

VOLUME 17, SUPPLEMENT 1, JUNE 2015

# BIPOLAR AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES DISORDERS

EDITORS

K. N. Roy Chengappa • Samuel Gershon

PITTSBURGH, USA

---

THE OFFICIAL JOURNAL OF  
The International Society for Bipolar Disorders

**17th Annual Conference  
of the International Society  
for Bipolar Disorders  
June 3–6, 2015  
Toronto, Canada**

**WILEY** Blackwell

# Welcome to the 17th Annual Conference of the International Society for Bipolar Disorders.

On behalf of the Scientific Program, Steering and Local Organizing Committees of the 17<sup>th</sup> Annual Conference of the International Society for Bipolar Disorders (ISBD), we would like to welcome you to Toronto for 4 days of engaging scientific programming

that offers something for everyone, including presentations on a diverse array of topics from leading experts, luminaries in the field of advocacy, hands-on workshops, social and networking opportunities, and a few surprises.

## Overview

We are pleased to announce that the opening evening of the conference will feature a special keynote presentation from Margaret Trudeau entitled “Changing My Mind,” during which she will share her personal life story, from becoming a prime minister’s wife at a young age, to the loss of both her son and her former husband, to her journey of acceptance and recovery from bipolar disorder. Other keynote presentations will include the following topics.

- What Have Observational Cohort Studies Taught Us About the Emergence and Course of Bipolar Disorder Among Youth
- The Future of Diagnosis in the Bipolar Spectrum
- Understanding the Neural Circuitry of Bipolar Disorder: Present and Future Neuroimaging Approaches
- Modeling Bipolar Disorder with Induced Pluripotent Stem Cells: Developmental and Functional Dimensions
- Apples and Pears Are Similar, But Not the Same (a Bipolar Disorder-Schizophrenia Borderlines talk)
- Is There a Schizophrenia/Bipolar Disorder Border?
- Revisiting Suicide Risk: Experience, Development and Psychopathology
- Tracking Behavioral Symptoms of Bipolar Disorder Using Automated Sensing and Delivering Personalized Interventions Using Smartphones

The opening evening will also include an expanded ISBD Awards Ceremony where we will again present the Samuel Gershon Junior Investigator Awards, the Mogens Schou Awards, the ISBD Kupfer-Frank Distinctive Contribution Award, and a new ISBD Scholars Award, which will recognize the efforts of a group

of inspiring individuals whose contributions in the areas of leadership, mentorship and clinical advancement are making a difference in their communities and by extension in the global community of those working to improve the lives of bipolar patients everywhere. The Awards Ceremony will be followed by our traditional welcome reception, providing delegates an opportunity to network, discuss topics from earlier in the day or just catch up with colleagues for a break in the action.

For those participating in an ISBD workshop or our International Satellite, the conference experience will begin even prior to the opening ceremony. The International Satellite is more than just a glimpse into the high quality scientific program to follow; it is an experience in its own right, featuring talks from Dr. Mauricio Tohen, Dr. Ayal Schaffer, Dr. Benjamin Goldstein, Dr. Gustavo Vazquez, Dr. Sagar Parikh and Dr. Manuel Sanchez de Carmona, President of the ISBD. The workshops will again include the extremely popular “State of the Art in Diagnosing, Assessing and Treating Bipolar Disorder: A Training Course to Improve your Skills as a Bipolar Expert,” as well as two new courses, “Implementing Longitudinal Clinical Assessment Programs in Bipolar Disorder” and “Evidence-Based Assessment of and Psychotherapy for Bipolar Disorder in Youth.”

Look for the familiar tracks system from the 16<sup>th</sup> Annual Conference in Seoul, which will allow delegates to hear a number of talks around specific topics, including clinical, basic science, special populations and treatment, as well as an entirely new track entitled “Experts by Experience.” Experts by Experience sets a new precedent for the ISBD meeting by integrating the voices of those with lived experience of bipolar disorders into the fabric of the meeting and creating unique opportunities for dialogue with clinicians and

others who dedicate their lives to those living with this challenging disease.

Of course, the conference will also feature staples from past meetings, including early morning brainstorming sessions, oral communications, poster sessions, industry satellites and the ISBD membership meeting, which is a chance for newcomers to learn more about ISBD and for returning members to get a deeper understanding of developments in the Society over the past year and our plans for the future.

We would like to thank all the delegates attending the 17<sup>th</sup> Annual Conference of the International Society for Bipolar Disorders, the members of our Conference committees, our ISBD staff, our board and our PCO, Kenes International, for making this extraordinary event possible.

***Manuel Sanchez de Carmona, MD***  
***President, ISBD***  
***Chair, Steering Committee***  
***Co-Chair, Scientific Program Committee***

***L. Trevor Young, MD, PhD***  
***Chair, Scientific Program Committee***  
***Co-Chair, Steering Committee***

***Sagar Parikh, MD, FRCPC***  
***Chair, Local Organizing Committee***  
***Co-Chair, Scientific Program Committee***  
***Co-Chair, Steering Committee***

***Vivek Singh, MD***  
***Co-Chair, Scientific Program Committee***  
***Co-Chair, Steering Committee***

***Ayal Schaffer, MD, FRCPC***  
***Co-Chair, Local Organizing Committee***



## CONFERENCE CHAIRS

### **L. Trevor Young, MD, PhD**

Chair, Scientific Program Committee  
Co-Chair, Steering Committee  
Dean of Faculty of Medicine, University of Toronto

### **Vivek Singh, MD**

Co-Chair, Steering Committee  
Co-Chair, Scientific Program Committee  
Associate Professor of Psychiatry, University of Texas  
Interim Vice Chair for Clinical Affairs, Medical Director of  
University Hospital Psychiatric Services  
Director of the Psychiatric Consultation Liaison Service and Chairman of the  
Institutional Review Board, University of Texas  
Health Science Center at San Antonio

### **Sagar Parikh, MD, FRCPC**

Chair, Local Organizing Committee  
Co-Chair, Scientific Program Committee  
Deputy Psychiatrist-in-Chief, University Health Network  
Director of Continuing Mental Health Education, University of Toronto  
Professor of Psychiatry, University of Toronto

### **Manuel Sanchez de Carmona, MD**

Chair, Steering Committee  
Co-Chair, Scientific Program Committee  
Bipolar Connection Clinical Group  
ISBD Mexico, Mexico City

### **Ayal Schaffer, MD, FRCPC**

Co-Chair, Local Organizing Committee  
Head, Mood and Anxiety Disorders Program, Sunnybrook  
Health Sciences Centre  
Deputy Psychiatrist-in-Chief, Sunnybrook Health Sciences Centre  
Associate Professor of Psychiatry, University of Toronto

## STEERING COMMITTEE

### **Manuel Sanchez de Carmona, MD, Chair**

Bipolar Connection Clinical Group  
ISBD Mexico, Mexico City, Mexico

### **L. Trevor Young, MD, PhD, Co-Chair**

Dean of Faculty of Medicine  
University of Toronto, Canada

**Vivek Singh, MD**  
Associate Professor of Psychiatry  
University of Texas Health Science Center at San Antonio, USA

**Trisha Suppes, MD, PhD**  
Professor, Psychiatry and Behavioral Sciences  
Stanford School of Medicine, USA

**Sagar Parikh, MD, FRCPC**  
Professor of Psychiatry  
University of Toronto, Canada

**Lakshmi Yatham, MBBS, FRCPC, MRCPsych**  
Professor of Psychiatry  
University of British Columbia, Regional Head  
Department of Psychiatry, VCH/PHC, Canada

#### **SCIENTIFIC PROGRAM COMMITTEE**

**L. Trevor Young, MD, PhD, Chair**  
Dean of Faculty of Medicine  
University of Toronto, Canada

**Manuel Sanchez de Carmona, MD, Co-Chair**  
Bipolar Connection Clinical Group  
ISBD Mexico, Mexico City, Mexico

**Vivek Singh, MD, Co-Chair**  
Associate Professor of Psychiatry  
University of Texas Health Science Center, San Antonio, USA

**Sagar Parikh, MD, FRCPC, Co-Chair**  
Professor of Psychiatry  
University of Toronto, Canada

**Ayal Schaffer, MD, FRCPC**  
Associate Professor of Psychiatry  
University of Toronto, Canada

**Lakshmi Yatham, MBBS, FRCPC, MRCPsych**  
Professor of Psychiatry  
University of British Columbia, Regional Head  
Department of Psychiatry, VCH/PHC, Canada

**David Kupfer, MD**  
Thomas Detre Professor of Psychiatry  
University of Pittsburgh School of Medicine, USA

**Ellen Frank, PhD**  
Professor, Department of Psychiatry  
University of Pittsburgh School of Medicine, USA

**Mauricio Tohen, MD, DrPH, MBA**  
Professor and Chairman, Department of Psychiatry  
University of New Mexico School of Medicine, USA

**Terrance Ketter, MD**  
Professor, Chief, Bipolar Disorders Clinic  
Stanford University School of Medicine, USA

**Benjamin Goldstein, MD, PhD, FRCPC**  
Associate Professor, Departments of Psychiatry and Pharmacology  
University of Toronto, Canada

**Allan Young, MD, ChB, MPhil, PhD, FRCPsych, FRCPC**  
Chair and Head of Psychiatry  
Imperial College, London, UK

**Willem Nolen, MD, PhD**  
Emeritus Professor, University Medical Center Groningen  
University of Groningen, The Netherlands

**Carlo Altamura, MD**  
Professor of Psychiatry  
University of Milan, Italy Chairman, Department of Psychiatry  
Fondazione IRCCS Ospedale Maggiore Policlinico of Milan, Italy

**Michael Wong, MB, BS (HK), MRCPsych (UK), FHKCPsych, FHKAM**  
Department of Psychiatry  
Queen Mary Hospital, Hong Kong  
The University of Hong Kong, Hong Kong

**Tadafumi Kato, MD, PhD**  
Senior Team Leader  
Lab for Molecular Dynamic of Mental Disorders  
RIKEN Brain Science Institute, Japan

**Kyooseob Ha, MD, PhD**  
Professor of Psychiatry, Seoul National University  
Director General, Seoul National Hospital, Korea

**Pichet Udomratn, MD**  
Professor of Psychiatry, Faculty of Medicine  
Prince of Songkla University, Thailand

**Phillip Mitchell, PhD**  
Scientia Professor and Head of the School of Psychiatry  
University of New South Wales, Sydney, Australia

**Gin Malhi, MD**  
Head of Department, Department of Psychiatry  
University of Sydney, Australia

**Michael Berk, MD**  
Professor of Psychiatry, School of Medicine  
Deakin University and University of Melbourne, Australia

**Flavio Kapczinski, MD, PhD**  
Professor, Department of Psychiatry and Behavioral Sciences  
University of Texas at Houston, Houston, USA

**Danilo Quiroz, MD**  
Assistant Professor, Department of Psychiatry  
Diego Portales University, Santiago, Chile

**Oscar Heeren, MD**  
Department of Psychiatry  
Cayetano Heredia University, Peru

**Beny Lafer, MD**  
Professor, Director, Bipolar Research Program  
University of São Paulo, Brazil

**Mohammed Alsuwaidan, MD, MPH, FRCPC**  
Academic Psychiatrist  
Kuwait Center for Mental Health, Kuwait

**Allen Doederlien**  
President  
Depression and Bipolar Support Alliance, USA

**Andrew Kcomt**  
Research Consultant  
Mood Disorders Association of Ontario, Canada

**Valerie Taylor, MD, PhD**  
Associate Clinical Professor, Psychiatry & Behavioural Neurosciences  
McMaster University, Canada

**Jan Scott, PhD, FRCPsych**  
Emeritus Professor of Psychological Medicine  
Newcastle University & Institute of Psychiatry, Newcastle upon Tyne, UK

**Aysegul Ozerdem, MD, PhD**  
Professor of Psychiatry  
Dokuz Eylul University Faculty of Medicine, Turkey

**Michael Bauer, MD, PhD**  
Director and Chairman  
University Hospital Carl Gustav Carus, Germany

## **REGIONAL ORGANIZING COMMITTEE**

**Sagar Parikh, MD, FRCPC, Chair**  
Professor of Psychiatry  
University of Toronto, Canada

**Ayal Schaffer, MD, FRCPC**  
Associate Professor of Psychiatry  
University of Toronto, Canada

**SohamRej, MD, MSc**  
Geriatric Psychiatry Fellow  
University of Toronto, Canada

**Benjamin Goldstein, MD, PhD, FRCPC**  
Associate Professor, Departments of Psychiatry and Pharmacology  
University of Toronto, Canada

**Lakshmi Yatham, MBBS, FRCPC, MRCPsych**  
Professor of Psychiatry  
University of British Columbia, Regional Head  
Department of Psychiatry, VCH/PHC, Canada

**Roger McIntyre, MD, FRCPC**  
Professor of Psychiatry and Pharmacology  
University of Toronto, Canada

**Martin Alda, MD, FRCPC**  
Professor and Killam Chair in Mood Disorders  
Dalhousie University, Canada

**Valerie Taylor, MD, PhD**  
Associate Clinical Professor, Psychiatry & Behavioural Neurosciences  
McMaster University, Canada

**Glenda MacQueen, MD, PhD, FRCPC**  
Vice Dean of Faculty of Medicine  
University of Calgary, Canada

**Roumen Milev, MD, PhD, FRCPC**  
Head of Department, Department of Psychiatry  
Queen's University, Canada

**Anny Duffy, MD**  
Associate Professor of Psychiatry  
University of Calgary, Canada

**Serge Beaulieu, MD, PhD, FRCPC**  
Associate Professor of Psychiatry  
McGill University, Canada

# Contents

<b>Keynote Lectures</b>	8
<b>Symposium I</b>	
Clinical neurodevelopmental phenotypes of bipolar disorder	11
<b>Symposium II</b>	
Big data in bipolar disorder	12
<b>Symposium III</b>	
Engaging families in the treatment of Bipolar Disorder	13
<b>Symposium IV</b>	
Bioenergetic anomalies in bipolar disorders: new evidence and implications	13
<b>Symposium V</b>	
Staging and neuroprogression in bipolar disorder	14
<b>Symposium VI</b>	
Creativity Artistic Genius and Bipolar Disorder	15
<b>Symposium VII</b>	
Who benefits from psychotherapy for bipolar disorder?	16
<b>Symposium VIII</b>	
Machine learning approaches for featuring bipolar disorder at personal level: is there any translational impact?	17
<b>Symposium IX</b>	
Bipolar, Borderline, Both? Clinical, Neurocognitive, and Genetic Overlaps and Divergences	18
<b>Symposium X</b>	
Cognitive impairment in bipolar disorder: is it preventable or treatable?	19
<b>Symposium XI</b>	
Predicting lithium response	20
<b>Symposium XII</b>	
Neuroinflammatory markers in bipolar disorders	21
<b>Symposium XIII</b>	
Web-based Support for Self-Management in Bipolar Disorder: new interventions and new horizons	22
<b>Symposium XIV</b>	
Accumulating data and dissipating controversy in pediatric bipolar disorder research	23
<b>Symposium XV</b>	
From I to we - from illness to wellness - psychoeducation, wellness measures, and the therapeutic alliance	24
<b>Symposium XVI</b>	
Practical clinical trials: multicenter, non-industry-funded pharmacological and psychological interventions in the post-genomics era	25
<b>Symposium XVII</b>	
Role of circadian rhythms and sleep in the course of bipolar disorders: from genes, through critical periods to treatment	26
<b>Symposium XVIII</b>	
An ISBD bipolar disorder in older adults taskforce update: how should current evidence guide practice and research?	27
<b>Symposium XX</b>	
Spirituality and Faith in Recovery: resilience, purpose, identity, and healing	28
<b>Symposium XXI</b>	
Results of the international society for bipolar disorders task force on suicide: systematic review and meta-analyses	29
<b>Symposium XXII</b>	
Socio-emotional cognition in bipolar disorder: what do we know and where to next?	30
<b>Symposium XXIII</b>	
Drug treatments for geriatric bipolar disorder: a perspective from the isbd geriatric bipolar taskforce	31
<b>Symposium XXIV</b>	
Bipolar depression: new vistas for the research and clinical ecosystem	32
<b>Symposium XXV</b>	
Experts by experience: consumer's experience of coping with suicidal thoughts	33
<b>Symposium XXVI</b>	
Clinical and biological factors as targets of intervention for bipolar spectrum disorders	34
<b>Symposium XXVII</b>	
Redefining mixed states in dsm-5: findings from 2 large datasets and discussion of the mixed features specifier	35
<b>Symposium XXVIII</b>	
Psychopathological and neurodevelopmental antecedents of bipolar disorder	36
<b>Symposium XXIX</b>	
Service Users as Powerful and Active Educators in the Health Professions and Beyond	37
<b>Symposium XXX</b>	
Varenicline for bipolar depression with comorbid nicotine dependence	38
<b>Symposium XXXI</b>	
Cross-cultural issues in family interventions for bipolar disorder	39
<b>Symposium XXXII</b>	
Advances on the management of bipolar disorder in pregnancy	39
<b>Symposium XXXIII</b>	
Laughing Like Crazy Stand Up Comedy Peer Support Program for People with Mental Illness: Research Results	40
<b>Symposium XXXIV</b>	
Inflammatory processes and bipolar disorder: etiological and treatment considerations	41
<b>Symposium XXXV</b>	
Understanding mood instability in bipolar disorder: from psychopathology to neurobiology to therapy	42
<b>Symposium XXXVI</b>	
Effective psychosocial interventions: tailoring to patient stages and needs while achieving optimal dissemination	43
<b>Brainstorming Sessions</b>	45
<b>Rapid Communications</b>	49
<b>Posters</b>	58
<b>Author Index</b>	143



# Keynote Lecture I

## Chair: Manuel Sanchez de Carmona

### Advocacy talk – Changing My Mind

**M Trudeau**

*Celebrated Canadian Mental Health Advocate*

Canadians fell in love with Pierre Elliott Trudeau's beautiful bride when he brought her to the world stage as the youngest First Lady in the history of the country. Yet, as time went by, Margaret was unprepared for public life, and plagued by mood swings. After three sons with Pierre, the marriage ended. She then remarried and had two more children. But the tragic loss of her son, Michel, in a skiing accident and the passing of Pierre Trudeau a few years later, were too much to bear, and she became severely ill.

Today, Margaret has rebuilt her life once again. Now, she brings her formidable life story to the stage in her quest to help others, sharing her message of resilience with the goal of helping to inspire others and to erase the stigma surrounding mental health issues.

### Pediatric bipolar disorder – what have observational cohort studies taught us about the emergence and course of bipolar disorder among youth

**B Birmaher**

*Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, USA*

Bipolar Disorder (BD) often onsets during adolescence, but it can take several years for it to be correctly diagnosed and treated,

resulting in deleterious consequences for the psychosocial functioning of the youth. Therefore, there is a need for studying the initial presentation and prodromal symptoms of this illness. The Bipolar Offspring Study (BIOS) is the largest existing high-risk study that prospectively follows offspring of parents with BD and offspring of community control parents. After adjusting for confounding factors (e.g., demographic variables, parental non-BD psychopathology), BIOS found that subsyndromal manic symptoms, depressive episodes, affective lability, irritability and behavior problems specifically increased the risk for BD in offspring of parents with BD. These results have important clinical implications for the treatment of BD and the study of the mechanisms underlying it.

Once a child is diagnosed with BD, it is important to understand the longitudinal trajectories and factors associated with the course of illness because these factors may be amenable to treatment. The Course and Outcome of Bipolar Youth (COBY) prospectively followed a large sample of youth with BD. During 9 years of follow-up, approximately 2/3 showed poor to moderate course and 1/3 were euthymic most of the time. Despite that some youth had a predominantly euthymic course, many showed poor longitudinal functioning, mainly due to the presence of comorbid disorders and other environmental factors. Interestingly, the fact that a subgroup of youth were euthymic most of the follow-up time suggests that a developmentally limited form of BD may exist. Factors associated with the different longitudinal mood trajectories as well as the longitudinal functioning will be discussed.

# Keynote Lecture II

## Chair: Sagar Parikh

### The future of diagnosis in the bipolar spectrum

**D Kupfer<sup>a</sup>, B Cuthbert<sup>b</sup>**

*<sup>a</sup>Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, USA, <sup>b</sup>RDoC Unit, National Institute of Mental Health, Bethesda, USA*

During the past five years, considerable attention has been devoted to the completion of the DSM-5 and the initiation of the RDoC process by the National Institute of Mental Health (NIMH). While it has sometimes appeared that they serve different purposes and lack crosswalks for the clinician or the researcher, the two approaches share a common commitment to facilitate progress that can lead to improved patient care. RDoC comprises an integrative, brain-behavior framework to study functional mechanisms within and/or across disorder categories – not to develop a substitute classification for the DSM-5 but rather to generate a research literature that can inform future revisions of the DSM, leading to

neuroscience-based, precision-medicine diagnostic strategies and treatment approaches.

The bipolar spectrum represents a superb example of opportunities for potentially important collaborations. Numerous changes were made for bipolar disorders in DSM-5, starting with the addition of a separate bipolar disorders chapter. Specific changes include adding activity/energy to the main criterion for mania, as well as changing the criteria for mixed states and adding new specifiers. The next steps could include the use of predictive biomarkers to improve outcome by enhanced treatment selection, and RDoC-informed clinical trials that target mechanisms in specific subgroups – possibly reflecting current subtypes, but also newly identified clusters based upon novel combinations of measures from different levels of analysis. For example, objective assessment of activity levels or neurocognitive measures in various mixed states could increase the likelihood of finding more specific treatments across the entire bipolar spectrum.

## Understanding the neural circuitry of bipolar disorder: present and future neuroimaging approaches

**M Phillips**

*Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, USA*

**Background:** The NIMH RDoC initiative advocates for a re-conceptualization of psychiatric disorders as dimensions of pathology that cut across conventionally-defined diagnostic categories. My laboratory has adopted conventional diagnostic and dimensional approaches to elucidate functional abnormalities in neural circuitries supporting cognitive and emotional processes, including reward processing, known to be aberrant in bipolar and mood spectrum disorders, with the goal of identifying biomarkers reflecting key pathophysiologic processes that may predict future functional and clinical outcome and ultimately provide neurobiological targets to guide treatment choice.

**Methods:** My presentation will focus on neuroimaging studies in (1) adults with bipolar disorder; (2) adults seeking treatment for

psychological distress, regardless of diagnosis; (3) youth at familial risk for bipolar disorder; (4) behaviorally and emotionally dysregulated youth across the diagnostic range.

**Results:** In adults, abnormally elevated reward circuitry activity was associated with a bipolar disorder diagnosis and having high scores on trait risk-taking and impulsive sensation seeking behaviors. Regions included ventral striatum (VS) and left ventrolateral prefrontal cortex, important for reward value-encoding and decision-making regarding potential outcomes. Youth at familial risk for bipolar disorder, and youth with greater behavioral and emotional dysregulation, showed abnormally elevated activity during reward processing in middle prefrontal cortical regions mediating attention to outcomes, and disrupted VS-ventrolateral prefrontal cortical connectivity. Greater reward-related VS-prefrontal cortical connectivity predicted future worsening of behavioral and emotional dysregulation in youth.

**Conclusions:** Neuroimaging studies are beginning to identify biomarkers reflecting underlying pathophysiologic processes across the bipolar and mood disorder spectrum, that can help predict future clinical and functional outcome.

# Keynote Lecture III

## Chair: Vivek Singh

### Basic research – modeling bipolar disorders with induced pluripotent stem cells: developmental and functional dimensions?

**M McInnis<sup>a</sup>, S O'Shea<sup>b</sup>**

*<sup>a</sup>Psychiatry, University of Michigan, Ann Arbor, USA, <sup>b</sup>Cell and Developmental Biology, University of Michigan, Ann Arbor, USA*

The capacity to study human disease is substantially enhanced with the development of model cellular systems wherein details of the pathophysiology may be deconstructed and the knowledge gained used to determine underlying disease mechanisms and drug discovery. A further benefit of a model system is the capability to study and compare physiological conditions and interventions at the molecular level. There are few models of psychiatric disorders that allow detailed study of pathophysiology and interventions at the individual patient level. Induced pluripotent stem cells (iPSC) offer the opportunity to derive models using specific tissue from independent mature cells; neuronal tissue may be derived from fibroblasts through iPSC reprogramming technologies. Neuronal cells derived from individuals with bipolar disorder clearly differ from those unaffected in several respects. There is greater reactivity in response to a stimulus to provoke an action potential; the reactivity appears to be modified by lithium. The measure of the reactivity is the calcium related amplitude and transient of the action potential; this may be of interest given that one of the genes implicated in bipolar disorder is the CACNA1C gene, a subunit of a voltage dependent calcium channel. The iPSC approach provides for the study of cellular developmental fate; neuronal cells from bipolar individuals have a preponderance to express ventral fate markers over markers that indicate a dorsal expression pattern. The molecular differences in bipolar disorder appear to be present at the earliest developmental stages of the nervous system.

The potential for preventive and personalized medicine is considerable. The limits of this technology are unknown in neuropsychiatric disorders and substantial basic research is needed before an

individual treatment plan based on the analysis of the individual iPSC model is routine.

### Apples and pears are similar, but not the same

**H Grunze**

*Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK*

Categorical classification systems in psychiatry come under increasing scrutiny as their validity and discriminatory power are questioned based on findings of overlapping candidate genes, neurobiology, neuroanatomy and, finally, clinical symptoms. Especially the validity of the schizophrenia-bipolar distinction remains controversial; e.g., Lake and Hurwitz (2006) postulated that a single disease, a mood disorder with a broad spectrum of severity, accounts for functional psychoses.

However, there are good arguments for a schizophrenic syndrome that is clearly distinguishable from affective disorders based on illness course and treatment response, e.g. to lithium (Johnstone et al, 1988). Epidemiological studies have shown that –different from bipolar disorders- the pattern of course and outcome in schizophrenia are more predictable. Brockington et al. (1979) were able to distinguish a similar cohort of patients on the basis of 2 year outcome data. Prospective follow up of juvenile cohorts with schizophrenia, schizoaffective disorders and bipolar disorder also demonstrated the distinctively higher functionality in bipolar disorder (Ledda et al, 2009). Although there is an overlap of candidate genes between schizophrenia and bipolar disorder, we are not yet in a position to judge to what degree this justifies or dismisses a spectrum vs. separable disorders.

Finally, a dimensional approach to SA by unifying affective and psychotic disorders may be attractive from a clinician's point of view, but categorical classifications remain to be crucial to research. The introduction of diagnostic categories by a dimen-

sional approach may lead to “double book keeping”: a dimensional diagnosis used for the medical practice and a categorical one for research and insurance reimbursement purposes. The future will tell whether DSM5’s attempt to combine categories and dimensions (“specifiers”) is of any help to solve this dilemma.

## **Is there a schizophrenia/bipolar disorder border?**

**M Tohen**

*Psychiatry, University of New Mexico, Albuquerque, USA*

Author will review the differences in the epidemiology, diagnosis, course and treatment between schizophrenia and bipolar disorders. Special emphasis will be made in diagnostic stability and response to different treatments in recent onset conditions.

# **Keynote Lecture IV**

## **Chair: L. Trevor Young**

### **Clinical biological – revisiting suicide risk: experience, development and psychopathology**

**G Turecki**

*Psychiatry, McGill University, Montreal, Canada*

Suicide and related behaviors are complex phenomena associated with different risk factors. While most individuals who display suicidal behavior do not have a history of early-life adversity, a significant minority does. Dr. Turecki will discuss results from his laboratory suggesting that early-life adversity increases risk of suicide by altering epigenetic processes in discrete genetic loci. Enduring differential gene expression regulation resulting from these altered epigenetic processes are likely to influence the development of stable emotional and behavioral phenotypes that, in turn, increase suicide risk. In this talk Dr. Turecki will discuss recent data suggesting that these mechanisms are at play in the regulation of aggressive behavior and other behavioral traits that increase risk for suicidal behavior.

### **Tracking behavioral symptoms of bipolar disorder using automated sensing and delivering personalized interventions using smartphones**

**T Choudhury**

*Cornell University, New York, USA*

Mobile and ubiquitous computing research has led to new techniques for cheaply, accurately, and continuously collecting data on

human behavior that include detailed measurements of physical activities, social interactions and conversations, as well sleep quality and duration. Continuous and unobtrusive sensing of social and physical functioning has tremendous potential to support the lifelong management of mental illnesses by: (1) acting as an early warning system to detect changes in mental well-being, (2) delivering context-aware, personalized micro-interventions to patients when and where they need them, and (3) by significantly accelerating patient understanding of their illness. These unique properties of mobile and ubiquitous computing seem particularly well suited for the management of bipolar disorder.

Developing effective health-care interventions is a complex task. Like any medical intervention, the successful introduction of mobile sensing technologies into mental health care needs to address factors related to patient and clinician acceptance. In order for passive sensing to have a major impact on serious mental illness, technologists need to bring a consideration of patients and their clinicians to bear on system development. This includes: providing individuals with control, being sensitive to the ways information is shown to the user, and recording only as much information as is needed to support clinical decision-making and privacy. Technologists are only beginning to address the challenges associated with striking the right balance between cutting-edge technology and patient needs. In this presentation, I will give an overview of our work on turning sensor-enabled mobile phones into well-being monitors and instruments for administering real-time/real-place interventions. I will also describe our efforts to develop strategies that strike a balance between the potential for ubiquitous sensing and user acceptance.

# Symposium I

## Clinical Neurodevelopmental Phenotypes of Bipolar Disorder

### Chair: Melvin McInnis

#### Developmental patterns of bipolar disorder

A Duffy, J Horrocks, S Doucette, D Keown-Stoneman, A Andreazza, T Young, P Grof

*University of Calgary, Calgary, Canada*

**Background:** Longitudinal studies of offspring of bipolar parents inform the natural history of illness development and the identification of associated multimodal risk indicators.

**Methods:** Assessment of bipolar parents attending specialty services was conducted using SADS-L interviews and best estimate diagnosis. Affected parents were divided on the basis of long-term response to lithium (LiR vs LiNR) to reduce heterogeneity. High-risk offspring completed KSADS-PL/SADS-L interviews and validated scales of perceived attachment and temperament. Exposure to parental illness over the first 10 years of life was estimated. In a subset, plasma protein levels of BDNF and inflammatory markers were determined.

**Results:** High-risk offspring who develop bipolar disorder did so in a predictable series of clinical stages, starting from non-specific childhood antecedents including sleep and anxiety disorders to minor mood and then depressive disorders. Multi-state models support a forward progression through defined stages. Offspring of LiNR develop a wider range of antecedent and end-stage psychopathology compared to offspring of LiR. Evidence suggests that perceived neglect from mother and high emotionality predict mood disorders. Further that early exposure (0–2 years) to parental illness is a risk factor for subsequent psychopathology. Finally, plasma levels of BDNF and IL-6 differentiated high-risk from controls and early from later stage illness.

**Conclusions:** Clinical staging produces a developmentally refined phenotype and advances studies of illness risk and progression. The study of candidate risk indicators over development is an important step in advancing understanding and treatment of mood disorders in high-risk youth.

#### Combined use of clinical and genetic information in the prediction of risk for bipolar disorder

Jl Nurnberger<sup>a</sup>, H Wilcox<sup>c</sup>, A Glowinsky<sup>d</sup>, P Mitchell<sup>e</sup>, J Fullerton<sup>e</sup>, L Hulvershorn<sup>a</sup>, M Kamali<sup>b</sup>, N Ghaziuddin<sup>b</sup>, D Koller<sup>a</sup>, T Foroud<sup>a</sup>, H Edenberg<sup>a</sup>

<sup>a</sup>University of Indiana, Indianapolis, USA, <sup>b</sup>University of Michigan School of Medicine, Ann Arbor, USA, <sup>c</sup>Johns Hopkins University, Baltimore, USA, <sup>d</sup>Washington University School of Medicine, St Louis, USA, <sup>e</sup>University of New South Wales, Sydney, Australia

As part of a five-site collaborative study, we have been following 300 adolescents/young close relatives of a bipolar proband (cases), along with 150 age-matched controls. We now have the following

clinical information on each subject: (1) lifetime diagnostic interview using the K-SADS-BP; (2) best estimate diagnoses plus quantitative ratings of lifetime severity of mood, anxiety, and behavioral symptoms; (3) diagnostician's summary of clinical features including chronicity, psychosis, comorbid substance abuse, disability, and course of illness; (4) detailed history of substance use; (5) history of medication treatment; (6) best estimate diagnostic assessment of each parent; (7) detailed history of suicidal behavior; (8) history of stressful life events; (9) follow-up diagnoses after 3–5 years. The lifetime risk for cases is about 30–40% and for controls about 7%. The use of additional clinical variables should help to identify subjects at the greatest clinical risk. Genetic information: We have previously summarized data from 33 single nucleotide polymorphisms chosen on the basis of a combined analysis from the Psychiatric Genomics Consortium (PGC BP group, 2011). These data discriminated affected persons, relatives, and high-risk cases from controls (Fullerton et al., submitted for publication). We now have data from the PsychChip, a newly designed platform that includes a genome-wide framework, with special focus on thousands of genomic areas suggested by previous studies of psychiatric disorders. A PsychChip comparison database approaching 100,000 subjects is expected to be available in 2015 through the PGC. We will describe the development of predictive algorithms using these combined datasets.

#### Australian longitudinal cohort: focus on structural and functional neuroimaging

P Mitchell<sup>a</sup>, G Roberts<sup>a</sup>, MLR Breakspear<sup>b</sup>, M Green<sup>a</sup>, A Lord<sup>b</sup>, W Wen<sup>a</sup>, A Frankland<sup>a</sup>

<sup>a</sup>University of New South Wales, Sydney, Australia, <sup>b</sup>Mental Health Institute of Medical Research, Brisbane, Australia

**Background:** There have been few neuroimaging reports of young people at high genetic risk of bipolar disorder (BP).

**Methods:** The Australian longitudinal cohort of 12–30 year-olds comprises 165 children or siblings of probands with confirmed BP, 135 from families with no mental illness, and 65 with established BP. This study investigated functional and structural imaging (sMRI and DTI) in these three groups.

**Results:** We have previously reported the fMRI finding of a significant lack of recruitment of the inferior frontal gyrus (IFG) when inhibiting responses to fearful faces in the high-risk participants compared with controls. We now study resting state functional connectivity of the IFG, finding functional dysconnectivity between the left IFG and a network of regions including bilateral insulae, dorsal anterior cingulate cortex, superior temporal gyri and the putamen. Dysconnectivity in high risk subjects was intermediate between those with BP and controls. Hypothesising that this functional deficit in the IFG reflects the convergence of

broader network dynamics underlying the coordination of emotion processing and cognitive control, we have also studied effective connectivity in the fMRI data. Using dynamic causal modelling we found that the models that embody nonlinear, hierarchical relationships show stronger empirical support in the healthy control group than the other models tested. DTI structural connectivity

analyses suggest impaired connections between the IFG and other regions.

**Conclusions:** These studies of young people at high risk of BP suggest functional and structural differences prior to the onset of this condition, with convergent evidence implicating involvement of the IFG.

## Symposium II

# Big Data in Bipolar Disorder

### Chair: John Richard Geddes

#### Stratifying risk using large-scale electronic health records data

**RY Perlis, T McCoy, A Wiste, M Ostacher, V Castro**

*Department of Psychiatry, Harvard University, Boston, USA*

**Background:** The availability of large numbers of longitudinal patient care records provides an emerging opportunity to stratify risk for adverse outcomes and facilitate more targeted treatment in the mood disorders.

**Method:** We will describe examples of the application of machine learning techniques to derive and validate risk stratification tools and decision support tools in the treatment of mood disorders. After providing an overview of how such models are derived, we will summarize strengths and limitations of this approach.

**Results:** We have developed a model that estimates risk for developing renal failure during lithium treatment with an area under the receiver operating characteristic curve exceeding 0.8, and identifies multiple modifiable risk factors. Related families of models estimating risk for outcomes such as falls and hospital readmission, using both coded and uncoded data types, will also be considered.

**Conclusion:** With attention to important considerations such as control of confounding, avoidance of overfitting, assessment of generalizability/portability, and means of visualization, large clinical data sets provide an opportunity to substantially improve clinical ability to stratify adverse outcome risk.

#### Assessing brain-behaviour volatility in bipolar disorder

**AC Nobre, C Harmer, N Nelissen, A Baker, M Woolrich, P Harrison, J Geddes**

*Department of Experimental Psychology, University of Oxford, Oxford, UK*

Our current understanding of the bipolar phenotype is largely based on retrospective assessment from patients. The availability of scalable methods of prospective monitoring of mood and behaviour, and the potential to link these to temporally ordered neuropsychological and neural processes, has the potential to transform our understanding of the mood instability that underlies clinical bipolar disorder. In the new CONBRIO programme, we will use the big data produced by prospective methods to derive a deeper understanding into the neurobiology of mood instability, generating valid new treatment targets as well as efficient experimental models for treatment developments. In particular we will explore the utility of the construct of mood instability identified to underpin the psychological profile of the disorder by large-scale prospec-

tive epidemiological methods. Young healthy adults meeting the DSM-5 criteria for bipolar II disorder (not medicated or in treatment) and well-matched control participants will be recruited through a common mechanism for intensive cognitive neuroscientific studies that will explore patterns of variability in neural, physiological, cognitive, and mood measures. We will test whether mood instability arises from deficits in the stability of neural systems and failures of specific regulatory mechanisms to sustain and balance emotional and cognitive functions. Initial results indicate that it is possible to measure daily fluctuations in behavioural measures and dynamical changes in neural networks to characterize patterns of volatility between groups.

#### The chronorecord experience: 10 years of electronic daily self-reported mood charting

**M Bauer**

*Carl Gustav Carus TU Dresden, Department for Psychiatry and Psychotherapy, Dresden, Germany*

With the rapid emergence and acceptance of IT technologies, alternative measures of mental state and behavior are being developed for screening, diagnosis, and monitoring. In contrast to symptoms reported by patients directly to psychiatrists, these measures will be based on data collected from computers and diverse sensors within smartphones, devices, and wearable technology, as well as data collected from Internet usage and activities. The fact that bipolar disorders (BD) are characterized by great variation in diurnal changes in mood, sleep and activity as well as episode frequency, severity, duration, and polarity, BD are prime candidates for using novel technologies that help to identify rapid changes in patient's behavior. The prospective assessment fluctuations of patients' mood and sleep allows for detailed assessment of frequency and pattern of illness. Simultaneous comparison of daily mood fluctuations and medications may help to optimize complex pharmacological therapy and to better detect nuances of partial response. Another benefit of daily self-reporting of mood is increased patient involvement in their care. For more than 10 years, we have explored the use of a home computer based system as a way to improve data collection and analysis in longitudinal studies of BD. Patients with BD showed high acceptance of a computer-based system for self-reporting of daily data. Automation of data collection can reduce missing data, eliminate errors associated with data entry and allows the use of familiar statistical techniques for analysis. Results of specific research questions and experiences with patient's views from 10-year experience will be presented.

# Symposium III

## Engaging Families in the Treatment of Bipolar Disorder

Chair: David Miklowitz

### The role of the family in treating people with bipolar disorder

**M Walker**

*International Bipolar Foundation, San Diego, USA*

Muffy Walker is Chairman of the *International Bipolar Foundation*. She will speak as a caregiver and patient advocate about the role of the family in treating people with BD. Inclusion of family members in identifying stressors and early warning signs of relapse, developing an emergency treatment plan, and assuring compliance with medications can be critical to a person's health. Not to be overlooked is the tremendous social stress that BD places on family members. Family treatment and advocacy from support groups can help caregivers and patients to cope in a healthy way.

### Communicating effectively with family members

**D Farb**

*Peer Support Worker, Mood Disorders Association of Ontario, Ontario, Canada*

Daniel Farb is a peer support worker in the Family Matters Program at the Mood Disorders Association of Ontario (MDAO). The MDAO assists individuals with mood disorders in communicating effectively with family members as part of their own recovery, and on helping family members maintain wellness while supporting a relative with mood difficulties. Mr. Farb has piloted a "Dealing with Family" program for individuals with chronic and

recurrent mood disorders to help strengthen family relationships, talk about self-stigma and shame, and develop assertiveness and self-advocacy skills. In addition to his personal experiences with mental health and recovery, Mr. Farb brings a wealth of experience being a supporter of a family member with a mood disorder.

### Family-focused therapy

**DJ Miklowitz**

*Psychiatry, University of California at Los Angeles (UCLA), Los Angeles, USA*

Dr. Miklowitz will describe his evidence-based program of family-focused therapy (FFT) as adjunctive to pharmacotherapy for bipolar adults and adolescents. FFT is composed of three consecutive modules: psychoeducation, communication training, and problem-solving skills training. FFT has several objectives: (1) identifying early warning signs and stress factors associated with illness recurrences; (2) implementing coping strategies to prevent full episodes; (3) family education regarding adherence with medications; (4) distinguishing personality, temperament, and variations in normal development from mood episodes; and (5) enhancing family relationships that protect against recurrences. Citing research from randomized trials, he will discuss the conditions under which FFT produces greater or lesser benefits in adults or adolescents with BD.

# Symposium IV

## Bioenergetic Anomalies in Bipolar Disorders: New Evidence and Implications

Chair: Bruce Cohen

### In vivo, stimulation induced abnormalities of brain bioenergetics in bipolar disorder

**D Ongur<sup>a</sup>, C Yuksel<sup>a</sup>, F Du<sup>a</sup>, BM Cohen<sup>b</sup>**

*<sup>a</sup>Schizophrenia & Bipolar Disorders Program, McLean Hospital, Belmont, USA, <sup>b</sup>Program for Neuropsychiatric Research, McLean Hospital, Belmont, USA*

Bioenergetic processes, including the production and utilization of ATP, play critical roles in brain function. Several lines of evidence

have implicated abnormalities in these processes in the pathophysiology of bipolar disorder (BD). Following ATP synthesis, the high-energy phosphate bond in ATP can be converted to a storage form, Phosphocreatine (PCr), by the enzymes creatine kinase (CK). At times of high energy demand, neurons maintain ATP concentrations by reversing the CK reaction and generating new ATP from PCr. 31P Magnetic Resonance Spectroscopy (MRS) provides a unique window into these processes in vivo. In a series of studies, we have explored them in euthymic stable patients with

bipolar I disorder (BD). Dr. Ongur will present data showing that at baseline ATP and PCr concentrations, as well as the CK reaction rates, appear normal in BD. However, the response of this system to heightened energy demand (probes using visual photic stimulation) is abnormal. Interestingly, pH of brain parenchyma is reduced in the occipital cortex in BD, even without visual stimulation. These findings suggest that bioenergetic function is partially compensated in BD at baseline. Acidic pH is the only sign of bioenergetic compromise at this stage. Straining the system with high energy demands unmasks underlying abnormalities. In our multidisciplinary collaboration, we have collected fibroblasts from the patients who participated in imaging studies. We are correlating CK enzyme activity ex vivo with our MRS measures in vivo, as we test for the convergence of key molecular and tissue findings in these studies.

### Bioenergetics and redox modulations in psychiatric illnesses

**AC Drevets<sup>a,b</sup>, G Scola<sup>a</sup>, LT Young<sup>a,b</sup>**

<sup>a</sup>Departments of Pharmacology and Psychiatry, University of Toronto, Toronto, Canada, <sup>b</sup>Centre for Addiction and Mental Health, Toronto, Canada

There is increasing evidence that energy dysfunction (i.e. altered bioenergetics) through mitochondrial dysfunction and consequent cellular redox modulation may play a role in the determination and expression of psychiatric illnesses. In recent years, sophisticated clinical measures are unveiling links between mitochondrial dysfunction, redox modulation and disease domains. Moreover, preclinical work is convergent in identifying redox modulations as a key element in neuronal connectivity and overall brain function. Thus, Dr. Drevets will provide an overview of the role of mitochondrial bioenergetics and redox modulations in psychiatric disorders, including the presentation of unpublished data that move the field forward in identifying these pathways as pathophysiological mechanisms in psychiatric disorders. She will first discuss clinical evidence of altered redox modulations and mitochondrial function in patients with mood disorders and schizophrenia, and then Dr. Drevets will discuss the link among mitochondrial bioenergetics, redox modulations and inflammatory pathways. Over-

all, Dr. Drevets will highlight the above-mentioned mechanisms as functionally-linked cellular processes likely to be involved in the biological changes that underlie the expression of behavioral traits characteristic of psychiatric disorders.

### Mitochondrially-mediated plasticity and the search for improved therapeutics for bipolar disorder

**W Drevets**

*Global Therapeutic Area Head, Neuroscience, Johnson & Johnson Pharmaceuticals Group, Titusville, USA*

Mitochondria play crucial roles in energy production, predominantly through the electron transport chain (ETC), and are crucial regulators of apoptosis, calcium signaling, and synaptic plasticity. They move throughout neurons to provide energy for intracellular signaling. In humans, growing evidence from genetic, postmortem, and neuroimaging studies suggests that subtle impairments in mitochondrial function may play an important role in the pathophysiology of bipolar disorder. Specifically, recent genetic studies have demonstrated that polymorphisms in mitochondria-related genes are risk factors for bipolar disorder, and postmortem studies found decreased ETC activity/expression and increased nitrosative and oxidative stress (OxS) in the brains of individuals with bipolar disorder. Bipolar disorder has also been associated with increased OxS, calcium dysregulation, and increased pro-apoptotic signaling in peripheral blood. Finally, neuroimaging studies have consistently found decreased energy and pH levels in the brains of individuals with bipolar disorder. In addition, the mood stabilizer lithium increases levels of B-cell lymphoma 2 (Bcl-2) and Bcl-2 associated athanogene (BAG-1), both of which regulate mitochondrial function and have neurotrophic effects in both rodents and humans; these effects may underlie lithium's effects on cellular resilience and affect the long-term course of bipolar disorder. Taken together, the evidence suggests that targeting mitochondrial function and specifically the role that mitochondria play in energy metabolism, synaptic plasticity, and cell survival may be key to developing new mood-stabilizing agents aimed at this promising novel target.

## Symposium V

# Staging and Neuroprogression in Bipolar Disorder

## Chair: Flavio Kapczinski

### Pathways to neuroprogression

**M Berk**

*School of Medicine, IMPACT Strategic Research Centre, Deakin University and University of Melbourne, Geelong, Australia*

On aggregate, major psychiatric disorders progress from an at-risk period, to the prodrome, a first episode, recurrence then chronicity. Along this path, the illness course and response patterns change, with poorer response in later stages where a greater risk of recurrence and more easily triggered recurrence are evident. In many

disorders, such as schizophrenia, bipolar disorder and depression, there is parallel evidence of both progressive neurostructural change and cognitive decline. There is an increasingly defined biological process of neuroprogression that appears to mediate this process. Its components include changes in apoptosis, inflammatory cytokines, corticosteroids, neurotrophins, neurogenesis, mitochondrial dysfunction and oxidative stress. Inflammatory oxidative and nitrosative stress can cause increased vulnerability to apoptosis, lipid peroxidation, DNA damage, telomere shortening, decreased BDNF and other neurotrophins and protein carbonyla-

tion. This can damage the anatomical substrates that for example modulate mood, further driving the cycle of illness. Many psychotropic agents such as lithium, antidepressants and atypical antipsychotics impact components of the neuroprogressive cascade. More interestingly, a series of repurposed and novel agents including N-acetyl cysteine, statins and anti-inflammatory agents such as statins and aspirin have neuroprotective potential.

## Overweight and obesity as risk factors for clinical and neurobiological illness progression in early-stage bipolar disorder

**D Bond**

*University of Minnesota, Laboratory for Neuropsychiatric Imaging, Minneapolis, USA*

**Aims:** Up to 75% of people with bipolar disorder (BD) are overweight or obese. Studies in patients with lengthy illnesses, typically 10–20 years in duration, show that obese patients have worse long-term outcomes than normal-weight patients, including more mood episodes, more frequent suicide attempts, lower medication response rates, and greater disability. However, the association of obesity with clinical outcomes early in the illness, when long-term disease patterns are established, has received less attention. As well, the impact of weight on neurobiological illness progression has not been explored.

**Methods:** We investigated (1) the association of weight with mood illness severity in a cohort of bipolar patients the 12 months after their diagnosis of bipolar disorder; (2) determined the impact of weight on neurobiological illness severity and progression, measured using MRI; and (3) examined serum inflammatory markers as potential mediating factors between obesity and illness progression.

**Results:** At recovery from their first mania, patients' mean BMI was within the normal range, and only a quarter were overweight/obese. However, during the first 12 months of maintenance treatment, patients gained a mean of 4.9 kg, and 47% experienced clinically significant weight gain (CSWG;  $\geq 7\%$  of baseline weight), resulting a 12-month overweight/obesity rate of over 50%. Patients with CSWG spent 23% more time with depression over 12 months than those without CSWG, and had significantly poorer psychoso-

cial functioning. At the brain level, patients with baseline overweight/obesity had extensive volume reductions compared to normal-weight patients in frontal, temporal, and subcortical limbic brain areas, and increased hippocampal glutamate/glutamine. Patients with 12-month CSWG had additional limbic brain volume loss compared to those without CSWG. Higher weight was strongly associated with greater serum inflammatory cytokines, which in turn predicted depressive relapse.

**Conclusions:** Increased weight is a potentially modifiable cause of clinical and neurobiological illness progression early in the course of bipolar disorder. Weight-related changes in serum biomarkers may mediate the association between obesity and outcomes in bipolar patients.

## Allostatic load and neuroprogression

**I Grande**

*Bipolar Disorders Unit, Hospital Clinic de Barcelona, Barcelona, Spain*

Many psychiatric disorders, such as bipolar disorder (BD), follow a progressive path. Clinical, neuroimaging and neurocognitive studies support the progressive nature of BD. Lithium and psychotherapy may be less effective if used later in the course of illness. Moreover, structural brain changes are not consistently found at illness onset and may evolve along with chronicity. Similarly, patients with BD may have cognitive deficits that become more apparent as long as the number of episodes increase. The allostatic load (AL) hypothesis contributes to the understanding of these modifications along the course of the illness. This concept provides a theoretical explanation of the “wear and tear” that occur in patients with chronic mental disorders regarding stressors, added factors such as substance use and the illness itself. These factors may induce modulations on the brain circuits that may lead to decreasing responsiveness to therapy, the observed structural changes and the associated cognitive decline. This remodeling furthermore increases the vulnerability to future illness episodes. In this lecture, we will portray the concept of allostasis, allostatic load (AL) and allostatic overload (AO) and their application to explain the dimensional impact and the neuroprogression of psychiatric illnesses, such as BD.

# Symposium VI

## Creativity, Artistic Genius and Bipolar Disorder

### Chair: Manuel Sanchez de Carmona

## Vincent van Gogh, biography, family history and artistic genius

**J Calabrese**

*Mood Disorders Program, Bipolar Disorders Research Center, Cleveland, USA*

**Objectives:** Detail the interface between van Gogh's psychiatric symptoms and his artistic genius. Describe the exponential increase in artistic productivity observed during van Gogh's most impaired disabling years of life. Carefully detail his Axis I disorders using contemporary diagnostic methodology. This presentation will review Vincent van Gogh's family history, his relationships with

the women in his life, his medical and psychiatric history, his failed careers, and their apparent impact or lack of impact on his artistic productivity.

## Pyotr I Tchaikovsky, musical creativity and his cyclic illness

**M Sanchez de Carmona**

*Psiquiatria, Centro Médico Infinito, Mexico City, Mexico*

**Objectives:** Review Tchaikovsky's biography, artistic creativity and its correlation with his history of mental illness, analyze the



relationship between his musical productivity and mood disorder symptomatology, and describe his interaction with his social environment, including the consequences and impairment due to his disorder. Composer Pyotr Ilych Tchaikovsky is widely considered the most popular Russian composer in history. His works includes *The Sleeping Beauty* and *The Nutcracker*. He struggled with a mood disorder and a complicated personal life. Tchaikovsky suffered from mood swings, anxiety and was hospitalized after he unsuccessfully attempted to commit suicide. His artistic productivity is clearly connected with his psychiatric symptoms and its impact on his functionality and social interaction.

## The Bipolar Roadshow – a creative approach to educating the audience and fighting stigma

M Kolbe

DGBS, Deutsche Gesellschaft für Bipolare Störungen, Zurich, Switzerland

A brief recall of my life as a bipolar composer and musician; retrospective of the Bipolar Roadshow which travelled throughout Germany in May, 2014.

# Symposium VII

## Who Benefits from Psychotherapy for Bipolar Disorder?

Chair: Andrew Nierenberg

### Extreme attributions and affective instability predict response to psychotherapy for depression in STEP-BD

DJ Miklowitz<sup>a</sup>, JP Stange<sup>b</sup>, LG Sylvia<sup>c</sup>, PV da Silva Magalhaes<sup>d</sup>, MW Otto<sup>e</sup>, E Frank<sup>f</sup>, NS Hansen<sup>g</sup>, DD Dougherty<sup>c</sup>, M Berk<sup>h</sup>, AA Nierenberg<sup>c</sup>, T Deckersbach<sup>c</sup>

<sup>a</sup>UCLA School of Medicine, Los Angeles, USA, <sup>b</sup>Department of Psychology, Temple University, Philadelphia, USA, <sup>c</sup>Massachusetts General Hospital, Harvard Medical School, Boston, USA, <sup>d</sup>Universidade Federal de Rio Grande de Sul, Porte Alegre, Brazil, <sup>e</sup>Boston University, Boston, USA, <sup>f</sup>University of Pittsburgh, Pittsburgh, USA, <sup>g</sup>University of Colorado, Boulder, USA, <sup>h</sup>Deakin University and University of Melbourne, Melbourne, Australia

Extreme pessimistic attributional style (e.g. “black and white thinking”) predicts increases in depressive symptoms in bipolar disorder, particularly when individuals experience life stressors. In STEP-BD, extreme attributions, assessed pre-treatment with the Attributional Style Questionnaire (ASQ), predicted lower likelihood of recovery ( $p = 0.01$ ) and longer time until recovery ( $p < 0.04$ ), independent of the effects of manic or depressive symptom severity at baseline. Patients with high affective instability also are at risk for poorer outcomes of depression treatment. In STEP-BD, instability of symptoms of depression and mania both predicted a lower likelihood of recovery and longer time until recovery, independent of the effects of symptom severity (for all comparisons,  $p < .05$ ).

### The role of age at onset, course of illness and sleep in response to psychotherapy in bipolar disorder

E Frank<sup>a</sup>, A Peters<sup>b</sup>, LG Sylvia<sup>c</sup>, PV da Silva Magalhaes<sup>d</sup>, DJ Miklowitz<sup>e</sup>, MW Otto<sup>f</sup>, NS Hansen<sup>g</sup>, DD Dougherty<sup>c</sup>, M Berk<sup>h</sup>, AA Nierenberg<sup>c</sup>, T Deckersbach<sup>c</sup>

<sup>a</sup>University of Pittsburgh, Pittsburgh, USA, <sup>b</sup>University of Illinois at Chicago, Chicago, USA, <sup>c</sup>Massachusetts General Hospital, Boston, USA, <sup>d</sup>Universidade Federal de Rio Grande de Sul, Porte Alegre, Brazil, <sup>e</sup>UCLA School of Medicine, Los Angeles, USA, <sup>f</sup>Boston University, Boston, USA, <sup>g</sup>University of Colorado, Boulder, Boulder, USA, <sup>h</sup>Deakin University and University of Melbourne, Melbourne, Australia

Response to pharmacotherapy appears to diminish with greater illness chronicity. However, less is known about whether patients' prior course of illness is related to responses to psychotherapy. Dr. Frank will focus on the role of previous mood episodes, age of illness onset, illness duration and sleep as predictors or moderators of the likelihood of recovery and time until recovery with STEP-BD intensive psychotherapy vs. collaborative care. Independently of treatment condition, participants with 1–9 prior depressive episodes were more likely to recover and had faster time to recovery than those with 20 or more prior depressive episodes. Participants with fewer than 20 prior manic episodes had faster time to recovery than those with 20 or more manic episodes. Longer illness duration predicted a longer time to recovery. Surprisingly, age of onset neither predicted the rate of or the time to recovery. Participants were more likely to recover in intensive psychotherapy than collaborative care if they had 10–20 prior episodes of depression (Number Needed to Treat NNT = 2.0), but equally likely to respond to psychotherapy and collaborative care if they had 1–9 (NNT = 32.0) or > 20 (NNT = 9.0) depressive episodes. There was no difference in recovery rates between intensive psychotherapy and collaborative care for normal sleepers (NNT = 100), but short sleepers (NNT = 4.6) and long sleepers (NNT = 5.3) were slightly more likely to recover with intensive psychotherapy than with collaborative care. Limitations of the findings and implications for treating clinicians will be discussed.

## Anxiety disorder and medical comorbidity predict response to psychotherapy for depression in STEP-BD

T Deckersbach<sup>a</sup>, A Peters<sup>b</sup>, LG Sylvia, PV da Silva Magalhaes<sup>c</sup>, DJ Miklowitz<sup>d</sup>, MW Otto<sup>e</sup>, E Frank<sup>f</sup>, NS Hansen<sup>g</sup>, DD Dougherty<sup>a</sup>, M Berk<sup>h</sup>, AA Nierenberg<sup>a</sup>

<sup>a</sup>Massachusetts General Hospital, Harvard Medical School, Boston, USA, <sup>b</sup>University of Illinois at Chicago, Chicago, USA,

<sup>c</sup>Universidade Federal de Rio Grande de Sul, Porte Alegre, Brazil,

<sup>d</sup>UCLA School of Medicine, Los Angeles, USA, <sup>e</sup>Boston University, Boston, USA, <sup>f</sup>University of Pittsburgh, Pittsburgh, USA,

<sup>g</sup>University of Colorado, Boulder, USA, <sup>h</sup>Deakin University and University of Melbourne, Melbourne, Australia

At least 50% of individuals with bipolar disorder have a lifetime anxiety disorder. Individuals with both bipolar disorder and a co-occurring anxiety disorder and those with medical conditions experience longer illness duration, greater illness severity, and poorer treatment response. This study investigates whether co-morbid lifetime anxiety in bipolar patients and those with medical conditions predicted and/or moderated psychotherapy treatment outcome

(intensive psychotherapy vs. collaborative care, a brief psychoeducational intervention). Participants with a lifetime anxiety disorder were more likely to recover with psychotherapy than with collaborative care (66% vs. 49% recovered over 1 year; Number Needed to Treat NNT = 5.88 [small – medium]). For patients without a lifetime anxiety disorder, there was no difference between rates of recovery in psychotherapy versus collaborative care (64% vs. 62% recovered; NNT = 50 [small]). Participants with one lifetime anxiety disorder were likely to benefit from intensive psychotherapy (84% vs. 53% recovered; NNT = 3.22 [medium – large]), whereas patients with multiple anxiety disorders showed no difference in response to the two treatments (54% vs. 46% recovered; NNT = 12.5 [small]). Higher medical comorbidity was associated with lower likelihood of recovery in both treatment conditions, but did not moderate treatment outcome. Higher body mass index was marginally associated with longer time until recovery. Intensive psychotherapy yielded superior recovery rates for individuals of normal body mass index (i.e. normal weight), but response rates to intensive psychotherapy and collaborative care did not differ among overweight and obese participants. Implications of psychiatric and medical comorbidity will be discussed.

# Symposium VIII

## Machine Learning Approaches for Featuring Bipolar Disorder at Personal Level: Is There Any Translational Impact?

Chair: Carlo Altamura

### Machine learning approach to help diagnose children and adolescents with bipolar disorder

J Soares

Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center-Houston, Houston, USA

**Objectives:** Pediatric bipolar disorder is currently diagnosed based on signs and symptoms, and without objective diagnostic biomarkers. In the present study, we investigated the utility of structural neuroanatomical signatures of the amygdala to objectively detect pediatric bipolar disorder.

**Methods:** Structural T1-weighted neuroimaging scans were obtained from 16 children and adolescents with unmedicated DSM-IV bipolar disorder (11 males, five females) and 16 matched healthy controls (11 males, five females). Voxel-based gray matter morphometric features extracted from a bilateral region-of-interest within the amygdala were used to develop a multivariate pattern analysis model which was utilized in predicting novel or ‘unseen’ individual subjects as either bipolar disorder or healthy controls.

**Results:** The model assigned 25 out of 32 subjects the correct label (bipolar disorder/healthy) translating to a 78.12% diagnostic accuracy, 81.25% sensitivity, 75.00% specificity, 76.47% positive predictive value, and 80.00% negative predictive value and an area under the receiver operating characteristic curve (ROC) of 0.81. The predictions were significant at  $p = 0.0014$  (2 test  $p$ -value).

**Conclusions:** These results reaffirm previous reports on the existence of neuroanatomical abnormalities in the amygdala of pediatric patients with bipolar disorder. Remarkably, the present study

also demonstrates that neuroanatomical signatures of the amygdala can predict individual subjects with bipolar disorder with a relatively high specificity and sensitivity. To the best of our knowledge, this is the first study to present a proof-of-concept diagnostic marker of pediatric bipolar disorder based on structural neuroimaging scans of largely medication-naïve patients.

### Using pattern recognition and neuroimaging to decode present and future symptom severity in behaviorally and emotionally dysregulated youth

M Phillips

University of Pittsburgh Medical School, Pittsburgh, USA

**Introduction:** We have used neuroimaging and pattern recognition techniques to classify individuals, case by case, into bipolar versus unipolar depression, and high versus low-bipolar-risk, categories. Here, we used these techniques to decode individual-level behavioral and emotional dysregulation severity based on patterns of reward-related activity.

**Methods:** 57 youth (mean 14.5 years) from the multi-site Longitudinal Assessment of Manic Symptoms (LAMS) study of behaviorally- and emotionally-dysregulated youth performed a block-design reward paradigm during neuroimaging. Pattern regression analyses comprised Relevance Vector Regression and cross-validation. Medication was a binary confounding variable (taking,

not taking). Decoded and actual clinical scores were compared. Permutation tests estimated significance. We also used a similar approach to determine whether patterns of reward circuitry functional connectivity could predict future behavioural and emotional dysregulation severity in 79 LAMS youth.

**Results:** In the first study, patterns of reward-related neural activity were identified that decoded behavioral and emotional dysregulation severity in LAMS youth at initial study screen ( $r = 0.44$ ,  $p = 0.002$ ), and close to the scanning session ( $r = 0.35$ ,  $p = 0.008$ ). Neural regions with the highest contribution to the model included cerebellum, sensory processing regions and fronto-limbic regions. In the second study, patterns of functional connectivity in reward circuitry significantly predicted individual youth-level emotional dysregulation severity at mean = 15.8 months post scan ( $r = 0.37$ ,  $p < 0.005$ ).

**Conclusions:** Together, these findings suggest that neuroimaging and pattern recognition techniques can help predict the future progression of behavioral and emotional dysregulation symptoms in individual youth. These neuroimaging measures could act as biologically-relevant markers to help predict likely future outcomes, and thereby guide treatment optimization from an early age in vulnerable young individuals.

## Classification of first episode psychosis: a multi-modal multi-feature approach

**P Brambilla**

*Department of Experimental & Clinical Medicine, ICBN, University of Udine, Udine, Italy*

**Introduction:** Currently, most of the classification studies of psychosis focused on chronic patients and employed single machine learning approaches. To overcome these limitations, we here compare, to our best knowledge for the first time, different classification methods of First Episode Psychosis (FEP) using multimodal imaging data exploited on several cortical and subcortical structures and white matter fiber bundles.

**Methods:** FEP patients and age-, gender-, and race-matched healthy participants were included in the study. Innovative machine learning techniques, including Multiple Kernel Learning (MKL) and linear support vector machine (SVM), were implemented on structural MRI (sMRI), diffusion tensor imaging (DTI), and dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI).

**Results:** Our results on sMRI and DTI show a discrimination accuracy greater than 90% between healthy subjects and patients with FEP (Peruzzo et al. Journal Neural Transmission 2014). Regions with an accuracy greater than 70% on different imaging sources and measures were middle and superior frontal gyrus, parahippocampal gyrus, uncinate fascicles and cingulum. Also, using DSC-MRI data, linear SVM reached an accuracy of 83% in the classification of patients and normal controls, with the highest accuracy associated with right frontal lobe and left parietal lobe (Squarcina et al. Submitted).

**Conclusions:** Our studies show that machine learning approaches integrating multimodal and multisource imaging data can classify FEP patients with high accuracy. Interestingly, specific grey matter structures, white matter bundles and perfusion indexes reach high classification reliability, potentially outlining a right prefronto-parieto-limbic network useful to classify FEP.

# Symposium IX

## Bipolar, Borderline, Both? Clinical, Neurocognitive, and Genetic Overlaps and Divergences

### Chair: Brian Palmer

#### Bipolar, borderline, both? Clinical, neurocognitive, and genetic overlaps and divergences

**B Palmer, S Kung, K Schak, R Alarcon, M Frye**

*Department of Psychiatry and Psychology, Mayo Clinic, Rochester, USA*

Given that bipolar disorder and borderline personality disorder are common causes of “treatment resistant” depression, we sought to identify (1) whether screening tests could be useful in identifying these disorders in the inpatient setting, and (2) what items on the tests could best differentiate one disorder from the other. To examine this, 757 sequential admissions to an inpatient psychiatric

Mood Disorder Unit completed both the Mood Disorder Questionnaire (MDQ) and the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). Using the discharge diagnosis of a board-certified psychiatrist as the gold standard, the MDQ with a cutoff of 7 had good sensitivity (86.7%) and adequate specificity (66.9%) for identifying the 130 patients with a bipolar disorder diagnosis, and the MSI-BPD with a cutoff of 7 also had good sensitivity (73.2%) and reasonable specificity (63.3%) for identifying the 60 patients with borderline personality disorder. Both screening tests were positive in 13.2% of cases. MDQ items related to self-confidence, racing thoughts, and distractibility were most associated with a negative screen on the MSI-BPD (i.e., bipolar but not borderline), while questions about impulsivity

(spending, risk-taking), irritability, and rapid speech offered were more likely to reflect positive MSI-BPD screens. Similarly, on the MSI-BPD, questions regarding identity disturbance and self-injury were associated with low likelihood of a positive MDQ screen (i.e., borderline but not bipolar), and items regarding non-suicidal impulsivity and feeling like things were unreal were most associated with a positive MDQ screen. These findings can help differentiate these disorders and have clear treatment implications.

### Distinguishing bipolar disorder and borderline personality disorder: utilising laboratory measures of cognition

**K Saunders<sup>a</sup>, R Rogers<sup>b</sup>, G Goodwin<sup>a</sup>**

<sup>a</sup>Oxford University Department of Psychiatry, Warneford Hospital, Oxford, UK, <sup>b</sup>School of Psychology, Adelaide Brigantia, UK

Bipolar disorder and borderline personality disorder are common psychiatric diagnoses. Despite contrasting etiologies they can be difficult to differentiate because of overlapping clinical presentations and symptoms. Diagnostic accuracy is important because of their polarized treatment approaches: long term treatment with mood stabilizers for bipolar disorder and psychotherapy for borderline personality disorder. Age and IQ matched women with bipolar disorder, borderline personality disorder and a healthy control group were compared in a series of cognitive tasks. Borderline personality disorder was associated with a failure to establish and maintain reciprocal cooperation in a game theoretic measure of social exchange. This behavioral change was not seen in euthymic bipolar disorder. Borderline personality disorder was also associated with an insensitivity to reward and losses in a risky decision-making task compared to the bipolar and healthy control group. Using a simple two-choice reaction task post error slowing was significantly amplified in the borderline group despite overall reaction times and error rates being similar in all three groups. Laboratory measures of social exchange, decision making and psychomotor performance highlight fundamental difficulties in borderline personality disorder not seen in euthymic bipolar disorder. These findings support the differentiation of bipolar disorder from borderline personality disorder and identify important potential treatment targets.

### Analysis of the genetic overlap of borderline personality disorder and bipolar disorder

**SH Witt<sup>a</sup>, F Frank<sup>a</sup>, J Treutlein<sup>a</sup>, S Heilmann<sup>b</sup>, A Forstner<sup>b</sup>, N Kleindienst<sup>c</sup>, T Mühleisen<sup>b</sup>, F Degenhardt<sup>b</sup>, M Jungkunz<sup>c</sup>, B Krumm<sup>d</sup>, S Cichon<sup>b,e</sup>, A Tadic<sup>f</sup>, N Dahmen<sup>f</sup>, CE Schwarze<sup>f</sup>, B Schott<sup>g,h</sup>, L Dietl<sup>h,i</sup>, MM Nöthen<sup>b</sup>, K Lieb<sup>f</sup>, S Roepke<sup>f</sup>, D Rujescu<sup>j</sup>, C Schmah<sup>e</sup>, MRM Bohus<sup>c</sup>**

<sup>a</sup>Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim | Heidelberg University, Mannheim, Germany, <sup>b</sup>Institute of Human Genetics and Department of Genomics, Life & Brain Center University of Bonn, Bonn, Germany, <sup>c</sup>Department of Psychosomatic Medicine, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany, <sup>d</sup>Department of Biostatistics, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany, <sup>e</sup>Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland, <sup>f</sup>Department of Psychiatry and Psychotherapy, University Medical Center, Mainz, Germany, <sup>g</sup>Leibniz Institute for Neurobiology, Magdeburg, Germany, <sup>h</sup>Department of Psychiatry, Charité-Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, <sup>i</sup>Department of Psychiatry, Campus Benjamin Franklin, Charité-Universitätsmedizin, Berlin, Germany, <sup>j</sup>Department of Psychiatry, University of Halle, Halle, Germany

Borderline personality disorder (BPD) displays high co-morbidity, and a substantial overlap in terms of phenomenology, with bipolar disorder (BD) which suggests a common genetic background of the two disorders. To investigate the hypothesis that BPD and BD share genetic variation we (i) analysed known genetic risk factors for BD in a well-characterized BPD case-control cohort and (ii) compared the genetic overlap of the two disorders using genome-wide SNP data. Five genome wide significant variants identified for BD (in CACNA1C, ANK3, and ODZ4) were analysed in 673 BPD cases and 748 controls. A nominally significant association with BPD was found for rs1006737 in CACNA1C ( $p = 0.0498$ ). Sex specific analysis revealed that this signal was present in females only. Moreover, 1,300 BPD patients were analysed using the Infinium PsychArray BeadChip. Genetic overlap of BPD and BD in genome-wide data is currently analysed using polygenic scores and GCTA. This is the first report of an association between a BD risk gene and BPD where selection was not based on a priori hypotheses about its function but on an unbiased hypothesis-free screening of the genome. Genome-wide association data of large samples of BPD will eventually identify new risk genes and the overlap between BPD and BD if it exists.

## Symposium X

# Cognitive Impairment in Bipolar Disorder: Is it Preventable or Treatable?

## Chair: Lakshmi Yatham

### Cognitive impairment in bipolar disorder

**E Vieta**

University of Barcelona, Barcelona, Spain

Cognitive impairment is common in bipolar disorder. Besides comorbid conditions (psychiatric and non-psychiatric) and medica-

tion side effects, the illness itself can be a major source of cognitive deficits (subthreshold symptoms, allostatic load and neuroprogression). Cognitive deficits can be treated by treating some of those underlying causes (improving comorbidities, simplifying medication regimens) and with cognitive and functional remediation. The prevention of cognitive impairment can be achieved by increasing

cognitive reserve, doing exercise and following a healthy diet, and adhering to medication and psychoeducation to prevent recurrences, which are a major cause of neuroprogression.

### Neuroprotection in the aftermath of first episode mania

**M Berk<sup>a</sup>, R Daglas<sup>b</sup>, M Yucel<sup>c</sup>, SM Cotton<sup>c</sup>**

<sup>a</sup>Deakin University, Geelong, Australia, <sup>b</sup>University of New South Wales, Sydney, Australia, <sup>c</sup>Monash University, Melbourne, Australia

Despite cognition being normal or even superior to controls prior to a first episode of mania, there is a decline in cognitive capacity and concomitant neuroimaging changes that are arguably steepest in the interval after a first episode of mania. What is unclear, is the extent to which these can be prevented and which agents might be most useful for doing so. In this presentation, I will report the outcomes of a single-blind, randomised control trial of maintenance therapy with lithium compared to quetiapine after a first episode of mania. Cognition and structural imaging were the primary endpoints. This study examined a number of paper and pencil tests of neurocognition as well as a computerised battery including Cogstate that assessed various domains of function such as attention, processing speed, memory and executive function. The assessments were conducted at baseline, 3 and 12 months. Results assessing the impact of each treatment relative to baseline and between the treatments will be presented. Given that cognition is a major symptomatic domain of bipolar disorder and has substantive effects on

quality of life, functioning and symptomatic outcomes, I would argue that the ability to influence the trajectory of cognitive change is of considerable clinical importance.

### Cognitive impairment in bipolar disorder: is it treatable?

**L Yatham**

University of British Columbia, Vancouver, Canada

Cognitive impairment in bipolar disorder is associated with substantial impairments in social and occupational functioning. Hence, it is critical to develop strategies that improve cognition in patients with bipolar disorder. I will present evidence from two different data sets to show that cognitive function can be improved in bipolar patients. The first data set comes from the first episode mania program at UBC. Patients that are part of this cohort are treated with evidence based pharmacotherapy and psychological treatments based on CANMAT guidelines. Patients are assessed using neurocognitive battery at baseline and at regular intervals. The data suggest that patients who remain episode free show significant improvement in cognitive function in various domains. The second data will come from a study that is assessing the effects of lurasidone on cognition in euthymic patients with bipolar disorder. Patients with who show impairments on cognitive testing are recruited in to this randomized controlled trial, and allocated lurasidone add-on or treatment as usual for 6 weeks. All patients are assessed using the ISBD-Neurocognitive battery at baseline and at 6 weeks. The results will be presented at the meeting.

## Symposium XI

### Predicting Lithium Response

Chair: Frank Bellivier, Marc Masson

#### Biomarkers of lithium response in bipolar I patients

**F Bellivier<sup>a</sup>, J Moreira<sup>a</sup>, C Beniz<sup>a</sup>, B Etain<sup>b</sup>, C Boudebessé<sup>b</sup>, C Courtin<sup>a</sup>, PA Geoffroy<sup>a</sup>, C Marie-Claire<sup>a</sup>**

<sup>a</sup>INSERM UMR-S1144, AP-HP, FondaMental Foundation, Paris, France, <sup>b</sup>INSERM U955, Team 15, AP-HP, FondaMental Foundation, Créteil, France

**Background:** A key issue for research in bipolar disorders (BD) is understanding the mechanisms of action of key treatments such as mood stabilizers. Many researchers view circadian dysrhythmias as a core feature of BD and circadian dysregulations represent an important pathophysiological abnormality of BD. Interestingly, lithium may exert its therapeutic action through modifications of the circadian clock- hence offering a putative mechanism of action for this treatment.

**Methods:** We undertook two studies: (i) a pilot study comparing the circadian characteristics of euthymic patients treated with lithium to a group of euthymic bipolar patients treated with anticon-

vulsant; patients were evaluated using the CSM, CTI and PSQI questionnaires and a 21 days actimetry, (ii) To explore the molecular signature associated with lithium efficacy, we also conducted an in vitro comparison of the transcriptional profile of cell-lines drawn from a group of lithium responders and non-responders. Candidate mRNA and miRNA will be studied with a focus on circadian genes.

**Results:** Lithium treated patient had an increased activity amplitude, a reduced within day activity variability and were more vigorous (CTI) as well as of morning type (CSM), by comparison with patients treated with anticonvulsant. Data will be presented from two ongoing studies of the transcriptional profile of cell lines before and after the introduction of lithium in the cell culture – which allows us to identify transcripts that differentiate cell cultures drawn from lithium responders and non-responders.

**Conclusions:** Lithium may exert its therapeutic action through modifications of the circadian clock.

## Neural basis of lithium response: clues from neurocognitive interrogation and neuroimaging

GS Malhi

Department of Psychiatry, Sydney Medical School, University of Sydney, Sydney, Australia

**Background:** Lithium remains the best long-term treatment for the maintenance of mood stability and prophylaxis in bipolar disorder. Lithium responders have been characterized clinically but only in broad terms and the biological underpinning of its effects remains unknown (Malhi & Geddes 2014).

**Objective:** To present preliminary neuroimaging and neurocognitive data from research in lithium treated patients and those with suicidality in the context of extant literature.

**Methods:** Data will be presented from two ongoing studies. Patients receiving varying doses of lithium treatment and those not on medication recruited specifically for functional MRI investigations have undergone neuroimaging and neurocognitive testing. Analyses contrasting both task-related and resting-state, to identify the impact of lithium on emotion processing networks within the brain will be presented. Correlations between these findings and clinical variables will be discussed in the context of known neurocognitive changes caused by lithium and findings from contemporary brain imaging and neurocognitive studies. Similarly neuroimaging data from patients experiencing varying degrees of suicidality will be presented and discussed in the context of a model specific to bipolar disorder (Malhi et al 2013).

**Results and Conclusions:** Understanding the neurobiological effects of lithium, particularly in the context of emotion circuitry, is important because of lithium's key role in mood stabilisation in bipolar disorder. Lithium is also likely to provide a key to understanding the brain processes that culminate in suicidal thinking (Malhi 2014).

**References:** Malhi GS & Geddes JR. British Journal of Psychiatry 2014, 205(5). (In press). Malhi GS. Bipolar Disorders 2015 (in press). Malhi GS et al. Bipolar Disorders. 2013; 15(5):559–74.

## Clinical barriers to optimal outcomes with lithium: strategies to address the efficacy-effectiveness gap

J Scott

Newcastle University & Institute of Psychiatry, Newcastle upon Tyne, UK

This paper will address barriers to optimal outcomes and potential solutions by exploring system-, patient- and clinician-related issues. At a system level, lithium effectiveness is undermined by late introduction of treatment. A systematic review of the literature (with 29 studies ranging from patient surveys to psychopharmacology data) will be presented on duration of untreated bipolar disorder (DUB), highlighting particular sub-groups at risk of prolonged DUB. At a patient level, a survey of the 'Bipolar Organization' (UK) demonstrates that lithium is more popular than atypical antipsychotics, but that non-adherence remains a problem. A health beliefs model is used to demonstrate how a 'necessity-concerns' framework can identify who is at risk of non-adherence and when this is likely to occur. Lastly, results from a study of personal and professional beliefs of clinicians demonstrates that professional and 'team' characteristics can influence the extent to which different clinicians endorse the use of different treatments in BD. Also, patients with lower adherence are associated with teams with inconsistent attitudes.

**References:** Clatworthy J et al (2009) Understanding medication non-adherence in bipolar disorders using a Necessity-Concerns Framework. J Affect Disord. 116:51–5. Scott J et al (2014) Duration of untreated bipolar disorders: operationalization of the concept and systematic review of the literature. Paper submitted. Tacchi MJ et al (2012) Improving the understanding of medication non-adherence among mental health professionals. J Mental Health. 21:600–7.

# Symposium XII

## Neuroinflammatory Markers in Bipolar Disorders

### Chair: Ghanshyam Pandey

## Immune-inflammatory risk factors in bipolar disorders: gene environment interactions

M Leboyer<sup>a</sup>, J Oliveira<sup>a,b</sup>, N Hamdani<sup>a</sup>, B Etain<sup>a</sup>, R Krishnamoorthy<sup>a</sup>, R Tamouza<sup>a</sup>

<sup>a</sup>Hopital Henri Mondor, Université Paris-Est, Fondation FondaMental, Paris, France, <sup>b</sup>Hopital Saint Louis, Université Paris-Diderot, Fondation FondaMental, Paris, France

Bipolar disorder (BD) is a multi-systemic chronic mood disorder associated with medical comorbidities, originating in a dys-immune context, thought to be at the crossroad of gene and environment interplays. Extensive research pinpointed the effect of infectious events and/or of early stressful experiences both interacting with specific immunogenetic background. We have analyzed several genetic variants encoding molecules of the innate and the adaptive immune processes and found that the following gene variants were associated with early onset bipo-

lar disorder (i) the Toll-like receptors (TLR 2 and 4), sensors for the initiation of immune responses (Oliveira et al., 2014); (ii) HLA-G molecules, immune tolerogenic molecules (Debnath et al., 2013), (iii) Human Leukocyte Antigen (HLA) which represent the final achievement of a specific immune response. We suggest that the genetic control of innate immune responses is of major importance in the development of early onset BD, due to deficient inflammatory responses against pathogens but also following interactions with stressors. In particular, we found that both TLR2 polymorphisms and the presence of early sexual abuse were associated with earlier age at onset (Oliveira et al, submitted). Altogether, within a gene-environment model of BD, we suggest that the initiation of the above-mentioned immune responses can be seen as being a pathogen-based triggering, modulated by immunogenetic variants and induced by environmental events such as infections and/or stress.

**Pro-inflammatory cytokines and matrix metalloproteinase-9 (MMP-9) during acute episode and remission in bipolar disorder**

**J Rybakowski<sup>a</sup>, A Remlinger-Molenda<sup>a</sup>, J Losey<sup>b</sup>**

<sup>a</sup>Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland, <sup>b</sup>Clinical Neuroimmunology, Poznan University of Medical Sciences, Poznan, Poland

Dysfunctions of immune system and synaptic plasticity have been demonstrated in the pathogenesis of bipolar disorder (BD). The matrix metalloproteinase-9 (MMP-9) is a novel player in synaptic plasticity and we showed an association between its gene and a predisposition to BD. In our study, the concentration of interleukin (IL)-6 was higher during the manic state as compared to control group and to immediate remission after mania, and there was a correlation between IL-6 concentration and the intensity of the manic state. Serum levels of both MMP-9 and interferon (IFN)- $\gamma$  in manic patients and immediate remission after mania did not show any differences compared to healthy controls. In other studies, elevated levels in mania were found of tumor necrosis factor (TNF) alpha and its soluble receptor (sTNF-R1), as well as soluble receptor of IL-2 (sIL-2R). We also found elevated serum levels of both MMP-9 and IFN- $\gamma$  in bipolar depression; for MMP-9 both in acute phase and in immediate remission after depression, especially

in patients on earlier stage of the illness, and for IFN- $\gamma$  only in acutely depressed subjects. IFN- $\gamma$  level was higher in depressed patients comparing to remission and in remission after depression IFN- $\gamma$  was higher than in the healthy controls. In depression, serum concentrations of MMP-9 and IFN- $\gamma$  showed positive correlation. Also, concentration of IL-1 beta was higher in depressed patients comparing to healthy subjects. In patients with sustained remission (most of them on lithium), cytokine and MMP-9 concentrations were not different from those of healthy subjects.

**Microglial activation and inflammation in bipolar disorder**

**F Kapczinski**

Psychiatry & Behavioral Sciences, University of Texas at Houston, Houston, USA

Converging evidence points to increased inflammatory activity in patients with bipolar disorder. However, the source of such low grade inflammation remains unknown. Recent data obtained from post mortem datasets and PET studies suggest that microglial activation in discrete regions of the brain may play an important role in this process. The literature in the field is reviewed and future directions of research are outlined.

# Symposium XIII

## Web-based Support for Self-Management in Bipolar Disorder: New Interventions and New Horizons

Chair: Greg Murray

**If you build it, will they come? Opening access to a new online Bipolar Wellness Centre**

**E Michalak<sup>a</sup>, G Murray<sup>b</sup>**

<sup>a</sup>Psychiatry, University of BC, Vancouver, Canada, <sup>b</sup>Psychology, Swinburne University of Technology, Melbourne, Australia

The Quality of Life in Bipolar Disorder (QoL.BD) is the field's first condition-specific measure of QoL in BD. Reliable and valid, the QoL.BD instrument has now been translated into numerous languages and shown international update. The next obvious step in the lifecycle of the scale was to produce a web-based application. We used an integrated knowledge translation approach to develop, trial and test the online administration of the QoL.BD. More than just an online assessment scale, the QoL tool serves as a 'gateway' into a sophisticated online Bipolar Wellness Centre. Within the Wellness Centre are housed cutting-edge resources to support self-management in each of the QoL.BD's 14 domains, tailored to the patient's specific QoL profile (i.e. strengths and deficits). Given the considerable investment in the development of the QoL Tool and Wellness Centre, we are particularly interested in evaluating implementation strategies to maximise access to self-management via the site. Four novel implementation strategies are being tested: 1. A series of 14 domain-specific webinars, delivered by expert clinician or person with BD; 2. A series of 6 'day-in-the-life-of' videos, where an actress with BD illustrates concrete examples of self-man-

agement in day-to-day settings; 3. A travelling roadshow co-delivered by expert clinicians and patients with BD and; 4. A 'living library', where users can 'check out' an expert clinician or person with BD via secure telehealth software to help tailor the resources to their specific context. Data will be presented on the development and impact of these intervention strategies.

**Augmenting psychoeducation with a mobile intervention for bipolar disorder: a randomized controlled trial**

**C Depp<sup>a,b</sup>, J Ceglowski<sup>a</sup>, VC Wang<sup>a</sup>, F Yaghouti<sup>a</sup>, BT Mausbach<sup>a</sup>, WK Thompson<sup>a</sup>, EL Granholm<sup>a,b</sup>**

<sup>a</sup>Psychiatry, University of California San Diego, San Diego, USA,

<sup>b</sup>VA San Diego Healthcare System, San Diego, USA

Mobile technology is a particularly promising route to delivering self-management interventions in BD, in particular to link self-monitoring of mood with personalized planned coping strategies. In this talk, we describe a recently completed clinical trial of a mobile intervention for BD called Personalized Real-Time Intervention for Stabilizing Mood (PRISM). PRISM helps users develop implementation intentions to detail specific behaviors that participants plan to engage in "risky" emotional states, and these plans

are delivered when symptoms are recorded prospectively on a mobile device. In this first randomized trial of an intervention that employed mobile devices in BD, we evaluated the feasibility, acceptability and efficacy of PRISM. In 82 consumers diagnosed with BD who completed a four-session psychoeducational intervention and were assigned to 10 weeks of either: (1) mobile device delivered interactive intervention linking patient-reported mood states with personalized self-management strategies, or (2) paper-and-pencil mood monitoring. Participants were assessed at baseline, 6 weeks (mid-point), 12 weeks (post-treatment), and 24 weeks (follow up) with clinician-rated depression and mania scales and self-reported functioning. Compared to the paper-and-pencil condition, participants in the augmented mobile intervention condition showed significantly greater reductions in depressive symptoms at 6 and 12 weeks (Cohen's  $d$  for both were  $d = 0.48$ ). Thus, the trial provides some promising support for the effectiveness of mobile interventions on bipolar depression. This talk will conclude with a discussion of techniques to overcome methodological challenges in developing and testing self-management mobile interventions for BD.

### Supporting self-management in bipolar disorder online: a review

G Murray<sup>a</sup>, ND Leitan<sup>a</sup>, EE Michalak<sup>b</sup>, L Berk<sup>c</sup>, M Berk<sup>c</sup>

<sup>a</sup>Psychology, Swinburne University of Technology, Melbourne, Australia, <sup>b</sup>Psychiatry, University of BC, Vancouver, Canada,

<sup>c</sup>Psychology, Deakin University, Geelong, Australia

Psychosocial interventions for people living with BD are effective, but relatively few people have access to the specialised services that deliver such treatments. Self-management offers an important alternative which, as well as decreasing peoples' reliance on clinicians, also serves to empower and support a sense of agency. The internet is a potentially powerful modality for delivering self-management programs as it provides low cost, round the clock, user-friendly and self-directed support. This talk will describe a recent review of how delivery of self-management strategies online can be optimised. This review examines data and theory on BD self-management from a recovery-oriented perspective, with a particular focus on optimising low-intensity delivery of self-management tools via the internet. The review suggests that health professional and/or peer support, tailoring programs to individual needs and the thoughtful creation of a vibrant online community are important tools for increasing engagement and effectiveness of online self-management materials. Safety and risk-management issues have received insufficient attention to date. Online self-management programs for BD are becoming more common, and have great potential to fill the gap caused by limited therapeutic services. Further research is urgently required to test the efficacy of methods for optimising online self-management offerings, such as health professional and/or peer support, individualised tailoring and the development of empowered online communities with strong risk-management processes.

## Symposium XIV

# Accumulating Data and Dissipating Controversy in Pediatric Bipolar Disorder Research

### Chair: Robert Post

### The state of assessment for pediatric bipolar disorder: it is time to throw away the old textbook

E Youngstrom<sup>a</sup>, A Van Meter<sup>b</sup>

<sup>a</sup>University of North Carolina at Chapel Hill, Chapel Hill, USA,

<sup>b</sup>Yeshiva University, New York, USA

Although Kraepelin described cases of pre-pubertal onset of manic syndromes, and case reports appeared in subsequent decades, the modern study of bipolar disorder in children and adolescents is only twenty years old. The knowledge base has increased geometrically since then. There are more than 7750 articles indexed in PubMed alone about bipolar disorder in children and adolescents at the time of writing this abstract, and the pace of publication continues to accelerate. This talk presents the results of a series of meta-analyses that distill the research evidence into a set of quantitative summaries and clinically actionable recommendations. In

2011, Van Meter et al. meta-analyzed 12 epidemiological studies (from 1500 reviewed hits) about rates of bipolar I and bipolar spectrum disorders in youths; six more studies have been published since; but the general conclusions remain similar. Likewise, Kowatch et al. (2005) published a preliminary meta-analysis of phenomenological features in pediatric bipolar disorder; now the available samples more than double the number of cases with research diagnoses of bipolar disorder included. Similar progress has been made in terms of assessment, where a meta-analysis started with 4094 hits and finished with 27 studies, 63 effect sizes,  $N = 10,232$  youths, of whom 1719 had PBD diagnoses, including parent, youth, and teacher report. We integrate these findings into a set of clinical recommendations for evidence-based assessment for PBD. These steps add less than five minutes and less than five dollars to the typical assessment, yet yield large gains in accuracy and agreement about next clinical action.



## Neurobiology of pediatric bipolar disorder: from cingulate to CRP

**B Goldstein**

*Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada*

This presentation will critically review the existing literature regarding neurobiology in pediatric bipolar disorder (BD). Findings regarding neurocognition, structural and functional neuroimaging, and peripheral biomarkers will be contextualized in comparison to the prevailing literature on these topics among adults with BD. Similar to adults, children and adolescents with BD demonstrate neurocognitive deficits, with large effect sizes evident in such domains as attention, executive function, and working memory. In addition, there is preliminary evidence that youth with BD display meaningful lags in the expected age-related improvement in these domains. Much of the research in the area of functional neuroimaging has sought to parse pediatric BD from complex presentations characterized by chronic and explosive irritability (i.e. Severe Mood Dysregulation). Similar to adults, studies in pediatric BD have begun examining neural circuitry using MRI approaches such as resting state functional connectivity and diffusion tensor imaging. Numerous studies from different research groups have provided evidence of anomalous neural physiology during tasks related to face processing, reward processing, response inhibition, set-shifting, and sustained attention. In contrast to numerous studies regarding neurocognition and neuroimaging, there is a disparity in peripheral biomarker research in comparison to these other neurobiological domains and in comparison to peripheral biomarker research among adults. There is preliminary evidence that inflammatory, neurotrophic, and oxidative stress markers, leading peripheral biomarkers in adults BD, are also salient to pediatric BD. The presentation will conclude with suggestions for future directions, including multi-modal biomarker

research, prospective repeated measures studies, and incorporation of neurobiological measures within clinical trials.

## Update and future directions in the treatment of pediatric bipolar disorder

**CP Zeni**

*Hospital de clinicas de porto alegre, ramiro barcellos 2350, 90035903 Porto Alegre, Brazil*

We intend to present an overview of the current data on the treatment of Bipolar Disorder in children and adolescents. Published data from randomized controlled trials (RCTs) in acute mania/hypomania with significant responses are available for lithium, topiramate, risperidone, olanzapine, and aripiprazole. Open trials of lithium and lamotrigine show that these drugs may be effective in the treatment of depressive episodes. No trials of selective serotonin reuptake inhibitors (SSRIs) have been conducted. In the treatment of comorbid ADHD, there are encouraging findings with mixed amphetamine salts and atomoxetine; conflicting results are observed with methylphenidate. Published RCTs of traditional mood stabilizers are scarce, but the best available evidence (results from meta-analytic regression) suggests that second-generation antipsychotics (SGAs) as a group are more effective in reducing manic symptoms. Risperidone was the only one included in head-to-head comparisons (vs. lithium and divalproex), showing superiority in terms of efficacy, but with more metabolic side effects, which were also more common in most of the SGAs. Long-term studies are scarce. Psychosocial intervention studies, even more scarce, will also be summarized. We will also present limitations on current knowledge and future directions for studies in this population.

# Symposium XV

## From I to We – From Illness to Wellness- Psychoeducation, Wellness Measures, and the Therapeutic Alliance

### Chair: Allen Doederlein

## Personal experience of wellness measures: using the DBSA Wellness Tracker

**A Doederlein<sup>a</sup>**

*Depression and Bipolar Support Alliance, Chicago, USA*

The Depression and Bipolar Support Alliance added the World Health Organization's Five-Point Well-Being Index, the WHO-5 Scale, to its Wellness Tracker self-management tool for mood disorders in 2014. DBSA President Allen Doederlein-a mental health advocate, speaker, and representative of DBSA's 3.1 million constituents who are, like him, mostly individuals who themselves live with a mood disorder-will personally chronicle and report on his experiences as a patient using the WHO-5 scale as an additional self-tracking mechanism added to his treatment program.

## Using wellness scales in clinical practice, with "listening to patients and their scales without getting weighed down"

**J Rakesh**

*Texas Tech University Health Sciences Center, Lubbock, USA*

Reduction and ideally elimination of debilitating and function-impairing symptoms are unquestionably principal aims of psychiatric treatment. Yet concurrent creation of wellness and resiliencies does not often make it into the clinical context. Using clinically-vetted, evidence-based instruments, such as the World Health Organization's Five-Point Well-Being Index or the Ryff Scales of Psychological Well-Being, provides both a concrete measure of progress in terms of wellness and a framework for a doctor to understand more of her or his patient's whole experience. Such

scales are also overwhelmingly favored by patients. We will explore the implementation of such scales in practice and their usefulness as a tool for fostering the therapeutic alliance and, ultimately, better treatment outcomes.

### **Veteran peer specialists and education**

**L Goodale**

*Depression and Bipolar Support Alliance, Chicago, USA*

Peer Specialists, or individuals with mental health conditions who have been trained and certified to help their peers achieve wellness and recovery within a structured treatment environment, are able

to help those they serve achieve greater gains in confidence and self-advocacy (Cook, 2009), knowledge and management of illness (Lucksted et al., 2009), and medication adherence and problem-solving (Druss, 2010), when compared to individuals receiving traditional services only. We will highlight DBSA's 2013–2014 work in training 500 Veteran Peer Specialists and explore the unique role peer support can play in advancing traditional treatment by expanding it to include not just illness, but wellness, too.

# **Symposium XVI**

## **Practical Clinical Trials: Multicenter, Non-Industry-Funded Pharmacological and Psychological Interventions in the Post-Genomics Era**

### **Chair: Michael Ostacher**

### **Comparative evaluation of quetiapine plus lamotrigine versus quetiapine monotherapy in people with bipolar depression: a randomized trial (CEQUEL)**

**JR Geddes, C Hinds, J Rendell, A Gardiner, M Voysey, MJ Attenburrow, GM Goodwin**

*Psychiatry, University of Oxford, Oxford, UK*

**Background:** Effective short- and longer-term treatments for bipolar depression remain limited. CEQUEL was designed to test the hypothesis that a combination of lamotrigine with quetiapine leads to better short-term response and longer term clinical outcomes than quetiapine alone. CEQUEL also investigated the effects of adding folic acid.

**Methods:** CEQUEL was a UK, multicentre, double-blind, randomized, placebo-controlled, parallel group, 2 × 2 factorial clinical trial. Patients with bipolar I or II disorder who required new pharmacological treatment for an acute depressive episode were eligible. Following 14 day run-in on quetiapine, participants were randomized to added lamotrigine (200 mg) or placebo for 12 months. The primary outcome was improvement in QIDS-SR16 depressive symptoms at 12 weeks. Secondary outcomes included improvement in depressive symptoms at 52 weeks.

**Results:** 202 patients were randomised (101 lamotrigine; 101 placebo). The modal daily dose of quetiapine was 300 mg. The mean difference in QIDS-SR16 between groups was: after 12 weeks, 1.6 points lower lamotrigine vs placebo (95% CI −3.4 to 0.23;  $p = 0.09$ ); after 52 weeks, 2.9 (95% −5.2 to −0.6;  $p = 0.013$ ). Folic acid was not superior to placebo and appears to reduce the effectiveness of lamotrigine in the first 12 weeks. The estimated effect of patients on lamotrigine who were not randomised to take folic acid was 4.1 points ( $p = 0.0041$ ).

**Discussion:** Adding lamotrigine to quetiapine treatment of acute bipolar depression substantially improves outcomes. Removing the interaction with folic acid demonstrated clear superiority at 12 weeks. The results of CEQUEL highlight the potential benefits of combination therapy in bipolar depression.

### **Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic six month trial of lithium vs. quetiapine for bipolar disorder**

**AA Nierenberg<sup>a,b</sup>, S McElroy<sup>c</sup>, TA Ketter<sup>d</sup>, RC Shelton<sup>e</sup>, T Deckersbach<sup>a</sup>, E Friedman<sup>d</sup>, M McInnis<sup>g</sup>, CL Bowden<sup>h</sup>, M Tohen<sup>i</sup>, JH Kocsis<sup>j</sup>, JR Calabrese<sup>k</sup>, G Kinrys<sup>a,b</sup>, WV Bobo<sup>l</sup>, V Singh<sup>h</sup>, M Kamali<sup>g</sup>, D Kemp<sup>k</sup>, B Brody<sup>j</sup>, NA Reilly-Harrington<sup>a,b</sup>, LG Sylvia<sup>a,b</sup>, LW Shesler<sup>a</sup>, EE Bernstein<sup>a</sup>, D Schoenfeld<sup>m</sup>, DJ Rabideau<sup>m</sup>, AC Leon<sup>l</sup>, S Faraone<sup>n</sup>, ME Thase<sup>d,o</sup>**

<sup>a</sup>Department of Psychiatry, Massachusetts General Hospital, Boston, USA, <sup>b</sup>Harvard Medical School, Boston, USA, <sup>c</sup>Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati and Lindner Center of HOPE, Mason, USA, <sup>d</sup>Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, USA, <sup>e</sup>Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, USA, <sup>f</sup>Department of Psychiatry, University of Alabama at Birmingham, Birmingham, USA, <sup>g</sup>Department of Psychiatry, University of Michigan, Ann Arbor, USA, <sup>h</sup>Department of Psychiatry, University of Texas Health Science Center, San Antonio, USA, <sup>i</sup>Department of Psychiatry, University of New Mexico Health Science Center, Albuquerque, USA, <sup>j</sup>Department of Psychiatry, Weill Cornell Medical College, New York, USA, <sup>k</sup>Department of

Psychiatry, Case Western Reserve University, Cleveland, USA, <sup>1</sup>Department of Psychiatry and Psychology, Mayo Clinic, Rochester, USA, <sup>m</sup>Department of Biostatistics, Massachusetts General Hospital, Boston, USA, <sup>n</sup>Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, USA, <sup>o</sup>Department of Psychiatry, University of Pennsylvania, Philadelphia, USA

**Background:** While lithium (Li) has been used extensively for bipolar disorder (BP) since the 1970s, second generation antipsychotics (SGAs) have supplanted Li since 1998. To date, no randomized comparative effectiveness study has compared Li and any SGA.

**Methods:** Within the duration of the study (September 2010–September 2013), participants with BP I or II (DSM-IV) were randomized for 6 months to receive Li (n = 240) or quetiapine (QTP; n = 242). Li and QTP were combined with other medications for BP consistent with typical clinical practice (adjunctive personalized treatment – APT, excluding any SGA for the Li + APT group and excluding Li or any other SGA for the QTP + APT group). Co-primary outcome measures included Clinical Global Impression-Efficacy Index (CGI-EI) and Necessary Clinical Adjustments (NCA) which measured number of changes in APT. Secondary measures included a full range of symptoms, cardiovascular risk, functioning, quality of life, suicidal ideation and behavior, and adverse events.

**Results:** Participants improved across all measures and over 20% had a sustained response. Primary (CGI-EI; p = 0.59, NCA; p = 0.15), and secondary outcomes changes were not statistically significantly different. For participants with greater manic/hypomanic symptoms, CGI-EI changes were significantly more favorable with QTP+APT (p = 0.02). Among those with anxiety, the

Li + APT group had fewer NCAs per month (p = 0.02). Lithium was better tolerated than quetiapine in terms of the burden of side effects frequency (p = 0.05), intensity (p = 0.01) and impairment (p = 0.01).

**Conclusions:** Despite adequate power to detect clinically meaningful differences, outcomes with Li + APT and QTP + APT were not significantly different across 6 months of treatment for BP.

## Psychosocial treatment for children who are vulnerable to bipolar disorder: neural correlates of psychosocial risk

**D Miklowitz**

*UCLA Semel Institute for Neuroscience and Human Behavior, Division of Child and Adolescent Psychiatry, David Geffen School of Medicine at UCLA, Los Angeles, USA*

Dr. Miklowitz will discuss his three-site trial of family-focused therapy versus a psychoeducational control treatment for youth who have a bipolar parent and are showing early signs of bipolar disorder, including subthreshold hypomanic and depressive mood swings. In this trial, children undergo an fMRI scan before and after treatment in both treatment conditions. He will present data on (a) associations between familial risk factors (e.g., expressed emotion in parents) and the responses of high-risk children to a within-scanner family problem solving task; and (b) early results on changes in neural activation patterns in an emotion processing task over a 4-month pre/post treatment interval.

# Symposium XVII

## Role of Circadian Rhythms and Sleep in the Course of Bipolar Disorders: From Genes, Through Critical Periods to Treatment

Chair: Frank Bellivier

### New interventions for disturbances in sleep and circadian rhythms in mood disorders

**M Gunnar**

*Norwegian University of Science and Technology, Trondheim, Norway*

Patients with bipolar disorder might experience sleep disturbances in all phases of the illness. Insomnia or hypersomnia in euthymia might increase the risk of new episodes of depression or mania in addition to reducing quality of life. In mania most patients experience reduced length of sleep and lack of stability in circadian rhythms. Clinically differences in the circadian patterns of motor activity between depressions with or without psychomotor retardation, mania and euthymia can be objectively recorded by novel technologies. Ongoing treatment trials will be described: Cognitive behavioral therapy for insomnia (CBT-I) in euthymic patients to improve quality of sleep, stabilize minor mood variations and prevent new episodes. This trial could document a new treatment for insomnia in bipolar disorder with possible effects on sleep and on

stability of mood. In addition instability of sleep in severe mania at intensive care units will be presented and the first published case from use of blue light-blocking treatment by means of orange-tinted glasses will be referred.

### From circadian genes, through chronotypes and sleep disruptions, to clinical outcomes in bipolar disorders

**B Etain**

*Pole de Psychiatrie – Hôpital Chenevier, Centre Expert troubles Bipolaires, INSERM U955, Créteil, France*

Bipolar disorders (BD) are accompanied by circadian deregulations and sleep disruptions, both during acute mood episodes and euthymic periods. It is hypothesized a pathway from circadian genes variants, through chronotypes and sleep disturbances, to various clinical outcomes in BD such as mood relapses, emotional

regulation, metabolic disturbances or response to mood stabilizers. We have performed several studies supporting the relevance of this pathway and used samples of remitted patients with BD to assess actigraphic and circadian parameters (phase preference, amplitude and stability of rhythms). We demonstrated associations between several circadian genes (TIMELESS, RORA, ASMT) and the susceptibility to BD. Using actigraphy, we demonstrated that patients with BD had longer sleep duration and latency but also higher variability in fragmentation index. We confirmed these results in a meta-analysis of nine published studies using actigraphy in patients in remission. Using questionnaires, we also demonstrated that patients with BD were more evening type, languid and less flexible in their rhythms. Interestingly, associated genes drove the circadian and sleep outputs in our sample, as shown by association between ASMT and sleep disruptions and associations between circadian genes and chronotypes. Finally, we will present preliminary data that established links between sleep, emotional reactivity and functioning but also between sleep and metabolic syndrome parameters. This presentation will highlight recent research on sleep and circadian rhythms in bipolar disorders and help in the comprehension of complex pathways going from circadian genetic susceptibility to clinical outcomes.

#### **Longitudinal assessment of circadian rhythms in women at risk for postpartum depression**

**B Frey**

*Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, Canada*

Postpartum depression (PPD) affects 7–15% of women in the general population, but women with bipolar and major depressive disorder are at an even greater risk. PPD confers major negative outcomes on mothers and their babies. For instance, children of mothers who suffered from PPD are at greater risk for development of affective, behavioural and cognitive problems. Moreover, several studies have found increased risk for infanticide and suicidal behaviour in this population, accounting for up to 20% of postpartum deaths. Therefore, it is imperative that proper risk factors for PPD are identified and the underlying biological mechanisms are better understood. In this study we investigated whether objective and subjective changes in circadian rhythms, as assessed with actigraphy and validated clinical questionnaires, from late pregnancy to early postpartum are associated with PPD. We investigated women with diagnosis of bipolar or major depression, as well as matched controls. All women were euthymic at the outset of the study. We found that both objective and subjective measures of circadian rhythms are associated with a significant increase in postpartum depressive symptoms only in women with bipolar and major depressive disorder, but not in healthy controls. This prospective study shows that specific identifiable measures of circadian rhythms are associated with increased risk for PPD and such risk is particularly high in women with mood disorders. Because all of these objective and subjective measures associated with risk are modifiable, treatment strategies targeting stabilization of the circadian system should be high priority in clinical management of this population.

## **Symposium XVIII**

# **An ISBD Bipolar Disorder in Older Adults Taskforce Update: How Should Current Evidence Guide Practice and Research?**

### **Chair: Kenneth Shulman**

#### **Epidemiology and significance of age of onset**

**S Strejilevich**

*Psychiatry, Neurosciences Institute, Favaloro University, Buenos Aires, Argentina*

More than 25% of people receiving treatment for bipolar disorders are aged 60 or older, and this percentage will increase due to the unprecedented ageing of the population. Bipolar disorder in older adults (OABD) represents a major health challenge as it may include the late stage of these disorders as well as a clinical form of other neuropsychiatric diseases. Most significantly, it may represent an illness subtype determined by late age at onset. We present the main findings of the Older Adults Task Force report related to the epidemiology of OABD which shows robust evidence that late age of onset is a distinct sub-type. While only minor differences in phenomenology exist between late and early onset bipolar disorder, significant genetic and cognitive factors may affect clinical course and response to treatment.

#### **Medical comorbidity, neuropathology, and biomarkers in older adults with bipolar disorder (OABD)**

**S Tsai**

*Psychiatry, Taipei Medical University and Taipei Medical University Hospital, Taipei, Taiwan*

Aging, medical morbidity, neuropathology, and pathophysiology of OABD may collectively exacerbate the health-related quality of life and outcomes in elderly patients with BD. These older adults represent a sub-population at risk of medical morbidity, including metabolic syndrome (up to 50%), hypertension (45–69%), diabetes mellitus (18–31%), cardiovascular disease (9–49%), respiratory illness (4–15%), arthritis (16–21%), endocrine abnormalities (17–22%), as well as atopic diseases such as allergic rhinitis and asthma (6–20%). Irrespective of the differences in prevalence of obesity, diet, life style, and medical care system between the Western and the Eastern countries, diabetes and coronary artery diseases seem to be racially-independent medical morbidities and

inherent to OABD. Although late-onset BD is associated with a higher burden of cerebrovascular disease than early-onset BD, silent cerebral infarctions may be present in over half of OABD, regardless of age at onset. Neuroimaging studies in OABD have revealed regional gray matter volume reduction, white matter hyperintensities, and biochemical alterations, e.g., reduced cerebral concentrations of N-acetyl aspartate (NAA) and elevated lactate levels. Metabolic abnormalities and systemic inflammation may also be critical risk factors and biomarkers for cerebrovascular disease in OABD. Concurrent medical morbidity can limit treatment options for OABD because of drug tolerability, drug-drug interactions, and altered drug-metabolism. Clinicians should address vascular risk factors and be sensitive to early signs of cerebrovascular disease, using imaging as necessary. Longitudinal neuroimaging studies in OABD need to better address the role of cerebrovascular burden in the etiology and prognosis of OABD.

## **Controversies regarding neuroprogression/ cognition dysfunction**

**A Gildengers**

*Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, USA*

Numerous published reports have revealed significant structural and functional brain abnormalities associated with bipolar disorder (BD) as well as related cognitive dysfunction. Structural brain abnormalities include, and are not limited to, enlarged lateral ventricles, increased occurrence of white matter hyperintensities, alterations in hippocampal and amygdala volumes, and changes in the white matter microstructure. These structural abnormalities may underlie functional abnormalities in brain circuits supporting emotion processing, emotion regulation, and reward processing along with changes in cognitive function (information processing, executive function, etc.). An area of controversy is whether these brain and cognitive changes are neurodevelopmental, disease-related, or a combination of both. While a neuroprogressive model for BD is enticing, not all studies support such a model. This presentation will review evidence pro and con for neuroprogression and progressive cognitive decline.

# **Symposium XX**

## **Spirituality and Faith in Recovery: Resilience, Purpose, Identity, and Healing**

### **Chair: Cheryl Tarr Magrini**

#### **The role of spirituality and faith on wellness, resiliency and purpose**

**C Magrini**

*Depression and Bipolar Support Alliance, Chicago, USA*

Based on fifty interviews (2013–2014), with individuals living with bipolar disorder, six core insights were identified related to spirituality/faith and a wellness lifestyle. Interviewees were questioned on their understanding of spirituality/faith; how they understand themselves as a spiritual person; to identify how spirituality influences their lifestyle practices for recovery and wellness, and their response to the experience of the interview. Connection as a theme was the foundational center of the interviews. Connection may be expressed or experienced in ways that support wellness, or may instead create barriers to wellness. Connection was expressed in three ways: to the source that is named and experienced in a wide breadth of ways; to oneself for the purpose of one's well-being that includes mind, body, and spirit; and to other individuals, a community, or encompassing the larger context of humanity or the natural world for their well-being. Resiliency and meaning and purpose emerged as significant expressions of these connective patterns. Selected from the six core insights Magrini will discuss connection in the context of: the breadth of spiritual understanding and the personal relationship with spirituality; resiliency and spirituality in the recovery process; and the role of meaning and purpose. Quotes from the interviewees that reflect their lived experience are a key component of the presentation.

#### **The diagnosis of bipolar disorder should never become one's identity**

**JS Tamerin**

*Depression and Bipolar Support Alliance, Chicago, USA*

Diagnosis is essential in medicine. A diagnosis may be heard as a neutral statement of fact or experienced with a sense of relief. The diagnosis of Bipolar Disorder is different because it conjures up negative emotions, images and stereotypes. Part of the challenge of dealing with bipolar illness is dealing with the impact of the diagnosis on the patient's identity. The patient must be helped to integrate this "highly loaded" diagnosis into a healthy and positive self-concept. This process is best accomplished with the assistance of a support group of peers who will help the patient see the disease as a "disorder" which must be faced and treated appropriately rather than as a scar and source of shame. Indeed, if faced properly many patients who attend a DBSA support group grow to the point where their challenge becomes a badge of courage rather than a source of humiliation.

#### **Healing and recovery: how we mend our minds**

**M Hornbacher**

*Depression and Bipolar Support Alliance, Chicago, USA*

What do we mean when we speak of recovery with regard to mental health? Marya Hornbacher will address the idea that we – people with and without mental illness – can engage in an ongoing process of healing the mind. Both individual experience and research show that healing and recovery do occur, and that more exploration of these concepts can result in more complete recovery for all.

# Symposium XXI

## Results of the International Society for Bipolar Disorders Task Force on Suicide: Systematic Review and Meta-Analyses

### Chair: Ayal Schaffer

#### Rates of suicide death in people with bipolar disorder: findings from the ISBD Task Force on Suicide

**A Schaffer**

*Mood & Anxiety Disorders Program, Psychiatry Sunnybrook Health Sciences Centre, Toronto, Canada*

**Objectives:** Bipolar disorder is associated with elevated risk of suicide deaths. One of the goals of the ISBD Task Force on Suicide was to report an updated analysis of suicide death rates and comparisons with other mental disorders.

**Methods:** A systematic review of studies published from Jan 1, 1980 to May 30, 2014 examining rates of suicide deaths in bipolar disorder samples. Using data from all eligible studies, we calculated pooled suicide rates (per 100 person-years) weighted by sample size and by exposure years. We further calculated these pooled suicide rates separately for men and women, using all studies in which sex-specific data was available.

**Results:** Our pooled analysis weighted by sample size (total  $n = 172,910$ ) identified a suicide rate of 0.152 per 100 person-years (95% CI = 0.023–0.471) and the pooled analysis weighted by number of exposure years (total of 1,143,728 person-years) identified a suicide rate of 0.164 per 100 person-years (95% CI = 0.005–0.324). Sex-specific data on suicide rates ( $n = 60,935$  BD subjects) weighted by exposure years identified a 1.7:1 ratio in men compared to women. The proportion of all suicides accounted for by people with BD varied considerably by sample composition, with a range of 3–14%.

**Discussion:** This updated analysis identified a lower estimated suicide rates in bipolar disorder than what was previously published. There is no doubt, however, that suicide rates vary across the course of a person's illness, therefore our results should only be considered as an estimated risk over an extended period of time.

#### Factors that influence the risk of suicide attempts or suicide in bipolar disorder

**E Isometsa**

*University of Helsinki, Helsinki, Finland*

**Objectives:** Bipolar disorder is associated with a high risk of suicide attempts and suicide death. The main objective of this study was to identify and quantify the demographic and clinical correlates of attempted and completed suicide in people with bipolar disorders.

**Methods:** Within the framework of the ISBD Task Force on Suicide, a systematic review of articles published since 1980 characterized by both key terms 'bipolar disorder' and 'suicide attempts or suicide' was conducted, and data extracted for analysis from all eligible articles. Demographic and clinical variables for which 3 studies with usable data were available were meta-analyzed using fixed

or random-effects models for association with suicide attempts and suicide deaths.

**Results:** Variables significantly associated with suicide attempts were: female sex, younger age of illness onset, depressive polarity of first illness episode, depressive polarity of current or most recent episode, comorbid anxiety disorder, any comorbid substance use disorder, alcohol use disorder, any illicit substance use, comorbid cluster B / borderline personality disorder, and first-degree family history of suicide. Suicide deaths were significantly associated with male sex and first-degree family history of suicide.

**Conclusions:** This study reports on the presence and magnitude of the correlates of suicide attempts and suicide deaths in BD. The findings do not address causation, and the heterogeneity of data sources should limit the direct clinical ranking of correlates. Our results nonetheless support the notion of incorporating diagnosis-specific data in the development of models of understanding suicide in BD.

#### Clinical interventions for suicide prevention in bipolar disorder

**L Vedel Kessing**

*Psychiatric Center Copenhagen, Copenhagen, Denmark*

**Objectives:** To review the literature on clinical interventions for suicide prevention in patients with bipolar disorder

**Method:** This work is part of the International Society of Bipolar Disorders task force on suicide. A subsection of the task force focused on examining the efficacy or effectiveness of clinical interventions in reducing the risk of suicide attempts or death from suicide among those with bipolar disorder. A systematic literature review of papers published from 1980 to May 2014 on suicide or suicide attempts in BD among people age 15 or older was conducted.

**Results:** Lithium has received the greatest attention as a possible anti-suicide treatment in bipolar disorder, yet uncertainty remains with regards to the relative anti-suicide effects compared to other active agents. Anticonvulsants (including divalproex sodium, carbamazepine and gabapentin) have also been extensively studied, with over a dozen published reports related to suicide. Fewer studies have examined the effects of antidepressants and atypical antipsychotics. There were very few studies specific to bipolar disorder on psychosocial treatments or on the role of screening. Summaries of findings will be reported in the symposium.

**Conclusions:** There is a growing literature on clinical interventions that may reduce the risk of suicide attempts and suicide in bipolar disorder. A paucity of adequately powered prospective studies limits the interpretation of findings, but positive signals in the literature support greater attention to studying suicide outcomes in treatment studies of bipolar disorder.

# Symposium XXII

## Socio-Emotional Cognition in Bipolar Disorder: What Do We Know and Where to Next?

Chair: Susan Rossell

### Behavioural indices of emotion processing in bipolar disorder

**T Van Rheenen<sup>a,b</sup>**

<sup>a</sup>Monash Alfred Psychiatry Research Centre, Central Clinical School, Monash University and the Alfred Hospital, Melbourne, Australia, <sup>b</sup>Brain and Psychological Sciences Research Centre, Swinburne University, Melbourne, Australia

**Background:** The ability to integrate information from different sensory channels is a vital process that serves to facilitate perceptual decoding in times of unimodal ambiguity. Despite its relevance to psychosocial functioning, multimodal integration of emotional information across facial and prosodic modes has not been addressed in bipolar disorder (BD). In light of this paucity of research we investigated multimodal processing behaviourally, in a BD cohort using a focussed attention paradigm.

**Methods:** BD patients and healthy controls completed a task assessing the cross-modal influence of emotional prosody on facial emotion recognition across congruent and incongruent facial and prosodic conditions, where attention was directed to the facial channel.

**Results:** There were no differences in multi-modal integration between groups at the level of accuracy, but differences were evident at the level of response time; emotional prosody biased facial recognition latencies in the control group only, where a fourfold increase in response times was evident between congruent and incongruent conditions relative to patients. **Conclusions:** The results of this study indicate that the automatic process of integrating multimodal information from facial and prosodic sensory channels is delayed in BD. Given that interpersonal communication usually occurs in real time, these results have implications for social functioning in the disorder.

### Elucidating bipolar disorder neurocognition using fMRI

**GS Malhi<sup>a,b</sup>**

<sup>a</sup>CADE Clinic, Head of Department of Psychiatry, Royal North Shore Hospital, St Leonards, Australia, <sup>b</sup>Discipline of Psychiatry, Sydney Medical School, University of Sydney, Sydney, Australia

**Background:** The clinical complexity of bipolar disorder (BD) has meant that examination of many simple but core cognitive functions has failed to adequately define the illness, but, increasingly sophisticated paradigms and means of analysis have been able to provide novel insights into the neural circuitry of the illness.

**Methods:** We recruited 16 adult patients with BD, 14 with borderline personality disorder (BPD), and 13 healthy controls (HC). Based on a priori assumptions we investigated fronto-limbic network emotion processing and regulation. Having acquired resting state and task related (emotional stroop) fMRI data, we initially

conducted a region of interest analysis and correlated findings to the difficulties in emotion regulation scale (DERS), and then conducted functional network connectivity (FNC) analysis and, again correlated FNC strength with DERS.

**Results:** Both patient groups displayed reduced left dorsolateral prefrontal cortex (dlPFC) activity but increased right ventrolateral prefrontal cortex (vlPFC) activity when engaged in task-related processing. However, a divergent pattern emerged involving heightened dorsomedial prefrontal cortex (mdPFC) activity in BD and diminished amygdala activity in BPD. These changes correlated reciprocally with DERS. FNC patterns also differentiated patients from healthy controls and changes correlated with impulsivity and emotional awareness and clarity.

**Conclusions:** The findings of our research demonstrate that complex constructs (e.g. affective lability and mood) core to BD can be differentiated and contribute to the development of a clinically meaningful model of BD circuitry.

### Functional abnormalities in neural circuitries supporting face emotion and reward processing in bipolar and bipolar at-risk youth: toward biomarkers of disease risk

**M Phillips**

Mood and Brain Lab, University of Pittsburgh and the University of Pittsburgh Medical Center, Pittsburgh, USA

**Background:** Elucidating in bipolar disorder (BD) and BD at-risk youth abnormalities in neural circuitries supporting key domains underlying socio-emotional functioning, face emotion and reward processing, can provide markers to inform risk detection and early interventions.

**Methods:** We recruited youth (8–17 years) from: (1) the Longitudinal Assessment of Manic Symptoms study (LAMS) of behaviorally- and emotionally-dysregulated BD and BD at-risk youth; (2) a study of youth offspring of BD parents. Youth performed face emotion processing and reward paradigms during neuroimaging. Analyses focused on key emotion processing (amygdala, ventrolateral prefrontal cortex:vlPFC), and reward (ventral striatum:VS, ventral and medial prefrontal cortices) regions.

**Results:** Face emotion: In LAMS, 15 mood stabilizer-/antipsychotic-unmedicated BD youth showed decreased right vlPFC activity to negative emotional faces versus 29 healthy ( $p = 0.007$ ) and 59 non-BD ( $p = 0.004$ ) youth. In 19 medicated BD youth, there were similar, although attenuated, findings. Reward: In 81 LAMS youth, greater right superior prefrontal-parietal-VS functional connectivity (FC) to reward predicted worsened emotional dysregulation at mean = 14.5 months' follow-up. 28 BD offspring showed significantly greater right frontal polar activity, and significantly greater inverse VS-right vlPFC FC, to reward and loss than 28 non-BD offspring and 23 healthy youth ( $p < 0.05$ ,

corrected). Preliminary data show that greater right frontal polar activity predicted greater 1 year follow-up anxiety.

**Conclusions:** Dysregulation of subcortical regions by right vIPFC may be a marker of BD in youth. Abnormally elevated right superior prefrontal and frontal polar functioning during reward processing may reflect heightened engagement with reward-relevant stimuli, and predict worsening clinical outcome in BD at-risk and BD youth.

# Symposium XXIII

## Drug Treatments for Geriatric Bipolar Disorder: A Perspective from the ISBD Geriatric Bipolar Taskforce

### Chair: Martha Sajatovic

#### Antipsychotic medications in late-life bipolar disorder

**M Sajatovic**

*Psychiatry, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center, Cleveland, USA*

Antipsychotic medications are a gold-standard and first-line treatment for bipolar disorder (BD) in the general population. However, in older BD adults, the role of antipsychotics is less clear. There are no prospective randomized, controlled trials specific to geriatric BD that can inform a relative assessment of benefits vs. burden of specific antipsychotic therapies. Based upon existing reports, there is positive efficacy data supporting the use of olanzapine, quetiapine, asenapine, and clozapine in acute late-life mania. For late-life BD depression there is positive efficacy data supporting the use of quetiapine, asenapine and lurasidone. Effective dosing in older adults samples is almost uniformly lower than with younger BD patients. As with younger patients, poor adherence to prescribed maintenance antipsychotic is pervasive in late-life BD, with nearly 1 in 2 individuals meeting thresholds for sub-optimal adherence. Adverse drug reactions are a general concern with advancing age, and antipsychotic-related side effects of particular relevance to BD elders include: (1) Elevated risk for metabolic abnormalities such as diabetes, (2) Potentially deleterious effects of antipsychotic drugs on cognition and brain integrity, (3) Greater propensity to develop extrapyramidal symptoms, and (4) The general risk of premature mortality among older individuals with dementia. While emerging data suggest that antipsychotic pharmacotherapies can reduce symptoms of mania and depression in older adults with BD, more data is needed on how antipsychotic drugs should be positioned within the BD treatment armamentarium relative to other compounds such as lithium and anticonvulsants, as well as to psychosocial therapies.

#### The role of anticonvulsants in late-life bipolar disorder

**RK Al Jurdi**

*Psychiatry, Michael E. DeBakey VA Medical Center, Houston, USA*

Excluding GERI-BD that compared valproate to lithium in elderly patients in acute manic or mixed episodes, there have been no sys-

tematic studies conducted in older adults with BD. Nonetheless, there has been an increase in the utilization of anticonvulsants and antipsychotics without enough data to support one class of medication versus the other. Several non-controlled studies have suggested the efficacy of valproate and carbamazepine in acute late-life mania, as monotherapy or in conjunction with lithium or an antipsychotic. Based on the limited available data, lamotrigine is recommended for acute bipolar depression and as add-on to lithium for bipolar disorder maintenance treatment. Elderly patients are more prone to side effects. Age-related changes in metabolism, increased probability of being on polypharmacy and related drug-drug interactions, and absence of age-specific medication dosing guidance contributes to a less than optimal tolerability and adherence to anticonvulsant regimen. Age-specific treatment guidelines that balance risks and benefits to maximize pharmacotherapy of late life bipolar disorder, such as anticonvulsants, are urgently needed.

#### Use of lithium in late-life bipolar disorder

**LV Kessing**

*Psychiatric Center Copenhagen, Rigshospitalet, Copenhagen, Denmark*

Lithium is a “gold standard” treatment also in late-life bipolar disorder but is generally used less among older individuals. Nevertheless, studies suggest that the prevalence of excellent response to lithium monotherapy in patients with late-life bipolar disorder is similar to the prevalence in younger patients. Further, data suggest that continued treatment with lithium may reduce the rate of suicide and the risk of developing dementia in the long run. It is currently unclear whether treatment with lithium in patients with late-life bipolar disorder is associated with a higher rate of renal failure than treatment in younger patients. New data on the risk of chronic renal disease in late-life bipolar disorder treated with lithium will be presented.

#### Anticonvulsive therapy in geriatric BD

Abstract Not Submitted.



# Symposium XXIV

## Bipolar Depression: New Vistas for the Research and Clinical Ecosystem

### Chair: Roger McIntyre

#### **The pharmacological treatments of bipolar depression: conventional, experimental, and innovative approaches**

**RS McIntyre**

*University of Toronto Head, Mood Disorders Psychopharmacology Unit, Toronto, Canada*

During the past ten years, three agents have received FDA regulatory approval for bipolar depression. Regulatory approval was granted on the basis of replicated pivotal trial data demonstrating efficacy, safety, and tolerability. Pharmacoepidemiological data indicate that bipolar adults often receive treatments for bipolar depression that are discordant with evidence-based guidelines, as well as regulatory approval. For example, conventional antidepressants are commonly prescribed to bipolar adults despite the fact that a sufficient evidence base supporting their use is not available. Adults with bipolar disorder disproportionately utilize healthcare purposes during depressive symptoms/episodes and very frequently are insufficiently responsive and/or intolerable of conventional approaches. Contemporary models of disease pathogenesis in bipolar disorder are suggesting that disturbances in a variety of interacting physiological systems (e.g. amino acid homeostasis (e.g. glutamate), immuno-inflammatory systems, cellular energetics, and insulin signaling), may be relevant to the pathogenesis and treatment of bipolar depression. A derivative of this observation is that pharmacological treatment approaches that restore homeostatic activity directly or indirectly may be capable of mitigating depressive systems and possibly modifying disease course. This presentation will provide an up-to-date summary of evidence supporting conventional treatments for bipolar depression and as well a succinct review of innovative and experimental pharmacological approaches that are currently a focus of research attention. The broader aim of this presentation is to provide a synthesis of clinically available treatments and a vista for future pharmacological approaches.

#### **Restoring cognition and functioning in bipolar depression**

**E Vieta**

*Department of Psychiatry, the Bipolar Disorders Program, and the Clinical Institute of Neuroscience, University of Barcelona, Barcelona, Spain*

Cognitive complaints are common in patients with bipolar disorder, especially during depressive episodes. Moreover, some patients show clinically relevant neurocognitive impairment even in the absence of memory-related symptoms. Major sources of cognitive and functional deficits are the presence of subthreshold depressive symptoms and comorbidities (hypothyroidism, diabetes, substance abuse)<sup>1</sup>. Sleep habits and exercise may also play a role. One of the main unmet needs in the management of bipolar disorder is the lack of available optimal treatment options for bipolar depression.

Currently, antidepressants, antipsychotics, and mood stabilizers are commonly prescribed for this condition. New agents are needed that improve remission rates and prevent new episodes, have fewer side effects than existing treatments, and are effective on the core symptoms of bipolar disorder, as well as on cognition, functioning, and physical health. Ideally, these new agents will prevent the high mortality rates associated with cardiovascular disease and suicide in bipolar disorder and promote treatment adherence through greater tolerability. Researchers are currently investigating a number of novel treatment targets, particularly the glutamatergic system, among others, in an attempt to develop a drug that will address these unmet needs in the management of bipolar depression<sup>2</sup>. Novel psychosocial interventions, such as functional remediation, may also be helpful<sup>3</sup>.

#### **References:**

- 1: Rosa AR, Magalhães PV, Czepielewski L, Sulzbach MV, Goi PD, Vieta E, Gama CS, Kapczinski F. Clinical staging in bipolar disorder: focus on cognition and functioning. *J Clin Psychiatry*. 2014 May;75(5):e450–6.
- 2: Vieta E. Emerging trends: novel molecular targets and moving beyond acute symptoms in bipolar depression. *J Clin Psychiatry*. 2014 Jul;75(7):e17.
- 3: Bonnin CM, Torrent C, Vieta E, Martínez-Arán A. Restoring functioning in bipolar disorder: functional remediation. *Harv Rev Psychiatry*. 2014 Nov–Dec;22(6):326–30.

#### **Guidelines, new findings and research priorities in the treatment of bipolar depression**

**G Goodwin**

*University of Oxford, Department Psychiatry, Oxford, UK*

The treatment of bipolar disorder reflects its complexity and the multi-dimensional character of its course and presentation in acute episodes. Guidelines are an important way in which treatment delivery may be enhanced. The recent NICE guidelines (1) and the plan for a revised BAP (British Association for Psychopharmacology) in 2015/16 will be presented. They summarize the current consensus and highlight the uncertainties around current approaches to the management of bipolar depression in particular. The NICE guidelines propose psychological treatments (Cognitive behaviour Therapy) as first line for bipolar depression. The justification for this extrapolation and uncertainties about bias in psychological treatment trial publications will be reviewed (2). New data on the role of individual psychoeducation will be presented. The pharmacological treatment of depression is still an area of considerable uncertainty. This relates primarily to the status of conventional antidepressants based on transmitter re-uptake inhibition. New data on lamotrigine will be presented that should help to underline its utility in the short and long term management of bipolar depression (the CEQUEL trial) in combination with quetiapine. Disclosure: The author has advised the companies involved in developing new drug treatments for bipolar disorder.

# Symposium XXV

## Experts by Experience: Consumer's Experience of Coping with Suicidal Thoughts

### Chair: Gregory Simon

#### Survey of consumers' experience of coping with suicidal thoughts

**G Simon<sup>a,b</sup>, C Specht<sup>a</sup>, A Doederlein<sup>a</sup>**

<sup>a</sup>*Depression and Bipolar Support Alliance, Chicago, USA*, <sup>b</sup>*Group Health Research Institute, Seattle, USA*

Of US residents who report suicidal thoughts, only half receive care from specialty mental health providers. For many, community resources, non-professional helpers, and self-care are the sole sources of support. Constituents of the Depression and Bipolar Support Alliance were invited to complete an anonymous online survey regarding experience of coping with suicidal thoughts. Of 611 respondents, 588 (96%) reported ever having thoughts of self-harm or suicide, 293 (48%) reported a prior suicide attempt or self-inflicted injury, 315 (52%) reported past hospitalization for suicide attempt, and 203 (33%) reported a history of forced or involuntary treatment. The most commonly reported sources of help were mental health professionals, family members, and peers. Half or fewer reported seeking help from emergency rooms or telephone crisis lines. Mental health providers and peers were most often described as somewhat or very helpful, while consumers gave the least favorable ratings to interactions with crisis lines, emergency rooms, and clergy. The most commonly reported self-care strategies included positive self-talk, prayer or meditation, social contact, physical activity, and scheduling positive or distracting activities. Most self-care activities were reported to be helpful, with prayer or meditation, physical activity, and social contact receiving the most favorable ratings. 73% of respondents agreed with the statement that suicide is often preventable, but 37% reported reluctance to speak with doctors or therapists regarding suicidal thoughts. These findings regarding consumers' experience have important implications for the design of services and for clinicians' advice to consumers regarding self-care strategies.

#### How a better understanding of suicide risk can inform the clinical care provided for people with bipolar disorder

**A Schaffer**

*Sunnybrook Health Sciences Center, Toronto, Canada*

The tragedy of suicide is not unique to bipolar disorder (BD), yet it is an inescapable reality that people who struggle with the illness are at elevated risk of suicide attempt and suicide. Efforts to better understand and prevent suicide must utilize the breadth of all available knowledge, and whenever possible incorporate diagnosis-spe-

cific information. The International Society for Bipolar Disorders Task Force on Suicide has recently completed a systematic review that summarized the rapidly expanding knowledge base in this area. Comprised of 20 experts from across 12 countries, the Task Force covered four key areas: (1) prevalence and characterization of suicide deaths and suicide attempts; (2) factors associated with suicide attempts or deaths; (3) neurobiology aspects; and (4) the impact of clinical interventions in bipolar disorder on suicide risk. Key findings from the Task Force will be presented, including the pooled suicide rate in BD, and a summary of the numerous sociodemographic and clinical factors that impact rates of suicide attempts and deaths. These results have important implications for developing suicide prevention strategies at the personal, clinical, and public health levels.

#### Understanding the lived experience of coping with suicidal thoughts

**K Wilma**

*Depression and Bipolar Support Alliance, Chicago, USA*

Evaluation of suicide risk is often one of the most difficult or stressful times in relationships between providers and consumers of mental health care. Providers' concerns about safety sometimes lead to more directive or even coercive approaches, and that may increase consumers' concerns about sharing sensitive information. Consumers may be forced to deal with unfamiliar providers at a time of significant stress. This presentation will describe the lived experience of coping with and seeking help for suicidal thoughts – based on the presenter's experience and the experiences of peers. Specific topics to be covered will include: descriptions of helpful and unhelpful consumer/provider interaction, effective support for consumer's self-care strategies, and encouraging use of peer supports.

# Symposium XXVI

## Clinical and Biological Factors as Targets of Intervention for Bipolar Spectrum Disorders

### Chair: Martin Preisig

#### Targets for intervention in mood disorders: evidence from objective measures of activity, mood, energy and sleep

K Merikangas<sup>a</sup>, L Cui<sup>a</sup>, D Lameira<sup>a</sup>, V Zippunikov<sup>b</sup>, F Lamers<sup>c</sup>, J Swendsen<sup>d</sup>

<sup>a</sup>National Institute of Mental Health, Bethesda, USA, <sup>b</sup>Johns Hopkins University School of Health, <sup>c</sup>VU University Amsterdam, Amsterdam, The Netherlands, <sup>d</sup>University of Bordeaux, Bordeaux, France

The role of physical activity in diverse mental disorders has been well recognized, particularly for bipolar disorder for which it may comprise a core feature. However, activity is only one component of a series of related homeostatic systems including sleep, energy, appetite, and mood that are regulated by hypothalamic circuits. The present study employs combined accelerometry and experiential momentary sampling to a non-clinical sample of probands and relatives with a broad range of mood disorders to address the following aims: (1) to identify the directional associations between sleep, energy, mood and activity evaluated objectively using mobile technologies; (2) to evaluate whether people with mood disorders, and those at high risk of mood disorders, manifest differential associations across these domains to identify targets for intervention in these disorders; and (3) to evaluate whether temperamental domains such as positive and negative affectivity are associated with differential relationships across these domains. The results reveal that after controlling for sleep and the outcome domain in the previous period, there was a uni-directional association between energy in one epoch and activity in the next; likewise, there was a direct association between activity in one epoch and mood in the next. No parallel direct associations emerged for activity predicting energy in the next epoch, or for mood predicting activity. These associations were much stronger among those with bipolar I disorder than for other subgroups of mood disorders. The implications of these results for targets of prevention and intervention are described.

#### The specificity of mania and early age of onset in high risk youth: a 10 year prospective study

M Preisig<sup>a</sup>, CL Vandeleur<sup>a</sup>, MPF Strippoli<sup>a</sup>, E Castelao<sup>a</sup>, M Gholam-Rezaee<sup>a</sup>, KR Merikangas<sup>b</sup>, P Marquet<sup>a</sup>, JM Aubry<sup>c</sup>

<sup>a</sup>Department of Psychiatry, University Hospital of Lausanne, Lausanne, Switzerland, <sup>b</sup>Genetic Epidemiology Research Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, USA, <sup>c</sup>Department of Mental Health and Psychiatry, University Hospital of Geneva, Geneva, Switzerland

**Background:** Recent family studies of mood disorders suggest independent familial aggregation of bipolar and unipolar mood disorders.

Using a prospective high-risk study design, our aim was to establish the incidence of mood disorders in offspring in function of the specific parental mood disorder and its age of onset.

**Methods:** Clinical information was collected on 81 treated probands with BPD, 64 with MDD and 63 medical controls as well as their 372 children who were 6–17 years old on inclusion (mean age: 10 years). Offspring were interviewed every 3 years (mean duration of follow-up was 10.6 years). Parental age of onset was dichotomized at the age of 21 years. Assessments of parents and offspring were based on direct diagnostic interviews. Shared gamma frailty models were adjusted for the effects of demographic characteristics in probands and offspring, the severity of mood disorders and the presence of comorbid disorders in probands as well as mood disorders in co-parents.

**Results:** Only offspring of parents with BPD revealed an increased risk of bipolar disorders. The increased risk of BPD in offspring of parents with BPD was entirely attributable to families where the parent had a BPD with an onset earlier than 21 years.

**Conclusions:** Our results further support the specific and independent familial aggregation of BPD and suggest that early onset is a highly relevant clinical feature which strongly affects the risk of offspring. Accordingly, the offspring of patients with early-onset bipolar disorders are likely to particularly benefit from preventive efforts.

#### The 24 hour sleep–wake cycle and circadian systems as targets for management of bipolar and other mood disorders

I Hickie

Brain & Mind Research Institute, University of Sydney, Sydney, Australia

**Background:** A major challenge is to identify those young persons who are at risk of developing major mood disorders, including bipolar disorder. Our model focuses on combining clinical staging with objective measurement of the 24 hour sleep–wake cycle and related circadian mechanisms.

**Methods:** We utilize longitudinal studies in clinical subjects, and twins, between the ages of 12–30 years. Clinical subjects are followed longitudinally with data collected for neurobiological and circadian studies. In adolescent twins we examine the longitudinal patterns of emerging changes in sleep–wake cycles and their relationships with major mood disorders.

**Results:** Clinical subjects with early phases of bipolar-type disorders are characterized by a range of features suggesting underlying circadian dysfunction, including delayed sleep phase and delayed onset of melatonin in the evening. Clinical interventions focus on use of circadian-targeted behavioral or pharmacological strategies. The twin studies demonstrate that while motor activation and sleep

disturbance features are common in adolescence, by themselves they are not indicative of bipolar or other major mental disorder.

**Conclusions:** Longitudinal clinical and twin studies of young people at risk of developing some unipolar or bipolar disorders suggest the importance of focusing on changing patterns of motor activation and underlying circadian and other neurobiological features.

**Disclosures** This body of work is supported largely by competitive grant funding from the Australian National Health and Medical Research Council. However, IH does hold investigator-initiated grant funding from Servier pharmaceuticals for investigation of the potential benefits of agomelatine in young persons with circadian-based depressive disorders.

# Symposium XXVII

## Redefining Mixed States in DSM-5: Findings from 2 Large Datasets and Discussion of the Mixed Features Specifier

### Chair: Trisha Suppes

#### Mixed depression in bipolar disorder: prevalence rate and clinical correlates during naturalistic follow up

S Miller<sup>a</sup>, T Suppes<sup>a</sup>, J Mintz<sup>b</sup>, G Helleman<sup>c</sup>, M Frye<sup>d</sup>, S McElroy<sup>e</sup>, W Nolen<sup>f</sup>, R Kupka<sup>g</sup>, G Leverich<sup>h</sup>, H Grunze<sup>i</sup>, L Altshuler<sup>c</sup>, P Keck<sup>e</sup>, R Post<sup>i</sup>

<sup>a</sup>VA Palo Alto Health Care System and Stanford University Medical Center Department of Psychiatry and Behavioral Sciences, Stanford, USA, <sup>b</sup>Department of Psychiatry, University of Texas Health Science Center, San Antonio, San Antonio, USA, <sup>c</sup>UCLA Department of Psychiatry, Los Angeles, USA, <sup>d</sup>Mayo Clinic Department of Psychiatry, Rochester, USA, <sup>e</sup>Lindner Center of HOPE, Cincinnati, USA, <sup>f</sup>University Medical Center Groningen, Groningen, The Netherlands, <sup>g</sup>Altrecht Institute for Mental Health Care and University Medical Centre, Altrecht, The Netherlands, <sup>h</sup>Biological Psychiatry Branch, NIMH, NIH, Bethesda, USA, <sup>i</sup>Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK, <sup>j</sup>George Washington School of Medicine, Washington, USA

**Objective:** The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), introduced the “with mixed features” specifier for major depressive episodes. The authors assessed the prevalence and phenomenology of mixed depression among patients with bipolar disorder, and qualitatively compared a range of diagnostic thresholds for mixed depression.

**Methods:** In a naturalistic study, 907 adult bipolar disorder outpatients participating in the Stanley Foundation Bipolar Network were followed longitudinally over 14,310 visits from 1995 to 2002. The Inventory of Depressive Symptomatology–Clinician-Rated Version (IDS-C) and Young Mania Rating Scale (YMRS) were administered at each visit.

**Results:** Mixed depression, defined as IDS-C score  $\geq 15$  and  $2 < \text{YMRS score} < 12$  at the same visit, occurred in 2,139 visits (14.9% of total visits, 43.5% of visits with depression) by 584 patients (64.4% of all patients). Women were more likely than men to experience subthreshold hypomania during visits with depression (40.7% versus 34.4%, gender  $\times$  depression interaction Wald chi-square = 8.47;  $p = 0.004$ ). Patients with  $\geq 1$  mixed depression visit had more visits symptomatic and less visits euthymic, compared to those with no mixed depression visits. A DSM-5-based definition of mixed depression (requiring  $\geq 3$  non-overlapping YMRS items concurrent with IDS-C  $\geq 15$ ) yielded a lower prevalence of mixed depression (6.6% of visits) but a similar relationship to gender.

**Conclusions:** Among bipolar disorder outpatients, concurrent hypomanic symptoms during visits with depression were common, particularly in women. The DSM-5 diagnostic criteria for depression with mixed features may yield inadequate sensitivity to detect patients with mixed depression, who may experience a more severe illness course and thus warrant careful monitoring.

#### Patterns of manic/hypomanic symptoms in depression using a pilot modification of the Hypomania Checklist – 32

ML Prieto<sup>a,b</sup>, EA Youngstrom<sup>c</sup>

<sup>a</sup>Department of Psychiatry, Universidad de los Andes, Santiago, Chile, <sup>b</sup>Department of Psychiatry & Psychology, Mayo Clinic College of Medicine, Rochester, USA, <sup>c</sup>Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, USA

**Objective:** The aim of this study was to explore the use of a modified self report screening instrument for bipolar disorder to assess current manic / hypomanic symptoms in patients with a depressive episode.

**Methods:** We evaluated 188 patients with Structured Clinical Interview for DSM-IV-TR disorders (SCID) confirmed bipolar or major depressive disorder. We assessed current hypomanic / manic symptoms using a modified version of the Hypomania Checklist-32 (mHCL-32). An Exploratory Factor Analysis (EFA) was conducted to identify clusters of mHCL-32 items that were endorsed concurrently. A Latent Class Analysis (LCA) was carried out to identify patients with similar mHCL-32 item endorsement patterns.

**Results:** The EFA identified 3 factors: factor #1 (“elation-disinhibition-increased goal directed activity”), factor #2 (“risk-taking-impulsivity-substance use”) and factor #3 (distractibility-irritability). The LCA yielded 3 classes (2 showing manic / hypomanic features). Class #1 patients endorsed items related to disinhibition and racing thoughts. Class #2 patients endorsed items associated with irritability and substance use.

**Conclusions:** The mHCL-32 scale allowed a comprehensive and convergent delineation of hypomanic / manic symptoms in depression. Different patterns of hypomanic / manic symptoms may occur in patients with depression, which may have treatment and prognostic implications. Further validation of these findings is needed.

## Implications and impressions of the ISBD Task Force DSM5 on mixed depression in bipolar disorder

MA Frye<sup>a</sup>, AC Swann<sup>b</sup>, B Lafer<sup>c</sup>, G Perugi<sup>d,e</sup>, M Bauer<sup>f</sup>, WM Bahk<sup>g</sup>, J Scott<sup>h</sup>, K Ha<sup>i</sup>, T Suppes<sup>j,k</sup>

<sup>a</sup>Department of Psychiatry & Psychology, Mayo Clinic Depression Center, Mayo Clinic, Rochester, USA, <sup>b</sup>Menninger Department of Psychiatry & Behavioral Sciences, Baylor College of Medicine, Houston, USA, <sup>c</sup>Department of Psychiatry, Bipolar Disorder Research Program, Institute of Psychiatry, University of São Paulo Medical School, São Paulo, Brazil, <sup>d</sup>Dipartimento di Psichiatria Università di Pisa, Pisa, Italy, <sup>e</sup>Institute of Behavioural Sciences "G. De Liso", Pisa, Italy, <sup>f</sup>Department of Psychiatry and Psychotherapy, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, <sup>g</sup>Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, <sup>h</sup>Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK, <sup>i</sup>Seoul National University Bundang Hospital, Seoul, Republic of Korea, <sup>j</sup>Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, USA, <sup>k</sup>VA Palo Alto Health Care System, Palo Alto, USA

**Objective:** While demarcated episodes of mania and depression have long been operationalized in diagnostic criteria, there is increasing recognition of the co-existence or rapid alternation of depressive and manic symptoms in the same episode. Until the development of DSM5, this mixed form was only recognized for mixed syndromal mania. Definitions of mixed states, especially those with prominent depression, are only beginning to be standardized and subsequently studied.

**Methods:** Literature searches based on bipolar disorder and the appearance of the term "mixed" and selected references from the articles found were combined with a series of conferences among the authors.

**Results:** The ISBD Task Force reviewed the concept and symptom structure of mixed states, described the relationship between mixed states and recurrent course of illness, and proposed diagnostic criteria for research or clinical use.

**Conclusions:** Definitions and properties of mixed states have generated controversy, but the stability of their characteristics over a range of clinical definitions and diagnostic methods shows that the concept of mixed states is robust. Now with a common set of DSM5 criteria, future research will rapidly clarify clinical correlates of mixed states in bipolar disorder.

# Symposium XXVIII

## Psychopathological and Neurodevelopmental Antecedents of Bipolar Disorder

### Chair: Martin Alda

## Antecedent psychopathology in offspring of parents with bipolar disorder and offspring of parents with major depressive disorder

R Uher

Dalhousie University, Departments of Psychiatry, Psychology & Neuroscience and Public Health & Epidemiology, Halifax, NS

Offspring of parents with bipolar disorder are not only at increased risk for developing bipolar disorder, but also report higher rates of antecedent psychopathology, including internalizing and externalizing disorders and affective lability in childhood and adolescence. Previous reports have been based on comparisons with offspring of healthy. Therefore, it is unknown if antecedents are specific to familial disposition to bipolar disorder or reflect a general familial risk of mood problems. To test the specificity of antecedents to family history, we compared rates of externalizing disorders, internalizing disorder and affective lability between offspring of parents with bipolar disorder (BP-O,  $n = 65$ , age  $12.2 \pm 4.7$ ) and offspring of parents with unipolar major depressive disorder (MDD-O,  $n = 57$ , age  $11.5 \pm 4.4$ ). We diagnosed internalizing problems in 21% of BP-O and 21% of MDD-O (difference OR = 1.02,  $p = 0.95$ ), externalizing problems in 28% of BP-O and 21% of MDD-O (difference OR = 1.43,  $p = 0.34$ ). We saw increased affective lability in 38% of BP-O and 39% of MDD-O (difference OR = 0.99,  $p = 0.99$ ). All antecedents were increased in both groups of high-risk offspring compared to offspring of healthy parents. In summary, most psychopathological antecedents generalize to offspring of parents with any major mood disorder. We have seen only small nonsignificant increase in the rate of externalizing disorders in offspring of parents with bipolar disorder. Rates of

internalizing symptoms and affective lability are increased to a similar degree in offspring of parents with bipolar and unipolar mood disorders.

## Using structural MRI to identify subjects at genetic risk for bipolar disorders – a two cohort, machine learning study

T Hajek<sup>a,b</sup>, C Cooke<sup>a</sup>, M Kopecek<sup>b</sup>, T Novak<sup>b</sup>, C Hoschl<sup>b</sup>, M Alda<sup>a,b</sup>

<sup>a</sup>Dalhousie University, Department of Psychiatry, Halifax, Canada,

<sup>b</sup>Charles University, Prague, Czech Republic

**Background:** Neuroimaging is of limited diagnostic use in psychiatry. This is due to clinical heterogeneity and low sensitivity/specificity of between-group neuroimaging differences. Machine learning (ML) may better translate neuroimaging to individual subjects. Studying the offspring of BD parents (high-risk HR design) decreases clinical heterogeneity and increases sensitivity for detection of endophenotypes. This is the first neuroimaging study using ML to identify subjects at genetic risk for BD.

**Methods:** We studied 45 unaffected and 36 affected relatives of BD probands recruited from 2 sites (Halifax, Canada; Prague, Czech Republic). Each subject was individually matched by age and sex to controls without personal or family history of psychiatric disorders. We applied support vector machines (SVM) and Gaussian process classifiers (GPC) to structural MRI.

**Results:** The SVM of white matter distinguished unaffected HR from control subjects (accuracy = 68.9%,  $p = 0.001$ ), with similar accuracy for the GPC (65.6%,  $p = 0.002$ ) or when analyzing data from each site separately. Differentiation of the more clinically het-

erogeneous affected familial subjects from healthy controls was less accurate (59%,  $p = 0.05$ ). Machine learning applied to gray matter did not distinguish either unaffected HR or affected subjects from controls. The regions, which most contributed to discrimination between the groups included white matter of the inferior frontal gyrus, cingulate, cerebellum, precuneus. Limitations: Although we recruited 126 subjects, ML benefits from large sample sizes.

**Conclusions:** Machine learning applied to white but not gray matter distinguished unaffected subjects at high and low genetic risk for BD based on regions previously implicated in the pathophysiology of BD.

### Anatomical evidence for an abnormal neurodevelopment in bipolar disorder

J Houenou<sup>a,b</sup>, C Henry<sup>a,b</sup>, S Sarrazin<sup>a,b</sup>, J Sun<sup>b</sup>, JF Mangin<sup>b</sup>, M Phillips<sup>c</sup>, M Wessa<sup>d</sup>

<sup>a</sup>INSERM U955 Team 15 “Psychiatry Genetics”, Créteil, France,

<sup>b</sup>Neurospin Neuroimaging Platform, CEA Saclay, 91191, Gif Sur

Yvette, France, <sup>c</sup>University of Pittsburgh Medical Center,

Pittsburgh, USA, <sup>d</sup>University of Mainz, Mainz, Germany

Neuroimaging studies have reported anatomical deviations in the brain of patients with bipolar disorder. The origin of the abnormal-

ities is yet unclear. They may be the result of abnormal neurodevelopment or stem from processes linked to the course of the disease, such as accelerated ageing, medication effect, impact of the episodes, socio-professional exclusion or comorbidities. Our objective was thus to explore anatomical evidence for abnormal neurodevelopment in patients with bipolar disorder. We studied the shapes of brain structures, which are supposed to be strongly driven by neurodevelopmental factors, as well as their link with cortical gyrification, which is also linked with early development. We analyzed a large multisite T1 and diffusion weighted MRI database that included 203 subjects (117 patients with bipolar disorder and 86 controls). In patients with bipolar disorder, we found alterations in the shape of the left cingulum ( $F = 4$ , effect size  $f = 0.1$ ,  $p = 0.05$ ), the left arcuate fasciculus ( $F = 16.2$ , effect size  $f = 0.3$ ,  $p = 0.0001$ ) and the bilateral uncinate fasciculus ( $F = 5$ , effect size  $f = 0.1$ ,  $p = 0.03$ ). For the latter one, we were able to show that its particular shape in bipolar disorder was associated with a specific gyrification pattern in the orbitofrontal lobe ( $p = 0.0006$ ). All these results bring evidence for neurodevelopmental alterations in both white and grey matter in bipolar disorder.

# Symposium XXIX

## Service Users as Powerful and Active Educators in the Health Professions and Beyond

### Chair: Sacha Agrawal

#### From surviving to advising: pairing people with lived experience of mental health and addiction issues as advisors to senior psychiatry residents

S Agrawal<sup>a</sup>, P Capponi<sup>b</sup>, D Farb<sup>c</sup>

<sup>a</sup>Psychiatry, University of Toronto and Centre for Addiction and Mental Health, Toronto, Canada, <sup>b</sup>Voices from the Street and Women Speak Out, Toronto, Canada, <sup>c</sup>Mood Disorders Association of Ontario, Toronto, Canada

Achieving the goal of a recovery-oriented mental health system requires a shift in postgraduate psychiatric education to engender among trainees a more person-centered stance toward people living with mental health and addiction issues. This project aimed to develop a novel educational model that pairs service users as advisors to psychiatry residents to enable residents to learn more deeply about the lived experience of people recovering from mental health and addiction issues and to reduce prejudice. Three successive cohorts of senior University of Toronto psychiatry residents ( $N = 49$  pairs) met with their advisors monthly for six months. The experience of the participants will be described and lessons learned from mounting a curriculum of this nature will be explored.

#### Peer to peer, peer to professional outreach

P Capponi

*Women Speak Out and Voices from the Street, Toronto, Canada*

In crowded drop-ins, supportive housing and the Toronto Community Housing Corporation, a panel of peers, women who have experienced years of life on the street, crack addictions, abuse and isolation, speak to clients about their lives and the challenges to their current health that poor nutrition, wretched conditions, and isolation have left them. They speak about their efforts to be seen by doctors in walk-in clinics and emergency departments, how unwelcome they felt and the atmosphere of suspicion they encountered. Then they speak about the present, their work with family doctors who know and accept them, advocate for them, and the positive difference this has created.

#### The power of veteran peer support

A Doerderlein

*Depression and Bipolar Support Alliance, Chicago, USA*

To reach, engage, and support individuals in recovery-focused, person-centered mental health services, new ways of work are needed, including partnerships among clinicians, program administrators, and individuals who have successfully utilized such services. One widely-recognized tactic to do so is to utilize trained and

certified peer specialists. The value of these individuals has been recognized by private and public mental health systems, including the United States Veterans Administration, with which the Depression and Bipolar Support Alliance worked in 2013–2014 to train

500 Veteran Peer Specialists. We will look at the numerous ways that peer support services have proven essential to transforming the VA's mental health programs to a more effective, person-centered, and wellness-focused model.

## Symposium XXX

# Varenicline for Bipolar Depression with Comorbid Nicotine Dependence

### Chair: Mark Frye

#### Varenicline for bipolar depression with comorbid nicotine dependence

**M Frye**

*Mayo Clinic, Rochester, USA*

This 12-week open-label study of varenicline included adults who met DSM IV TR criteria for bipolar I/II depression and tobacco dependence stable on mood-stabilization treatment. Varenicline (Chantix®) was dosed per package insert guidelines with visits at baseline and every 2 weeks (total 7 total visits). In addition to the study medication, all subjects received cognitive behavioral counseling focused on problem solving and avoiding relapse. The primary outcome measure was 7-day point prevalence self-reported abstinence rate confirmed by exhaled breath CO < 10 parts/million (ppm). Nine subjects (4F/5M, mean age  $38.8 \pm 13.8$  yrs) enrolled and started study medication. Baseline mean MADRS (9.9; SE = 1.5) and YMRS (1.9; SE = 0.6) were consistent with subsyndromal depression. While only 3/9 subjects met the primary outcome measure, there was an overall significant reduction from baseline to endpoint in the number of cigarettes smoked per day, urge to smoke, and CO levels (all  $p < 0.01$ ). While there was no significant change in MADRS and there was no suicidal behavior. Our preliminary data appear to suggest that varenicline may be effective and safe from a mood stabilization standpoint for smoking cessation in bipolar depressed patients. While only 1/3 of our subjects achieved abstinence, we did see evidence of significant cigarette reduction, which may be an alternative harm reduction outcome to further study.

#### A randomized, double-blind, placebo-controlled clinical trial of varenicline in persons with bipolar disorder motivated to quit smoking

**KNR Chengappa**

*University of Pittsburgh Medical Center, Pittsburgh, USA*

Virtually no adequately powered clinical trials for smoking cessation have been undertaken in bipolar disorder. Warnings for neuropsychiatric adverse events likely dampened enthusiasm for varenicline. The efficacy and safety of varenicline in euthymic bipolar subjects motivated to quit smoking was assessed in this study. Clinically stable adult patients with DSM-IV Bipolar disorder ( $n = 60$ ) who smoked  $\geq 10$  cigarettes per day were randomized to a 3-month, double-blind, placebo-controlled varenicline trial and a 3-month follow-up. Smoking cessation counseling was provided to

all. In addition to self-report, smoking cessation was verified using a carbon monoxide (CO) meter (CO < 10 ppm). At 3-months (i.e. end of treatment), significantly more subjects quit smoking with varenicline (15/31, 48.4%) than with placebo (3/29, 10.3%), OR = 8.1 (95% CI, 2.03, 32.5),  $p = 0.002$ . At 6-months (i.e. end of non-treatment follow up), 6/31 (19.4%) varenicline-treated subjects remained abstinent compared to 2/29 (6.90%) assigned to placebo, OR = 3.2 (95% CI, 0.60, 17.6),  $p = 0.17$ . Psychopathology scores remained stable. Ten serious adverse events occurred ( $n = 6$ , varenicline,  $n = 4$ , placebo). Abnormal dreams occurred significantly more often in varenicline-treated subjects (18/31, 61.3%) than those receiving placebo (9/29, 31%), Fisher's exact  $p = 0.04$ . Eight varenicline treated and five placebo-assigned subjects expressed fleeting suicidal ideation, a non-significant difference. Varenicline shows efficacy for initiating smoking cessation in bipolar patients, but medication trials of longer duration are warranted for maintaining abstinence. Vigilance for neuropsychiatric adverse events is prudent when initiating varenicline in this patient population.

#### Predictors of smoking in bipolar disorder with comorbid substance abuse

**I Salloum**

*University of Miami School of Medicine, Miami, USA*

The aim of this study was to examine predictors of smoking in bipolar disorder with comorbid substance dependence. The sample consisted of forty one patients with bipolar disorder and comorbid substance dependence who were treated with mood stabilizers and followed for three months. We examined predictors of smoking behavior as assessed by the Fagerström Test for Nicotine Dependence (FTND) and the Timeline Methods of daily smoking. Predictors included age, gender, ethnicity, race, education, bipolar type (depressed vs. manic) and comorbidity (cocaine vs. alcohol). Sixty six percent were smokers. Smoking was highest among males (71%), non-Hispanics (70%), with less years of education (71%), depressed (65%) and those with alcohol dependence (66%) and cocaine dependence (65%). The odd ratio of male to female smoking at baseline was 2.6, and that for Hispanic vs. non-Hispanic was 0.32. The odd ratio of smoking among depressed patients was 2.97 at baseline and still persisted high during the last four weeks of the study with an odd ratio of 3.98. Younger patients smoked more heavily than older patients. Male patients, non-Hispanics, non-White, with less than 12 years of education and those with depression reported more severe use as indicated by the FTND item such

as time to first cigarette smoked after awakening. This study highlights the high rate of smoking in bipolar disorder with comorbid substance abuse and points to the association of bipolar depres-

sion, younger age, male gender, non-Hispanic ethnicity and lesser than 12 years of education with smoking behavior.

## Symposium XXXI

### Cross-Cultural Issues in Family Interventions for Bipolar Disorder

Chair: Aysegul Ozerdem

#### Cross-cultural issues in family interventions for bipolar disorder

A Ozerdem<sup>a</sup>, AN Sharma<sup>b</sup>, DJ Miklowitz<sup>c</sup>

<sup>a</sup>Psychiatry Department, Dokuz Eylul University Medical School, Izmir, Turkey, <sup>b</sup>Academic Child and Adolescent Mental Health, Newcastle University, Newcastle upon Tyne, UK, <sup>c</sup>UCLA Semel Institute for Neuroscience and Human Behavior, Division of Child and Adolescent Psychiatry, Los Angeles, USA

A cultural perspective in psychiatry is important for identifying novel and effective treatment approaches for diverse populations across the world. Family-focused treatment (FFT) is useful as an adjunct to pharmacotherapy in symptom stabilization, relapse prevention, and functional enhancement in patients with adult and adolescent bipolar disorder. FFT targets family's knowledge of bipolar disorder and interactions between the symptomatic individual and his/her caregivers. Knowledge of illness and family interactions are likely to be influenced by such cultural variables as how the illness and the role of the individual in the family are perceived. FFT has been used in two different countries (UK and Turkey) outside the US where it was first coined, providing a model for discussing cross-cultural issues in psychotherapy for bipolar disorder. Dr. Aditya Sharma from the UK and Dr. Aysegul Ozerdem from Turkey will present their experiences of applying FFT in two patient populations (adolescents in UK and adults in Turkey) from both clinical and research points of view and discuss the modifications they had to make throughout the treatment course, and

outcomes of each respective experience. The third speaker from US (Dr. David Miklowitz) will discuss how the similarities and differences in applying FFT across cultures can be used as a model for the development of other novel interventions for bipolar disorder.

#### Cross-cultural adaptations to psychotherapy

DJ Miklowitz

Psychiatry, UCLA School of Medicine, Los Angeles, USA

Dr. Miklowitz will be the discussant. He will focus on the similarities and differences in applying FFT across cultures, and how to use information gleaned from the cross-cultural experiences of the Turkish and UK studies of FFT can be used in the adaptation of other psychosocial treatments. For example, cultures may vary on whether they see bipolar disorder as a biologically and genetically-based illness, and may place greater emphasis on environmental factors. The Western ideal of good family communication (e.g., good eye contact, "I feel" statements, specific about one's complaints and suggesting behavioral changes in another family member) may be viewed as signs of disrespect when expressed by an offspring to a parent. Some Eastern cultures may emphasize acceptance strategies (e.g., mindfulness meditation) over change strategies (e.g., cognitive restructuring). The clinician needs to be aware of these differences and prepared to modify the treatment protocol to adapt to strongly held cultural beliefs.

## Symposium XXXII

### Advances in the Management of Bipolar Disorder in Pregnancy

Chair: Arianna Di Florio

#### Bipolar disorder during pregnancy and postpartum: prevention, pathophysiology and treatment of episodes

V Bergink<sup>a,b</sup>

<sup>a</sup>Erasmus Medical Center, Department of Psychiatry, Rotterdam, The Netherlands, <sup>b</sup>National Center for Register-Based Research, Aarhus University, Aarhus, Denmark

Women with bipolar disorder are at high risk for relapse during pregnancy if they taper of medication. Further, after delivery, women with bipolar disorder are at extreme high risk for affective and/or psychotic episodes. A major goal of peripartum psychiatric care for bipolar women is the development of effective prophylaxis algorithm that optimally balances the risks and benefits for the mother and the fetus. Using our recent data, we will discuss pharmacologic treatment recommendations during pregnancy and the



postpartum period. The majority of women presenting with severe mental illness immediately postpartum do not have a psychiatric history. This presentation will highlight results which indicate that the first time occurrence of severe mental illness in the early postpartum period is a marker of possible underlying bipolarity. Outcomes from a prospective postpartum psychosis cohort study from Rotterdam, the Netherlands will be discussed. We have evaluated treatment response and remission during the acute phase of illness, as well as relapse events through a nine-month follow-up period. In addition, we recently identified abnormal immune responses in women with first onset PP compared to controls. Our data highlight a model for postpartum episodes by which an abnormal set point of the immuno-endocrine axis is the ultimate trigger for the acute onset of mania or psychosis in women with an underlying genetic susceptibility for bipolar disorder.

### **The role of psychosocial treatments in the prevention of bipolar relapse following childbirth**

**P Boyce**

*Sydney Medical School, The University of Sydney, Sydney, Australia*

Psychosocial treatments (Psychoeducation, Social Rhythm Therapy, Family therapy and CBT) are effective in preventing bipolar relapse. Pregnancy is an ideal time to apply these interventions, either in combination with medication, or on their own to prevent relapse following childbirth. Psychosocial treatments can target factors that are known to trigger relapse among bipolar women. Triggering factors include sleep disruption, interpersonal difficulties and a failure to recognise early warning signs. The impact of these triggering factors can be reduced by the application of psychoeducation, learning how to recognise early warning signs, and developing strategies to deal with them when they arise; social

rhythms therapy to develop a stable sleep wake cycle (as well as developing strategies to ensure a stable sleep wake cycle in immediate postpartum period) and CBT to deal with stresses that may arise during the pregnancy and stress inoculation for potential postpartum stresses. In this presentation these strategies will be outlined along with a series of cases demonstrating their application.

### **What factors influence vulnerability to postpartum episodes in bipolar women?**

**I Jones**

*National Centre for Mental Health, MRC Centre in Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK*

It has long been recognised that childbirth is a time of considerable risk for women with bipolar disorder, with severe postpartum episodes (postpartum or puerperal psychosis) occurring following 25% to 50% of deliveries. This represents a many hundred-fold increase compared with the general population rate of around 1 in 1000, and highlights the importance of considering issues regarding pregnancy and childbirth in women with bipolar disorder. In this talk I will review the evidence confirming that women with bipolar disorder are at very high risk of episodes of severe postpartum affective disorder and examine what is known about the factors that influence this risk. Studies from our group have demonstrated that familial (genetic) factors influence vulnerability to the puerperal trigger and based on these findings we are conducting molecular genetic studies to identify the genetic variants that confer risk. This line of research has the potential to uncover the nature of the puerperal trigger, allow a more individualised estimation of risk for women with bipolar disorder, and provide further information relating to the aetiology of mood disorders in relation to childbirth and at other times.

## **Symposium XXXIII**

# **Laughing Like Crazy Stand Up Comedy Peer Support Program for People with Mental Illness: Research Results**

### **Chair: Lisa Hawke**

### **Evaluation of the efficacy of the laughing like crazy stand-up comedy training program**

**L Hawke<sup>a,b</sup>**

*<sup>a</sup>University Health Network, Toronto, Canada, <sup>b</sup>Université de Saint-Boniface, Winnipeg, Canada*

Dr. Hawke will present the results of the formal research project assessing the impacts of Laughing Like Crazy. In a collaborative project between MDAO and academic partners at the University Health Network, Dr. Hawke led a mixed-methods research project evaluating the effects of the Laughing Like Crazy program. A total of 40 participants completed a series of questionnaires before and after the program and participated in focus group interviews.

Among them, 30 (75%) completed the entire Laughing Like Crazy program. Participants reported extremely high rates of satisfaction, as well as statistically significant improvements on nearly every measure. Improvements included greater self-confidence, reduced anxiety and depression, and more frequent use of humour to deal with stressful situations. Furthermore, at the end of the program participants reported using humour in a more adaptive way and using less maladaptive humour. Focus group discussions revealed improved symptom management, personal development, a sense of achievement, a sense of community, and enjoyment of a very inspiring experience. In summary, MDAO's Laughing Like Crazy stand-up comedy training program has many positive effects for participants and is a unique, powerful recovery program in the

MDAO suite of services. Based on these positive results, preliminary planning is under way to begin program dissemination to Ontario affiliate groups.

### **The laughing like crazy program from peer, facilitator and supervisor perspectives**

**E Wedge Årdal**

*Mood Disorders Association of Ontario, Toronto, Canada*

Emma will describe the Laughing Like Crazy program from peer, facilitator and supervisor perspectives. Emma has a background in women's studies and philosophy, is a graduate of the Peer Recovery Education for Employment & Resilience (PREPER) program, and has experience as direct provider of peer support services. Involved in Laughing Like Crazy since 2008, she has facilitated the program for five years and trained some 120 comedians. She has also led the comedians through over 100 performances before diverse audiences, such as the Ontario Psychiatric Association, the Consumer-Survivor Information Centre and Humber River Regional Hospital. Emma is now responsible for supervising six Laughing Like Crazy program facilitators and ensuring ongoing program consistency and effectiveness. Based on her substantial program experience, Emma will describe the mechanics of program participation and facilitation, providing an inside look at the Laughing Like Crazy experience. She will also describe the program docu-

mentation process and the steps MDAO is taking to prepare for disseminating the program effectively across the province.

S097

### **Laughing like crazy: a live comedy performance**

**L Hawke**

*Mood Disorders Association of Ontario, Toronto, Canada*

To round out the symposium, four Laughing Like Crazy program graduates will perform original comedy routines. Comedians will be selected from among the some 120 comedians active in the Laughing Like Crazy Graduates group in spring 2015. Comedians' courageous performances will present the dark and light side of living with a mental illness, viewing even serious issues such as hospitalization, suicide and trauma through the lens of humor. This unique component of the conference symposium will put the audience in direct contact with actual Laughing Like Crazy participants and demonstrate the program's ability to empower participants, entertain audiences, and bring people together. A question and answer period will be provided to give the audience the opportunity to talk to the comedians about their experience participating in the Laughing Like Crazy program, then taking their comedy routines on the road.

# **Symposium XXXIV**

## **Inflammatory Processes and Bipolar Disorder: Etiological and Treatment Considerations**

### **Chair: Victoria Cosgrove**

### **Exploring inflammatory pathways in bipolar disorder**

**T Suppes<sup>a,b</sup>, V Cosgrove<sup>a,b</sup>, J Hallmayer<sup>a</sup>**

<sup>a</sup>*Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, USA,* <sup>b</sup>*Bipolar and Depression Research Program, VA Palo Alto Health Care System, Palo Alto, USA*

Bipolar disorder is among the top ten diseases listed worldwide by the WHO for morbidity and mortality. The recent work by Padmos and colleagues (2008) suggests that an expression of proinflammatory genes in monocytes may be specific to bipolar disorder and be part of the vulnerability of developing the illness. These promising early leads suggest novel treatment targets, and importantly provide a vital new direction to explore addressing of the pathophysiology of an illness historically considered to be genetically determined. We will present preliminary findings from a hypothesis-generating study replicating for the first time the recent findings of Padmos and colleagues of this mRNA signature expression, but uniquely the proposed study was carried out with patients on no medications and a uniform bipolar diagnostic group. We will explore a putative role for inflammatory immune pathways in BDII versus healthy controls by assessing the presence of a signature of aberrantly-expressed mRNAs of inflammatory, trafficking, survival, and mitogen-activated kinase pathway genes in 10 medication-free individuals with BD and 10 healthy controls having similar distributions of age, sex, and ethnicity. We will also examine the impact on the mRNA expression signature within individ-

ual patients after initiation of medications (3 weeks) and after expected clinical response of depressive symptomatology (~8 weeks). This pilot study adds important information to our understanding of this grouping of mRNA inflammatory signature genes in bipolar disorder and provides the first longitudinal work measuring medication impact and state versus trait impact.

### **Inflammation: implication for pathogenesis in novel treatments in bipolar disorder**

**R McIntyre**

*Mood Disorders Psychopharmacology Unit, University of Toronto, Toronto, Canada*

Disturbances in immune-inflammatory systems have been implicated in the pathogenesis, phenomenology, co-morbidity and treatment of bipolar disorder the plausibility of immune-inflammatory systems in this regard is buttressed by convergent results from pre-clinical studies as well as in vivo studies in human volunteers indicating that brain substrates implicated in the pathogenesis of bipolar disorder are engaged by inflammatory systems. Available treatment options in bipolar disorder represent incrementalism of development when compared to older treatments. There is a pressing need to better characterize disease pathogenesis in bipolar disorder to provide opportunity for transformative treatment and prevention efforts. It is unlikely that immune-inflammatory disturbances are relevant to most individual with bipolar disorder and

more likely to represent a relevant pathway for a sub population. The future of bipolar characterization should prioritize stratification followed by personalization. There is a need to inform stratification with biomarkers and possibly bio signatures. It is plausible that biomarkers could include inflammatory systems. This presentation will provide a focused and directed look at inflammation with specific implications for domains in bipolar disorder and as well as opportunities for prevention and treatment. This presentation will also present preliminary results of a proof of concept study involving infliximab as part of a placebo evaluating the effect of this treatment on key domains e.g. cognition, affective processing in bipolar disorder.

### **Does cognitive behavioral therapy alter stress-induced inflammatory response in pediatric bipolar disorder?**

**V Cosgrove, J Pearlstein, K Chang**

*Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, USA*

Cognitive-behavioral therapy (CBT) may be effective in ameliorating depressive symptoms as well as staving off the full expression

of bipolar disorder (BD) in youth. CBT teaches skills and techniques to manage and reduce how an individual responds to stress in the environment. Altering response to environmental and psychosocial stress via CBT may alter levels of expression in inflammatory protein production (cytokines) associated with such stress. This may elucidate mechanisms of response to CBT, ultimately determining who is most likely to benefit, improving depressive symptoms, and possibly avoiding progression to full BD in high risk youth. The specific, objective of this study is to determine whether participation in group CBT alters inflammatory response to a laboratory psychosocial stress test in youth with or at high risk for BD and if this alteration is related to a decrease in depressive symptoms. Thirty-six youth with or at high risk for BD completed a 10-session CBT group and pre- and post-group Trier Social Stress Tests (TSSTs). Mean age at study entry was 15.21 (1.97). At study entry, mean levels of pro-inflammatory TNF- $\alpha$  and IL-6 were 4.35 (1.61) and 3.80 (7.78), respectively, while mean anti-inflammatory IL-10 was 4.87 (5.23). Cytokine levels measured after 30, 60, and 90 minutes post-stressor will be presented. Results from this study examine biological correlates of response to CBT, potentially leading us closer to a mechanism of treatment and/or prevention of BD in youth.

## **Symposium XXXV**

# **Understanding Mood Instability in Bipolar Disorder: From Psychopathology to Neurobiology to Therapy**

Chair: Guy Goodwin

### **Mental imagery and mood instability: a case series of imagery-focused cognitive therapy for bipolar disorder**

**M Di Simplicio<sup>a</sup>, S Hales<sup>b</sup>, S Blackwell<sup>a</sup>, K Young<sup>b</sup>, A Lau-Zhu<sup>a</sup>, H Mitchell<sup>a</sup>, G Goodwin<sup>b</sup>, EA Holmes<sup>a,b</sup>**

*<sup>a</sup>Cognition and Brain Sciences Unit, Medical Research Council, Cambridge, UK, <sup>b</sup>Psychiatry, University of Oxford, Oxford, UK*

Mental imagery (the experience of 'seeing through the mind's eye') is associated with a greater emotional response than are verbal thoughts (Holmes & Matthews, 2005). Intrusive mental images characterise numerous mental disorders, from social anxiety to post-traumatic stress disorder, and have been proven a useful target for cognitive therapy to reduce anxiety (Clark et al., 2006) and depression (Brewin et al., 2009). Anxiety is a common feature of bipolar disorder potentially worsening mood instability, yet it remains neglected in psychological treatment approaches (Stratford, Cooper, Di Simplicio, Blackwell, Holmes in press). We proposed that excessive levels of vivid mental images can act as 'emotional amplifier' in bipolar disorder, contributing to the escalation of anxiety and mood symptoms (Holmes, et al., 2008). Compared to individuals with unipolar depression, bipolar patients report more compelling 'flashforwards' (future images) of both a negative suicidal (Hales et al., 2012) or positive nature (Ivins et al.,

2014). MAPP (Mood Action Psychology Programme) is a case series study of imagery-focused cognitive therapy for bipolar disorder. Fourteen patients with bipolar disorder underwent a brief intervention (10–12 sessions) reducing dysfunctional and improving functional mental images associated with anxiety, low and elevated mood. Weekly depression, mania and anxiety symptoms were collected from four weeks baseline through the study duration and patients were followed up for six months; functioning and suicidality measures were also assessed. Data will be presented following our prediction that targeting mental imagery via cognitive therapy will reduce bipolar anxiety and improve eventual mood stability.

### **Mechanisms underlying the dynamics of bipolar disorder: a look on emotional and motivational dysregulation**

**M Wessa**

*Clinical Psychology and Neuropsychology, Johannes Gutenberg-University Mainz, Mainz, Germany*

Emotional and motivational dysregulation have been proposed as core mechanisms underlying the development and chronic course of bipolar disorder. Substantial empirical evidence, also from our

own group, suggests that such dysregulation is present during euthymic illness phases but also in healthy individuals at risk to develop bipolar disorder. We will present data from different behavioral and neuroimaging studies in euthymic patients with bipolar-I disorder showing that despite very low levels of residual symptoms the affective quality of the previous episode predicts response patterns to reward on a behavioral and neural level (as measured with functional magnetic resonance imaging). Patients with a previous manic episode were more reactive to reward, indicated by choosing rewarding stimuli more often and by increased amygdala activity in response to rewarding outcomes. This effect was evident even when taking other illness-related variables, such as number of episodes, predominant quality of the episodes or age of illness onset, into consideration. Further, euthymic bipolar-I disorder patients vary in their patterns of emotional processing depending on the affective quality of the previous episode. These data will be discussed in the light of research perspectives that include prospective study designs using behavioral and potentially neuroimaging measures of emotional and motivational dysregulation at multiple time points to unravel the pathogenic mechanisms of the dynamics of bipolar disorder.

### **Emotional reactivity in euthymic bipolar patients: two emotional dysregulation profiles associated with impaired functioning**

**K M'bailara<sup>a</sup>, A Desage<sup>b</sup>, L Zanouy<sup>b</sup>, I Minois<sup>b</sup>, M Bouteloux<sup>b</sup>, A Jutant<sup>b</sup>, S Gard<sup>b</sup>, C Henry<sup>c</sup>**

<sup>a</sup>Psychology, University of Bordeaux, Bordeaux, France, <sup>b</sup>Fondation FondaMental, Hospital Ch. Perrens, Bordeaux, France, <sup>c</sup>Fondation FondaMental, Hospital A. Chenevier, Créteil, France

Emotional reactivity is defined by the emotional intensity with which an individual reacts to the environment. It is now well established that bipolar patients have exhibit a stronger emotional reactivity than healthy subjects (Henry et al, 2012; Holmes et al., 2011; M'bailara et al., 2009). To refine this observation, it seems important to determine whether there are different patterns of emotional dysregulation: hypo versus hyper reactivity. The link between emotion and adaptation being well demonstrated, one needs to refine the descriptions of emotional dysregulation profiles, to understand the functional differences between patients. The objective of this study was to test the link between emotional reactivity profiles and level of functioning in euthymic patients with a diagnosis of bipolar disorder. This study was conducted with euthymic bipolar patients (FACE-BD cohort). Emotional reactivity was assessed with the MATHYS (Multidimensional Assessment of Thymic State) and the individual functioning with the FAST. The results shows that the distribution of functioning scores differ between groups (Kruskal-Wallis test 11.7; df = 2, p = 0.003). At the same time, patients with hypo-reactivity (MATHYS 24) have a general level of impaired functioning, particularly for the dimensions of autonomy, work, cognitive functioning and interpersonal relationships). There are therefore several profiles of emotional dysregulation in patients. Thus, taking into account the bidirectional state of bipolar patients it would serve us well to rely on the results of the emotional reactivity profiles in order to adequately plan for their treatment.

# **Symposium XXXVI**

## **Effective Psychosocial Interventions: Tailoring to Patient Stages and Needs while Achieving Optimal Dissemination**

### **Chair: Sagar Parikh**

### **An evidence map of psychosocial interventions for the earliest stages of bipolar disorders**

**J Scott**

*Newcastle University & Institute of Psychiatry, Newcastle upon Tyne, UK*

Bipolar disorder (BD) is one of the four most burdensome global problems in individuals under 25 years. 1. In psychosis and depression, psychological interventions are effective low risk, high benefit approaches to at risk, first episode and other early onset cases. This paper reviews therapies for these early stages of BD. As therapy for this target group is an emerging field, it was not possible to apply gold standard approaches to data synthesis. Instead, 'evidence mapping' was employed to identify the 'extent, distribution and methodological quality' of available evidence. 2. The evidence map showed that 18 different therapy models have been employed in 29 completed or ongoing studies: 10 are in at risk populations, five in first episode BD, and 14 in early onset cases. The main models employed are family, cognitive-behavioural, and interpersonal therapies, but only family therapies has been tested across all early

stages using randomized controlled trials. Of 19 completed studies, seven are RCTs, but only one had a sample size >100. Despite the paucity of completed high quality research, descriptions of interventions for early stages of BD in 15–25 year olds suggests that well-adapted, age-appropriate interventions are available. Potential gaps are that few models precisely target normative developmental processes that may increase risk of BD (eg delayed sleep phase, ruminative response style), or offer detailed strategies for managing substance use or physical health and activity 3.

### **Treating late stage patients: the role of psychotherapy**

**F Colom**

*Institute for Neuroscience, University of Barcelona, Barcelona, Spain*

Several psychological interventions including cognitive-behavioral therapy, patients' group psychoeducation and caregivers' psycho-

education have shown some prophylactic efficacy in the early stages of bipolar disorders. Unfortunately, the vast majority of approaches fail at showing similar efficacy on those patients presenting a large number of past episodes and an important degree of functional and cognitive impairment. This population is usually refractory to standard pharmacological therapy and, hence, palliative psychosocial approaches are badly needed the sooner the better. An integrative model of palliative psychotherapy should include functional rehabilitation, psychoeducative and behavioral techniques and family support. It should also promote healthy habits, including the regular practice of physical exercise. Moreover, given the problems in social cognition which persist even when the patient is asymptomatic, a more significant effort to address these issues should be made. On the other hand, functional remediation and psychoeducation may take different places in the available arsenal of psychotherapies for bipolar disorders. Whilst psychoeducation may be the first choice treatment as a prophylactic add-on for many bipolar patients (mostly for those in early and medium stages of the illness), functional remediation is the treatment of choice for patients showing a clear cognitive and functional impairment who would probably respond poorly to psychoeducation.

### **Promoting effective uptake of psychosocial interventions: key patient, provider, and systems approaches**

**S Parikh**

*University of Toronto, Toronto, Canada*

Significant research has identified multiple psychosocial interventions that improve outcomes in BD, but cost and complexity have hindered their implementation. Population health approaches focus on using multiple strategies, at the patient, provider, and system levels, to facilitate uptake. This paper will review key patient strategies that include use of peer-to-peer dialogue, interactive internet and paper-based self-help methods, and non-traditional approaches involving dramatic theatrical approaches. At the provider level, approaches which reduce cost in training and delivery of treatments will be reviewed. Innovations in service delivery, with use of groups and different treatment providers, can aid feasibility of interventions. Finally, the systems level of approaches demands a weaving together of strategies and tools that allow for uptake and reinforcement of psychosocial interventions at a manageable cost, involving using tools such as E-health and internet strategies together with specific patient and provider approaches. These population health inspired practices can optimize the use of psychosocial interventions in bipolar disorder.

# Brainstorming Session I

## The Problem of Defining and Detecting Relapse in Maintenance Studies

Chair: Gary Sachs

### Novel approach to design and assessment for relapse prevention trials

**A Mahableshwarkar**

*Takeda, Deerfield, Chicago, USA*

Prevention of relapse in patients with bipolar disorder who have been treated and stabilized for acute episodes (whether for mania or depression) has been studied as a method to demonstrate the utility of long-term treatment of medications that are effective in short-term treatment. Such a randomized withdrawal design has been the standard design for all treatments that have been approved for prevention of relapse. A relapse in such studies is usually defined by a specific score on selected rating scales for mania or depression (HAM-D, MADRS, YMRS, etc.). This presentation will discuss a trial for an add-on treatment for prevention of relapse that is currently ongoing. This trial has a novel design in that currently stable patients are randomized to either placebo or treatment in addition to ongoing physician's choice treatment. The trial also assesses relapse based on clinician and patient scored scores on the YMRS and MADRS. The presentation will compare relapse rates based on the two approaches and discuss relative merits of each method.

### Challenges with outcomes for longitudinal follow up of interventions for patients with mood disorders

**A Nierenberg<sup>a,b</sup>**

*<sup>a</sup>Psychiatry, Harvard Medical School, Boston, USA, <sup>b</sup>Psychiatry, Massachusetts General Hospital, Boston, USA*

To prevent mood episode relapses or recurrences for those with major depressive disorder (MDD) or bipolar disorder (BD) is a laudable goal and a desirable outcome. But to conduct the efficacy studies that show that interventions prevent relapses/recurrences, patients are usually asked to remain in a study until they develop an actual episode that meets full diagnostic criteria –something that they may not agree to at the start (volunteer bias) or may not stick around for once they start to feel worse (leaving the study prematurely). Alternatives to using the return of a full episode as an outcome include: 1) worsening that falls short of developing a full episode (“roughening”); 2) the clinical need for an intervention; or 3) all cause discontinuation from the protocol. Pragmatic trials that assess how well interventions perform under usual clinical care) present further difficulties because clinicians can usually intervene when patients start to feel worse after feeling well – with one method of measuring outcomes called Necessary Clinical Adjustments. Naturalistic studies such as registries or the Patient Centered Outcomes Research Institute funded MoodNetwork will also need to have clearly defined long-term outcomes for relapse/recurrence. This presentation will discuss the challenge of choosing thresholds for outcomes for controlled and naturalistic studies to examine relapse/recurrence of mood disorders.

# Brainstorming Session II

## How to Manage Bipolar Disorder in Pregnancy and Postpartum Disorder

Chair: Bart Geerling

### Pharmacotherapy for pregnant and nursing women with bipolar disorder

**WV Bobo<sup>a</sup>, A Stevens<sup>b</sup>, B Geerling<sup>b</sup>**

*<sup>a</sup>Department of Psychiatry and Psychology, Mayo Clinic, Rochester, USA, <sup>b</sup>SCBS, Dimence, Deventer, the Netherlands*

Treatment of bipolar pregnant women is a challenge. What is the risk of no treatment with pharmacotherapy and how are risk and

benefit of pharmacotherapy studied in context of pregnancy (observational, rather than randomized, studies). Reproductive safety of mood stabilizers and antipsychotics used to treat bipolar disorder will be discussed, as structural and neurobehavioral teratogenesis, adverse neonatal events. Also lactational safety of mood stabilizers and antipsychotics used to treat bipolar disorder will be discussed.

### **Weighing the risks**

**A Stevens<sup>a</sup>, B Geerling<sup>a</sup>, WV Bobo<sup>b</sup>**

<sup>a</sup>*SCBS, Dimence, Deventer, the Netherlands*, <sup>b</sup>*Department of Psychiatry and Psychology, Mayo Clinic, Rochester, USA*

Pregnancy and postpartum period are challenging periods in women with a bipolar disorder. Decisions must be made whether continuing or stopping medication during pregnancy weighing the risk of medication for the (unborn) child and the risk of the illness

(becoming depressed or manic/psychotic) for the mother. We discuss the pro's and contra's of continuing or stopping medication and if continue medication we discuss which medication is best to use. We discuss possible alternatives for medication. We also present a format of a prevention plan. In this plan the stress and protective factors will be written, the prodromes (of manic or depressive decompensation) and what to do if these prodromes occur for each period (pregnancy, delivery and postpartum).

## **Brainstorming Session III**

### **Primary Care: Collaborative Detection and Management of the Larger Half of Bipolar Disorders**

**Chair: James Phelps**

#### **Integrating bipolar management in a busy primary care practice**

**D Dietch**

*Lonsdale Medical Centre, Turnbridge Wells, Kent, UK*

Using a day in the life of a primary care physician as a living example of this process, we will examine the ways in which bipolar disorder is handled in an urban primary care clinic. Obstacles to detection of bipolar disorders in this setting; and use of education and cooperation to address those obstacles, will be reviewed. The ways a primary care provider must manage complexity and uncertainty will be emphasized.

#### **Improving the early diagnosis and initial treatment of bipolar disorder**

**D Smith**

*Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK*

Early detection of bipolar disorder is crucial to improving outcomes; and immediately upon detection comes the need for extensive psychoeducation. How can this be delivered efficiently, especially in the context of patients being detected in primary care? We will examine the tools that have been developed for bipolar screening, and how they perform. Then we will present results from clinical trials of web-based psychoeducation efforts and recent data from the Scottish Mental Health Research Network.

## **Brainstorming Session IV**

### **Mineralocorticoid Receptor (Mr)/Glucocorticoid Receptor (Gr) Dysregulation in Bipolar Affective Disorders: Consequences and the Impact of Childhood Adversity?**

**Chair: Ian Ferrier**

#### **Early life stress in bipolar patients: HPA axis response to GR and MR agonists**

**MF Jurueña**

*Stress and Affective Disorders (SAD) Program, Department Neurosciences and Behavior, University of Sao Paulo, Sao Paulo, Brazil*

Evidence indicates that early life stress (ELS) can induce persistent changes in the HPA axis in adults and that could trigger Bipolar Affective Disorders. These appear to be related to the impairment binding to glucocorticoid (GR) and mineralocorticoid receptors (MR). The aim of this study was to evaluate the impact of ELS in HPA axis response to challenges with GR and MR agonists in

bipolar patients. Patients were recruited into two groups according to ELS history assessed by the Childhood Trauma Questionnaire (CTQ). The cortisol measures in the saliva were evaluated after placebo, fludrocortisone (MR agonist), or dexamethasone (GR agonist). Bipolar showed a lower salivary cortisol upon waking after placebo compared with controls. Moreover, cortisol awakening responses (CAR) after MR agonist were found to be lower in patients than in controls. CAR after placebo, GR agonist, MR agonist we found in a Linear Regression model that patients with ELS show differences between placebo vs. MR agonist but not after GR agonist; in patients, without ELS the data show differences between placebo vs. MR agonist; but now as well in placebo vs. GR agonist. Our findings indicate that MR activity is impaired in bipolar patients compared with controls. In patients with ELS, there was suppression by MR agonist, indicating that patients with ELS are sensitive to MR agonists. In contrast with bipolar patients without ELS, we found suppression after both MR and GR agonist. These data suggested that in ELS an imbalance exists between MR and GR with MR dysfunction.

## MR function in bipolar affective disorders

**S Watson**

*Department Psychiatry, Newcastle University, Newcastle upon Tyne, UK*

Much research has explored the function of the hypothalamic pituitary adrenal axis in bipolar disorder. Dysfunction of the glucocorticoid receptor has been reported but there is no clear consensus regarding the functional integrity of mineralocorticoid receptors. More recent evidence has suggested the ratio of receptor activity is also crucial. Neuropsychological performance is impaired in bipolar disorder and may be related to alterations in this ratio. We used dexamethasone and fludrocortisone as pharmacological probes alongside a neuropsychological test battery to examine the integrity of glucocorticoid receptor and mineralocorticoid receptor function in recovered patients with bipolar disorder ( $n = 18$ ) and healthy controls ( $n = 18$ ). We found that patients suppressed cortisol comparably to controls in response to both drug challenges, though different neuropsychological profiles emerged in each group. Furthermore, a self-reported history of emotional abuse was related to both these outcomes; engendering enhanced suppression of cortisol and improvement of spatial memory after dexamethasone in patients. This would suggest emotional abuse specifically impacts glucocorticoid receptor function. Possible reasons for our result will be discussed.

# Brainstorming Session V

## Neural Predictors and Moderators of Treatment Response to Psychotherapy for Bipolar Depression

### Chair: Thilo Deckersbach

#### Neural predictors of response to psychotherapy for depression in bipolar disorder

**A Nierenberg<sup>a</sup>, A Peters<sup>b</sup>, J Stange<sup>c</sup>, LG Sylvia<sup>c</sup>, MW Otto<sup>d</sup>, DJ Miklowitz<sup>e</sup>, DD Dougherty<sup>a</sup>, T Deckersbach<sup>a</sup>**

<sup>a</sup>Massachusetts General Hospital/Harvard Medical School, Boston, USA, <sup>b</sup>University of Illinois at Chicago, Chicago, USA, <sup>c</sup>Temple University, Philadelphia, USA, <sup>d</sup>Boston University, Boston, USA, <sup>e</sup>UCLA School of Medicine, Los Angeles, USA

Cognitive impairment, contributes to impairments in psychosocial functioning in bipolar disorder. Little is known about the functional neuroanatomy that underlies concentration and memory difficulties and how cognitive difficulties impact response to psychotherapy for depression in bipolar disorder. Before randomization to either cognitive-behavior therapy or supportive psychotherapy, depressed patients with DSM-IV bipolar I disorder (see symposium overview), completed an affective attention task and a memory paradigm in conjunction with fMRI. MRI data were acquired using a 3.0-T whole-body scanner (Trio-System) equipped for echo planar imaging (Siemens Medical Systems, Iselin NJ) with a 3-axis gradient head coil. In the affective attention fMRI paradigm, subjects were shown three-digit numbers. The task was to decide which number was different than the two other numbers. The numbers were superimposed on neutral or negatively affectively valenced pictures taken from the International Affective Pic-

ture System (IAPS). In the fMRI memory paradigm, subjects were presented with word lists and asked to rehearse and organize the words for a subsequent memory test. During negatively valenced IAPS pictures relative to neutral IAPS pictures, they exhibited an activation increase in the anterior insula, pregenual anterior cingulate (ACC; affective division of the ACC), dorsal ACC (cognitive division of the ACC), as well as in the dorsolateral prefrontal cortex (BA 9/46) compared to control participants.

#### Cognitive functioning predicts response to psychotherapy for depression in bipolar disorder

**LG Sylvia<sup>a</sup>, A Peters<sup>b</sup>, JP Stange<sup>c</sup>, A Peckham<sup>d</sup>, DJ Miklowitz<sup>e</sup>, MW Otto<sup>f</sup>, DD Dougherty<sup>a</sup>, A. Nierenberg<sup>a</sup>, T Deckersbach<sup>a</sup>**

<sup>a</sup>Massachusetts General Hospital, Harvard Medical School, Boston, USA, <sup>b</sup>University of Illinois at Chicago, Chicago, USA, <sup>c</sup>Temple University, Philadelphia, USA, <sup>d</sup>Berkeley University, Berkeley, USA, <sup>e</sup>UCLA School of Medicine, Los Angeles, USA, <sup>f</sup>Boston University, Boston, USA

Depression is consistently related to lower overall psychosocial functioning in bipolar disorder. Another emerging determinant of



functioning is cognitive impairment. 30%–40% of patients with bipolar disorder have cognitive difficulties even when they are not depressed or manic. This involves impairments in attention, memory and executive functioning. Patients with cognitive impairments have lower psychosocial functioning, including occupational functioning and higher rates of disability. In our randomized controlled trial of cognitive-behavior therapy vs. supportive psychotherapy for depression in DSM-IV bipolar I disorder, pre-treatment, patients completed a neuropsychological test battery including measures of attention, memory and executive functioning. Tests included the Repeatable Battery of Neuropsychological Status (RBANS), the California Verbal Learning Test II, and selected subtests of the Delis-Kaplan Executive Functioning System (DKEFS, e.g., color word test, and card sorting). We hypothesized

that patients with more neuropsychological impairment would benefit less from CBT compared to supportive psychotherapy. Preliminary results indicate, that, contrary to our hypothesis, patients with more impaired neuropsychological functioning, in particularly memory, had a greater improvement in HAM-D 17 depression scores with both CBT and supportive psychotherapy from pre-treatment to the end of treatment (e.g. RBANS story recall,  $r = -0.48$ ,  $p = 0.02$ ). Similarly, larger decreases in HAM-D 17 scores from pre-treatment to the 3-months follow-up were predicted by lower pretreatment cognitive functioning (e.g. RBANS total,  $r = -0.45$ ,  $p = 0.03$ ), and less cognitive inhibition (color word test,  $r = -0.48$ ,  $p = 0.03$ ). We will present the full set of neuropsychological predictor and moderator findings and discuss their meaning and clinical implication.

## Brainstorming Session VI

# Hormones and Mood in Bipolar Disorder: From Neurobiology to Treatment

### Chair: Thilo Deckersbach

#### Co-morbid bipolar and premenstrual dysphoric disorder: from hormones to brain circuits and behavior

**BN Frey<sup>a,b,c</sup>**

<sup>a</sup>Women's Health Concerns Clinic, St. Joseph's Healthcare, Hamilton, Canada, <sup>b</sup>Mood Disorders Program, St. Joseph's Healthcare, Hamilton, Canada, <sup>c</sup>Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Canada

A large community-based study found that women who met criteria for premenstrual dysphoric disorder (PMDD) were 8 times more likely to be diagnosed with bipolar disorder (BD) than those who did not have PMDD. Consistently, two independent studies found that the prevalence of PMDD was higher among women with BD compared to the rates from the general population. A seminal study showed that ovarian suppression with leuprolide blocked premenstrual worsening in women with PMDD, and exogenous administration of estradiol (E2) and progesterone (P) induced a re-emergence of mood symptoms in women with PMDD but not in women with no history of PMDD. These results provided compelling evidence for a direct role of sex hormones in the development of PMDD. Although the neurobiological mechanisms underlying the association between BD and PMDD are unknown, it is conceivable that some women with BD may be particularly sensitive to hormonal fluctuations that accompany the premenstrual period. In the present study, we conducted an fMRI study investigating brain connectivity in women with BD with and without PMDD using an emotional Stroop task. All women were euthymic for at least 2 months to avoid effects of mood episodes on brain function. All women were scanned twice, once premenstrually and once in the mid-follicular phase. We also collected E2, P, and Allopregnanolone on the day of the brain scans to investigate the association between sex hormones and brain function. The main results and the association between sex hormones and brain function in this population will be discussed.

#### Bipolar disorder during the menopausal transition and its endocrinological changes: what we know, what we need to know

**W Marsh**

Department of Psychiatry, University of Massachusetts, Worcester, USA

Little is known about the clinical course of BD through the menopausal transition, yet every woman with BD has gone through or expects to go through menopause, and other times of hormonal fluctuation are associated with an increased risk of mood disruption in BD. Studies in women without BD clearly indicate an elevated risk for depression during the transition and in the years shortly thereafter. The association of unipolar depressive symptoms and reproductive endocrinological and inflammatory markers has been examined with several approaches but remains unclear. Yet the administration of hormone therapy has been found to significantly reduce depressive symptoms in women during the menopausal transition. In this session, menopausal staging and hormonal course will be defined. Author's results in prospectively examining mood and reproductive hormones during the menopausal transition in women with BD indicate a higher rate of depressive symptoms during the late menopausal transition and early post-menopausal years compared to the early transition as well as reproductive years. Mood elevation symptoms were also increased during the late transition and early post menopause women. The finding of no significant association of mood severity in bipolar disorder and key reproductive hormones will be discussed. Key questions of a) what the next step should be in elucidating mood course through the menopausal transition including the role of sex hormones and b) the potential treatment implications, including hormone therapy, for women with BD during the menopausal transition, will be discussed.

# Rapid Communication I

## Sleep and circadian effects on neural reward functioning: towards a chronobiology of reward for bipolar disorder

G Murray<sup>a</sup>, G Malhi<sup>b</sup>, S Johnson<sup>c</sup>, S Rossell<sup>d</sup>, N Leitan<sup>d</sup>, C Keating<sup>d</sup>

<sup>a</sup>Psychological Sciences, Swinburne University, Hawthorn, Australia, <sup>b</sup>Psychiatry, University of Sydney, Sydney, Australia,

<sup>c</sup>Psychology, University of California Berkeley, Berkeley, USA,

<sup>d</sup>Psychology, Swinburne University, Hawthorn, Australia

**Aims:** To understand the neurobiology of bipolar disorder, we must start to conceptualise its multiple underpinning processes. Sleep and biological rhythms are intimately connected to pathologies of mood, but the mechanisms of this interaction are poorly understood. The present study reviewed research into one particular pathway – modulation of reward functioning by sleep and biological rhythms – with the aim of articulating next steps in the ‘chronobiology of reward’.

**Methods:** A systematic review of neuroimaging research into the chronobiology of reward was conducted, and findings situated in the broader context of genetic, neurotransmitter and behavioural research.

**Results:** Neuroimaging research has largely focused on the relationship between sleep restriction and reward functioning, with only two studies testing circadian effects. In contrast, non-imaging research in animals and humans provides multi-level evidence of circadian modulation of reward. The literature as a whole provides strong support for biological rhythm modulation of reward, but more sophisticated designs are required to parse sleep homeostatic and circadian effects.

**Conclusions:** Better understanding of the interaction between biological rhythms and affective functioning has the potential to refine treatments for bipolar disorder. Existing research hints at multiple strategies by which fragile endogenous rhythmicity might be therapeutically scaffolded. Future studies should take advantage of non-intrusive neuroimaging paradigms, and adopt more complex designs measuring genes, objective behaviour and self-report to clarify mechanisms of the temporal priming of mood.

## A measure of total peripheral inflammation is associated with weight and depressive relapse in early-stage bipolar disorder

DJ Bond<sup>a</sup>, AC Andreazza<sup>b</sup>, J Hughes<sup>c</sup>, T Dhanoa<sup>d</sup>, IJ Torres<sup>d</sup>, JM Kozicky<sup>d</sup>, LT Young<sup>b</sup>, RW Lam<sup>d</sup>, LN Yatham<sup>d</sup>

<sup>a</sup>Psychiatry, University of Minnesota, Minneapolis, USA,

<sup>b</sup>Psychiatry, University of Toronto, Toronto, Canada, <sup>c</sup>School of Public Health, University of Minnesota, Minneapolis, USA,

<sup>d</sup>Psychiatry, University of British Columbia, Vancouver, Canada

**Aims:** Bipolar disorder (BD) is characterized by increased peripheral and CNS inflammation, which are believed to be central to disease etiology and progression. BD is also associated with high rates of obesity, itself a systemic inflammatory condition. Our objectives were: 1) to determine if peripheral inflammation in BD is mood illness-related or secondary to elevated body mass index (BMI), and 2) to investigate the impact of inflammation on prospectively-measured relapse into depression and mania.

**Method:** We created a composite measure of total peripheral inflammation in 49 BD patients enrolled in a first-episode mania program, by normalizing and combining their serum levels of 7

inflammatory cytokines: TNF- $\alpha$ ,  $\gamma$ -interferon, monocyte chemo-attractant protein-1 (MCP-1), IL-1 $\alpha$ , IL-2, IL-6, and IL-8. The study was approved by the University of British Columbia Clinical research Ethics Board, and written informed consent was obtained from all participants.

**Results:** Using a linear regression model that controlled for the effects of psychotropic medications, we found that higher BMI ( $p = 0.01$ ), but not current or past-6-month mood symptoms, significantly predicted greater peripheral inflammation. Furthermore, greater inflammation predicted more time with prospectively-ascertained depressive symptoms over the subsequent 12 months ( $p = 0.02$ ).

**Conclusions:** These results demonstrate that elevated BMI is a major contributor to inflammation in early-stage BD, more so even than mood illness severity. They further support our measure of total peripheral inflammation index as a useful instrument for predicting relapse. Finally, they provide a plausible biological rationale for the well-known association between obesity and increased depressive burden in BD.

## Nonlinear dynamics of mood regulation in bipolar disorder

A Ortiz<sup>a</sup>, K Bradler<sup>b</sup>, J Garnham<sup>c</sup>, C Slaney<sup>c</sup>, M Alda<sup>a</sup>

<sup>a</sup>Department of Psychiatry Mood Disorders Program, Dalhousie University, Halifax, Canada, <sup>b</sup>Department of Physics, Saint Mary's University, Halifax, Canada, <sup>c</sup>Mood Disorders Program, Capital District Health Authority, Halifax, Canada

**Objectives:** We sought to study the underlying dynamic processes involved in mood regulation in subjects with bipolar disorder and healthy control subjects using time-series analysis and to then analyze the relation between anxiety and mood using cross-correlation techniques.

**Methods:** We recruited 30 healthy controls and 30 euthymic patients with bipolar disorder. Participants rated their mood, anxiety, and energy levels using a paper-based visual analog scale; and they also recorded their sleep and any life events. Information on these variables was provided over a three-month period on a daily basis, twice per day. We analyzed the data using Box–Jenkins time series analysis to obtain information on the autocorrelation of the series (for mood) and cross correlation (mood and anxiety series).

**Results:** Throughout the study, we analyzed 10,170 data points. Self-ratings for mood, anxiety, and energy were normally distributed in both groups. Autocorrelation functions for mood in both groups were governed by the autoregressive integrated moving average (ARIMA) (1,1,0) model, which means that current values in the series were related to one previous point only. We also found a negative cross-correlation between mood and anxiety.

**Conclusions:** Mood can be considered a memory stochastic process; it is a flexible, dynamic process that has a ‘short memory’ both in healthy controls and euthymic patients with bipolar disorder. This process may be quite different in untreated patients or in those acutely ill. Our results suggest that nonlinear measures can be applied to the study of mood disorders.

## Medication-free depressed unipolar and bipolar subjects are distinguished by default mode network connectivity

H Ruhe<sup>a</sup>, M Rive<sup>b</sup>, L Schmaal<sup>c</sup>, D Veltman<sup>c</sup>, A Schene<sup>d</sup>

<sup>a</sup>Department of Psychiatry (UCP) Program for Mood and Anxiety Disorders, University Medical Center Groningen (UMCG), Groningen, Netherlands, <sup>b</sup>Department of Psychiatry Program for Mood Disorders, Academic Medical Center (AMC) University of Amsterdam, Amsterdam, Netherlands, <sup>c</sup>Department of Psychiatry, VU Medical Center (VUMC) Vrije Universiteit Amsterdam, Amsterdam, Netherlands, <sup>d</sup>Department of Psychiatry, Radboud University Medical Center Nijmegen, Nijmegen, Netherlands

**Background:** Recent studies indicated that pattern recognition techniques of fMRI data for individual classification may be valuable to discriminate major depressive (MDD) and bipolar disorder (BD). Importantly, medication may have affected previous classification results, as MDD and BD samples use different classes of medication. Therefore, here we focused on medication-free subjects.

**Aim:** To distinguish MDD and BD subjects based on pattern recognition techniques of resting state networks and to investigate whether classification would be mood state dependent.

**Methods:** We applied support vector machine learning to investigate the discriminative power of three resting-state networks implicated in mood disorders (default mode network (DMN), salience network (SN), lateralized frontoparietal networks (FPN)) in depressed and remitted medication-free MDD and BD (depressed: N = 20; remitted: N = 44). This study was approved by the local institutional ethical review board and all participants provided written informed consent.

**Results:** Depressed MDD and BD subjects could be classified based on DMN functional connectivity with 85% prediction accuracy. Prediction accuracy using the FPNs and SN did not exceed chance level. Remitted MDD and BD could not be discriminated based on any of our networks of interest.

**Conclusion:** For the first time we show that depressed MDD and BD subjects who were medication-free can be differentiated based on resting-state functional connectivity. Moreover, results indicate that research concerning diagnostic neuroimaging tools to distinguish MDD and BD should consider mood state, since remitted MDD and BD could not be distinguished. Of importance is that our results cannot be directly generalized to medication-naïve or first-episode subjects, which merits further research.

## Growth and differentiation abnormalities in neural precursor cell lines from bipolar I disorder patients: implications for impaired neurogenesis

M Tseng<sup>a</sup>, J Warsh<sup>a</sup>, D Ganeshan<sup>a</sup>, MA Green<sup>a</sup>, IJ Witterick<sup>b</sup>, RD McCurdy<sup>c</sup>

<sup>a</sup>Cellular and Molecular Pathophysiology Neuroscience, Campbell Family Mental Health Research Institute, Toronto, Canada,

<sup>b</sup>Department of Otolaryngology-Head & Neck Surgery, University of Toronto, Toronto, Canada, <sup>c</sup>Center for Neurobiology-Department of Psychiatry Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA

**Aims:** Impaired neurogenesis related to signal transduction and cell cycle abnormalities has been implicated in postmortem brain and neural stem cell studies of bipolar disorder (BD). BDNF and intracellular calcium signaling play important roles in cell proliferation, differentiation and viability. To test more directly whether altered neurogenesis occurs in BD, we examined growth and viability, morphological changes and immunocytochemical markers of neuronal differentiation in olfactory-epithelium derived neural precursor

sors (ONP) as a disease model from BD I patients and healthy controls (HC).

**Method:** Subjects' diagnoses or HC status was confirmed by SCID-I patient and non-patient versions, respectively. ONP cell lines were generated from nine BD-I patients and eleven sex- and age-matched HC providing olfactory epithelial samples via nasal biopsy. After regrowth from cryopreserved stock without differentiation, ONP growth and viability were determined at 6–8 passages in culture after 24 hr and 7 days exposure to 1 mM lithium. The CAMH Research Ethics Committee approved the study and participants provided written, informed consent.

**Results:** Nestin, MAP2,  $\beta$ -III Tubulin, GFAP, Vimentin and NeuN immunostaining in representative cultures before and during differentiating conditions confirmed ONP phenotype and development of mature neuronal phenotypes. Repeated measures ANOVA revealed significantly higher apparent ONP growth (9.3%,  $p = 0.001$ ) in lithium vs. vehicle-treated ONPs and particularly in BD-I (190%, time by diagnosis interaction,  $p = 0.011$ ) compared with HC, but no significant treatment by group interaction effect. Cell viability was  $\geq 96\%$  in all conditions. There were no diagnostic differences in BDNF expression or  $[Ca^{2+}]_B$ , although lithium induced a modest, statistically significant increase in  $[Ca^{2+}]_B$ . Representative neural precursor lines from BD-I and HC pairs subjected to a standardized neuronal differentiation induction following exposure to EGF/FGF and subsequently to sonic hedgehog showed slower and shorter neuritic-like outgrowth and atypical morphologies in BD-I compared with those from HC.

**Conclusions:** The enhancing effect of lithium on human ONP growth *in vitro*, supports that its therapeutic action may also involve promoting neurogenesis. Higher apparent ONP growth in BD-I versus HC suggests dysregulated signal transduction and/or cell cycle dynamics, possibly affecting neurogenesis in BD-I. Our findings further support the use of ONPs for neuropsychiatric disease modeling and drug discovery.

## Comparative evaluation of quetiapine plus lamotrigine versus quetiapine monotherapy in people with bipolar depression: a randomized trial (CEQUEL)

JR Geddes, J Rendell, C Hinds, M Voysey, A Gardiner, MJ Attenburrow, GM Goodwin, E Tunbridge, PJ Harrison

Psychiatry, University of Oxford, Oxford, United Kingdom

**Background:** CEQUEL investigated if the combination of lamotrigine with quetiapine leads to better short-term response and longer term clinical outcomes than quetiapine alone.

**Methods:** CEQUEL was a multicentre, double-blind, randomized, placebo-controlled, parallel group,  $2 \times 2$  factorial clinical trial with concurrent economic, biochemical and genetic analysis. Eligible patients were those with DSM-IV bipolar disorder I/II (BDI/II) who required new pharmacological treatment for an acute depressive episode, aged 16 or over. Following 14 day run-in on quetiapine, participants were randomized to added lamotrigine (200 mg) or placebo. Allocated treatment was continued for 12 months. The primary outcome was improvement in depressive symptoms at 12 weeks from randomisation using QIDS-SR16. QIDS data was collected by participants using the True Colours SMS/email system.

**Results:** 202 patients were randomised (101 lamotrigine; 101 placebo). The groups were balanced by minimisation for bipolar subtype; age, gender, concurrent medications, medication history and mood episodes. Diagnoses bipolar disorder type 1: bipolar 2 was approximately 3:1. The modal daily dose of quetiapine was 300 mg. The mean difference in QIDS-SR16 between groups was: after 12 weeks, 1.6 points lower lamotrigine vs placebo (95% CI

–3.4 to 0.23;  $p = 0.09$ ; after 52 weeks, 2.9 (95% –5.2 to –0.6;  $p = 0.013$ ). Folic acid was not superior to placebo. There was an unexpected significant interaction between folic acid and lamotrigine. Folic acid reduced the effectiveness of lamotrigine in the first 12 weeks. In the presence of such an interaction between treatments the best estimate of the effect of lamotrigine at 12 weeks is

the estimate taken from only patients who were not randomised to take folic acid (mean diff –4.1  $p = 0.0041$ ).

**Discussion:** Adding lamotrigine to quetiapine treatment of acute bipolar depression substantially improves outcomes. Removing the interaction with folic acid demonstrated clear superiority at 12 weeks.

## Rapid Communication II

### Executive dysfunction in late onset mania is related to reduced structural interhemispheric connectivity

J Ramirez-Bermudez<sup>a</sup>, C Berlanga-Flores<sup>a</sup>, O Marrufo<sup>b</sup>, C Atriano<sup>a</sup>, D Martinez<sup>a</sup>, R Carrillo<sup>b</sup>, J Taboada<sup>b</sup>, R Favila<sup>b</sup>, P Alvarado<sup>b</sup>, A Guadamuz<sup>b</sup>

<sup>a</sup>Neuropsychiatry, National Institute of Neurology and Neurosurgery, Mexico City, Mexico, <sup>b</sup>Brain Imaging, National Institute of Neurology and Neurosurgery, Mexico City, Mexico

**Aims:** To explore relationships between executive function and white matter integrity in late onset mania.

**Methods:** 22 patients with late onset mania (>50 years old) and 22 age-paired healthy controls were included in the study. Executive function was measured by means of the Frontal Assessment Battery (FAB). Neuroanatomy measures were obtained by means of structural MRI, using the FLAIR sequence to describe the quantity of white matter hyperintense lesions, and Magnetic Resonance Diffusion Tensor Imaging (DTI) in order to obtain the values of fractional anisotropy (FA), which is considered a quantitative measure of white matter integrity. TBSS analysis was done by means of FSL software from Oxford University, in order to process DTI images. SPSS software was used to analyze the relationship between brain imaging data and clinical data.

**Results:** We found significant differences between patients and controls regarding the FAB scores for motor programming ( $p = 0.023$ ) and inhibitory control ( $p = 0.023$ ). Patients had a higher number of hyperintense lesions in the right inferior frontal gyrus ( $p = 0.042$ ), as well as a higher total amount of hyperintense lesions in the FLAIR sequence ( $p = 0.038$ ). The total score of the FAB showed a significant inverse correlation with right inferior frontal gyrus lesions ( $r = -0.506$ ,  $p = 0.001$ ). Patients showed significantly inferior FA values in right and left corpus callosum, at the level of minor forceps, according to TBSS analysis. Significant correlations were found between FAB total score and FA in the left corpus callosum (minor forceps) ( $r = 0.712$ ,  $p$

**Conclusions:** Late onset mania patients have executive dysfunction, probably related to reduced integrity white matter fibers involved in interhemispheric and fronto-limbic structural connectivity. Hyperintense lesions in the right inferior frontal gyrus may be of critical relevance for the understanding of this syndrome.

### Kidney and thyroid function in patients receiving lithium therapy for more than 10 years

J Rybakowski<sup>a</sup>, M Abramowicz<sup>a</sup>, A Kraszewska<sup>a</sup>, M Chlopocka-Wozniak<sup>a</sup>

Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland

**Aims:** In many patients with bipolar disorder, lithium administration for the prevention of manic and depressive episodes is a long term procedure, with some patients receiving this drug for 20 years or more. The aim of this study was to carry out a cross-sectional assessment of kidney and thyroid function in a group of patients

with bipolar mood disorder who have been receiving lithium for 10 years or more.

**Methods:** The study comprised 47 patients (15 male, 32 female), with bipolar mood disorder, aged 39–85 ( $62 \pm 13$ ) years, receiving lithium for 10–42 ( $20 \pm 9$ ) years. A comparison of parameters of kidney function and thyroid function was made between patients receiving lithium for 10–19 years (28 patients) and 20 years or more (19 patients). For kidney function, serum concentration of creatinine and specific gravity of the urine sample was measured, and estimated glomerular filtration rate (eGFR) calculated. Thyroid stimulating hormone (TSH), free thyroxine (fT3) and free triiodothyronine (fT4) were measured by the microparticle enzyme immunoassay. Thyroid peroxidase (TPO) antibodies, thyroglobulin (TG) antibodies and TSH receptor (TSH-R) antibodies were measured by the radioimmune assay.

**Results:** Concentration of creatinine was higher and eGFR was lower in patients receiving lithium for 20 years or more, and such a difference was more pronounced in male patients. No difference as to the specific gravity of the urine was found. Some features of hypothyroidism were found in 7 female patients (22%) and in none of males. There were no differences in thyroid hormones and thyroid autoantibodies between patients receiving lithium for 10–19 years and those taking the drug for 20 years or more.

**Conclusions:** The results confirm an association between the duration of lithium therapy and impairment of kidney function reflected in higher serum creatinine and lower eGFR as well as the greater susceptibility of female subjects for disturbances of thyroid hormones during lithium therapy. However, in contrast to the effect of lithium on kidney function our results do not show an association between the duration of long-term lithium therapy and thyroid dysfunction.

### Hierarchical gating of emotional and cognitive processes in those at genetic risk of bipolar disorder

PB Mitchell<sup>a</sup>, M Breakspear<sup>b</sup>, G Roberts<sup>a</sup>, MJ Green<sup>a</sup>, VT Nguyen<sup>b</sup>, A Frankland<sup>a</sup>, F Levy<sup>a</sup>, R Lenroot<sup>a</sup>

<sup>a</sup>Psychiatry, University of New South Wales, Sydney, Australia,

<sup>b</sup>Psychiatry, Berghofer QIMR, Brisbane, Australia

**Aims:** Identifying the neurobiological correlates of genetic risk for bipolar disorder (BD) may help elucidate the emotional and cognitive vulnerabilities that precede the development of the disorder. The inferior frontal gyrus (IFG) – a key cortical hub for the integration of cognition and emotion – exhibits both structural and functional changes in BD. This region is also functionally impaired in unaffected first-degree relatives, showing diminished engagement during motor inhibition to emotional stimuli. We hypothesised that this deficit reflects the dysfunction of broader network dynamics underlying the coordination of emotion perception and cognitive control.

**Methods:** We hence studied effective connectivity in fMRI data acquired from 41 first degree relatives of BD patients and 45

matched controls. Dynamic causal modelling (DCM) was used to model the neuronal interaction between key regions associated with fear perception (the anterior cingulate, AC), motor inhibition (the left dorsolateral prefrontal cortex, DLPFC) and the region upon which these influences converge, namely the IFG.

**Results:** Network models that embody nonlinear, hierarchical relationships found stronger empirical support in the control group than the other models tested. We observed a marked difference in the at-risk group in the hierarchical influence of the AC on the effective connectivity from the DLPFC to the IFG. Further analyses suggest that non-specific, non-hierarchical mechanisms compensate for this network disturbance.

**Conclusions:** In this first study of effective connectivity in those at high genetic risk for BD, we thus establish a specific network disturbance suggesting dysfunction in the processes that support hierarchical relationships between emotion and cognitive control.

### Modelled cost-effectiveness evaluation of bipolar disorder treatments to guide health policy

ML Chatterton<sup>a</sup>, C Mihalopoulos<sup>a</sup>, J Barendregt<sup>b</sup>, M Berk<sup>c</sup>, PB Mitchell<sup>d</sup>, J Khoo<sup>e</sup>, R Carter<sup>a</sup>

<sup>a</sup>Health Economics Unit, Deakin University, Burwood, Australia,

<sup>b</sup>School of Population Health, University of Queensland, Brisbane, Australia, <sup>c</sup>IMPACT Strategic Research Centre, Deakin University, Geelong, Australia, <sup>d</sup>School of Psychiatry, University of New South Wales, Sydney, Australia, <sup>e</sup>Toowong Specialist Clinic, Toowong Private Hospital, Brisbane, Australia

**Aims:** This analysis evaluates the cost-effectiveness of acute and maintenance treatments for bipolar disorder (I and II) to assist in efficient allocation of resources to reduce the burden of this condition.

**Methods:** A population based model was developed to estimate the cost per disability adjusted life year (DALY) averted for efficacious therapies to treat adults with bipolar disorder across all phases: acute mania, acute depression, maintenance. The model is based on the 2013 Australian population with the Global Burden of Disease (GBD) prevalence estimates applied by age and gender. All-cause mortality attributable to bipolar disorder was incorporated as well as the decreased rate of suicide attributable to lithium. Disability weights from GBD were used to calculate DALYs. The evaluation takes an Australian health sector perspective and uses standard costs for medications and other medical services obtained from Australian sources. All treatments with proven efficacy were sourced from the most current systematic reviews/meta-analyses and supplemented with expert clinical input. Treatments evaluated included monotherapy with atypical antipsychotics, anticonvulsants, and lithium as well as specific combination therapies evaluated in randomized controlled trials. Psychological therapies were evaluated as adjunctive to medications. Electroconvulsive therapy was evaluated as a treatment in the depressive phase only. The base case used 67.7% as a level of treatment seeking based on a 2007 Australian national survey and 41% treatment adherence. We assumed that non-adherence decreased effectiveness but incurred the full cost.

**Results:** Preliminary results suggest that among monotherapies, valproate produced the lowest cost per/DALY, \$AUD 53,000/DALY (CI \$35,000–\$84,000). Oxcarbazepine plus lithium provided the lowest cost among combinations \$104,000/DALY (CI dominant – \$446,000). Adding a disorder specific psychotherapy was less cost effective than pharmacotherapy alone for lower cost treatments (lithium, valproate) and more cost effective for aripiprazole, olanzapine, quetiapine, and combinations. Adherence costs will be varied in future analysis and presented.

**Conclusions:** All treatments exceeded the commonly accepted \$AUD 50,000/DALY threshold for implementation. In economic terms, valproate would be recommended as initial therapy based on its low ICER relative to other treatments. Higher cost therapies, including most combinations, should be implemented with a psychological intervention to improve cost-effectiveness.

### Emotional reactivity and inflammation in subsyndromal bipolar patients: clinical relevance of a dimensional approach

AA Dargel<sup>a</sup>, O Godin<sup>b</sup>, C Boudebasse<sup>c</sup>, B Etain<sup>d</sup>, JM Azorin<sup>d</sup>, K M Bailer<sup>e</sup>, F Bellivier<sup>f</sup>, C Passerieux<sup>g</sup>, V Aubin<sup>h</sup>, P Courtet<sup>i</sup>, M Leboyer<sup>j</sup>, C Henry<sup>j</sup>

<sup>a</sup>Translational Psychiatry Laboratory, INSERM U955 AP-HP Hôpital H. Mondor/A. Chenevier Pôle de psychiatrie and FondaMental Foundation, National Institute for Translational Medicine-Hospital de Clínicas de Porto Alegre-Molecular Psychiatry Laboratory-Graduate Program in Medicine-Department of Psychiatry-Federal University of Rio Grande do Sul (Brazil), Créteil, France, <sup>b</sup>Institut Pierre Louis d'Epidémiologie et de Santé Publique, UPMC Univ Paris 06 UMR\_S 1136 and FondaMental Foundation, Créteil, France, <sup>c</sup>Translational Psychiatry Laboratory, INSERM U955-AP-HP Hôpital H. Mondor/A. Chenevier Pôle de psychiatrie and FondaMental Foundation, Créteil, France, <sup>d</sup>CRN2M UMR\_7286, AP-HP Hôpital Sainte Marguerite Pôle de psychiatrie Aix-Marseille Université CNRS and FondaMental Foundation, Marseille, France, <sup>e</sup>Laboratory of Psychology Health and Quality of Life EA 4139, Université Bordeaux Segale-Hôpital Charles Perrens Pôle 3-4-7 de psychiatrie and FondaMental Foundation, Bordeaux, France, <sup>f</sup>Neurosciences, AP-HP GH Saint-Louis-Lariboisière-Fernand Widal Pôle Neurosciences and FondaMental Foundation, Paris, France, <sup>g</sup>Université Versailles-Saint-Quentin-en-Yvelines EA 4047, Centre Hospitalier de Versailles and FondaMental Foundation, Versailles, France, <sup>h</sup>Pôle de psychiatrie, Centre Hospitalier Princesse Grace and FondaMental Foundation, Monaco, Monaco, <sup>i</sup>Psychiatric Emergency Department CHRU Montpellier, Inserm U1061 Université Montpellier and FondaMental Foundation, Montpellier, France, <sup>j</sup>Translational Psychiatry Laboratory, Université Paris-Est UMR\_S955 INSERM U955-AP-HP Hôpital H. Mondor/A. Chenevier Pôle de psychiatrie and FondaMental Foundation, Créteil, France

**Aims:** To examine emotional reactivity (ER) as a dimension that may contribute to the better characterization of subsyndromal mood symptoms in bipolar disorder (BD) patients during remission, and to explore the association between ER and levels of C-reactive protein (CRP, a biomarker of low-grade inflammation) including as to whether CRP is a biosignature of emotional reactivity in BD.

**Method:** We included n = 743 adult remitted BD outpatients of FondaMental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD), a French National BD Network. Mood states were evaluated by the Multidimensional Assessment Tool of Thymic States (MATHYS), a validated scale comprising five quantitative dimensions (ER, cognition speed, psychomotor activation, motivation, and sensory perception). The MATHYS ER sub-score (0–40) refers to the ER intensity (lower/higher than normal) across mood states. CRP was measured by using standard enzyme immunoassay. Cluster analyses were performed in JMP Pro 9 and SAS, using Ward's linkage with Euclidean distance.

**Results:** Cluster analysis was carried out identifying three clusters of BD patients with meaningful ER profiles: Cluster-1 (n = 547), normal ER (mean = 21.2, SD = ±2.6); Cluster-2 (n = 104), HypoER (mean = 12.4, SD = ±4.0); and Cluster-3 (n = 92), HyperER (mean = 32.1, SD = ±5.3). BD patients with HypoER (Cluster 2) or HyperER (Cluster 3) had significantly greater levels of residual

depressive or manic symptoms than individuals with *normal ER* (Cluster 1) ( $p < 0.0001$ ). CRP levels ( $n = 355$ ) were significantly increased in BD patients with *HyperER* (mean = 4.6, SD =  $\pm 4.8$ ;  $p < 0.05$ ) in comparison with the other two clusters *HypoER* (mean = 2.5, SD =  $\pm 2.8$ ) or *normal ER* (mean = 2.9, SD =  $\pm 3.4$ ).

**Conclusions:** ER appears to be a pertinent dimension to discriminate subsyndromal mood symptoms in remitted BD patients. CRP could be a biological validator of *HyperER* in BD, and the association between ER-CRP levels may be useful proxy to examine the relationship between specific symptom profiles and chronic inflammation, a potential biological state associated with BD. This is a cross-sectional study and, therefore, the direction of the association could not be inferred. Additionally, all study participants were using medications, which may have affected some of the results. These novel findings could be clinically relevant, if tested and confirmed by future studies.

### Risk of myocardial infarction and stroke in bipolar disorder: a population-based cohort study

ML Prieto<sup>a</sup>, LA Schenck<sup>b</sup>, JL Kruse<sup>c</sup>, JP Klaas<sup>d</sup>, AM Chamberlain<sup>b</sup>, WV Bobo<sup>e</sup>, VL Roger<sup>e</sup>, RD Brown<sup>d</sup>, WA Rocca<sup>b</sup>, MA Frye<sup>c</sup>

<sup>a</sup>Faculty of Medicine/Department of Psychiatry, Universidad de los Andes, Santiago, Chile, <sup>b</sup>Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, USA, <sup>c</sup>Department of Psychiatry and Psychology, Mayo Clinic College of Medicine Rochester, USA, <sup>d</sup>Department of Neurology, Mayo Clinic College of Medicine, Rochester, USA, <sup>e</sup>Department of Medicine, Mayo Clinic College of Medicine, Rochester, USA

**Objective:** To estimate the risk of fatal and non-fatal myocardial infarction (MI) and stroke in patients with bipolar I disorder compared to people without bipolar I disorder.

**Method:** We utilized a population-based cohort in Olmsted County, MN, USA. We identified 335 participants with bipolar I disorder between 1966 and 1996 through a medical records linkage system, confirmed by medical record review by a psychiatrist, and 335 year of birth and sex-matched referents. MI and stroke were ascertained by medical records review by trained abstractors or neurologist. Follow up stopped at an incident MI or stroke, death, lost to follow up or by December 31, 2013. We carried out Cox proportional hazards models to assess the hazard ratio (HR) for MI or stroke, adjusting for potential confounders.

**Results:** We found an increased risk of MI/stroke in patients with bipolar I disorder [HR 1.54, 95% confidence interval (CI) 1.01, 2.33;  $p = 0.04$ ]. After adjusting for alcohol use disorder, hypertension, diabetes and smoking at baseline, the risk was no longer increased (HR 1.18, 95% CI 0.75, 1.86;  $p = 0.45$ ). Patients with history of psychosis showed an increased risk of MI/stroke at a trend level (HR 1.75, 95% CI 0.98, 3.13;  $p = 0.06$ ), while patients without psychosis showed a non-significant increase of the risk of MI/stroke (HR 1.36, 95% CI 0.74, 2.50;  $p = 0.32$ ).

**Conclusion:** Patients with bipolar I disorder showed an increased risk of fatal or non-fatal MI/stroke. Patients with history of psychosis may have an increased risk that may not be fully explained by exposure to cardiovascular risk factors.

## Rapid Communication III

### Bipolar disorder subtypes in an Australian sample of children and adolescents: rating scale data at time of first service presentation

SJ Hirneth<sup>a</sup>, PL Hazell<sup>a</sup>, TL Hanstock<sup>b</sup>, TJ Lewin<sup>c</sup>

<sup>a</sup>Discipline of Psychiatry, University of Sydney, Sydney, Australia, <sup>b</sup>School of Psychology, University of Newcastle, Newcastle, Australia, <sup>c</sup>Centre for Translational Neuroscience and Mental Health, University of Newcastle and Hunter New England Mental Health Services, Newcastle, Australia

**Aims:** To investigate clinical characteristics of clients with bipolar I disorder (BP-I), bipolar II disorder (BP-II) and bipolar disorder not otherwise specified (BP-NOS) recruited from The Bipolar Program (TBP), a community mental health clinic in Newcastle, Australia specialising in assessing and treating children and adolescents with bipolar disorder (BD).

**Methods:** Systematic assessment data (client demographics, standardised symptom rating scales, and psychosocial functioning measures) were obtained for clients meeting criteria for BD ( $n = 88$ ; 63 female) aged 8–18 years ( $M = 14.8 \pm 2.5$ ).

**Results:** All BD subtypes had high levels of psychopathology, with overall scores in the clinical range for child behaviour checklist (CBCL) total problems for parent-report (PR) ( $M = 72.6 \pm 9.5$ ) and youth self-report (YSR) ( $M = 70.6 \pm 9.8$ ). BD-NOS partici-

pants scored significantly higher ( $M = 74.7 \pm 6.9$ ) on CBCL-PR total problems compared to BD-II ( $M = 67.2 \pm 11.4$ ,  $p = 0.004$ ) but not compared to BD-I ( $M = 71.6 \pm 9.8$ , n.s.). BD-NOS had higher levels of CBCL-PR internalising problems ( $M = 74.04 \pm 9.3$ ) compared to BD-I ( $M = 68.7 \pm 10.0$ ,  $p = 0.032$ ) and BD-II ( $M = 67.4 \pm 10.2$ ,  $p = 0.029$ ). Participants across all BD subtypes scored in the moderately elevated range on Beck Youth Inventory subscales for Anxiety ( $M = 63.3 \pm 13.2$ ), Depression ( $M = 67.3 \pm 13.4$ ), Anger ( $M = 64.5 \pm 10.5$ ) and Disruptive Behaviour ( $M = 63.4 \pm 13.5$ ). Consistent with rating scale scores, participants had low scores on Global Assessment of Functioning ( $M = 53.4 \pm 9.8$ ) and had high rates of self-harming/suicidal gestures (69.3%), suicidal ideation (73.9%) and psychotic symptoms (35.2%).

**Conclusions:** All BD groups reported high levels of psychopathology overall, scoring at clinically significant levels across many symptom domains, with associated high levels of functional impairment, self-harm/suicidality and psychosis. BD-NOS participants reported the highest levels of overall symptomatology and internalising problems, highlighting the need for further research focus on this population. The current study is supported by a research grant from the Australian Rotary Health Research Fund – Mental Health Evaluation Grants Scheme.

## The orbit project: pilot evidence for feasibility and efficacy of a novel international online mindfulness-based intervention for late stage bipolar disorder

G Murray<sup>a</sup>, N Leitan<sup>a</sup>, M Berk<sup>b</sup>, N Thomas<sup>b</sup>, E Michalak<sup>c</sup>, L Berk<sup>d</sup>, S Johnson<sup>e</sup>, S Jones<sup>f</sup>, N Allen<sup>g</sup>, M Kyrios<sup>h</sup>

<sup>a</sup>Psychological Sciences, Swinburne University, Hawthorn, Australia, <sup>b</sup>Psychiatry, Deakin University, Burwood, Australia, <sup>c</sup>Psychiatry, University of British Columbia, Vancouver, Canada, <sup>d</sup>Psychiatry, Deakin University, Melbourne, Australia, <sup>e</sup>Psychology, University of California Berkeley, Berkeley, USA, <sup>f</sup>Psychology, Lancaster University, Lancaster, United Kingdom, <sup>g</sup>Psychology, University of Oregon, Oregon, USA, <sup>h</sup>Psychology, Australian National University, Canberra, Australia

**Background:** People in the late stage of Bipolar Disorder (BD) are poorly served by current interventions: They are unlikely to benefit from traditional psychotherapies, exhibit increased relapse risk and poorer quality of life (QoL). To meet this need, our international team developed ORBIT (online, recovery-focused, bipolar individualised therapy) in close consultation with end-users. ORBIT targets QoL through emotion regulation, sleep and sense-of-self mechanisms, and is delivered in a brief, multi-media web format. Here, we report on an open Phase II trial of ORBIT.

**Methods:** Inclusion criteria were: self-reported primary diagnosis of BD, experienced 6 or more episodes of BD, under the care of a medical practitioner, access to a computer and internet, proficient in English, 18–65 years of age, and willing to commit to a 3-week intervention. To test international feasibility, ORBIT was hosted and ethically approved at Swinburne University, while participants were recruited through our network in Canada. Primary outcome was change (baseline – post-treatment) on the Brief QoL:BD (Michalak & Murray, 2010).

**Results:** Twenty-six people consented to participate. Average age was 46.6 years ( $SD = 12.9$ ), and 75% (valid percent) were female. Ten participants were lost to follow-up, with complete pre- and post-intervention data obtained from 16 (38.5% attrition). Completers analysis found QoL was improved post-treatment ( $M = 42.63$ ,  $SD = 8.68$ ) compared with baseline ( $M = 39.19$ ,  $SD = 9.22$ ),  $t(15) = 2.88$ , 95% CI: .89–5.98,  $p = 0.011$ . Improvement was of large magnitude (partial  $\eta^2 = 0.36$ ), and exceeded the ‘one SEM’ criterion for minimally important change. Intention-to-treat analyses (LOCF,  $n = 26$ ) also found statistically significant improvement in QoL ( $p = 0.014$ , partial  $\eta^2 = 0.22$ ). All completers reported they would recommend the program to others with BD.

**Conclusion:** Pilot testing suggests ORBIT is feasible, acceptable, efficacious and now warrants full development and definitive international trial.

## Common genetic variants associated with bipolar disorder and coexisting medical conditions

ML Prieto<sup>a,c</sup>, E Ryu<sup>b</sup>, J Pathak<sup>b</sup>, GD Jenkins<sup>b</sup>, A Batzler<sup>b</sup>, AB Cuellar-Barboza<sup>d</sup>, MA Frye<sup>a</sup>, JM Biernacka<sup>a,b</sup>

<sup>a</sup>Department of Psychiatry and Psychology, <sup>b</sup>Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, USA, <sup>c</sup>Department of Psychiatry, Universidad de los Andes, Santiago, Chile, <sup>d</sup>Department of Psychiatry, Universidad Autónoma de Nuevo León, Nuevo León, Mexico

**Background:** Patients with bipolar disorder (BD) have a high prevalence of comorbid medical illness, mainly cardiovascular disease and diabetes. However the mechanisms behind these comorbidities are not known. The purpose of this study was to determine the association of BD-susceptibility genetic variants with various medi-

cal disease phenotypes using a genome-wide scan approach based on electronic health records (EHR) data.

**Methods:** Data from 6,957 Caucasian subjects were used to test association of 124 phenotypes derived from EHRs with 39 single nucleotide polymorphisms (SNPs) that were previously reported to be associated with BD according to the NHGRI GWAS catalog, and had bipolar disorder association  $p$ -value less than  $10^{-4}$  in a prior Psychiatric Genomics Consortium analysis. For each phenotype, subjects with  $\geq 2$  corresponding International Classification of Diseases (ICD) codes in the EMR that were at least 30 days apart were classified as cases. Logistic regression was used to test the association of each SNP with each phenotype. Odds ratios (ORs) and nominal  $p$ -values are presented.

**Results:** The BD risk allele at SNP rs736408 in ITIH3 gene showed the strongest association with “other gastrointestinal disorder” ( $OR = 1.15$ ;  $p = 8.7 \times 10^{-5}$ ). An association was also observed between the rs7042161 BD risk allele in SVEP1 and “essential hypertension” ( $OR = 1.15$ ;  $p = 1.8 \times 10^{-4}$ ).

**Discussion:** Our analyses identified SNPs with potential pleiotropic effects. The ITIH3 gene is related to proinflammatory processes including inflammatory bowel disease. The ITIH3 – hyaluronic acid complex is found in colonic mucosae in inflammatory bowel disease. SVEP1 regulates ICAM1, which is associated with high blood pressure, and interacts with SMAD3, which is associated with hypertensive cardiac fibrosis. While replication of these findings is needed, the associations described might be a factor contributing to the comorbidity of BD with gastrointestinal and cardiovascular disease.

## Association between suicide attempts and family functioning in bipolar disorder

M Berutti, B Lafer, V Alves Pereira, FG Nery

Psychiatry, Medicine School, São Paulo, Brazil

**Objectives:** Suicidal behavior is highly prevalent among BD patients. Familial environmental factors may play a role in suicidal behavior among BD patients. The objective of this study was to investigate the association between family functioning and personal history of suicide attempts (SA) in bipolar disorder (BD) patients

**Methods:** Thirty-one BD type patients with lifetime history of SA (mean age  $\pm$  SD:  $41 \pm 8$  y.o., female: 77.8%) were compared to 31 BD type I with no lifetime history of SA (mean age  $\pm$  SD:  $41 \pm 10$  y.o., female: 53.3%). Subjects were recruited from the Bipolar Disorder Program (PROMAN), Department of Psychiatry, University of São Paulo Medical School, Brazil. We used the Family Assessment Device (FAD), a self-report questionnaire that evaluate several dimensions of family functioning, including Problem Solving, Communication, Roles, Affective Responsiveness, Affective Involvement, Behavior Control, and General Functioning, to evaluate family functioning.

**Results:** BD patients with lifetime SA presented more psychiatric hospitalizations, higher frequency of psychotic symptoms, and higher scores on depressive, manic and suicide ideation scores than BD patients without lifetime SA. BD patients with lifetime SA presented significantly higher scores in several subscales of the FAD, including Problem Solving, Communication, Roles, Affective Responsiveness and General Functioning when compared with BD patients without SA. Among the BD patients with lifetime SA, the FAD subscale of Roles was positively correlated with years since last SA, and negatively correlated with number of SAs.

**Conclusion:** History of SA in BD patients is associated with worse performance in several domains of family functioning, including Problem Solving, Communication, Roles, Affective Responsiveness and General Functioning. Although we cannot determine the causality of this association, these findings may help to identify environmental factors involved in suicidal behavior in BD patients.

## Target engagement with anterior cingulate GLX: a placebo controlled proton-1 magnetic resonance spectroscopy study of uridine for adolescent bipolar depression

D Kondo, R Huber, X Shi, A Prescott, Y Sung, P Renshaw

*The Brain Institute, University of Utah, Salt Lake City, USA*

**Aims:** Among persons between 10 and 24 years of age, bipolar disorder (BD) is the 4th leading cause of worldwide medical disability. The onset is prior to age 20 in ~2/3 of cases, and 71% of first episodes are depressive. Yet there are no approved treatments for adolescent bipolar depression. Validation of biomarkers, i.e. treatment targets, would aid development of novel therapeutics. Experts recommend targeting the glutamatergic and purinergic systems, in seeking new treatments. In line with NIMH's emphasis on Experimental Medicine study designs, the aims of this trial were: 1) To assess uridine's "target engagement" with the neurochemical entity GLX (glutamate + glutamine), measured with proton-1 magnetic resonance spectroscopy (1H-MRS); and 2) To obtain pilot uridine clinical, safety and tolerability data, for use in planning future studies.

**Methods:** Adolescents aged 13–20 with bipolar depression were randomized to uridine 500 mg twice daily or placebo. 1H-MRS brain scans were performed at baseline, and repeated following 6 weeks of treatment.

**Results:** N = 24 adolescents were enrolled. At baseline, BD subjects had increased anterior cingulate cortex (ACC) GLX, compared with healthy controls ( $p < 0.001$ ). After 6 weeks of treatment, the uridine group had a lower mean Children's Depression Rating Scale-Revised (CDRS-R) raw score compared with placebo ( $p = 0.05$ ). In the uridine group, there was a trend toward correlation between change in ACC GLX and change in CDRS-R ( $p = 0.09$ ). There was also a trend toward reduced suicidal ideation in the uridine vs. placebo groups ( $p = 0.08$ ). There were no clinically significant abnormalities on serum, urine or ECG testing.

**Conclusions:** In adolescents with bipolar depression, uridine was well-tolerated and was associated with decreased CDRS-R scores. Five meta-analytic reviews have unanimously concluded that brain GLX is increased in BD, compared with healthy controls and major depressive disorder. Further study of uridine is warranted, based on the suggestion it may engage this target. A limitation of this study is small sample size. Discussion is provided, focused on the published neural effects relevant to BD that are common to uridine, lithium and ketamine. These shared mechanisms provide added rationale for uridine as a treatment for BD.

## Early-stage bipolar disorder patients who gain weight over 12 months experience greater limbic brain volume loss than patients without weight gain

DJ Bond<sup>a</sup>, IJ Torres<sup>b</sup>, RW Lam<sup>b</sup>, LN Yatham<sup>b</sup>

<sup>a</sup>Psychiatry, University of Minnesota, Minneapolis, USA,

<sup>b</sup>Psychiatry, University of British Columbia, Vancouver, Canada

**Aims:** Obese bipolar disorder (BD) patients experience a more severe mood illness than normal-weight patients, including more mood episodes, lower medication response rates, and more frequent suicide attempts. We previously reported cross-sectional data showing that early-stage BD patients had body mass index (BMI)-related volume reductions in limbic brain areas, suggesting that the structural brain changes typical of BD were exacerbated with increased weight. However, BD is a progressive illness, and whether additional weight gain is associated with greater limbic brain volume loss over time has not been investigated.

**Methods:** We used 3-Tesla MRI to measure brain volumes at recovery from the first manic episode and 12 months later in N = 41 BD patients. We obtained similar measurements from N = 23 age- and gender-matched non-BD comparison subjects. Using voxel-based regression analyses ( $p < 0.001$  FWE-corrected, minimum cluster size = 500 voxels), we examined the association between BMI change over 12 months and brain volume loss. In patients, the analyses were controlled for other factors that could impact volume changes, including relapse into mania and depression, and the use of mood stabilizers and second-generation antipsychotics. The study was approved by the University of British Columbia Clinical research Ethics Board, and written informed consent was obtained from all participants.

**Results:** In patients, increased BMI over 12 months was associated with greater gray matter (GM) and white matter (WM) volume losses in frontal, temporal, and sub-cortical limbic brain areas. BMI-related cerebellar WM reductions were particularly pronounced. In comparison subjects, BMI-related GM and WM losses were less extensive and were confined primarily to non-limbic brain areas.

**Conclusions:** Identifying predictors of clinical and neurobiological disease progression in BD, particularly modifiable ones, is a major priority. Weight gain early in the course of BD is a potentially modifiable driver of illness progression. Further work is urgently needed to determine whether weight loss interventions, as adjuncts to pharmacotherapy, can improve disease course in people with BD.

# Rapid Communication IV

## New approaches in fighting stigma

M Selo<sup>a</sup>, M Kolbe<sup>b</sup>, M Walker<sup>c</sup>

<sup>a</sup>Advocacy, Werner Alfred Selo Foundation, New York, USA,

<sup>b</sup>German Society for Bipolar Disorders (DGSB), Germany,

<sup>c</sup>International Bipolar Foundation, San Diego, USA

While it is true that stigma has been reduced greatly over the past 20 years, it is also true that stigma still prevails in many places. We hope to share anti-stigma strategies with the participants and discuss what has worked and what has not in various regions of the world. We hope to come to some universal guidelines to bust stigma. With this symposium we want to present new approaches in different countries showing various efforts to promote a healthy

attitude toward mental illness and improve mental wellbeing, including in the work place. Martin Kolbe will present the "Martin Kolbe Bipolar Roadshow", which comprises musical and poetical elements and has been most successful in Germany. Marylou Selo will speak about the second stage of the Swiss Anti-Stigma campaign entitled "Depression in the Work Place". Stephanie Wooley will present the various "Anti-Stigma Events" which are held in France and Belgium. Muffy Walker will present the events the International Bipolar Foundation (IBPF) has organized to improve mental health and attitudes toward mental health, among others the "Say it Forward" campaign and the "Stigma Buster 5K-walk/run" in the U.S.



# **Premenstrual mood symptoms after menarche association with early onset and perinatal mood disorders in women with bipolar disorder – findings from STEP-BD**

**R Dias<sup>a</sup>, B Lafer<sup>a</sup>, GS Sachs<sup>b</sup>, AA Nierenberg<sup>b</sup>, H Joffe<sup>c</sup>**

<sup>a</sup>Psychiatry Bipolar Disorder Research Group, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, <sup>b</sup>Bipolar Clinic and Research Program, Massachusetts General Hospital Harvard Medical School, Boston, USA, <sup>c</sup>Women's Hormone and Aging Research Program, Department of Psychiatry Brigham and Women's Hospital, Boston, USA

**Aims:** Premenstrual and perinatal-related mood disorders have been described in women with Bipolar Disorder (BD), but evidence to support a strong link between them in this population is limited. The aim of this study is to investigate this association.

**Methods:** The relationship between premenstrual and perinatal mood exacerbation was analyzed in 205 premenopausal women with BD, with at least one prior pregnancy and enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (mean age 32.33, SD 5.8). Associations were evaluated with logistic regression analysis and Bayes network.

**Results:** The frequency of any premenstrual and perinatal disorder was 94.6%, with 74.6% of women reporting premenstrual mood symptoms in the first 5 years after menarche (Premenstrual-Menarche-Sx), 73.2% premenstrual mood exacerbation (Premenstrual-Exacerbation-Sx), 58.8% severe mood symptoms on postpartum period (Postpartum-Sx), 53.2% severe mood symptoms during pregnancy (Pregnancy-Sx) and 43.9% severe mood symptoms when using hormonal contraceptives (Hormonal-Contraceptives-Sx) and 85.9% at least 2 disorders. In total, 559 pregnancies and 324 children were reported. The analysis did not reveal an association common to all reproductive events, but several variables were significantly associated, such as Premenstrual-Menarche-Sx with, Premenstrual-exacerbation-Sx with Pregnancy-Sx, Pregnancy-Sx with Postpartum-Sx, and Premenstrual-Menarche-Sx with early onset of BD.

**Conclusion:** Neurophysiological distinction in reproductive hormones between premenstrual and perinatal periods could partly explain these results. Other factors associated with premenstrual mood symptoms, especially the postpartum period, should be considered to clarify reproductive-related mood changes in women with BD. Further research is needed to evaluate this complex network of interactions.

## **Uric acid and clinical correlates in bipolar patients from the FACE-BD cohort**

**J Loftus<sup>a</sup>, B Etain<sup>b</sup>, I Cussac<sup>a</sup>, R Belzeaux<sup>c</sup>, P Courtet<sup>d</sup>, S Gard<sup>e</sup>, JP Kahn<sup>f</sup>, F Bellivier<sup>g</sup>, C Passerieux<sup>h</sup>, FACE-BD<sup>i</sup>**

<sup>a</sup>Princess Grace Hospital, Fondation FondaMental Department Psychiatry, Monaco, <sup>b</sup>Fondation FondaMental, Université Paris, France, <sup>c</sup>Hôpital Sainte Marguerite, Assistance Publique Hôpitaux de Marseille, France, <sup>d</sup>Emergency Psychiatric Department, Université Montpellier, France, <sup>e</sup>Hôpital Charles Perrens, Centre Expert Trouble Bipolaire, France, <sup>f</sup>CHU de Nancy, Hôpitaux de Brabois, Université de Lorraine, France, <sup>g</sup>AP-HP, GHSaint-Louis-Lariboisière-Fernand Widal, P. Fondation, France, <sup>h</sup>Université de Versailles Saint-Quentin, France, <sup>i</sup>CHU de Grenoble, France

Recent research has implicated the purinergic system in the pathophysiology of bipolar disorder. Elevated uric acid has been reported in mania in first episode medication naïve subjects and xanthine oxidase inhibitors have shown efficacy as an adjunctive treatment to lithium in the treatment of mania. Elevated uric acid levels have also been suggested as potential trait markers for the disorder. Genetic, environmental and iatrogenic factors influence

uric acid levels. The aim of this study is to explore the relationship between uric acid levels and biological and clinical variables in a large sample of bipolar patients.

**Methods:** Data was analysed from 945 subjects with DSM-IV bipolar disorder recruited from FondaMental French network of bipolar centres. Comparative statistical tests were performed to determine the clinical correlates uric acid levels using a quantitative approach. Female and male subjects were analysed separately. Multivariate analysis was also performed with the inclusion of variables significant in the univariate analysis and adjustment for age.

**Results:** Uric acid was significantly elevated in bipolar I subjects ( $p = 0.05$ ). A weak correlation was observed between age in female subjects and uric acid levels ( $0.13$ ,  $p = 0.0027$ ). No significant relationship was found between uric acid levels and first episode, age of onset, duration of illness or medication. Uric acid levels were significantly correlated with creatinine, body mass index (BMI) and glucose levels. The correlation was more pronounced in female subjects. Multivariate analysis adjusting for somatic variables and age did not find a significant relationship between bipolar I and uric acid levels.

**Conclusions:** Elevated uric acid levels in this sample were related to somatic variables. Age of onset, duration, episode type and medication did not impact on uric acid levels. Women seemed more at risk of elevated uric acid levels in this sample.

## **Comparative efficacy and acceptability of psychological interventions for long term treatment of bipolar disorder: a network meta-analysis**

**A Cipriani<sup>a</sup>, DJ Miklowitz<sup>b</sup>, H McMahon<sup>a</sup>, A Chaimani<sup>c</sup>, S Stockton<sup>a</sup>, G Salanti<sup>d</sup>, JR Geddes<sup>a</sup>**

<sup>a</sup>Department of Psychiatry, University of Oxford, Oxford, United Kingdom, <sup>b</sup>Semel Institute, University of California Los Angeles, Los Angeles, USA, <sup>c</sup>Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece

**Background:** Despite consistent reports of efficacy in bipolar disorder, psychosocial treatments are by their nature complex and prone to intellectual bias. It still remains unclear which content ingredients are essential to a successful outcome and how the different treatment options rank against to each other.

**Aims:** The objective of this review was to compare the efficacy and acceptability of different psychological interventions in the long term treatment of bipolar disorder. To overcome the limitations of the available evidence, we carried out a network meta-analysis, a methodological approach to integrate information from within-trial direct comparisons with indirect comparisons derived from studies comparing either of the two interventions with a common comparator. This statistical technique was previously used to investigate the effectiveness of pharmacological treatments in mania and bipolar disorder, and also psychological interventions in depression and PTSD.

**Methods:** We registered the protocol in PROSPERO ([www.crd.york.ac.uk/PROSPERO/](http://www.crd.york.ac.uk/PROSPERO/)), an international database of systematic reviews aimed at avoiding unplanned duplication and enabling comparison of reported review methods with what was originally planned. We searched the Cochrane Central Register of Controlled Trials until November 2014. Only randomised controlled trials comparing specific psychological interventions against any control intervention for long term treatment of bipolar disorder in patients aged 18 years or older were included. Long term treatment was defined as a duration of follow up of at least 3 months. Two reviewers independently selected the references. Network meta-analysis was performed using STATA.

**Results:** We managed to group interventions with common ingredients (i.e. common methods, assumptions or structure). In order not to be biased by the retrieved evidence, the interventions were merged “a priori” through a consensus process within the review group, before carrying out the statistical analyses. Results from network meta-analysis were presented as summary relative effect sizes for each possible pair of treatments and ranking probabilities were estimated for all interventions, using the surface under the cumulative ranking curve and mean ranks.

**Conclusion:** We found that the various psychological interventions in bipolar disorder had common elements that could differentiate these approaches from treatment as usual but also specific elements that could distinguish them from one another.

### Galantamine-ER for cognitive deficits in bipolar disorder

DV Iosifescu<sup>a</sup>, JW Murrough<sup>a</sup>, T Deckersbach<sup>b</sup>, B Iacoviello<sup>a</sup>, K Huryk<sup>a</sup>, AA Nierenberg<sup>b</sup>

<sup>a</sup>Psychiatry Mood and Anxiety Disorders Program, Icahn School of Medicine at Mount Sinai, New York, USA, <sup>b</sup>Psychiatry Bipolar Clinic and Research Program, Massachusetts General Hospital, Boston, USA

**Aims:** Subjects with bipolar disorder experience significant cognitive dysfunction, even when euthymic, but few studies have evaluated potential treatments for such deficits. We completed a two-site, 16-week, randomized, placebo-controlled study to evaluate the efficacy of galantamine ER, an acetylcholinesterase inhibitor, for the treatment of cognitive deficits in euthymic subjects with bipolar disorder.

**Methods:** N = 73 euthymic subjects with bipolar disorder (52% female, age 46.5 years, SD=12.6), who reported subjective cognitive deficits, provided IRB-approved informed consent. 80% of subjects were BPI and 20% BPII. Subjects were randomized 1:1 to adjuvant galantamine ER or placebo (in addition to their existing mood stabilizing treatment) for a 16-week treatment study with flexible doses (8–24 mg/day). At every monthly visit subjects were administered neuropsychological tests of attention (Conners CPT) and self report scales for functional impairment (The Range of Impaired Functioning Tool, LIFE-RIFT). Tests for episodic memory (CVLT) were administered only at baseline and endpoint to reduce learning effects. We used mixed-effects linear regression to compare treatment groups on the repeated assessments of CPT and LIFE-RIFT; changes in CVLT were assessed with ANOVA.

**Results:** Bipolar subjects treated with galantamine experienced significant improvement in attention (CPT omission and commission errors) compared to placebo over the 16 week treatment, after adjusting for confounders ( $p = 0.035$ ). Galantamine treated patients showed no significant improvement on CVLT or in self-reported functional impairment (LIFE-RIFT) compared to placebo. Galantamine was well tolerated, with rates of adverse effects or new onset mood episodes not significantly different from placebo.

**Conclusion:** Sixteen weeks of treatment with galantamine ER was associated with significant improvements in measures of attention but not in episodic memory or subjective functional impairment.

**Source of funding:** Supported by NIMH R01 MH079157 (Dr. Iosifescu)

### Mood regulatory actions of nucleus accumbens deep brain stimulation

R Kale<sup>a</sup>, A Kouzani<sup>b</sup>, M Frye<sup>a</sup>, K Walder<sup>c</sup>, M Berk<sup>c</sup>, S Tye<sup>a</sup>

<sup>a</sup>Department of Psychiatry and Psychology, Mayo Clinic, Rochester, USA, <sup>b</sup>School of Engineering, Deakin University, Waurn Ponds, Australia, <sup>c</sup>School of Medicine, Deakin University, Waurn Ponds, Australia

The mood regulatory mechanisms of deep brain stimulation (DBS) therapy are yet to be fully understood. DBS is shown to have antidepressant actions in severe, treatment-resistant depression (TRD). Interestingly, DBS of mesoaccumbens neurologic targets, including the nucleus accumbens (NAc), have also been shown to induce mania in vulnerable individuals. The nucleus accumbens (NAc) is a critical node in the mesocorticolimbic system and plays a major role in mediating antidepressant behavioral responses in the forced swim test (FST), a preclinical screen for antidepressant efficacy. This study investigates the antidepressant effects of NAc DBS in an established animal model of TRD. Wistar rats were divided into 4 groups: TRD-DBS ( $n = 9$ ), TRD-Sham ( $n = 8$ ), TRD ( $n = 10$ ), and Control ( $n = 10$ ). Bilateral stimulating electrodes were implanted into the NAc of TRD-Sham and TRD-DBS animals. Antidepressant-resistance and depression behaviors were induced through adrenocorticotrophic-hormone (ACTH-(1–24); 100 µg/day; 2nd and 3rd weeks) administration and concurrent social isolation (all 3 weeks) respectively. DBS was administered throughout the 2nd week of ACTH treatment via a back mounted rodent DBS system. 24-hour locomotor activity counts were obtained using infra-red detectors and weekly sucrose preference tests were performed throughout the 3 week protocol. Open field and FST were completed at the end of the 3 weeks. Brains were then removed and stored at  $-80^{\circ}\text{C}$ . NAc tissue levels of brain-derived and glial-derived neurotrophic factors (BDNF and GDNF, respectively) were quantified using western blot. Results demonstrate significant increases in locomotor activity for TRD-DBS animals (DBS-Vs-Sham:  $p = 0.0248$ ). Lowered immobility was observed during FST for TRD-DBS animals (DBS-Vs-Sham:  $p = 0.0188$ ). ACTH-induced BDNF expression increased in the outer region substructure NAc-shell ( $p = 0.0487$ ) and decreased in the inner region substructure NAc-core ( $p = 0.0275$ ) compared to controls. These data support antidepressant actions of NAc DBS in TRD. Local changes in neurotrophic factors may contribute to these mechanisms. Importantly, observed increases in locomotor activity over the 3 weeks highlight the potential for mesoaccumbens DBS to impact behaviors such as locomotor activity which may contribute to risk for induction of mania. Preliminary analysis of concurrent effects of daily dopamine reuptake inhibitor GBR12909 (16 mg/kg) administration coupled with NAc DBS demonstrates dopamine-mediated augmentation of these mania-like behaviors.

# Poster Session I

## Does sleep deprivation lower corticosterone levels in mice?

B Akers<sup>a</sup>, S Krupp<sup>b</sup>, Y Gao<sup>a</sup>, M Roberts<sup>a</sup>, R El-Mallakh<sup>a</sup>

<sup>a</sup>Psychiatry, University of Louisville, Louisville, USA, <sup>b</sup>Anatomical Sciences and Neurobiology, University of Louisville, Louisville, USA

**Background:** We have previously reported that sleep fragmentation utilizing the moving bar method (and modeling sleep apnea), lowers corticosterone levels in mice. This was significantly lower than corticosterone levels after rapid eye movement (REM) sleep deprivation (which models reduced sleep that may lead to bipolar relapse). In that initial study, neither group was significantly different from baseline.

**Methods:** Young adult Black Swiss male mice were REM sleep deprived for 1 or 3 days utilizing the inverted flowerpot method. Immediately at the end of the sleep deprivation period, the mice were sacrificed by decapitation and blood collected for subsequent determination of serum corticosterone levels utilizing immunoassay (DetectX, Arbor Assays).

**Results:** Approximately 20 baseline, 20 one-day sleep deprived, and 20 three-day sleep deprived mice were examined. Corticosterone levels are currently being measured and the results will be presented at the meeting.

**Discussion:** Sleep deprivation is associated with behavioral changes (immediate increase in activity and subsequent reduction in activity), and has been proposed to be an animal model of mania, and possibly bipolar illness. It is expected that REM sleep deprivation will be associated with elevated corticosterone levels.

## Experimental meningitis during childhood triggers depressive-like behaviour in adult life

T Barichello<sup>a</sup>, JS Generoso<sup>b</sup>, LR Simoes<sup>b</sup>, D Domingui<sup>b</sup>, SS Valvassori<sup>b</sup>, J De Quevedo<sup>a</sup>

<sup>a</sup>Department of Psychiatry and Behavioral Sciences, The university of Texas Health Science Center at Houston, Houston, USA,

<sup>b</sup>Graduate Program in Health Sciences, Universidade do Extremo Sul Catarinense, Criciuma, Brazil

Pneumococcal meningitis is a severe infection of the central nervous system (CNS) presenting with high mortality rates and neurological sequelae. Infectious diseases could play a significant role in the aetiology of neuropsychiatric disorders.

**Aim:** Based on these observations, our presupposition is that meningitis during childhood could induce depressive-like behaviour in adult life. The aim of this study was to investigate depressive-like behaviour, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell line-derived neurotrophic factor (GDNF) expression in the hippocampus and the adrenocorticotrophic hormone (ACTH) and corticosterone in the blood, and the response to imipramine treatment in adulthood rats subjected to pneumococcal meningitis during infancy.

**Methods:** Infant Wistar rats received artificial cerebrospinal fluid as a placebo or *Streptococcus pneumoniae* suspension at a concentration of  $1 \times 10^6$  colony-forming units (CFU). Eighteen hours after induction, the animals received antibiotic treatment as usual for 7 days. On day forty-six of life, the animals received imipramine or NaCl sterile solution for 14 days (47th–60th). At day 60 of life, the animals were evaluated on the consumption of sweet food

(anhedonia) and submitted to a forced swimming task. Immediately after the behavioural tasks, the animals were sacrificed to evaluate the BDNF, NGF, and GDNF expression in the hippocampus and ACTH and corticosterone in the blood.

**Results:** The meningitis group presented depressive-like behaviour through decreased sucrose intake and increased immobility time in the forced swimming task; the BDNF and GDNF decreased in the hippocampus and the ACTH and corticosterone levels increased in the blood. The imipramine treatment reversed the depressive-like behaviour, re-established the hippocampal BDNF and GDNF expression, and normalised the ACTH and corticosterone levels in the blood.

**Conclusion:** In this research, we demonstrated that adult rats subjected to experimental pneumococcal meningitis during infancy presented depressive-like behaviour and pathophysiological findings similar to those of patients with depression as well as a response to imipramine treatment. Meningitis infection during childhood could trigger pathophysiological events that lead to depression in adulthood. Further studies are necessary to investigate in depth the mechanisms underlying this phenomenon.

## HTR1b allelic imbalance in bipolar disorder and suicide

A Bani-Fatemi, V De Luca

Neuroscience, CAMH, Toronto, Canada

**Background:** Several studies have suggested that suicidal behaviour is partially determined by genetic factors, supporting a search for candidate genes involved in the neurobiology of suicidal behaviour. HTR1B has been highlighted in the literature as being involved in suicidal behaviour. We analyzed the parent-of-origin effects (POE) in suicide attempters and the differential expression of HTR1B rs6296 alleles in suicide victims.

**Methods:** We compared the C861G (rs6296) allele-specific mRNA levels in the frontal cortex of suicide ( $n = 13$ ) and non-suicide victims ( $n = 13$ ) from the Stanley Medical Research post-mortem brain collection. We also conducted a family-based association study performing QTD analyses of the rs6296 polymorphism in 277 nuclear families with at least one subject affected by bipolar disorder considering the suicidal behaviour severity scores as quantitative phenotype.

**Results:** We did not find any altered C/G expression ratio in suicide victims compared to controls ( $p = 0.370$ ); however, the subjects with comorbid alcohol abuse ( $p = 0.009$ ) and drug abuse ( $p = 0.03$ ) showed higher C/G ratio. There was no preferential transmission of C861G polymorphism and the severity of suicidal behaviour, when we considered paternal ( $p > 0.05$ ) or maternal meiosis ( $p > 0.05$ ).

**Discussion:** This is the first study investigating the allelic ratio in HTR1B. However, these data do not support a role for allelic imbalance or POE of HTR1B for suicidal behaviour in bipolar disorder.

## Relationships between mood symptoms, weight, and serum adipokines in early-stage bipolar disorder

DJ Bond<sup>a</sup>, AC Andreazza<sup>b</sup>, J Hughes<sup>c</sup>, T Dhanoo<sup>d</sup>, IJ Torres<sup>d</sup>, JM Kozicky<sup>d</sup>, LT Young<sup>b</sup>, RW Lam<sup>d</sup>, LN Yatham<sup>d</sup>

<sup>a</sup>Psychiatry, University of Minnesota, Minneapolis, USA,

<sup>b</sup>Psychiatry, University of Toronto, Toronto, Canada, <sup>c</sup>School of Public Health, University of Minnesota, Minneapolis, USA,

<sup>d</sup>Psychiatry, University of British Columbia, Vancouver, Canada

**Aims:** There is a bidirectional relationship between mood disorders and obesity, with each increasing the risk of developing the other. This suggests that they share pathophysiologic mechanisms. Adipose tissue-derived hormones, or adipokines, regulate appetite via the hypothalamus, and also have activity in limbic brain regions, making them potential mediators of the link between obesity and mood disorders. However, the precise relationships between mood, weight, and adipokines are unknown.

**Methods:** We measured the serum levels of five adipokines – adiponectin, lipocalin-2, resistin, adipsin, and leptin – in 50 bipolar disorder (BD) patients enrolled in a first-episode mania program, and examined (1) whether time in recent mood episodes, current body mass index (BMI), and medication treatment predicted adipokine levels, and (2) whether adipokine levels predicted subsequent weight change and time spent with depression and hypo/mania. The study was approved by the University of British Columbia Clinical research Ethics Board, and written informed consent was obtained from all participants.

**Results:** The number of past-6-month days with depression predicted adipokine levels in aggregate ( $p = 0.05$ ) and lower adipsin ( $p < 0.01$ ), an insulin secretagogue, in particular. Second-generation antipsychotic use predicted greater resistin, a pro-inflammatory adipokine ( $p = 0.02$ ). BMI was not significantly associated with adipokine levels. Higher leptin predicted greater 12-month weight gain independently of baseline BMI ( $p = 0.04$ ), while lower leptin ( $p = 0.02$ ) and adiponectin ( $p = 0.04$ ) predicted increased time with depression.

**Conclusions:** This was the first prospective study to examine the relationships between mood, weight, and adipokines in mood disorders patients. Our findings indicate that mood- and antipsychotic-induced adipokine changes may contribute to metabolic abnormalities in BD. They further suggest that adipokines influence mood illness course. Adipokines deserve further study as potential mood-regulating molecules.

## Lipid peroxidation biomarkers in adolescents with or at high-risk for bipolar disorder

A Andreazza<sup>a</sup>, R McNamara<sup>b</sup>, J Leffler<sup>c</sup>, K Cullen<sup>d</sup>, P Croarkin<sup>c</sup>, J Geske<sup>e</sup>, J Biernacka<sup>c</sup>, M Frye<sup>c</sup>, M DelBello<sup>b</sup>

<sup>a</sup>Psychiatry, University of Toronto, Toronto, Canada, <sup>b</sup>Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, USA, <sup>c</sup>Psychiatry and Psychology, Mayo Clinic, Rochester, USA, <sup>d</sup>Psychiatry, University of Minnesota, Minneapolis, USA, <sup>e</sup>Biomedical Statistics and Informatics, Mayo Clinic, Rochester, USA

**Aims:** This study examined measures of lipid peroxidation in adolescents at varying risk for BD (healthy control, high risk, ultra-high risk, and symptomatic).

**Methods:** Whole blood was obtained from medication-free adolescents (ages 9–23 years):  $n = 15$  with no DSM-IV diagnosis and a biological parent with BD-I ('high risk'),  $n = 20$  with a current diagnosis of MDD or Depressive Disorder NOS and a biological parent with BD-I ('ultra-high risk'), and  $n = 16$  with a current diagnosis of BD-I (manic or mixed episode). Patients were recruited from the inpatient psychiatric units of the University of

Cincinnati Hospital and Cincinnati Children's Hospital Medical Center and affiliated outpatient treatment centers. Symptom ratings were obtained with the Young Mania Rating Scale and the 28-item Hamilton Depression Rating Scale. Healthy controls  $n = 13$  with no personal or family history of BD-I were recruited from the greater Cincinnati area. Serum levels of lipid peroxidation (lipid hydroperoxides, LPH, 8-isoprostane, 8-Iso, 4-hydroxy-2-nonenal, 4-HNE) were measured using colorimetric (LPH) or ELISA assays (4HNE, 8-ISO). We also measured serum levels of protein oxidation (carbonylation) using standard immunoblotting analysis and inflammatory marker using multiplex ELISA from Miliplex – Millipore. The investigators were blind to group identity, diagnosis and demographic variables of subjects during all experiments and measurements. Samples were coded numerically in a random manner and the code lifted only during data analyses after all experiments were completed. Analysis of variance and covariance models were used to test for overall differences in the biomarker levels across the 4 risk level groups.

**Results:** Four group unadjusted ( $p = 0.02$ ) and age/gender adjusted ( $p = 0.009$ ) group comparisons of lipid peroxidation (LPO) demonstrated significant differences. There were no significant differences among 4-HNE, 8-ISO, Carbonyl group, and assays of other inflammatory markers.

**Conclusions:** In contrast to findings from adult studies that have shown high LPO levels, we found that LPO was low in adolescents with fully syndromal BD than controls, while the at-risk groups' levels fell in-between. Quantifying lipid peroxidation in longitudinal studies using larger, more diverse samples could explicate the developmental pathophysiology of bipolar disorder and assist with the development of diagnostic biomarkers for early identification.

## A feasibility study evaluating differential proteomic expression in mood disorders

M Frye

Psychiatry and Psychology, Mayo Clinic, Rochester, USA

**Introduction:** Biomarkers could potentially enhance the diagnostic assessment and treatment recommendations for major depression and bipolar disorder.

**Methods:** In collaboration with the biomarker testing laboratory Rules Based Medicine and their proprietary Multi Analyte Profiling (MAP) platform, patients with unipolar ( $n = 52$ ) or bipolar depression (BP-I  $n = 46$ , BP-II  $n = 49$ ) and controls ( $n = 144$ ) were recruited. Clinical assessments included Structured Diagnostic Interview for DSM-IV-TR, Inventory for Depressive Symptoms (IDS), Young Mania Rating Scale (YMRS). One 7.5 cc tube of blood was drawn into a serum separator for proteomic multiplex analysis utilizing the DiscoveryMAPTM v 1.0. Diagnosis was predicted based on individual proteins using logistic or multinomial models; multiple testing was addressed using Bonferroni method.

**Results:** The protein growth differentiation factor 15 (GDF-15), hemopexin, hepsin, matrix metalloproteinase-7 (MMP-7), retinol-binding protein 4 (RBP-4), and transthyretin (TTR) all showed statically significant differences among the compared groups. Within this set of analytes, differences were most striking between BP-I and controls (GDF-15  $P = 3.41E-05$ , hemopexin  $P = 2.70E-05$ , hepsin  $P = 1.91E-05$ , MMP-7  $P = 0.0001$ , RBP-4  $P = 1.56E-07$ , TTR  $P = 1.48E-06$ ); however, there was also a difference found between BP-II and controls (GDF-15  $P = 0.0017$ , hepsin  $P = 0.003$ , MMP-7  $P = 0.0017$ ).

**Conclusion:** These preliminary results, while from a small sample and not adjusted for medication state, do suggest feasibility in testing for proteomic differences in mood disorders vs healthy controls and in particular bipolar I depression.

## Identification of circadian gene variants in bipolar disorder in Latino populations

R Gonzalez<sup>a</sup>, SD Gonzalez<sup>b</sup>, E Villa<sup>b</sup>, RJ Leach<sup>c</sup>, D Flores<sup>d</sup>, A Jerez<sup>e</sup>, H Raventos<sup>f</sup>, A Ontiveros<sup>g</sup>, H Nicolini<sup>h</sup>, M Escamilla<sup>a</sup>

<sup>a</sup>Psychiatry, Texas Tech University Health Science Center, El Paso, USA, <sup>b</sup>Biomedical Sciences, Texas Tech University Health Science Center, El Paso, USA, <sup>c</sup>Cellular and Structural Biology, UT Health Science Center at San Antonio, San Antonio, USA, <sup>d</sup>Los Angeles Biomedical Research Center at Harbor, University of California Los Angeles Medical Center, Torrance, USA, <sup>e</sup>Psychiatry, Centro Internacional de Trastornos Afectivos y de la Conducta Adictiva, Guatemala, Guatemala, <sup>f</sup>Centro de Investigación en Biología Celular y Molecular y Escuela de Biología, Universidad de Costa Rica, San Jose, Costa Rica, <sup>g</sup>Psychiatry, Instituto de Información e Investigación en Salud Mental AC, Monterrey, Mexico, <sup>h</sup>Psychiatry, Grupo de Estudios Médicos y Familiares, Carracci, Mexico

**Background:** Rhythm disruption is a hallmark of bipolar disorder (BD). The precision of the circadian timing system is in large part dictated by the expression of circadian genes. Alterations in circadian genes can impact biological rhythms. Given the rhythm disturbances that characterize BD, genes encoding components of molecular clocks are good candidate genes for the illness.

**Methods:** A family based association analysis of circadian gene single nucleotide polymorphisms (SNPs) and BD was conducted. The sample included Latino pedigrees recruited from the United States, Mexico, Guatemala, and Costa Rica. 868 individuals from 206 pedigrees (465 BP phenotype and 403 unaffected family members) were genotyped. Family based single marker association testing was performed. Ancestral haplotypes (SNPs found to be in strong LD defined using confidence intervals) were also tested for association with BD.

**Results:** Multiple suggestive associations between circadian gene SNPs and BD were noted. These included CSNK1E (rs1534891,  $p = 0.00689$ ), ARNTL (rs3789327,  $p = 0.021172$ ), CSNK1D (rs4510078,  $p = 0.022801$ ), CLOCK (rs1777927,  $p = 0.031664$ ). Individually, none of the SNPs were significantly associated with BD after correction for multiple testing. However, a 4-locus CSNK1E haplotype encompassing the rs1534891 SNP showed a significant association with BD (Z-score = 2.685, permuted  $p = 0.0076$ ). Additionally, a 3-locus haplotype in ARNTL also showed significant association with BD (Z-score = 3.269, permuted  $p = 0.0011$ ).

**Conclusions:** The results suggest that ARNTL and CSNK1E variants may be associated with BD. Variations in ARNTL and CSNK1E have previously been associated with the illness. Further studies are warranted to assess the relationships between ARNTL, CSNK1E and BD in Latino populations.

## Metabolic markers in patients with bipolar disorder across mood states

S Lee<sup>a</sup>, T Ha<sup>a</sup>, Y Park<sup>a</sup>, T Chung<sup>a</sup>, E Kim<sup>a</sup>, J Kim<sup>b</sup>, H Lee<sup>a</sup>, K Ha<sup>a</sup>

<sup>a</sup>Psychiatry, Seoul National University Bundang Hospital, Seongnam-si Gyeonggi-do, Korea, <sup>b</sup>Biomedical Research Institute, Seoul National University Bundang Hospital, Seongnam-si Gyeonggi-do, Korea

**Background:** Patients with bipolar disorder (BD) are at high risk for obesity. The aim of this study was to examine associations between serum levels of adiponectin, leptin, ghrelin, and TNF- $\alpha$  in patients with BD.

**Methods:** Body mass index (BMI) and adiponectin, leptin, ghrelin, TNF- $\alpha$  levels were assessed in 90 patients with BD and 73 control group. Metabolic markers were compared between the two groups and across mood states.

**Results:** BMI was higher and obesity was more frequent in the patients with BD than in the control group. Adiponectin, ghrelin and TNF- $\alpha$  levels were lower and leptin level was higher in the patients with BD than control group. After adjusting for BMI in a multivariate analysis of covariance, ghrelin and TNF- $\alpha$  levels were still lower in patients with BD than control group. There was no significant difference in serum levels of adiponectin, leptin, ghrelin, and TNF- $\alpha$  between euthymic and depressive state in patients with BD.

**Conclusion:** Our findings suggest that ghrelin and TNF- $\alpha$  are closely associated with BD as a potential trait marker.

## Tumor necrosis factor-A (TNF-A) level and psychovegetative disorders in patients with chronic cerebral ischemia

Y Morozova

Neurology and Neurosurgery, RSMU, Moscow, Russia

Aim of study was to learn the neurological, immune features and psychovegetative disorders of Chronic Cerebral Ischemia (CCI). We observed Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) level (mean value) and frequency of psychovegetative symptoms in 108 patients with CCI who have been divided on 3 groups: (1) Control group-40 health persons and TNF- $\alpha$  level is  $0.648 \pm 0.003$  pg/l, (2) CCI I stage(st) – 33 patients with mild cognitive impairment and TNF- $\alpha$  is  $0.705 \pm 0.001$  pg/l (3) CCI II st-35 patients with moderate cognitive impairment and TNF- $\alpha$  is  $1.220 \pm 0.0004$  pg/l.

**Methods:** Inquirer, neurological exam, psychologist test, psychiatrist consultate, immunoenzymatic method.

**Result:** 17 patients with CCI I st. and 29 with CCI II st. had sleep disorders and TNF- $\alpha$   $0.684 \pm 0.003$  pg/l. Anxiety-TNF- $\alpha$   $0.728 \pm 0.003$  pg/l, 12 patients with CCI I st. and 23 patients with CCI II st. had anxiety and TNF- $\alpha$   $0.728 \pm 0.003$  pg/l. 28 patients with CCI I st. and 29 patients with CCI II st. had asthenia and TNF- $\alpha$   $0.702 \pm 0.003$  pg/l. 3 patients with CCI I st. and 11 patients with CCI II st. had panic attack and TNF- $\alpha$   $1.104 \pm 0.0004$  pg/l. Nobody with CCI I st. and 7 patients with CCI II st. had depression and TNF- $\alpha$   $1.132 \pm 0.0004$  pg/l.

**Conclusion:** The obtained facts show that the rise of proinflammatory cytokine TNF- $\alpha$  is associated with psychovegetative disorders (sleep disorders, asthenia, anxiety, depression, panic attack) and can be as a result of autoimmune inflammatory in brain of patients with CCI.

## Gene expression alterations related to affective state in rapid cycling bipolar disorder patients and compared with healthy control subjects

K Munkholm<sup>a</sup>, L Pejts<sup>b</sup>, M Vinberg<sup>a</sup>, LV Kessing<sup>a</sup>

<sup>a</sup>Rigshospitalet, Psychiatric Center Copenhagen, Copenhagen, Denmark, <sup>b</sup>Department of Infectious Diseases, Centre of Inflammation and Metabolism Rigshospitalet, Copenhagen, Denmark

**Aims:** Recent findings have indicated a role for epigenetic mechanisms regulating patterns of gene expression that may play a role in the pathophysiology of bipolar disorder. We recently demonstrated downregulation of prostaglandin D synthase (PTGDS) mRNA expression in rapid cycling bipolar disorder. Here, we aimed to investigate gene expression alterations of a larger set of genes, constituting twenty genes related to neuroplasticity, inflammation, oxidative stress and other pathways speculated to be involved in bipolar disorder pathophysiology. We specifically aimed to identify genes that exhibit state-related alterations in mRNA expression in rapid cycling bipolar disorder and additionally to investigate possible alterations between mRNA expression

in rapid cycling bipolar disorder patients and healthy control subjects.

**Methods:** mRNA expression of a set of twenty genes was measured in peripheral blood mononuclear cells of 37 well-characterized rapid cycling bipolar disorder patients and 40 age- and gender matched healthy control subjects using RT-qPCR. Repeated measurements of mRNA expression were obtained in various affective states (hypomania, mania, depression and euthymia) during 6–12 months and compared with repeated measurements in healthy control subjects. Methodological care was taken to standardize sampling- and laboratory conditions, minimizing risk of bias and in to control statistical analyses for potential confounders. Patients were overall on stable medication during the study, minimizing a potential effect of medication on mRNA levels. The study protocol was approved by the Committee on Health Research Ethics of the Capital Region of Denmark (protocol no. H-4-2010-006). All participants provided written informed consent.

**Results:** Laboratory analysis is ongoing. Results will be presented at the ISBD 2015 conference. **Conclusions:** State-related changes in gene expression may point to markers of disease activity, while trait-related alterations could indicate vulnerability pathways. Identification of novel genes may inform on pathways involved in bipolar disorder pathophysiology.

### Association of brain-derived neurotrophic factor (BDNF) Val66Met polymorphism with early-onset bipolar disorder

M Nassan<sup>a</sup>, P Croarkin<sup>a</sup>, J Luby<sup>b</sup>, M Veldic<sup>a</sup>, P Joshi<sup>c</sup>, S McElroy<sup>d</sup>, R Post<sup>e</sup>, J Walkup<sup>f</sup>, K Cercy<sup>g</sup>, J Geske<sup>g</sup>, K Wagner<sup>h</sup>, A Cuellar-Barboza<sup>i</sup>, L Casuto<sup>d</sup>, C Lavebratt<sup>j</sup>, M Schalling<sup>j</sup>, P. Jensen<sup>k</sup>, J Biernacka<sup>a</sup>, M Frye<sup>a</sup>

<sup>a</sup>Department of Psychiatry and Psychology, Mayo Clinic, Rochester, USA, <sup>b</sup>Department of Psychiatry, Washington University School of Medicine, St. Louis, USA, <sup>c</sup>Department of Psychiatry and Psychology, Department of Psychiatry and Behavioral Sciences, Children's National Medical Center, Washington District of Columbia, USA, <sup>d</sup>Psychiatry, Linder Center of HOPE, Mason, USA, <sup>e</sup>Psychiatry, Bipolar Collaborative Network, Bethesda, USA, <sup>f</sup>Psychiatry, Weil Cornell Medical College, New York, USA, <sup>g</sup>Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, USA, <sup>h</sup>Division of Biomedical Statistics and Informatics, Department of Psychiatry and Behavioral Sciences, The University of Texas Medical Branch, Galveston, USA, <sup>i</sup>Psychiatry, The University of Texas Medical Branch, Universidad Autónoma de Nuevo Leon, Nuevo Leon, Mexico, <sup>j</sup>Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, <sup>k</sup>Psychiatry, The REACH Institute, New York, USA

**Aims:** Brain-derived neurotrophic factor (BDNF) Val66Met (rs6265) functional polymorphism has been implicated in early-onset bipolar disorder. However, results of studies are inconsistent. We aimed to further explore this association.

**Methods:** DNA samples from the Treatment of Early Age Mania (TEAM) and Mayo Clinic Bipolar Disorder Biobank were investigated for association of rs6265 with early-onset bipolar disorder. Bipolar cases were classified as *early onset* with the definition of first manic or depressive episode at age  $\leq 19$  years (vs adult-onset cases at age  $> 19$  years). After quality control, 69 TEAM early-onset bipolar disorder cases, 732 Mayo Clinic bipolar disorder cases (261 early onset and 471 adult onset), and 776 control cases were included in the analysis of association, assessed with logistic regression assuming log-additive allele effects. Protocols and procedures were approved by the Mayo Clinic and TEAM study Institutional Review Boards. All participants provided informed consent.

**Results:** Comparison of TEAM cases with controls suggested association of early-onset bipolar disorder with the rs6265 minor allele

(odds ratio [OR], 1.55;  $p = 0.04$ ). Although comparison of early-onset adult bipolar disorder cases from Mayo Clinic vs controls was not statistically significant, the OR estimate indicated the same direction of effect (OR, 1.21;  $p = 0.19$ ). When the 2 early-onset TEAM and Mayo Clinic Bipolar Disorder Biobank groups were combined and compared with the control group, the association of the minor allele rs6265 was statistically significant (OR, 1.35;  $p = 0.03$ ).

**Conclusions:** These preliminary analyses of a relatively small sample with early-onset bipolar disorder are suggestive that functional variation in BDNF is implicated in bipolar disorder risk and may have a more significant role in early-onset expression of the disorder.

### Comparison of cholesterol and other biological variables between bipolar depressive inpatients with and without current suicide attempt

E Nieto, L Plans, A Gómez, I Ibañez, M Gallardo

Psychiatry, Althaia Xarxa Assistencial de Manresa, Manresa, Spain

**Aims:** To determine whether there are significant differences in cholesterol and other biological blood parameters between bipolar depressive inpatients with and without current suicide attempt.

**Methods:** 1. Patients: We selected all patients admitted to our hospitalization unit between 2009 and 2013 diagnosed according to DSM IV of Bipolar I or Bipolar II disorder with depressive episode. 2. Methods: The next day of admission a blood test determining the levels of glucose, cholesterol, HDL-cholesterol, triglycerides, total protein, albumin, T4 and TSH, was performed in all these patients. 3. Statistical analysis: Using Student's *t*-test we compared the levels of different biological variables between bipolar depressives with current (immediately previous at Hospitalization) suicide attempt ( $N = 34$ ) and those without current suicide attempt ( $N = 136$ ).

**Results:** Between depressed bipolar inpatients with and without current suicide attempt significant differences were found in age ( $p < 0.015$ , mean of 43.5 vs 49.6 years respectively). No significant differences were found in gender (73, 5% women vs 66.9% women respectively). No significant differences were found in percentage of patients treated with lithium (20.6% vs 31.6% respectively) bipolar depressives with current suicide attempt differed significantly from the others in that they had significantly lower levels of protein (mean of 6.19 vs 6.48  $p < 0.03$ ) and albumin (mean of 3.52 vs 3.76  $p < 0.006$ ). There were no significant differences between bipolar depressive with and without current suicide attempt in levels of cholesterol (mean of 191 vs 195), glucose, HDL-cholesterol, triglycerides, T4 and TSH. We conducted a multinomial logistic regression analysis including the existence of current suicide attempt as the dependent variable. As independent factors we included sex and as covariates the age and albumin and protein levels. After this analysis only a significantly lower levels of albumin ( $p < 0.027$ ) and a lower age ( $p < 0.005$ ) remained significantly associated with presence of current suicide attempt in bipolar depressive inpatients.

**Conclusion:** Bipolar depressed inpatients with current suicide attempt are significantly younger and have significantly lower levels of albumin than those without current suicide attempt.

## Childhood IQ and manic features in young adulthood: birth cohort study

DJ Smith<sup>a</sup>, J Anderson<sup>a</sup>, S Zammit<sup>b</sup>, TD Meyer<sup>c</sup>, J Pell<sup>a</sup>, D Mackay<sup>a</sup>

<sup>a</sup>Institute of Health and Wellbeing Mental Health, University of Glasgow, Glasgow, United Kingdom, <sup>b</sup>MRC Centre for Neuropsychiatric Genetics, Cardiff University, Cardiff, United Kingdom, <sup>c</sup>Department of Psychiatry and Behavioral Sciences, University of Texas, Houston, USA

**Objective:** Biographical studies and more recent empirical studies have identified that intellectual ability and creativity may be associated with risk of developing bipolar disorder. Within a large birth cohort, we aimed to assess whether childhood IQ (including both verbal IQ and performance IQ) at age eight was predictive of lifetime features of mania assessed in young adulthood (ages 22–23). We hypothesized that verbal IQ might be a specific marker for the later development of manic features.

**Methods:** We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a large UK birth cohort, to test for an association between measures of childhood IQ at age eight and lifetime manic features assessed at age 22–23 years ( $n = 2,401$ ). An ordinary least squares (OLS) linear regression model was used, with normal childhood IQ (range 90–109) as the referent group. We adjusted analyses for confounding factors, including sex, ethnicity, handedness, maternal social class at recruitment, maternal age, maternal history of depression and maternal education.

**Results:** There was an overall positive association between IQ score assessed at age eight and mean scores for lifetime manic features assessed at age 22/23, which persisted after adjusting for confounding factors. This association was most pronounced for verbal IQ but was also in evidence for performance IQ and full-scale IQ. Findings were also consistent for imputed data analyses and the association occurred for both males and females.

**Conclusions:** Childhood IQ was positively associated with a dimensional measure of lifetime manic features assessed during young adulthood. A higher score for verbal IQ in childhood may represent a marker of risk for the later development of bipolar disorder. This finding has implications for future genetic studies of the interface between intelligence, creativity and bipolar disorder and may help to inform early intervention approaches to bipolar disorder.

## Impact of individual-family psychoeducational psychotherapy (IF-PEP) and omega3 fatty acids on children with bipolar disorder-not otherwise specified or cyclothymic disorder

LE Arnold<sup>a</sup>, AT Vesco<sup>b</sup>, AS Young Ryan<sup>a</sup>, A Seidenfeld<sup>c</sup>, H Wolfson<sup>a</sup>, WP Gardner<sup>d</sup>, M Fristad<sup>a</sup>

<sup>a</sup>Psychiatry and Behavioral Health Division of Child & Adolescent Psychiatry, The Ohio State University, Columbus, USA,

<sup>b</sup>Psychology, The Ohio State University, Columbus, USA,

<sup>c</sup>Psychiatry and Behavioral Health Division of Child and Adolescent Psychiatry, The Ohio State University, Columbus, USA, <sup>d</sup>Research Institute, Children's Hospital of Eastern Ontario, Ottawa, Canada

**Aims:** Determine the impact of individual-family psychoeducational psychotherapy (IF-PEP) and omega3 fatty acids (Ω3) on clinical outcomes for children aged 7–14 with bipolar disorder not otherwise specified (BP-NOS) or cyclothymic disorder (CYC).

**Methods:** Twenty-three children completed comprehensive screen and baseline assessments then were randomized to IF-PEP or active monitoring (AM) AND Ω3 or placebo (PBO), resulting in 4 treatment groups. The two Ω3 groups received two capsules of 500 mg Ω3 (350 mg EPA; 50 mg DHA; 100 other Ω3) twice daily for a total daily dose of 2000 mg Ω3 (1400 mg EPA; 200 mg DHA; 400 other Ω3). The two PBO groups received capsules twice daily matched for odor and appearance. Families in IF-PEP were

offered up to 24 therapy sessions (half for the child with the parent joining at the beginning and end; half for the parent); AM families received feedback after the baseline assessment regarding the child's diagnosis. Referrals were made for all families to coordinate end-of-study care. Follow-up assessments occurred at weeks 2, 4, 6, 9 and 12 (end of study). Blood draws, physical exams and dietary monitoring occurred at baseline and week 12.

**Results:** Children receiving IF-PEP and Ω3 were significantly improved at week 12 compared to those receiving AM and PBO (Kiddie Depression Rating Scale [KDRS],  $p = 0.05$ ;  $d = 0.79$ ). Children receiving Ω3 and AM were nominally more improved at week 12 compared to those receiving PBO and AM ( $d = 0.38$ ). When children receiving PEP vs AM (regardless of medication condition) were compared, children who received PEP showed greater improvement in depressive symptoms (KDRS:  $p = 0.036$ ,  $d = 0.59$ ). When children receiving Ω3 vs PBO (regardless of psychotherapy condition) were compared, the nominal advantage of Ω3 was nonsignificant (KDRS:  $d = 0.19$ ). Side effects were mild; nausea, diarrhea and decreased appetite were more common for children receiving Ω3 relative to PBO ( $p < 0.05$ ). Side-effect severity (on a 0–6 scale, with 1–2 being mild) ranged from 0.4 to 1.2 for the Ω3 group.

**Conclusions:** No evidence-based treatment guidelines currently exist for children with BP-NOS/CYC. These pilot results suggest IF-PEP in combination with Ω3 may ameliorate mood severity, particularly for depressive symptoms.

## Tick-borne infections and pediatric bipolar disorder

R Greenberg

Psychiatry, Medical Arts Psychotherapy Associates PA, Summit, USA

**Background/Aim:** A growing body of evidence suggests that infectious triggers and subsequent inflammatory responses may play important roles in several health conditions, including psychiatric illness. This study explored possible links between exposure to tick-borne pathogens and pediatric bipolar disorder.

**Methods:** A retrospective case series of 17 bipolar youth from a single Northeast US practice was used to examine rates of exposure to tick-borne pathogens. Bipolar diagnoses were based on DSM-IV TR criteria using information from parent questionnaires, clinical interviews with parents and children, and school reports. Patients provided specimens between February 2013 and December 2014 to measure exposure to tick-borne pathogens, including *Borrelia burgdorferi* (Lyme Disease), *Babesia*, *Bartonella*, *Mycoplasma Pneumoniae*, *Anaplasma*, and *Ehrlichia*. Lyme testing was performed using ELISA and Western Blot IgG/IgM; *Babesia* and *Bartonella* were ascertained by IgG/IgM titers and fluorescent in-situ hybridization (FISH) tests; other pathogens were tested using IgG/IgM titers. Testing was performed at Lab Corp, Mayo Medical, and/or Igenex Laboratories. Diagnosis of tick-borne illness was based on clinician evaluation of symptoms, physical examination, and laboratory results. Descriptive statistics were used to summarize the data.

**Results:** The sample had Bipolar I ( $n = 10$ ) or Bipolar II ( $n = 7$ ) disorders; average age at diagnosis was 7.2 years (range 5–12). Eighty-two percent were male. Serological evidence of exposure to one or more tick-borne pathogens was found in 14 of the 17 (82%) patients. The most common pathogens were: *Babesia* ( $n = 9$ ), *Mycoplasma Pneumoniae* ( $n = 7$ ), *Bartonella* ( $N = 4$ ), and *Lyme* ( $n = 3$ ). Twelve of the 14 serologically positive patients completed clinical evaluation. Eighty-three percent of those evaluated were diagnosed with tick-borne illnesses.

**Caveats:** This research needs to be extended to evaluate tick-borne illness exposure in bipolar cases vs. matched controls without psy-



chiatric disease using standardized serological testing. Results require replication in broader populations and geographic regions. Prospective data will ultimately be needed to establish causality and identify potential mechanisms.

**Conclusions:** The high rate of tick-borne illness in pediatric bipolar patients observed in this case series is provocative. If confirmed, this association may suggest gene-environment interactions and could have implications for the prevention and treatment of pediatric bipolar disorder.

### Elevated levels of oxidative stress, inflammation and sub-clinical vascular impairment among adolescents with bipolar disorder

J Hatch<sup>a</sup>, G Scola<sup>b</sup>, O Olowoyeye<sup>c</sup>, A Andreazza<sup>b</sup>, A Moody<sup>c</sup>, B Goldstein<sup>a</sup>

<sup>a</sup>Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada,

<sup>b</sup>Psychiatry, Centre for Addiction and Mental Health, Toronto,

Canada, <sup>c</sup>Medical Imaging, University of Toronto, Toronto, Canada

**Aims:** Bipolar disorder (BD) is characterized by substantial burden of hypo/manic and depressive symptoms and by premature and excessive mortality from cardiovascular disease (CVD). Characterizing biomarkers of BD is pertinent to understanding the increased CVD risk and disease progression. Inflammation and oxidative stress are key potential biomarkers.

**Methods:** 60 adolescents (13–19 years old), with no CVD (40 adolescents with BD, and 20 controls) were recruited. Diagnoses were determined using semi-structured interviews (K-SADS-Present and Lifetime Version). Standard procedures were used for ultrasound measurements of carotid intima media thickness (cIMT) and flow-mediated dilation (FMD). Serum levels of inflammation and oxidative stress were determined using ELISA. Non-parametric analyses (Kruskal–Wallis and Mann–Whitney *U* tests) were performed using SPSS 22.

**Results:** cIMT and FMD were not significantly different between groups. Lipid hydroperoxides (mean<sub>controls</sub> = 6.4, SD = 3.6, mean<sub>BD</sub> = 10.5, SD = 4.9;  $\chi^2(3) = 8.8$ ,  $p = 0.03$ ), Interleukin (IL) 1-alpha (mean<sub>controls</sub> = 247.2, SD = 175.3, mean<sub>BD</sub> = 463.1, SD = 253.9;  $\chi^2(3) = 10.1$ ,  $p = 0.018$ ) and IL-6 (mean<sub>controls</sub> = 4.9, SD = 6.4, mean<sub>BD</sub> = 8.9, SD = 7.7;  $\chi^2(3) = 15.1$ ,  $p = 0.002$ ), but not 4-hydroxynonenal, were significantly greater in the BD group compared to controls. Notably, lipid hydroperoxides are greater in BD I than BDII, which are both greater than BDNOS and controls ( $\chi^2(3) = 8.8$ ,  $p = 0.03$ ).

**Conclusion:** Adolescents with BD have significantly greater levels of oxidative stress and inflammation, compared to healthy controls. Oxidative stress and inflammation should be investigated further as biomarkers of BD, which may sub-serve the BD-CVD link.

### Bipolar disorder subtypes in an Australian sample of children and adolescents: rating scale data at time of first service presentation

SJ Hirneth<sup>a</sup>, PL Hazell<sup>a</sup>, TL Hanstock<sup>b</sup>, TJ Lewin<sup>c</sup>

<sup>a</sup>Discipline of Psychiatry, University of Sydney, Sydney, Australia,

<sup>b</sup>School of Psychology, University of Newcastle, Newcastle,

Australia, <sup>c</sup>Centre for Translational Neuroscience and Mental Health, University of Newcastle and Hunter New England Mental Health Services, Newcastle, Australia

**Aims:** To investigate clinical characteristics of clients with bipolar I disorder (BP-I), bipolar II disorder (BP-II) and bipolar disorder not otherwise specified (BP-NOS) recruited from The Bipolar Program (TBP), a community mental health clinic in Newcastle, Australia specialising in assessing and treating children and adolescents with bipolar disorder (BD).

**Methods:** Systematic assessment data (client demographics, standardised symptom rating scales, and psychosocial functioning measures) were obtained for clients meeting criteria for BD ( $n = 88$ ; 63 female) aged 8–18 years ( $M = 14.8 \pm 2.5$ ).

**Results:** All BD subtypes had high levels of psychopathology, with overall scores in the clinical range for child behaviour checklist (CBCL) total problems for parent-report (PR) ( $M = 72.6 \pm 9.5$ ) and youth self-report (YSR) ( $M = 70.6 \pm 9.8$ ). BD-NOS participants scored significantly higher ( $M = 74.7 \pm 6.9$ ) on CBCL-PR total problems compared to BD-II ( $M = 67.2 \pm 11.4$ ,  $p = 0.004$ ) but not compared to BD-I ( $M = 71.6 \pm 9.8$ , n.s.). BD-NOS had higher levels of CBCL-PR internalising problems ( $M = 74.04 \pm 9.3$ ) compared to BD-I ( $M = 68.7 \pm 10.0$ ,  $p = 0.032$ ) and BD-II ( $M = 67.4 \pm 10.2$ ,  $p = 0.029$ ). Participants across all BD subtypes scored in the moderately elevated range on Beck Youth Inventory subscales for Anxiety ( $M = 63.3 \pm 13.2$ ), Depression ( $M = 67.3 \pm 13.4$ ), Anger ( $M = 64.5 \pm 10.5$ ) and Disruptive Behaviour ( $M = 63.4 \pm 13.5$ ). Consistent with rating scale scores, participants had low scores on Global Assessment of Functioning ( $M = 53.4 \pm 9.8$ ) and had high rates of self-harming / suicidal gestures (69.3%), suicidal ideation (73.9%) and psychotic symptoms (35.2%).

**Conclusions:** All BD groups reported high levels of psychopathology overall, scoring at clinically significant levels across many symptom domains, with associated high levels of functional impairment, self-harm/suicidality and psychosis. BD-NOS participants reported the highest levels of overall symptomatology and internalising problems, highlighting the need for further research focus on this population. The current study is supported by a research grant from the Australian Rotary Health Research Fund – Mental Health Evaluation Grants Scheme.

### Psychopathology among offspring of parents with bipolar I disorder and community controls

JD Palacio, C Peña, AM Díaz, C Lopez Jaramillo

Psychiatry, Universidad de Antioquia, Medellín, Colombia

**Introduction:** Reports in the literature have shown that Bipolar Offspring's (BO) present a wide range of psychopathology. Comparison studies between BO and Parent Control Offspring's (PCO) have allowed to identifying specific psychopathological features in this risk group.

**Objective:** To compare the psychopathological characteristics between BO's group and PCO's group using the Kiddie-SADS and the Diagnostic Interview for Psychiatric Disorder (DIGS).

**Methods:** A descriptive-correlational, cross-sectional comparative study was performed with 127 BO and 150 PCO, (6–30 years old). Subjects were evaluated with Spanish validated diagnostic instruments (K-SADS and DIGS). The sample was collected in from the “Paisa” genetic isolated, in Colombia.

**Results:** The group of BO showed higher frequencies of bipolar disorder (prevalence ratio [OR] = 17.70; confidence interval [CI] 95%, 1.02 to 306.83), substance use disorder (OR = 9.52, 95% CI 2.93 to 30.90), oppositional defiant disorder (OR = 4.10, 95% CI 1.70 to 9.89), posttraumatic stress disorder (OR = 3.90, 95% CI 1.30 to 11.66), alcohol use disorder (OR = 3.84, 95% CI 1.28 to 11.48), attention deficit/hyperactivity disorder (OR = 2.26, 95% CI 1.37 to 3.75) and major depressive disorder (OR = 2.25, 95% CI 1.13 to 4.50). Regarding subthreshold symptoms, major differences were found in bipolar disorder (OR = 20.08, 95% CI, 2.71 to 148.80), agoraphobia/panic disorder (OR = 27.56, 95% CI, 1.64–463.13), and conduct disorder (OR = 2.50, 95% CI 1.44 to 4.33).

**Conclusion:** These findings confirm previous reports in the literature, which have shown that BO have higher risk for developing affective and non-affective disorders than control subjects, and also for presenting subthreshold symptoms of any psychiatric disorder.



**References:** Birmaher, B., et al. (2009). Lifetime Psychiatric Disorders in School-aged Bipolar Offspring. *AGP*, 66(3), 287–296. Singh, M. K., et al. (2007). Psychopathology in children of bipolar parents. *JAD*, 102(1–3), 131–6. Petresco, S., et al. (2009). Psychopathology in offspring of bipolar women from a Brazil. *Rev Bras Psiqu.*, 31(53), 240–246.

## Factors associated with obstetrical complications among adolescents with bipolar disorder

G O' Hagan, A Scavone, V Timmins

Psychiatry Centre for Youth Bipolar Disorder, Sunnybrook Research Institute, Toronto, Canada

**Aims:** Exposure to obstetrical complications (OCs) has been found to be etiologically significant in schizophrenia. Research into OCs and bipolar disorder (BD) however, has produced mixed findings, with small sample sizes, in mainly adult populations. This study compares the prevalence of OCs among adolescents with vs. without BD, and further examines the correlates of OCs among adolescents with BD.

**Methods:** One hundred and twelve adolescents, age 13–19 years, with a BD diagnosis ( $16.5 \pm 1.5$  years,  $N = 112$ , 67.0% female) and 60 controls ( $15.5 \pm 1.8$  years,  $N = 60$ , 46.8% female) were recruited from the Centre for Youth Bipolar Disorder (CYBD), a tertiary sub-specialty clinic at Sunnybrook Health Sciences Centre, Toronto. Data was extracted from CYBD research registries. Research ethics approval was obtained and participants and parents provided written informed consent prior to study commencement. Diagnoses were assessed using the KSADS-PL. OCs were assessed by administering the Child and Adolescent Health Screening Report to care-givers. Chi-square analyses and independent samples t-tests were employed to examine demographic and clinical correlates of OCs.

**Results:** There was no significance difference between BD adolescents and controls in relation to exposure to OCs (39.3% vs. 33.3%,  $\chi^2 = 0.592$ ,  $p = 0.441$ ). Among adolescents with BD, presence vs. absence of OCs was associated with: BD II subtype (56.8% vs. 30.9%,  $\chi^2 = 7.425$ ,  $p = 0.006$ ), ADHD (38.6% vs. 19.1%,  $\chi^2 = 5.190$ ,  $p = 0.023$ ), substance dependence (34.1% vs. 16.2%,  $\chi^2 = 4.810$ ,  $p = 0.028$ ), and with family history of depression (88.6% vs. 72.1%,  $\chi^2 = 4.360$ ,  $p = 0.037$ ), hypomania (34.1% vs. 16.2%,  $\chi^2 = 4.810$ ,  $p = 0.028$ ) and schizophrenia (18.2% vs. 4.4%,  $\chi^2 = 5.719$ ,  $p = 0.017$ ).

**Conclusions:** This preliminary study identifies several clinical correlates of OCs among adolescents with BD. Higher rates of familial depression, hypomania, and schizophrenia among BD adolescents with OCs provide tentative support for a diathesis-stress model (family psychiatric history  $\times$  OC) of early-onset BD in a subset of subjects. Future studies are warranted that include larger samples, OC severity ratings, and examination of the differential illness course and/or treatment response among BD adolescents with vs. without OCs.

## Transdiagnostic levels of parent- and youth-reported sleep problems in outpatient adolescents

M Ong<sup>a</sup>, E Youngstrom<sup>a</sup>, A Van Meter<sup>b</sup>, S Salcedo<sup>a</sup>, T Halverson<sup>a</sup>, J Youngstrom<sup>a</sup>, R Findling<sup>c</sup>

<sup>a</sup>Psychology, University of North Carolina at Chapel Hill, Chapel Hill, USA, <sup>b</sup>Psychology, Yeshiva University Ferkauf Graduate School of Psychology, Bronx, USA, <sup>c</sup>Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, USA

**Aims:** Sleep disturbances are associated with multiple psychiatric diagnoses among adults (Breslau, Roth, Rosenthal, & Andreski,

1996) and youth (Alfano, Ginsburg, & Kingery, 2007). The presence of sleep problems correlates with a wide range of health outcomes, including mood disorders, attention problems, and, to a lesser extent, other behavioral disorders (Aubrecht, Jenkins, & Nelson, 2014; Landgraf, McCarthy, & Welsh, 2014). This study used linear regressions to investigate parent and child report of sleep problems in youth with mood disorder diagnoses using rationally derived sleep scales from two well-established measures of behavior.

**Methods:** Participants (age 5–18) were youth and their caregivers in a consecutive case series recruited from a combination of a community mental health center and university medical facility as part of a larger project (R01 MH066647, PI: EAY). Sleep problems were measured via the parent and child-reported General Behavior Inventory (GBI; Depue et al., 1981), Achenbach Child Behavior Checklist (CBCL), and Youth Self Report (YSR; Achenbach & Rescorla, 2001). In this study, youth were grouped based on presence of either DSM-IV bipolar spectrum disorder (BSD), attention-deficit hyperactivity disorder (ADHD), major depressive disorder (MDD), oppositional defiant disorder (ODD), or conduct disorder (CD), each coded as present/absent to allow for comorbidity.

**Results:** Using caregiver-reported GBI, hierarchical regressions indicated that BSD ( $B = 3.7$ ), MDD ( $B = 2.8$ ) and ADHD ( $B = 1.2$ ) status incrementally predicted sleep problems ( $ps < 0.0005$ ), but ODD and CD did not. Conversely, using youth-reported GBI, MDD ( $B = 1.5$ ) status incrementally predicted sleep problems ( $p < 0.05$ ), but BSD, ODD, ADHD and CD did not. Using caregiver reported CBCL, hierarchical regressions indicated that BSD ( $B = 1.2$ ), ADHD ( $B = 0.50$ ), CD ( $B = 0.76$ ) and MDD ( $B = 1.2$ ) status incrementally predicted sleep problems (BSD & MDD:  $p < 0.005$ ; ADHD & CD:  $p < 0.05$ ), but ODD did not. Conversely, using youth report (YSR), BSD ( $B = 0.77$ ) status predicted sleep problems ( $p < 0.05$ ), but not ADHD, ODD, CD and MDD.

**Conclusions:** Sleep problems were associated with multiple psychiatric diagnoses. Bipolar disorder, major depression, and ADHD showed the largest incremental effects after accounting for comorbidity. We replicated findings across two widely used instruments, and also across caregiver and youth report, indicating these are robust results.

## Preliminary findings regarding the impact of CACNA1C rs1006737 bipolar disorder susceptibility gene on hippocampal and amygdala volume in adolescents

X Qu<sup>a</sup>, A Scavone<sup>a</sup>, B MacIntosh<sup>b</sup>, D Korczak<sup>c</sup>, J Kennedy<sup>d</sup>, B Goldstein<sup>a</sup>

<sup>a</sup>Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada, <sup>b</sup>Heart and Stroke Foundation Centre for Stroke Recovery, Sunnybrook Research Institute, Toronto, Canada, <sup>c</sup>Psychiatry, Hospital for Sick Children, Toronto, Canada, <sup>d</sup>Neuroscience Research, Centre for Addiction and Mental Health, Toronto, Canada

**Background:** Recently, a single nucleotide polymorphism (SNP) in a calcium gene (CACNA1C rs1006737) has been associated with BD in multiple genome wide association studies. Among adults, CACNA1C rs1006737 risk allele carriers (AG/AA) have demonstrated structural differences in amygdala and hippocampus when compared to non-carriers (GG). Small amygdala volume is a highly replicated finding amongst youth with BD. No prior studies have examined the association between CACNA1C and neuroimaging phenotypes among youth.

**Methods:** Twenty-nine adolescents (13–21 years) were enrolled (16 control + 13 bipolar disorder [BD]). Genotypes were determined

from saliva samples. T1 structural MRI was performed in a 3T Phillips scanner. FreeSurfer was used to determine subcortical volumes in 4 *a priori* regions of interest (bilateral hippocampus and amygdala). Risk allele carriers (AA/AG) were grouped together.

**Results:** Genotyping revealed 12 risk allele carriers (3 AA/9 AG) and 17 non-carriers (GG). Risk allele carriers demonstrated significantly greater bilateral hippocampal volume when compared to non-carriers (left hippocampus:  $p = 0.04$ , right hippocampus:  $p = 0.004$ ). No significant difference was observed between groups (AA/AG vs. GG) in amygdala volumes (left amygdala:  $p = 0.36$ , right amygdala:  $p = 0.47$ ). 15 additional participants are anticipated by the time of presentation.

**Conclusions:** These preliminary findings suggest that the CACNA1C risk allele may be associated with increased hippocampal volume in adolescents. Larger studies are warranted in order to parse the relationship of BD diagnosis and of genotype with brain structure among adolescents.

### Parent versus youth reported sleep patterns as correlates of sleep, mood, and quality of life

S Salcedo<sup>a</sup>, G Perez Algorta<sup>b</sup>, EA Youngstrom<sup>a</sup>, TF Halverson<sup>a</sup>, M Ong<sup>a</sup>, RL Findling<sup>c</sup>

<sup>a</sup>Psychology, University of North Carolina at Chapel Hill, Chapel Hill, USA, <sup>b</sup>Faculty of Health and Medicine, Lancaster University, Lancaster, United Kingdom, <sup>c</sup>Psychiatry, Johns Hopkins University and Kennedy Krieger Institute, Baltimore, USA

**Aims:** This study examined the reliability and agreement in parent versus youth reports of sleep problems, as well as how these scales relate to mood, global functioning, comorbidity, and quality of life.

**Methods:** This secondary analysis utilized data from a multi-site study examining the prevalence and clinical characteristics of bipolar disorders in youths (ages 4–18;  $N = 828$ ) who sought treatment for various behavioral and emotional problems in outpatient mental health centers (Youngstrom et al., 2005). Youths and their caregivers completed the K-SADS interview to examine the presence of DSM-IV diagnoses and global functioning (Kaufman et al., 1997). The sleep scales (parent and youth reports) from the General Behavior Inventory (GBI; Meyers & Youngstrom, 2008) and the Achenbach System of Empirically-Based Assessment (CBCL & YSR; Gregory & O'Connor, 2002) measured sleep problems. The K-SADS Mania Rating Scale (KMRS) and Depression Rating Scale (KDRS; Axelson et al., 2003) assessed manic and depressive symptom severity, and the parent report KINDL measured quality of life (Ravens-Sieberger & Bullinger, 1998). Youths ages 11+ completed self-report questionnaires. Cronbach's alphas quantified the internal consistency of the CBCL and GBI sleep scales, and Pearson's correlations measured the relationships between the parent and youth-reported sleep scales, KMRS, KDRS, and KINDL total scores.

**Results:** The GBI sleep scales showed higher internal consistency (Parent  $\alpha = 0.82$ ; Youth  $\alpha = 0.80$ ) than the six CBCL sleep items (Parent  $\alpha = 0.58$ ; Youth  $\alpha = 0.75$ ). Parent and youth-report GBI sleep scores were significantly correlated,  $r = 0.24$ ,  $p < 0.001$ , as were CBCL scores between parent and youth reports,  $r = 0.31$ ,  $p < 0.001$ . Both parent and youth report GBI and CBCL sleep scores were positively correlated with KMRS ( $r_s = 0.18$  to  $0.38$ ;  $p_s < 0.001$ ) and KDRS scores ( $r_s = 0.22$  to  $0.42$ ;  $p_s < 0.001$ ) and negatively correlated with KINDL scores ( $r_s = -0.12$  to  $-0.43$ ;  $p_s < 0.01$ ).

**Conclusions:** Youths' report of sleep problems is moderately correlated with caregiver endorsement of youths' sleep problems. Furthermore, increased sleep problems per either informant correspond to increased manic and depressive symptom severity and lower quality of life. Further research should examine how cross-informant reports of sleep change across age and determi-

nants underlying the relationships between adolescent sleep problems and mood and functioning in bipolar disorder.

### Prevalence and correlates of cigarette smoking among Canadian adolescents with bipolar disorder

A Scavone, V Timmins, B Swampillai, BI Goldstein

Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada

**Aims:** Little is known about smoking among adolescents with bipolar disorder (BP). We therefore sought to examine the prevalence and correlates of smoking among Canadian adolescents with BP.

**Methods:** Participants were adolescents ages 13–19 years, including 114 with BP-I, -II, or -NOS ( $16.28 \pm 1.51$  years, 65.8% female) and 61 psychiatrically healthy controls (HC;  $15.62 \pm 1.88$  years, 47.5% female). Ethics review board approval was obtained and all participants and their parents provided written informed consent prior to study procedures. Diagnoses and smoking status were determined via the KSADS-PL. The Life Problems Inventory (LPI) measured mood dysregulation and the Children's Global Assessment Scale measured global functioning. A Safety Assessment Form outlined lifetime aggression and suicidality. Demographic and clinical correlates of cigarette smoking were examined using Chi-square analyses and independent samples t-tests. Variables associated with smoking ( $p < 0.1$ ) among BP participants were included in logistic regression analyses.

**Results:** Fifty-four BP participants (47.4%) and three HC participants (4.9%) reported ever having tried a cigarette. Controlling for age, sex, and race, BP participants continued to be significantly more likely to be smokers vs. HCs ( $p < 0.001$ ). Among BP participants, smoking was associated with a greater prevalence of comorbid conduct disorder, oppositional defiant disorder, substance use disorder, lifetime homicidal ideations, non-suicidal self-injurious behaviours, impulsivity, emotional dysregulation, and total LPI scores. Smokers were significantly less likely to have used a second generation antipsychotic, lithium, and stimulants. Those that smoked reported poorer global functioning at intake and the year prior to intake, as well as greater depression scores at intake. After regression analyses, smoking was significantly associated with depression scores at intake ( $p = 0.02$ ) and trait impulsivity ( $p < 0.001$ ).

**Conclusions:** These findings from a Canadian sample replicate previous U.S. findings. Dimensional lability was prominent among adolescents that smoked, including anger and disinhibition, suggesting that preventative strategies targeting lability may be beneficial in this group of adolescents. Participants that smoked reported more severe depression and worse global functioning, suggesting a worse course of BP illness among adolescents that smoke. Given the high rates of smoking and challenges of smoking cessation in this population, preventive interventions and early cessation strategies are warranted.

### Characterizing exercise-induced feelings after a single bout of exercise in healthy adolescents and adolescents with bipolar disorder

M Subramaniapillai<sup>a</sup>, M Duncan<sup>a</sup>, K Arbour-Nicotopoulos<sup>a</sup>, B Goldstein<sup>a</sup>, B MacIntosh<sup>c</sup>, D Korczak<sup>d</sup>, A Scavone<sup>b</sup>, G Faulkner<sup>a</sup>

<sup>a</sup>Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Canada, <sup>b</sup>Department of Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada, <sup>c</sup>Canadian Partnership for Stroke Recovery, Sunnybrook Health Sciences Centre, Toronto, Canada, <sup>d</sup>Department of Psychiatry, Sick Kids Hospital, Toronto, Canada

Exercise may be a practical, non-pharmacological strategy for symptom and health management for adolescents with bipolar dis-

order (BD). The purpose of this study was to determine if adolescents with BD experience changes in exercise-induced feelings from an acute bout of exercise similar to their healthy peer group. Thirty-two adolescents with BD (Age (SD) = 16.91 (1.4), 14 males and 18 females) and twenty-six healthy adolescents (Age (SD) = 15.73 (1.8), 13 males and 13 females) participated. Participants completed the Exercise-Induced Feeling Inventory (EFI) before and after a 20-minute bout of moderate intensity exercise (heart rate goal of 60–80% of the age estimated maximum ( $220 - 0.7 \times \text{age}$ )) on a cycle ergometer. Repeated-Measures ANOVA was conducted on the four main EFI categories (Positive Engagement, Revitalization, Physical Exhaustion and Tranquility). No significant between-group differences emerged among the four categories between adolescents with BD and the control group ( $p > 0.05$ ). However, there was a significant effect of time for Positive Engagement, Revitalization, and Tranquility. Further post-hoc paired t-tests revealed a significant improvement in Revitalization post-exercise compared to baseline testing within the BD group (Mean Change (SD) = 0.37 (0.77),  $p = 0.01$ ). Among the healthy control group, there was a significant improvement in Revitalization (Mean Change (SD) = 0.40 (0.77),  $p = 0.01$ ) and Positive Engagement (Mean Change (SD) = 0.32 (0.45),  $p = 0.01$ ). Notably, greater individual variability was seen in the BD group on the EFI compared to the control group. In conclusion, the lack of between group differences in the two groups may indicate that adolescents with BD experience similar exercise-induced emotional benefits as their healthy peers. Exercise may be used by adolescents with BD to regulate their mood-related symptoms. Future experimental research is needed to confirm this and to identify the possible implications for exercise adherence in this population.

### Bipolar and recurrent depression: chronobiological aspect

**S Andruskevicius, V Meiner, G Vindasiene**

*Republican Vilnius Psychiatric Hospital, Vilnius, Lithuania*

**Objective:** To study circadian rhythms of the parameters of spectral analysis of heart rate variability in the treatment of bipolar and recurrent depression.

**Methods:** 52 patients have been studied (F 31.3–31.4, F 33.0–33.2). Mean age  $45.7 \pm 11.2$  years. The patients have been divided into two groups: group 1 consisted of 23 patients with recurrent depressive disorder, and group 2 included 29 patients with bipolar affective disorder. Assessing the autonomous regulation of the cardiovascular system the spectral analysis of heart rate variability was applied. The power spectrum density (PSD) of LF (low frequency) and HF (high frequency) range was established. The patients were examined at 1 a.m., 7 a.m., 1 p.m., 7 p.m. prior to the beginning of treatment, at the end of the first week of treatment and at discharge from the hospital. In order to determine the daily curve of changes in the indices under investigation the control group (15 mentally healthy people, mean age  $44.9 \pm 9.3$  years) was examined at 1 a.m., 4 a.m., 7 a.m., 9 a.m., 11 a.m., 1 p.m., 3 p.m., 4 p.m., 5 p.m., 7 p.m. in summer.

**Results:** Prior to the therapy de-synchronization of the circadian rhythms of the parameters of spectral analysis of heart rate variability and the “sleep-wake” rhythm has been observed. This manifested itself in the shift of the phase of the circadian rhythms of the parameters under study towards the earlier time of the day. Prior to the beginning of treatment de-synchronization of the circadian rhythms under study was more pronounced in the night/morning hours in the group 1, and in the day/evening hours in the group 2. This difference persisted in the course of positive therapeutic dynamics.

**Conclusions:** Depressive patients diagnosed as bipolar affective disorder had more pronounced circadian disorders in daytime and in the evening.

**References:** 1. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task force of the European society of cardiology and the North American society of pacing and electrophysiology. *Eur Heart J.* 1996; 17: 354–81.

### Association of Clock, ARNTI, and NPAS2 gene polymorphisms and seasonal variations in mood and behavior

**H Kim<sup>a</sup>, H Lee<sup>a</sup>, C Cho<sup>a</sup>, S Kang<sup>b</sup>, H Yoon<sup>a</sup>, Y Park<sup>c</sup>, S Lee<sup>c</sup>, J Moon<sup>a</sup>, H Song<sup>a</sup>, E Lee<sup>d</sup>, L Kim<sup>a</sup>**

<sup>a</sup>Psychiatry, Korea University College of Medicine, Seoul, Korea,

<sup>b</sup>Psychiatry, Gachon University College of Medicine, Incheon, Korea,

<sup>c</sup>Psychiatry, Inje University College of Medicine, Ilsan, Korea,

<sup>d</sup>Preventive Medicine, Korea University College of Medicine, Seoul, Korea

Seasonal affective disorder (SAD) is a condition of seasonal mood changes characterized by recurrent depression in autumn or winter that spontaneously remits in spring or summer. Evidence has suggested that circadian gene variants contribute to the pathogenesis of SAD. In this study, we investigated polymorphisms in the *CLOCK*, *ARNTL*, and *NPAS2* genes in relation to seasonal variation in 507 healthy young adults. Seasonal variations were assessed with the Seasonality Pattern Assessment Questionnaire. The prevalence of SAD was 12.0% (winter-type 9.3%, summer-type 2.8%). No significant difference was found between the groups in the genotype distribution of *ARNTL* rs2278749 and *NPAS2* rs2305160. The T allele of *CLOCK* rs1801260 was significantly more frequent in seasonals (SAD + subsyndromal SAD) compared with non-seasonals ( $p = 0.020$ , odds ratio = 1.89, 95% confidence interval = 1.09–3.27). Global seasonality score was significantly different among genotypes of *CLOCK* rs1801260 but not among genotypes of *ARNTL* rs2278749 and *NPAS2* rs2305160. However, statistical difference was observed in the body weight and appetite subscales among genotypes of *ARNTL* rs2278749 and in the body weight subscale among genotypes of *NPAS2* rs2305160. There was synergistic interaction between *CLOCK* rs1801260 and *ARNTL* rs2278749 on seasonality. To our knowledge, this study is the first to reveal an association between the *CLOCK* gene and seasonal variations in mood and behavior in the Korean population. Although we cannot confirm previous findings of an association between SAD and the *ARNTL* and *NPAS2* genes, these genes may influence seasonal variations through metabolic factors such as body weight and appetite. The interaction of the *CLOCK* and *ARNTL* genes contributes to susceptibility for SAD.

### Late life bipolar disorders evolving into frontotemporal dementia mimic

**A Dols<sup>a</sup>, YAL Pijnenburg<sup>b</sup>, K WA<sup>b</sup>, FT Gossink<sup>a</sup>, ML Stek<sup>a</sup>**

<sup>a</sup>Old Age Psychiatry GGZinGeest, VU University Medical Center, Amsterdam, Netherlands, <sup>b</sup>Neurology, VU University Medical Center, Amsterdam, Netherlands

**Aims:** Although bipolar disorder has been understood classically as a cyclic disease with full recovery between mood episodes, in the last decade evidence has accumulated supporting progressive features. The pathophysiological changes observed in bipolar disorder (brain structural alterations, cognitive deficits, immunological deregulation) converge to a model of accelerated aging. The clinical picture of advanced or end stage bipolar disorder will be heterogeneous with possible deficits in cognition and behaviour.

**Methods:** From our neuropsychiatric outpatient clinic, we describe 4 cases with a long standing history of bipolar disorder who gradually developed a clinical picture including apathy, disinhibition, loss of empathy, stereotypical behavior and compulsiveness fulfilling the criteria for possible behavioral variant of Frontotemporal Dementia (bvFTD) (Rascovsky et al 2011).

**Results:** All cases were diagnosed with bipolar I disorder at least 10 years before the onset of the current symptoms. Two cases had an early onset of disease. All cases presented with cognitive complaints (memory or disorientation) with hardly any burden. Their spouses, on the contrary, observed a radical change in behavior that was very different from previous mood episodes. Symptoms of apathy (sitting on the couch all day), disinhibition (masturbating in public, excessive eating or smoking), loss of empathy, stereotypical behavior (urge of excessive cleaning) and compulsiveness (living by a rigid daily routine) were very severe and interfering with social functioning. Symptoms could not be accounted for by recent mood swings, psychotic episodes, or switches of medication. In all cases, at least 3 years of follow-up yielded no progression. Repeated neuroimaging was within normal limits. CSF biomarker studies were not suggestive of underlying neurodegenerative pathology. C9orf status was negative in all cases.

**Conclusions:** Combinations of apathy, disinhibition, loss of empathy, stereotypical behavior and compulsiveness, fitting with a diagnosis of possible bvFTD, may be present in later stages of bipolar disorder. A neurodegenerative nature seems unlikely based on repeated normal neuroimaging and the absence of rapid clinical progression. Pathophysiologically, functional involvement of the frontal-subcortical networks in bipolar disorder might play a role.

### Glycogen synthase kinase-3 $\beta$ and mood states in bipolar disorder – a longitudinal case–control study

**A Jacoby, K Munkholm, M Vinberg, LV Kessing**

*Psychiatric Center Copenhagen, Copenhagen, Denmark*

**Objectives:** Glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) is a promising new biomarker involved in mood states in bipolar disorder. Furthermore strong evidence suggest that lithium down regulates GSK-3 $\beta$  indicating that GSK-3 $\beta$  may play a central role in the mechanism of action of lithium and hence in the treatment of bipolar disorder. The present study aims to investigate the possible association between GSK-3 $\beta$  activity and mood alterations in patients with bipolar disorder and to compare the activity of GSK-3 $\beta$  in bipolar patients in remission with the activity of GSK-3 $\beta$  in healthy individuals. We hypothesize that the activity of GSK-3 $\beta$  in peripheral blood varies with mood states in bipolar patients and that the activity of GSK-3 $\beta$  is slightly increased in the remitted state of individuals with bipolar disorder compared with healthy control individuals.

**Methods:** The study has included a total of 60 patients with bipolar disorder aged 18–60 years, hospitalised with a manic or mixed episode at a psychiatric ward in the Capital Region of Denmark. 35 healthy age- and gender matched control individuals were recruited via the Blood Bank of the Capital Region of Denmark. Patients were followed prospectively during the hospitalisation period and in a 6–12 months period following discharge from hospital with assessment during mood episodes and remitted phases. Blood testing and ratings were performed during the initial manic or mixed episode, during remission and during subsequent depressive, manic, hypomanic and mixed episodes. In healthy control individuals, the same tests were performed at the initial interview and after three months.

**Results:** The study is ongoing, the follow-up was terminated December 2014 and the first results will be presented at the conference.

**Perspectives:** This is the first study using a prospective design assessing GSK-3 $\beta$  in manic, hypomanic, mixed, depressive and

remitted states of patients with bipolar disorder, in this way taking intra-individual as well as inter-individual differences into account. The study is expected to contribute to the understanding of the neurobiological mechanisms underlying bipolar disorder and potentially to new treatment strategies and assessment of treatment response.

### Differences between bipolar patients with or without rapid-cycling feature in clinical features, comorbidity, and family history

**E Kim, T Ha, S Lee, T Chung, S Jang, H Lee, Y Park, J Kim, K Ha**

*Psychiatry, Seoul National University Bundang Hospital,*

*Seong-nam si Gyeonggi-do, Korea*

Rapid-cycling in bipolar disorder (BD) was often related to a worse course. This study was designed to investigate the differential effects of the Rapid-Cycling feature on clinical variables in patients with bipolar disorders. We collected data from 251 bipolar patients who had visited the Mood Disorders Clinic of Seoul National University Bundang Hospital. The subjects consisted of 96 patients with BD I, 126 patients with BD II and 29 patients with BD NOS who met the DSM-IV criteria. Group mean differences in demographic and clinical variables were compared between patients with and without rapid-cycling feature. Rapid-cycling feature was associated with BD II, atypical depression and left handedness. In acute depressive phase, HAMD and BDRS scores of patients with rapid-cycling feature were higher than patients without rapid-cycling feature. However, there were no differences between groups in the onset age, illness duration, substance misuse and history of suicide attempt. Our results suggest that patients with rapid-cycling feature experience severer depressive symptoms and need more clinical attention.

### Translational implications of ACTH-driven mania

**R Morgan, N Thusius, S Tye, M Frye**

*Psychiatry and Psychology, Mayo Clinic, Rochester, USA*

**Aims:** Excess cortisol, adrenocorticotrophic hormone (ACTH), or corticotropin releasing hormone (CRH), as seen in Cushing's syndrome, can be associated with a number of psychiatric symptoms, most notably depression, and has been investigated as a potential marker for relapse to depression. Despite evidence that CRH stimulation and other similar hypothalamic-pituitary-adrenal (HPA) axis challenges can predict manic relapse, syndromal mania and/or psychosis have been less frequently observed and systematically studied.

**Methods:** We present 2 cases of mania associated with an ectopic ACTH secreting tumor. We additionally present data from animal studies investigating the role of ACTH in mood dysregulation. In these preclinical studies, male Sprague-Dawley rats (~250 g) were administered either 100  $\mu$ g ACTH-(1-24) or saline (0.9%) for 14 days. Using Fast Scan Cyclic Voltammetry we assessed effects on nucleus accumbens dopamine efflux. Drawing on data from this clinical and preclinical work, we analyze these cases through the lens of HPA axis – dopamine network interactions in an effort to develop hypotheses concerning varied patient responses to aberrant HPA signalling.

**Results:** Case I is a 56-year-old woman who presented de novo with two similar manic episodes characterized by thought disorganization, hyperreligiosity, hypersexuality, bizarre behavior, and hypokalemia, hyperglycemia, and hypertension. An ACTH-producing pulmonary carcinoid tumor was surgically removed with complete resolution of manic symptoms and successful mood stabilizing treatment taper. Case II is a 61-year-old woman with an 18-year history of bipolar disorder, type I. Her most recent episode of

mania was qualitatively different than prior episodes characterized by disorganization, paranoia, bizarre behavior, hypokalemia, hyperglycemia, and hypertension. She was found to have an ACTH-producing small-cell lung carcinoma and died 11 months after diagnosis. In our animal studies, ACTH treatment induced substantial dysregulation of mesoaccumbens dopamine neurotransmission. Specifically, transient dopamine efflux was attenuated relative to controls, but hypersensitive to increasing intensity of electrical stimulation.

**Conclusions:** Based on these preclinical data, we hypothesize that ACTH-mediated hypersensitivity of the dopamine system may contribute to the development of psychosis and mania in vulnerable individuals, including the presented cases. Further research exploring the mechanisms through which ACTH can induce mania is needed to better understand the pathophysiology mediating this state.

### Case report: successful remission of a manic episode due to a short-time coercive intervention in a 75-years old patient

**T Veselinovic, A Kirner, M Paulzen, G Gründer**

*Psychiatry Psychotherapy and Psychosomatics, RWTH Aachen University, Aachen, Germany*

The symptoms of bipolar disorders are often severe and difficult to control. Especially challenging is the treatment of non-compliant patients. In a significant part of those patients coercive measures will be unavoidable. The decision concerning the choice of the right substance and the appropriate dosage but also the duration of the coercive treatment is not always easy to make. We report a case of a 75-years old female patient who was involuntary admitted to an acute psychiatric ward with pronounced manic (YMRS 52) and psychotic (PANSS 106) symptomatology. Because of acute self-endangerment and aggressive behavior a mechanical restrain and coercive medication were necessary. During the first four days after admission the patient received 5 mg diazepam and in the sum 22.5 mg olanzapine i.m. Due to the sufficient decline of the acute endangerment, continuing coercive measures were not justifiable. The patient rejected further medication intake. On day 7 we observed a considerable symptoms improvement (YMRS 37, PANSS 91) and the symptom decline proceeded until day 35 (YMRS 13, PANSS 36), when the patient left the hospital, persistently refusing any medication intake. Nevertheless, she agreed in the establishment of several psychosocial supporting measures. The exploration of the illness history revealed at least 33 years illness duration with 5 hospitalizations. Twice a manic syndrome with psychotic symptoms was the admission reason. In both cases the symptoms improved sufficiently after a short time antipsychotic treatment. During the major part of her life the patient refused the medication intake. We present this case as a interesting example of a successful short-time treatment of a acute bipolar mania in a patient who experienced just a few disease episodes, which were heavy but rapidly controllable. In each psychotic episode, only a few doses of effective antipsychotics were sufficient to reduce the symptoms. Possibly we could consider a shortening of the intensive treatment time in some bipolar patients, taking into account they individual illness course. This could be especially a meaningful approach in patients requiring coercive interventions, so that here a stronger effort could be put into establishment of psychosocial supportive measures.

### Moodswings 2.0: an online intervention for bipolar disorder

**S Lauder<sup>a</sup>, V Cosgrove<sup>b</sup>, E Gliddon<sup>c</sup>, D Grimm<sup>b</sup>, S Dodd<sup>c</sup>, T Suppes<sup>b</sup>, M Berk<sup>c</sup>**

*<sup>a</sup>Department of Psychiatry, University of Melbourne, Parkville, Australia, <sup>b</sup>Bipolar and Depression Research Program, VA Palo Alto Health Care System, Palo Alto, USA, <sup>c</sup>IMPACT Strategic Research Centre, Deakin University, Geelong, Australia*

**Aims:** The primary aim of this study is to assess if the three components of the MoodSwings 2.0 online self-help program for bipolar disorder have an additive benefit on improvement in depression and mania scores across 12 months. Exploratory aims include health services utilization, evidence of relapse (time to intervention), functionality, quality of life and medication adherence.

**Methods:** Participants diagnosed with bipolar I, II or NOS are being recruited internationally, with a total recruitment target of 300. As of January 1 2015, 247 participants had been randomized. MoodSwings 2.0 is a 3-arm randomized parallel group stepped design. Participants are randomized to discussion board only, discussion plus psychoeducation, or discussion, psychoeducation and interactive tools. One discussion board is allocated per arm. Psychoeducation material includes five core learning modules, plus four quarterly booster modules. Interactive tools include mood monitoring, problem solving, and illness profiles, identifying triggers and warning signs. Psychoeducation and interactive material is released bi-weekly across a 10 week period, followed by booster psychoeducation material released at 3, 6, 9 and 12 months. Participants have access to the program for 12 months. Outcomes are assessed quarterly via blind rated phone interview, as well as online self-report. This project has received approval from the Barwon Health Human Research Ethics Committee and the Department of Veterans Affairs Institutional Review Board. All participants complete informed consent prior to randomization.

**Conclusions:** Online enhancements in MoodSwings 2.0, as well as a larger sample size including an attention control (discussion board only arm), may lead to a greater understanding of these interventions as an adjunctive treatment tool. This research is supported by the National Institute of Mental Health (R34MH091384 and R34MH091284).

### Psychosis and previous episodes does not mediate neurocognitive impairment at first treatment bipolar I disorder

**C Demmo, I Melle, C Simonsen, L Kvitland, OA Andreassen, T Vik Lagerberg, T Ueland**

*Psychosis Research Unit, Oslo University Hospital, Oslo, Norway*

**Aims:** Recent studies have shown neurocognitive impairment to be present in first treatment bipolar I patients. However, explanatory factors for this impairment have received little attention. We hypothesized that psychosis and previous episodes could be mediating factors in neurocognitive functioning in first treatment bipolar I disorder and evaluated the impact of these features by comparing their presence in bipolar I disorder with first treatment schizophrenia and healthy controls.

**Methods:** A total of 303 participants, 101 with a broad DSM-IV schizophrenia spectrum disorder, 101 with bipolar I disorder and 101 healthy controls (mean age: 29.9 years, gender: 43.6% males), were recruited to the Thematically Organized Psychosis (TOP) Study. Diagnoses were obtained with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) and neurocognitive functioning was assessed with a comprehensive test battery. The groups were matched on sex and age before comparing neurocognitive functioning using multivariate analysis of variance (MANOVA). All participants received a complete oral description of the

study prior to giving written informed consent. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data inspectorate.

**Results:** The first treatment bipolar I group performed in between the first treatment schizophrenia group and healthy controls on all measures. Compared to healthy controls they showed impaired neurocognitive functioning across measures of verbal learning and memory, executive functioning, processing speed, attention and working memory. Within the first treatment bipolar I group, no differences in neurocognitive functioning were observed in psychotic versus non-psychotic patients, or between those having experienced previous episodes versus first episode patients.

**Conclusion:** The first treatment bipolar I group showed a pattern of neurocognitive performance falling between patients with first treatment schizophrenia and healthy controls on all measures. This confirms previous findings indicating that neurocognitive dysfunction is present at the time of first treatment. This pattern of performance was not mediated by psychosis or previous episodes and accordingly does not explain the neurocognitive impairment in this group.

### Influence of cognitive reserve on neuropsychological deficits: findings from a five year longitudinal study of bipolar disorder

KH Hinrichs<sup>a</sup>, A Hayek<sup>a</sup>, B Pester<sup>a</sup>, K Angers<sup>a</sup>, Z Lai<sup>a</sup>, DF Marshall<sup>a</sup>, M Kamali<sup>a</sup>, SA Langenecker<sup>b</sup>, MG McInnis<sup>a</sup>, KA Ryan<sup>a</sup>

<sup>a</sup>Psychiatry, University of Michigan, Ann Arbor, USA, <sup>b</sup>Psychiatry, University of Illinois at Chicago, Chicago, USA

**Aims:** The theory of Cognitive Reserve (CR) asserts that individual characteristics such as premorbid IQ, education, and occupation have an impact on preservation or decline of cognitive abilities over time. While evidence for CR has been observed in neurological disorders, relatively little research has focused on CR in relation to neuropsychiatric disorders. Prior research on the influence of CR variables on schizophrenia has shown that high IQ is associated with a decreased risk of developing schizophrenia, and better functional outcomes. Individuals with Bipolar Disorder (BP) tend to demonstrate reduced performances on neuropsychological measures, but it is unclear if these deficits are influenced by CR factors. Previous research in this area has yielded mixed results, with some support for IQ and education as moderating factors. The present study sought to examine the neurocognitive performances of individuals with BP over time and to determine if cognitive changes were associated with CR variables.

**Methods:** Fifty-two euthymic individuals diagnosed with BP and 25 healthy controls (HC) were recruited as part of the Prechter Longitudinal Study of Bipolar Disorder at the University of Michigan. Participants underwent a comprehensive clinical/diagnostic evaluation and they were administered a battery of neuropsychological tests at two time points, five years apart. Eight neurocognitive factor scores were calculated from neuropsychological test data (capturing executive functioning, attention, memory, fine motor dexterity, and emotion processing).

**Results:** Results of two sample t-test analyses revealed that the BP group obtained lower scores on measures of fine motor dexterity and processing speed/interference resolution (a subcategory of executive functioning) compared to HC at both time points. Further, results of multiple variable regression models showed that each increase of 10 IQ points was associated with improvement in auditory memory at year 5 by 0.16 ( $p = 0.03$ ). Conversely, each increase of 10 IQ points was associated with a decline in conceptual reasoning ability at year 5 by 0.21 ( $p = 0.01$ ). Education and occupational status were not related to neurocognitive impairment.

**Conclusions:** These results suggest that CR factors may influence changes in neurocognitive ability in BP over time, but further

research is necessary to determine other influences on neurocognitive impairment in BP.

### A preliminary evaluation of the efficacy of repetitive transcranial magnetic stimulation in treating a depressive episode in bipolar II disorder

S Hu<sup>a</sup>, J Lai<sup>b</sup>, D Xu<sup>c</sup>, H Qi<sup>a</sup>, BS Peterson<sup>d</sup>, Y Xu<sup>a</sup>

<sup>a</sup>Department of Psychiatry, First Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China, <sup>b</sup>Zhejiang University, School of Medicine, Hangzhou, China, <sup>c</sup>Department of Psychiatry, Columbia University & New York State Psychiatric Institute, New York, USA, <sup>d</sup>Institute of the Developing Mind, Children's Hospital Los Angeles University of Southern California, Los Angeles, USA

**Aims:** The efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) in treating a depressive episode of Bipolar Disorder is unclear. The aim of this study was to explore the clinical and cognitive responses following rTMS administration, combined with quetiapine, in patients with Bipolar II Disorder during a depressive episode.

**Methods:** Thirty-eight patients identified with depressive episode in Bipolar II Disorder were enrolled, and randomly assigned into three groups: (1) left high-frequency rTMS ( $n = 13$ ), (2) right low-frequency rTMS ( $n = 12$ ), and (3) sham stimulation ( $n = 13$ ). All three groups were given quetiapine concomitantly. Clinical efficacy was evaluated using the 17-item Hamilton Depression Rating Scale (HDRS-17) and the Montgomery-Asberg Depression Rating Scale (MADRS). Cognitive functioning was assessed with the Wisconsin Card Sorting Test (WCST), Stroop Word-Color Interference Test (Stroop), Continuous Performance Test (CPT), and Trail Making Test (TMT).

**Results:** No significant difference was found among three groups in HDRS-17 or MADRS scores at any of the evaluation time-points, or in response or remission rates. Further analyses on factor scores of HDRS-17 revealed that the left high-frequency group scored lower than the right low-frequency group in anxiety/somatization and cognition factors after the 2-week treatment, whereas the sleep factor score in the sham-stimulation group was significantly lower than in the left high-frequency group ( $p < 0.05$ ).

**Conclusions:** Both left high-frequency and right low-frequency stimulation were not superior to quetiapine monotherapy in improving either depressive symptoms or cognitive performance for patients in a Bipolar II depressive episode.

### Are risk related decision making and reward sensitivity different between bipolar and unipolar depression?

R Yeni Elbay<sup>a</sup>, S Kesebir<sup>b</sup>

<sup>a</sup>Psychiatry, Erenkoy Mental and Neurological Disease Training and Research Hospital, Istanbul, Turkey, <sup>b</sup>NPIstanbul Neuropsychiatry Hospital, Üsküdar University, Istanbul, Turkey

**Objective:** The aim of this study is to research if unipolar and bipolar depression cases become distinct or not in terms of risk related decision making and reward sensitivity.

**Methods:** Present study included 25 patients with bipolar disorder and 25 patients with unipolar disorder in depressive episode who admitted to our outpatients clinic with given informed consent, diagnosed according to DSM-IVTR and 25 healthy subjects. Iowa Gambling Task (IGT), Hamilton Depression Rating Scale (HDRS), Snaith-Hamilton Pleasure Scale (SHPS), and Barratt Impulsiveness Scale (BIS) are administered to all patients in depressive episode and controls.

**Results:** IGT scores were lower in bipolar depression than unipolar depression and healthy controls. HDRS and SHPS scores were similar in bipolar and unipolar depression but higher than healthy controls. BIS scores were higher in bipolar depression than unipolar depression, and they were higher in unipolar depression than healthy controls. There is a weak and reverse correlation between pre-intuition scores of IGT and BIS scores in bipolar depression. It is similar in unipolar depression. In addition, mentioned relationship progresses also at intuition phase. A weak correlation between scores of SHPS and comprehension phase of IGT is also detected.

**Conclusion:** Risk related decision making and reward sensitivity are more disturbed in bipolar depression than unipolar. This disturbance is also observed in different phases of risk related decision making.

### Are ERP and cognitive performance related and differentiated in different phase of bipolar disorder?

E Kaymak Koca<sup>a</sup>, S Kesebir<sup>b</sup>

<sup>a</sup>Psychiatry, Erenkoy Mental and Neurological Disease Training and Research Hospital, Istanbul, Turkey, <sup>b</sup>Psychiatry NPIstanbul Hospital, Üsküdar University, Istanbul, Turkey

**Objective:** The aim of this study is to investigate the event-related evoked potentials (ERP) in depressive, manic and remission phase of bipolar disorder and evaluate with Frontal Assessment Battery (FAB) and Stroop test.

**Methods:** 20 depressive, 20 manic and 20 euthymic patients (at least 8 week) diagnosed with Bipolar Disorder according to DSM-IVTR and 20 healthy controls recruited in the study. HRSR, YMRS, FAB and Stroop test were used. N100, N200, P200 and P300 were recorded using "oddball two tones discrimination work" method. Evoked potentials records were taken with three channel (Fz, Pz, Cz).

**Results:** FAB performance was M=D<R<HC. Stroop IF was M>D>R>HC, total time was D>M=R=HC. N200 was D<M=R=HC and P300 was M=D=R>HC. No correlation was found between cognitive performance and ERP values in mania, however YMRS was related with Stroop IF and P300. In depressive phase, there was a strong and inverse correlation between FAB and N100. FAB and N100 were related with HDRS. In remission, there was a strong and inverse correlation FAB and N200, Stroop performance and N100. In healthy controls, FAB was related with P300, Stroop performance was related with N200, P200 and P300.

**Conclusion:** FAB and Stroop test scores and ERP values were different in depressive, manic and remission phase of illness than healthy subjects. Beside the relation between cognitive test scores and ERP, severity of mood disorder was also related with cognitive test scores and ERP values.

### The relationship between objective and subjective cognitive functioning and quality of life in bipolar disorder and healthy volunteers

S Mackala, S Ahn, C Hidiröglu, E Michalak, L Yatham, I Torres

Psychiatry Mood Disorders Clinic, University of British Columbia, Vancouver, Canada

**Aims:** Individuals with bipolar disorder (BD) can show cognitive impairments, which have the potential to significantly impair one's functioning and well-being. There are mixed findings on the relationship between subjective and objective cognitive functioning in BD, and less is known about the influence of cognitive complaints on quality of life (QOL). The purpose of this study was to evaluate objective and subjective cognitive functioning in BD and their association with QOL.

**Methods:** Outpatients with BD (n = 75) and healthy volunteers (n = 41) completed subjective (Cognitive Failures Questionnaire; CFQ) and objective cognitive measures (verbal learning and executive functioning). Group differences on objective and subjective measures between patients and healthy volunteers were assessed through independent-sample t-tests. Significant predictors of QoL (Quality of Life in Bipolar Disorder questionnaire) were assessed through multiple hierarchical regression.

**Results:** There were no significant differences on verbal learning (t (114) = -1.71) and executive functioning (t (114) = -0.58) between outpatients and healthy volunteers; however, patients reported greater cognitive complaints (CFQ; t (112) = 6.71) and lower QOL (t (114) = -5.44). When euthymic outpatients (n = 53) and healthy volunteers were compared (to account for the potential effect of depression), outpatients still reported greater cognitive complaints and poorer QOL than healthy volunteers. The differences for CFQ (t (90) = 4.71) and QOL (t (92) = -3.64) represented large-sized effects (CFQ d = -0.96; QOL d = 0.75). After accounting for symptoms of depression (R<sup>2</sup> = 0.54, p < 0.001) and objective cognitive performance (ΔR<sup>2</sup> = 0.01, p > 0.05), subjective cognitive complaints further predicted QoL (ΔR<sup>2</sup> = 0.04, p < .01) in outpatients.

**Conclusion:** Objective cognitive measures failed to predict QOL, which may be due to the fact that outpatients performed comparable to healthy controls in this sample. This suggests that poorer cognitive functioning may predict poorer QOL only if objective performance is significantly impaired. Despite comparable objective cognitive functioning between outpatients and healthy volunteers, patients showed more subjective cognitive complaints (CFQ) which predicted poorer QOL, even after controlling for mood symptoms. Overall, findings suggest that subjective cognitive assessments may help to guide treatment strategies. Further research should aim to determine whether change in patient's subjective cognitive appraisals may improve patient QOL.

### Increased cognitive decline in elderly patients with bipolar disorder: a six-year prospective follow-up study

P Nunes, LP Coelho, RB Ladeira, I Aprahamian, B Lafer, OV Forlenza

Psychiatry, Psychiatry University of Sao Paulo Medical School, Sao Paulo, Brazil

**Aims:** Bipolar disorder (BD) is associated with a higher prevalence of cognitive deficits, especially in executive function, attention and memory, which seem to be present even in euthymic or unmedicated patients. Elderly BD patients have also an increased risk for dementia. There are few prospective studies of cognitive functions in elderly bipolars and the characteristics of its possible decline are yet to be determined. The aim of this study is to evaluate prospectively during 6 years cognitive functions of non-demented euthymic elderly BD patients and compare with age matched healthy controls.

**Method:** 20 BD I or II patients (DSM-IV criteria), and 24 healthy control subjects (with similar age and no mood disorder) had 60 years of age or more and no dementia (CDR < 1.0). Cognition was assessed at baseline, 3 and 6 years later with the Mini-Mental State Examination (MMSE) and the Cambridge Examination for Mental Disorders in the Elderly semi-structured interview, which yields scores for the Mini-Mental State Examination (MMSE) (maximum 30 points) and the Cambridge Cognitive Test (CAMCOG) (maximum 107 points). BD patients had to be euthymic (Hamilton and Young Scales Scores <7) at the time of cognitive evaluation.

**Results:** In BD group, there was no significant decrease in scores from MMSE and CAMCOG after 3-year follow-up. However, within 6 years, a reduction in MMSE (from 25.7 ± 2.9 to

$22.8 \pm 4.0$ ,  $p < 0.001$ ) and in CAMCOG (from  $84.7 \pm 13.5$  to  $76.7 \pm 14.8$ ,  $p = 0.001$ ) was observed. Higher decline was found in the CAMCOG subsets orientation ( $p = 0.018$ ), comprehension language ( $p = 0.007$ ), short term memory ( $p = 0.003$ ), praxis ( $p = 0.006$ ) and abstraction ( $p = 0.027$ ). No cognitive decline was found in the healthy control group, even though they had higher schooling.

**Conclusions:** A greater cognitive decline was found in elderly patients with BD. These results are consistent with epidemiological cross-sectional studies in BD. The domains of greater decline are similar to the ones found in the most prevalent dementias such as of Alzheimer's type.

## Learning from positive and negative feedback in patients with bipolar-I disorder and their relatives

V Scholz, J Linke, B Kollmann, M Wessa

*Department of Psychology Faculty of Clinical Psychology and Neuropsychology, University Mainz, Mainz, Germany*

**Background:** Previous evidence show alterations in feedback-based learning processes in patients with bipolar-I disorder (BD-I), unaffected relatives and healthy individuals with a hypomanic temperament. However, until now, it remains unclear how exactly learning from positive and negative feedback is disrupted in patients and what implications might arise from this. Furthermore, the question remains whether certain motivational learning processes might be considered a risk factor for developing BD-I disorder.

**Methods:** In the present study we investigated euthymic BD-I patients, unaffected first-degree relatives (BD-REL) of BD-I patients and a group of healthy controls (HC). HC did not differ significantly from BD-I or BD-REL in age and all groups had approximately the same gender ratio. The experimental task used in this study involved a probabilistic selection task in which subjects had to learn to select one stimulus from different stimulus pairs based on positive and negative feedback, which they received for their choices. They were instructed to identify stimuli that were most likely to be rewarded with positive feedback while avoiding those with a higher likelihood of negative feedback.

**Results:** BD-I patients did not differ significantly from HC in their reaction to positive feedback but showed altered reactions towards negative feedback. They were less likely to adapt their stimulus choice after receiving negative feedback. BD-REL showed altered reactions to both positive and negative feedback that differed significantly from HC. More precisely, REL displayed a higher affinity to stick to a positively rewarded stimulus while failing to change their behavior in response to negative feedback they received.

**Discussion:** BD-I patients displayed an altered reaction pattern in response to negative feedback, possibly indicating that they include negative feedback to a lesser extent in their motivational choices. Meanwhile, positive feedback-processing of BD-I strongly resembled HC. This might be explained by the high percentage of patients taking lithium (48%), known to dampen response to positive feedback in unipolar depression. The fact that we could show altered feedback-processing in BD-I patients and first-degree relatives suggests that disrupted feedback-processing might be considered a risk factor for developing BD-I.

## Impaired spatial processing in bipolar disorder

A Tereszko<sup>a</sup>, AA Chrobak<sup>a</sup>, S Jezioro<sup>a</sup>, G Siwek<sup>a</sup>, K Siuda-Krzywicka<sup>b</sup>, A Arciszewska<sup>c</sup>, M Siwek<sup>c</sup>, D Dudek<sup>c</sup>

<sup>a</sup>Jagiellonian University Medical College, Students' Scientific Association of Affective Disorders, Kraków, Poland, <sup>b</sup>Université Pierre et Marie Curie, Ecole des Neurosciences a Paris, Paris, France, <sup>c</sup>Jagiellonian University Medical College, Department of Affective Disorders, Kraków, Poland

**Aim:** Bipolar Disorder (BD) patients exhibit mental deficits in periods between episodes of mania or depression, ie in euthymic state. Our goal is to expand the knowledge of specific areas of those dysfunctions – in this particular study, spatial processing.

**Method:** 31 BD patients in euthymia and 27 healthy controls performed a digital two-dimensional Mental Rotation task consisting of 64 trials. We used The Psychology Experiment Building Language (PEBL) Mental Rotation task. In this task, subjects were presented with either two identical figures or mirror images, rotated against one another in 8 angles, each differing by 45 degrees. They were asked to distinguish whether the figures were the same or different (mirror images). The number of correct answers and reaction times were measured.

**Results:** Patients with BD revealed significantly lower number of accurate responses ( $M = 42.94$ ;  $Mdn = 44$ ;  $SD = 11.16$ ) compared to healthy controls ( $M = 54.67$ ;  $Mdn = 57$ ;  $SD = 7.07$ ), regardless of the angle at which the figures were rotated relative to each other ( $p < 0.001$ ). Additionally, patients showed different pattern of response time depending on the angle of the pairs of figures. Response time of patients with BD was significantly longer in 5 out of 8 conditions compared to healthy controls ( $p < 0.05$ ). Groups did not differ in case of  $180^\circ$ ,  $135^\circ$  and  $-135^\circ$  angles.

**Conclusions:** Our results indicate that BD patients reveal mental rotation impairments, most noticeable in case of small angles. Difficulties with rotation of the figures mentally can be one sign of impaired spatial processing and can be easily assessed with mental rotation task given to the patient.

## Semantic or affective: which word characteristic impact the most the priming effect in hypomanic trait population? an ERP study

S Terrien<sup>a</sup>, P Gobin<sup>a</sup>, S Mathey<sup>b</sup>, C Besche-Richard<sup>a</sup>

<sup>a</sup>Laboratoire Cognition Santé et Socialisation, Université de Reims Champagne-Ardenne, Reims, France, <sup>b</sup>Lettres et Sciences Humaines Laboratoire de Psychologie Santé et Qualité de Vie, Université de Bordeaux, Bordeaux, France

**Aims:** There are few studies on semantic memory in bipolar disorders (BD) while thought and language disorders are common (Bora et al., 2010; Ivleva et al., 2012), suggesting semantic disturbances in this disease. Only two studies have been published on the semantic priming effects in BD: one behavioral (Andreou et al., 2013) and one in event-related potential (ERP) (Ryu et al., 2012) suggesting abnormal automatic semantic processing in manic patients. Many studies have been conducted on emotional processes in BD. In an emotional priming task with facial stimuli, Kim et al. (2010) showed that BD patients had impaired cognitive control on emotional processing rather than automatically spreading of activation of emotion. It will be interesting to dissociate affective and semantic processes in the same experimental task in a population who presents risk to develop bipolar disorder. To investigate this dissociation, we used a method inspired of a study conducted by Rossel and Nobre (2004) on healthy population: affective and semantic priming. Actually, there are no studies on the neurophysiologic processes mediating the processing of affective and semantic priming in population with hypomanic personality traits. The aim of this study is to explore affective and semantic priming processes in relation with the level of hypomanic traits in a general population.



**Methods:** Healthy participants will be evaluated with hypomanic personality scale (HPS). ERPs will be recorded during a primed lexical decision task on negative or positive target words presented in four experimental conditions: affective related pairs, semantic related pairs, affective and semantic related pairs, affective and semantic unrelated pairs. Each target word (e.g., contagion) was preceded by an affective related word (e.g., imprudent), by a semantic related word (e.g., transmission), by an affective and semantic related word (e.g., infection) or by an unrelated word (e.g., edge).

**Results:** We expect to observe that high hypomanic participants, compared with low hypomanic ones, will exhibit particularities on the modulation of amplitude of N400 and Late Positive Component.

**Conclusions:** The major discussion points will concern the modifications of ERP component modulation by semantic and affective integration as cognitive markers of a vulnerability to bipolar disorders.

### Affective lability is associated with alcohol- and cannabis use disorder in bipolar disorder

SR Aminoff<sup>a</sup>, TV Lagerberg<sup>a</sup>, M Aas<sup>a</sup>, T Bjella<sup>a</sup>, C Henry<sup>b</sup>, M Leboyer<sup>b</sup>, F Bellivier<sup>c</sup>, OA Andreassen<sup>a</sup>, I Melle<sup>a</sup>, B Etain<sup>b</sup>

<sup>a</sup>Division of mental health and addiction, Oslo University Hospital, Oslo, Norway, <sup>b</sup>Pôle de Psychiatrie, AP-HP Hôpital H. Mondor – A. Chenevier DHU Pepsy, Creteil, France, <sup>c</sup>Pôle Neurosciences, AP-HP GH Saint-Louis-Lariboisière-Fernand Widal, Paris, France

**Aims:** Patients with bipolar disorder (BD) report use of alcohol, cannabis and other substances to dampen core symptoms of the disorder, primarily depressive, but also manic symptoms. One possible core symptom in patients with BD is intraepisodic affective lability. In this study we investigated whether alcohol, cannabis and other substance use disorders are more common in BD patients who experience higher intraepisodic affective lability than in patients with lower degrees of such experiences. We also explored whether the experience of frequent emotional shifts between depression and hypomania (elation), depression and anxiety, and anger were related to different types of misuse.

**Methods:** A French and Norwegian sample of 390 patients with BD (mean±SD age: 41.6 ± 13.0; gender: 40% males; diagnosis: 75% bipolar I, 20% bipolar II, and 0.8% bipolar NOS, 4.2% information missing) was included. Affective lability was measured with the Affective Lability Scale (ALS; 18 item version), divided into total score and the three subscales 1) anger, 2) depression – elation and 3) depression- anxiety. Lifetime alcohol (19%), cannabis (14%) or other (6%) substance use disorders was assessed using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) or the Diagnostic Interview for Genetic Studies (DIGS).

**Results:** We found a significant correlation ( $r_s = 0.137$ ,  $p < 0.01$ ) between lifetime alcohol use disorders and increased ALS total score, as well as increased scores on the subscales anger, depression – elation, and depression- anxiety. Lifetime cannabis use disorder was significantly ( $r_s = 0.110$ ,  $p < 0.05$ ) associated with increased scores on the depression-elation subscale only. Use disorders involving other substances had no association with ALS.

**Conclusions:** Alcohol use disorder in patients with BD were significantly associated with increased affective lability as shown by higher scores on the ALS total score and all subscales. Cannabis use disorder was associated with subscale depressive-elation only. Future studies are needed to address the dynamics of this relationship.

### Stressful life events and associated illness morbidity in bipolar disorder: implications for future epigenetic quantification of disease burden

A Grzenda<sup>a</sup>, S McElroy<sup>b</sup>, J Geske<sup>c</sup>, M Veldic<sup>d</sup>, J Biernacka<sup>c</sup>, M Frye<sup>d</sup>

<sup>a</sup>Psychiatry & Psychology, Mayo Clinic, Rochester, USA,

<sup>b</sup>Department of Psychiatry, Lindner Center of HOPE, Mason,

USA, <sup>c</sup>Division of Biomedical Statistics and Informatics, Mayo

Clinic, Rochester, USA, <sup>d</sup>Psychiatry and Psychology, Mayo Clinic, Rochester, USA

**Aims:** Examine the relationship between the number and severity of self-reported stressful life events and associated illness morbidity features in patients with bipolar (BP) I or II disorder.

**Methods:** Data were aggregated from the 1,225 patients with SCID-confirmed diagnoses of bipolar I ( $n = 863$ ) or bipolar II ( $n = 362$ ) disorder currently enrolled in the Mayo Clinic Individualized Medicine Bipolar Biobank. A structured diagnostic interview and clinical questionnaire confirmed diagnosis and illness variables. A patient-completed questionnaire gathered demographic information and quantified the severity of positive and negative stressful life events during the first and last 12 months of BP illness. Multiple logistic and linear regression models were used to study the association of stress with illness morbidity features, including rapid cycling, psychosis, mood instability sum (e.g., mixed episodes, cycle acceleration, increased severity), co-morbid anxiety disorders, and substance use disorders.

**Results:** After adjustments for age and gender, the number of stress events within the first 12 months of BP illness was only significantly associated with anxiety disorders ( $OR = 1.035$ ,  $p = 0.0056$ ), whereas the number of stress events in the last 12 months of BP illness was significantly associated with rapid cycling ( $OR = 1.027$ ,  $p = 0.0173$ ), anxiety disorders ( $OR = 1.058$ ,  $p < 0.0001$ ), and substance abuse ( $OR = 1.035$ ,  $p = 0.0037$ ). Mean severity of stress events in the last 12 months of illness is significantly associated with rapid cycling ( $OR = 1.543$ ), anxiety disorders ( $OR = 1.44$ ), substance use disorders ( $OR = 1.175$ ), and mood instability ( $\beta = 0.390$ ) (all  $p$ -values  $< 0.0001$ ). Cumulative stress, defined as the total number of stress events in the first 12 and most recent 12 months of BP illness, was significantly associated with anxiety disorders ( $OR = 1.027$ ,  $p = 0.002$ ) and substance abuse disorders ( $OR = 1.015$ ,  $p = 0.0151$ ).

**Conclusions:** Both the number and severity of stressors at the onset and recent time of bipolar illness was associated with multiple illness co-morbidities well known to increase negative treatment outcomes. Delineation of positive versus negative stressful events with corresponding epigenetic quantification at critical gene loci may prove useful measures in studying disease susceptibility and progression as well as assist in the development of initial frameworks for treatment trial design.

### Metabolic syndrome and bipolar disorder: the role of childhood trauma

S Kesebir

Training and Research Psychiatry, Erenköy Mental and Neurological Disease Training and Research Hospital, Istanbul, Turkey

Studies for prevalence and causal relationship established that addressing comorbidities of mental illnesses with medical disease will be another revolution in psychiatry. Increasing number of evidence shows that there is a bidirectional connection between mood disorders and some medical diseases. Glucocorticoid/insulin signal mechanisms and immunoenflammatory effector systems are junction points that show pathophysiology between bipolar disorder and general medical situations susceptible to stress. A subgroup of

mood disorder patients are under risk of developing obesity and diabetes. Their habits and life styles, genetic predisposition and treatment options are parameters that define this subgroup. Medical disease in adults had a significant relationship to adverse life experiences in childhood. This illustrates that adverse experiences in childhood are related to adult disease by two basic etiologic mechanisms: (1) conventional risk factors that actually are compensatory behaviors, attempts at self-help through the use of agents and foods; and (2) the effects of chronic stress.

### Examining migraine in bipolar disorder

**S Knott<sup>a</sup>, I Jones<sup>a</sup>, L Jones<sup>b</sup>, K Gordon-Smith<sup>b</sup>, L Forty<sup>a</sup>, N Craddock<sup>a</sup>**

<sup>a</sup>*Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, United Kingdom*, <sup>b</sup>*Department of Psychiatry, University of Birmingham, Birmingham, United Kingdom*

**Aims:** Epidemiological and clinical studies demonstrate a high degree of comorbidity between bipolar disorder (BD) and migraine. Research also suggests that bipolar patients with comorbid migraine may experience a different clinical profile to those without; suggesting that comorbid migraine may represent a more homogeneous subtype of BD. We aimed to further evaluate these comorbid phenomena, by (1) identifying migraine prevalence in a large UK bipolar sample, (2) determining bipolar clinical characteristics differentiating individuals with BD, according to the presence or absence of comorbid migraine and (3) comparing bipolar characteristics between migraine subtypes, with and without aura.

**Methods:** The study utilised clinical data collected through the Bipolar Disorder Research Network; a large, well-defined sample of UK subjects (N = 1428) with a DSM-IV diagnosis of BD. Lifetime presence of migraine was assessed using a validated, self-report questionnaire and diagnosed according to International Headache Society criteria.

**Results:** Migraine prevalence was found at 19.4% (N = 277), with N = 153 meeting criteria for migraine with aura. A multivariate model revealed the characteristics that best predicted presence of migraine were: younger age (OR = 0.971,  $p = 0.0003$ ); being female (OR = 1.939,  $p = 0.008$ ); BPII diagnosis (OR = 1.745,  $p = 0.006$ ); higher number of depressive episodes (OR = 1.015,  $p = 0.011$ ); history of suicide attempt (OR = 1.546,  $p = 0.025$ ); and history of anxiety (OR = 1.623,  $p = 0.03$ ). Comparison of illness variables between migraine subtypes revealed the above associations were predominantly due to the individuals with migraine with aura (MA). The MA group experienced significantly more episodes of depression (12.1 vs. 9.5,  $p < .01$ ) and mania (7.5 vs. 5.1,  $p < .05$ ); and a higher rate of attempted suicide (66.7% vs. 53.3%,  $p < .027$ ), panic disorder (26.8% vs. 13.3%,  $p < .05$ ), and smoking (63.1% vs. 43.1%,  $p < .01$ ).

**Conclusions:** Results demonstrate an approximate two-fold increase in migraine prevalence in the BD sample, compared to the general population. Findings suggest differences in the clinical course of BD in individuals with comorbid migraine compared to those without this comorbidity and that these associations are driven by those with migraine with aura. Comorbid patients may represent a more aetiological homogeneous subgroup, which may be useful in genetic and other studies. Current work focuses on identifying potential genetic associations for the BD/migraine phenotype in a genome-wide association study.

### Cannabis use disorder is associated with greater illness severity in tobacco smoking patients with bipolar disorder

**T Lagerberg<sup>a</sup>, R Ickick<sup>b</sup>, OA Andreassen<sup>c</sup>, PA Ringen<sup>a</sup>, B Etain<sup>d</sup>, M Aas<sup>a</sup>, C Henry<sup>d</sup>, TD Bjella<sup>a</sup>, I. Melle<sup>c</sup>, F Bellivier<sup>b</sup>**

<sup>a</sup>*NORMENT KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, Norway*, <sup>b</sup>*GH Saint-Louis-Lariboisière-Fernand Widal, Inserm U1144, Paris, France*, <sup>c</sup>*NORMENT KG Jebsen Centre for Psychosis Research, University of Oslo Oslo University Hospital, Oslo, Norway*, <sup>d</sup>*AP-HP Hopitaux Universitaires Henri Mondor, Inserm U1144, Paris, France*

**Aims:** This study aimed to investigate whether tobacco smoking influences the relationship between cannabis use disorders (CUD) and greater illness severity in bipolar disorder (BD) such as earlier onsets, higher frequency of illness episodes, increased prevalence of mixed and psychotic episodes, and suicide attempts.

**Methods:** A large combined sample of French and Norwegian patients with BD I and II, recruited from in- and out treatment units was investigated (N = 1067). Diagnoses were based on DSM IV, and patients were interviewed for demographic and illness characteristics. Selecting patients with lifetime daily tobacco use (n = 642), the relationship between lifetime CUD and clinical expressions was investigated, controlling for potential confounders including earlier onsets and other substance use disorders.

**Results:** In bivariate analyses, CUD was significantly associated with an earlier onset of the BD, a higher frequency of manic episodes (in bipolar I disorder), depressive episodes and hospital stays per illness year, and a higher prevalence of psychotic episodes. After controlling for other potential confounders, the relationships with earlier onsets ( $B = -5.60$  95% CI =  $-7.65$  to  $-3.64$ ), increased risk for a high frequency of hospital stays (OR = 2.93, 95% CI: 1.85 to 4.64) and manic episodes in BD I (OR = 1.93, 95% CI: 1.15 to 3.23) remained statistically significant.

**Conclusion:** This is to our knowledge the first study to demonstrate that the relationship between CUD and greater illness severity in BD is not fully explained by tobacco smoking or other potential confounders. This implicates that cannabis use disorders in BD should be prevented and treated.

### Comorbid anxiety disorders in Canadians with bipolar disorder: prevalence, impact and psychological treatment

**MD Provencher<sup>a</sup>, LD Hawke<sup>b</sup>, S Parikh<sup>c</sup>**

<sup>a</sup>*Psychology, Université Laval, Quebec, Canada*, <sup>b</sup>*Psychology, Mood Disorders Association of Ontario, Toronto, Canada*, <sup>c</sup>*Psychiatry, University of Toronto, Toronto, Canada*

This presentation examines the impact of anxiety disorders (AD) comorbid to bipolar disorder (BD) in a large, nationally representative sample. The purpose is to describe the sociodemographic and clinical profiles of Canadians living with bipolar disorder and with or without comorbid anxiety disorders, to identify the characteristics uniquely associated with comorbid anxiety, and examine treatment patterns. Data from the Canadian Community Health Survey, conducted among 38,492 Canadians, was analyzed. Individuals meeting the criteria for bipolar disorder (N = 808) were compared based on the presence or absence of an assessed AD (social phobia, panic disorder, agoraphobia). Results show that individuals with BD and a comorbid AD fare worse in terms of BD relapses, suicidality, and sleep disturbance, and are more likely to be taking psychiatric medication. They have more impairment in their work and social functioning and rate their health and life satisfaction lower. Despite the greater severity, they are not receiving additional psychological treatment, they feel they are not receiving the treatment they need, and they report more barriers to

treatment. This study confirms the critical impact of comorbid anxiety on the course of bipolar disorder in a large, nationally representative sample and reveals that the psychological treatment needs of this population are not being met. I will conclude this presentation by reviewing psychological treatment options for comorbid AD with BD and present the results of a pilot study of CBT for comorbid GAD.

### Clinical differences between inpatients with bipolar disorder with and without comorbid PTSD

MK Reddy<sup>a</sup>, LM Weinstock<sup>b</sup>, IW Miller<sup>b</sup>, TD Meyer<sup>a</sup>, JC Soares<sup>a</sup>

<sup>a</sup>Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, Houston, USA,

<sup>b</sup>Department of Psychiatry and Human Behavior, Brown University and Butler Hospital, Providence, USA

There are elevated rates of posttraumatic stress disorder (PTSD) among patients with bipolar disorder (BD), according to data from epidemiological and clinical samples. However, little is known about the clinical correlates that may distinguish patients with comorbid PTSD and BD from those with BD alone. The present study sought to elucidate those differences and examined risk factors such as psychosis, history of suicide attempts, and comorbid personality disorders in predicting comorbid PTSD in a sample of 230 psychiatric inpatients. Results found that patients with comorbid PTSD and BD were significantly more likely to be female, to be depressed (vs. manic), to have a comorbid personality disorder, and to have a history of suicide attempt. Also, BD patients with PTSD were significantly less likely to present for their inpatient hospital stay with psychosis. These effects remained significant after controlling for mood episode polarity, suggesting that findings were not fully explained by the higher incidence of depression in the comorbid PTSD group. Patients with comorbid PTSD and BD appear to be a high risk population with need for enhanced monitoring of suicidality. These findings will be discussed in relation to theories of PTSD development and clinical implications will be presented.

### Medical comorbidity and acute medical health service utilization in late-life bipolar disorder: a comparison of lithium, valproate, and other pharmacotherapies

C Yu<sup>a</sup>, KI Shuman<sup>b</sup>, N Herrmann<sup>b</sup>, Z Harel<sup>c</sup>, HD Fischer<sup>d</sup>, K Fung<sup>e</sup>, A Gruneir<sup>d</sup>, S Rej<sup>b</sup>

<sup>a</sup>Psychiatry, McGill University, Montreal, Canada, <sup>b</sup>Psychiatry, University of Toronto, Toronto, Canada, <sup>c</sup>Nephrology, University of Toronto, Toronto, Canada, <sup>d</sup>Epidemiology, Institute for Clinical Evaluative Sciences, Toronto, Canada, <sup>e</sup>Statistics, Institute for Clinical Evaluative Sciences, Toronto, Canada

**Background:** Bipolar disorder is associated with high rates of medical comorbidity, particularly in late life. Little is known about medical health service utilization and potential effects of bipolar pharmacotherapy. We hypothesize that lithium use will not be associated with higher rates of medical hospitalization.

**Methods:** Population-based retrospective cohort study of 1,388 bipolar disorder patients aged  $\geq 66$ , discharged from a psychiatric hospitalization in Ontario, Canada between 2006 and 2012. Patients were divided into lithium users, valproate users, and non-lithium/non-valproate users. The main outcome was acute non-psychiatric, medical/surgical hospitalization during 1-year follow-up. Bivariate and Cox-regression analyses were performed.

**Results:** Patients had high rates of medical hospitalization (20%). However, lithium and valproate were not associated with shorter

times to medical hospitalization after controlling for age, sex, past medical hospitalization, and antipsychotic use. There were almost no differences between lithium, valproate, and non-lithium/non-valproate users in terms of reason for medical hospitalization, 1-year acute medical health utilization outcomes, and medical comorbidity rates.

**Conclusion:** Lithium and valproate use are not associated with higher rates of medical comorbidity or acute medical health care utilization in late-life bipolar disorder, which has high rates of acute medical health service utilization. A proactive approach may prevent medical service utilization in severe late-life bipolar disorder.

### Prevalence and impact of comorbid alcohol use disorder in 284 bipolar I and II patients: a prospective, naturalistic 4 year follow-up study

C Simhandl<sup>a</sup>, J Radua<sup>b</sup>, B König<sup>a</sup>, B Amann<sup>b</sup>

<sup>a</sup>Bipolar Zentrum Wiener Neustadt, BIPOlar Zentrum Wiener Neustadt, Wiener Neustadt, Austria, <sup>b</sup>CIBERSAM, FIDMAG Research Foundation, Barcelona, Spain

**Background:** Alcohol Use disorder (AUDs) may very well increase the likelihood of affective episodes in bipolar disorder, but prospective data on survival are inconsistent.

**Methods:** The authors examined the prevalence of AUDs and their impact on the risk of relapse. Out of five hundred fifteen consecutively admitted bipolar patients two hundred eighty-four ICD-10 bipolar I ( $n = 161$ ) and II ( $n = 123$ ) patients were followed-up naturalistically over a period of 4 years by one research team.

**Results:** The prevalence of AUDs was higher in bipolar II disorder than in bipolar I disorder (26.8% vs. 14.9%;  $\chi^2 = 5.46$ ,  $p = 0.019$ ), with a global prevalence of AUDs of 20.1% in the whole sample. Only 8.7% of bipolar I patients suffered from alcohol abuse (AA) and 6.2% from alcohol dependency (AD) whereas 13% bipolar II had AA and 13.8% AD. Male bipolar subjects had a statistically significant higher prevalence of AUD than female patients (38.3% vs. 12.8%;  $\chi^2 = 21.84$ ,  $p$ -value  $< 0.001$ ). The presence of AUDs was associated with increased risk of depressive relapse in bipolar I patients (Cox regression analysis hazard ratio = 2.7,  $p = 0.005$ ).

**Limitations:** Exact alcohol units were not evaluated and defined dosages of drugs or blood sampling during all visits were not performed.

**Conclusions:** Our data support previous reports of a negative impact of AUDs on the long-term course of bipolar patients, in this case with more bipolar I depressive episodes. This underlines the importance of detection and treatment of alcohol use disorder in bipolar patients at an early stage of any of the disorders.

### Using eye movement assessment to better discriminate between adult patients with bipolar disorder and those with attention-deficit hyperactivity disorder

S Soncin<sup>a</sup>, A Marin<sup>b</sup>, D Munoz<sup>a</sup>

<sup>a</sup>CNS, Queen's University, Kingston, Canada, <sup>b</sup>Psychiatry, Queen's University, Kingston, Canada

**Background:** There is significant overlap between symptoms in adult Attention Deficit/Hyperactivity Disorder (ADHD) and Bipolar Disorder (BD) that complicate accurate diagnosis. Meta-analysis supports the idea that the onset age, response to treatment and outcome of BD may be influenced by co-occurrence with ADHD. Hence, there is a pressing need to further elucidate the exact nature of the clinical overlaps in these diagnosis categories and for tools to help diagnosis.

**Methods:** We have investigated the cognitive and emotional control of saccades using well developed paradigms. 20 ADHD and 20 eu-

thymic BD subjects, men and women aged 18–55 years were recruited from the Adult Outpatient Psychiatry clinics at Hotel Dieu Hospital in Kingston. 25 control subjects were recruited from the community. All the patients and the controls were screened with the M.I.N.I. Plus, Version 5.0.0. Subjects have performed an interleaved pro-/anti-saccade task while viewing a computer screen. The attentional performance during behavioral trials was manipulated by embedding emotional distracters in the central visual field during instructed fixation.

**Results:** Control subjects had the shortest SRTs for correct pro- and anti-saccades and they generated the fewest direction errors in the anti-saccade task. BD patients had the longest SRTs and they made the most direction errors, and ADHD patients were between the control and BD values. The face manipulations have differential effects on SRT and error rates in the anti-saccade task only and most notably with the BD group, although the ADHD also shows some modulation of error rate with face emotion.

### A psychosocial strategy to improve cardiovascular risk factors in bipolar disorder

**L Sylvia, ME Gigler, E Bernstein, A Nierenberg, T Deckersbach**

*Department of Psychiatry, Massachusetts General Hospital, Boston, USA*

Several serious medical conditions disproportionately affect patients with bipolar disorder, including diabetes, hypertension, and cardiovascular disease (CVD). CVD is one of the leading causes of premature death in patients with bipolar disorder, pharmacological treatments for bipolar disorder contributing further to patients' already increased CVD risk. Despite evidence that lifestyle interventions improve CVD in the general population, few integrative psychosocial treatments address these conditions in bipolar disorder. The Nutrition, Exercise and Wellness Treatment (NEW Tx) has the potential to reduce the cardiovascular risk in bipolar disorder. NEW Tx, a 20-week, individual CBT-based treatment, is comprised of three modules: (1) Nutrition (identify healthy foods, define a balanced diet, and discuss serving sizes); (2) Exercise (emphasize regular exercise and its role in improving mood); (3) Wellness (CBT skills for healthy decision-making). Future iterations of NEW Tx should include skills for coping with stressors and focus more on social support and sleep hygiene. We conducted several pilot trials, updated the manual based on participant feedback, and are currently conducting a randomized controlled trial (RCT) comparing NEW Tx to treatment as usual. Further results and their implications will be discussed.

### Alcohol use and consumption in mood disorder first-time psychiatric evaluations: Mexican retrospective cohort

**P Zarate, F Canale, AB Cuellar-Barboza**

*Psychiatry, Universidad Autonoma de Nuevo Leon, Monterrey, Mexico*

**Aims:** The comorbid condition of alcohol use and mood disorder is well established in the US population. Few studies, however, compare this association in the Mexican population. We explore the prevalence of alcohol abuse in first-time psychiatric consults, in a Mexican retrospective cohort, and compare it between bipolar (BD), unipolar (UD) and other mood disorders (OD).

**Methods:** This is a retrospective cohort from medical records of first-time psychiatric evaluations. Subjects were selected from the Outpatient Service of the Department of Psychiatry of the University Hospital of the Universidad Autónoma de Nuevo León, Monterrey, Mexico from January 2014 to December 2014. Our outpatient service is a regional center that evaluates patients from the north east of Mexico. We performed a query to determine every

mood disorder that met DSM-IV-TR diagnostic criteria in first-time consults and included patients 18 years and older; the resulting medical records were reviewed manually. Clinical variables including alcohol consumption were self-reported. Standardized chi-square, t-test and ANOVA were used for analysis.

**Results:** We found 425 mood disorder first-time evaluations. 80% of these sample have UD; 12.4% BD and 7.6% other OD. 68.9% were females, mean age of  $37.2 \pm 14.4$  years. 50.1% were alcohol users, 61.9% were women and 38% men. There were no differences in social demographic variables between diagnoses. Between diagnosis there was no differences in alcohol use (56.6% BD vs 43.7% OD vs 49.7% UD; 2.43,  $p = 0.6$ ). BD patients report significantly higher consumption of 2 or more substances (22.64% BD vs 18.75% OD vs 6.74% UD; 18.87,  $p = 0.0008$ ). Similarly OD and BD patients show higher rates of self-reported heavy drinkers (5 or more drinks on same occasion) (BD 28.3% vs OD 31.5% vs UB 14.71%; 12.34,  $p = 0.01$ ).

**Conclusion:** Although there was no difference between alcohol use and axis I diagnosis, it seems that BD patients are prone to heavy drinking vs. UD patients. These results are similar to those reported in the US population.

### Predictors and outcomes of long duration of undiagnosed of bipolar disorders in China

**W Hong, YR Fang**

*Mood Disorder, Shanghai Mental Health Center Shanghai Jiao Tong University School of Medicine, Shanghai, China*

**Aims:** With the recent attention to misdiagnose of bipolar disorder (BPD), long duration of undiagnosed of BPD (DUBP) were reported in some studies. This survey investigated the DUBP and the predictors and outcomes of long DUBP across mainland China.

**Method:** 3906 participants from 26 participating hospitals throughout China were enrolled in this study. We systematically collected socio-demographic and clinical data from medical records and questionnaires.

**Result:** The mean age at first onset was 26.737 years. The type of first episodes of 58.1% patients was Mania/hypomania. The mean DUBP was 40.52 months. 82.7% patients reported that they had been hospitalized for bipolar disorder. Frequent of mood episodes averaged 5.44. Current suicidal ideation or suicide behavior was identified clinically in 6.5% of all subjects. 6.3% female patients experienced postpartum depression. Patients from psychiatric special hospital, older patients, female patients, patients with later manic/ypomanic episode, patients with later depressive episode were independently associated with long duration of undiagnosed of BP. These factors together explained 32.4% of the variance in DUBP. Long DUBP was associated with more recurrences ( $r = 0.392$ ,  $p < 0.001$ ), more risk for mixed episode or rapid cycling ( $Z = -3.279$ ,  $p = 0.001$ ), more risk to be hospitalization ( $r = 0.039$ ,  $p < 0.05$ ) and more risk complicated treatment ( $r = 0.107$ ,  $p < 0.001$ ).

**Conclusion:** Psychiatric special hospital, older patients, female patients, patients with later manic/ypomanic episode, patients with later depressive episode were independently associated with long duration of undiagnosed of BP. Long durations of undiagnosed of Bipolar disorder is found to be associated with a more severe course and outcome in bipolar disorder.

# Strengths and limitations of more inclusive (counting “overlapping” mood elevation symptoms) compared to DSM-5 definition of mixed depression in bipolar disorder patients

H Kim<sup>a</sup>, W Kim<sup>b</sup>, KC Goffin<sup>c</sup>, L Yuen<sup>c</sup>, JN Holtzman<sup>c</sup>, F Hooshmand<sup>c</sup>, S Miller<sup>c</sup>, PW Wang<sup>c</sup>, T Ketter<sup>c</sup>

<sup>a</sup>Psychiatry, Inje University, Goyang, Korea, <sup>b</sup>Psychiatry, Inje University, Seoul, Korea, <sup>c</sup>Psychiatry and Behavioral Sciences, Stanford University, Stanford, USA

**Aims:** The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) compared to the fourth edition adopted a more inclusive approach to mixed symptoms, including addition of mixed depression, by using a “with mixed features” for major depressive episodes. However, this approach to mixed depression has already been criticized as being overly exclusive, due to it not counting important but “overlapping” (i.e., may also occur during depression) mood elevation symptoms such as irritability, psychomotor agitation, and distractibility. We assessed the strengths and limitations of a more inclusive (counting “overlapping” mood elevation symptoms) compared to DSM-5 definition of mixed depression in bipolar disorder (BD) outpatients.

**Methods:** BD outpatients were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation. Prevalence and clinical correlates of baseline depressive episodes “with mixed features” were compared using a inclusive threshold (counting “overlapping” mood elevation symptoms) compared to the less inclusive DSM-5 threshold.

**Results:** Among 153 depressed BD outpatients, a more inclusive threshold compared to the less inclusive DSM-5 threshold, yielded a more than three-fold higher mixed depression rate (22.9% versus 7.2%,  $p < 0.0001$ ), and had several important statistically significant clinical correlates compared to pure depressive episodes, such as more lifetime anxiety disorder comorbidity (94.3% versus 72.0%,  $p < 0.01$ ) and current irritability (91.4% versus 44.1%,  $p < 0.0001$ ) and less current antidepressant use (20.0% versus 51.7%,  $p < 0.001$ ) which were not statistically significant using the less inclusive DSM-5 threshold.

**Conclusions:** Further studies are warranted to assess our observation that more compared to less inclusive “with mixed features” thresholds for bipolar depression may have more statistically significant clinical correlates, and the extent to which differences in effect sizes versus statistical power contribute to this phenomenon.

# A preliminary examination of auditory verbal hallucinations (AVH) in bipolar disorder and depression: analysis of the 2010 survey of high impact psychosis (SHIP) data

S Russell<sup>a</sup>, W Toh<sup>a</sup>, N Thomas<sup>a</sup>, J Badcock<sup>b</sup>, D Castle<sup>c</sup>

<sup>a</sup>Brain and Psychological Sciences Research Centre, Swinburne University, Melbourne, Australia, <sup>b</sup>CCRN, Royal Perth Hospital, Perth, Australia, <sup>c</sup>Psychiatry, St Vincents, Melbourne, Australia

**Aims:** Auditory verbal hallucinations (AVHs) are known to occur in in bipolar disorder (BD) and major depressive disorder (MDD), but there has been scant research conducted in the area. Research examining the phenomenology of in mood disorders is required to advance diagnostic boundaries and potential treatment avenues. This paper aims to compare the prevalence and severity of hallucinations, and AVHs in particular, across mood and psychotic disorders. Specific attention was given to (i) a running commentary, (ii) third-person voices, and (iii) accusatory voices. A secondary aim was to examine patterns of associated delusional themes, as well as any sex differences.

**Methods:** Participants were 1550 Australians, aged 18–64 years, assigned to one of four groups on the basis of diagnosis: (i) bipolar disorder (BD), (ii) depressive psychosis (DP), (iii) schizophrenia

(Sz), and (iv) schizoaffective disorder (SAD). Relevant data collected from the 2010 Australian Survey of High Impact Psychosis (SHIP) was analysed.

**Results:** Point and lifetime prevalence estimates of hallucinations were in the order  $BD < DP < SAD < Sz$ .  $BD = “DP < SAD = Sz,” > < /dp < sad < sz.>$

**Conclusion:** A notable finding in this data set was that accusatory voices as well as persecutory delusions were the most prominent in all groups. Future research should examine age of AVH onset as well as other types of AVHs, whilst taking into account participants’ specific mood states.

# Comparison of bipolar disorder with schizophrenia and major depressive disorder on affective temperaments and schizotypy

J Rybakowski, D Dembinska-Krajewska

Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland

**Aims:** The aim of the study was to assess affective temperaments by means of the Temperament Evaluation of the Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A) and schizotypy traits by means of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE), in patients with bipolar disorder (BD) compared with schizophrenia (SCH) and major depressive disorder (MDD). In view of recent clinical and genetic findings, we tried to elucidate possible similarities and differences between patients with BD and those with SCH and MDD.

**Methods:** The study involved 167 people, including 52 patients with BD (22 men), 58 patients with SCH (35 men), and 57 patients with MDD (24 men). The TEMPS-A scale which measures five types of affective temperaments: depressive, cyclothymic, hyperthymic, irritable and anxious and the O-LIFE scale which measures four dimensions of schizotypy: unusual experiences, cognitive disorganization, introverted anhedonia and impulsive nonconformity were employed to all subjects.

**Results:** Comparison between patients with bipolar disorder and schizophrenia showed only statistically higher scores of irritable temperament and impulsive nonconformity in the BD group. A comparison of patients with BD and MDD showed significantly higher scores of cyclothymic and irritable temperaments as well as impulsive nonconformity in the bipolar group. Higher scores of hyperthymic temperament in BD compared with MDD group did not reach the level of statistical significance.

**Conclusions:** A lack of significant differences in 4 out of 5 affective temperaments and 3 out of 4 schizotypy dimensions studied between patients with BD and SCH may correspond with the results of studies showing similarities between these two illnesses, including some features of common genetic predisposition. On the other hand, the differences in cyclothymic, irritable, and to some extent, hyperthymic temperaments as well as impulsive nonconformity between patients with BD compared with MDD may be used for prediction for a risk of subsequent conversion to BD, in MDD patients having higher scores of these dimensions of affective temperament and schizotypy.

# Sleep dysregulation and assessment in pediatric bipolar disorder

AR Van Meter<sup>a</sup>, EA Youngstrom<sup>b</sup>, RL Findling<sup>c</sup>

<sup>a</sup>Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, USA, <sup>b</sup>Psychiatry and Psychology, University of North Carolina at Chapel Hill, Chapel Hill, USA, <sup>c</sup>Psychiatry, Johns Hopkins University/Kennedy Krieger Institute, Baltimore, USA

**Background:** Sleep disturbance, including irregular sleep and nightmares, as well as decreased need for sleep, are common among

young people with bipolar disorder (BD); a meta-analysis of studies ( $N = 20$ ) on pediatric mania suggests that more than half of youth with BD are affected by sleep disturbance. Additionally, though decreased need for sleep is not required for a diagnosis of BD, it is specific to BD – whereas many BD symptoms tend to overlap significantly with other childhood disorders. Accurate assessment of decreased need for sleep and sleep disturbance may offer important information in the challenging diagnosis of pediatric BD. It also may indicate a core pathophysiological process with treatment implications.

**Method:** All procedures were approved by the IRB. Youths (5 to 18) were drawn from a psychiatric research center (Sample One;  $N = 630$ ) and an urban community mental health center (Sample Two;  $N = 808$ ). Families completed a K-SADS interview (Kaufman, et al., 1997). Sleep scales (parent and youth report) from the Achenbach System of Empirically-Based Assessment (Gregory & O'Connor, 2002) and the General Behavior Inventory (Meyers & Youngstrom, 2008) were calculated. Receiver operating characteristic analyses assessed the ability of the sleep scales to distinguish youth with BD.

**Results:** The P-GBI sleep scale discriminated youth with BD from youth with other diagnoses in Sample One ( $AUC = 0.71$ ,  $p < 0.001$ ) and Sample Two ( $AUC = 0.74$ ,  $p < 0.001$ ). The CBCL sleep scale performed similarly; Sample One ( $AUC = 0.63$ ,  $p < 0.001$ ) and Sample Two ( $AUC = 0.65$ ,  $p < 0.001$ ). Importantly, the P-GBI discriminated BD from MDD in both samples ( $ps = 0.001$ ), the CBCL did in Sample Two ( $p = 0.003$ ). The adolescent GBI discriminated youth with BD in Sample One only ( $AUC = 0.61$ ,  $p = 0.001$ ); Sample Two ( $AUC = 0.56$ ,  $p = 0.08$ ). The YSR discriminated youth with BD in Sample Two only ( $AUC = 0.61$ ,  $p = 0.001$ ); Sample One ( $AUC = 0.53$ ,  $p = 0.47$ ).

**Conclusion:** Sleep scales derived from the Parent GBI, a free questionnaire, and the CBCL, a commonly used assessment measure, both discriminated youth with BD from youth with other disorders. The ability of the P-GBI to distinguish between BD and MDD is especially important; this can be a difficult differential diagnosis. A sleep measure, or subscale, could be a helpful addition to the evidence-based assessment of BD.

## Early intervention in psychoses – the Singapore experience

S Basu, S Verma

*Early Psychoses Intervention Programme, Institute of Mental Health, Singapore, Singapore*

**Introduction:** Psychoses is a debilitating illness and we looked at the data available and found that Failures in Care were caused by Prolonged delays in accessing effective treatment, Traumatic and often alienating initial treatment strategies, Poor continuity of care and Poor engagement of the patient in treatment. Consequences of Delay of delay in Care caused Slower and Less Complete Response, Increased Relapse and Increased Treatment Resistance.

**Aim:** Evaluate do we need early intervention in Psychosis? This has been implemented and we would like to share the experience.

**Methods:** In Singapore the Early Psychosis Programme (EPIP) was started in 2001 and our goals were to Raise awareness of psychosis, Reduce stigma associated with psychosis, Reduce the DUP (duration of untreated psychoses) in Singapore, Improve the outcome and quality of life of those with psychosis and therefore reduce the burden of care for their families, To provide Early Detection, Use the Staging Model of Schizophrenia and Provide phase-specific care – 3 phases Prior to EPIP (Early Psychosis Intervention Programme), In Singapore, mean (SD) duration of DUP of patients with Schizophrenia was 32.6 (54.8) months, median of 12 months.

**Results:** Since the inception of EPIP in 2001, 3,098 individuals have been screened and 2,271 accepted into the programme. 91.9%

(339/369) are engaged with EPIP services, 85.8% (247/288) had significant reduction (remission) in symptoms, 83.7% (241/288) experienced significant improvement in functioning, 76.5% (277/362) returned to performing age appropriate roles (back to school or gainfully employed).

## Illness episodes but not duration of treatment delay is associated with symptom severity in recent onset BDI after one year of treatment

L Kvittland, PA Ringen, SR Aminoff, C Demmo, T Hellvin, TV Lagerberg, OA Andreassen, I Melle

*NORMENT KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, Norway*

**Aims:** Treatment delay (TD) is associated with poorer course of illness in Schizophrenia. As Bipolar Disorder I (BDI) is a relapse-remitting disorder, both number of episodes before treatment (EBT) and duration of untreated illness (DUI) could be measures for TD in BD. We aimed at exploring the relationship between DUI and EBT and symptoms and functioning, at inclusion and follow up, in a representative sample of first treatment BDI patients.

**Methods:** 62 patients with first treatment BDI from the Thematically Organized Psychosis Study were evaluated within one year of onset (baseline – T1), and re-assessed after one year (T2). The SCID-I was used for DSM-IV diagnosis and for identifying previous episodes. Affective symptoms were measured by the YMRS and the IDS-C and psychotic symptoms by the PANSS. Both first affective (FA) and first manic (FM) episode were separately investigated as BDI TD start points, adequate pharmacological treatment was chosen as the endpoint. Patients were divided into those with one previous affective or psychotic episode, 2–5 previous episodes or 6 or more previous episodes based on the distribution of number of episodes in scatterplots against symptom scores. Participants consented to participate in the study was approved by the Regional Committee for Medical Research Ethics.

**Results:** Mean DUI for FA was 206 weeks (SD: 345); Mean DUI for FM was 109 weeks (SD: 261). Mean EBT was 7 (SD: 11). Both FA and FM correlated positively with IDS-C at T2 (p).

**Discussion:** The main finding of our study is that the EBT could be a more important predictor for the course of recent onset BDI than DUI. Based on our findings we speculate if increased efforts on treatment at the first episode, rather than identifying an ultra-high risk group are vital.

## The association between duration of untreated bipolar disorder and clinical variables: data from a Brazilian sample

GC Medeiros, S Barbieri, B Lafer, KM Almeida

*Psychiatry, Institute of Psychiatry at the University of São Paulo, São Paulo, Brazil*

**Aims:** Evidence from developed countries suggests that bipolar disorder (BD) is usually untreated for long periods of time after its onset. This delay in treatment has been correlated with poor clinical outcomes such as more suicidal behavior, more social difficulties and a higher number of mood episodes. However, the concept of duration of untreated bipolar disorder (DUB) is still understudied and there is no data regarding DUB in developing countries, which is worrisome since the mental health care in these regions is usually less effective than in developed countries. The objective of this study is to verify the magnitude of DUB in Brazil and analyze the association between an extended DUB and clinical variables.

**Methods:** We studied 152 outpatients with BD I or II recruited from the Bipolar Disorder Program (PROMAN) at the Institute of

Psychiatry – University of São Paulo Medical School. All participants were assessed for demographics; DUB (interval between the onset of BD and the first pharmacological treatment with a mood stabilizer) and 13 relevant clinical variables. We performed analysis of correlation to assess the relationship between DUB and other continuous variables. With respect to the association between DUB and categorical variables, we executed Mann–Whitney test.

**Results:** The mean age and mean DUB of the sample were, respectively, 38.9 ( $\pm 10.8$ ) and 10.4 ( $\pm$ SD 9.8) years. DUB presented a median value of 7, a minimum value of 0 and a maximum value of 43. A longer DUB was significantly associated with early onset of BD ( $p < 0.001$ ), the presence of a first degree relative with BD ( $p = 0.012$ ) and of depression as first mood episode ( $p = 0.004$ ). Additionally, a longer DUB was also statistically associated with poorer clinical outcomes such as rapid cycling ( $p = 0.004$ ) and comorbidity with anxiety disorders ( $p = 0.016$ ) as well as lower levels of current full remission ( $p = 0.021$ ).

**Conclusions:** Time from onset of illness until first treatment is a modifiable variable and better medical education and more structured medical services may reduce its duration and, consequently, have relevant positive clinical impact.

### A comparison of caregivers of patients with bipolar disorder and Alzheimer's disease: similar levels of burden and greater distress in bipolar disorder

GD Santos, RB Ladeira, JG Almeida, I Aprahamian, OV Forlenza, B Lafer, P Nunes

Psychiatry, Psychiatry University of Sao Paulo Medica School, Sao Paulo, Brazil

**Aims:** Caregivers are an essential element in health care. The challenges of Alzheimer's Disease (AD) caregivers are well recognized in the literature but not of elderly Bipolar Disorder (BD) patients. The objective of this study is to compare burden and distress of caregivers of elderly BD and AD patients.

**Methods:** Patients had 60 years of age or more and attained DSM-IV criteria for BD or mild to moderate AD. They were evaluated by a blind examiner with the Geriatric Depression Scale (GDS), Beck Anxiety Inventory (BDI), CDR, Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), Functional Assessment Short Test (FAST), WHOQOL-BREF and with socio-demographic variables. The caregiver that spent the greater time with each patient was selected, and was evaluated with the Zarit Burden Interview (ZBI), NPI Caregiver Distress item (NPI-D), GDS, BAI, WHOQOL-BREF.

**Results:** Patients with BD ( $n = 36$ ) compared with AD ( $n = 39$ ) patients had a better cognitive status ( $p = 0.028$ ), greater scores in GDS ( $p < 0.001$ ), BAI and NPI ( $p = 0.002$ ), and smaller scores in WHOQOL-BREF ( $p < 0.001$ ). Caregivers of BD patients were younger than AD patients ( $51.1 \pm 14.4$  and  $64.7 \pm 13.3$  years,  $p < 0.001$ ) and spent less hours of caring per day ( $5.9 \pm 8.3$  and  $13.9 \pm 10.2$ ,  $p < 0.001$ ). In spite of that, ZBI was similar ( $p = 0.097$ ) and NPI-D was greater in BD caregiver group ( $p = 0.019$ ). ZBI and NPI-D were correlated with hours of caring ( $r = 0.293$ ,  $p = 0.011$  and  $r = 0.299$ ,  $p = 0.009$ ), patient's FAST ( $r = 0.284$ ,  $p = 0.013$  and  $r = 0.595$ ,  $p < 0.001$ ) and NPI ( $r = 0.392$ ,  $p = 0.001$  and  $r = 0.862$ ,  $p < 0.001$ ). ZBI was also correlated to caregiver BAI ( $r = 0.444$ ,  $p < 0.001$ ), GDS ( $r = 0.571$ ,  $p < 0.001$ ) and WHOQOL-BREF ( $r = -0.431$ ,  $p = 0.001$ ) but not with patient's BAI and GDS.

**Conclusions:** Being the caregiver of elderly BD or AD patient is associated with great burden. Contrary to our initial hypothesis, distress was greater in BD caregivers. Factors associated with it were impairment in patient's functionality and neuropsychiatric symptoms, number of hours of caring and caregiver depression

and anxiety. Our results point to the benefit for psychosocial interventions for patients and caregivers.

### Electrocardiographic changes of old patients with bipolar disorder compared with schizophrenic ones

SY Tsai<sup>a</sup>, PH Chen<sup>b</sup>, ML Chen<sup>c</sup>, KH Chung<sup>a</sup>, SH Huang<sup>a</sup>

<sup>a</sup>Psychiatry, Taipei Medical University and Hospital, Taipei, Taiwan, <sup>b</sup>Psychiatry, Taipei Medical University Hospital, Taipei, Taiwan, <sup>c</sup>Cardiology, Cathay General Hospital, Taipei, Taiwan

**Aims:** Both bipolar and schizophrenic patients are vulnerable to cardiovascular morbidity. However, comparisons of standard 12-lead electrocardiogram (ECG) analyses in old patients with bipolar disorder and schizophrenia remain limited. We attempted to investigate what ECG characteristics exist in old patients with bipolar disorder.

**Methods:** We recruited outpatients with bipolar I disorder or schizophrenia (DSM-IV) aged over 50 years to undergo standard 12-lead ECG study. A board-certified cardiologist blind to the clinical data of patients analyzed the ECG recordings. The ECG diagnosis of coronary heart disease is defined by having pathological Q waves, non-specific ST-T changes, ST and/or T wave inversion of any degree, left bundle branch block, and old myocardial infarction.

**Results:** We totally recruited 52 bipolar patients with mean age of  $60.9 \pm 9.1$  years and 74 schizophrenic ones with mean  $57.3 \pm 8.4$  years old. Abnormal ECG was noted in 53.9% of bipolar subjects and 56.8% of schizophrenic ones. The proportions of patients with the ECG-defined coronary heart disease in bipolar group (30.8%) and schizophrenic one (39.2%) were comparable. Conduction defects except left bundle branch block were more common found in bipolar group (15.4%) than in schizophrenic one (5.4%) (Fisher's exact test,  $p = 0.05\%$ ). There was no significant difference in proportion of significant ECG change between two groups, including premature ventricular beats, QT prolong, and left ventricular hypertrophy.

**Conclusion:** Coronary heart disease is more often detected by ECG in bipolar and schizophrenic old patients than 5 to 10% reported in general population after the middle ages. Various pathophysiology and medication effects may partially explain that old bipolar patients rather than schizophrenic ones have cardiac conduction defect.

### Women are at higher risk for rapid cycling than men: new data from the mayo clinic individualized medicine biobank for bipolar disorder

A Erol<sup>a</sup>, SJ Winham<sup>a</sup>, SL McElroy<sup>b</sup>, MA Frye<sup>a</sup>, ML Prieto<sup>c</sup>, AB Cuellar-Barboza<sup>d</sup>, J Geske<sup>a</sup>, N Mori<sup>b</sup>, JM Biernacka<sup>a</sup>, WV Bobo<sup>a</sup>

<sup>a</sup>Psychiatry & Psychology, Mayo Clinic, Rochester, USA,

<sup>b</sup>Psychiatry, Lindner Center of HOPE and University of Cincinnati School of Medicine, Cincinnati, USA, <sup>c</sup>Psychiatry, Universidad de los Andes Facultad de Medicina, Santiago, Chile, <sup>d</sup>Psychiatry, Universidad Autonoma de Nuevo Leon, Monterrey, Mexico

**Aims:** Although evidence indicates that female bipolar patients have a higher prevalence of rapid cycling, there is controversy regarding the interaction between gender and bipolar disorder subtype. Our aim was to examine sex differences in the risk of rapid cycling in patients with bipolar I or II disorder (BP-I or BP-II), independent of other risk factors in a large sample of 1,225 patients.

**Methods:** We analyzed data from the first 1,225 patients with SCID-confirmed diagnoses of bipolar I or II disorder enrolled in the Mayo Clinic Individualized Medicine Biobank for Bipolar

Disorder. Demographic and clinical variables were ascertained using clinical interviews and standardized questionnaires; height and weight were assessed to determine body mass index (BMI). Demographic and clinical characteristics and rates of rapid cycling were compared between sex groups (female, male) overall and within subgroups defined by bipolar disorder subtype (BP-1 or BP-2). Multiple logistic regression analysis was used to assess the independent effect of sex on the risk of rapid cycling after controlling for other risk factors.

**Results:** 863 subjects had BP-1 (58.3% women), and 362 had BP-2 disorder (66.6% women). In univariate analyses, women had a significantly higher rate of rapid cycling than did men (398/744 [54.5%] vs. 221/481 [46.6%],  $p = 0.009$ ). Overall rates of rapid cycling were higher in patients with BP-2 than BP-1 (57.7% vs. 48.1%), and sex differences in the rate of rapid cycling were more pronounced in patients with BP-2 (60.0% vs. 52.5%,  $p = 0.18$ ) than BP-1 (51.7% vs. 44.6%,  $p = 0.04$ ), although power to detect statistically significant differences was reduced due to lower sample size of BP-2 subjects. Female sex was a significant predictor of rapid cycling after adjusting for age at enrollment, bipolar disorder subtype, current BMI, having any comorbid psychiatric disorder, and current antidepressant use (adjusted OR = 2.10, 95% CI 1.78 to 2.60).

**Conclusions:** Female sex was associated with significantly higher risk of rapid cycling in a sample of 1,225 patients with bipolar disorders. This association remained statistically significant after adjusting for bipolar disorder subtype and other risk factors for rapid-cycling.

## Quetiapine in the acute treatment of bipolar postpartum depression

V Sharma<sup>a</sup>, M Khan<sup>b</sup>

<sup>a</sup>Psychiatry, University of Western, London, Canada, <sup>b</sup>Psychology, Western University, London, Canada

**Aim:** Despite its common occurrence following childbirth, there are no published studies on the pharmacotherapy of bipolar depression. We sought to study the effectiveness and tolerability of quetiapine in the treatment of bipolar depression with postpartum onset (defined as onset of depression in the first four weeks after childbirth), among patients treated in a naturalistic setting.

**Methods:** We conducted a retrospective chart review of 18 consecutive outpatients with a DSM-5 diagnosis of bipolar disorder, being treated with quetiapine monotherapy for a depressive episode.

**Results:** Fifteen of the 18 patients were rated as “very much” or “much” improved after 8 weeks of treatment, and one patient discontinued quetiapine after 3 weeks. The dose of quetiapine ranged from 25 to 500 mg, with exactly half of the sample receiving either 50 or 75 mg, and most of the remaining half receiving 100–150 mg. The most common side effects were weight gain (2 patients), somnolence (1 patient), and restless leg syndrome (1 patient).

**Conclusions:** Quetiapine appears to be safe and effective in the acute treatment of bipolar postpartum depression.

## Overlap of precipitating factors in mania and partial seizures: in pursuit of shared pathophysiology

ECS Bostock<sup>a</sup>, KC Kirkby<sup>b</sup>, MI Garry<sup>a</sup>, BV Taylor<sup>c</sup>

<sup>a</sup>Psychology, University of Tasmania, Hobart, Australia,

<sup>b</sup>Psychiatry, University of Tasmania, Hobart, Australia,

<sup>c</sup>Neurology, Menzies Research Institute, Hobart, Australia

**Aims:** Comparisons of aetiological factors may cast light on brain regions and processes through which disorders develop. A standard classification of aetiology considers predisposing, precipitating and perpetuating factors. Precipitating factors, proximate to

illness episodes, prompt the change from vulnerability to frank illness. Comparison of precipitants has been studied for epilepsy and migraine. Similarities recommending this approach for mania in bipolar disorder (BD) and partial (focal) seizures (PS) arising from the temporal lobes include: chronic course punctuated by acute episodes; sensory, perceptual, cognitive and affective symptoms; response to anticonvulsants. Common mechanisms inferred include neurotransmitters and kindling. Investigations comparing mania and PS may highlight relevance of temporal lobe mediated processes and pathology. This study compares precipitating factors of manic episodes, and of PS in diagnosed epilepsy to identify the extent and nature of their overlap.

**Methods:** Review based on literature search of PubMed and Google Scholar.

**Results:** Precipitating factors for both mania and PS were stress, sleep deprivation, antidepressant medication and, tentatively, emotion. For mania alone goal-attainment events, spring and summer season, postpartum, and drugs including steroids and stimulants. For PS alone winter season, menstruation and specific triggers in complex reflex epilepsies.

**Conclusions:** The overlap of precipitating factors in mania and PS imply common brain processes may contribute to both.

## Ataxia signs in bipolar disorder

AA Chrobak<sup>a</sup>, G Siwek<sup>a</sup>, A Tereszko<sup>a</sup>, S Jeziorko<sup>a</sup>, K Siuda-Krzywicka<sup>b</sup>, A Arciszewska<sup>c</sup>, M Siwek<sup>c</sup>, D Dudek<sup>c</sup>

<sup>a</sup>Students' Scientific Association of Affective Disorders, Jagiellonian University Medical College, Cracow, Poland, <sup>b</sup>Ecole des Neurosciences a Paris, Université Pierre et Marie Curie Paris, Cracow, Poland, <sup>c</sup>Department of Affective Disorders, Jagiellonian University Medical College, Cracow, Poland

**Aims:** Studies indicate occurrence of motor dysfunctions in bipolar disorder (BD) patients, as well as functional and structural impairments of cerebellum. The aim of our study is to evaluate ataxia signs in BD patients.

**Methods:** 30 euthymic BD patients and 26 healthy controls matched for age and gender were evaluated with a use of International Co-operative Ataxia Rating Scale (ICARS). BD patients were under quetiapine, olanzapine or clozapine treatment. Additionally valproic acid and carbamazepine has been accepted.

**Results:** BD patients showed significantly higher scores in total ICARS score than healthy controls ( $p < 0.001$ ). BD patients presented higher scores in kinetic functions subscale ( $p < 0.001$ ) and oculomotor disorders subscale ( $p < 0.001$ ) than healthy controls.

**Conclusion:** BD patients presented ataxia signs most particularly noticeable in kinetic and oculomotor functions.

## Child sexual abuse and suicidal attempts in Brazilian bipolar type I patients

D Duarte, M Neves, F Neves, M Albuquerque, H Correa

Mental Health of de Faculty of Medicine of Federal University of Minas Gerais Molecular Medicine, HC-UFMG, Belo Horizonte, Brazil

**Objective:** To study the association between childhood traumatic events (CTE) and suicidal attempts (SA) in Brazilian bipolar I patients (BD-I).

**Method:** Euthymic BD-I patients were assessed for lifetime SA and five trauma subtypes' frequency and severity. The instruments of evaluation were Mini International Neuropsychiatry Interview (MINI-Plus), Childhood Trauma Questionnaire (CTQ), Socio-demography questionnaire, Beck's Suicide Intent Scale, Beck's Suicide Lethality Scale, Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HAM-D).



**Results:** Among 47 BD-I patients included in this study 23 (48.9%) presented lifetime SA, and 21 (44.6%) was positive for CTE. When compared categorical variable between SA and CTE we found no statistical significance ( $p = 0.67$ ), otherwise, using numerical values, BD-I subjects that presented higher CTQ scores in sexual abuse had more lifetime SA (Mean 11.26 SD 8.26) when compared with BD-I patients without trauma (Mean 6.92 SD 5.15) with  $p = 0.036$ .

**Conclusion:** BD-I patients that suffered childhood sexual trauma have a tendency toward SA in Brazilian population. This finding suggests that attention should be given to the presence of CTE in BD-I patients and that new approach focused on prevention should be developed.

### Childhood trauma, severe clinical and dimensional expression of bipolar disorders and moderation by genetic factors

**B Etain<sup>a</sup>, M Aas<sup>b</sup>, F Bellivier<sup>c</sup>, I Melle<sup>b</sup>, C Henry<sup>d</sup>, O Andreassen<sup>b</sup>**

<sup>a</sup>INSERM U955, France, <sup>b</sup>Institute of Clinical Medicine, University of Oslo, Division of Mental Health and Addiction, Oslo University Hospital, Norway, <sup>c</sup>Service de Psychiatrie et d'addictologie, APHP – Hopital Fernand Widal – Lariboisière, France, <sup>d</sup>Pole de Psychiatrie and Inserm U955, APHP, Groupe Hospitalier Henri Mondor, France

Bipolar disorders (BD) are determined by environmental factors that interact with genetic variants. Childhood traumatic events are suggested as major risk factors although their role on the clinical expression of BD and the influence of genetic modulators are unknown. In this context, exploring pathways from trauma to clinical expression through intermediate dimensions and genetic modulation is a relevant strategy. We used a four steps approach using the Childhood Trauma Questionnaire in normothymic patients and controls. (1) Multiple trauma were frequent in patients as compared to controls. Among subtypes only emotional abuse was associated with BD with a dose-effect. (2) Emotional and sexual abuses were associated with a greater severity of BD i.e. an earlier age at onset, greater suicidality, rapid cycling, more depressive episodes. (3) Regression analyses showed an interaction between emotional trauma and short/short genotype of SLC6A4 gene on the age at onset of BD. Interactions was also found with immunity-related genes. (4) We demonstrated that the higher the exposure to trauma was, the higher affective instability (measured using the Affective Lability Scale and the Affect Intensity Measure), as well as higher impulsivity and hostility traits. Our results demonstrated the importance of childhood trauma as a risk factor for BD, but also for a more severe/unstable/impulsive clinical expression. This might be particularly relevant for carriers of specific stress responsiveness-related genotypes. The effects of trauma on the clinical expression could be modeled within a pathway that incorporated non-specific dimensions of susceptibility such as affective lability or impulsivity.

### Entropy and periodicity analysis to investigate mood variability in bipolar disorder

**D Kreindler<sup>a</sup>, A Munshi<sup>b</sup>**

<sup>a</sup>Department of Psychiatry Division of Youth Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada, <sup>b</sup>Department of Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada

**Introduction:** Bipolar disorder is a mental illness characterized by mood fluctuations. The physical mechanisms that underlie these mood fluctuations have yet to be described. Rigorous characterization of the dynamics of mood in bipolar disorder may help us to constrain the classes of candidate systems capable of giving rise to mood in health and bipolar disorder. Prior work has demonstrated

that mood fluctuations in both bipolar disorder and healthy controls show evidence of self-similarity. Furthermore, in biological systems, a shift from normal functioning to pathology is typically associated with decreased entropy – i.e., increased predictability.

**Methods:** Two sets of data were analyzed: the first (“MHT”) consisted of daily mood ratings from 148 participants ages 14–65 with bipolar disorder ( $n = 27$ ), mood instability ( $n = 13$ ), and healthy controls ( $n = 108$ ) over intervals of 6–18 months; the second (“VS”), a single record of 3024 mood ratings from a male diagnosed with Bipolar Disorder Type II, collected over 25 years of active mood cycling and three years of remission, with one entry each time the reporter’s mood changed. All participants consented to participation; the research was approved by Sunnybrook’s Research Ethics Board. Sample entropy (SampEn) and power law exponents of periodograms (“alpha”) of each of the mood records were calculated; for VS, alpha and SampEn were calculated for mood ratings for 14 two-year epochs, as well as SampEn of intervals between mood changes.

**Results:** SampEn and alpha for the MHT time series did not reveal significant difference between diagnostic groups ( $p > 0.15$ ;  $p > 0.45$ ). Alpha was generally confined to the interval  $(-1, 0)$ . For the VS set, alpha was largely confined to the interval  $(-1, 0)$  over the entire 28-year interval; changes in mood ratings became progressively more predictable (i.e., SampEn diminished) beginning approximately five years after onset of illness, while predictability of intervals between mood changes followed a more complicated pattern.

**Discussion:** Our results are consistent with mood having a ‘history’: in general, long-term trends predominate over shorter-term fluctuations. The lack of difference in SampEn between groups is unexpected and requires replication. The longitudinal VS results, while a single case, offer an intriguing picture of how bipolar disorder can quantitatively evolve over time.

### Differences between bipolar patients with or without suicide attempt in clinical features, comorbidity, and family history

**HJ Lee<sup>a</sup>, EJ Kim<sup>a</sup>, TH Ha<sup>a</sup>, S Lee<sup>a</sup>, T Chung<sup>a</sup>, SL Jang<sup>a</sup>, YS Park<sup>a</sup>, J Kim<sup>b</sup>, K Ha<sup>c</sup>**

<sup>a</sup>Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, Korea, <sup>b</sup>Biomedical Research Institute, Seoul National University Bundang Hospital, Seongnam, Korea, <sup>c</sup>Neuropsychiatry, Seoul National Hospital, Seoul, Korea

Bipolar disorder is a chronic and heterogenous condition, characterized by recurrent mood episode and is strongly associated with suicide. This study was designed to investigate the differential effects of the history of suicidal attempts on clinical features in bipolar patients. We collected data from 251 bipolar patients who had visited the Mood Disorders Clinic of Seoul National University Bundang Hospital. The subjects consisted of 96 patients with BD I, 126 patients with BD II and 29 patients with BD-NOS who met the DSM-IV criteria. Group mean differences in demographic and clinical variables were compared between patients with and without history of suicide attempt. 34.3% patients with history of suicide attempt. The patients with a history of suicide attempt had a younger onset age and more depressive episodes compared to patients without suicide attempt. Suicide attempt was related to mixed episode, psychiatric comorbidity and family history of suicide. Through analysis of 117 patients in acute depressive phase, we found that the suicidal patients had a lower GAF scores, however their depressive symptoms were not severer than those of patients without suicide attempt. In current study, distinctive characteristics of bipolar patients with history of suicide attempt were confirmed. Our results suggest suicide in bipolar patients was closely related to functional impairment rather than depressive symptoms.

## The trajectory of quality of life in bipolar disorder

G Murray<sup>a</sup>, E Morton<sup>a</sup>, S Bowe<sup>a</sup>, E Michalak<sup>b</sup>, R Lam<sup>b</sup>, S Beaulieu<sup>c</sup>, V Sharma<sup>d</sup>, P Cervantes<sup>e</sup>, L Yatham<sup>b</sup>

<sup>a</sup>Psychological Sciences, Swinburne University, Hawthorn, Australia, <sup>b</sup>Psychiatry, University of British Columbia, Vancouver, Canada, <sup>c</sup>Bipolar Disorders program, Douglas Hospital, Verdun, Canada, <sup>d</sup>Psychiatry, Regional Mental Health Care, London, Canada, <sup>e</sup>Mood Disorders unit, McGill University, Montreal, Canada

**Background:** Little is known about the trajectory of quality of life (QoL) amongst people with bipolar disorder (BD), or the impact of symptoms on this trajectory. The results of a large scale, prospective, naturalistic multisite study addressing these questions are reported here.

**Methods:** Participants were recruited from 12 sites across Canada, with diagnosis of BD I or BD II confirmed on the MINI. Participants were under the care of a psychiatrist, with individual patient treatment plans following consensus guidelines. Data was collected every 3 months for a minimum of a year. Mental (MCS) and physical (PCS) QoL was measured using the SF-36. Symptom data was recorded for mania (YMRS) and depression (HamD17, MADRS). Multilevel modelling was used to analyse the rate of change of MCS and PCS over time.

**Results:** A total of 362 participants were recruited: mean age 42.75 (SD = 12.18), 207 female (57.2%). Across 1823 visits (M = 4.95, SD = 2.73), MCS exhibited a positive linear trajectory, while PCS did not vary systematically over time. Significant inter-individual variability was found in baseline and growth rates for MCS, with a trend for lower baseline levels to be associated with steeper increase across time. Investigation of temporal relationships between QoL and symptoms suggested bidirectional effects: The linear trajectory of MCS became non-significant when controlling for mania and depression symptoms at the preceding visit, while the preceding visit's MCS predicted symptoms.

**Conclusion:** The present naturalistic study demonstrates for the first time that people receiving consensus treatment for BD report linear improvements in mental quality of life across extended periods. The data also permitted investigation of dynamic interactions between QoL and symptoms, generating novel hypotheses for future research. Methodologically, the study highlights multilevel modelling as a tool for interrogating within-subject trajectories across multiple clinical variables.

## Positive emotion persistence in depression? Examination of emotion reactivity across bipolar and unipolar depression

LM Weinstock<sup>a</sup>, IW Miller<sup>a</sup>, J Gruber<sup>b</sup>

<sup>a</sup>Department of Psychiatry and Human Behavior, Brown University and Butler Hospital, Providence, USA, <sup>b</sup>Department of Psychology and Neuroscience, University of Colorado at Boulder, Boulder, USA

**Aims:** Bipolar disorder (BD) and major depressive disorder (MDD) evidence distinct disruptions in positive emotion responding that may potentially differentiate the two. Indeed, there is robust support for *attenuated* reactivity of positive emotions in MDD, whereas recent studies reveal a pattern of *potentiated* reactivity of positive emotions in BD. Yet it is unclear to what extent this response pattern in BD is evident during periods of depression, as relevant research has been conducted primarily with non-clinical or euthymic patient samples.

**Methods:** To further advance this line of inquiry, the current study used an experimental paradigm to examine emotion reactivity to standardized emotional films in currently depressed participants with BDI (n = 30) and MDD (n = 30), and in healthy controls (CTL; n = 30). In a counterbalanced order, participants viewed

positive (i.e., goal attainment theme) and negative (i.e., loss theme) films, and completed pre- and post-film self-reported emotion ratings.

**Results:** Results from repeated measures ANOVAs revealed that, across films, both BD and MDD evidenced potentiated positive emotion reactivity as compared to the CTL group. Further, in comparison to the CTL group, both BD and MDD evidenced attenuated negative emotion reactivity, but in response to the sad film only.

**Conclusions:** Consistent with prior research, study data provide additional evidence for potentiated positive emotion responding in BD, and suggest that this response pattern may also be evident during a depressive episode. Yet somewhat unexpectedly, study data further suggest that individuals with BD and MDD may evidence similar patterns of positive and negative emotion responding across an emotion challenge paradigm. This study adds to a growing literature focused on models of positive emotion persistence and dysregulation across the mood disorders.

## Association study of ZNF804A gene with bipolar I and II disorder in the Korean population

JH Baek<sup>a</sup>, K Lee<sup>a</sup>, I Huh<sup>b</sup>, S Ryu<sup>a</sup>, E Cho<sup>a</sup>, T Park<sup>b</sup>, K Ha<sup>c</sup>, KS Hong<sup>a</sup>

<sup>a</sup>Psychiatry, Samsung Medical Center, Seoul, Korea, <sup>b</sup>Statistics, Seoul National University, Seoul, Korea, <sup>c</sup>Psychiatry, Seoul National University, Seoul, Korea

**Aims:** Evidence from Genome-wide association study (GWAS) indicates that the zinc-finger protein 804A gene (ZNF804A) is associated with psychotic disorders including bipolar disorder (BD). We investigated the genetic association between the ZNF804A and BD in the Korean population, and performed a subgroup analysis for bipolar I disorder (BD1) and bipolar II disorder (BD2).

**Methods:** A total of 330 patients with BD and 483 healthy controls were recruited for this study. Nineteen tag single nucleotide polymorphisms (SNPs) across the overall region of ZNF804A and two more SNPs (rs7597593 and rs1344706) showing association with BD in previous studies were genotyped. We used logistic linear regression analysis under three types of genetic model (additive, dominant, and recessive models) for the BD1, BD2 and combined groups.

**Results:** For BD1, 10 SNPs of ZNF804A showed nominally significant association under additive and dominant models. rs2369595 on intron 1 represented the lowest p value ( $2.52 \times 10^{-3}$ ) under the dominant model. No association remained statistically significant after Bonferroni correction. Weaker association trends were observed for combined BD group and BD-II group.

**Conclusions:** These results suggest that genetic variants in ZNF804A are associated with susceptibility to BD1. Further studies with a larger sample size for each BD subgroups are required to clarify differential effect of ZNF804A on BD1 and BD2.

## Increased expression of serotonin and dopamine receptors on leukocytes from euthymic bipolar disorder patients

I Barbosa<sup>a</sup>, FTL Guimaraes<sup>b</sup>, NP Rocha<sup>a</sup>, VA Mendonça<sup>c</sup>, GB Melo<sup>d</sup>, AL Teixeira<sup>a</sup>

<sup>a</sup>Laboratório Interdisciplinar de Investigação Médica, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, <sup>b</sup>Nutrição, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Brazil, <sup>c</sup>Fisioterapia, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Brazil, <sup>d</sup>Fisiologia, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Brazil

**Introduction:** A growing body of evidence suggests that serotonergic and dopaminergic systems are involved in the pathophysiol-

ogy of bipolar disorder (BD). The aim of the present study was to evaluate serotonergic and dopaminergic systems in peripheral leukocytes from euthymic BD patients and healthy control subjects.

**Methods:** 21 euthymic (15 women / 6 men, 48.95,  $\pm$ 9.14 years) BD type I patients, and 22 (14 women / 8 men, 46.95,  $\pm$ 8.58 years) healthy controls matched by age and gender were enrolled in this study. BD patients were assessed with the Mini-International Neuropsychiatry Interview, and the Young Mania Rating Scale and the Hamilton Depression Rating Scale. The expression of serotonin receptors 5HT 1A, 5HT 2A, 5HT 2B, 5HT 1C and dopamine receptors D 2, D 3, and D 4 were evaluated by flow cytometry in total leukocytes.

**Results:** BD patients present a mean 23.14 years ( $\pm$ 11.46) length of illness. In comparison with controls, peripheral leukocytes from BD patients showed increased expression of serotonergic receptors: 3.11 fold-increase of 5-HT1A (p).

**Conclusion:** Leukocytes might be a probe of the central nervous system. The present study suggest serotonergic and dopaminergic dysfunctions in BD illness.

### Glutamate induced apoptosis in human olfactory neuroepithelial progenitors derived from bipolar and non bipolar subjects

Y Gao<sup>a</sup>, W Winstead<sup>b</sup>, Z Lei<sup>c</sup>, C Lu<sup>d</sup>, F Roisen<sup>d</sup>, R El-Mallakh<sup>d</sup>

<sup>a</sup>Psychiatry, University of Louisville, Louisville, USA, <sup>b</sup>Surgery, University of Louisville, Louisville, USA, <sup>c</sup>Obstetrics and Gynecology, University of Louisville, Louisville, USA, <sup>d</sup>Anatomical Sciences and Neurobiology, University of Louisville, Louisville, USA

**Aims:** Bipolar disorder (BD) is characterized by marked parenchymal brain loss. The lack of necrosis in post mortem examination suggests an apoptotic process. There is emerging evidence supports that mood stabilizers have antiapoptotic actions. Glutamatergic system abnormalities have been consistently associated with BD. But the mechanism of glutamate excitotoxicity on BD is still elusive.

**Methods:** Olfactory neuroepithelial progenitors (ONPs) were obtained by biopsy from type I bipolar patients and non-bipolar controls matched for age, gender, and passage number (n = 3, respectively). ONPs were exposed to 0.1M glutamate alone for 6 hours, 1 mM lithium alone for 3 days, or pretreated lithium for 3 days followed by glutamate. The apoptotic rate was measured by DNA fragmentation assays using an ELISA kit. The protein levels relevant to apoptotic pathway were determined by western blotting, such as BCL-2, AKT, B-RAF, cleaved-caspase-3, cleaved-PARP.

**Results:** 0.1 M glutamate treatment for 6 h induced apoptosis in ONPs. Moreover, the level of apoptotic damage in ONPs derived from BD was significantly greater than that from normal subjects ( $124.71 \pm 11.42$  vs  $36.43 \pm 12.52$ ,  $p < 0.05$ ). The protein levels of cleaved-caspase-3 were significant higher in BD-ONPs compare to non-BD-ONPs with glutamate treatment ( $3.25 \pm 0.95$  vs  $1.27 \pm 0.17$ ,  $p < 0.05$ ). Lithium (1 mM) pretreatment significantly increase B-RAF and BCL-2 protein expression in BD-ONPs than that in non-BD-ONPs ( $1.60 \pm 0.12$  vs  $1.05 \pm 0.13$ ,  $5.15 \pm 2.83$  vs  $0.81 \pm 0.18$ ,  $p < 0.05$ ).

**Conclusions:** ONPs derived from BD are more susceptible to glutamate-induced apoptosis. Lithium is more effective in increasing B-RAF and BCL-2 expression in BD-ONPs. The further study of the relevant mechanism will help to understand glutamate-induced apoptosis in BD.

### EEG coherence of drug-free and drug related patients with bipolar disorder

S Kesebir<sup>a</sup>, RM Demirer<sup>b</sup>

<sup>a</sup>Psychiatry NPIstanbul Hospital, Üsküdar University, Istanbul, Turkey, <sup>b</sup>Biomedical Engineering, Gelişim University, Istanbul, Turkey

**Objective:** Unlike most of the studies which are based on the coherence comparison between healthy subjects and patients, our aim is this work is to study the BD by finding invariants and variants by calculating coherence between drug-free and drug-related patients.

**Methods:** We compared EEG coherence of patients with BD in resting/normal condition and in hyperventilation condition for alpha, gamma, and beta frequency bands in frontal, central, and occipital regions. We used cross power spectral density to see power of the signals in the regions of the brain and coherence analysis with sampling frequency 128 Hz for 40 patients to determine how coherent changes in brains' left and right hemispheres after the treatment. Participants included 40 bipolar disorder, first manic episode patients. Patient's data recorded before and after the antimanic medication. The recording process ended at 16 scalp points by using international standard 10–20 system of electrode placement at sampling frequency of 128 Hz. 16 channels are generated by calculating the differences of two electrodes. We selected 3 electrode pairs to analyze frontal, central, and occipital regions of the brain. EEG recordings completed with 3 conditions, during 20 minutes time frame for each patient.

**Results:** There is active power density at alpha band before the treatment. After the treatment the activity could be observed with smaller magnitude. Peaks at 50 Hz were significant result of the power spectral density analysis. We obtained important frequency values that are 9–10 Hz in alpha band, 22–24 Hz in beta band, and 33–36 Hz gamma band, which non-stationary coherence patterns are shown before and after treatment recordings for both conditions. In frontal region, magnitude of the before and after treatment coherence signals were smaller at beta frequency interval. There are peaks at 41 Hz gamma band along the all brain regions in both before and after data. When patients were in resting condition, left and right hemispheres coherences for frontal, central and occipital regions have larger values than hyperventilation condition.

**Conclusion:** There is active power density at alpha band before the treatment in bipolar patient. After the treatment the activity could be observed with smaller magnitude.

### Interaction between HPA axis, adverse lipid profile, metabolic syndrome and female gender in bipolar disorder

A Ozerdem

Dokuz Eylül University, Turkey

Increased cardiovascular risk and increased premature mortality among patients with bipolar disorder (BD) particularly females compared to normal population and men with BD requires further attention to elucidate the underlying mechanisms. Rate of metabolic syndrome has been reported to be lower among young age female patients compared to the same age male patients although both groups present higher rates compared to healthy controls. Increased BMI and central obesity on the contrary are shown to be more prevalent in female BD patients compared to male patients. Data on adverse lipid profile in female patients compared to male patients is contradictory. Illness state (depression versus mania versus euthymia) may be affecting the findings. Medications used in treatment of bipolar disorder are known to be associated with weight gain, increased risk for metabolic syndrome, and development of diabetes. However, the impact of illness pathogenesis itself

and the medication effect on any of the abovementioned adversities are not fully understood. The moderating effect of estrogen, on the HPA axis activation resulting in increased cortisol levels also needs a more focused research as it seems to be affected by the presence or absence of stress. Dr. Ozerdem, during her presentation will discuss the interplay between HPA axis activity, metabolic syndrome, and adverse lipid profile in bipolar disorder with a special focus on the role of estrogen and point at potential areas for research for development of better clinical care.

### Resting state medial prefrontal functional connectivity variability over time: deficits and relationship to cognition in bipolar disorder

LT Eyler<sup>a</sup>, S Kovacevic<sup>b</sup>, B McKenna<sup>c</sup>, K Lu<sup>d</sup>, TT Liu<sup>d</sup>

<sup>a</sup>MIRECC & Psychiatry, San Diego VA & UC San Diego, San Diego, USA, <sup>b</sup>Psychiatry, San Diego Veterans Medical Research Foundation, San Diego, USA, <sup>c</sup>Psychiatry, UC San Diego, San Diego, USA, <sup>d</sup>Radiology, UC San Diego, San Diego, USA

**Aims:** Neuroimaging studies in euthymic bipolar disorder (BD) patients can reveal trait-like abnormalities and help explain inter-episode cognitive deficits. In particular, the degree of functional communication between the medial prefrontal (MPF) cortex and other nodes of the default mode network (DMN) at rest has been shown to be abnormal. Most studies examined only the average degree of concordance between resting signals over time, but network functional connectivity is known to vary from moment to moment. We compared this moment-to-moment variability between BD and healthy comparison (HC) participants and examined how it relates to cognitive performance in the BD group.

**Methods:** Using a multiband sequence modeled after the Human Connectome Project resting-state fMRI protocol, we scanned 21 euthymic BD I patients (7M/14F, 47 years old) and 20 demographically similar HC (6M/14F, 47 years old) for 10 minutes (833 timepoints). Processing included distortion and motion correction, temporal and spatial filtering, and statistical removal of heart and respiratory rate signals, white matter and ventricular signals, and motion parameters. The time series was averaged within eleven DMN nodes, and the MPF signal was correlated with the 10 other regional signals across the entire time course and using a sliding window approach to estimate changes in correlation across 19 sub-epochs. The temporal variance of these values was compared between groups and related to performance on measures of processing speed.

**Results:** Temporal variability in correlation strength between the MPF and other regions of the DMN was lower in BD than in HC participants. Correlation strength estimated across the entire 10 minute scan was not different between groups. Within the BD group, participants with the lowest temporal variability in connection strength between the MPF and posterior cingulate cortex had the slowest processing speed.

**Conclusions:** BD participants showed less dynamic range in the strength of connections between MPF and the rest of the DMN, and those with the least temporal variability in correlation strength with a key posterior node of the DMN had the poorest cognitive performance. Temporal variability in functional connectivity may be an important phenotype to understand the neural underpinnings of cognitive deficits in BD.

### Alterations in the effective connectivity of the fronto-insular network following targeted theta-burst transcranial magnetic stimulation

SJ Iwabuchi<sup>a</sup>, DP Auer<sup>b</sup>, F Raschke<sup>b</sup>, S Lankappa<sup>c</sup>, L Palaniyappan<sup>a</sup>

<sup>a</sup>Psychiatry and Applied Psychology Translational Neuroimaging in Mental Health, Institute of Mental Health University of Nottingham, Nottingham, United Kingdom, <sup>b</sup>Radiological Sciences Division of Clinical Neuroscience, University of Nottingham, Nottingham, United Kingdom, <sup>c</sup>Psychiatry, Nottinghamshire Healthcare NHS Trust, Nottingham, United Kingdom

**Background and aims:** Recent neuroimaging studies have identified the insula as a key brain region in the pathophysiology of depression and bipolar disorder and may be a crucial target for the treatment of depression. The modulation of the insular networks may have widespread effects on the connectivity of other disrupted networks, and ultimately reduce symptom burden in depression. Using a connectivity based approach, we sought proof of concept for the neuromodulation of the insula through transcranial magnetic stimulation (TMS). Our aim was to develop a connectivity-informed neuromodulation approach for TMS to reduce depressive symptom burden. To this end, we report a proof of concept study in healthy controls.

**Methods:** In a sample of 21 healthy controls, we investigated the effects of intermittent theta-burst TMS (iTBS) on fronto-insular effective connectivity using resting-state functional MRI (rs-fMRI) and Granger causal analysis (GCA). Images were acquired on a GE 3T MR750 scanner (five minute rs-fMRI scan duration) and preprocessed using DPARSF software. For each subject, GCA was seeded from the right anterior insula (rAI) to locate the highest peak intensity within the DLPFC, which was used as the target location for iTBS. We also ran an inverse GCA from each DLPFC target region to the rAI to form a reciprocal fronto-insula network. The Granger coefficients were extracted using 6 mm spherical regions of interest from rAI and frontal target regions and compared between sham and real iTBS.

**Results:** Results showed significant dampening of the negative influence of the DLPFC on the rAI following iTBS ( $p = 0.017$ ). Moreover, there was a trend toward a reduced positive influence of the rAI on the DLPFC ( $p = 0.095$ ). This suggests that iTBS has a direct effect on the effective connectivity between the DLPFC and rAI via an inhibitory mechanism on the reciprocal influence between the rAI and DLPFC.

**Conclusions:** Our results demonstrate that the application of a single session of targeted iTBS on the frontal cortex can modulate the effective connectivity of the rAI, a key target region in depression. These findings offer great promise for optimizing TMS efficacy in treating patients with affective disorders such as depression and bipolar disorder.

### Specificity of reduced fronto-limbic and inter-hemispherical connectivity for bipolar I disorder

J Linke<sup>a</sup>, T Netemeyer<sup>b</sup>, P Kanske<sup>c</sup>, C Poupon<sup>d</sup>, M Wessa<sup>a</sup>

<sup>a</sup>Department of Clinical Psychology and Neuropsychology, Institute for Psychology, Mainz, Germany, <sup>b</sup>Department of Neurobiology and Behavior, Hopkins Lab, Ithaca, USA, <sup>c</sup>Department of Social Neuroscience, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, <sup>d</sup>Neurospin Le Duda, UNIRS, Paris, France

Reduced white matter integrity of the anterior limb of the internal capsule (ALIC), uncinate fasciculus (UF) involved in memory integration and emotion regulation, and corpus callosum was not only reported in patients with bipolar I disorder (BD-I), but also among their healthy relatives. However, it remained unclear, whether these abnormalities are specific for bipolar disorder or rather pose a vul-

nerability for affective disorders in general. To address this issue we compared diffusion tensor imaging data of 21 euthymic BD-I patients (mean age: 44.5 (10), 9 male), 21 remitted patients with major depression (MD; mean age: 44 (9), 7 male) and 21 healthy controls (mean age: 43 (10), 9 male). After processing the data with tract based spatial statistics, we used a region of interest approach and observed significant lower fractional anisotropy in BD-I patients compared to patients with MD in ALIC ( $x = -15$ ,  $y = 15$ ,  $z = -1$ , 29 voxel,  $p_{\text{min FWE-corrected}} = 0.032$ ), UF ( $x = 29$ ,  $y = 14$ ,  $z = -7$ , 52 voxel,  $p_{\text{min FWE-corrected}} = 0.027$ ), and corpus callosum ( $x = 7$ ,  $y = -30$ ,  $z = 23$ , 3921 voxel,  $p_{\text{min FWE-corrected}} < 0.01$ ). Additional whole-brain analysis also revealed significant lower white matter integrity in the superior longitudinal fasciculus (SLF), a fiber bundle involved in the integration of the auditory and speech areas of the brain, in BD-I patients compared to MD patients ( $x = 35$ ,  $y = -21$ ,  $z = 26$ , 1605 voxel,  $p_{\text{min FWE-corrected}} = 0.025$ ). Compared to healthy controls, BD-I patients also showed lower fractional anisotropy values in ALIC ( $x = 20$ ,  $y = 16$ ,  $z = 7$ , 42 voxel,  $p_{\text{min FWE-corrected}} = 0.027$ ), UF ( $x = 28$ ,  $y = 15$ ,  $z = -8$ , 18 voxel,  $p_{\text{min FWE-corrected}} = 0.031$ ), and corpus callosum ( $x = 9$ ,  $y = -12$ ,  $z = 28$ , 441 voxel,  $p_{\text{min FWE-corrected}} = 0.04$ ). For patients with MD we observed increased white matter integrity in the ALIC ( $x = -17$ ,  $y = 5$ ,  $z = 11$ , 46 voxel,  $p_{\text{min FWE-corrected}} = 0.024$  and corpus callosum ( $x = 20$ ,  $y = -41$ ,  $z = 29$ , 922 voxel,  $p_{\text{min FWE-corrected}} = 0.014$ ), when compared to healthy controls. In sum, these results confirm specificity of reduced white matter integrity in the ALIC, UF, corpus callosum and SLF in BD-I and underline the importance of reduced white matter network connectivity within etiological models of BD-I.

### The effect of an acute bout of aerobic exercise on sustained attention and motor inhibition among adolescents with and without bipolar disorder

AWS Metcalfe<sup>a</sup>, BJ MacIntosh<sup>b</sup>, A Scavone<sup>c</sup>, X Ou<sup>c</sup>, BI Goldstein<sup>c</sup>

<sup>a</sup>Brain Sciences, Sunnybrook Research Institute, Toronto, Canada,

<sup>b</sup>Department of Physical Sciences, Sunnybrook Research Institute, Toronto, Canada, <sup>c</sup>Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada

**Aims:** Medial frontal dysfunction during attention & executive control tasks is reported in adolescents with bipolar disorder (BD). Aerobic exercise in healthy participants (HC) can improve neurocognitive function, and exercise benefits in those with BD have been widely discussed. This study combines this research to examine exercise effects in adolescents with and without BD using BOLD fMRI of the *sustained attention to response task* (SART) before and 30 minutes following aerobic exercise.

**Methods:** Participants: fifty 13–19 year-olds ( $M = 16.5$ ,  $SD = 1.6$ , 42% male, 30 BD adolescents – active mania excluded; 20 HCs). SART: button presses during rapid serial presentation of numbers 1–9, but inhibition for the number 3; practice controlled for session effects. Exercise: 20 minutes at 60 revolutions per minute on stationary bicycle-ergometer maintaining 60–80% of age-estimated maximum heart rate. Analysis: ANOVAs for behavioral and BOLD fMRI data.

**Results:** Post-commission-error RT decreased after exercise across groups. Planned comparisons found higher activation in rostral ACC, dorsal ACC and PCC for adolescents with BD > HC pre-exercise and BDpre > BD post-exercise, but no difference BDpost > HCpre. Event analysis of commission-errors produced the same pattern in PCC.

**Conclusions:** Exercise mitigated over-reactivity to error in behaviour. Findings of medial frontal cortex dysfunction in BD adolescents were replicated. Novel findings revealed reductions in

cingulate activation for adolescents with BD post-exercise that approximated HC baseline. These results provide a scientific basis for brain related changes in behaviors realized after a single session of exercise. Future investigations will examine longitudinal cascading effects of regular exercise on everyday symptoms in adolescents with BD.

### The TPH2 G703T polymorphism is associated with working memory in bipolar disorder and control cohorts

TE Van Rheenen<sup>a</sup>, K Bozaoglu<sup>b</sup>, SL Rossell<sup>a</sup>

<sup>a</sup>Brain and Psychological Sciences Research Centre, Swinburne University, Melbourne, Australia, <sup>b</sup>Genomics and Systems Biology, Baker IDI, Melbourne, Australia

**Objective:** Tryptophan Hydroxylase 2 (TPH2) has been implicated in bipolar disorder (BD), and affects cognition in healthy samples. To date, there have been no studies investigating the influence of the TPH2 G703T polymorphism on neurocognition in BD. We present the first examination of the association between G703T and a candidate cognitive endophenotype for BD; working memory.

**Method:** Forty nine BD patients and 53 healthy controls were genotyped for rs4570625 and its association with performance on the Letter Number Span (LNS) was tested.

**Results:** There was a significant allelotype effect for the LNS, with T allele carriers performing better on this measure than those absent of the T allele. There was no group by allelotype interaction.

**Conclusions:** These novel findings suggest that genetic variation in the TPH2 gene is associated with cognitive performance in BD and healthy controls. Research in larger samples is needed to establish whether these results remain consistent.

### Abnormal high energy phosphate molecule metabolism during regional brain activation in patients with bipolar disorder

C Yuksel<sup>a</sup>, F Du<sup>a</sup>, C Ravichandran<sup>a</sup>, J Goldbach<sup>a</sup>, T Thida<sup>a</sup>, P Lin<sup>a</sup>, B Dora<sup>a</sup>, S Gruber<sup>a</sup>, D Ongur<sup>a</sup>, B Cohen<sup>a</sup>

<sup>a</sup>Psychiatry, McLean Hospital/Harvard Medical School, Boston, USA

Converging evidence suggests bioenergetic abnormalities in bipolar disorder (BD). In the brain, phosphocreatine (PCr) acts a reservoir of high-energy phosphate (HEP) bonds, and creatine kinases (CK) catalyze the transfer of HEP from adenosine triphosphate (ATP) to PCr and from PCr back to ATP, at times of increased need. This study examined the activity of this mechanism in BD by measuring the levels of HEP molecules during a stimulus paradigm that increased local energy demand. 23 patients diagnosed with BD-I and 22 healthy controls (HC) were included. Levels of phosphorus metabolites were measured at baseline and during visual stimulation in the occipital lobe using <sup>31</sup>P MRS at 4T. Changes in metabolite levels showed different patterns between the groups. During stimulation, HC had significant reductions in PCr but not in ATP, as expected. In contrast, BD patients had significant reductions in ATP but not in PCr. In addition PCr/ATP ratio was lower at baseline in patients, and there was a higher change in this measure during stimulation. This pattern suggests a disease related failure to replenish ATP from PCr through CK enzyme catalysis during tissue activation. Further studies of HEP at baseline and during stimulation and directly examining the CK flux in BD are required to confirm and extend this finding.

## Finding hidden patterns using network analysis of mood disorders symptoms

JH Baek<sup>a</sup>, B Babadi<sup>b</sup>, A Nierenberg<sup>a</sup>

<sup>a</sup>Psychiatry, Massachusetts General Hospital, Boston, USA,

<sup>b</sup>Center for brain science, Harvard University, Boston, USA

**Aims:** Psychiatric symptom patterns in bipolar I (BP-I), II (BP-II) and major depressive disorders (MDD) have been widely studied but differential diagnosis based on cross-sectional symptoms have still been a clinical challenge. Current approaches to psychiatric symptoms may limit our ability to explore complex patterns within symptom presentations of mood disorders. Network approaches can reveal patterns that would otherwise be hidden in a various biological systems. In this study, we aimed to apply network analysis to mood disorder symptoms to explore their similarities and differences.

**Methods:** Using customized algorithms in MatLab environment, we applied the network analysis techniques to psychopathology data of patients with mood disorder (BP-I, BP-II and MDD) from the Epidemiological data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) wave 1 study. Demographic characteristics and each symptom criterion from DSM-IV diagnostic criteria were used as nodes (total 59 nodes), and positive partial correlation coefficients, an indicator of co-occurrence of each pair of symptoms after controlling the contribution of other symptoms were used as edges. For each diagnosis lifetime and 12 month symptom networks were separately constructed.

**Results:** Of lifetime symptom networks, MDD network had greater numbers of edges (55 nodes, 118 edges) than BP-I (56 nodes, 98 edges) and BP-II networks (50 nodes, 68 edges) ( $\chi^2 = 14.16$ ,  $p = 0.001$ ), indicating a more heterogeneous symptom presentation in MDD. Most nodes were located in distinct clusters, indicating most symptoms were inter-connected. In lifetime symptom networks, symptoms of generalized anxiety disorder had the highest Eigenvector centrality, meaning these nodes serve as “hubs” of comorbidity in mood disorders. A similarity index showed that BP-I, BP-II and MDD network had quite different structures from one another.

**Conclusions:** Although mood symptoms are considered the cardinal feature of mood disorders, generalized anxiety symptoms were central to the symptom networks, highlighting the importance of anxiety symptoms in mood disorders. Symptom network structures may differ by time frame. The network approach provides a new way of seeing characteristics of psychiatric symptoms as a whole and may help developing a novel and more accurate psychiatric disease classification system.

## Voice analysis using smartphones as an electronic biomarker of illness activity in bipolar disorder – the MONARCA studies

M Faurholt-Jepsen<sup>a</sup>, M Vinberg<sup>a</sup>, M Frost<sup>b</sup>, O Vinther<sup>c</sup>, EM Christensen<sup>a</sup>, J Bardram<sup>b</sup>, LV Kessing<sup>a</sup>

<sup>a</sup>Psychiatric Center Copenhagen, Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark, <sup>b</sup>PIT Laboratory, IT University of Copenhagen, Copenhagen, Denmark, <sup>c</sup>Technical University of Denmark, Technical University of Denmark, Copenhagen, Denmark

**Background:** Objective methods for measuring illness activity in bipolar disorder are lacking. Smartphones offer unique opportunities for collecting automatically generated objective data, such as number of phone calls/day; number of text messages/day; amount of movement/day; amount of data traffic/day etc., during naturalistic setting and with real-time data. The present study aimed at investigating correlations between different voice parameters dur-

ing phone calls and clinically rated depressive and manic symptoms in patients with bipolar disorder.

**Methods:** A total of 29 patients with bipolar disorder were recruited from The Copenhagen Clinic for Affective Disorder, Denmark during the period from October 2013 to October 2014. All patients used the MONARCA system on smartphones for daily electronic self-monitoring of depressive and manic symptoms for a three-month period and automatically generated objective data, including voice parameters, were collected simultaneously in real-time and naturalistic settings. Depressive and manic symptoms were clinically rated fortnightly using the Hamilton Depression Rating Scale 17-item and Young Mania Rating Scale, respectively and self-rated depressive and manic symptoms were assessed using Becks Depressive Inventory 42-item and Altman Self-Rating scale for Mania, respectively.

**Results:** All of the included patients completed the study. Analyses are ongoing, and results will be presented at the ISBD 2015 conference.

**Conclusions:** Automatically generated objective data collected using smartphones is a promising method for measuring illness activity in patients with bipolar disorder. If voice analyses collected in naturalistic settings correlate with clinically rated depressive and manic symptoms this may serve as an electronic biomarker of illness activity in patients with bipolar disorder.

## The pros and cons of online recruitment

E Gliddon<sup>a</sup>, S Lauder<sup>b</sup>, V Cosgrove<sup>c</sup>, D Grimm<sup>c</sup>, S Dodd<sup>a</sup>, T Suppes<sup>c</sup>, M Berk<sup>a</sup>

<sup>a</sup>IMPACT Strategic Research Centre, Deakin University, Geelong, Australia, <sup>b</sup>Department of Psychiatry, University of Melbourne, Parkville, Australia, <sup>c</sup>Bipolar and Depression Research Program, VA Palo Alto Health Care System, Palo Alto, USA

**Aims:** Online recruitment in internet-based psychosocial interventions can be extremely valuable, however it also presents a unique set of challenges. This poster discusses the pros and cons of online recruitment, citing the experiences of the MoodSwings online self-help program for bipolar disorder.

**Methods:** Online recruitment offers a unique set of challenges and opportunities, especially when utilizing social media outlets such as Facebook and Twitter. While the internet can provide valuable recruitment resources, converting expressions of interest into research participants is not easy. In a randomized controlled trial using the MoodSwings 2.0 online intervention for bipolar disorder, social media outlets as well as well-established websites related to mental illness were utilized to aid recruitment. This project has received approval from the Barwon Health Human Research Ethics Committee and the Department of Veterans Affairs Institutional Review Board. All participants complete informed consent prior to randomization.

**Results:** 80% of the total recruitment target of 300 was reached in 10 months. Each time trial information was shared online, the program received an influx of new registrations, totalling 1400 registrations of interest in less than 12 months. Interestingly, only 4% of registrants have gone on to become participants as of January 1, 2015.

**Conclusions:** Online studies require different approaches to design and implementation from face-to-face studies. While online recruitment can yield a large number of potential participants in a short period of time, it remains unclear how to achieve the best results in turning expressions of interest into research participants. This research is supported by the National Institute of Mental Health (R34MH091384 and R34MH091284).

## Actigraphy can identify differences in motor activity in acute episodes of mood disorders

K Krane-Gartiser<sup>a</sup>, TEG Henriksen<sup>b</sup>, A Vaaler<sup>a</sup>, OB Fasmer<sup>c</sup>, G Morken<sup>a</sup>

<sup>a</sup>Department of Neuroscience/ Department of Psychiatry, Norwegian University of Science and Technology and St Olavs University Hospital, Trondheim, Norway, <sup>b</sup>Department of Psychiatry, Valen Hospital University of Bergen and Haukeland University Hospital, Bergen, Norway, <sup>c</sup>Department of Psychiatry, University of Bergen and Haukeland University Hospital, Bergen, Norway

**Aims:** Actigraphy is a promising tool for monitoring phase shifts and changes following treatment in mood disorders. We aimed to compare recordings of motor activity in unipolar depression with and without motor retardation, mania, bipolar depression, and healthy controls, using linear and nonlinear analytical methods.

**Methods:** 24-hour actigraphy recordings from 82 acutely admitted inpatients with mood disorders were compared to 28 recordings from healthy controls. The patient population consisted of 52 inpatients with unipolar depression, who were separated in 25 with clinically assessed motor retardation and 27 without motor retardation, 18 inpatients with mania and 12 with bipolar depression. Mean activity and several measures of variability and complexity were calculated for the 24-hour recordings and 64-minute periods of continuous motor activity in the morning and evening.

**Results:** Comparing the patients with unipolar depression, the patients with motor retardation had a reduced mean activity level and higher intra-individual variability, as given by increased standard deviation (SD) and root mean square successive difference (RMSSD) during 24 hours, compared to patients without motor retardation. All depression groups demonstrated significantly lower mean activity compared to healthy controls, but higher variability shown by increased SD and RMSSD. All patient groups had a higher RMSSD/SD ratio compared to controls. In the active morning period, the unipolar depressed patients without motor retardation and the patients with mania displayed significantly increased complexity of time series compared to the motor-retarded patients with unipolar depression, and the patients with bipolar depression, respectively.

**Conclusions:** We have found distinctly different activity patterns in hospitalized patients in acute episodes of mood disorders, according to diagnostic group and compared to healthy comparison subjects. Patients with and without motor retardation can be distinguished objectively using actigraphy. Findings in unipolar depressed inpatients without motor retardation closely resemble those of inpatients with mania and previously studied schizophrenia and glutamatergic antagonism.

## Acceptability and tolerability of ambulatory monitoring in bipolar disorder: a patient perspective

K Saunders<sup>a</sup>, AC Bilderbeck<sup>a</sup>, P Panchal<sup>a</sup>, D Brett<sup>a</sup>, GD Clifford<sup>b</sup>, CJ Harmer<sup>a</sup>, AC Nobre<sup>a</sup>, PJ Harrison<sup>a</sup>, JR Geddes<sup>a</sup>, GM Goodwin<sup>a</sup>

<sup>a</sup>Department of Psychiatry, University of Oxford, Oxford, United Kingdom, <sup>b</sup>Institute of Biomedical Engineering, University of Oxford, Oxford, United Kingdom

**Aims:** To investigate the experience of using remote mood- and activity-monitoring devices for research purposes among patients with bipolar disorder, and to explore barriers to wider use.

**Methods:** Qualitative study of 20 people with bipolar disorder who were interviewed following 3 months of monitoring. Monitoring involved daily and weekly ratings of mood (via a smartphone 'App' and by text message/email, respectively) as well as ambulatory movement and sleep (measured via a wrist-worn accelerometer).

ter, a wearable pedometer, and the smartphone's in-built accelerometer). Interviews were semi-structured and included questions regarding the acceptability and tolerability of monitoring. Transcripts of interviews were analysed by two independent raters using a framework technique to gain an in depth understanding of the patient experience of mood and activity monitoring, and to identify any potential barriers to using such approaches in routine clinical practice.

**Results:** Monitoring was endorsed by majority of participants. The devices were well tolerated and participants reported enjoying using them. Use of the devices appeared to facilitate understanding of their condition and many participants described significant behavioural changes associated with using the devices, in particular when devices provided clear and meaningful feedback. Behavioural changes that were described included increased physical activity, weight loss, decreased alcohol use and improved sleep hygiene. Concerns were raised about how monitoring might be misinterpreted during psychotic episodes and the need for devices to require minimal user input. The majority of participants chose to continue using the devices as part of an optional 9 month study extension.

**Conclusions:** Monitoring of mood, activity and sleep is acceptable and tolerable for individuals with bipolar disorder. Monitoring appears to promote positive behavioural change without the need for additional psychoeducation. Such approaches show great promise in enhancing our understanding of bipolar disorder, and in the promotion of self-management among patient groups.

## Reducing default rates in patients discharged from an early psychosis unit to continuity care

S Basu, SB Ali, S Verma

Early Psychoses Intervention Programme, Institute of Mental Health, Singapore, Singapore

**Objective:** To reduce default rate of patients discharged from Early Psychosis Intervention Program (EPIP) at Institute of Mental Health (IMH) to Continuity Care from 25% to 0% in 6 months and sustain the improvement over the a period of two years.

**Design:** All patients discharged from Early Psychosis Intervention Program (EPIP) at Institute of Mental Health (IMH) to Continuity Care were included and flow chart of the processes leading to discharge were tabulated. A survey was given to patients to evaluate their needs and a cause and effect diagram, a pareto chart was done and the top 4 causes for default were targeted. PDSA cycles were done after implementation.

**Intervention:** The Interventions included changing the word 'Discharge' to 'Transfer of care', having designated persons assigned to follow up patients when they are discharged from the specialized service, use of relapse signature cards and token of appreciation given to patients if they were compliant with their appointments.

**Main outcome measures:** Default at first appointment with downstream care was measured.

**Results:** The default rate was 0% as all the patients discharged from Early Psychosis Intervention Program (EPIP) kept their scheduled appointments. The pre-intervention default rates were 25%. We were able to sustain this from the time of the interventions till date.

**Conclusions:** The interventions were perceived as effective and efficient as rates of default drastically reduced from 25% to 0% as targeted.

## Psychosocial and cognitive remediation for recurrent mood disorders: pilot findings and project outline

K Douglas<sup>a</sup>, R Porter<sup>a</sup>, M Crowe<sup>a</sup>, M Inder<sup>a</sup>, J Jordan<sup>a</sup>, B Beaglehole<sup>a</sup>, C Lacey<sup>a</sup>, R Mulder<sup>a</sup>, C Bowie<sup>b</sup>

<sup>a</sup>Psychological Medicine, University of Otago, Christchurch, New Zealand, <sup>b</sup>Psychology, Queen's University, Kingston, Canada

**Aim:** Guidelines for the treatment of mood disorders typically recommend a combination of medication and psychotherapy. While these treatment modalities are effective in treating selected aspects of mood disorders, cognitive functioning tends to remain impaired after symptomatic recovery. Cognitive impairment has been associated with occupational and interpersonal deficits. This presentation will outline a large-scale study commencing in mid-2015 in Christchurch, New Zealand, examining the effectiveness of a one-year Functional Recovery Package (FRP) in treating recurrent mood disorder patients (recurrent major depressive disorder and bipolar disorder). Results from an open-label pilot study assessing the feasibility of a Cognitive Remediation intervention (which is to be included in the large-scale study) in an equivalent patient sample will also be presented.

**Method:** For the large-scale study, 180 patients with a recurrent mood disorder, upon discharge from specialist mental health services in Christchurch, will be randomised to receive the FRP or treatment as usual (TAU). FRP will consist of three components: (1) Specialist Medication Management delivered by psychiatrists, (2) Interpersonal and Social Rhythms Therapy delivered by psychologists or nurses, and (3) Cognitive Remediation. Primary outcome measures will include the Functioning Assessment Short Test, cost-analysis of service use, neuropsychological functioning, and relapse rates. In the open-label pilot study, patients with recurrent mood disorders who were discharged from mental health services undertook a 10-week Cognitive Remediation intervention. This involved flexible weekly sessions with a therapist and three additional online practice sessions per week using a computerised cognitive exercise package. Patients completed neuropsychological assessment and several measures of clinical and daily functioning before and after completion of the Cognitive Remediation intervention.

**Results:** Findings relate to the open-label pilot study. Patients ( $n = 10$ ) found the online format manageable and engaging and all have been able to engage in three weekly practice sessions. Patient recruitment has only recently ended, and analysis of clinical, daily functioning, and neuropsychological measures are underway. Findings will be reported in this presentation.

**Conclusions:** These studies recognise the importance not only of improving clinical state in patients who suffer from recurrent mood disorders, but also to independently target cognitive functioning to improve real-world outcomes.

## Bipolar disorder influences weight loss in the nationally implemented MOVE!® program for veterans

C Janney<sup>a</sup>, R Owen<sup>b</sup>, N Bowersox<sup>c</sup>, D Ratz<sup>a</sup>, A Kilbourne<sup>a</sup>, C Richardson<sup>a</sup>

<sup>a</sup>CCMR/HSRD, VA, Ann Arbor, USA, <sup>b</sup>Center for Mental Healthcare and Outcomes Research, VA, Little Rock, USA,

<sup>c</sup>CCMR/SMITREC/Office of Mental Health Operations, VA, Ann Arbor, USA

**Aims:** To investigate the relationship between bipolar disorder (BD) and weight loss in overweight/obese veterans enrolled in MOVE!®, a national weight loss program available throughout the Veterans Health Administration (VHA) health care system.

**Methods:** MOVE!® participants with at least 2 MOVE!® visits enrolled during Fiscal Years 2008–2012, who had BMI  $\geq 25$  kg/m<sup>2</sup>, and who were 18–69 years of age ( $n = 46772$ ) were included in these analyses. VHA administrative data identified Veterans with BD (ICD-9-CM codes=296.0–296.1, 296.4–296.89, 301.11, 301.13), schizophrenia/schizoaffective disorders (SZO) (ICD-9-CM=295) or no mental health disorders (MHD). Weight changes at 6- and 12-months by MHD diagnosis were modeled using repeated measures controlling for demographics, and medical and psychiatric comorbidities.

**Results:** BD was diagnosed in 3529 (7.6%) veterans. At baseline enrollment, veterans with BD ( $240.8 \pm 48.0$  lbs.) or SZO ( $241.0 \pm 47.4$  lbs.,  $n = 2315$ ) weighed less than those with no MH ( $248.2 \pm 49.6$  lbs.,  $n = 40,928$ ) ( $p < 0.01$ ). Over the one year evaluation period, the pattern of weight loss was statistically different between veterans with BD compared to veterans with no MHD ( $p < 0.01$ ). At 6-months, average weight loss among veterans with BD ( $-3.0 \pm 0.2$  lbs.) was less than those with no MHD ( $-3.6 \pm 0.1$  lbs.,  $p < 0.01$ ). Between 6- and 12-months, veterans with BD continued to lose weight, on average, while those with no MHD were regaining weight, on average. Overall, average weight loss was modest for veterans with BD ( $-3.8 \pm 0.3$  lbs.), SZO ( $-3.5 \pm 0.3$  lbs.), or no MHD ( $-3.1 \pm 0.1$  lbs.) at 12 months ( $p < 0.01$ ). Clinically significant weight loss ( $\geq 5\%$  from baseline) at 12-month was achieved by 23.6%, 23.8%, and 18.9% of veterans with BD, SZO, or no MHD, respectively ( $p < 0.01$ ).

**Conclusion:** These findings highlight that modest weight loss for individuals with BD or SZO is obtainable within a nationally implemented weight loss intervention. Veterans with BD or SZO exhibited delayed weight loss at 6-months but continued to lose weight at 12-months compared to veterans with no MHD.

## Tardive dyskinesia and tardive dystonia with second-generation antipsychotics in bipolar disorder patients unexposed to first-generation antipsychotic

Y Cho<sup>a</sup>, A Lee<sup>a</sup>, J Kim<sup>a</sup>, J Kim<sup>b</sup>, M Choi<sup>c</sup>, S Yoon<sup>d</sup>, K Ha<sup>b</sup>, K Hong<sup>a</sup>

<sup>a</sup>Department of Psychiatry, Samsung Medical Center, Seoul, Korea,

<sup>b</sup>Department of Neuropsychiatry, Seoul National University

Bundang Hospital, Seoul, Korea, <sup>c</sup>Center for Clinical Research,

Samsung Biomedical Research Institute, Seoul, Korea, <sup>d</sup>Department of Psychiatry, Samsung Medical Center, Seoul, Korea

**Objective:** Second-generation antipsychotics (SGAs) are frequently used in the treatment of bipolar disorder. However, there is still no consensus on the risk of tardive dyskinesia and dystonia with SGAs in bipolar disorder. This study aimed to investigate, in a naturalistic out-patient clinical setting, prevalence rates and associated factors of tardive dyskinesia and dystonia with SGAs in patients with bipolar disorder.

**Methods:** The authors assessed 78 non-elderly patients with bipolar ( $n = 71$ ) or schizoaffective disorder ( $n = 7$ ) who received SGAs with a combined use of mood stabilizers for more than three months without previous exposure to first-generation antipsychotics. Tardive movement symptoms were assessed using the Abnormal Involuntary Movement Scale (AIMS), Extrapyramidal Symptom Rating Scale (ESRS). Hospital records longer than one recent year describing any observed tardive movement symptoms were reviewed.

**Results:** A current or past history of tardive dyskinesia and/or tardive dystonia associated with SGAs was identified in 13 subjects (16.7%). These patients were being treated with ziprasidone, risperidone, olanzapine, quetiapine, paliperidone at the time of the onset of the movement symptoms. Tardive dyskinesia was mostly in the orolingual area, and the most frequently observed tardive dystonia was oromandibular area. A past history of acute dystonia



was significantly associated with tardive dyskinesia and dystonia. A antecedent lithium use also showed trend of association with tardive movement syndromes.

**Conclusion:** Tardive dyskinesia or dystonia was observed in a substantial portion of bipolar disorder patients who had been treated with SGAs. A history of acute dystonia and the antecedent lithium treatment seem to increase the risk of tardive movement syndromes.

### The value of early improvement as a predictor of short-term response during treatment of bipolar depression with lurasidone

DV Iosifescu<sup>a</sup>, J Tsai<sup>b</sup>, A Pikalov<sup>c</sup>, H Kroger<sup>d</sup>, J Cucchiaro<sup>e</sup>, A Loebe<sup>f</sup>

<sup>a</sup>Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, USA, <sup>b</sup>Medical Affairs, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>c</sup>Clinical Development and Medical Affairs, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>d</sup>Clinical Development, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>e</sup>Clinical Development, Sunovion Pharmaceuticals Inc., Fort Lee, USA

**Aims:** To evaluate the utility of early improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Global Impressions Bipolar Version, Severity of Illness (CGI-BP-S) scale as predictors of response to lurasidone in bipolar depression.

**Methods:** Patients with bipolar I depression were randomized to 6 weeks of double-blind treatment with lurasidone in a monotherapy study (20–60 mg/d and 80–120 mg/d vs placebo), and in an adjunctive therapy study (20–120 mg/d vs placebo; with lithium or valproate). For both studies, the relationship between early improvement (at Week 2) and response at Week 6 was assessed using 2 criteria (MADRS improvement  $\geq 25\%$ ; CGI-BP-S improvement  $\geq 1$ -point). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of early improvement for the prediction of endpoint response ( $\geq 50\%$  reduction from baseline in MADRS total score) were estimated. Receiver operating characteristic (ROC) curves were used to evaluate the performance characteristics of early improvement criteria for the prediction of endpoint response, reported as area under the ROC curve ( $AUC_{ROC}$ ).

**Results:** In the monotherapy study, the proportion of patients showing early improvement at Week 2 using the MADRS  $\geq 25\%$  criterion was 47.6%, and the proportion using the CGI-BP-S  $\geq 1$  criterion was 52.0%. For prediction of endpoint response at Week 2, the MADRS  $\geq 25\%$  criterion had 64.9% sensitivity, 78.6% specificity, 82.0% PPV, 59.7% NPV, and  $AUC_{ROC}=0.877$ ; and the CGI-BP-S  $\geq 1$  improvement criterion had 62.8% sensitivity, 64.3% specificity, 72.7% PPV, 53.4% NPV, and  $AUC_{ROC}=0.852$ . In the adjunctive therapy study, the proportion of patients showing early improvement at Week 2 using the MADRS  $\geq 25\%$  criterion was 51.7%, and the proportion using the CGI-BP-S  $\geq 1$  criterion was 64.3%. For prediction of endpoint response at Week 2, the MADRS  $\geq 25\%$  criterion had 68.5% sensitivity, 78.4% specificity, 85.1% PPV, 58.0% NPV, and  $AUC_{ROC}=0.919$ ; and the CGI-BP-S  $\geq 1$  improvement criterion had 77.2% sensitivity, 58.8% specificity, 77.2% PPV, 58.8% NPV, and  $AUC_{ROC}=0.883$ .

**Conclusions:** Week 2 improvement was found to robustly predict clinical response at Week 6 in patients treated with lurasidone for bipolar depression. Both definitions of early improvement (CGI-BP-S; MADRS) performed similarly in predicting response. Further analyses are needed determine the utility of early improvement for clinical decision-making.

### Effect of lurasidone on metabolic parameters in patients with bipolar depression

JW Newcomer<sup>a</sup>, J Tsai<sup>b</sup>, A Pikalov<sup>c</sup>, H Kroger<sup>d</sup>, J Cucchiaro<sup>e</sup>, A Loebe<sup>f</sup>

<sup>a</sup>Clinical Biomedical Science, Charles E. Schmidt College of Medicine Florida Atlantic University, Boca Raton, USA, <sup>b</sup>Medical Affairs, Sunovion Pharmaceuticals Inc, Marlborough, USA, <sup>c</sup>Clinical Development and Medical Affairs, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>d</sup>Clinical Development, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>e</sup>Clinical Development, Sunovion Pharmaceuticals Inc., Fort Lee, USA

**Aims:** To evaluate the extent to which treatment with lurasidone was associated with clinically relevant shifts in body mass index (BMI) and metabolic laboratory values in patients with bipolar depression.

**Methods:** Data were analyzed from 3 studies in patients with bipolar depression who were randomized to 6 weeks of double-blind, placebo-controlled treatment with lurasidone (20–120 mg/d), either as monotherapy (one study, N = 499), or adjunctive therapy with lithium or valproate (two studies, combined N = 694). Patients completing these 3 acute studies continued to receive 6 months of treatment with lurasidone 20–120 mg/d in an open-label extension study (N = 813). Normal, borderline, or abnormal BMI or laboratory values, respectively, were defined as follows for BMI (18.5–25 vs 25–30 vs  $\geq 30$  kg/m<sup>2</sup>), cholesterol (6.4%). The proportions of patients who shifted between normal and borderline-or-abnormal values were analyzed, from double-blind baseline to Week 6, and from double-blind baseline to Month 6 of the extension study.

**Results:** At Week 6 in the monotherapy study, the proportion of patients treated with lurasidone vs placebo, respectively, who shifted from normal-to-borderline/abnormal were as follows for BMI (7.5% vs. 4.9%), cholesterol (25.4% vs 15.2%), triglycerides (30.4% vs 38.6%), LDL (21.0% vs 25.0%), and glucose (20.6% vs 17.4%); and the proportion who shifted from borderline/abnormal-to-normal were as follows for BMI (2.2% vs. 1.1%), cholesterol (13.3% vs 9.3%), triglycerides (18.1% vs 20.0%), LDL (16.9% vs 16.9%), and glucose (48.3% vs 39.4%). At Month 6, the proportion on lurasidone monotherapy who shifted from normal-to-borderline/abnormal vs borderline/abnormal-to-normal, respectively, were as follows for BMI (12.5% vs. 1.5%), cholesterol (22.4% vs 8.1%), triglycerides (33.0% vs 19.7%), LDL (30.0% vs 23.2%), and HbA1c (16.1% vs 28.1%). The shift pattern was similar among patients treated in the adjunctive therapy study at both Week 6 and Month 6.

**Conclusions:** These data add to the substantial and growing body of information regarding the metabolic safety of lurasidone.

### Long-term use of lurasidone in patients with bipolar disorder: safety and effectiveness over 2 years of treatment

A Pikalov<sup>a</sup>, J Tsai<sup>b</sup>, Y Mao<sup>c</sup>, J Cucchiaro<sup>d</sup>, A Loebe<sup>e</sup>

<sup>a</sup>Clinical Development and Medical Affairs, Sunovion Pharmaceuticals Inc., Fort Lee, USA, <sup>b</sup>Medical Affairs, Sunovion Pharmaceuticals Inc., Marlborough, USA, <sup>c</sup>Clinical Development, Sunovion Pharmaceuticals Inc., Fort Lee, USA

**Aims:** To evaluate the safety and effectiveness of lurasidone over 2 years of treatment in patients with bipolar disorder who initially presented with a major depressive episode.

**Methods:** Patients with bipolar I depression were enrolled in one of three 6-week, double-blind, placebo-controlled trials (monotherapy with lurasidone, 1 study; adjunctive therapy with lurasidone and lithium or valproate, 2 studies); followed by a 6-month open-label extension study of lurasidone in flexible daily doses of 20–120 mg.

Six month study completers were then treated for an additional 18 months with flexible, once-daily doses of lurasidone in the range of 20–80 mg. Concomitant therapy with mood stabilizers and antidepressant medications was permitted throughout the open-label studies. The Clinical Global Impression–Severity (CGI-S) scale was included as a measure of treatment efficacy.

**Results:** A total of 941/1199 patients (78.5%) completed the 6 week acute treatment studies (lurasidone, 77.4%; placebo, 80.0%), of whom 817 entered the 6-month extension study, with 559/817 (68.4%) completing. A total of 122 patients entered the 18-month continuation study (52.5% male; mean age, 41.3 years; 76.2% receiving adjunctive therapy with lithium or valproate). Overall, 19.7% of patients discontinued during 18 months of treatment, including 6.6% due to adverse events and 1.6% due to insufficient efficacy. An additional 58 patients (47.5%) were ongoing at the time the study was terminated by the sponsor. Among patients who entered the 18-month continuation study, the mean CGI-S score at baseline of the acute study was 4.3, and improved to 2.8 at baseline of the 6-month extension study, and was 2.1 at baseline of the 18-month continuation study. At 18-month endpoint, the mean CGI-S score was 1.7 (observed case [OC] analysis; LOCF, 1.9). Median change in weight, from acute baseline to 18-month continuation endpoint was +0.10 kg (OC,  $n = 55$ ); median change in cholesterol was  $-3.0$  mg/dL, and median change in triglycerides was +26.0 mg/dL (OC,  $n = 54$  for both).

**Conclusions:** Up to 2 years of treatment with lurasidone was safe and well-tolerated in this bipolar depression population, with minimal effects on weight and metabolic parameters. Efficacy was maintained during extended treatment with lurasidone.

### Categorical improvement across mania symptoms: pooled analyses of cariprazine phase II/III trials

S Zukin<sup>a</sup>, K Lu<sup>b</sup>, A Ruth<sup>c</sup>, M DeBelle<sup>d</sup>, S Durgam<sup>e</sup>, I D'Souza<sup>f</sup>

<sup>a</sup>Forest Research Institute, Jersey City, USA, <sup>b</sup>Biostatistics, Forest Research Institute, Jersey City, USA, <sup>c</sup>Prescott Medical Communications Group, Chicago, USA, <sup>d</sup>Medical Division, Gedeon Richter Plc, Budapest, Hungary, <sup>e</sup>Clinical Development, Forest Research Institute, Jersey City, USA, <sup>f</sup>Medical Affairs – CNS, Forest Research Institute, Seattle, USA

**Aims:** Cariprazine, a dopamine D<sub>3</sub>/D<sub>2</sub> receptor partial agonist with preferential binding to D<sub>3</sub> receptors, has demonstrated efficacy in 3 positive Phase II/III clinical trials in patients with manic or mixed episodes associated with bipolar I disorder. This pooled post hoc analysis assessed clinically relevant symptom improvement in individual YMRS items by evaluating the percent of patients that shifted from a more severe symptom category at baseline to a less severe category at end of study.

**Methods:** Pooled 3-week data ( $N = 1037$ ) from 3 double-blind, randomized, placebo-controlled trials (NCT00488618, NCT01058096, NCT01058668) was analyzed. All cariprazine doses (3–12 mg/d) were pooled. For categorical shift analyses, the percentage of patients that shifted from at least moderate severity (YMRS item score  $\geq 2$  [items scored 0–4] and  $\geq 4$  [items scored 0–8]) at baseline to mild/no symptoms (score  $< 2$  [0–4 items] and  $< 4$  [0–8 items]) at Week 3 were determined for all 11 YMRS items. Additional analyses included the percentage of patients that shifted from at least moderate to mild/no symptoms concurrently on all 4 core YMRS symptoms (irritability, speech, content, and disruptive-aggressive behavior) and the percentage of patients with mild/no symptomatology at endpoint concurrently on all 11 items.

**Results:** The percentage of patients that shifted from moderate or worse severity at baseline to mild/no symptoms at Week 3 was significantly higher for cariprazine vs placebo on each of the YMRS single items. Odds ratios (OR) ranged from 1.6 (increased motor

activity-energy) to 2.7 (irritability); all  $p < 0.001$ . Category shifts on all 4 YMRS core items concurrently were observed in a significantly greater percentage of cariprazine (50.5%) vs placebo (29.1%) patients (OR = 2.43;  $p = 0.0002$ ). The percentage of patients with mild/no symptoms on all 11 YMRS domains at endpoint was also significantly higher in the cariprazine (22.5%) vs placebo (13.5%) group (OR = 1.85;  $p = 0.0004$ ).

**Conclusions:** In this novel post hoc YMRS category shift analysis, a significantly greater proportion of cariprazine-treated compared with placebo-treated patients showed clinically meaningful categorical improvements on all 11 YMRS symptom domains. These results suggest that cariprazine is associated with clinically meaningful improvements across a broad spectrum of mania symptoms.

### Patterns of improvement in patients with acute depressive episodes of bipolar I disorder and bipolar II disorder

C Datto<sup>a</sup>, J Mullen<sup>b</sup>, W Pottorf<sup>c</sup>, S LaPorte<sup>d</sup>, C Liss<sup>d</sup>

<sup>a</sup>US Medical Affairs, AstraZeneca Pharmaceuticals, Wilmington, USA, <sup>b</sup>R&D, AstraZeneca Neuroscience, Cambridge, USA, <sup>c</sup>Medical Information, AstraZeneca Pharmaceuticals, Wilmington, USA, <sup>d</sup>Biometrics and Information Sciences, AstraZeneca Pharmaceuticals, Wilmington, USA

**Aims:** Few studies of acute depressive episodes of bipolar disorder (BD) include patients with either BD type I or II. Five studies were examined of BDI and II patients treated with quetiapine (QTP; immediate and extended release), placebo, and either lithium or paroxetine to illustrate clinical patterns of response and safety profiles.

**Methods:** Primary results of the 5 randomized, 8-week, bipolar depression studies are reported elsewhere [1–5]. Here efficacy and safety are examined according to BDI and II status. QTP 300 mg and 600 mg treatment arms were pooled because their efficacy was similar [1–4]. Efficacy assessments included MADRS, CGI-BP-S, and HAM-A scores and safety was assessed by adverse event (AE) and discontinuation adverse event (DAE) rates.

**Results:** In the first 4 weeks of treatment, BDII patients randomized to lithium demonstrated slowest rates of symptom improvement, measured by change in MADRS score. BDI and II patients randomized to QTP demonstrated fastest symptom improvement in the first 4 weeks. In the last 4 weeks, BDI or II patients randomized to placebo and paroxetine showed slower symptom improvement, while those treated with lithium nearly reached symptom improvements achieved by those randomized to QTP. Similar patterns of response were seen for CGI-BP-S and HAM-A scores. Proportions of BDI patients reporting any AE were: QTP 76.7%, placebo 72.4%, lithium 54.0%, and paroxetine 71.1%; DAE rates were 9.9%, 3.8%, 5.7%, and 11.8%, respectively. Proportions of BDII patients reporting any AE were 74.5%, 66.5%, 65.3%, and 66.7%, respectively; DAE rates were 14.2%, 4.1%, 10.2%, and 4.4%. Patterns of AEs were consistent with known side-effect profiles of these agents.

**Conclusion:** BDII patients initially have slower response to treatment, but by 8 weeks reach improvement levels similar to BDI, with the exception of paroxetine in BDII patients. No clear pattern of tolerability differences was identified between BDI and BDII by randomized treatments. Sponsored by AstraZeneca.

**References:** [1] Calabrese JR, *Am J Psychiatry*. 2005;162:1351–60; [2] Thase ME, *J Clin Psychopharmacol*. 2006;26:600–9; [3] Young AH, *J Clin Psychiatry*. 2010;71:150–62; [4] McElroy SL, *J Clin Psychiatry*. 2010;71:163–74; [5] Suppes T, *J Affect Disord*. 2010;121:106–15.

## Effects of food on the pharmacokinetics and bioavailability of quetiapine XR: clinical relevance of dosing instructions

C Datto<sup>a</sup>, W Pottor<sup>b</sup>, S LaPorte<sup>c</sup>, J Mullen<sup>d</sup>

<sup>a</sup>US Medical Affairs, AstraZeneca Pharmaceuticals, Wilmington, USA, <sup>b</sup>Medical Information, AstraZeneca Pharmaceuticals, Wilmington, USA, <sup>c</sup>Biometrics and Information Sciences, AstraZeneca Pharmaceuticals, Wilmington, USA, <sup>d</sup>R&D, AstraZeneca Neuroscience, Cambridge, USA

**Aims:** Quetiapine extended release (XR) administered once daily has the same area under the plasma concentration-time curve (AUC) and elimination half-life ( $t_{1/2}$ ) as an equivalent total daily dose of quetiapine immediate release (IR) administered twice daily, following the recommended prescribing information [1,2]. However, the pharmacokinetics and bioavailability of quetiapine XR can be influenced by caloric intake.

**Methods:** The effect of food (high-fat [800–1000 calories] meal and fasting) on the steady-state pharmacokinetics and bioavailability of quetiapine XR 50 and 300 mg tablets was explored in 30 patients (80% male, mean age 44.6 years) with schizophrenia or schizoaffective disorder [1,3]. Additional studies were conducted in 20 healthy volunteers (Cohort A, 50 mg) and 13 patients with schizophrenia or schizoaffective disorder (Cohort B, 300 mg) to further examine differences in quetiapine XR with a light meal (no fat,  $\leq 300$  calories) or fasting (no food/liquid 10 h before and for 4 h after administration) conditions [1,4].

**Results:** Under fasting conditions, quetiapine XR demonstrated linear pharmacokinetics with respect to maximum plasma concentration ( $C_{max}$ ), minimum plasma concentration ( $C_{min}$ ) and AUC [3]. However, a high-fat meal produced statistically significant increases in the quetiapine XR steady-state  $C_{max}$  of 44% and 52% and AUC of 20% and 22% for 50 mg and 300 mg tablets, respectively [1,3]. In comparison, a light meal had no significant effect on the  $C_{max}$  or AUC of quetiapine XR [1,4].

**Conclusion:** Because of the influence of caloric intake on the pharmacokinetics and bioavailability of quetiapine XR formulation, it is recommended that quetiapine XR be taken without food or with a light meal [1]. Sponsored by AstraZeneca.

**References:** [1] Quetiapine XR Prescribing Information 2013; [2] Figueroa C, Biol Psychiatry. 2009;33:199–204; [3] Data on file, AstraZeneca LP; [4] Juckel G, Poster presentation at: 14th Biennial Winter Workshop on Schizophrenia and Bipolar Disorders; February 3–7, 2008; Montreux, Switzerland.

## Long-term lithium response in the bipolar disorder research network study

A Di Florio<sup>a</sup>, K Gordon-Smith<sup>b</sup>, L Forty<sup>c</sup>, L Jones<sup>b</sup>, N Craddock<sup>c</sup>, I Jones<sup>c</sup>

<sup>a</sup>Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, USA, <sup>b</sup>Department of Psychiatry, University of Birmingham, Birmingham, United Kingdom, <sup>c</sup>Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, United Kingdom

**Context:** Lithium has been a first-line maintenance treatment for bipolar disorder for decades. Given the great variability in effectiveness and tolerability from person to person, it is essential to know in advance who will benefit from a long-term treatment. Research into the biological determinants of lithium response has however been hindered by difficulties in defining and assessing the phenotype of interest.

**Aims:** (1) to report the development of a new, simple and pragmatic scale to assess long-term lithium effectiveness (2) to test the association between lithium response and clinical characteristics of bipolar disorder.

**Methods:** 4169 participants with bipolar disorder, recruited in our research on genetic and non-genetic factors in major affective disorders, the Bipolar Disorder Research Network, underwent a semi-structured interview and case notes were reviewed. Best-estimate diagnoses were made according to DSM-IV criteria and key clinical variables, including lithium response, were rated. Mean statistics ranged between 0.81 and 0.99 for categorical variables; mean intra-class correlation coefficients were between 0.91 and 0.97 for continuous variables. A five-point scale measuring the level of evidence for lithium effectiveness was developed and used to assess lithium response. The Clm function from the ordinal package in R was employed to test the association between lithium response and clinical variables.

**Results:** Of the 2715 participants who had ever taken lithium, 50.6% (N = 1375) showed at least subjective evidence of good response, while in only 7.3% (N = 198) there was no evidence of response. We found an inverse ordinal association between lithium response as measured with our scale and alcohol use disorders ( $p < 0.001$ ), rapid cycling ( $p < 0.001$ ) and history of panic attack disorder ( $p < 0.002$ ).

**Conclusions:** Our findings support a simple and pragmatic definition of lithium effectiveness that includes levels of evidence of response.

## A double-blind, placebo-controlled study of cariprazine monotherapy for the treatment of bipolar I depression

S Durgam<sup>a</sup>, A Lipschitz<sup>a</sup>, H Guo<sup>b</sup>, W Earley<sup>a</sup>, I Laszlovszky<sup>c</sup>, G Németh<sup>c</sup>, LN Yatham<sup>d</sup>

<sup>a</sup>Clinical Development, Forest Research Institute, Jersey City, USA, <sup>b</sup>Biostatistics, Forest Research Institute, Jersey City, USA, <sup>c</sup>Medical Division, Gedeon Richter Plc, Budapest, Hungary, <sup>d</sup>Psychiatry, University of British Columbia, Vancouver, Canada

**Aims:** Cariprazine (CAR), a dopamine D<sub>3</sub> and D<sub>2</sub> receptor partial agonist antipsychotic with preferential D<sub>3</sub> receptor binding, is in late-stage clinical development for the treatment of schizophrenia and bipolar mania. This Phase II study evaluated the efficacy, safety, and tolerability of CAR in patients with bipolar I depression.

**Methods:** This was an 8-week multinational, randomized, double-blind, placebo (PBO)-controlled, parallel-group, fixed-dose study in adult patients with bipolar I disorder (NCT01396447). Patients were randomized to PBO or CAR 0.75, 1.5, or 3.0 mg/d. The primary and secondary efficacy parameters were change from baseline to Week 6 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and Clinical Global Impressions-Severity (CGI-S), respectively, analyzed using a mixed-effects model for repeated measures (MMRM) in the intent-to-treat (ITT) population; p values were adjusted for multiple comparisons.

**Results:** The ITT population comprised 571 patients (PBO = 141, CAR: 0.75 mg/d = 140, 1.5 mg/d = 145, 3.0 mg/d = 145); 73% of patients completed the study (PBO = 72%, CAR: 0.75 mg/d = 73%, 1.5 mg/d = 80%, 3.0 mg/d = 64%). The LSMD (95% CI) for MADRS total score change from baseline to Week 6 was statistically significant in favor of CAR 1.5 mg/d versus PBO (−4.0 [−6.3, −1.6]; adjusted  $p = 0.0030$ , unadjusted  $p = 0.0010$ ). CAR 3.0 mg/d LSMD versus PBO was not significant following multiplicity adjustment (−2.5 [−4.9, −0.1]; adjusted  $p = 0.1122$ , unadjusted  $p = 0.0374$ ); CAR 0.75 mg/d was similar to PBO. Cohen's  $d$  effect sizes for the CAR 0.75-, 1.5-, and 3.0-mg/d groups after 6 weeks of treatment were 0.20, 0.42, and 0.26, respectively. A similar pattern of significance versus PBO was seen on the CGI-S (CAR: 1.5 mg/d = −0.4 [−0.6, −0.1], adjusted  $p = 0.0132$ ; 3.0 mg/d = −0.3 [−0.5, −0.0], unadjusted  $p = 0.0489$ ). In post hoc analyses, significant improvement for CAR 1.5 mg/d versus PBO was seen on 6 of 10 MADRS single items ( $p < 0.05$  each). The adverse events (AEs) that occurred at  $\geq 10\%$  in any CAR group

were akathisia and insomnia. Serious AEs were reported in 5 PBO patients and 1, 2, and 2 CAR 0.75-, 1.5-, and 3.0 mg/d-patients, respectively.

**Conclusions:** CAR 1.5 mg/d demonstrated consistent efficacy versus PBO across outcomes and was generally well tolerated, suggesting potential efficacy for the treatment of bipolar depression.

## N-acetylcysteine in depressive symptoms and functionality: a systematic review and meta-analysis

**B Fernandes, O Dean, S Dodd, M Berk**

*Department of Psychiatry, Deakin University and Barwon Health, Geelong, Australia*

**Aims:** To assess the utility of n-acetylcysteine (NAC) for depressive symptoms in psychiatric conditions.

**Methods:** A computerized literature search was conducted in Medline, Embase, the Cochrane Library, Scielo, PsycINFO, Scopus, and Web of Knowledge. No year or country restrictions were used. The Boolean terms used for the electronic database search were: (NAC OR n-acetylcysteine OR acetylcysteine) AND (depression OR depressive OR depressed) AND (trial). The last search was performed in November of 2014. Double-blind, randomized, placebo-controlled trials using NAC for depressive symptoms regardless the main psychiatric condition. Using keywords and cross-referenced bibliographies, 38 studies were identified and examined in depth. Of those, 33 articles were rejected because inclusion criteria were not met. Finally, 5 studies were included. Data were extracted independently by 2 investigators. The primary outcome measure was change in depressive symptoms. Functionality, quality of life, manic and anxiety symptoms were also examined. A full review and meta-analysis were performed. Standardized mean differences (SMDs) and Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

**Results:** Five studies fulfilled our inclusion criteria for the meta-analysis, providing data on 574 participants, of whom 291 were randomised to receive NAC, and 283 to placebo. The follow-up varied from 12 to 24 weeks. Two studies included subjects with BD and current depressive symptoms, one subjects with MDD in a current depressive episode, and two subjects with depressive symptoms in the context of other psychiatric condition (one trichotillomania and one heavy smoking). Treatment with NAC improved depressive symptoms as assessed by MADRS and HDRS when compared to placebo (SMD = 0.37, 95% CI 0.19 to 0.55,  $p < 0.001$ ). Subjects receiving NAC presented better scores regarding the CGI-S of depressive symptoms at the follow-up than subjects on placebo (SMD = 0.22, 95% CI 0.03 to 0.41,  $p < 0.001$ ). In addition, global functionality was better in NAC than in placebo. There were no changes in quality of life. With regard to side effects, only minor side effects were associated with NAC (OR 1.61, 95% IC 1.01 to 2.59,  $p = 0.049$ ).

**Conclusions:** NAC ameliorates depressive symptoms and improves functionality, with a relatively moderate impact and good tolerability.

## Absolute weight change, $\geq 7\%$ weight gain, and self-reported weight gain of second-generation antipsychotics in bipolar disorder

**K Gao<sup>a</sup>, F Fang<sup>b</sup>**

*<sup>a</sup>Psychiatry Mood Disorders Program, Case Western Reserve University, Cleveland, USA, <sup>b</sup>Psychiatry, Hongkou District Mental Health Center of Shanghai, Shanghai, China*

**Objectives:** To assess absolute weight change (AWC),  $\geq 7\%$  weight gain (WG), and self-reported WG of antipsychotics in mania, bipolar depression, and bipolar maintenance.

**Methods:** Studies were identified through PubMed search. AWC,  $\geq 7\%$  WG, and self-reported WG were extracted from original publications. Difference(s) in AWC between an active treatment and placebo/comparator was based on original significance test or re-calculated with t-test. Differences in  $\geq 7\%$  WG, and/or self-reported WG were estimated with the number needed to treat to harm (NNH).

**Results:** Forty mania, 15 bipolar depression, and 18 maintenance studies had AWC,  $\geq 7\%$  WG, and/or self-reported WG. In mania studies, aripiprazole, olanzapine, and quetiapine caused significant WG based on AWC and  $\geq 7\%$  WG at least in one study. Of 33 active treatments in mania with both AWC and  $\geq 7\%$  WG, 28 treatments had agreement in significance between AWC and  $\geq 7\%$  WG. Of 25 treatments with both  $\geq 7\%$  WG and self-reported WG, 18 treatments had a smaller NNH with  $\geq 7\%$  WG than that with self-reported WG. In bipolar depression, olanzapine, olanzapine-fluoxetine combination, and quetiapine caused significant WG based on AWC and  $\geq 7\%$  WG. Of 15 treatments with AWC and  $\geq 7\%$  WG, 10 had agreement between AWC and  $\geq 7\%$  WG. Of 5 treatments with  $\geq 7\%$  WG and self-reported, all 5 had a smaller NNH with  $\geq 7\%$  WG than that with self-reported. In maintenance studies, aripiprazole, olanzapine, quetiapine, paliperidone, and risperidone long-acting-injection caused significant WG based on AWC and  $\geq 7\%$  WG. Of 18 treatments with AWC and  $\geq 7\%$  WG, 12 had agreement between AWC and  $\geq 7\%$  WG. Of 16 treatments with  $\geq 7\%$  WG and self-reported, 12 treatments had a smaller NNH with  $\geq 7\%$  WG than that with self-reported.

**Conclusions:** AWC,  $\geq 7\%$  WG, self-reported WG provided inconsistent findings in risks for antipsychotic-induced WG.  $\geq 7\%$  weight gain was more reliable and provided more clinical relevant information than self-reported WG and AWC. Short-term weight change did not predict long-term weight gain. Measuring weight at each visit should be a good standard for managing antipsychotic-induced WG.

## Rates of recurrence in bipolar disorder: systematic analysis and comparison between long-term prospective, naturalistic studies vs. randomized controlled trials (RCTs)

**GH Vazquez<sup>a</sup>, J Holtzman<sup>b</sup>, M Lolich<sup>a</sup>, T Ketter<sup>b</sup>, RJ Baldessarini<sup>c</sup>**

*<sup>a</sup>Research Center for Neuroscience and Neuropsychology, University of Palermo, Buenos Aires, Argentina, <sup>b</sup>Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, USA, <sup>c</sup>Department of Psychiatry, Harvard Medical School, Boston, USA*

**Background:** Bipolar disorder (BD) is a severe, recurrent or chronic, lifelong illness. Despite many options for the treatment of bipolar disorder of proven efficacy, long-term control of the illness, especially its depressive components, is surprisingly limited.

**Methods:** We systematically computer-searched for prospective naturalistic studies of long-term treatment of BD patients for at least two years. Ten such studies met inclusion criteria for analysis of clinical outcomes and of related sociodemographic and clinical variables. Of these studies, the necessary data were extracted in order to construct a database and to perform a combined analysis of the most relevant sociodemographic and clinical variables, including the rate of recurrence following two-years of maintenance treatment. Such data were compared to the corresponding data from 15 randomized control trials with two years of follow-up that were compiled in a parallel systematic review.

**Results:** Among 3,904 subjects in prospective, naturalistic observational studies (mean age 41.9 years, 51.4% women, 81.3% type I BD, mean onset age of 28.2 years), the pooled recurrence rate was 54.1%: 63.6% of recurrent episodes were depressive and 36.4% were manic or hypomanic. In comparison, among the 15 included randomized control trials, the overall rate of recurrence was found

to be 42.9% among 4,907 subjects (mean age 40.2 years, 53.5% women, 98.2% type I BD, with a mean onset age of 26.7 years), with 48.2% of recurrent episodes being depressive and 51.8% being manic or hypomanic.

**Discussion:** The recurrence rate of affective episodes during long-term treatment of patients with bipolar I and II disorder in prospective, naturalistic observational studies was substantial at 54% while in RCTs was 43%, with depressive compared to manic recurrences being more common, independent of methodology. These results remark the necessity of more effective or better-accepted, maintenance treatments for BD patients, especially for bipolar depression and highlight the difference on recurrence rates between naturalistic and RCTs long term follow up studies.

### Remission and recovery in lurasidone-treated patients with bipolar depression: post-hoc analysis of a 6-week, placebo-controlled trial followed by a 6-month extension

**A Loebel<sup>a</sup>, C Siu<sup>b</sup>, K Rajagopalan<sup>c</sup>, A Pikalov<sup>d</sup>, J Cucchiari<sup>e</sup>, T Ketter<sup>f</sup>**

<sup>a</sup>Chief Medical Officer, Sunovion Pharmaceuticals Inc., Fort Lee, USA, <sup>b</sup>Data Science and Analytics, COS Consulting, Montreal, Canada, <sup>c</sup>Health Economics and Outcomes Research, Sunovion Pharmaceuticals Inc., Marlborough, USA, <sup>d</sup>Clinical Development and Medical Affairs, Sunovion Pharmaceuticals Inc., Fort Lee, USA, <sup>e</sup>Clinical Operations, Sunovion Pharmaceuticals Inc., Fort Lee, USA, <sup>f</sup>Psychiatry and Behavioral Sciences, Stanford University, Stanford, USA

**Aims:** The objective of this post-hoc analysis was to evaluate symptomatic and functional remission and recovery in patients with bipolar depression treated with lurasidone.

**Methods:** Outpatients meeting DSM-IV-TR criteria for bipolar I depression, with or without rapid cycling, were randomized to 6 weeks of once-daily, double-blind treatment with lurasidone 20–60 mg (LUR20-60), lurasidone 80–120 mg (LUR80-120) or placebo (PBO). A total of 318 subjects enrolled in a subsequent 6-month, open-label extension study. Subjects initially treated with placebo were started at extension baseline with flexible once-daily doses of lurasidone 40–160 mg/d (PBO-LUR; N = 107). Symptomatic and functional recovery was defined as meeting criteria for both symptomatic remission (Montgomery-Asberg Depression Rating Scale [MADRS] total score ≤ 12) and functional remission (Sheehan Disability Scale [SDS] mean score ≤ 3 and all SDS domain scores ≤ 3 representing no more than mild impairment) sustained for at least 3 months (i.e., at months 3 and 6 of the open extension study).

**Results:** At end of the 6-week acute phase, a significantly higher proportion of subjects met both symptomatic (MADRS total score ≤ 12) and functional (mean SDS total score ≤ 3 and all SDS domain scores ≤ 3 for mildly impairment) remission criteria in the lurasidone group (33%, N = 273 pooling the LUR20-60 and LUR80-120 groups) compared to the placebo group (15%, N = 143, p).

**Conclusions:** These findings derived from a 6-week acute and 6-month extension study period suggest that lurasidone is associated with substantial rates of symptomatic and functional remission and recovery in patients with bipolar depression. Predictors of response were identified.

### Efficacy and safety of asenapine 5 mg bid and 10 mg bid in adults with a manic or mixed episode associated with bipolar I disorder

**R McIntyre<sup>a</sup>, R Landbloom<sup>b</sup>, M Mackle<sup>b</sup>, X Wu<sup>c</sup>, L Kelly<sup>b</sup>, L Snow-Adami<sup>b</sup>, M Mathews<sup>d</sup>, C Hundt<sup>e</sup>**

<sup>a</sup>Mood Disorders Psychopharmacology Unit University Health Network, University of Toronto, Toronto, Canada, <sup>b</sup>Merck, Whitehouse Station, USA, <sup>c</sup>Forest Research Institute an affiliate of Actavis Inc., Jersey City, USA, <sup>d</sup>Formerly with Forest Research Institute an affiliate of Actavis Inc., Jersey City, USA

**Aims:** Asenapine is an atypical antipsychotic for acute treatment of manic or mixed episodes associated with bipolar I disorder, available at a starting dose of 10 mg twice daily (bid) with the option to down-titrate to 5 mg bid. In asenapine pivotal trials, patients could have been titrated from 10 mg bid to 5 mg bid if clinically indicated although <10% had their dose reduced to 5 mg bid.<sup>1,2</sup> Therefore, we aimed to further characterize, by a fixed-dose design, the efficacy and safety of asenapine 5 mg bid and 10 mg bid vs placebo in adults currently experiencing an acute manic or mixed episode.

**Methods:** This was a phase IIb, international, double-blind, fixed-dose, parallel-group, 3-week placebo-controlled trial of asenapine 5 and 10 mg bid in adults with a current manic (DSM-IV-TR 296.4x) or mixed (DSM-IV-TR 296.6x) episode. The primary outcome was difference in asenapine vs placebo in change from baseline to day 21 in the Young-Mania Rating Scale (YMRS). Other outcomes included the difference in asenapine vs placebo in the Clinical Global Impression Scale for Bipolar Severity (CGI-BP-S) and rate of YMRS responders.

**Results:** Both asenapine 5 and 10 mg bid were superior to placebo in improving mania as measured by the mean change from baseline to day 21 in YMRS score (−10.9, −14.4, and −14.9 for placebo, asenapine 5 mg bid, 10 mg bid, respectively). Both asenapine doses had superior improvement in CGI-BP-S overall scores at day 21 (−1.1, −1.6, −1.7 for placebo, asenapine 5 mg bid, and 10 mg bid, respectively). Neither asenapine dose had significantly more YMRS responders at day 21 than placebo. Oral hypoesthesia, sedation, akathisia, somnolence, and headache were the most commonly reported adverse events.

**Conclusions:** Asenapine 5 and 10 mg bid were efficacious in treating mania associated with bipolar I disorder and were generally well tolerated. This study further characterized, by a fixed-dose design, the efficacy and safety profile of asenapine 5 mg bid vs placebo in patients with bipolar I disorder.

**References:** 1. McIntyre RS, et al. *Bipolar Disord.* 2009;11:673–686. 2. McIntyre RS, et al. *J Affect Dis.* 2010;122:27–38.

### Use of asenapine in acute affective disorders

**S Ovejero<sup>a</sup>, M Iza<sup>a</sup>, R Alvarez<sup>b</sup>, L Mata<sup>c</sup>, S Sánchez-Alonso<sup>c</sup>**

<sup>a</sup>Psychiatry Inpatient Unit, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, <sup>b</sup>Psychiatry Inpatient Unit, Hospital Rey Juan Carlos, Móstoles, Spain, <sup>c</sup>Psychiatry Outpatient Unit, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

**Objectives:** The main objective of this study is to make a naturalistic evaluation of the use of asenapine in a short-term psychiatric inpatient unit in Madrid, Spain. In this study we will evaluate the efficacy of asenapine in affective disorders and the presence of adverse effects during use in acute patients in daily clinical practice.

**Methods:** Data was gathered among 55 psychiatric inpatients sample treated consecutively with asenapine. A description of the sample obtained was performed. Diagnostics among the sample were schizoaffective disorder (n = 7), bipolar disorder (n = 36), and single maniac episode (n = 12). Within mood episodes the diagnostics were psychotic mania (n = 37), non-psychotic mania (n = 8), hypomania (n = 2), psychotic depression (n = 6) and non-

psychotic depression ( $n = 2$ ). Asenapine was withdrawn in 5 patients due to lack of efficacy (2), adverse effects (2) or presence of a social problem (1).

**Results:** The average inpatient stay is 11.40 days. When the dose of asenapine is increased within five days after the start of treatment, the average hospital stay is reduced to 8.06 days ( $t$  Student test;  $p = 0.012$ ). Significant differences (ANOVA;  $p = 0.002$ ) in the average length of stay were found by type of mood episode: psychotic mania, 10.58 days; non-psychotic mania, 7.29 days; hypomania 5.00 days; psychotic depression 21.67 days; and non-psychotic depression, 15.00 days. At hospital discharge ( $n = 50$ ), 24% of patients were on monotherapy absolute with asenapine ( $n = 12$ ). Antipsychotic monotherapy at discharge is found in 86% of the sample ( $n = 43$ ). At hospital discharge, 26% patients treated with asenapine were readmitted ( $n = 13$ ). Of these, 8 patients were readmitted for discontinued treatment, 4 for presenting a relapse, and one to present a shift cycle. Patients who discontinued treatment were readmitted within 59.4 days, patients who relapsed did so within 113.0 days, and the patient who made a shift cycle readmitted within 11.0 days.

**Conclusions:** Inpatients treated with asenapine have a short hospital stay. Early increase of asenapine doses reduces the average hospital stay. The use of asenapine as antipsychotic monotherapy in a short-term hospitalization unit may open new options of treatment for affective disorders.

### Who will benefit from antidepressants in the acute treatment of bipolar depression? A follow up observational data analysis of STEP-BD

F Wu<sup>a</sup>, E Laber<sup>a</sup>, I Iipkovich<sup>b</sup>, E Severus<sup>c</sup>

<sup>a</sup>Department of Statistics, North Carolina State University, Raleigh, USA, <sup>b</sup>Center for Statistics in Drug Development, Quintiles, Morrisville, USA, <sup>c</sup>Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Dresden, Germany

**Aims:** There is substantial uncertainty regarding the efficacy of antidepressants in the acute treatment of bipolar depression. In our recent paper (Wu et al., 2015, in press, International Journal of Bipolar Disorders), we used data from the acute depression randomized care (RAD) pathway of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (Sachs et al., 2007, NEJM), to estimate an optimal dynamic treatment regime via Q-learning. The estimated optimal dynamic treatment regime presents some evidence that patients in RAD pathway of STEP-BD with a (hypo)manic episode prior to onset of the current depressive episode should not be given an antidepressant in addition to a mood stabilizer, while all the other patients would benefit from an additional antidepressant. The goal of our current analyses is to validate this finding, using an independent sample, but a similar methodology regarding outcome criteria and rating instruments.

**Methods:** In STEP-BD study, there is another pathway named standardized care pathway (SCP), which is an observational study. We construct a dataset named SAD (Standard Acute Depression) Pathway, which contains patients in SCP pathway that satisfy RAD pathway entering criteria. Using this dataset, we construct three different models to validate the performance of the findings in RAD pathway via Inverse Probability Weighting (IPW) as well as Augmented Inverse Probability Weighting (AIPW), which are two popular methods for estimating the mean outcome of a dynamic treatment regime.

**Results:** The analyses are still ongoing, but preliminary results indicate that there is some uncertainty in reproducing the findings from RAD, and that the results are dependent on the estimation method used.

**Conclusions:** There are some differences between RAD dataset and SAD dataset which may affect the results from SAD data analysis.

In the future, we will estimate optimal treatment regime based on SAD dataset.

### Predictors of long-term work disability among patients with bipolar disorder – a prospective study

P Arvilommi<sup>a</sup>, K Suominen<sup>b</sup>, O Mantere<sup>c</sup>, H Valtonen<sup>b</sup>, S Leppämäki<sup>d</sup>, E Isometsä<sup>e</sup>

<sup>a</sup>Department of Mental Health and Substance Abuse Services, National Institute of Health and Welfare, Helsinki, Finland,

<sup>b</sup>Psychiatric and Substance Abuse Services Helsinki City Department of Social Services and Healthcare, Helsinki, Finland,

<sup>c</sup>Department of Mental Health and Substance Abuse Services, National Institute of Health and Welfare, Helsinki, Finland,

<sup>d</sup>Department of Psychiatry, Helsinki University Hospital, Helsinki, Finland, <sup>e</sup>Department of Psychiatry, University of Helsinki, Helsinki, Finland

**Objectives:** Bipolar Disorder (BD) is one of the leading causes of disability worldwide. Vocational ability is an important area of functioning, but the predictors of long-term work disability have been little studied among patients with BD. We investigated clinical predictors of long-term work disability among BD patients in psychiatric secondary-level care.

**Method:** The Jorvi Bipolar Study (JoBS) is a naturalistic prospective cohort study ( $N = 191$ ) representing adult (18–59 years) psychiatric in- and outpatients with DSM-IV BD I and II in three Finnish cities. Within the JoBS, we studied the prevalence of disability pensions at baseline, and predictors for being granted a disability pension during an 18-month follow-up of the 151 patients in labor force at baseline. Cox proportional hazards models were used to determine predictors for onset of disability pension.

**Results:** At baseline, 21% (40/191) of the patients already had a disability pension. During the follow up 38 more patients (25% of the 151 followed) were granted a disability pension. The predictors included older age, subjective work disability, high number of psychiatric hospitalizations; generalized anxiety disorder (GAD), avoidant personality disorder and borderline personality disorder. However, the predictors differed depending on bipolar subtype, age and sex.

**Conclusion:** BD I and II are associated with a major risk of long term-work disability, the proportion of patients with a disability pension approaching one half over time in this Finnish cohort. Age, subjective work disability, comorbidities and severe clinical course are likely to be the main predictors, but predictors may vary depending on the subgroup studied.

### Opportunities for suicide prevention in bipolar disorder: an examination of health care contacts during the year prior to suicide deaths

A Schaffer<sup>a</sup>, M Sinyor<sup>a</sup>, P Kurdyak<sup>b</sup>, J Sareen<sup>c</sup>, J Bolton<sup>c</sup>, S Vigod<sup>b</sup>, A Cheung<sup>b</sup>, S Grigoriadis<sup>b</sup>, A Rhodes<sup>b</sup>, J Cairney<sup>d</sup>

<sup>a</sup>Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada,

<sup>b</sup>Psychiatry, University of Toronto, Toronto, Canada, <sup>c</sup>Psychiatry, University of Manitoba, Winnipeg, Canada, <sup>d</sup>Psychiatry, McMaster University, Hamilton, Canada

**Introduction:** People with bipolar disorder (BD) carry a high risk of suicide, and efforts at optimizing suicide prevention approaches are paramount. Such efforts within the health care system require more data on what types of mental health care services are accessed by people with BD prior to suicide, and who does or does not access these services. This knowledge can aid in the development of targeted suicide prevention strategies for specific points of care.

**Objective:** To characterize the past year mental health care utilization of people with BD who died by suicide, and to examine the differences between groups who did or did not come into contact with various types of mental health care services.

**Methods:** Data were obtained from a linked dataset of all BD suicides in the City of Toronto, Canada from 1998 to 2012 with the health care administrative databases for the Province of Ontario. The principal exposure variable was contact with any mental health care during the 12-months preceding the date of suicide. Secondary measures included specific contact types: mental-health related primary care physician contact, outpatient psychiatrist contact, Emergency Department (ED) visit for a mental health reason or suicide attempt, or hospitalization with a mental-health related primary discharge diagnosis.

**Results:** There were  $n = 176$  BD suicides in the linked dataset, which accounted for 6.2% of all suicides during the years of study. Nearly all people with BD (97.7%) had some form of mental health care contact in the year prior to suicide death; 43.8% had an inpatient admission; 47.8% had a mental-health related ED visit; 75.6% saw an outpatient psychiatrist; and 75% had a mental-health related primary care physician contact. The presentation will report on differences between the group of people who did or did not contact these services.

**Conclusions:** Almost all people with BD who die by suicide have had contact with the mental health care system during the year prior to death, with broad exposure to primary care, specialty care, and ED / inpatient services. These results highlight the importance at directing significant suicide prevention efforts at these specific windows of opportunity.

### Suicide risk in bipolar disorder during treatment with lithium and valproate

**J Song<sup>a</sup>, A Sjölander<sup>a</sup>, S Bergen<sup>a</sup>, H Larsson<sup>a</sup>, M Landén<sup>b</sup>, P Lichtenstein<sup>a</sup>**

<sup>a</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, <sup>b</sup>Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden

**Objectives:** Previous studies suggest that lithium treatment is associated with reduced risk of suicide among patients with bipolar disorder. However, strong conclusions are limited due to non-representative subjects and the inevitable confounding by indication. Also, the association between valproate treatment and suicide risk has been less studied, and results are inconsistent. This study aims to investigate the association between lithium and valproate medication and risk of concomitant suicidal behavior. To control for confounding, the rate of suicide-related events during treated periods were compared with the rate during untreated periods in the same individual.

**Methods:** By linking multiple national registers in Sweden, we established a cohort of 34,306 individuals with bipolar disorder, aged 15 to 100 years and followed between 2005 and 2009 for treatment status by lithium or valproate medication and suicide-related events (suicide attempt and completed suicide). Incidence rate of suicide-related events during treated periods was compared with that during untreated periods at both population and within-individual level.

**Results:** Among the 34,306 individuals with bipolar disorder, 4,356 suicide-related events occurred during 109,307 person years of follow-up. After adjustment for age category, sex, number of previous treatment periods and previous suicidal behavior, use of lithium treatment was significantly associated with decreased rates of suicide-related events at both the population level (hazard ratio 0.69, 95% confidence interval 0.62–0.77) and the individual level (0.72, 0.61–0.85). This was not true for valproate treatment. The rate of suicide-related events was significantly different during lithium

treatment periods compared with that during valproate treatment periods ( $p = 0.03$ ). When we restricted analyses to completed suicides, the within individual comparison showed a decreased risk of completed suicide by 90% for the use of lithium treatment (0.10, 0.04–0.27). Sensitivity analyses yielded similar results after adjustment for other antipsychotic, antidepressant and antiepileptic treatments.

**Conclusions:** This study provides further evidence that the use of lithium treatment is associated with reduced rate of suicide-related events among bipolar patients. This phenomenon was not obvious for valproate treatment. Psychiatrists prescribing mood stabilizers should be aware that different types of medications can have different effects on reducing suicidal behavior.

### Delayed sleep phase identified as a subtype of sleep disturbance in bipolar disorder

**MK Steinan<sup>a</sup>, G Morken<sup>a</sup>, TV Lagerberg<sup>b</sup>, I Melle<sup>b</sup>, OA Andreassen<sup>b</sup>, A Vaaler<sup>a</sup>, J Scott<sup>c</sup>**

<sup>a</sup>Department of Psychiatry, St Olavs University Hospital, Trondheim, Norway, <sup>b</sup>KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, Norway, <sup>c</sup>Institute of Neuroscience, Newcastle University, Newcastle, United Kingdom

Models of Bipolar Disorder (BD) highlight that sleep disturbances may be a marker of underlying circadian dysregulation, and sleep disturbances are common during and between BD episodes. Delayed Sleep Phase (DSP) is however rarely reported on. This study examines the prevalence of DSP in BD cases with sleep problems and explores features that distinguish DSP from other sleep disturbances.

**Methods:** A cross-sectional study of 404 adults with BD I or II who met published clinical criteria for insomnia, hypersomnia or DSP.

**Results:** About 10% of BD cases met criteria for DSP. The DSP group was younger and had a higher mean Body Mass Index (BMI) than the insomnia or hypersomnia groups. Also, DSP cases were more likely to be prescribed mood stabilizers and antidepressant than insomnia cases. Any exploratory analysis of pre-selected depressive symptoms indicated that DSP was more likely to be associated with impaired energy and activity levels.

**Conclusions:** The DSP group identified in this study can be differentiated from hypersomnia and insomnia groups on the basis of clinical and demographic features. The association of DSP with younger age, higher BMI and impaired energy and activity also suggest that this clinical profile may be a good proxy for underlying circadian dysregulation. This study highlights the clinical and research need for more detailed differentiation of the diverse sleep profiles associated with BD.

### Development of an online interactive self-help program for significant others:

**www.iCARE4bipolar.com**

**L Berk<sup>a</sup>, E Gliddon<sup>b</sup>, T Suppes<sup>c</sup>, V Cosgrove<sup>c</sup>, T Deckersbach<sup>d</sup>, D Austin<sup>a</sup>, A Lewis<sup>a</sup>, S Lauder<sup>a</sup>, D Grimm<sup>c</sup>, M Berk<sup>b</sup>**

<sup>a</sup>School of Psychology, Deakin University, Geelong, Australia, <sup>b</sup>IMPACT Strategic Research Centre, Deakin University, Geelong, Australia, <sup>c</sup>VA Palo Alto Health Care System, Bipolar and Depression Research Program, Palo Alto, USA, <sup>d</sup>Harvard University, Massachusetts General Hospital, Boston, USA, <sup>e</sup>University of Melbourne, Department of Psychiatry, Melbourne, Australia

**Background:** Close family and friends who are a primary source of support for an adult with bipolar disorder commonly find it challenging to deal with the symptoms and illness consequences. Many report distress, isolation and depression, and turn to the privacy and convenience of the Internet for guidance and support. This

poster reports on the development of [www.iCARE4bipolar.com](http://www.iCARE4bipolar.com), a comprehensive interactive online self-help program to assist significant others to learn about bipolar disorder, provide support and take care of themselves, currently being trialed in a pilot RCT.

**Method:** The development of [www.iCARE4bipolar.com](http://www.iCARE4bipolar.com) involved: (1) A Delphi study (N = 143) combining research literature, and suggestions and consensus of experienced clinicians, significant others and people with bipolar disorder to form a passive information resource [www.bipolarcaregivers.org](http://www.bipolarcaregivers.org). (2) A formative evaluation of [www.bipolarcaregivers.org](http://www.bipolarcaregivers.org) by end-users (N = 536) to assess its usefulness and relevance and how to improve it. (3) The upgrading of [www.bipolarcaregivers.org](http://www.bipolarcaregivers.org) to create [www.iCARE4bipolar.com](http://www.iCARE4bipolar.com) to incorporate end-user recommendations, and beta-testing of the new website for use in the RCT.

**Results:** High rates of consensus between Delphi panels resulted in 86% of the 626 survey items forming the content of [www.bipolarcaregivers.org](http://www.bipolarcaregivers.org). In the evaluation study, 84–97% reported finding the various sections of the website useful, but they recommended including more specific information and interactive exercises to help them apply the information to everyday life, plus an active support aspect. Currently, the original website receives over 9000 visits a month and nearly a fifth are returning visitors, however, the average time on the site is a few minutes. [www.iCARE4bipolar.com](http://www.iCARE4bipolar.com) is a modularized self-help program that combines information on [www.bipolarcaregivers.org](http://www.bipolarcaregivers.org) with interactive practice exercises, and a moderated discussion board.

**Conclusion:** [www.iCARE4bipolar.com](http://www.iCARE4bipolar.com) evolved from [www.bipolarcaregivers.org](http://www.bipolarcaregivers.org) and input from significant others themselves. This comprehensive self-help program is being compared to the passive information only [www.bipolarcaregivers.org](http://www.bipolarcaregivers.org) to assess its impact on reducing the distress of significant others and enhancing their coping and quality of life. The iCARE4bipolar model may potentially be a way to inform, support and up-skill family and friends to play a vital informal supportive role without jeopardizing their wellbeing or relationship with the person.

### A feasibility randomised controlled trial of a culturally adapted psycho-education for bipolar disorder

MI Husain<sup>a</sup>, IB Chaudhry<sup>b</sup>, MO Husain<sup>c</sup>, N Mehmood<sup>d</sup>, SH Ansari<sup>d</sup>, RR Rahman<sup>e</sup>, MM Hamirani<sup>f</sup>, T Kiran<sup>d</sup>, S Ahmed<sup>d</sup>, P Haddad<sup>b</sup>, F Naeem<sup>g</sup>, N Husain<sup>b</sup>

<sup>a</sup>Centre for Affective Disorders, Institute of Psychiatry Psychology and Neuroscience, London, United Kingdom, <sup>b</sup>Department of Psychiatry, University of Manchester, Manchester, United Kingdom, <sup>c</sup>Department of Psychiatry, Greater Manchester West NHS Foundation Trust, Manchester, United Kingdom, <sup>d</sup>Department of Psychiatry, Pakistan Institute of Learning and Living, Karachi, Pakistan, <sup>e</sup>Department of Psychiatry, Dow Institute of Health Sciences, Karachi, Pakistan, <sup>f</sup>Department of Psychiatry, Abbasi Shaheed Hospital, Karachi, Pakistan, <sup>g</sup>Department of Psychiatry, Queen's University, Kingston, Canada

**Background:** Studies on psycho-education indicate that such interventions may improve outcomes in bipolar patients. However, there has been a lack of structured, controlled clinical trials demonstrating the efficacy of culturally adapted psycho-education in preventing relapse in patients with bipolar I and II disorder in the low and middle-income countries.

**Aim:** To determine the feasibility and acceptability of a culturally adapted psycho-education intervention to prevent relapse of bipolar disorder in patients in Karachi, Pakistan.

**Methods:** Thirty-one bipolar I and II outpatients in remission (Young Mania Rating Scale score <6, Hamilton Depression Rating Scale-17 score <8) for at least 6 months prior to inclusion in the study were recruited from outpatient psychiatric units in Karachi.

Participants were receiving standard pharmacologic treatment. Participants were randomized to receive, in addition to standard psychiatric care, 12 weekly sessions of culturally adapted psycho-education or treatment as usual (TAU). Subjects were assessed every two weeks during the 12-week treatment period. Outcome measures were assessed using Young Mania Rating Scale (YMRS), Knowledge, Attitudes and Practice (KAP) surveys and a self-reported measure of medication adherence.

**Results:** 17 participants were randomised to the intervention group whilst 14 participants were randomised to TAU group. Data is currently being collected and results are expected to be ready for presentation at the conference.

**Implications:** Evidence based guidelines recommend psycho-education for bipolar disorder but there is limited reported research from low and middle-income countries. To our knowledge this is the first RCT of a manual assisted culturally adapted psychological intervention from Pakistan.

### The long-term effects of psychoeducation on number of hospitalizations: a randomized controlled trial comparing group or individual treatment for patients with bipolar disorder

H Kallestad<sup>a</sup>, E Wullum<sup>a</sup>, JH Bjørngaard<sup>b</sup>, TC Stiles<sup>c</sup>, G Morken<sup>a</sup>

<sup>a</sup>Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway, <sup>b</sup>Department of Public Health and General Practice, Norwegian University of Science and Technology, Trondheim, Norway, <sup>c</sup>Department of Psychology, Norwegian University of Science and Technology, Trondheim, Norway

**Background:** Psychoeducation is recommended adjunct treatment for patients with bipolar disorder, but it is still unclear what format of psychoeducation works best and for which populations it works best.

**Aims:** To test if 18 sessions of group based psychoeducation is more effective than three sessions of individual psychoeducation in reducing the long-term number of hospitalizations, and to test if there are subtypes of patients where group therapy is more effective.

**Method:** A randomized controlled trial of 77 patients with bipolar I or II disorder who were randomized to group (experimental condition, n = 38) or individual psychoeducation (control condition, n = 39). The primary outcome was number of hospitalizations during the two first years after treatment started. Baseline characteristics on number of prior hospitalizations, affective episodes 6 months before treatment, affective state at treatment entry, levels of functioning, harmful substance use, medication compliance, and symptom severity was assessed. A regression analysis was used to test if type of treatment could predict number of hospitalizations after treatment; and if substance use, diagnostic subtype, and prior hospitalizations moderated outcomes.

**Results:** There were no differences between the two groups on any of the baseline characteristics. In the unadjusted analyses, there were no differences between mean number of hospitalizations between the individual treatment (n = 0.87, SD = 1.9) and group treatment (n = 1.08, SD = 2.0) (t (74) = 0.48, p = 0.63). However, in the adjusted analysis, patients receiving individual psychoeducation had fewer hospitalizations compared to patients receiving group based psychoeducation ( $\beta = 0.52$ , p = 0.0003), and this was moderated by number of prior hospitalizations ( $\beta = -0.51$ , p = 0.001) and diagnostic subtype ( $\beta = 0.24$ , p = 0.02), with patients with more prior hospitalizations and bipolar II disorder having less hospitalizations with individual treatment. The regression model explained 46% of the variance in hospitalizations.

**Conclusion:** Contrary to our assumptions, three sessions of individual psychoeducation was more effective than 18 sessions of group based psychoeducation in reducing future hospitalizations for



patients with bipolar disorder, especially for patients with bipolar II disorder and frequent prior hospitalizations.

### The evolution of illness representations: a therapeutic lever in psychoeducation

K M'baïlara<sup>a</sup>, F Colom<sup>b</sup>, E Rouan<sup>c</sup>, A Follentant<sup>a</sup>, I Minois<sup>d</sup>, B Etain<sup>e</sup>, S Gard<sup>d</sup>, C Henry<sup>e</sup>, A Desage<sup>d</sup>, J Scott<sup>f</sup>

<sup>a</sup>Psychology, University of Bordeaux, Bordeaux, France,

<sup>b</sup>Department of Psychiatry Institute of Neuroscience Hospital Clinic University of Barcelona IDIBAPS CIBERSAM, Bipolar Disorders Unit, Barcelona, Spain, <sup>c</sup>Psychology, University of Paris 8, Paris, France, <sup>d</sup>Psychiatry, Hospital C.Perrens, Bordeaux, France, <sup>e</sup>U955 and Pôle de Psychiatrie, INSERM and Hôpital Henri Mondor-Albert Chenevier Assistance Publique Hôpitaux de Paris, Créteil, France, <sup>f</sup>Newcastle University & Institute of Psychiatry, Academic Psychiatry Institute of Neuroscience & Centre for Affective, Newcastle & London, United Kingdom

The effectiveness of psychoeducation on illness course is recognized (Colom et al., 2003; Colom et al., 2009). Nonetheless, only little research on therapeutic processes has led to conclusive findings about the improvement in the psychosocial functioning of psychoeducation groups' participants. The knowledge input regarding the disorder and the work done on the representation of the disorder are action and facilitation mechanisms. However, are they therapeutic levers? The present study gauges the evolution of representations on the psychosocial functioning of patients and families facing bipolar disorder who participated to a 6 months psychoeducation program consisting of 12 sessions (FondaMental Campus, French program). The sample comprises 44 participants (patients and family). The psychoeducation sessions lead to improve their knowledge of bipolar disorders and, above all, to change their subjective representation of the illness (particularly controllability and understanding). This modification of representation (Scott, 2005) significantly predicts a good psychosocial functioning and a good quality of life after the program. This exploratory study's interest lies in the finding that, out of these two variables, only the evolution of illness representation is a relevant lever in psychoeducation effectiveness processes. While bearing the educational dimension in mind, it is about ensuring that the relation's psychological dimension to the illness stands at the heart of the psychoeducation approach offered to the participants. Information per se is not enough.

### Verbal learning and memory abilities and the outcome of psychological treatments in bipolar disorder – data from a RCT

T Meyer<sup>a</sup>, IE Bauer<sup>a</sup>, M Hautzinger<sup>b</sup>

<sup>a</sup>Department of Psychiatry & Behavioral Sciences, University of Texas HSC, Houston, USA, <sup>b</sup>Department of Clinical Psychology, University of Tuebingen, Tuebingen, Germany

**Introduction:** A number of studies have shown that patients with bipolar disorder (BD) exhibit neuropsychological deficits including impaired executive functioning, verbal learning and memory. While it is unclear whether these deficits are indicators of vulnerability, severity of the disorder or consequences of biological changes associated with the disease (e.g. neuroprogression), poor cognitive functioning can potentially affect treatment adherence and the patient's ability to effectively and jointly work with a physician and/or therapist to improve treatment outcome. Verbal learning and memory are related to communication, and communication is essential for most psychological interventions which often are also labelled as 'talking therapies'. We therefore examined whether the outcome of psychological interventions aimed at

reducing recurrence of mood episodes was affected by verbal learning and memory performance.

**Method:** N = 76 euthymic patients with BD were randomized to either Cognitive Behavior Therapy (CBT) or Supportive Therapy (ST) [Meyer & Hautzinger, 2012]. In addition to diagnostic and clinical measures (e.g. SCID-I, HAMD, YMRS) patients underwent cognitive tests assessing their verbal learning/memory functioning (*Auditive Verbal Learning Test* (AVLT, Heubrock, 1992)) and global intelligence (*Leistungsprüfsystem* (LPS, Horn, 1972)). Patients received 20 sessions of CBT or ST over 9 months and were followed up for another 2 years.

**Results:** We previously found that, while in treatment, CBT tended to prevent recurrence of mood episodes to a greater extent than ST. However, this effect disappeared during the 2 year follow-up [Meyer & Hautzinger, 2012]. First exploratory analyses suggest that cognitive functioning might be related to post-treatment self-rated ( $p = 0.10$ ) and observer-rated depressive symptoms ( $p < 0.05$ ) after controlling for therapy condition, age of onset and number of episodes. Final results including recurrence rates at follow-up in this sample will be presented and discussed at the conference.

### Diagnosis-specific, individualized peer support for bipolar disorder

K Pring-Mill, P Termansen

Peer Support, Pacific Bipolar Foundation, North Vancouver, Canada

**Aims:** The *Friends of Bipolar* peer support program provides practical, educational, and emotional support specific to bipolar disorders in a one-on-one setting. It aims to offer compassionate care, comprehensive education about self-management, and support during transitions between inpatient and community care.

**Methods:** In 2013, our team recruited potential peer supporters based on their effective self-management of bipolar disorder and their desire to support others. These individuals enrolled in our training course, which includes psychosocial intervention, peer support techniques, comorbid disorders, and coping strategies for bipolar disorder. The eight-week course consists of twice-weekly, two-hour seminars taught by local experts, followed by an exam. From the first two courses, the program recruited a team of 15 peer supporters, each of whom supports 1–3 clients at a time. Supporters meet weekly with clients for 90-minute sessions, assisting with setting goals, evaluating mood, and teaching self-management methods, including tools drawn from cognitive-behavioural and psychosocial approaches. A coordinator oversees clients' progress, evaluating case notes and addressing challenging cases. Clients are interviewed every three months to determine any changes in well-being and to consider the impact of this unique diagnosis-specific, individualized peer support program.

**Results:** Clients report positive changes in their well-being and quality of life, such as improved moods and feeling less isolated. They express appreciation for the empathy, non-judgment, and guidance provided by their peers. Clients acknowledge the value of implementing self-management strategies; knowing that they have agency in their recovery empowers them to manage their symptoms and commit to treatment. Peer support has enhanced crisis management; weekly peer support allows for consistent monitoring, such that peer supporters alert clinicians of early warning signs. Peers have also eased transitions from inpatient to community care.

**Conclusions:** This pilot project has garnered significant positive feedback, and our team plans to offer the program to other mental health organizations throughout Canada. One-on-one, diagnosis-specific peer support is beneficial in conjunction with a clinical

treatment plan, and our team intends to pursue quantitative research to further evaluate its effectiveness in improving bipolar symptoms and decreasing hospitalization.

### A qualitative study of reasons for nonadherence to psychiatric and cardiovascular risk factors treatment among patients with bipolar disorder in Puerto Rico

SI Ralat<sup>a</sup>, CA Depp<sup>b</sup>, G Bernal<sup>c</sup>

<sup>a</sup>Department of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico, <sup>b</sup>Department of Psychiatry, University of California San Diego, USA, <sup>c</sup>Department of Psychology, University of Puerto Rico Rio Piedras Campus, San Juan, Puerto Rico

**Aims:** Cardiovascular Disease (CVD) risk factors in Bipolar Disorder (BD) patients are about twice as common as that in the general population. Latinos with BD are more likely to be nonadherent to psychiatric medication and other medical conditions. The aim of this study is to identify the patients' perspectives on the reasons for nonadherence to psychiatric and CVD risk treatment in outpatients with BD in Puerto Rico.

**Methods:** Four focus groups were held for a total of 20 patients ranging from 23 to 60 years old, recruited from CMHC of Carlos Albizu University and ASSMCA outpatient sites in Puerto Rico. IRB approved this study. All subjects signed written informed consent. Participants had BD, Type I/II and one or more of the following CVD risk factors: hypertension, obesity, diabetes, high level of cholesterol, smoking, poor diet, lack of physical activity, or a high level of stress. Audio-recordings of focus groups were transcribed and a content analysis was performed.

**Results:** Themes emerging from the focus groups included that patients perceived physical illness as more "serious" than BD. Reasons identified for lack of adherence varied by patient views of treatment (e.g., limited understanding about the purpose of medication, limited motivation to adhere in the absence of physical symptoms); stigma against taking medications (e.g., view of diabetes as a disease of the elderly); provider poor orientation (e.g., confusion about explanation for medication) and lack of support (e.g., no one else does diet). For BD medications, the most commonly identified causes of nonadherence were: stigma to the psychiatric condition (e.g., fear to be labeled as "crazy" by their families and others); views of the illness (e.g., denial of condition); provider relationship factors (e.g., feeling as though "no one listen to the needs of patients"); side effects; poor support from family members, (e.g., pressure to stop their medication). Participants stated that mood symptoms influence adherence for both BD and CVD risk factors.

**Conclusion:** Patients' reasons for nonadherence to treatments for CVD risk and BD were somewhat unique, suggesting need for integrated interventions targeting patient, provider, and family barriers to adherence in patients with both conditions.

### Understanding family functioning in bipolar disorder: a comparison of bipolar patients, family caregivers and healthy controls

M Reñares, CM Bonnin, F Colom, D Hidalgo-Mazzei, B Solé, E Jiménez, C Torrent, M Comes, A Martínez-Arán, J Sánchez-Moreno, E Vieta

Department of Psychiatry Hospital Clínic Barcelona, Bipolar Disorder Programs Institute of Neurosciences IDIBAPS CIBERSAM, Barcelona, Spain

**Aims:** Functional improvement has become one of the aims of the treatment of bipolar disorder. However, scant attention has been

given to family functioning, even though it has a role in the illness outcome and is simultaneously affected by the disorder. The aims of this study were to compare family functioning reported by euthymic bipolar patients and healthy controls; analyse the relationship between clinical variables and family functioning; and explore the level of congruence in the perception of family environment between bipolar patients and their relatives.

**Methods:** The sample comprised 82 adult euthymic bipolar patients, 82 family caregivers of these patients and 47 healthy controls. Socio-demographic, clinical and treatment data were collected. All participants completed the Family Environment Scale.

**Results:** There were low discrepancies between relatives' and patients' reported scores in family functioning subscales, the pattern being very similar. However, significant differences were found between bipolar patients and controls. Inter-group differences were significant for the subscales cohesion ( $p < 0.005$ ), expressiveness ( $p = 0.002$ ), conflict ( $p = 0.038$ ), intellectual-cultural orientation ( $p = 0.001$ ) and active-recreational orientation ( $p < 0.005$ ), and almost significant in organization ( $p = 0.064$ ), all favourable for the control group. Significant associations were found between family environment and clinical variables.

**Conclusions:** Perception of family environment between euthymic bipolar patients and their caregivers is similar but significant differences exist between patients and healthy controls. Clinical variables of severity were related to family environment although the cross-sectional design impedes to determine causality direction. These findings contribute to increasing the understanding of family functioning in bipolar disorder and highlight the importance of family intervention.

### Emotion processing is not related to self-reported measures of social functioning in bipolar disorder

K Angers<sup>a</sup>, B Pester<sup>a</sup>, A Hayek<sup>a</sup>, D Marshall<sup>a</sup>, K Hinrichs<sup>a</sup>, M McInnis<sup>b</sup>, M Kamali<sup>b</sup>, S Langenecker<sup>c</sup>, K Ryan<sup>a</sup>

<sup>a</sup>Psychiatry Neuropsychology, University of Michigan, Ann Arbor, USA, <sup>b</sup>Psychiatry, University of Michigan, Ann Arbor, USA, <sup>c</sup>Psychiatry, University of Illinois-Chicago, Chicago, USA

**Aims:** Individuals with bipolar illness (BD) are less accurate at identifying facial emotions compared to healthy controls and those with unipolar depression. Social and cognitive deficits observed in BD can be as severe as those observed in schizophrenia. Accurately processing facial expressions plays a crucial role in social interactions, though the link between the two has been largely understudied in BD. This study examined the relationship between mood state, emotion processing, and social functioning in a large sample of BD patients.

**Methods:** A sample of 164 individuals diagnosed with bipolar I/II were taken from the Prechter Longitudinal Study of BD. Mania and depression were assessed using the Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HDRS). The Facial Emotion Processing Test (FEPT), which involves identification of four emotions: happy, sad, angry, and fearful was administered and all patients completed the Life Functioning Questionnaire (LFQ), which examines life functioning in 4 domains, but only social difficulties with family and friends were used for this study.

**Results:** Bivariate correlations showed depression scores were not related to accuracy in identifying the four emotions, but higher depression scores were significantly related to higher social difficulties (difficulties with family,  $r = 0.39$ , difficulties with friends,  $r = 0.33$ ). In contrast, YMRS was significantly negatively correlated with fear accuracy ( $r = -0.17$ ) and sad accuracy ( $r = -0.19$ ), indicating that higher mania scores showed more inaccuracies identifying these emotions. YMRS was not significantly related to self-

reported measures of social difficulties. There was no relationship between face accuracy and social difficulties.

**Conclusions:** Mood is significantly related to emotion processing and to self-report of social functioning, but dependent on mood polarity. Mania was related to greater inaccuracy in identifying fear and sad emotions. We might expect this to impact social relationships; however, higher mania scores were not related to social difficulties. In contrast, depression showed no relationship to emotion processing, but there was a relationship to social difficulties. Overall, using self-report measures of social difficulties may not reflect the level of objective difficulties with emotion processing among individuals with varying levels of depression and mania.

### **Additive effects of polygenetic risk and childhood trauma on clinical characteristics in severe mental disorders**

**M. Aas, M. Tesli, S. Djurovic, F. Bettella, O.A. Andreassen, I. Melle**  
*NORMENT-K.G.JEBSEN Psychosis Research Centre, Institute of Clinical Medicine, University of Oslo and Oslo University Hospital, Norway*

Childhood trauma has been linked to increased risk of bipolar disorder and schizophrenia, as well as more severe clinical features of the disorders. It is well known that these disorders are highly heri-

table, with overlapping polygenetic risk. Aim of this study: Investigate the relationship between polygenetic risk and a history of childhood trauma on clinical features in patients with bipolar and schizophrenia. 215 patients with a broad DSM-IV schizophrenia spectrum disorder or bipolar disorder (mean  $\pm$  age:  $26.0 \pm 10.4$ ; gender: 54% males) were consecutively recruited to the NORMENT, TOP research study. All patients had at least one psychotic episode. A history of childhood trauma was collected using the Childhood Trauma Questionnaire. Polygenic risk scores were calculated based on results from the independent Psychiatric Genomics Consortium schizophrenia and bipolar case-control studies. Clinical characteristics were assessed by the DSM-IV, the Positive And Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF). Patients with high polygenic risk score reporting a history of childhood trauma had significantly more severe clinical features, such as lower GAF scores, more positive symptoms from the PANSS, and lower age of onset, compared to all other groups. They also had a greater risk of smoking cannabis lifetime, and had significantly longer duration of untreated psychosis (DUP), as well as poorer premorbid functioning in adolescence. Our data demonstrate additive effects of polygenic risk and a history of childhood trauma on more severe clinical features in patients with a severe mental illness.

# Poster Session II

## Dopaminergic animal models of mania

**J Quevedo**

*Psychiatry, The University of Texas Medical School at Houston, Houston, USA*

Animal models of mania should be able to produce an equivalent clinical phenomenon (face validity) resembling pathophysiological aspects of the illness (construct validity) and treatment responses (predictive validity). Nevertheless, inducing manic symptoms by increasing dopaminergic activity may reflect in some extent the clinical phenomenon, pathophysiological processes and treatment responses to dopamine blockers observed in acute mania. As a consequence, validated animal models of mania have relied on the effects of stimulant administration over the behavior of rodents on the open field test. The administration of stimulants to rodents produces an increase in the brain dopamine (DA) efflux, inhibition of DA reuptake or DA degradation by the enzyme monoamine oxidase that may induce increase in locomotor activity and psychomotor agitation mimicking manic symptoms. In recent years, our research group has studied neurochemical changes involved in the pathophysiology of bipolar disorder using the animal model of mania induced by amphetamine. We have engaged in the study of different molecules and systems, including brain derived neurotrophic factor (BDNF), B-cell lymphoma 2 (Bcl-2), histone deacetylase (HDAC), protein kinase C (PKC), Glycogen synthase kinase-3 (GSK-3), oxidative stress and mitochondrial alterations. From these studies we have also studied new substances with potential as mood stabilizers. The number of potential new drugs tested in animal models is growing, which helps further our knowledge of the pathophysiology of bipolar disorder and supports the development of better drugs for the treatment of this disorder.

## Intracerebroventricular administration of ouabain as an animal model for mania

**S REI-Mallakh**

*Psychiatry, University of Louisville School of Medicine, Louisville, USA*

Human bipolar illness is characterized by mood state and diagnosis-associated abnormalities of cellular cation distribution and transport. These include reduced sodium pump activity and expression and increased intracellular sodium and calcium. These observations lead to the use of intracerebroventricular (ICV) administration of ouabain, a potent sodium pump inhibitor, to model human bipolar illness. Ouabain, was administered intracerebroventricularly to male rats. Activity is determined by locomotion in an open field. Animals were treated with lithium, haloperidol, olanzapine, cariprazine, or memantine. Cerebral glucose uptake was also examined after ouabain administration with [18F]-Fluorodeoxyglucose positron emission tomography (FDG PET). Ouabain increased locomotion 300% over baseline. Lithium, haloperidol, cariprazine, and memantine prevented the ouabain-induced hyperlocomotion response. Olanzapine did not. FDG PET revealed reduce glucose uptake throughout the cortex. Inhibition of central nervous system sodium pump with ouabain models human abnormalities in animals. The resulting behavioral and biochemical responses are a plausible animal model of mania. The data with medications suggests that this model is useful for preclinical screening of potential anti-manic agents.

## An efficient test battery for rapid characterization of new generation of non-toxic antipsychotics derived from clozapine

**J Eschbach<sup>a</sup>, S Muller<sup>b</sup>, J Peter<sup>c</sup>, P Eftekhari<sup>a</sup>**

*<sup>a</sup>Inoviem Scientific, ISIS Institut de sciences et d'ingénierie supramoléculaire, Strasbourg, France, <sup>b</sup>Centre National de la Recherche Scientifique (CNRS) Immunopathologie et Chimie Thérapeutique, IBMC, Strasbourg, France, <sup>c</sup>Laboratory of Excellence Medalis, IBMC, Strasbourg, France*

The aim of this study was to develop a new animal model which allow the selection of new analogs of clozapine with less or non-side effects yet unchanged clinical efficiency. Current available preclinical models are complex and not optimal to develop new therapy for schizophrenia. In our model the ideal analog of clozapine should have a longer latency for inducing extrapyramidal symptoms. In this regard we have generated an animal model for translational drug development based on a simple and rapid battery of tests using drug induced extrapyramidal effects such as locomotor activity and catalepsy. We tested the effects of clozapine and its two metabolites N-Desmethylclozapine and clozapine N-oxide in male MRL/lpr and C57BL/6 mice strains (n = 12 respectively). In sensorimotor tasks, C57BL/6 following clozapine treatment (5, 10 and 15 mg/kg) showed a rapid impairment in string agility, and impairment in balance beam test, while it has very mild effect on MRL/lpr mice. The MRL/lpr mild response to clozapine might be explained by the presence of circulating autoantibodies against serotonergic, adrenergic, angiotensin G-protein coupled receptors (GPCR), which we have detected and were previously described as pharmacologically active on their targeted receptors. No autoantibodies against the melanocortin-4 receptor (control GPCR) were detected in this strain. Based on these results combination of both strains makes a suitable *in vivo* screening method to evaluate potential treatments for clozapine treated subset of patients with schizophrenia. Combined with NPOT (Nematic Protein Organization Technic) a label free cutting edge technology by which the OFF target responsible for agranulocytosis, can be identified, this model will allow a rapid development of a new generation of clozapine analogs.

## Deep brain stimulation in ACTH-treated rats induce mania-like behavior: role for mitochondrial dysfunction in cycling mood states

**Y Kim<sup>a</sup>, S McGee<sup>b</sup>, J Czechor<sup>b</sup>, A Walker<sup>a</sup>, R Kale<sup>c</sup>, S Sutor<sup>d</sup>, K Walder<sup>b</sup>, A Kouzani<sup>c</sup>, M Berk<sup>e</sup>, S Tye<sup>d</sup>**

*<sup>a</sup>School of Psychology, Deakin University, Melbourne, Australia, <sup>b</sup>Molecular and Medical Research Strategic Research Centre, Deakin University, Geelong, Australia, <sup>c</sup>School of Engineering, Deakin University, Geelong, Australia, <sup>d</sup>Department of Psychiatry & Psychology, Mayo Clinic, Rochester, USA, <sup>e</sup>IMPACT Strategic Research Centre, Deakin University, Geelong, Australia*

The hypothalamic-pituitary-adrenal (HPA) axis is implicated in stress reactivity, antidepressant treatment response and is believed to play a central role in the pathogenesis of depressive and bipolar states. In rats, chronic treatment with adrenocorticotrophic hormone (ACTH) disrupts antidepressant efficacy and induces HPA axis abnormalities similar to the findings in patients with unipolar and bipolar depression. To model resistant depression, ACTH (100 µg/d) was administered for 21 days to male Wistar rats.

Animals were divided randomly into ACTH and saline control groups where a subset of them received surgery with deep brain stimulation (DBS) or sham electrodes. Antidepressant efficacy of imipramine (10 mg/kg) was assessed in the Open Field Test (OFT) and Forced Swim Test (FST) on day 15. Imipramine-resistant animals subsequently received 7 days of high frequency nucleus accumbens (NAc) DBS (130 Hz; 200  $\mu$ A; 90 $\mu$ sec) followed by OFT and FST. ACTH pre-administration blocked imipramine-mediated reductions of immobility in the FST ( $n = 23$ ;  $p < 0.05$ ). NAc stimulation significantly decreased immobility time in ACTH-treated animals ( $n = 8$ ;  $p < 0.05$ ). No significant reduction in immobility, however, was observed in the sham group ( $n = 8$ ;  $p < 0.05$ ). Interestingly, a proportion (30%;  $n = 7$ ) of the ACTH-treated animals (DBS & Sham) displayed heightened locomotor activity in the OFT, and exaggerated escape behaviors in the FST. Further investigations of mitochondrial function in the prefrontal cortex showed that ACTH-treated rats had lower capacity for ATP production compared with the saline treatment group. In addition, there was a high capacity for substrate oxidation, ATP production and low mitochondrial proton leak in the ACTH-treated rats with hyperactive locomotor activity. These findings highlight the potential efficacy of NAc DBS for treating animals that were resistant to imipramine. The induction of a mania-like phenotype was suggested by the observations of hyperactivity, augmented antidepressant response behaviors and mitochondrial function, altogether indicative of a disruption to mesoaccumbens signaling in ACTH-treated animals. Therefore, mitochondrial dysfunction may play a role in the impairment of cellular plasticity and resilience manifested in the context of mood-related disorders.

### Oxidative DNA guanine base damage and base excision repair (BER) in euthymic patients with bipolar disorder

D Ceylan<sup>a</sup>, G Tuna<sup>b</sup>, G Kırkalı<sup>c</sup>, Z Tunca<sup>d</sup>, M Dizdaroğlu<sup>c</sup>, G Can<sup>d</sup>, E Arat<sup>d</sup>, A Özerdem<sup>d</sup>

<sup>a</sup>Psychiatry, Gümüşhane State Hospital, Gümüşhane, Turkey,

<sup>b</sup>Biochemistry, Dokuz Eylül University, Izmir, Turkey, <sup>c</sup>Biochemical Science Division, National Institute of Standards and Technology, Gaithersburg, USA, <sup>d</sup>Psychiatry, Dokuz Eylül University, Izmir, Turkey

**Background:** Base excision repair (BER) mechanism repairs DNA by removing damaged bases with the help of specific enzymes. The human-8-oxoguanine DNA N-glycosylase I (hOGG1) is a specific BER enzyme for guanine base, whereas endonuclease VIII-like I (NEIL1) repairs damaged adenine and guanine bases. We aimed to investigate oxidative guanine damage in relation to repair enzymes in bipolar disorder (BD).

**Method:** Medicated patients with BD who were euthymic for at least 6 months ( $n = 17$ ) and healthy controls ( $n = 19$ ) were included. Expressions of the NEIL1 and hOGG1 mRNA transcripts were measured in blood samples by QRT-PCR using a LightCycler (Graph1-2). DNA samples were isolated from leukocytes using salting-out method. Damaged DNA bases [8-hydroxyguanine (8-OHGua), 2,6-diamino-4-hydroxy-5-formamidopyridine (FapyGua)] were measured using GC-MS/MS. Groups were compared using MannWhitney-U and Chi-square tests. hOGG1 ( $\Delta$ Ct), NEIL1 ( $\Delta$ Ct), 8-OHGua and FapyGua levels were analyzed using multivariate analysis of variance.

**Results:** Groups did not differ with regard to gender or smoking status. Controls were significantly younger than the patients. NEIL1, 8-OHGua/106 and FapyGua/106 levels were not significantly different between patients and controls (Table 1). Patients showed significantly (43%) lower levels of hOGG1 expression than controls (Graph 2). Expressed levels of hOGG1 correlated nega-

tively with the 8-OHGua/106 base levels only in patients ( $r = -0.601$ ,  $p = 0.001$ ) but not in controls ( $r = 0.218$ ,  $p = 0.455$ ).

**Conclusion:** Significantly lower levels of hOGG1 enzyme and its negative correlation with the 8-OHGua levels in medicated euthymic patients may point at involvement of defected BER mechanisms in the oxidative DNA damage processes in BD.

### Cerebral dopamine neurotrophic factor (CDNF) levels are increased in bipolar disorder

M Sehmbi<sup>a</sup>, A Siddiqui<sup>a</sup>, K Terpstra<sup>a</sup>, RK Mishra<sup>b</sup>, BN Frey<sup>b</sup>

<sup>a</sup>MinDS Neuroscience Graduate Program, McMaster University, Hamilton, Canada, <sup>b</sup>Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, Canada

**Background/Aims:** The dopaminergic system has been implicated in the pathophysiology of Bipolar Disorder (BD) via pharmacological and functional MRI studies. Cerebral dopamine neurotrophic factor (CDNF) protects midbrain dopamine neurons *in vivo*. Following administration of 6-hydroxydopamine, CDNF restores the function of dopaminergic neurons and prevents further degeneration. CDNF also displays anti-inflammatory properties both in cell culture and *in vivo* studies. Here we investigated levels of peripheral CDNF RNA expression in individuals with BD and healthy controls.

**Methods:** We measured levels of CDNF RNA expression in whole blood in a total of 76 participants via RT-PCR: 37 individuals with BD, and 39 healthy controls. For patients with BD, psychiatric status was confirmed with the Structured Clinical Interview for DSM-IV (SCID). The severity of depressive symptoms was assessed via the Montgomery-Asberg Depression Rating Scale (MADRS), and the Hamilton Depression Rating Scale (HDRS). BD patients in all mood states were included in the study.

**Results:** An ANCOVA model with CDNF RNA expression as the dependent variable and age and sex as covariates showed a significant group effect ( $F_{1,71} = 11.7$ ,  $p = 0.001$ ). Age was significantly associated with CDNF RNA expression ( $F_{1,71} = 15.3$ ,  $p = 0.0002$ ). Sex was not significantly associated with CDNF RNA expression ( $F_{1,71} = 0.6$ ,  $p = 0.44$ ). CDNF RNA expression was significantly correlated with both MADRS ( $r_s(35) = 0.35$ ,  $p = 0.03$ ) and HDRS scores ( $r_s(35) = 0.48$ ,  $p = 0.003$ ) in individuals with BD.

**Conclusions:** No previous studies have investigated CDNF in BD. Our results indicate that levels of CDNF expression are increased in individuals with BD. A previous study shows that valproic acid can upregulate CDNF expression in the rat CNS *in vivo*. Perhaps the use of medications that interact with the dopaminergic system may explain in part the increased expression of CDNF observed in individuals with BD.

### Mitochondrial DNA sequence analysis of patients with bipolar disorder

M Frye<sup>a</sup>, E Ryu<sup>b</sup>, G Jenkins<sup>b</sup>, J Evans<sup>b</sup>, S McElroy<sup>c</sup>, M Nassan<sup>a</sup>, W Highsmith<sup>d</sup>, J Biernacka<sup>b</sup>

<sup>a</sup>Department of Psychiatry & Psychology, Mayo Clinic, Rochester, USA, <sup>b</sup>Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, USA, <sup>c</sup>Department of Psychiatry & Psychology, Lindner Center of HOPE, Mason, USA, <sup>d</sup>Department of Molecular Genetics, Mayo Clinic, Rochester, USA

**Background:** Clinical, genetic and neuroimaging data suggest mitochondrial dysfunction is related to bipolar disorder (BD), and the mitochondrial dysfunction hypothesis has been proposed as an explanation for the underlying heterogeneity of the clinical manifestations of BD and related psychiatric traits. An association of BD and schizophrenia with a deletion of almost 5000 bp, known as the “common deletion,” which includes the mitochondrial DNA

gene NADH dehydrogenase subunits 3, 4, and 5 (MT-ND3,4,5), has been investigated by several studies.

**Methods:** To evaluate the association of mitochondrial DNA (mtDNA) variation with secondary clinical features common in BD, we sequenced the mtDNA of 227 subjects with BD. We tested for association of the common haplogroups and common polymorphisms with BMI as well as psychosis ( $N = 110$  BD with psychosis vs  $N = 111$  BD with no psychosis), and rapid cycling ( $N = 138$  BD with rapid cycling vs  $N = 96$  BD with no rapid cycling).

**Results:** Although none of the associations were significant after correction for multiple testing, there was marginal evidence of association of the U haplogroup with psychosis ( $p = 0.02$ ). Top association signals for single nucleotide variants (SNVs) included association of psychosis with variants in the ND3, ND4 and ND5 genes, within the common deletion region ( $p < 0.05$ ).

**Conclusions:** Ongoing analyses are focused on gene-level associations that take into account rare variants in mtDNA, as well as whole mtDNA comparisons between phenotypically distinct subgroups of BD.

### Associations among reward-based learning, mood and anxiety symptoms, and their relation to brain neurophysiology in schizophrenia and bipolar disorder

MH Hall<sup>a</sup>, A Whittton<sup>a</sup>, S Mallya<sup>a</sup>, S Douglas<sup>a</sup>, K Spencer<sup>b</sup>, B Cohen<sup>a</sup>, D Levy<sup>a</sup>, J Smoller<sup>c</sup>, D Öngür<sup>a</sup>, D Pizzagalli<sup>a</sup>

<sup>a</sup>Psychiatry, McLean Hospital Harvard Medical School, Belmont, USA, <sup>b</sup>Psychiatry, VA Boston Healthcare System Harvard Medical School, Boston, USA, <sup>c</sup>Psychiatry, Massachusetts General Hospital Harvard Medical School, Boston, USA

**Background:** Evidence suggests that impaired reward-based learning [RL] is particularly salient in mood disorders and that reduced RL correlates with increased anhedonic symptoms. However, the pattern of RL and its relation to anhedonia in patients with schizophrenia (SZ) is unclear. Moreover, few studies have investigated the association between RL and event-related potentials (ERPs) thought to be endophenotypes for schizophrenia (e.g., P3, sensory gating, and gamma oscillation). In this study we examined the associations between RL, mood and anxiety symptoms, and ERP responses in a large cohort of patients with SZ and BPD, and healthy individuals.

**Methods:** One hundred and twelve patients with BPD, 81 patients with SZ, and 141 control subjects were evaluated. Each completed the following tasks: clinical assessment, the Snaith–Hamilton Pleasure Scale (SHPS), the Mood and Anxiety Symptom Questionnaire (MASQ), a computerized probabilistic reward task, and an EEG recording. Sensory gating, P3, and gamma oscillation were processed from an auditory dual-click, an odd ball, and a steady-state 40 Hz paradigm, respectively. RL (i.e., response bias, RB) was assessed using mixed ANOVA with group as the between- and block as the within-subject factors, respectively. Associations between overall RL (total RB score), mood symptoms and each ERP phenotype were examined using Pearson partial correlations. Age, sex, and discriminability (an index of task difficulty) were included as covariates.

**Results:** SZ and BPD patients exhibited similar patterns of RL compared to controls. Significant negative correlations were found between SHPS and RL (total RB score) and between MASQ total score and RL in healthy controls (partial  $R = -0.28$ ,  $p < 0.001$  in both), but not in SZ or BPD patients. These results were unrelated to dose of antipsychotic medication. Controlling for the effect of mood and anxiety symptoms, RL was significantly associated with sensory gating response (partial  $R = -0.12$ ,  $p = 0.03$ ).

**Conclusions:** The results suggest that patients with SZ and BPD show intact RL. Among healthy individuals, increased anhedonic symptoms are associated with reduced RL. Overall, increased RL is related to greater inhibitory gating response. These results support a link between reward systems and inhibitory mechanisms.

### Neuromapping of endophenotypes for affective disorders: a twin study of neurocognitive, neuroimaging, cellular and epigenetic markers (the NEAD study)

I Meluken, N Meinhard, KW Miskowiak, M Vinberg, LV Kessing

Psychiatric Center Copenhagen, Copenhagen, Denmark

**Aims:** We aim to investigate candidate endophenotypes for affective disorders, across different levels of investigation. At the epigenetic and cellular levels, we examine DNA methylation, histone modification and microRNA and biomarkers related to oxidative stress, neuroinflammation, and metabolic respectively. Using structural and functional magnetic resonance imaging (MRI) and cognitive testing, we investigate gray matter volume as well as neural and behavioral measures of affective cognition, including emotional biases, affective regulation, mental imagery and reward processing. Three main hypotheses will be tested: 1) Candidate endophenotypes are associated with the degree of genetic disposition, 2) Abnormalities in these endophenotypes are interrelated on different levels, 3) Unaffected twins discordant for unipolar and bipolar disorder will differ in their profiles of endophenotypes.

**Methods:** Monozygotic twins are recruited through record linkage between the Danish Twin Register and the Danish Psychiatric Register. Twins discharged from a Psychiatric hospital between 1994 and 2011, diagnosed with either unipolar or bipolar disorder and in clinical remission (HDRS and YMRS scores  $\leq 14$ ), are eligible for inclusion. We aim to include 200 participants, of which 120 will undergo MR scan: Forty twin-pairs concordant ( $n = 40$ ) or discordant ( $n = 40$ ) for unipolar disorder, forty twin-pairs concordant ( $n = 40$ ) or discordant ( $n = 40$ ) for bipolar disorder and twenty twin-pairs ( $n = 40$ ) with no psychiatric history. One the day of inclusion, diagnosis is assessed with a SCAN interview, supplemented by medical records. Blood samples and a spot urine sample are obtained. The participants then undergo comprehensive neurocognitive testing using a battery of computerized affective cognition tests, and manual tests of non-emotional cognition. During functional MRI (fMRI), participants are given four tests to investigate self-referent incidental memory, emotional face processing, emotion regulation and reward processing. Data on gray matter volume is obtained with T1 and T2 structural scans.

**Results and conclusion:** The project is in its early inclusion phase, with 9 participants included. No emerging results or conclusions are yet available for publication.

### Protein S100 level and psychovegetative disorders in patients with chronic cerebral ischemia

Y Morozova

Neurology and Neurosurgery, RSMU, Moscow, Russia

Psychovegetative syndromes are common developments of Chronic Cerebral Ischemia (CCI), but its pathogenesis is not clear. We observed protein S100 level and frequency of psychovegetative symptoms in 108 patients with Chronic Cerebral Ischemia (CCI). All patients age 20–60 years; male-17, female-91 have been divided on 3 groups: (1) Control group-40 health persons and mean value S100 is  $0.694 \pm 0.001$  unit of optical density (UOD). (2) CCI I stage(st) – 33 patients with mild cognitive impairment and mean value S100 is  $0.740 \pm 0.002$  UOD. (3) CCI II stage-35 patients with

moderate cognitive impairment and mean value S100 is  $0.764 \pm 0.001$  UOD ( $p < 0.001$ ). We revealed correlation protein S100 level with frequency of sleep disorders, anxiety, asthenia, depression, panic attack in patients with CCI.

**Methods:** Inquirer, neurological exam, psychologist test, psychiatrist consultate, immunoenzymatic method.

**Result:** Sleep disorders — mean value S100 is  $0.717 \pm 0.001$  UOD, 17 patients with CCI I st. and 29 with CCI II st. Anxiety — mean value S100  $0.724 \pm 0.002$  UOD, 12 patients with CCI I st. and 23 patients with CCI II st. Asthenia — mean value S100 is  $0.716 \pm 0.002$  UOD, 28 patients with CCI I st. and 29 patients with CCI II st. Panic attack — mean value S100 is  $0.732 \pm 0.002$  UOD, 3 patients with CCI I st. and 11 patients with CCI II st. Depression — mean value S100 is  $0.778 \pm 0.001$  UOD ( $p < 0.001$ , nobody with CCI I st. and 7 patients with CCI II st).

**Conclusion:** Intensity of cognitive impairments and protein S100 level correlates with psychovegetative symptoms such as sleep disorders, asthenia, anxiety, depression, panic attack. The obtained facts show that the rise of neurobiochemical marker of brain damage protein S100 is associated with psychovegetative disorders grow and can be as a result of neurodegenerative processes in brain of patients with CCI.

### A feasibility study evaluating peripheral biomarkers in depression subtypes

M Nassan<sup>a</sup>, S Feeder<sup>a</sup>, G Jenknis<sup>b</sup>, D Choi<sup>a</sup>, S Kung<sup>a</sup>, M Veldic<sup>a</sup>, B Palmer<sup>a</sup>, P Croarkin<sup>a</sup>, W Bobo<sup>a</sup>, K Moore<sup>a</sup>, S Tye<sup>a</sup>, S Sutor<sup>a</sup>, J Biernacka<sup>a</sup>, M Frye<sup>a</sup>

<sup>a</sup>Psychiatry and Psychology, Mayo Clinic, Rochester, USA,

<sup>b</sup>Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, USA, <sup>c</sup>Division of Biomedical Statistics and Informatics and Department of Psychiatry and Psychology, Mayo Clinic, Rochester, USA

**Objectives:** The aim of this study was to explore the feasibility of utilizing peripheral biomarkers to enhance the diagnostic assessment, severity evaluation and treatment recommendations for depression subtypes.

**Methods:** In collaboration with the biomarker testing laboratory of Myriad Rules Based Medicine, depressed patients with MDD ( $n = 52$ ) or bipolar depression ( $n = 95$ ) were recruited. Clinical assessments included: Structured Diagnostic Interview for DSM-IV-TR (SCID), Inventory for Depressive Symptoms (IDS) and Patient health questionnaire (PHQ-9). Subjects with SCID diagnosis of atypical depression ( $n = 10$ ) were compared with subjects without atypical depression ( $n = 65$ ). To further explore the neurovegetative symptoms of atypical depression, we compared depressed subjects with decreased sleep and weight or appetite ( $n = 27$ ) vs subjects with increased sleep and weight or appetite ( $n = 20$ ). Furthermore, association of peripheral biomarkers with current depression severity as per IDS and PHQ-9 total scores was studied in all 147 subjects. One 7.5 cc tube of blood was drawn for proteomic multiplex analyses of 320 proteins utilizing the DiscoveryMAPTM v 1.0. Endpoint measures were predicted based on individual proteins using linear, logistic or multinomial logistic regression models; multiple testing per end point was addressed using False Discovery Rate (q-value). Participants provided informed consent to enrol in this study that was approved by the Institutional Review Board at Mayo Clinic.

**Results:** BMI, as a possible confounder, was not associated with any of the endpoint measures. After adjusting for primary diagnosis (MDD, BP-I and BP-II), subjects with atypical depression had lower levels of Cystatin-A with statistical significance suggestive of an association ( $q = 0.054$ ). When exploring the neurovegetative

symptoms, subjects with increased sleep and weight or appetite had higher levels of Thrombospondin-4 ( $q = 0.042$ ) than those with decreased sleep and weight or appetite. Although we did not find a significant association between protein levels and depression severity, our results suggest a possible negative correlation of Interferon gamma Induced Protein-10 with IDS severity ( $q = 0.067$ ), as well as negative correlation of Cadherin-1 ( $q = 0.065$ ) and positive correlation of Fatty Acid-Binding Protein-adipocyte ( $q = 0.065$ ) with PHQ-9 severity.

**Conclusions:** Limited by small sample size, these preliminary results suggest feasibility in testing for proteomic differences between depression subtypes and in evaluating depression severity.

### BDNF moderates the association between oxidative stress and cognition in adolescent bipolar disorder

D Newton, M Naiberg, B Goldstein

Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada

**Aims:** Oxidative stress and brain-derived neurotrophic factor (BDNF) have both been implicated in bipolar disorder (BD) pathophysiology. Similarly, cognitive dysfunction, particularly in frontal-executive tasks, is evident within and between mood episodes in BD. Schizophrenia research has shown interactions between oxidative stress and BDNF, and associations with cognition. No study has examined these interactions in BD youth; a population that may yield enhanced signal detection from decreased effects of aging and disease burden.

**Methods:** Serum levels of lipid hydroperoxides (LPH) and BDNF were measured in 30 BD adolescents and 25 control participants. Cognition was assessed using the Intra-Extra Dimensional (IED) task from the Cambridge Neuropsychological Test Automated Battery. Participants were divided into sub-groups based on BDNF levels using a median split. Mann-Whitney *U*-tests were used to compare between-groups, and Spearman correlations to compare LPH and cognition. Significant correlations were analysed using general linear models (GLM).

**Results:** Between-group comparisons of LPH, BDNF, and IED measure were not significant. LPH and BDNF significantly correlated only in controls ( $\rho = 0.402$ ,  $p = 0.047$ ). Within those with low BDNF in the combined sample, LPH significantly correlated with better IED total trials ( $\rho = -0.391$ ,  $p = 0.044$ ) and total trials adjusted for stages completed ( $\rho = -0.400$ ,  $p = 0.039$ ). Within controls with low BDNF, LPH significantly correlated with better total trials ( $\rho = -0.693$ ,  $p = 0.006$ ), total trials adjusted ( $\rho = -0.667$ ,  $p = 0.009$ ), total errors ( $\rho = -0.602$ ,  $p = 0.023$ ), and total errors adjusted ( $\rho = -0.576$ ,  $p = 0.031$ ). Within BD subjects with high BDNF, LPH significantly correlated with worse IED completed stage trials ( $\rho = 0.755$ ,  $p = 0.001$ ) and pre-extra dimensional shift errors ( $\rho = 0.588$ ,  $p = 0.017$ ). Within those with high BDNF in the combined sample, LPH significantly correlated with worse IED completed stage trials ( $\rho = 0.462$ ,  $p = 0.015$ ). GLM analysis showed a significant interaction of BDNF and LPH for all significant correlations in controls, and IED completed stage trials in the complete sample.

**Conclusions:** LPH may negatively influence set-shifting and reversal learning in BD youth, whereas the reverse association is evident among healthy controls. Moreover, BDNF may influence these associations. Further studies involving larger samples and longitudinal, repeated-measures study designs are warranted to better understand the directionality of these associations. Studies of antioxidant therapeutic approaches as possible treatments for cognitive dysfunction in BD are warranted, especially among those with high BDNF.



## Differences between manic and depressive bipolar inpatients in biochemical blood parameters

E Nieto, L Plans, I Ibañez, A Gómez, M Gallardo

Psychiatry, Althaia Xarxa Assistencial de Manresa, Manresa, Spain

**Aims:** To determine whether there are significant differences in biochemical blood parameters between manic inpatients and bipolar depressed inpatients

**Methods:** We included all patients admitted to our Psychiatric Unit between 2009 and 2013 diagnosed according to DSM IV criteria of Bipolar I manic (N = 244) or depressive (N = 72) episode. In all patients was performed a blood analysis at next day after hospitalization that included the determination of the following levels: -Glucose, Cholesterol, HDL and Triglycerides -Protein and Albumin -TSH and T4 Statistical analyses; To find significant differences on the parameters listed above between the two groups of bipolar inpatients we used the Independent Student's *t* test.

**Results:** Between manic and depressed bipolar inpatients significant differences were found in age ( $p < 0.000$ , mean of 42.4 vs 52.2 years respectively) and gender ( $p < 0.05$ , 54.2% men and 42.7% men respectively). No significant differences were found between bipolar manic and bipolar depressed patients in percentage of patients treated with lithium (44.8% and 40% respectively). There were no significant differences between bipolar manic and bipolar depressed inpatients in levels of glucose, triglycerides, protein and TSH levels. The manic patients had cholesterol levels and HDL levels significantly lower than depressed patients (mean of 170.7 vs 194.8,  $p < 0.001$ , and mean of 45.7 vs 50.6,  $p < 0.05$ , respectively). The manic patients had albumin levels and T4 levels significantly higher than depressed patients (mean of 3.91 vs 3.77  $p < 0.03$ , and mean of 0.97 vs 0.87,  $p < 0.006$ , respectively). We conducted a multinomial logistic regression analysis including the existence of mania as the dependent variable. As independent factors we included sex and lithium treatment, and as covariates the age and Cholesterol, HDL, albumin and T4 levels. After this analysis only a significantly higher levels of T4 ( $p < 0.024$ ) and a lower age ( $p < 0.008$ ) remained significantly associated with mania versus depression.

**Conclusion:** Bipolar I patients hospitalized for mania are significantly younger and with higher levels of T4 than those admitted by a depressive episode.

## Peripheral neuroplasticity-related biomarkers in children and adolescent bipolar disorder: a nested school-based controlled study

PM Pan<sup>a</sup>, G Cunha<sup>a</sup>, R Mansur<sup>a</sup>, A Gadelha<sup>a</sup>, G Sallum<sup>b</sup>, A Teixeira<sup>c</sup>, M Kauer-Sant'Anna<sup>d</sup>, R Grassi-Oliveira<sup>b</sup>, R Bressan<sup>a</sup>, E Brietzke<sup>a</sup>

<sup>a</sup>Psychiatry, Federal University of São Paulo (UNIFESP), São Paulo, Brazil,

<sup>b</sup>Psychiatry, National Institute of Developmental Psychiatry (INPD), Porto Alegre, Brazil,

<sup>c</sup>Psychiatry, Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil,

<sup>d</sup>Molecular Psychiatry Unit and National Science and Technology Institute for Translational Medicine (INCT-TM), Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

**Aims:** To compare serum levels of Brain-derived Neurotrophic Factor (BDNF), Thiobarbituric Acid Reactive Species (TBARS), cytokines and their receptors between children and adolescents with BD with a healthy control group. Levels of those biomarkers were also compared in three groups according to Latent Class Analysis (LCA) of manic symptoms (high severity, low/moderate severity and absence of manic symptoms).

**Methods:** Cross-sectional study analyzing data from the High Risk Cohort (HRC), a school-based survey of 6–14 years of age children ( $n = 2,512$ ). An enriched subsample of 625 subjects also provided

peripheral blood samples. Development and Well-Being Assessment (DAWBA) was used to investigate DSM-IV-defined psychiatric diagnosis including BD I-II and Not Otherwise Specified (NOS). Children with BD ( $n = 14$ ) were compared to Typically Developed Children (TDC;  $n = 37$ ) matched for age, gender, and socioeconomic status. From the mania section of DAWBA, we extracted three groups of children via LCA: high severity of manic symptoms ( $n = 24$ ), low/moderate severity ( $n = 94$ ) and absence of manic symptoms ( $n = 37$ ). Serum neuroplasticity-related biomarkers such as TBARS, BDNF, cytokines [Interleukin-6 (IL-6), Interleukin-10 (IL-10), Eotaxin-1 (CCL-11) and Tumor Necrosis Factor-alpha (TNF-alpha)] and their soluble receptors (TNFR-1 and TNFR-2) were compared among the groups. Statistical comparisons were performed using Mann-Whitney's *U* test and Kruskal-Wallis (H) test. For Mann-Whitney tests we also report Effect Size (ES).

**Results:** Compared with TDC group, children and adolescents with BD presented statistically significant higher levels of TBARS ( $U = 88.5$ ,  $p = 0.021$ ,  $ES = 0.43$ ), IL-6 ( $U = 373.5$ ,  $p = 0.021$ ,  $ES = 0.32$ ) and Eotaxin-1 ( $U = 95.000$ ,  $p = 0.006$ ,  $ES = 0.40$ ) and lower levels of sTNFR2 ( $U = 67.000$ ,  $p = 0.001$ ,  $ES = 0.50$ ). There were no statistically significant differences between the groups in BDNF, TNF-alpha and IL-10 levels. LCA analysis showed a gradient in changes in biomarkers according to severity of manic symptoms. Significant differences between the groups were found in IL-6 ( $H = 6.90$ ,  $p = 0.032$ ), Eotaxin-1 ( $H = 8.84$ ,  $p = 0.012$ ) and sTNFR2 ( $H = 18.47$ ,  $p < 0.001$ ).

**Conclusions:** The results of this study suggest that neuroplasticity-related biomarkers are able to differentiate individuals with BD from TDC in a non-clinical setting. In addition, we observed a gradient in the abnormalities of biomarkers and severity of mania, even in individuals without diagnosis of BD.

## The role of metabolic parameters in influencing circulating cytokine levels in depressed and euthymic individuals with bipolar I/II disorder

JK Soczynska<sup>a</sup>, SH Kennedy<sup>a</sup>, M Li<sup>b</sup>, MP McAndrews<sup>c</sup>, RS McIntyre<sup>a</sup>

<sup>a</sup>Institute of Medical Science, University of Toronto, Toronto,

Canada, <sup>b</sup>Psychiatry, University Health Network, Toronto, Canada,

<sup>c</sup>Neuropsychology, University Health Network, Toronto, Canada

**Background:** Replicated evidence indicates that bipolar disorder (BD) is associated with abnormalities in several inflammatory cytokines, however, a specific biomarker profile that aids diagnosis and treatment selection, remains to be elucidated. Identification of subpopulations associated with specific inflammatory cytokine abnormalities may advance the utility of these biomarkers in clinical settings. A replicated body of evidence indicates that BD is associated higher rates of metabolic and inflammatory-based conditions, including obesity and metabolic syndrome. The aims of this investigation were to identify a cytokine profile that differentiates BD from healthy controls, and to determine if higher BMI and the co-occurrence of metabolic syndrome in BD is associated with a distinct cluster of inflammatory cytokines.

**Method:** A total of 75 individuals with DSM-IV-TR-defined bipolar I/II disorder (BD) [meeting criteria for a major depressive episode ( $n = 29$ , HAMD-17  $\geq 20$ ) or 4 weeks of prospective verification of euthymia ( $n = 46$ )] and 31 healthy controls (HC) were enrolled. Plasma cytokine levels were measured using the human cytokine 30 V-PLEX immunoassay (Meso Scale Discovery). The presence of metabolic syndrome was operationalized in accordance with the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP-III) criteria.

**Results:** A model comprised of IL-6, MIP-1 $\alpha$ , IL-15, and IL-17A best differentiated BD from HC. Increased IL-6 levels were evident during depressive and euthymic states, while reduced levels of the



latter cytokines were associated with euthymia (Nagelkerke Pseudo  $R^2 = 0.797$ ,  $p < 0.001$ ). The presence of metabolic syndrome in BD ( $n = 24$ , 32.0%) was associated with significantly increased levels of TNF- $\alpha$  ( $p = 0.001$ ), IL-7 ( $p = 0.004$ ), and IL-8 ( $p = 0.001$ ), however, only TNF- $\alpha$  (OR = 1.70, 95% CI: 0.988–2.92) approached significance as an independent predictor of metabolic syndrome after adjusting for medical comorbidity, BMI, and illness state (Nagelkerke  $R^2 = 0.501$ ,  $p < 0.001$ ). Increasing BMI was predicted by higher levels of IL-6 ( $\beta = 0.340$ ,  $p = 0.004$ , Model:  $R^2 = 0.316$ ,  $p = 0.001$ ) and CRP ( $\beta = 0.408$ ,  $p < 0.001$ , Model:  $R^2 = 0.366$ ,  $p < 0.001$ ) after adjusting for the presence of metabolic syndrome, other medical comorbidities, current atypical antipsychotic use, and BD illness state.

**Conclusions:** This study replicates previous reports implicating inflammatory cytokines in the pathophysiology of BD, most notably in individuals who exhibit increased adiposity and metabolic abnormalities.

### Does long-term treatment with recombinant human erythropoietin (EPO) impact on inflammatory markers and plasma brain derived neurotrophic factor (BDNF) levels in patients with affective disorders?

**M Vinberg, P Weikop, L Kessing, K Miskowiak**

*Psychiatric Center Copenhagen, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark*

We have demonstrated that 8 weekly infusions of recombinant human erythropoietin (EPO) improve cognition in patients with affective disorders. This study aims to investigate whether this effect is associated with EPO-associated changes in inflammatory markers and plasma brain derived neurotrophic factor (BDNF) levels in these patients. Forty currently depressed patients with treatment resistant depression (TRD) (Hamilton Depression Rating Scale-17 items (HDRS-17) score  $\geq 17$ ) and 43 patients with bipolar disorder (BD) in partial remission (HDRS-17 and Young Mania Rating Scale (YMRS)  $\leq 14$ ) were enrolled in the trial. Patients were randomized to receive eight weekly EPO (Eprex; 40,000 IU) or saline (0.9% NaCl) infusions in a double-blind, placebo controlled, parallel-group design. High sensitive C-reactive protein, IL-6, IL-18 and BDNF levels were measured at baseline and at weeks 5, 9 and at follow up, week 14.

**Results:** Data analyses are in process and the results will be presented at the congress ClinicalTrials.gov: NCT 00916552.

### Two factor model of sleep problems in youths: hypersomnia/fatigue and insomnia/sleep problems show distinct diagnostic correlates

**TF Halverson<sup>a</sup>, EA Youngstrom<sup>a</sup>, A Van Meter<sup>a</sup>, S Salcedo<sup>a</sup>, M Ong<sup>a</sup>, RL Findling<sup>c</sup>**

<sup>a</sup>Psychology, University of North Carolina – Chapel Hill, Chapel Hill, USA, <sup>b</sup>Psychology, Yeshiva University, Bronx, USA,

<sup>c</sup>Psychiatry, John Hopkins University, Baltimore, USA

**Background:** Symptoms of sleep dysregulation are common in youths with bipolar disorder (BD) or depression. However, important differences in the type of sleep disturbance may exist across diagnoses. Identifying these differences could help with diagnostic clarification, which is often difficult. The present study investigated the factor structure of caregiver-reported sleep problems in youths, as well as whether the factors showed distinct associations with psychiatric diagnoses.

**Method:** Youths (ages 5–17) and their primary caregivers ( $N = 825$ ) from an outpatient clinical sample completed K-SADS interviews (Kaufman, et al., 1997) to determine DSM-IV Axis I

diagnoses. Primary caregivers completed the General Behavior Inventory (GBI; Meyers & Youngstrom, 2008) and Childhood Behavior Checklist (CBCL; Achenbach, 1991) about their child. Exploratory factor analysis of sleep items drawn from the GBI and CBCL revealed a two-factor solution. Individual factors based on 13 items were labeled Insomnia/Sleep Problems and Hypersomnia/Fatigue. Receiver operating characteristic analyses assessed the ability of each factor to discriminate youth with BD or unipolar depression from other diagnoses.

**Results:** Each individual factor (i.e., Insomnia/Sleep Problems and Hypersomnia/Fatigue) successfully discriminated youth with BD, youth with unipolar depression, and youth with any mood disorder from other diagnoses with areas under the curve (AUCs) 0.61–0.70 ( $p < 0.01$ ). Venkatraman's Test comparing AUCs revealed that Hypersomnia/Fatigue discriminated youths with unipolar depression, as well as youths with any mood disorder, significantly better ( $p$ 's  $< 0.05$ ) than Insomnia/Sleep Problems. Both factors discriminated youth with BD from other youth equally well. Exploratory analyses examined discriminatory strength of each factor as a function of child age; performance was similar in both prepubertal and adolescent youths.

**Conclusion:** A two-factor structure derived from sleep items on the CBCL and GBI successfully discriminated youth with BD, youth with unipolar depression, and youth with any mood disorder from other disorders. The results underline the central role sleep dysregulation plays in childhood mood disorders and indicates that there may be qualitative differences in the type of sleep disturbance associated with depression versus BD. The two-factor structure may be a useful tool for evidence-based assessment differentiating between mood disorders.

### Prevalence and clinical correlates of non-suicidal self injury in adolescents with bipolar disorder

**A Iskrac, V Timmins, A Scavone, B Goldstein**

*Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada*

**Aims:** There is an absence of research investigating the correlates of non-suicidal self injury (NSSI) in adolescents with bipolar disorder (BD), as only the Course and Outcome of Bipolar Illness in Youth study found that a suicide attempt, greater severity of depressive symptoms, a mixed episode, and poor psychosocial functioning were associated with NSSI. The purpose of this study is to examine the prevalence and clinical correlates of NSSI among adolescents with BD.

**Methods:** There were 116 adolescents included from ages 13–19 years ( $16.3 \pm 1.5$  years, 66.4% female) with BDI ( $n = 30$ ), BDII ( $n = 46$ ), or BDNOS ( $n = 40$ ) determined by the K-SADS-PL interview. Participants were recruited from a tertiary sub-specialty clinic for adolescents with BD. Lifetime NSSI was systematically ascertained in conjunction with the K-SADS-PL. Correlates of NSSI were examined using chi-square analyses and independent samples t-tests. The study was approved by REB and all subjects signed written informed consent prior to participation.

**Results:** Lifetime NSSI was reported by 50.9% of adolescents with BD. BD subjects with NSSI were significantly more likely to be female ( $p < 0.001$ ) and were significantly younger ( $p = 0.003$ ) than subjects without NSSI. BD subjects with NSSI also reported significantly higher rates of passive death wishes ( $p < 0.001$ ), active suicidal ideation ( $p < 0.001$ ), and suicide attempts ( $p < 0.001$ ). Furthermore, BD subjects with NSSI were significantly more likely to have BDII ( $p = 0.033$ ), a current major depressive episode ( $p = 0.009$ ), panic disorder ( $p = 0.003$ ), agoraphobia ( $p = 0.025$ ), GAD ( $p = 0.015$ ), and PTSD ( $p = 0.025$ ), but were significantly less likely to have lifetime ADHD ( $p = 0.039$ ). With regards to treatment, BD subjects with NSSI were significantly less likely to

be on lifetime psychiatric medications ( $p = 0.028$ ), lithium ( $p = 0.047$ ), and stimulants ( $p = 0.040$ ). Finally, BD subjects with NSSI were significantly less likely to have a first or second-degree family history of mania ( $p = 0.015$ ).

**Conclusions:** Despite the high prevalence of NSSI among adolescents with BD and its association with other clinical correlates of suicidality, adolescents with NSSI were significantly less likely to receive psychiatric treatment. Future prospective studies are warranted to better understand the treatment of adolescent BD subjects with NSSI and the psychiatric factors that confer risk for NSSI.

## Nutritional behaviours among adolescents with bipolar disorder

**K Martin, J Woo, V Timmins, A Scavone, B Goldstein**

*Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada*

**Introduction:** The long-term health of individuals is greatly influenced by nutrition, particularly during adolescence.<sup>1</sup> This is a critical period of biological change, and optimal nutrition is required for adequate growth and development. Although adolescents with bipolar disorder (BP) are at increased risk for obesity and early cardiovascular disease, no prior study has examined nutrition in this population.

**Aim:** This study investigates nutritional behaviour patterns among adolescents with BP in comparison to adolescents without personal or family history of a major psychiatric disorder.

**Methods:** Participants included 131 adolescents, 13–19 years old (82 BP, 49 controls). Gold-standard semi-structured interviews were held to establish BP diagnoses. The self-reported quick Weight, Activity, Variety & Excess (WAVE) Screener assessed dietary habits, yielding total nutritional scores, and variety, excess, household food insecurity subscales. Pearson  $\chi^2$  tests were used to compare categorical variables,  $t$ -tests for normally distributed continuous variables, and Mann–Whitney  $U$  tests for ordinal or skewed continuous variables. Adolescent participants and a parent/guardian provided written informed consent. The study was approved by the local research ethics board.

**Results:** Controls had significantly higher total WAVE ( $t = 2.623$ ,  $DF = 129$ ,  $p = 0.010$ ) and excess subscale scores (Mann–Whitney  $U = 1.319$ ,  $p = 0.001$ ). Regarding variety and household food insecurity subscales, there were no significant differences between groups. Exploratory within-group analyses demonstrated that among numerous potential clinical and familial correlates, only self-reported impulsivity/emotional dysregulation ( $t = 3.38$ ,  $DF = 129$ ,  $p = 0.039$ ) was associated with nutritional behaviour.

**Conclusion:** Adolescents with BP appear to have poorer nutrition in comparison to controls, and this difference is largely attributable to dietary excess. This demonstrates the need to discuss nutrition education and strategy implementation to improve nutritional health among adolescents with BP, particularly for those with high levels of impulsivity/emotional dysregulation.

**References:** Gidding SS, Dennison BA, Birch LL, Daniels SR, Gilman MW, Lichtenstein AH, Rattay KT, Steinberger J, Stettler N, Van Horn L. Dietary Recommendations for Children and Adolescents A Guide for Practitioners: Consensus Statement from the American Heart Association. *Circulation*. 2005; 122(13): 2061–2075.

## Correlates of disruptive mood dysregulated disorder (DMDD) phenotype among adolescents with bipolar disorder

**RHB Mitchell, A Iskric, A Scavone, V Timmins, B Goldstein**

*Psychiatry, Sunnybrook Health Sciences Centre University of Toronto, Toronto, Canada*

**Aims:** To compare adolescents meeting modified criteria for disruptive mood dysregulation disorder (DMDD) to those without modified DMDD, in a clinical population of adolescents with bipolar disorder (BD).

**Methods:** DMDD criteria were modified and applied to a sample of 116 adolescents with BD-I ( $n = 30$ ), BD-II ( $n = 46$ ) or BD-NOS ( $n = 40$ ) recruited from a tertiary teaching hospital. Diagnoses were determined by the KSADS-PL. DMDD Criteria A–G were derived from the KSADS Oppositional Defiant Disorder (ODD) screening interview and supplement, as well as narrative summaries. Chi-square analyses or  $t$ -tests ( $p < 0.05$ ) were conducted as appropriate, followed by logistic regression.  $p$ -values were adjusted using the false discovery rate (FDR) approach.

**Results:** Twenty-five percent (27/108) met criteria for DMDD phenotype (DMDDP). Eight were excluded due to missing data. DMDDP was not associated with BD subtype or with family history of BD. In univariate analyses, DMDDP was associated with lower functioning, increased family conflict, assault history, and attention deficit and/or hyperactivity disorder (ADHD) (FDR adjusted  $p$ -values:  $<0.0001$ ,  $<0.0001$ ,  $0.007$ ,  $0.007$ ). Lifetime substance abuse and medication use approached significance (adjusted  $p < 0.051$ ). Per logistic regression, after controlling for sex, age and race, DMDDP was independently associated with ADHD (OR 3.3; CI =  $0.98$ – $10.9$ ;  $p < 0.05$ ), lower functioning ( $p < 0.001$ ), and greater family conflict ( $p < 0.006$ ).

**Conclusions:** Despite the positioning of DMDD as phenotypically and biologically distinct from BD, these phenotypes commonly overlap in clinical settings. This overlap is not explained by BD-NOS or by non-familial BD. Despite the sample size limitations, these findings tentatively suggest that comorbid DMDDP warrants increased resources and targeted interventions to mitigate the associated functional impairment and family conflict.

## Psychosocial treatment utilization among adolescents with bipolar disorder

**D Omrin, A Iskric, J Collins, V Timmins, A Scavone, B Goldstein**

*Psychiatry Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada*

**Aims:** We sought to examine lifetime psychosocial treatment history, as well as clinical correlates associated with the utilization of different forms of psychosocial treatment, among adolescents at the time of diagnostic assessment for bipolar disorder (BD).

**Methods:** Adolescents aged 13–19 years ( $16.3 \pm 1.5$  years, 67.3% female;  $N = 113$ ) were recruited from a tertiary subspecialty clinic. Diagnoses were determined using the KSADS-PL. Lifetime psychosocial treatment history was ascertained systematically during the KSADS interview. Psychosocial treatment history was classified as having participated in individual, family, group, other and unknown (specific type not reported) therapies. Participants were categorized into having received 0, 1, 2, or  $>3$  different types of psychosocial treatment. Correlates of treatment history were examined using chi-square, one-way ANOVAs, and G-test analyses.

**Results:** At time of assessment, 88 (78%) adolescents had received at least one kind of psychosocial treatment (90.9% individual, 11.4% family, 9.1% group, 11.4% other, and 34.1% unknown). The number of types of psychosocial treatment was significantly associated with a history of suicide attempt (LR-stat=7.91,  $p = 0.048$ ), physical or sexual abuse (Fisher exact test  $p = 0.050$ ),

and a comorbid diagnosis of any anxiety disorder (LR-stat = 8.79,  $p = 0.032$ ). Patients who received more than 3 different types of psychosocial treatment (1 vs. 2 vs. >3) had a higher rate of suicide attempt (11.1% vs. 26.3% vs. 40% respectively), physical or sexual abuse (14.3% vs. 0% vs. 26.8% respectively), and a comorbid diagnosis of any anxiety disorder (67.9% vs. 68.4% vs. 90.2% respectively) compared with patients who received two or fewer forms of psychosocial treatment.

**Conclusions:** While most adolescents had received some form of psychosocial treatment, few received family therapy, a modality with extensive research support as an effective and promising early intervention treatment for adolescents diagnosed with and at high risk for developing BD. Reasons for this discrepancy in what treatments are utilized are uncertain. Future studies are warranted in order to determine the underlying motivations for specific psychosocial treatment modality selection. Similarly, additional research is warranted to determine whether psychosocial treatment exposure influences clinical outcomes in adolescents with BD.

### Suicide and adolescent bipolar disorder: is substance use a moderator for suicide in the bipolar spectrum

T Piersaint

*Psychology, Carlow University, Pittsburgh, USA*

Adolescence is known as a transitional period in a child's life, often viewed as the bridge between childhood and adulthood. At the core of this transition, these teens begin to explore their social relationships, exploring the world in search of independence and a sense of self (Kroger, Martinussen, & Marcia, 2010). For nearly 1.8% of youth worldwide, this transitional period presents with unbalanced emotions and, in extreme cases, these teens are often diagnosed with bipolar disorder (BD) (Diler & Birmaher, 2012; Dijk, 2009). Bipolar disorder in the adolescent population is considered a public health concern for many factors, including its high comorbidity rate with substance use disorder, and high rates of suicide (Axelson et al., 2006; Pavuluri, Birmaher, & Naylor, 2005; Goldstein et al., 2008). Current research assesses correlations between substance use and suicide in bipolar subtypes (types I and II), but only in adult populations. This research assesses adolescents with a diagnosis of bipolar spectrum, inclusive of BD-I, BD-II, Cyclothymia, and BD-NOS, with a history of substance use and suicide (includes attempts, ideation, and self injurious behaviors). It is hypothesized that adolescents with a substance use history will present with higher rates of suicidality versus those with the bipolar diagnosis and no comorbidity of substance use disorder. A secondary data analysis, with data spanning over four years (2010–2014) will be analyzed using the following statistical tests: One-way Multivariate Analysis of Variance (MANOVA) to assess differences in suicide rates within adolescent groups with bipolar spectrum disorder, and a comorbidity of substance use and without substance use; and Multiple Regression to assess correlation between suicide attempts (includes self-injurious behaviors, and suicidal ideations) in adolescents with bipolar spectrum disorder with and without a comorbidity of substance use. A positive correlation is expected to be found between adolescents with bipolar disorder with comorbid substance use and suicidality.

### Evidence for a cohort effect: a child network for assessing naturalistic treatment in the community

R Post<sup>a</sup>, R Kupka<sup>b</sup>, P Keck Jr<sup>c</sup>, S McElroy<sup>c</sup>, L Altshuler<sup>d</sup>, M Frye<sup>e</sup>, M Rowe<sup>f</sup>, T Suppes<sup>g</sup>, W Nolen<sup>h</sup>, R Findling<sup>i</sup>

<sup>a</sup>Bipolar Collaborative Network, George Washington University, Bethesda, USA, <sup>b</sup>Department of Psychiatry, VU University Medical Center, Amsterdam, Netherlands, <sup>c</sup>Biological Psychiatry Program, University of Cincinnati Medical College, Cincinnati, USA, <sup>d</sup>Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, USA, <sup>e</sup>Department of Psychiatry, Mayo Clinic, Rochester, USA, <sup>f</sup>George Washington University, Bipolar Collaborative Network, Bethesda, USA, <sup>g</sup>Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, USA, <sup>h</sup>University Medical Center, University of Groningen, Groningen, Netherlands, <sup>i</sup>Psychiatry and Behavioral Sciences, Johns Hopkins Medicine, Baltimore, USA

**Introduction:** There is a robust literature indicating that childhood onset bipolar disorder is common in the U.S. and perhaps more so than in some European countries. This evidence includes: comparative data, epidemiological studies (including BP-NOS), at risk studies, and clinical populations. A cohort effect is rarely mentioned as a possible contributor and treatment strategies of these increasingly younger children have not been described.

**Methods:** 968 outpatients (average age 41, range 18–80) with bipolar disorder gave informed consent for Network participation and completed questionnaires on age of onset and family history of psychiatric illness. We examined whether (1) age of onset of bipolar disorder and (2) parental and grandparental loading for positive history of psychiatric illness was related to more recent birth cohorts (i.e., patients who were younger at Network entry).

**Results:** More recently born patients did have an early onset of their bipolar and did have direct lineage relatives with more psychiatric disorders ( $p < 0.001$ ).

**Discussion:** These data add to a growing literature for the existence of cohort effects in bipolar disorder. Given this increasing incidence and earlier age of onset we have started a Child Network for weekly parental ratings on a secure website of children 2–12 with mood disorders or at risk for them. Type of treatment (if any) and its tolerability is elicited. This will provide some of the first data on how the youngest children with mood disorders are being treated in the community. Please encourage parents to join this Network; informed consent is available at [bipolarnews.org](http://bipolarnews.org).

### A pharmacologic algorithm for youth at-risk for bipolar disorder

CD Schneck<sup>a</sup>, MK Singh<sup>b</sup>, KD Chang<sup>b</sup>, MP DelBello<sup>c</sup>, DJ Miklowitz<sup>d</sup>

<sup>a</sup>Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, USA, <sup>b</sup>Psychiatry, Stanford University, Stanford, USA, <sup>c</sup>Psychiatry, University of Cincinnati College of Medicine, Cincinnati, USA, <sup>d</sup>Psychiatry, UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, USA

**Objective:** Depression and brief periods of (hypo)mania are linked to an increased risk of progression to bipolar I or II disorder (BD) in children of bipolar parents. At present, little empiric evidence exists to guide the pharmacologic management of children at high risk for bipolar disorder. The rationale in developing a pharmacologic treatment algorithm for high-risk children are discussed and results from its first use are presented.

**Method:** Participants were 40 youth (mean 12.3 years, range 9–17) with BD not otherwise specified, major depression or cyclothymia who had a first-degree relative with BD I or II, and active mood symptoms (Young Mania Rating Scale [YMRS] > 11 or Child

Depression Rating Scale [CDRS] > 29). Patients were enrolled in a randomized trial examining the effects of a 4-month family-focused therapy (FFT) program versus a control condition on the 1-year course of mood symptoms. Some youth whose symptoms caused [DJM1] significant academic/psychosocial dysfunction were offered medications or may have had existing medications altered in order to decrease symptom severity. Treatment psychiatrists were guided by a medication algorithm to treat depressive or (hypo)manic symptoms, depending on the underlying mood diagnosis (major depressive disorder or BP NOS). Treatment of anxiety and attention-deficit hyperactivity disorder were also addressed in the algorithm.

**Results:** At study entry, 60% of the participants were taking at least one psychiatric medication, and nearly an identical number were taking medications at study end (59%). Patients with BP NOS and major depressive diagnoses were equally likely to have their medications altered during the course of the study ( $2.27 \pm 1.6$  medication changes vs.  $2.27 \pm 1.9$ , respectively). No patients had antidepressant [MS2] – induced or stimulant-induced mania during the course of the study.

**Conclusions:** Following a pharmacologic algorithm in treating children at high-risk for bipolar disorder may reduce the likelihood of medication-induced manic or depressive episodes.

### Clinical correlates of first episode polarity in adolescents with bipolar disorder

V Timmins, J Collins, A Scavone, B Goldstein

Psychiatry Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada

**Aims:** Prior evidence indicates there are differences in the clinical profile of adults with bipolar disorder (BD) depending on the polarity of the first affective episode. Among adults with BD, depressive onset (DO) is more common than mania onset (MO). No studies have examined this topic in adolescents with BD. We sought to examine the clinical correlates of first episode polarity in a sample of Canadian adolescents with BD.

**Methods:** Subjects were 91 adolescents aged 13–19 with a diagnosis of BD-I, -II, or -NOS via the KSADS-PL. All subjects provided written informed consent to participate in a clinical research registry that was approved by the local research ethics board. Subjects were divided into three groups based on the polarity of their first episode of mood symptoms: DO, MO, and mixed onset (MXO). The Life Problems Inventory (LPI) assessed borderline personality traits via self-report. Chi square analyses, ANOVAs, and likelihood ratio significance tests were performed. Post hoc pairwise *t* tests were performed using the Holm correction.

**Results:** DO was the most common polarity onset (53.8%), followed by MO (26.4%) and MXO (19.8%). Adolescents with MO had increased use of SSRI antidepressants when compared with those in the DO and MXO groups (58.3% vs. 24.5% vs. 27.8%,  $\chi^2 = 8.61$ ,  $p = 0.014$ ). There were significant differences between the LPI scores of each group ( $F = 3.89$ ,  $p = 0.025$ ). Post hoc tests determined that those in the DO group had significantly higher LPI scores than the MXO group ( $p = 0.027$ ) while there were no significant differences between MO and MXO. The DO group was more likely to have a family history of a suicide attempt when compared with the MO and MXO groups (36.7% vs. 16.7% vs. 11.1%,  $\chi^2 = 6.03$ ,  $p = 0.049$ ). There were no significant differences in comorbidities and other family history factors between the three groups.

**Conclusions:** In this sample, there are few characteristics associated with first episode polarity. Although larger replication studies are warranted, present findings suggest that first episode polarity may not be a clinically significant characteristic in adolescent BD.

### Errors in identifying emotion in body postures and facial expressions among youth with pediatric bipolar disorder

LS Schenkel<sup>a</sup>, TL Towne<sup>a</sup>, AM Herbert<sup>a</sup>, JB Pelz<sup>b</sup>

<sup>a</sup>Psychology, Rochester Institute of Technology, Rochester, USA,

<sup>b</sup>Imaging Science, Rochester Institute of Technology, Rochester, USA

**Aims:** The ability to accurately identify nonverbal emotional cues is essential for successful social interaction. Facial emotion processing impairments have been consistently demonstrated among patients with pediatric bipolar disorder (PBD). However, less is known about other domains of nonverbal emotion recognition in this group. Therefore, we investigated emotion identification for body postures in addition to facial expressions among PBD patients and matched healthy comparison (HC) subjects.

**Methods:** Type I and type II patients with PBD ( $n = 25$ ) and intellectually and demographically matched HC subjects ( $n = 25$ ) completed the body postures and faces subtests of the Diagnostic Analysis of Nonverbal Accuracy-2 (DANVA2) scale and the Nim-Stim Set of Facial Expressions, along with diagnostic and clinical assessments.

**Results:** Compared to HC, PBD patients made significantly more errors identifying emotion in body postures and faces, with findings being the most robust for sad, happy, and fearful stimuli. Among PBD patients only, poorer performance on all three emotion labeling tasks was associated with greater manic symptoms. Poorer performance on the facial emotion tasks, but not the body postures, was associated with parent reports of peer difficulties.

**Conclusions:** In addition to impairments in facial emotion recognition, PBD youth also show impairments in the ability to correctly identify emotion from body postures. Facial emotion processing impairments appear to be a better indicator of real-world psychosocial difficulties than emotional body poses. However, both are related to increased manic symptomatology. Psychosocial interventions should target multiple domains of nonverbal emotion identification as part of a comprehensive social skills treatment program.

### Emotional dysregulation in adolescents, a common potential denominator between eating disorders and bipolar spectrum

JA Vargas Castro

Child & Adolescent Psychiatry and Psychology, Hospital General de Catalunya/Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

**Background:** Emotional dysregulation is often present in mental disorders suffered by children and adolescents. Such dysregulation can be observed in eating disorders like anorexia nervosa, rumination, avoidant-restrictive, and also in bulimia nervosa, binge eating disorder, pica, and other specified, and unspecified eating disorders (ED). Emotional dysregulation can also be seen in the bipolar spectrum, highlighting similarities between a softer bipolar spectrum in its sub-threshold forms and eating disorders syndromes and sub-syndromes in adolescents. This research stems from those premises in order to evaluate the emotional dysregulation (measured by the HCL-32) and eating habits (measured through the BEDS) in a population with ED.

**Methods:** This transversal, observational study investigates a group of patients between 12 and 19 years of age, all of whom were diagnosed with ED before they turned 18 and receive inpatient treatment ( $n = 40$ ). The group was divided into two subgroups: Group I: Anorexia Nervosa-AN ( $n = 17$ ) and Group II: Bulimia Nervosa-BN ( $n = 23$ ).

**Results:** Group I-AN showed higher scores in HCL-32, which is not positively correlated with the BEDS scale's findings. Group II BN and others, presented high scores in HCL-32, showing a posi-

tive correlation with the BEDS scale's findings ( $r = 0.518$ ;  $p = 0.011$ ), mainly in the subscale symptoms of hypomania associated with a lack of inhibition, self-control and attentional capacity (HCL-32-Factor 2) ( $r = 0.461$ ;  $p = 0.027$ ).

**Conclusions:** Emotional dysregulation is a factor to be considered in the diagnosis and clinical management of patients with ED: Anorexia Nervosa, Bulimia Nervosa and other eating disorders, as they may imply other comorbid conditions. Furthermore, Bulimia Nervosa, especially in cases with emotional dysregulation could be related to hypomania or a bipolar spectrum.

## Women with history of mood disorders show greater circadian rhythm disruption across the perinatal period: preliminary analyses of a longitudinal study

E Krawczak<sup>a</sup>, W Simpson<sup>a</sup>, L Minuzzi<sup>b</sup>, MP Hidalgo<sup>c</sup>, BN Frey<sup>b</sup>

<sup>a</sup>MiNDS Neuroscience Graduate Program, McMaster University, Hamilton, Canada, <sup>b</sup>Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, Canada, <sup>c</sup>Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

**Objective:** The primary aim of this study was to determine if women with a history of mood disorders show greater objective or subjective circadian rhythm and sleep disruption from pregnancy to postpartum, as compared to healthy controls.

**Methods:** Nineteen women (11 healthy controls, 8 with a history of major depressive or bipolar disorder) have been enrolled in this cohort study. All women were euthymic at initial assessment. The study includes two visits: one during the third trimester of pregnancy ( $\geq 26$  weeks gestation) and one during the postpartum period (6–12 weeks). At each visit, participants completed the subjective Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) and Pittsburgh Sleep Quality Index (PSQI) questionnaires, as well as were fitted with an actigraph (Respironics) to objectively measure their sleep and the circadian rhythmicity of their activity for a period of 3 weeks.

**Results:** Analysis of subjective BRIAN and PSQI scores revealed that women with history of mood disorders showed greater disruption in circadian rhythms and sleep both during pregnancy and the postpartum period in comparison to controls ( $p = 0.02$  and  $p = 0.03$ , respectively). Likewise, analysis of sleep variables revealed that women with mood disorders have a lower sleep efficiency during pregnancy ( $p = 0.04$ ) and postpartum ( $p = 0.01$ ), with marginally lower total sleep time ( $p = 0.07$ ). Finally, cosinor analysis of the actigraphy data also revealed that women with mood disorders showed marginally significant differences in their mesor (i.e. difference in mean activity) ( $p = 0.056$ ) and amplitude (i.e. difference in peak activity) ( $p = 0.0573$ ). There was no group  $\times$  time interaction on either subjective or objective measures.

**Conclusions:** Previous studies have demonstrated that women with mood disorders show increased subjective sleep disruption during the perinatal period. However, studies aiming to determine if sleep disruption predicts postpartum depression have yielded mixed results. Here we show that subjective and objective parameters of circadian rhythms are persistently disrupted in women at risk for postpartum depression.

## Are winter and summer type different in SAD?

YB Gülşen Küçükbaş<sup>a</sup>, S Kesebir<sup>b</sup>

<sup>a</sup>Psychiatry, Erenköy Mental and Neurological Disease Training and Research Hospital, Istanbul, Turkey, <sup>b</sup>Psychiatry NPIstanbul Hospital, Üsküdar University, Istanbul, Turkey

**Objective:** The aim of this study was to examine the differentiation of sociodemographic, clinical and temperamental characteristics of

patients diagnosed with winter type seasonal affective disorder (SAD) and summer type SAD.

**Methods:** 32 winter type and 42 summer type totally 74 patients with SAD according to DSM-IVTR were evaluated in this study. Diagnosis of SAD confirmed by Seasonal Pattern Assessment Questionnaire (SPAQ). All patients were examined Mood Disorder Record and Following Form (SCIP-TURK), Pittsburgh Sleep Quality Index (PSQI), Eating Attitude Test (EAT), Arizona Sexual Experiences Scale (ASEX), Temperament Autoquestionnaire of Memphis, Paris, Pisa and San Diego (TEMPS-A) and, Global Assessment of Functioning (GAF).

**Results:** Summer type SAD was more frequent in our sample (56.8%). Unipolar/Bipolar ratio, family history, early age onset and, frequency of depressive episode were more frequently in summer type SAD. Frequency of manic and hypomanic episode and childhood trauma were more frequently in winter type SAD. Atypical subtype was more frequently in summer type SAD whereas the melancholic subtype was found to be similar in both type of SAD. Scores of EAT and ASEX between two groups were not different. Total duration of sleep was found to be similar, but sleep latency was found to be longer in winter type SAD. Cyclothymic and irritable temperament scores were to be higher in summer type SAD. GAF scores were found to be higher in summer type SAD. On the other hand, having a job, being married and living in city center were more frequently in summer type SAD.

**Conclusion:** Winter and summer type SAD differ from each other in terms of sociodemographic, clinical and temperamental characteristics of patients.

## Clinical characteristics of bipolar I vs II disorder in an Italian sample

B Dell'Osso<sup>a</sup>, L Cremaschi<sup>a</sup>, C Dobrea<sup>a</sup>, M Cigliobianco<sup>a</sup>, TA Ketter<sup>b</sup>, AC Altamura<sup>a</sup>

<sup>a</sup>Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti Università degli Studi di Milano Dipartimento di Salute Mentale, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, <sup>b</sup>Bipolar Disorders Clinic Stanford Medical School, Stanford University, Stanford, USA

**Aims:** Bipolar Disorder (BD) is a chronic and highly disabling mood disorder, associated with the highest risk of suicide among psychiatric disorders. The hypothesis that Bipolar I and II Disorders simply represent more and less severe forms of illness, respectively, has been increasingly questioned over the last years. For instance, clinical characteristics including number and duration of depressive episodes, age at onset, specific patterns of comorbidity and suicide attempt rates were found to be at least equally severe in BDII vs I in different studies (Goodwin & Jamison, 2007). On the other hand, it has been recently pointed out that American patients with BD may show more severe expressions of BD compared to European patients (Post et al., 2014). The present study was, therefore, aimed to assess and compare a series of different socio-demographic and clinical features in a large sample of Italian patients with BD.

**Methods:** The sample consisted of 202 euthymic bipolar patients (129 with BDI, 73 with BDII), attending the psychiatric services of Policlinico in Milan. They underwent a psychiatric and psychometric assessment, during which their main socio-demographic and clinical data were collected. Statistical analyses were performed using SPSS.

**Results:** Clinical variables of the total sample appeared to be largely consistent with the existing body of evidence in literature. Of note, comparison between patients showed statistical significance with respect to: duration of untreated illness (DUI) (BDII>I:  $p = 0.001$ ), duration of last episode (BDII>I:  $p = 0.003$ ), current global assessment of functioning score (BDII>I:  $p.000$ ), number of

hospitalizations lifetime (BDI>II:  $p=0.017$ ), polarity of first (i.e., depressive; BDI>II:  $p=0.000$ ) and last episode (i.e., depressive; BDII>I:  $p=0.000$ ), and lifetime presence of psychosis (BDI>II:  $p=0.000$ ). Other variables, including lifetime number of suicide attempt and any comorbidity (either psychiatric and medical), did not show significant differences in BDI vs II patients ( $p>.05$ ).

**Conclusions:** Our findings seem to support the notion that BD I and II represent equally severe forms of illness, with different clinical characteristics and peculiar expressions of severity. In particular, our BDII patients had a longer DUI, a more frequent last depressive episode and a similar suicide attempt rate, compared to BDI patients, warranting further investigation in the field.

### Differential effect of lithium and Quetiapine on brain corticostriatal networks resting-state connectivity in first episode mania patients

O Dandash<sup>a</sup>, A Fornito<sup>b</sup>, R Daglas<sup>c</sup>, C Pantelis<sup>d</sup>, P McGorry<sup>d</sup>, M Berk<sup>e</sup>, M Yucel<sup>b</sup>

<sup>a</sup>Psychiatry, University of Melbourne, Melbourne, Australia,

<sup>b</sup>School of Psychology, Monash University, Clayton, Australia,

<sup>c</sup>Psychiatry, ORYGEN Youth Health Melbourne Health,

Melbourne, Australia, <sup>d</sup>Psychiatry, ORYGEN Youth Health

University of Melbourne, Melbourne, Australia, <sup>e</sup>School of Medicine, Deakin University Barwon Health, Geelong, Australia

**Introduction:** First-episode Mania (FEM; Bipolar Disorder Type I) patients exhibit abnormally elevated, expansive, or irritable mood accompanied with extreme energy, racing thoughts and forced speech. These behavioural disturbances have been linked to disturbed functional connectivity in brain corticostriatal networks; in particular, an affective network linking ventromedial prefrontal cortex with ventral striatum. Lithium has been the first-line treatment for BPD. More recently the antipsychotic drug Quetiapine has also been found to be effective in the treatment of mania. However, the neurobiological mechanisms underlying the efficacy of both drugs remains largely unknown. This study utilises functional MRI to delineate the shared and differential effect of Lithium and Quetiapine on the functional connectivity of corticostriatal networks.

**Method:** 41 FEM participant and 30 healthy control were recruited at baseline. Patients were stabilized for a minimum of two weeks then randomly assigned to either Lithium or Quetiapine treatment for 12 months. MRI scan were conducted at baseline, 3 month (patient only) and 12 months on a 3T Siemens scanner. Eyes closed resting-state fMRI was acquired and corticostriatal functional connectivity was mapped in relation to 4 seed regions per hemisphere placed in dorsal and ventral striatal regions. General Liner Model was built to examine the time effect, group effect and time by group interaction using SPM8 & SPSS v20.

**Results:** Collapsed across treatment groups, FEM patients showed reduced functional connectivity in dorsal (cognitive) network linking the caudate nucleus with the dorsolateral prefrontal cortex when compared to healthy participants. In addition, patients exhibited abnormally increased connectivity of ventral corticostriatal networks linking the ventral striatum with the orbitofrontal cortex and thalamus. Longitudinally, we found a significant time by treatment interaction in the connectivity of both the dorsal and ventral networks, such that the connectivity abnormalities normalized to a greater extent following Lithium compared to Quetiapine after 3 and 12 months.

**Conclusion:** FEM patients exhibit alterations in the functional connectivity of both the ventral and dorsal corticostriatal networks. These changes may underlie the disturbances in emotional and cog-

nitive processing seen in patients. Lithium appears to be more effective than Quetiapine in normalizing the observed functional connectivity alterations.

### Bipolar II disorder, ketogenic diet, and social rhythm therapy: case study

E van Gent<sup>a</sup>, C de Bruin<sup>b</sup>

<sup>a</sup>Biological Psychiatry, Faneurop, Arnhem, Netherlands, <sup>b</sup>Outpatient Clinic, Dimence, Deventer, Netherlands

In the treatment of bipolar II disorder is the balance between effects and side effects essential for therapy compliance.

**Aim:** In co-operation with the patient to be studied, to find which is the optimal treatment. A 26 year old Dietetics student with rapid cycling bipolar II disorder, asked if the ketogenic diet works as a treatment for bipolar disorder. He refused medication. In the literature are a number of theoretical articles because the ketogenic diet works for epilepsy and some anti-epileptics work for bipolar disorder. There is a success case study with 2 patients where the diet as given is added to the existing therapy. Another study where the diet was not working and a study where the patient became psychotic with the diet. Bright light prior to bedtime and reduced sleep can, for some bipolar patients, stimulate a hypomanic episode.

**Methods:** Ketogenic diet. Laboratory tests to detect cholesterol and ketogenic chains in urine. Life chart: one and a half years before and one and half years after ketogenic diet. No other medications. Special glasses in the evening to reduce the blue light from the computer.

**Results:** After 1½ years he had only one hypomanic episode, shortly after the start of the diet, normally 3–5 in a year. The severity and duration of depressive episodes was reduced by half.

**Discussion:** The ketogenic diet for this patient seems to be a good supplement to existing therapy. Although he used the diet he also used the glasses to get enough sleep. Whether the results and the compliance with this therapy is better than the conventional treatment must be shown by patients and more research.

### Factors influencing HAMD score in BP depression an acute treatment

J Kim, T Ha, S Lee, T Chung, H Lee, S Jang, Y Park, K Ha

Psychiatry, Seoul National University Bundang Hospital, Seongnam si Gyeonggi-do, Korea

**Purpose:** To find the influencing factors on the acute treatment response in bipolar depression.

**Method:** Prospectively, we observed acute treatment course of 228 bipolar depressive patients and evaluated HAMD score at baseline, 1 month, 2 months and 6 months. To find the factors that determine remission or not at 1 month, chi square and independent *T*-test analysis were used and find the factor that influence on HAMD score after 6 months treatment, mixed effects model was used.

**Result:** 58.9% were remitted at 1 month, 59.3% were remitted at 2 months, and 66.2% were remitted at 6 months. Age, psychiatric co-morbidity and past suicide attempt were significantly different according to remission or not at 1 month. It was found through mixed effects model, age, sex, global CGI, medical and psychiatric co-morbidity influenced on HAMD score after 6 month treatment.

**Conclusion:** Our finding suggests that HAMD score at 6 month is influenced by age, sex, global CGI, medical and psychiatric co-morbidity. But further study will be needed.

## An item response theory evaluation of the young mania rating scale and the Montgomery-Asberg Depression Rating Scale in STEP-BD

JJ Prisciandaro, BK Tolliver

*Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, USA*

**Aims:** The Young Mania Rating Scale (YMRS) and Montgomery Asberg Depression Rating Scale (MADRS) are among the most widely used outcome measures in clinical trials for Bipolar Disorder (BD). Nonetheless, very few studies have examined the measurement characteristics of the YMRS and MADRS in individuals with BD using modern psychometric methods. The present study evaluated the YMRS and MADRS in the Systematic Treatment Enhancement Program for BD (STEP-BD) study using Item Response Theory (IRT).

**Methods:** 3,716 STEP-BD participants with baseline YMRS and MADRS data were available for the present analysis. The Graded Response Model (GRM), a generalization of the two-parameter logistic IRT model for ordinal data, was fit separately to YMRS and MADRS item responses. Category response curves, which represent the probability of a participant at a given symptom severity level responding in a particular response category, and item information curves, which represent the reciprocal of the standard error of measurement at each point along the latent symptom severity spectrum, were calculated for each item.

**Results:** (1) Although items contained between 5 and 9 response categories, most response categories were non-informative (i.e., there was no point along the severity continuum at which participants were more likely to choose that category relative to neighboring categories). (2) Several items provided very little psychometric information (e.g., YMRS “insight,” “appearance”; MADRS “reduced appetite,” “reduced sleep”). (3) Test information for participants with below average (e.g.,  $< -1$  SD [MADRS],  $< 0$  SD [YMRS]) or substantially above average (e.g.,  $> 2$  SD) symptom severity was very low. Relative to the YMRS, the MADRS provided psychometric information along a wider band of the symptom severity continuum.

**Conclusions:** The present study demonstrated that, in outpatients with BD: (1) most or all YMRS and MADRS items could employ 2–3 category response scales without any loss of test information, (2) several YMRS and MADRS items could be eliminated without significant reduction of information, and (3) additional response options and/or items would be needed to adequately measure depressive and manic symptomatology in individuals with below or above average symptom severity. These conclusions should be considered tentative until replicated.

## Rationale and design of OxLith: a randomised placebo controlled trial exploring the short-term physical and psychological effects of lithium on mood instability

JR Geddes, J Rendell, A Cipriani, KEA Saunders, MJ Attenburrow, AC Bilderbeck, GM Goodwin, AC Nobre, CJ Harmer, PJ Harrison

*Department of Psychiatry, University of Oxford, Oxford, United Kingdom*

Notwithstanding its toxicity in overdose and many side-effects, lithium remains the most effective pharmacological treatment for bipolar disorder and it significantly reduces suicidal behaviour. Despite having been in clinical use for many years, little is known about the early effects of lithium or its mode of action. Mood instability is an important clinical feature of bipolar disorder which persists in euthymia. Better mood stabilisation may improve clinical outcomes, and changes in mood stability over a short period in response to lithium may predict long-term therapeutic efficacy.

**Aims:** 1To use new technologies to explore the acute effects of lithium on mood stabilisation. 2To identify the early biological, physiological and cognitive effects of lithium.

**Method:** Double blind randomised placebo controlled trial of lithium carbonate in the treatment of mood instability in patients (aged 16 years or older) with bipolar disorder. Forty bipolar participants with mood instability will be recruited from a single centre and allocated to lithium or placebo for 6 weeks. All participants will undergo deep phenotyping. OxLith will use clinical, cognitive, neural, behavioural and pathophysiological outcome measures. Mood variability will be captured weekly using the True Colours system ([www.truecolours.nhs.uk](http://www.truecolours.nhs.uk)) and daily using the Positive and Negative Affect Schedule (PANAS). The underlying neuropsychology and neurobiology of mood stabilisation will be explored using a tablet device pre-loaded with a series of short cognitive tasks which will be completed daily, plus MEG and MRI scans 4 weeks after randomisation. Participants will wear a variety of devices including smart watches and accelerometers which will remotely monitor sleep and motor activity. Cheek swabs and saliva samples taken before and during treatment will be used to monitor circadian gene expression, melatonin and cortisol levels. Early physiological changes to renal, thyroid, parathyroid functions and inflammatory markers will be measured from blood samples. Data analysis will use novel mathematical approaches. In addition to eliciting the clinical effect and mechanism of action of lithium on mood instability, the trial will provide a paradigm for generating an experimental medicine model which can be used to expedite the development of new and safer medicines for bipolar disorder.

## The promise of the PCORnet MoodNetwork

A Nierenberg<sup>a</sup>, LG Sylvia<sup>a</sup>, A Doederlein<sup>b</sup>, S Edgman-Levitan<sup>c</sup>, A Muskin<sup>d</sup>, L Jewell<sup>e</sup>, M Walker<sup>f</sup>, D Goodman<sup>g</sup>, M Farahbakhsh<sup>h</sup>, R Tovey<sup>h</sup>, C Hearing<sup>a</sup>, R Montana<sup>a</sup>, T Deckersbach<sup>a</sup>

<sup>a</sup>Bipolar Clinic and Research Program, Massachusetts General Hospital, Boston, USA, <sup>b</sup>President, Depression Bipolar Support Alliance, Chicago, USA, <sup>c</sup>Stoekel Center for Primary Care, Massachusetts General Hospital, Boston, USA, <sup>d</sup>Executive Director, Anxiety Depression Association of America, Chicago, USA, <sup>e</sup>Patient Advocate, Depression Bipolar Support Alliance, Chicago, USA, <sup>f</sup>President, International Bipolar Foundation, San Diego, USA, <sup>g</sup>Patient Advocate, MoodNetwork, Boston, USA, <sup>h</sup>Director of Communications, MoodNetwork, Boston, USA

In bipolar disorder, as in the rest of medicine, most research fails to guide clinical care. As stated by Tricoci and colleagues who comment on guidelines in cardiology, “the current system generating research is inadequate to satisfy the information needs of caregivers and patients in determining benefits and risks of drugs, devices, and procedures” (Tricoci et al. 2009). We need a new research paradigm beyond meta-analyses of efficacy studies. The audacious initiative from the Patient Centered Outcomes Research Institute (PCORI) to form a network of networks ([www.PCORnet.org](http://www.PCORnet.org)) that includes a Mood Patient Powered Research Network (MoodNetwork; [www.moodnetwork.org](http://www.moodnetwork.org)). The MoodNetwork will provide a national infrastructure to address clinical questions of most importance to people who have mood disorders as they partner with their clinicians. The ultimate goal of the MoodNetwork is to improve the lives of people with mood disorders through prospective comparative effectiveness trials embedded within routine care (Wang et al. 2009) and through patient reported outcomes as well as outcome data from electronic medical records (EMR) (McMurray et al. 2013) when available. The main aim of the Mood Network is to bring together at least 50,000 participants who have or have had mood disorder diagnoses and who are willing and able to consider participating in prospective comparative effectiveness

studies. The main strategy to achieve this extraordinary aim is to collaborate with multiple mental health advocacy groups with their broad reach through their membership and websites to provide opportunities for appropriate individuals to volunteer. Clinicians can also refer their patients to obtain patient reported outcomes. From the very start, people with diagnoses have been true partners in this initiative and are instrumental in determining priorities and the scope of patient-reported outcome measures to be collected. The Mood Network will evolve to include the perspective of clinicians, not only to disseminate and implement findings from comparative effectiveness studies, but also to allow clinicians to help determine the research agenda. Clinicians, patients, researchers, and healthcare systems can use the MoodNetwork to help patients with a system of patient reported outcomes that patients can use to track their progress.

### Pilot study on the applicability of the screen for cognitive impairment in psychiatry (SCIP) in a clinical population with bipolar disorder (BD)

A Abdel-Malek<sup>a</sup>, S Saury<sup>a</sup>, A Djouini<sup>b</sup>, S Potvin<sup>c</sup>, S Renaud<sup>d</sup>, A Daigneault<sup>d</sup>, S Beaulieu<sup>d</sup>, V Tourjman<sup>c</sup>

<sup>a</sup>Pavillion Newman, Douglas Mental Health University Institute, Montreal, Canada, <sup>b</sup>Research Center, Centre de recherche Fernand Séguin, Montreal, Canada, <sup>c</sup>Psychiatry Department, Hôpital Louis-H. Lafontaine Centre Universitaire en Santé Mentale de Montréal, Montreal, Canada, <sup>d</sup>Psychiatry Department, McGill University, Montreal, Canada

**Introduction:** Cognitive impairment can impact the clinical course of many psychiatric conditions and is a determinant factor of functioning. There is growing evidence that individuals with BD have cognitive deficits. Nevertheless, evaluation of cognition is time-consuming, costly and constrained by accessibility of expertise. The SCIP is a 15-minute pen-and-paper evaluation tool shown to help in screening patients that may require more extensive cognitive assessment.

**Objectives:** The goal of this study is to determine the feasibility of using the French version of the SCIP to evaluate cognitive functions in a clinical population affected by BD.

**Materials and Methods:** So far 18 francophone patients were recruited from the Bipolar Disorder outpatient clinic at the Douglas Mental Health Institute in Montreal, Quebec. Of the 18 patients, eight had a diagnosis of BDI, seven of BDII, two of BDNOS and one of Schizoaffective disorder as defined by the DSM-IV-TR. Four patients were in a depressive episode, one was in a hypomanic episode and 13 were euthymic. A Global Assessment of Functioning (GAF) and a Clinical Global Impression (CGI) were also completed by the treating physician who was blind to the results of the SCIP. Patients were asked to complete a questionnaire regarding their experience with the SCIP and their perception of their cognitive functions. All results were collected on REDCap. Preliminary descriptive statistics were run on the sample population and questionnaire scores.

**Results:** The sex ratio among the participants was 1:1 and the mean age was 54.4 years with a standard deviation of 10.5. The mean time for taking the test was 14 minutes with a standard deviation of 2.16. Out of 18 participants, 16 completed all the sub-tests of the SCIP while two were unable to complete the fifth sub-test due to visual or motor impairment. All participants were cooperative and 77.8% thought that the SCIP would help the treating team understand their cognitive functioning better.

**Conclusion:** The brevity of the French version of the SCIP and the responsiveness from the francophone population suggest that the SCIP can be integrated into a routine clinical evaluation of patients with BD.

### Association between mood variability and emotional processing among individuals diagnosed with bipolar disorder

AC Bilderbeck, ZE Reed, H McMahon, L Atkinson, J Price, JR Geddes, GM Goodwin, CJ Harmer

Department of Psychiatry, University of Oxford, Oxford, United Kingdom

Aberrant emotional biases have been reported in bipolar disorder (BD), but results are inconsistent, possibly due to relatively small sample sizes, and the effects of current symptomology. However, there is no previous research investigating how the extent of symptom fluctuations in bipolar disorder might relate to emotional biases.

**Aim:** To investigate in a large cohort of bipolar patients whether variance in weekly symptoms are related to emotional processing as measured by a simple laboratory task. Further, to compare emotional processing in BDI and BDII after controlling for key demographic and clinical variables.

**Methods:** Participants (N = 327; BDI = 206 or BDII = 121) completed an 'emotional memory' task, as part of an established Emotional Task Battery. Sixty positively or negatively valenced words were presented and, after a 15 minute delay, participants were asked to recall as many words as possible. Using ANOVA and linear regression analyses, we explored the influence of demographic and clinical factors on recall of positive vs. negative words. We also explored the influence of symptom variability, calculated as the standard deviation of depressive (QIDS) and manic (AMRS) scores for weeks +0 (baseline) to +6, and 0 to +12. Symptom measurements were made prospectively using the True Colours system ([www.truecolours.nhs.uk](http://www.truecolours.nhs.uk)).

**Results:** No effects of diagnosis (BDI vs. BDII) were observed. Higher depressive scores at weeks +1 ( $F(1,215) = 4.24$ ,  $p = 0.04$ ) and +3 ( $F(1,214) = 8.66$ ,  $p < 0.01$ ) were associated with greater negative recall bias. Greater variability in manic symptoms for weeks 0–6 ( $F(1,191) = 5.21$ ,  $p = 0.02$ ) and 0–12 ( $F(1,174) = 6.93$ ,  $p = 0.01$ ) were also associated with greater negative bias in free recall. These effects remained robust after the substantial effects of gender, age, and level of education had been statistically accounted for. Medication also influenced performance; lithium was associated with poorer overall recall ( $\beta = -0.18$ ,  $p = 0.03$ ,  $R^2 = 0.27$ ), but did not explain the relationship between mood variation and negative recall bias.

**Conclusions:** Emotional processing biases in bipolar disorder may be related to temporally local, or more chronic, instability in mood. This instability, at least for manic symptoms, was related to greater negative emotional bias in this large sample. Findings prompt further investigation into the underpinnings and functional significance of mood instability.

### Disrupted organization of visual perception in patients with bipolar disorder

S Jang, S Lee, Y Park, J Kim, T Chung, K Ha, T Ha

Psychiatry, Seoul National University Bundang Hospital, Seongnam si Gyeonggi-do, Korea

**Aims:** Bipolar disorder is related to cognitive impairments of various domain. We investigated if patients with bipolar disorders have qualitative changes in perceptual organization.

**Methods:** 25 patients with bipolar disorders and 20 healthy controls performed a shape matching test that has been designed to study the perception of hierarchical patterns using two Korean letters. In the paradigm, two different small letters were arranged to form two large different forms, thus making conflict between global and local shapes. The rate of global response and response time was measured and compared.



**Results:** Patients with bipolar disorders showed a lower rate of global responses and a longer response time. Depressive symptoms deepened the choice of local shapes.

**Conclusions:** Our findings suggest that there may be a disruption in perceptual organization of global precedence in bipolar disorders that tends to worsen in depressive states. Further neurobiological underpinnings need to be studied.

### Are power spectral density of EEG and cognitive function different in bipolar disorder I and II?

S Şayakçı Gürdal<sup>a</sup>, S Kesebir<sup>b</sup>

<sup>a</sup>Psychiatry, Erenköy Mental and Neurological Disease Training and Research Hospital, Istanbul, Turkey, <sup>b</sup>Psychiatry NPIstanbul Hospital, Üsküdar University, Istanbul, Turkey

**Objective:** The aim of this study is to investigate the EEG power spectral density and cognitive functions in remission period of bipolar disorder I and II and also to reveal whether they differentiate between each other and to investigate whether there is any relationship between peak power values of power spectral density (PSD-PPV) and cognitive functions.

**Methods:** Present study included 25 patients with bipolar disorder type I and 25 patients with bipolar disorder type II in remission period who following in our outpatients clinic, diagnosed according to DSM-IVTR and were in remission for at least 8 weeks (HDRS < 8 and YMRS < 5). Wisconsin Card Test, Stroop Test and Verbal Memory Processes Test (VMPT) were used. Six patients were excluded because of they have a psychotropic medication that impact to EEG.

**Results:** PSD-PPV recorded by the F3C3, F4C4, F7T3 and P3O1 electrodes was found to be higher in BD I group than BD II where as T4T6 electrodes was found to be higher in BD II group than BD I. In WCT, total number of responses and total number of non-perceverative responses were found to be higher in BD I group than BD II. In BD II group the number of completed category and percentage of conceptually responses were found to be higher than BD I group. In VMPT, total learning and recognition points were found to be higher in BD I group. Also, the highest point of learning and long-term memory were found to be higher in BD II group. There was a moderately correlation between total time of Stroop test and PSD-PPV of F3C3 both in BD I and II group. A weak relationship was found between Stroop interference and PSD-PPV of F3C3.

**Conclusion:** In BD I, the PSD-PPV that detected from right and left frontal, left frontotemporal and left parietooccipital areas correspond pathological activity in beta band, but in BD II, PSD-PPV that detected from right mediotemporal area correspond pathological activity in beta band BD I and II patients are found to be different according to the electrophysiological properties and cognitive functions in remission.

### Association between personality traits and depression in bipolar patients

I Lima<sup>a</sup>, APG Jelihovschi<sup>b</sup>, JN Fernandes<sup>a</sup>, C Soraggi<sup>b</sup>, FS Neves<sup>c</sup>, LF Malloy-Diniz<sup>c</sup>

<sup>a</sup>Molecular Medicine Post-Graduation Programme, Faculty of Medicine – Federal University of Minas Gerais, Belo Horizonte, Brazil, <sup>b</sup>Laboratory of Neuropsychological and Clinical investigations – National Institute of Science and Technology – Molecular Medicine, Faculty of Medicine – Federal University of Minas Gerais, Belo Horizonte, Brazil, <sup>c</sup>Department of Mental Health, Faculty of Medicine – Federal University of Minas Gerais, Belo Horizonte, Brazil

**Aim:** Investigate differences in personality in depressed, non-depressed and controls.

**Methods:** Sixty-seven patients – depressed (N = 55) and non-depressed (N = 12) – and 20 controls participated of this study. For clinical assessment it was used a structured interview – MINI Plus 5.0. The Beck Depression Inventory (BDI), The Young Mania Rating Scale (YMRS) and Temperament and Character Inventory (TCI) was filled in by participants. The latter measures seven traits: Harm Avoidance (HA), Reward Dependence (RD), Novelty Seeking (NS), and Persistence (PS), Cooperativeness (CO), Self-Directedness (SD) and Self Transcendence (ST)). The local ethics committee approved this study. Analyses of Variance (ANOVA) and Bonferroni *Post-hoc* analyses were performed.

**Results:** Depressed differed from non-depressed patients and controls in HA, NS and SD- higher scores in the first two measures and lower in SD.

**Conclusions:** The results suggest that HA, NS and SD maybe the traits most influenced by depressive symptomatology. These traits may be associated with depressive impairments.

### Neuropsychological performance in genetically at high-risk and ultra-high-risk offspring of parents with bipolar disorder

K Lin<sup>a</sup>, G Xu<sup>b</sup>, K Chen<sup>b</sup>, W Lu<sup>b</sup>, G Miao<sup>b</sup>, L Ting<sup>b</sup>, B Lai<sup>b</sup>, L Zhong<sup>c</sup>, K So<sup>d</sup>, T Lee<sup>a</sup>

<sup>a</sup>Psychology, The University of Hong Kong, Hong Kong, Hong Kong China, <sup>b</sup>Affective disorders, Guangzhou Psychiatric Hospital, Guangzhou, China, <sup>c</sup>Psychology, Minnan normal university, Fujian, China, <sup>d</sup>The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong, Hong Kong China

**Background:** Little is known about whether cognitive impairments predate the onset of bipolar disorder (BP), although numerous studies have shown cognitive deficits such as on executive function existing on established BP. We previously found that the two domains—processing speed and visual spatial memory—could not recover to the healthy level in a 6-week antidepressant treatments trial.

**Objective:** To establish whether processing speed and visual spatial memory predate the onset of BP.

**Methods:** In a two-year follow-up study on offspring of parents with bipolar disorder, we investigated those offspring either had developed into bipolar disorder or expressed subthreshold syndrome and those who manifested no or mild symptoms, defined as ultra-high-risk (UHR) and high-risk (HR) offspring respectively in according with the clinical staging models. Cognitive function was assessed by the MATRICS Consensus Cognitive Battery (MCCB).

**Result:** HR offspring showed no impairment in processing speed and visual spatial memory ( $p > 0.05$ ); however, UHR offspring displayed deficits on both of the domains.

**Conclusions:** our data suggest cognitive deficits is unlikely to be inherited abnormalities, but related to disease progression.

### Triglyceride levels are associated with working memory among adolescents with bipolar disorder

M Naiberg, D Newton, B Goldstein

Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada

**Aims:** Abnormal lipid (low-density lipoprotein (LDL); high-density lipoprotein (HDL); triglycerides (TG); total cholesterol (TC)) levels are common in bipolar disorder (BD). Lipid abnormalities have been associated with cognitive dysfunction, including working memory. It has been shown that high levels of TG may reduce insulin sensitivity, which has been further associated with impaired neurocognitive performance. We therefore aim to determine a link between lipids and working memory in adolescents with and without BD.

**Methods:** 29 BD adolescents (ages 13–20) and 25 healthy control adolescents (ages 13–19) completed the Spatial Span (SSP) task, using the Cambridge Neuropsychological Automated Testing Battery (CANTAB). This task assesses working memory capacity. Levels of LDL, HDL, TG and TC were obtained and analyzed dimensionally using International Diabetes Federation cut-offs. Mann-Whitney U-tests and Spearman correlations were performed using SPSS 22.

**Results:** BD adolescents had significantly higher TG levels ( $1.14 \pm 0.64$  mmol/L) compared to healthy control adolescents ( $0.76 \pm 0.37$  mmol/L) ( $U = 228.5$ ,  $p = 0.020$ ). TG levels were significantly correlated with SSP span length test scores in the BD group ( $p = -0.400$ ,  $p = 0.035$ ), but not in the control group ( $p = -0.006$ ,  $p = 0.976$ ). In the BD group, individuals with, vs. without, high TG levels ( $>1.70$  mmol/L) performed poorer on the SSP task (average score for longest sequence successfully recalled:  $4.67 \pm 0.82$  vs.  $6.95 \pm 1.40$ ;  $U = 13.00$ ,  $p = 0.002$ ). This result was non-significant in the control group ( $U = 4.0$ ,  $p = 0.400$ ). No significant associations were observed between memory and LDL, HDL or TC levels.

**Conclusions:** This study provides preliminary insights regarding one of the leading challenges in BD, cognitive impairment. Overall, TG levels are negatively associated with working memory in BD adolescents, but not in healthy controls. Larger prospective studies, and studies examining the impact of optimizing TG levels on cognition among BD adolescents, are warranted.

## Semantic inhibition in relation to hypomanic personality traits: an event related potential study

D Raucher-Chéné<sup>a</sup>, S Terrien<sup>b</sup>, F Gierski<sup>b</sup>, S Caillies<sup>b</sup>, A Kaladjian<sup>a</sup>, C Besche-Richard<sup>b</sup>

<sup>a</sup>Psychiatric Department, University Hospital of Reims, Reims, France, <sup>b</sup>Cognition Health Socialization (C2S EA6291) Laboratory, University of Reims Champagne-Ardenne, Reims, France

**Aims:** Hypomanic personality describes people who are cheerful, optimistic, extraverted, self-confident and energetic, although sometimes also irritable, rude and reckless or irresponsible. This personality is generally associated with an increased risk of subsequently developing bipolar disorder (Miller and Chapman, 2001). In bipolar disorder, semantic processing impairments are perceived by speech disorders such as loss of associations or tangentiality. Semantic processing involves mechanisms of access to the representation as activation and inhibition, and semantic inhibition failures in bipolar disorder are the objects of a growing literature (Wang et al., 2013). In a preliminary fMRI study, we found correlations between scores on the Hypomanic Personality Scale (HPS; Eckblad & Chapman, 1986) and cerebral activations implicated in semantic processing (Raucher-Chéné et al., 2014). These results suggest that participants with high HPS score may share similar processes with bipolar patients to deal with semantic information. The aim of this study was to further explore the relations between hypomanic personality traits and semantic inhibition deficiencies by using electroencephalography in order to investigate the temporal course of this potential deficiency.

**Methods:** An Event Related Potential linguistic paradigm involving semantic inhibition processes was proposed to a group of healthy participants who differ in their levels of self-reported Hypomanic personality.

**Results:** We expect correlations between scores on the HPS and cerebral electrophysiological waves implicated in semantic processing (N400 and Late Positive Component).

**Conclusions:** Exploration of semantic inhibition in hypomanic personality participants may contribute to a better knowledge of cognitive processes deficiencies implicated in mood disorders.

## Auditory attention deficits in bipolar disorder

GP Siwek<sup>a</sup>, AA Chrobak<sup>a</sup>, K Siuda-Krzywicka<sup>b</sup>, S Jezioro<sup>a</sup>, A Tereszko<sup>a</sup>, A Arciszewska<sup>c</sup>, L Luty<sup>d</sup>, M Siwek<sup>c</sup>, D Dudek<sup>c</sup>

<sup>a</sup>Students' Scientific Association of Affective Disorders, Jagiellonian University Medical College, Kraków, Poland, <sup>b</sup>Ecole des Neurosciences a Paris, Université Pierre et Marie Curie, Paris, France, <sup>c</sup>Department of Affective Disorders, Jagiellonian University Medical College, Kraków, Poland, <sup>d</sup>Department of Mathematical Statistics Faculty of Agriculture and Economics, University of Agriculture in Krakow, Kraków, Poland

**Aims:** Cognitive deficits are present in bipolar disorder (BD) even in the state of euthymia. Emerging data suggests impairment in various cognitive domains, such as executive functions, implicit and explicit learning, however only a few works examined performance of BD patients in auditory-attention-related tasks. In our study, we set out to investigate the presence of attention deficits in BD patients.

**Methods:** 31 DSM-V euthymic BD patients and 16 healthy controls (HC) were enrolled in the study. Subjects performed digital version of auditory oddball task: patients were presented two types of audio stimuli: more frequent, low-pitched sound (filler) and randomly delivered, high-pitched sound (oddball). Patients were asked to respond correspondingly to the presented stimuli (left mouse button for filler and right mouse button for oddball and had 1s for response. Reaction times, numbers of errors and misclicks (additional responses during that were collected during stimulus presentation phase) were collected.

**Results:** BD patients presented slower median reaction times (MRT) to both types of the stimuli: (Filler MRT for BD = 4507.0 vs. HC = 3602.4,  $p = 0.001$  and Oddball MRT for BD = 5531.2 vs. HC = 4569.3,  $p = 0.017$ ). Also, BD group was characterized by higher amount of misclicks (mean misclicks for BD = 18.9 vs. HC = 2.4  $p = 0.002$ ). No significant differences in number of errors to both types of stimuli were found.

**Conclusion:** In this study bipolar disorder patients presented impairment of auditory attention, especially noticeable in terms of reaction times and accuracy (number of misses).

## Mood symptoms confer risk for suicidal ideation in bipolar disorder: multi-wave data from STEP-BD

JP Stange<sup>a</sup>, EM Kleiman<sup>b</sup>, LG Sylvia<sup>c</sup>, PV Magalhães<sup>d</sup>, M Berk<sup>e</sup>, AA Nierenberg<sup>c</sup>, T Deckersbach<sup>c</sup>

<sup>a</sup>Psychology, Temple University, Philadelphia, USA, <sup>b</sup>Psychology, Harvard University, Boston, USA, <sup>c</sup>Psychiatry, Massachusetts General Hospital & Harvard Medical School, Boston, USA, <sup>d</sup>Psychiatry, National Institute for Translational Medicine Hospital de Clínicas de Porto Alegre Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, <sup>e</sup>Department of Clinical and Biomedical Sciences, Barwon Health and The Geelong Clinic University of Melbourne, Melbourne, Australia

**Aims:** Little is known about specific mood symptoms that may confer risk for suicidal ideation (SI) among patients with bipolar disorder receiving treatment according to contemporary practice guidelines. We evaluated prospectively whether particular symptoms of depression and mania precede the onset or worsening of SI among adults with or without a history of making a suicide attempt.

**Methods:** We examined prospective data from a large ( $N = 2,741$ ) cohort of patients participating in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). We evaluated history of suicide attempts at baseline, and symptoms of depression and mania (including SI) at baseline and follow-up visits. Hierarchical linear modeling tested whether mood symptoms at

a given visit predicted levels of SI at subsequent visits, and whether the strength of such associations differed based on suicide attempt history, after accounting for the influence of other mood symptoms and previous SI.

**Results:** Higher levels of SI across follow-up were predicted by suicide attempt history, baseline SI, baseline depression and mania symptom severity, number of lifetime (hypo)manic episodes, number of lifetime depressive episodes, earlier age of onset, illness duration, number of comorbid axis I conditions, and number of medical conditions, accounting for up to 7.7% of the overall variance in SI. Beyond overall symptom severity and SI at the previous visit, guilt, reduced self-esteem, psychomotor retardation and agitation, increases in appetite, and distractibility predicted more severe levels of prospective SI. Problems with concentration, distraction, sleep loss, distractibility, and decreased need for sleep predicted SI more strongly among individuals with a suicide attempt history, accounting for an additional 12% of the variance in SI.

**Conclusions:** Several specific mood symptoms may confer risk for the onset or worsening of SI among treatment-seeking patients with bipolar disorder. Individuals with a previous suicide attempt may be at greater risk in part due to greater reactivity to mood symptoms in the form of SI. However, effect sizes for symptoms were small, suggesting the need to identify additional proximal predictors of SI that have greater clinical utility. Future work should consider whether targeting and ameliorating these symptoms might reduce suicide risk in BD.

## Assessment of cognitive impairment in manic episode from bipolar affective disorder

M Vrabie<sup>a</sup>, V Marinescu<sup>b</sup>, A Talasman<sup>b</sup>, I Miclutia<sup>a</sup>

<sup>a</sup>Department of Psychiatry, University of Medicine & Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania, <sup>b</sup>Department of Psychiatry, University of Medicine & Pharmacy "Carol Davila", Bucharest, Romania

**Background:** There is important data which indicate that patient with bipolar affective disorder present cognitive impairment during all phases of illness, including manic episodes.

**Aim:** Identifying specific domains of cognitive dysfunction for manic episodes in bipolar disorder.

**Method:** We examined 100 bipolar (depressive, manic/hypomanic, euthymic) patients (according to DSM IV TR). The cognitive battery included standardized test of IQ, executive functioning, working memory, attention, visual memory and verbal memory. Demographic data (including gender, age, years of education, socioeconomic status and current employment) were systematically obtained. Data about psychiatric history, past and current treatment, psychosis history, illness duration, age of onset and family history were collected. We analyzed statistically these data and assessed the relationships between cognitive impairment and manic episodes and identified specific domains of cognitive dysfunction for manic episode.

**Results:** Bipolar patients present cognitive deficits in domains of attention, verbal and learning memory and executive function (including working memory, executive control, verbal fluency, mental manipulation, cognitive flexibility), across all phases of the illness. Manic episodes have the the most impact on neuropsychological function. Verbal learning, verbal memory and sustained attention were particularly deteriorated in manics. Cognitive deficits are more frequent in manic patients with longer durations of mood disturbance and are negatively correlated with executive function, psychomotor speed, concentration and attention. Selective attention deficits during acute episodes don't normalize during euthymia. Deterioration of executive functioning is related of hospitalization for mania. Verbal memory is associated with a higher number of past manic episodes. Attention and executive function

are deteriorated by the recurrence of manic episodes. Higher number of hospitalization is negatively correlated with visual and verbal memory, verbal fluency, spatial memory, psychomotor speed, executive function, regardless of episode type.

**Conclusions:** Bipolar patients exhibit important neurocognitive dysfunctions during their lives. There are persistent cognitive deficits over the course of bipolar affective disorder and specific cognitive impairment of each phase of the illness, including mania.

## Impact of comorbid anxiety disorders in prospective suicide attempts

LN Abreu<sup>a</sup>, B Lafer<sup>a</sup>, A Burke<sup>b</sup>, MF Grunebaum<sup>b</sup>, L Sher<sup>c</sup>, GM Sullivan<sup>b</sup>, ME Sublette<sup>b</sup>, R Pietrobond<sup>d</sup>, JR Vissoci<sup>d</sup>, JJ Mann<sup>b</sup>, MA Oquendo<sup>b</sup>

<sup>a</sup>University of Sao Paulo, Institute of Psychiatry, Sao Paulo, Brazil,

<sup>b</sup>Molecular Imaging and Neuropathology Division, New York State Psychiatry Institute, New York, USA, <sup>c</sup>Mount Sinai School of Medicine, James J. Peters Veteran's administration Medical Center, New York, USA, <sup>d</sup>Duke University Medical Center, Duke University Medical Center, Durham, USA

**Background:** Suicide attempts (SA) have been associated with comorbidity with anxiety disorders in both major depression (MDD) and bipolar disorder (BD). Our aim is to verify prospectively the impact of lifetime and current comorbid anxiety disorders on prospective suicide attempts in a sample of patients with MDD and BD.

**Method:** A two-year prospective study evaluated 655 patients with either MDD (N = 491, 75%) or BD (N = 164, 25%). Of these patients, two hundred and thirty-five (45.5%) had any lifetime anxiety disorders and 196 (38%) had any current anxiety disorders. Assessments were performed after 3 months, 12 months and 24 months. The main outcome was the presence of suicide attempts during the follow-up. Kaplan-Meier survival analysis and Log rank test were used to elucidate the relationship between presence of lifetime anxiety disorders and current anxiety disorders and subsequent suicide attempts. We performed a secondary analysis considering the subgroups of MDD and BD patients separately to verify if there were any differences between anxiety disorders, diagnostic of MDD or BD and prospective suicide attempts.

**Results:** There were 64 suicide attempts during the follow-up, 18 (28.12%) in the BD subgroup and 46 (71.87%) in the MDD subgroup. For the whole sample, 421 patients were censored (86.6%) and the median survival time was 28 months. There were no differences in survival curves for presence of lifetime anxiety disorders (p = 0.530) and presence of current anxiety disorders (p = 0.769). Considering the subgroups of MDD and BD patients, survival curves comparing the diagnostic (p = 0.723), lifetime anxiety disorders (p = 0.377) and current anxiety disorders (p = 0.575) did not differ.

**Conclusion:** Our results suggest that current and lifetime comorbid anxiety disorders were not risk factors for prospective suicide attempts in patients with either MDD or BD. The role of comorbidity with anxiety disorders and its relationship with prospective suicide attempts in patients with mood disorders requires further study.

## Prevalence and socio-demographic and clinical correlates of eating disorder comorbidity in bipolar disorder patients

D Balzafigore<sup>a</sup>, H Kim<sup>b</sup>, K Goffin<sup>a</sup>, N Rasgon<sup>a</sup>, T Ketter<sup>a</sup>

<sup>a</sup>Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, USA, <sup>b</sup>Department of Psychiatry, Inje University School of Medicine, Seoul, Korea

**Aims:** Eating disorders (EDs) are common in bipolar disorder (BD), and may be associated with earlier BD onset, more depres-

sive episodes, suicide attempts, rapid cycling, anxiety/substance use disorder comorbidity, and weight disturbance. We assessed prevalence and socio-demographic and clinical correlates of EDs in BD outpatients.

**Methods:** BD outpatients ( $n = 503$ ) were recruited from the Stanford University Bipolar Clinic and were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation. The STEP-BD protocol and a subsequent similar Stanford-specific centralized database protocol were approved by the Stanford University Administrative Panel on Human Subjects, and patients provided verbal and written informed consent prior to participation. Prevalence, socio-demographic, and clinical characteristics were compared between outpatients with versus without a lifetime ED.

**Results:** Among 503 BD outpatients, 76 (15.1%) had a lifetime ED. Most BD + ED patients were female (86.8%). BD patients with compared to without EDs had earlier BD onset ( $14.3 \pm 5.1$  versus  $18.6 \pm 8.8$  years,  $p < 0.0001$ ), a 90% higher risk of BD onset before age 13 years (35.5% versus 18.7%,  $p < 0.01$ ), more comorbid anxiety (78.9% versus 62.3%,  $p < 0.01$ ), alcohol use (51.3% versus 34.4%,  $p < 0.01$ ), and personality (21.1% versus 9.8%,  $p < 0.01$ ) disorders, a prior suicide attempt (47.4% versus 27.8%,  $p < 0.0001$ ), and more rapid cycling during the prior year (40.3% versus 23.8%,  $p < 0.01$ ). Lifetime presence of ED was not significantly different between bipolar I and bipolar II patients. There was no significant difference in body mass index (BMI) between the groups.

**Conclusions:** Our findings support previous studies suggesting that EDs are common in patients with BD and may be associated with an earlier age of BD onset and more severe bipolar course. Further studies are needed to explore the implications of ED comorbidity for treatment response.

## Identification of a novel candidate epigene for antipsychotic-induced insulin resistance in bipolar disorder

K Burghardt<sup>a</sup>, J Goodrich<sup>b</sup>, D Dolinoy<sup>b</sup>, V Ellingrod<sup>c</sup>

<sup>a</sup>Pharmacy Practice, Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, USA, <sup>b</sup>School of Public Health, University of Michigan, Ann Arbor, USA, <sup>c</sup>College of Pharmacy, University of Michigan, Ann Arbor, USA

**Aims:** The rate of diabetes is elevated in bipolar disorder and contributes to a more complicated course of psychiatric illness and shorter life expectancies. The second generation antipsychotics (SGAs) are known to further increase this baseline risk of diabetes in bipolar disorder. The mechanism behind this adverse effect may be related to abnormalities in the folate cycle and thus DNA methylation. This study aimed to assess the effect of SGA use and insulin resistance on DNA methylation using two different DNA methylation interrogation techniques.

**Methods:** Bipolar subjects on either SGAs or mood stabilizer monotherapy were assessed for insulin resistance using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Global methylation levels were assessed using the Luminometric Methylation Assay. 76 SGA-treated bipolar I subjects were used for a follow-up epigenome-wide association study (EWAS) using the Illumina 450K beadchip in peripheral blood samples to identify the top differentially methylated regions.

**Results:** For the global methylation analysis, 115 bipolar I subjects were included. The average age was  $43.1 \pm 12.2$  years, 67% were female and 81% were Caucasian. A multivariate linear regression found that global methylation was significantly influenced by HOMA-IR ( $p = 0.0072$ ), smoking ( $p = 0.0320$ ) and an interaction between hip-to-waist ratio and SGA use ( $p = 0.0167$ ). For the EWAS, the average age was  $44.2 \pm 11.1$ , 60% were female and

90% were Caucasian. A total of 2 CpG probes were found to be differentially methylated based on HOMA-IR. The top gene hit was found in the Fatty Acyl CoA Reductase 2 (FAR2) gene.

**Conclusions:** This is the first study to show a relationship between SGA use, insulin resistance and global DNA methylation followed by an EWAS to identify differentially methylated regions for future study. The top EWAS gene hit is linked to the metabolism of fatty acids. Fatty acids are closely linked to insulin resistance and disruption of their metabolism through epigenetic regulation could be a possible explanation for SGA-induced insulin resistance. Future work is needed to identify site-specific methylation differences based on gold-standard assessments of insulin resistance (e.g., hyperinsulinemic euglycemic clamp) in candidate tissues involved in the pathophysiology of insulin resistance.

## Sexual abuse prevalence in bipolar disorder first-time psychiatric evaluations: a Mexican retrospective cohort

F Canale, P Zarate, AB Cuellar-Barboza

Psychiatry, Universidad Autonoma de Nuevo Leon, Monterrey, Mexico

**Aims:** Sexual abuse has a high prevalence among bipolar patients; however, few studies have compared this prevalence with other mood disorders. Moreover, most reports have been performed in occidental first world countries. We explored the prevalence of sexual abuse in first-time psychiatric consults, in a Mexican retrospective cohort, and compare it between bipolar (BD), unipolar (UD) and other mood disorders (OD).

**Methods:** This is a retrospective cohort from medical records of first-time psychiatric evaluations. Subjects were selected from the Outpatient Service of the Department of Psychiatry of the University Hospital of the Universidad Autónoma de Nuevo León, Monterrey, Mexico from January 2014 to December 2014. Our outpatient service is a regional center that evaluates patients from the north east of Mexico. We performed a query to determine every mood disorder that met DSM-IV-TR diagnostic criteria in first-time consults and included patients 18 years and older; the resulting medical records were reviewed manually. Clinical variables including sexual abuse were self-reported. Standardized chi-square, *t*-test and ANOVA were used for analysis.

**Results:** We found 425 mood disorder first-time evaluations. 80% of this sample was diagnosed with UD; 12.4% BD; and 7.6% OD; the majority (68.9%) were females, with a mean age of  $37.2 \pm 14.4$  years. There was no significant difference in socio-demographic variables between diagnoses. UD and OD patients showed significantly more comorbidity in axis I vs. bipolar patients (65.6% OD vs. 61.4% UD vs. 41.5% BD,  $p = 0.01$ ). 75 (17.6%) evaluations reported sexual abuse and 83% of these were female. Although not significantly increased, a trend was observed showing higher sexual abuse in BD patients (BD 30% vs. UD 15% vs. OD 15%;  $8.810$ ,  $p = 0.06$ ). Among those that reported age of sexual abuse the mean was of 8.62 years ( $n = 49$ ).

**Conclusions:** We show a prevalence of sexual abuse of 17.6% in mood disorder patients. Bipolar patients seem to have a higher history of sexual abuse (30%) than unipolar patients (15%). A larger and prospective sample is needed to better explore this concerning finding.

## Binge behavior, binge eating disorder, and bulimia in bipolar disorder

S McElroy<sup>a</sup>, D Bond<sup>b</sup>, S Crow<sup>b</sup>, S Winham<sup>c</sup>, W Bobo<sup>d</sup>, L Seymour<sup>d</sup>, N Mori<sup>a</sup>, J Biernacka<sup>c</sup>, M Frye<sup>d</sup>

<sup>a</sup>Department of Psychiatry and Psychology, Lindner Center of HOPE, Mason, USA, <sup>b</sup>Department of Psychiatry and Psychology, University of Minnesota, Minneapolis, USA, <sup>c</sup>Division of Biomedical Statistics and Informatics Department of Health Sciences Research, Mayo Clinic, Rochester, USA, <sup>d</sup>Department of Psychiatry and Psychology, Mayo Clinic, Rochester, USA

**Aims:** DSM-5 now recognizes binge eating disorder. Our earlier work identified a clinical diagnosis of binge eating disorder (BED) in 9.5% patients with bipolar disorder. The stress and functional impairment (i.e., suicidality, psychosis, mood instability, substance abuse) of this comorbidity eating disorder is substantial. The goal of this study was to explore the relationship between bipolar disorder and a spectrum of eating disorders (binge behavior, binge eating disorder, and bulimia nervosa) utilizing the Eating Disorder Diagnostic Scale (EDDS).

**Methods:** 1,123 patients participating in the Mayo Clinic Bipolar Biobank completed structured diagnostic interviews and questionnaires for demographic and illness related variables. The EDDS, a patient self-report with good psychometric properties (internal consistency, test-retest reliability), was used to identify a spectrum of eating disorders including: binge behavior (endorsing times eating large quantities of food with concurrent loss of control), and DSM-5 based binge eating disorder (BED) and bulimia nervosa.

**Results:** Binge behaviors, eating large quantities of food, was endorsed in 527/1123 (46.9%), loss of controls in 375/1091 (34.3%), or both behaviors in 331/1091 (30.3%) of bipolar patients. Frequencies of loss of control as binge behavior was reported 1 day/week (15%), 2 days/week (12.8%), and 3 days/week (7.9%). Binge eating disorder was identified in 285/1080 patients (26.3%). Bulimia nervosa was identified in 113/1063 patients (10.6%).

**Conclusions:** To our knowledge, this is the first study utilizing the EDDS to assess a spectrum of eating disorders including binge behavior and now DSM-5 recognized binge eating disorder in bipolar disorder. The BED prevalence rate of 26% is significantly higher than our earlier work (9.5%), which had relied on a clinical diagnosis as opposed to a patient self-report. Further research is encouraged to delineate the extent of clinical comorbidity and functional disability associated with the spectrum of eating disorders in bipolar disorder.

## Increased atherogenic index of plasma (AIP) and atherogenic coefficient (AC) in major depression and bipolar disorder, especially when comorbid with tobacco use disorder

S Nunes

Avenida Adhemar de Barros, Londrina, Brazil

Abstract Incomplete.

## Can statins prevent lithium-associated diabetes insipidus? Findings from the McGLIDICS study

D Elie<sup>a</sup>, M Segal<sup>a</sup>, NCP Low<sup>a</sup>, I Mucsi<sup>b</sup>, C Holcroft<sup>c</sup>, KI Shulman<sup>d</sup>, KJ Looper<sup>a</sup>, S Reij<sup>d</sup>

<sup>a</sup>Psychiatry, McGill University, Montreal, Canada, <sup>b</sup>Nephrology, University of Toronto, Montreal, Canada, <sup>c</sup>Biostatistics, Consultant Biostatistician, Boston, USA, <sup>d</sup>Psychiatry, University of Toronto, Toronto, Canada

**Background:** Lithium is a highly effective medication for mood disorders. However, nephrogenic diabetes insipidus (NDI) commonly complicates chronic lithium use with dehydration, hypernatremia,

and chronic kidney disease (CKD). Recent mice studies have shown statins to be helpful in genetic forms of NDI, however statins have not yet been studied in lithium users.

**Methods:** We used cross-sectional data from 71 geriatric and adult lithium users enrolled in the McGLIDICS study. We analyzed the correlation between statin use and urine osmolality, including multivariate analyses controlling for age, lithium level and duration.

**Results:** Patients were aged 20–95 years (mean 60.9), 54.9% were female, 88.6% had bipolar disorder, mean lithium duration and serum level were 10.6 years and 0.62 mmol/L, respectively. Seventeen patients used statins, with atorvastatin 10–40 mg/day (n = 10) and rosuvastatin 5–20 mg/day (n = 5), being the main ones used. Statin users and non-users had similar overall UOsm: 507.9 mOsm/kg vs. 513.35 mOsm/kg,  $t = 0.10$ ,  $p = 0.92$ . On multiple linear regression, statin use was not associated with UOsm. Strikingly though, 0% (0/17) of statin users compared to 20.4% (11/54) on non-users had UOsm < 300 mOsm/kg (Fisher's Exact  $p = 0.055$ ). A typical logistic regression could not be performed, since statin use was a “perfect predictor” – all UOsm < 300 mOsm/kg events occurred in statin non-users.

**Conclusion:** From this exploratory analysis, statins appear to have a protective effect against lithium-associated NDI. Statins are particularly appealing since they are cheap, relatively safe, and may protect against other comorbidities (e.g. cardiovascular events). Trials could confirm whether statins can treat/prevent lithium-associated NDI and its consequences.

## Comorbid anxiety disorder associates with poor sleep quality in euthymic bipolar disorder patients

PMB Rocha<sup>a</sup>, FS Neves<sup>b</sup>, H Corrêa<sup>b</sup>

<sup>a</sup>Faculdade de Medicina, IMES, Ipatinga, Brazil, <sup>b</sup>Faculdade de Medicina, UFMG, Belo Horizonte, Brazil

Sleep disturbances have been reported as frequent symptoms in Bipolar Disorder (BD) even during euthymia and associated with greater recurrence of mood episodes and a poorer outcome. In the past decades numerous studies reported high rates of axis I and II psychiatric disorders in BD patients compared to the general population, including substance use, personality and anxiety disorders. In this sense, the occurrence of comorbid anxiety disorders in BD is relevant because some prospective studies showed they could be related to higher symptomatology burden and a worse course of illness. Recent evidences showed that the negative impact of a comorbid anxiety disorder extends to the interepisodic phases of the disorder. Thus, given the clinical relevance of comorbid anxiety disorders and sleep disturbances during the interepisodic phase of BD, we decided to evaluate if the presence of a comorbid anxiety disorder could adversely impact sleep function in euthymic BD patients. In order to achieve this intent we subdivided a sample of 105 euthymic BD patients into “good sleepers” (PSQI ≤ 5) and “poor sleepers” (PSQI > 5) assessed by the Pittsburgh Sleep Quality Index (PSQI) and performed a multivariate analyses having comorbid anxiety disorder as well as some other potential risk factors for sleep disturbances as covariates. Psychiatric diagnosis was assessed by the MINI-Plus structured interview for both groups, based on the DSM-IV criteria. Euthymia was established as a score lower than 7 in both Young and Hamilton mood scales simultaneously, as well as the lack of criteria for a current major mood episode assessed by the MINI-plus. All procedures were preapproved by local ethics committee and informed consent was obtained for all the subjects. Statistical analysis was performed by SPSS software with a significance level of 0.05. Multivariate analysis showed that a comorbid anxiety disorder diagnosis significantly associated with poor sleep quality in euthymic BD patients (OR 5.379;  $p$ -value = 0.016). Several researchers have raised the impor-

tance of addressing adequately the psychiatric comorbid conditions in BD as they are associated with a poor prognosis. We found preliminary evidence that a comorbid anxiety disorder could adversely impact sleep quality of euthymic BD patients.

### Self-managing bipolar disorder and comorbid diabetes: older and wiser?

**M Martha Sajatovic, D Gunzler, D Einstadter, C Thomas, R McCormick, C Blixen, AT Perzynski, S Kanuch, K Cassidy, NV Dawson**

*University Hospitals, Case Medical Center, Cleveland, USA*

Among those with serious mental illnesses such as bipolar disorder (BD), metabolic disturbances are common, and are amplified by unhealthy behaviors such as smoking, reduced physical activity, and poor diet. Medical comorbidity in BD inflates costs due to over-utilization of hospital-based or crisis services. BD elders have high rates of diabetes. Helping individuals with BD to better self-manage their mental and physical health could potentially improve outcomes and control costs. Targeted training in illness management (TTIM) is a behavioral treatment that blends psychoeducation, problem identification/goal-setting, and behavioral modeling which has been adapted to the primary care setting, and targeted for seriously mentally ill individuals with comorbid diabetes. These investigators have recently completed enrollment (N = 200) in a National Institute of Mental Health (NIMH) randomized controlled trial (RCT) assessing effects of TTIM compared to usual care. In the baseline TTIM intervention sample, 48% of individuals were > age 55 years. Older individuals had lower hemoglobin A1c scores (mean 7.3, SD 1.6) compared to younger individuals (mean 8.7, 2.6), p

### Understanding adolescent bipolar disorder (BD-A): when is a dual diagnosis of autism spectrum disorder (ASD) appropriate?

#### Experiences from the USA and UK

**AS Le Couteur<sup>a</sup>, MK Singh<sup>b</sup>, AN Sharma<sup>a</sup>**

*<sup>a</sup>Academic Child and Adolescent Mental Health, Newcastle University, Newcastle upon Tyne, United Kingdom, <sup>b</sup>Pediatric Bipolar Disorders Program, Stanford University, USA*

Youth with Adolescent onset Bipolar Disorder (BD-A) often have co-occurring mental health and neurodevelopmental disorders. In addition, Bipolar Disorder is associated with enduring psychosocial dysfunction. Some groups have reported an association of psychosocial dysfunction in Bipolar Disorder with neurocognitive and facial emotion labelling deficits but other groups have not replicated this finding. This session will focus on understanding the rates of social interaction and communication deficits in BD-A and what the potential clinical implications of these deficits are on assessment, management and psychosocial function in BD-A. In particular, it will report findings from US on the psychosocial deficits, UK epidemiology data for Paediatric Bipolar I Disorder and the speakers will facilitate a discussion on whether new insights can be gained to inform clinical academic practice? Dr Manpreet Singh will present clinical data from the Stanford Paediatric Bipolar Disorders Program on the rates of ASD diagnoses within cases of BD-A and also present data on Theory of Mind deficits seen in subjects at risk of developing Bipolar Disorders. Dr Aditya Sharma will report findings from the Regional North East of England Adolescent Bipolar Service and the UK Surveillance Study of the Incidence of Paediatric Bipolar I Disorder. He will then discuss the impact of a dual diagnosis of BD-A & ASD including modifications to psychoeducational approaches to interventions e.g. the Family Focussed Treatment for Adolescents with Bipolar Disorder.

### Demographic and clinical characteristics associated with comorbid cannabis use disorders (CUDs) in hospitalized patients with bipolar disorder

**LM Weinstock<sup>a</sup>, BA Gaudiano<sup>a</sup>, G Epstein-Lubow<sup>a</sup>, SJ Wenzel<sup>b</sup>, IW Miller<sup>a</sup>**

*<sup>a</sup>Department of Psychiatry and Human Behavior, Brown University and Butler Hospital, Providence, USA, <sup>b</sup>Department of Psychology, Lafayette College, Easton, USA*

**Aims:** The elevated prevalence of substance use in bipolar disorder (BD) has been well documented, with evidence that rates of comorbid substance use disorders (SUDs) are among the highest in BD relative to the other major psychiatric disorders. As in the general population, cannabis represents the most common *illicit* substance of abuse in BD. An emerging literature suggests that cannabis use is associated with several negative consequences for BD, including new manic episode onset, psychosis, and functional disability. Yet much less is known about cannabis use disorders (CUDs) in this population, especially in more acutely ill samples. The aim of this study was to evaluate correlates of CUDs in a sample of psychiatrically hospitalized patients with bipolar I disorder (BDI).

**Methods:** A retrospective chart review was conducted for patients with BDI admitted to the inpatient or partial hospitalization programs at Butler Hospital in Providence, RI, USA during the 2010 calendar year. Using a computer algorithm, a hospital administrator extracted relevant demographic and clinical data from the electronic medical record for analysis. To be considered eligible for inclusion, patients must have been 18 years or older and given a primary diagnosis of BDI at both hospital admission and discharge. The resulting sample included 230 unique cases for analysis.

**Results:** Overall, 36 (16%) had a CUD diagnosis. Results from univariate analyses revealed that those with a comorbid CUD were significantly more likely to be younger, to be in a manic/mixed episode, to present with psychosis, and to have comorbid nicotine dependence, alcohol use disorder, and other SUDs. Those with a CUD were significantly less likely to have an anxiety disorder diagnosis. Results from multivariate analyses controlling for the presence of concurrent other SUDs were largely consistent with univariate results.

**Conclusions:** Patients with BD and comorbid CUDs appear to be a high risk population with need for enhanced monitoring of mania, psychosis, and additional substance use behavior. Given increasing acceptance of cannabis use among legislators and the public, and the current limited availability of evidence based interventions targeted toward CUDs in BD, enhanced psychoeducation and other treatment development efforts appear to be warranted.

### Prevention is better than cure-target is: elimination of self-defeating behaviors-stress-anxiety-depression and other disorders @ 25% to 35% at global level

**M Ashraf**

*The Ultimate Solutions, PK*

ELIMINATION OF SELF-DEFEATING BEHAVIORS, S-A-D @ 25% / 35% AT GLOBAL LEVEL BY USING available paraphernalia at best levels AND THE MODEL IS SYNERGY. Future: Resources available; need to utilize all resources. .... just like we launched several successful campaigns against different severe diseases suppose to be AIDS and likewise. Target Result in: Elimination of Self-Defeating Behaviors – Frustration – Stress – Anxiety – Depression @ 40% to 50% at global level. AND at the same time we will make a very major development in the shape of: Formation of: A Newly World Wide Centralize Forum – Just like – The United Nations – Resulting in the shape of more strength,

more power, more cooperation and have well planned, well Coordinated, Well Organized Results and Developments throughout the world. Yes, together we can make our future destiny in a way as we need and want to see. Thank you very much.

### Strengths and limitations of more versus less inclusive definitions of mixed depression (not counting “overlapping” mood elevation symptoms) in bipolar disorder patients

W Kim<sup>a</sup>, H Kim<sup>b</sup>, KC Goffin<sup>c</sup>, L Yuen<sup>c</sup>, JN Holtzman<sup>c</sup>, F Hooshmand<sup>c</sup>, S Miller<sup>c</sup>, PW Wang<sup>c</sup>, TA Ketter<sup>c</sup>

<sup>a</sup>Psychiatry, Inje University, Seoul, Korea, <sup>b</sup>Psychiatry, Inje University, Goyang, Korea, <sup>c</sup>Psychiatry and Behavioral Sciences, Stanford University, Stanford, USA

**Aims:** The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) adopted a more inclusive approach to mixed symptoms, including addition of mixed depression, by using a “with mixed features” specifier for major depressive episodes. However, this approach to mixed depression has been criticized as being overly exclusive, due to it not counting important but overlapping (i.e., may also occur during depression) mood elevation symptoms such as irritability, psychomotor agitation, and distractibility. Assuming only non-overlapping mood elevation symptoms ought to be counted, we assessed the prevalence, demographics, and clinical correlates of mixed versus pure depression in bipolar disorder patients, using the DSM-5 (at least 3 non-overlapping mood elevation symptoms) and more inclusive (at least 2 or 1 non-overlapping mood elevation symptom(s)) definitions.

**Methods:** BD outpatients were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation. Prevalence and clinical correlates of baseline depressive episodes “with mixed features” were compared using more inclusive thresholds (requiring only one or two non-overlapping mood elevation symptoms) compared to the less inclusive DSM-5 threshold (requiring three non-overlapping mood elevation symptoms).

**Results:** Among 153 BD patients with syndromal depression, counting only non-overlapping mood elevation symptoms, our most inclusive ( $\geq 1$  symptom) and more inclusive ( $\geq 2$  symptoms) thresholds compared to the less inclusive DSM-5 threshold, yielded significantly higher mixed depression rates (34.6% and 14.4% versus 7.2%), which in turn yielded potentially important statistically significant clinical correlates for mixed compared to pure depressive episodes (e.g. more lifetime anxiety disorder comorbidity and current irritability, and less current antidepressant use (most inclusive threshold only)), which were not statistically significant using the less inclusive DSM-5 threshold. However, our most inclusive threshold was associated with the potential confound of less often having a college degree for patients with mixed versus pure depression (28.3% versus 55.0%,  $p < 0.01$ ).

**Conclusions:** Further studies are warranted to assess our observation that more compared to less inclusive “with mixed features” thresholds for bipolar depression may have more statistically significant clinical correlates, and the extent to which differences in effect sizes versus statistical power contribute to this phenomenon.

### The Internal State Scale: exam of its psychometric characteristics in a large mood disorder, tertiary care sample and its ability to discriminate among mood phases

S Paterniti<sup>a</sup>, JC Bissier<sup>b</sup>

<sup>a</sup>Psychiatry Mood and Anxiety Disorders Program, University of Ottawa, Ottawa, Canada, <sup>b</sup>Psychiatry, University of Ottawa, Ottawa, Canada

**Aims:** The Internal State Scale (ISS) was developed to assess the severity of manic and depressive symptoms simultaneously. The goal of this study is to examine the psychometric properties of the ISS in a large mood disorder sample referred to a tertiary care structure.

**Methods:** Between 2006 and 2012, 310 individuals diagnosed with Major Depressive Disorder (MDD) and 174 subjects diagnosed with Bipolar Disorder (BD) completed the Internal State Scale (ISS) during an assessment at the ROMHC Mood Disorders Program, which provides tertiary care to resistant to treatment population. The Structured Clinical Interview for DSM-IV-TR was used to assess diagnosis.

**Results:** Sixty-seven percent of the sample were women; the mean age was 40.9 (SD = 12.4). The ISS internal consistency as measured by Cronbach alpha was 0.76. The Principal Component Analysis of the ISS revealed three factors (Activation, Well Being and Perceived Conflict), similarly to the original analysis from Bauer et al (1991). The depression subscore (DI) correlated positively with the Quick Inventory of Depressive Symptomatology total score (0.57,  $p < 0.001$ ), the Automatic Thoughts Questionnaire total score (0.58,  $p < 0.001$ ) and the Outcome Questionnaire total score (0.56,  $p < 0.001$ ). The Wellbeing (WB) subscore correlated with the same scales, but negatively ( $-0.50$ ,  $-0.47$ ,  $-0.49$ , respectively,  $p < 0.001$  for the three correlations). Interestingly, the subscale Activation (ACT) correlated positively with the QIDS total score (0.26,  $p < 0.001$ ) and the Penny Worry Questionnaire total score (0.27,  $p < 0.001$ ), which measures the intensity of worries. We assessed the agreement between the classification of mood states (euthymic, manic/hypomanic/mixed, depressed) based on the ISS algorithm (ATC cut-off = 155 and WB score cutoff = 125) and on the physician rating based on the SCID. If we consider the clinician rating as the “gold” standard, 58% percent of depressed patients, 28% of the manic/hypomanic/mixed patients and 21% of the euthymic patients were correctly identified by the ISS algorithm.

**Conclusions:** The ISS exhibited good psychometric properties (robust factor structure, good internal consistency), but the ability to discriminate among different mood phases on the basis of this self-rating scale seems to remain a major challenge.

### Definition of research diagnostic criteria for cyclothymic disorder

AR Van Meter<sup>a</sup>, EA Youngstrom<sup>b</sup>, B Birmaher<sup>c</sup>, MA Fristad<sup>d</sup>, SM Horwitz<sup>e</sup>, TW Frazier<sup>f</sup>, LE Arnold<sup>d</sup>, RL Findling<sup>g</sup>

<sup>a</sup>Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, USA, <sup>b</sup>Psychiatry and Psychology, University of North Carolina at Chapel Hill, Chapel Hill, USA, <sup>c</sup>School of Medicine, University of Pittsburgh, Pittsburgh, USA, <sup>d</sup>Psychiatry, The Ohio State University, Columbus, USA, <sup>e</sup>School of Medicine, New York University, New York, USA, <sup>f</sup>Center for Pediatric Behavioral Health, Cleveland Clinic, Cleveland, USA, <sup>g</sup>Psychiatry, Johns Hopkins University/Kennedy Krieger Institute, Baltimore, USA

**Background:** Epidemiological studies suggest that cyclothymic disorder (CYC) may be the most prevalent subtype of bipolar disorder (BD). However, CYC is rarely diagnosed clinically, especially in youth. This may be because CYC criteria can be difficult to apply. Development of concrete criteria for CYC could increase

accurate use of the diagnosis. The objective of this study was to determine whether a research definition of CYC (RDCyc), based on DSM-5 criteria, could be quantified and validated in youth.

**Method:** Data from the IRB-approved LAMS study (Horwitz, 2010) were well-suited for this study: most participants experienced baseline manic symptoms, putting them at risk for RDCyc, and the design allowed the duration criteria to be evaluated prospectively. Participants ( $N = 685$ ) completed evaluations every six months. This report includes data collected through the two-year follow-up (ages 8–14). RDCyc criteria (required at two consecutive follow-ups) were: (1) At least one core symptom of mania (elated mood, irritability, increased energy) and depressed mood; (2) at least one additional symptom of mania and one of depression; (3) impairment. Participants could not meet criteria for [hypo]mania or major depression at any point. RDCyc youth were compared to other youth (BD I/II, BD NOS/CYC, disruptive behavior disorders [including ADHD], depression) using ANOVA and chi-squared analyses.

**Results:** RDCyc youth ( $n = 34$ ) had symptoms consistent with other BD youth, equivalent quality of life scores, and rates of parent psychopathology ( $p$ 's  $> 0.05$ ). The only significant difference among the BD subtypes was that RDCyc youth were less likely to be prescribed mood stabilizers than youth with BD I or II ( $p = 0.001$ ). RDCyc participants had higher CDRS-R scores than DBD youth ( $p < 0.001$ ), higher YMRS scores than youth with DBD ( $p = 0.001$ ) or depression ( $p = 0.042$ ), and lower QoL than youth with DBD. RDCyc youth were more likely to have a parent with psychopathology than youth with DBD ( $p = 0.02$ ).

**Discussion:** The results indicate that RDCyc criteria identify a group of youth who share more in common with BD (I, II, NOS) youth than youth with other diagnoses. Simplifying the criteria for CYC may improve diagnostic accuracy, facilitate appropriate treatment, and build understanding of this prevalent but largely ignored diagnosis.

## Lithium therapy: the nephrologist's point of view

**F Assuncao, FS Neves**

*Psychiatry Mental Health, Federal University of Minas Gerais, Belo Horizonte, Brazil*

The lithium therapy remains the gold standard for the treatment of bipolar disorder at all stages of the disease, and despite the potential serious adverse effects. Renal function is a major concern in patients using lithium. It is controversial whether the lithium can lead to long-term renal insufficiency. In addition to using lithium, bipolar patients are at increased risk of cardiovascular disease, substance abuse, diabetes, hypercholesterolemia, obesity and uric acid that can also damage the renal function. Moreover, studies show that patients with metabolic syndrome have a higher risk of developing chronic kidney disease. The objective of the study was to evaluate a service specializing in the treatment of bipolar disorder the prevalence of alterations in renal function and other conditions that may affect it in the long run.

**Methods:** We studied 26 bipolar patients taking lithium regularly following the recommendations of guidelines for preservation of renal function (urea / serum creatinine every six months plus general recommendations to avoid poisoning lithium). All patients were subjected to the following laboratory tests: TSH, free T4, PTH, ionized calcium, phosphorus, 25-hydroxy-vitamin D, uric acid, urea, serum creatinine, LDL, HDL, triglycerides, sodium, potassium, bicarbonate, hemoglobin, fasting glucose and urinalysis.

**Results:** In the total sample, 65% had chronic kidney disease, 43% had 25-hydroxy-vitamin D deficiency, 41% had PTH elevation, 71% had LDL above 100 mg/dL, 87% had HDL below 60 mg/dL, 50% had hypertriglyceridemia, 28% had fasting glucose above

100 mg/dL, 44% had hypercalcemia, 11% had hyperuricemia and 65% had BMI above 24.

**Conclusions:** The key to prevention or delay of severe kidney disease is early detection and aggressive intervention – while there's still time to slow down the progression to kidney failure. A significant number of the studied sample had direct alterations in renal function and others that could impair renal function in the long run. The study suggests that current recommendations for the maintenance of renal function should be revisited and that randomized clinical trials should be done to investigate whether a early psychiatric diagnosis of chronic kidney disease and their causal factors could slow the progression this disease in bipolar patients.

## Multimodal group intervention in first-episode psychosis: a randomized clinical trial of effectiveness

**E Leclerc, C Noto, Q Cordeiro, E Brietzke**

*Psychiatry and Medical Psychology, UNIFESP, Sao Paulo, Brazil*

**Aims:** Evaluate the effectiveness of MIRA (Multimodal Intervention to Raise the Adherence), a brief group intervention for First Episode Psychosis patients, designed to delay the next episode by targeting factors associated to nonadherence.

**Methods:** The design is a randomized controlled trial of parallel groups. 90 stabilized FEP patients between 16 and 35 years old will be randomly assigned to the MIRA intervention group or the control group (treatment as usual). The intervention will consist of five weekly group sessions of 10 patients and include psychoeducation, one session with relatives, progressive muscle relaxation, and other techniques from motivational interviewing and cognitive-behavioral therapy. Other modalities of the intervention are text messages (reminders of the sessions), emails (including videos and links) and a closed forum on Internet. Outcome assessments will be performed on a 1-year period (at 3, 6 and 12 months). The main outcome is the time until relapse (hospitalization or evaluation by the psychiatrist). Other outcomes include: adherence to treatment (in %, self-rated and by psychiatrist), Positive And Negative Symptoms Scale (PANSS), Young Mania Rating Scale (YMRS), the Clinical Global Impression (CGI), and the Global Assessment of Functioning (GAF). The two groups will be compared on all outcomes at different time points. A survival analysis will be performed to evaluate the time to relapse. Approval from the Ethics Committee of UNIFESP has been requested and is awaited in the next weeks. Each patients will have to sign a written informed consent to be included in the study. As soon as approval is released the study will start, and results are expected for 2016 or beginning of 2017.

## Impulsivity predicts the onset of (hypo)manic episodes in individuals with bipolar spectrum disorder

**TH Ng<sup>a</sup>, JP Stange<sup>a</sup>, CL Black<sup>a</sup>, RB Weiss<sup>b</sup>, LY Abramson<sup>c</sup>, LB Alloy<sup>a</sup>**

<sup>a</sup>*Department of Psychology, Temple University, Philadelphia, USA,*

<sup>b</sup>*Department of Psychiatry, McLean Hospital/Harvard Medical School, Belmont, USA,* <sup>c</sup>*Department of Psychology, University of Wisconsin-Madison, Madison, USA*

**Aims:** A growing body of studies suggests that people with bipolar disorder show higher impulsivity than healthy controls. This study provides the first examination of whether impulsivity prospectively predicts time to onset of (hypo)manic and major depressive episodes in a sample of people with bipolar spectrum disorders.

**Methods:** One hundred and twenty-one young adults diagnosed with cyclothymia or bipolar II disorder completed measures of depressive and manic symptoms, family history of mood disorder, and impulsivity at Time 1 and were followed prospectively with



semi-structured diagnostic interview assessments of mood episodes and treatment seeking every four months for an average of 38 months.

**Results:** Survival analyses indicated that impulsivity significantly predicted a shorter time to onset of episodes of (hypo)mania but not major depression, after controlling for baseline depressive and manic symptoms, family history of mood disorder, and treatment seeking.

**Conclusions:** Impulsivity provides vulnerability to onsets of (hypo) manic episodes.

### Mood episodes triggered by sleep loss: heterogeneity within bipolar disorder

KJ Swaden Lewis<sup>a</sup>, A Di Florio<sup>a</sup>, L Forty<sup>a</sup>, K Gordon-Smith<sup>b</sup>, L Jones<sup>b</sup>, N Craddock<sup>a</sup>, I Jones<sup>a</sup>

<sup>a</sup>Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, United Kingdom, <sup>b</sup>Department of Psychiatry, University of Birmingham, Birmingham, United Kingdom

**Aims:** The role of sleep disturbance in bipolar disorder has become a topic of interest amongst researchers. However, despite sleep disturbance being a frequently reported antecedent of manic and depressive episodes, prospective studies yield inconsistent results. These inconsistent findings may be due to individual differences in bipolar diagnosis. We therefore aimed to use a large clinical sample to examine whether sleep loss triggering mood episodes differed among individuals diagnosed with bipolar I (BD-I) or bipolar II (BD-II) disorder.

**Methods:** 2571 participants in the bipolar disorder research network (BDRN) study (64.7% BD-I, 31.7% BD-II) participated in a retrospective interview that included questions on triggers of high and low mood. DSM-IV diagnosis of BD-I or BD-II was derived from case notes and interview data. We compared rates of sleep loss as a trigger of mood episodes according to gender, diagnosis, and episode polarity.

**Results:** Twenty-two per cent of individuals reported sleep loss as a trigger of high mood, which was more commonly reported by females than males (OR = 1.42, 95% CI = 1.15–1.76). In addition, when controlling for gender, individuals with BD-I were 2.89 times more likely to report episodes of high mood triggered by sleep loss (95% CI, 2.72–3.69) compared to those with BD-II. Low mood triggered by sleep loss was reported by 14% of the sample and also more commonly reported amongst females (OR = 1.38, 95% CI = 1.05–1.80). In contrast to the findings for manic episodes, however, individuals with BD-II were more likely than those with BD-I to report episodes of low mood triggered by sleep loss (OR = 1.35, 95% CI = 1.06–1.72).

**Conclusions:** Sleep loss was more commonly reported as a trigger of high mood than low mood, and as a trigger of high mood in BD-I and low mood in BD-II. In addition, across the bipolar spectrum, women appear more susceptible to mood episodes triggered by sleep loss than men. These findings should be incorporated into future research examining the relationship between sleep and mood in bipolar disorder.

### Factors associated with greater burden of caregivers of elderly bipolar patients: the importance of functionality and neuropsychiatric symptoms

GD Santos, JG Almeida, I Aprahamian, OV Forlenza, B Lafer, P Nunes  
Psychiatry, Institute of Psychiatry University of Sao Paulo Medical School, Sao Paulo, Brazil

**Aims:** There are few studies of caregivers of patients with bipolar disorder (BD), especially elders. With increasing age there are often

health changes and a decrease in autonomy due to various reasons. This increases the need of care, often given by a relative. The aim of this study is to explore which factors bring higher burden to caregivers of elderly BD outpatients.

**Methods:** Patients were 60 years of age or more and attained DSM-IV criteria for BD. They were evaluated with the Geriatric Depression Scale (GDS), Beck Anxiety Inventory (BAI), CDR, Neuropsychiatric Inventory (NPI), Functional Assessment Short Test (FAST), Cumulative Illness Rating Scale (CIRS), WHOQOL-BREF. Years since BD diagnosis and number of psychiatric admissions were also measured. The caregiver that spent the greater time with each patient was selected for the study, and was evaluated with the Zarit Burden Interview (ZBI), GDS, Beck-Anxiety, WHOQOL-BREF, CIRS. The number of tasks that the caregiver does for the patient and hours of caring/week were also measured.

**Results:** 36 BD patients (70.3 ± 6.2 years) and their caregivers (51.1 ± 14.8 years, 69.4% women) were assessed. ZBI was associated with patients' severity of dementia (CDR) ( $p = 0.032$ ), and directly correlated with NPI ( $r = 0.508$ ,  $p = 0.002$ ) and functional impairment (FAST) ( $r = 0.466$ ,  $p = 0.004$ ) but not with GDS or BAI. ZBI was directly correlated with caregiver's GDS ( $r = 0.576$ ,  $p < 0.001$ ) and BAI ( $r = 0.360$ ,  $p = 0.031$ ), caregiver's CIRS ( $r = 0.387$ ,  $p = 0.020$ ), number tasks he/she does ( $r = 0.480$ ,  $p = 0.003$ ) and inversely correlated with caregivers' WHOQOL-BREF ( $r = -0.406$ ,  $p = 0.014$ ).

**Conclusions:** In this group of elderly BD patients, symptoms frequently seen in dementia (as measured by CDR, NPI) were more associated with caregiver burden than depressive, manic or anxiety symptoms often used as measures of treatment goals for adults. Attention should be given to potential treatable causes of burden, as could be caregiver depression, anxiety or medical comorbidities (CIRS). Moreover, looking for support in services or social relationships in order to decrease in the number of tasks the caregiver does for patient could decrease burden and improve caregiver's quality of life. Information on caregiver burden can help in developing services and establishing intervention programs for orientation and support.

### MAC-PMSS: preliminary analyses of a new DSM-5-based tool to monitor concurrent mood and premenstrual symptoms

OR Allega<sup>a</sup>, D Dhaliwal<sup>b</sup>, K Gusenbauer<sup>c</sup>, L Minuzzi<sup>d</sup>, BN Frey<sup>d</sup>

<sup>a</sup>McMaster Neuroscience Graduate Program, McMaster University, Hamilton, Canada, <sup>b</sup>Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, Hamilton, Canada, <sup>c</sup>Faculty of Health Sciences, McMaster University, Hamilton, Canada, <sup>d</sup>Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, Canada

**Background:** Females with bipolar and major depressive disorder are more likely to experience premenstrual exacerbation of their mood symptoms. Prospective daily rating of symptoms for at least two consecutive cycles is a requirement for the diagnosis of premenstrual dysphoric disorder. The objective of the current study is to validate a tool developed to concurrently monitor both mood and premenstrual symptoms in females with mood disorders.

**Methods:** To date, ten females with bipolar disorder or major depressive disorder, age 16 or older with regular menstrual cycles, have completed two consecutive months of prospective charting with the McMaster Premenstrual and Mood Symptom Scale (MAC-PMSS) and the Daily Record of Severity of Problems (DRSP). Inter-scale reliability between MAC-PMSS and DRSP was assessed with Cohen's kappa statistic. Reliability of MAC-PMSS depressive scores were correlated against HAMD, and manic scores against YMRS.

**Results:** Late-luteal and mid-follicular phase summary scores on MAC-PMSS provided substantial agreement with DRSP summary scores (late-luteal “depressed mood, hopelessness, self-depreciating thoughts”:  $\kappa = 0.600$  ( $p < 0.001$ ), 95% CI (0.242, 0.958), late-luteal “loss of interest in usual activities”:  $\kappa = 0.851$  ( $p < 0.001$ ), 95% CI (0.577, 1.125), mid-follicular “emotional lability”:  $\kappa = 0.697$  ( $p < 0.001$ ), 95% CI (0.323, 1.071). HAMD scores were positively correlated with the depressive segment of the mood chart ( $r = 0.698$ ,  $p = 0.025$ ). YMRS scores positively correlated with the mania segment of the mood chart ( $r = 0.648$ ,  $p = 0.043$ ).

**Conclusions:** These preliminary results support the MAC-PMSS as a reliable tool for females to simultaneously measure both mood and premenstrual symptoms. This new tool will enable clinicians to proper diagnose and monitor treatment response of premenstrual symptoms in women with mood disorders.

### Sex differences in symptoms and function in age groups of patients with bipolar disorder and schizophrenia

G Morken<sup>a</sup>, HK Schoeyen<sup>b</sup>

<sup>a</sup>Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway, <sup>b</sup>Department of Psychiatry, Stavanger University Hospital, Stavanger, Norway

**Background:** The frequencies of schizophrenia and bipolar disorders in the two sexes seem to be similar, although men are observed to have an earlier age of onset in schizophrenia. Less is known of sex differences between the illnesses in use of hospital services in different age groups. In Norway, in-patient treatment for psychiatric illnesses is publically funded and catchment area based. Patients receive in-patient treatment either in hospitals where most of the wards have closed doors or in community health centers where the wards have open doors.

**Aims:** To describe age and sex differences between bipolar disorder, schizophrenia and the rest of the psychiatric admissions to Norwegian hospitals and community health centers.

**Methods:** In the Norwegian Patient Register, all in-patient admissions for the 5 million inhabitants are registered with day of admission, length of stay and diagnosis. Each individual has a personal identification number. Both number of admissions and number of days as inpatients will be distributed on diagnosis and analyzed for each year of birth. In cross sectional descriptions of patients at Stavanger University Hospital and St Olav University Hospital in Trondheim, in-depth descriptions of patients at the hospitals and community health centers are collected.

**Results:** Preliminary results from the two hospitals indicate that both in number of admissions and days as inpatients, patients with schizophrenia are more often men and younger than patients with bipolar disorder. In the bipolar group there is a female dominance increasing with age. Results from the national registry will be presented at the meeting.

**Conclusion:** Analyses from the Norwegian Patient Register represent use of psychiatric health services for 5 million inhabitants. Both admissions and days as inpatients indirectly reflect relapses and days as inpatients reflect long-lasting periods or chronic low function. By comparing hospital departments with closed doors and community health centers where the wards have open doors, it is possible to classify the level of care needed for patient groups divided on diagnosis and year of birth. Results from the two university hospitals will add detailed information in the two diagnostic groups.

### The effect of resilience on quality of life in patients with bipolar disorder: a controlled study

B Cha<sup>a</sup>, D Lee<sup>b</sup>, JW Choi<sup>b</sup>, CS Park<sup>a</sup>, BJ Kim<sup>a</sup>, CS Lee<sup>a</sup>, SJ Lee<sup>a</sup>, J Jang<sup>b</sup>, JH Wang<sup>b</sup>

<sup>a</sup>Psychiatry, Gyeongsang National University College of Medicine, Jinju, Korea, <sup>b</sup>Psychiatry, Gyeongsang National University Hospital, Jinju, Korea

**Objectives:** Few studies have examined the effect of resilience on quality of life (QOL) in patients with bipolar disorder (BD). This study aimed to investigate the association between resilience and QoL in patients with BD and matched healthy controls (HC).

**Methods:** Sixty-eight euthymic patients with BD and 68 age, sex and length of education-matched HC were recruited. Through semi-structured interviews, the sociodemographic and clinical variables of the two groups were investigated. All participants completed the Connor–Davidson Resilience Scale (CD-RISC), the World Health Organization QOL-Brief Form (WHOQOL-BREF), and the Barratt Impulsiveness Scale. Multiple regression analysis was conducted to investigate the correlation between QOL and resilience.

**Results:** The BD group showed lower QOL scores in all domains compared to the HC group. In both groups, CD-RISC scores showed a significantly positive correlation with WHOQOL-BREF total and subdomains scores. The effect sizes of a correlation analysis on the WHOQOL-BREF total, physical domain, and environmental domain scores each against CD-RISC scores of the BD group were twice as big as those of the control group. As a result of multiple regression analysis, in the BD group, CD-RISC scores independently showed correlations with WHOQOL-BREF total scores and all subdomains.

**Conclusions:** The results suggest that resilience in patients with BD has positive association with QoL and that the extent of correlation is more marked than that of the control group. Our study indicates a need for various strategies to reinforce resilience to improve the low QOL of patients with BD.

### Age at onset in first episode bipolar disorder: effect of recall bias and cultural influences

V De Luca

Psychiatry, CAMH, Toronto, Canada

**Background:** Many studies have used the admixture analysis to separate age-at-onset (AAO) subgroups in bipolar disorder, but none of them examined first episode patients.

**Objective:** The purpose of this study was to investigate the influence of clinical variables on AAO in first episode bipolar patients.

**Methods:** The admixture analysis was applied to identify the model best fitting the observed AAO distribution of a sample of 194 patients with DSM-IV diagnosis of bipolar disorder and the Finite Mixture Model was applied to assess the effect of eleven clinical covariates on AAO.

**Results:** Using the BIC method, the model that was best fitting the observed distribution of AAO was a mixture of three normal distributions. We identified three AAO groups: early age-at-onset (EAO) ( $\mu = 17.9.0$ ,  $\sigma = 2.79$ ), intermediate-age-at-onset (IAO) ( $\mu = 28.2$ ,  $\sigma = 3.84$ ), and late-age-at-onset (LAO) ( $\mu = 47.4$ ,  $\sigma = 7.75$ ), comprising 67%, 24%, and 9% of the sample respectively. All eleven clinical covariates showed statistically significant association with the AAO in the univariate finite mixture models.

**Conclusions:** This study confirms that bipolar disorder can be classified into three groups based on AAO distribution. The data reported in our paper provide more insight into the use of clinical factors in modeling clinical subgroups of AAO.

## The relation between impulsivity and suicide intent in bipolar patients: the role of childhood trauma

G Yıldırım<sup>a</sup>, S Kesebir<sup>b</sup>

<sup>a</sup>Psychiatry, Erenkoy Mental and Neurological Disease Training and Research Hospital, Istanbul, Turkey, <sup>b</sup>Psychiatry NPIstanbul Hospital, Üsküdar University, Istanbul, Turkey

**Objective:** The aim of this study was to investigate the relation between suicidal intent and impulsivity in bipolar patients with or without childhood trauma (CT), and to determine whether the relation between suicidal intention and impulsivity in patients with CT varies with the subtype of CT and its age range.

**Method:** Patients diagnosed with BD according to DSM-IV and who gave informed consent were consecutively evaluated. Patients evaluated were required to be in remission period for at least eight weeks. Diagnostic interview for 150 patients meeting this criteria was made with SCID-I, information on the disease was collected with SKIP-TURK (Mood Disorders diagnosis and follow up form). Subsequently, each case was administered SIS (Suicidal Intent Scale) and BIS (Barrat Impulsivity Scale). The presence and subtype and age range of CT was investigated with CTQ (Childhood Trauma Questionnaire) and TEC (Traumatic Experiences Checklist).

**Results:** In CT+ patients, SIS and BIS scores were found to be higher than those in CT- patients. In linear regression analysis, while unfavorable effect of all CT subtypes was shown on SIS score, physical, sexual and emotional abuse were shown to have an adverse effect on BIS scores. A relation between SIS and BIS scores was found solely in CT- patients. When subtypes of CT trauma were evaluated separately, in patients with emotional neglect, a strong inverse relation was found between SIS and BIS scores. As to patients with an history of sexual abuse, direct relation between BIS and SIS scores was demonstrated in them. As the age range when CT occurred becomes later, the relation between suicidal intent and impulsivity becomes less marked.

**Conclusion:** In patients diagnosed with BD, the relation between suicid intent and impulsivity is influenced by presence of CT, subtype of CT and age range of CT.

## Differential prevalence and demographic and clinical correlates of antipsychotic use in bipolar I disorder versus bipolar II disorder

DY Park<sup>a</sup>, KC Goffin<sup>b</sup>, L Yuen<sup>b</sup>, JN Holtzman<sup>b</sup>, F Hooshmand<sup>b</sup>, S Miller<sup>b</sup>, PW Wang<sup>b</sup>, TA Ketter<sup>b</sup>

<sup>a</sup>Psychiatry, Seoul National Hospital, Seoul, Korea, <sup>b</sup>Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, USA

**Aims:** To assess prevalence and demographic and clinical correlates of antipsychotic (AP) use in bipolar disorder (BD) patients with bipolar I disorder (BDI) compared to bipolar II disorder (BDII).

**Method:** BD patients referred to Stanford Bipolar Disorder Clinic during 2000–2011 were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation. Prevalence and demographic and clinical correlates of current AP use were assessed and compared for BDI versus BDII.

**Results:** Among 503 BD outpatients (mean  $\pm$  SD age  $35.6 \pm 13.1$  years; 58.3% female; 48.3% BDI, 51.7% BDII; with illness duration  $17.7 \pm 13.1$  years; Clinical Global Impression for Bipolar Disorder-Overall Severity score  $3.9 \pm 1.5$ , and taking  $2.6 \pm 1.7$  prescription psychotropics), rates of AP use in BDI compared to BDII were almost twice as high (53.1% versus 24.6%,  $p < 0.0001$ ). 0 patients taking (N = 129) compared to not taking (N = 114) APs, less often were married (27.1% versus 42.1%,

$p = 0.018$ ), employed full time (20.2% versus 36.0%,  $p = 0.001$ ), or had a college degree (78.3% versus 87.7%,  $p = 0.046$ ); more often had lifetime comorbid substance use disorder (49.6% versus 36.0%,  $p = 0.046$ ), history of psychosis (70.5% versus 57.0%,  $p = 0.036$ ), and lifetime psychiatric hospitalization (78.3% versus 56.1%,  $p < 0.0001$ ); and were more often taking complex pharmacotherapy ( $\geq 4$  psychotropics, 37.2% versus 24.1%,  $p < 0.05$ ). In contrast, these demographic and clinical correlates of AP use were not statistically significant among patients with BDII. However, patients taking compared to not taking APs were taking a greater number of current psychotropics in both the BDI ( $3.0 \pm 1.5$  versus  $2.5 \pm 1.6$ ,  $p < 0.01$ ) and BDII ( $3.2 \pm 1.6$  versus  $2.3 \pm 1.9$ ,  $p = 0.003$ ) subgroups.

**Conclusion:** AP use in patients with BDI but not BDII is associated with higher rates of unfavorable illness characteristics (lifetime comorbid substance use disorder, history of psychosis, lifetime psychiatric hospitalization, and complex pharmacotherapy). However, demographic factors could contribute importantly to these clinical correlates of AP use in BPI. In contrast, among patients with BDII, these demographic and most clinical characteristics were not related to AP use.

## Childhood trauma predicts neuroticism in bipolar disorder

B Pester<sup>a</sup>, K Angers<sup>a</sup>, A Hayek<sup>a</sup>, K Hinrichs<sup>a</sup>, K Ryan<sup>a</sup>, M Kamali<sup>b</sup>, M McInnis<sup>b</sup>, D Marshall<sup>a</sup>

<sup>a</sup>Psychiatry Neuropsychology, University of Michigan, Ann Arbor, USA, <sup>b</sup>Psychiatry, University of Michigan, Ann Arbor, USA

**Aims:** Individuals with psychiatric disorders have shown similar personality trait profiles, with neuroticism being particularly high. There is a large body of literature examining the genetic and environmental underpinnings of personality traits, which may or may not be illness specific. Childhood trauma may be a potential environmental factor that has neurodevelopmental implications and adversely impacts personality and severity of psychiatric disorders later in life. The present study aimed to elucidate personality traits specific to those with bipolar disorder (BD) and healthy controls (HC) with or without a history of childhood trauma.

**Methods:** Groups were selected from the Prechter Longitudinal Study of BD at the University of Michigan and matched on age, education, gender, and IQ. Two hundred twenty-nine individuals with BD and 89 HCs completed a diagnostic interview, the Childhood Trauma Questionnaire (CTQ), and the NEO Personality Inventory. Four comparison groups were created using a 1.0 standard deviation cut-off of the mean of the total CTQ score (e.g., BD high trauma, BD normative range, HC high trauma, HC normative range).

**Results:** After controlling for depression, a significant group effect was found for neuroticism ( $p < 0.001$ ), with higher neuroticism scores in the BD groups. Within the BD sample, those with high trauma had more chronic mood symptoms, a greater number of years ill, a younger age of BD onset, and more manic episodes compared to the normative group ( $p$ 's  $< 0.05$ ). The BD high trauma group also had significantly higher neuroticism scores compared to the BD normative group ( $p = 0.003$ ). When examining the entire BD sample, hierarchical linear regressions revealed that childhood trauma significantly predicted neuroticism beyond relevant clinical correlates ( $p < 0.001$ ).

**Conclusions:** In our sample, those with BD scored higher in neuroticism compared to those without psychiatric illness. Among those with BD, individuals with a history of trauma displayed a more severe course of BD illness and higher neuroticism scores compared to those with no history of trauma, suggesting that early trauma may adversely impact the severity of illness and development of personality traits in bipolar individuals. Future research is

necessary to understand the mechanism through which trauma and personality are linked in BD.

### Characteristics of and possible contributing factors to chronic insomnia in patients with bipolar disorder

CB Schaffer<sup>a</sup>, LC Schaffer<sup>b</sup>, TE Nordahl<sup>a</sup>, NM Stark<sup>b</sup>

<sup>a</sup>Department of Psychiatry and Behavioral Sciences, University of California Davis School of Medicine, Sacramento, USA,

<sup>b</sup>Psychiatry, Sutter Community Hospitals, Sacramento, USA

**Aims:** Chronic insomnia is prevalent and causes considerable subjective distress, metabolic conditions, cognitive impairment and daytime dysfunction. The control of chronic insomnia in Bipolar Disorder (BD) patients is important since it can activate manic symptoms and increase suicide risk. In this prospective study, several variables will be compared to identify contributing psychosocial, clinical and biological factors to and characteristics of chronic insomnia in BD patients.

**Methods:** Forty-four adult outpatients with any DSM-IV BD diagnosis participated in the study. Insomniacs and noninsomniacs were paired by gender, age and participation date. Chronic insomnia was defined by research and clinical criteria. Demographic data were obtained. Sleep and mood scales were utilized. Psychiatric and medical histories were collected. Biological markers measured included C-reactive protein (CRP), selected cytokines and salivary cortisol levels.

**Results:** Twenty-four females and twenty males participated. Participants' average age was 50. Both groups contained a similar distribution of BD subtypes and BD daytime mood symptoms. The insomniacs' current episode of insomnia averaged 269.96 months (SD = 183.80). Sixteen insomniacs and eight noninsomniacs reported a family history of chronic insomnia. The Sleep Hygiene Index revealed no differences between the two groups. Insomniacs' average total sleep (6.95 hours) was significantly less than the noninsomniacs' (7.56 hours). Noninsomniacs were more likely taking antidepressants (11 vs. 3). The two groups had similar numbers of signs and symptoms of metabolic syndrome. Perceived stressful life events did not differ between groups. The overall severity score on the CGI-BP did not differ significantly between groups. Of the twelve female pairs, nine insomniacs had higher CRPs. There was an unexpected trend for elevated Cortisol Awakening Response (CAR) in the noninsomniacs ( $p = 0.1$ ).

**Conclusions:** The insomniacs slept less on average, despite taking sedative hypnotics. The insomniacs' average current episode of insomnia was remarkably long in duration (22.50 years). Antidepressants were not a contributing factor to chronic insomnia, nor were poor sleep hygiene habits. Type and severity of mood symptoms and metabolic findings were not associated with sleep patterns. Insomniacs had a greater family history of chronic insomnia. The results provide motivation for future investigation of CRP and cortisol levels in larger data sets.

### Efficiency of defense mechanisms activism type in bipolar disorder (case report)

S Trifu<sup>a</sup>, D Brailanu<sup>b</sup>, S Alexandra<sup>b</sup>, BM Gulei Gradinaru<sup>b</sup>, A Gutt<sup>b</sup>

<sup>a</sup>Psychiatry, UMF Carol Davila, Bucharest, Romania, <sup>b</sup>Psychology, Sapunari Psychiatric Hospital, Calarasi, Romania

**Motivation of topic:** It is well known that the usual period of bipolar disorder debut is between the third and fourth decade of age. Often, when the first episode is a manic episode, it occurs over a certain personality structure, using mechanism from *activism field* and psychomotor agitation represents only a failure in managing these defenses.

**Objective:** We wish to present a case report of a 37 years old female patient, without pathological personal antecedents or known psychiatric family history, which presents a severe manic episode with hetero-aggressiveness and behavioral disruption, sudden onset (in maximum two days), which necessitate non voluntarily emergency psychiatric hospitalization.

**Hypothesis:** We think that a personality structure that functioned marked, since adolescence, with hypo-manic mechanism, activism type and hyper involvement in social functioning, also presents a potential fragility/vulnerability to decompensate under stress, in time there are no sufficient amount of compulsion energy to cope with external triggers.

**Results:** Cerebral neuroimaging investigation (CT, EEG) and also psychiatric evaluation (hetero anamnesis, map of life, psychological examination) come in support of hypothesis that the patient have a powerful Ego and a dominant manner of controlling and works on denial mechanisms, multiple reactionary forms and affects isolation, which, though effective for a long period of time, univocally and excess used, become insufficient to cope with any psycho-traumatizing situation.

**Conclusions:** Regarding psychodynamic functioning of this patient, we identify a vicious circle, in which excess of using the known old defense mechanisms (in absence of superior or situational adapted ones), this leads in extreme to psychopathological decompensation and expressed in a manic episode with a severe narrowing of the field of consciousness.

### Association study of ApoE gene polymorphisms and neurodevelopmental markers in BPAD

A Waghmare<sup>a</sup>, A Antony<sup>b</sup>, YCJ Reddy<sup>c</sup>, JP John<sup>c</sup>, S Jain<sup>c</sup>

<sup>a</sup>Department of Psychiatry, Smt. Kashibai Navale Medical College, Pune, India, <sup>b</sup>Department of Psychiatry, Sree Gokulam Medical College, Trivandrum, India, <sup>c</sup>Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India

**Introduction:** Endophenotypes are considered as a bridge between phenotype and genotype. These are helpful in understanding neurobiological underpinnings of a disorder. Aim: To study the association between ApoE gene polymorphisms and neurodevelopmental markers (neurological soft signs – NSS and minor physical anomalies – MPAs) for bipolar affective disorder (BPAD). Hypothesis: NSS and MPAs would be higher in bipolar patients than controls and presence of ApoE  $\epsilon 4$  allele would be associated with higher NSS and MPAs. It was also hypothesized that the frequency of ApoE  $\epsilon 4$  allele would be higher in patients than in controls.

**Methods:** Ethical approval was obtained from institute's ethics committee. After getting written informed consent 60 euthymic BPAD I patients and 42 healthy controls were assessed by applying neurological evaluation scale (NES) and modified Waldrop scale (MWS). Genetic analysis for ApoE genotype was done.

**Results:** There was no difference in groups with and without ApoE  $\epsilon 4$  allele in terms of total NSS ( $p = 0.27$ ) or MPA ( $p = 0.85$ ) score. Total NSS ( $p < 0.001$ , Cohen's  $d = 1.32$ ) and MPA ( $p < 0.001$ ,  $d = 0.83$ ) scores were significantly higher in BPAD patients than in controls. MPAs around ears ( $p < 0.001$ ,  $d = 1.01$ ) and mouth ( $p = 0.001$ ,  $d = 0.77$ ) were higher in patients than controls. High arched palate was the commonest MPA found. NSS subgroup scores were also higher in BPAD patients than in controls except in sensory integration and parietal lobe NSS scores.

**Conclusions:** There was no association between ApoE  $\epsilon 4$  allele and severity of MPA-NSS. This may be due to smaller sample size or probably ApoE may not be involved in the pathways leading to NSS or MPAs in BPAD. The higher NSS scores in BPAD I patients demonstrate neurological dysfunction in BPAD. The high scores even in euthymic phase of disorder demonstrate the per-

siveness of this neurological dysfunction. The higher MPAs in BPAD patients point towards neuro-developmental basis of the disorder.

## Harnessing the power of CBPR approaches in bipolar disorders

EMS Johnson<sup>a,b</sup>

<sup>a</sup>Psychology, University of Berkeley, California, USA, <sup>b</sup>Psychiatry, University of BC, Vancouver, Canada

Across various domains of health care and policy, community-based participatory research (CBPR) has become increasingly popular and influential. CBPR is defined by an emphasis on including stakeholders, including patients, family members, close others, and clinicians, in every stage of planning and executing research. For those with lived experience, CBPR can support empowerment and recovery, and address internalized and social stigma. By engaging community members in the research process, CBPR challenges the idea that research leadership must be limited to those with a traditional academic background; by acknowledging lived experience as valid expertise, CBPR may also diminish power imbalances and hierarchical structures. Further, peer researchers often are required to develop new skills, and this process may enhance self-efficacy, positive perceptions of identity, and occupational or social opportunities. For researchers, CBPR can shape more pragmatic research questions, enrich the understanding of the research team, strengthen grant proposals, and enhance philanthropy. CBPR also benefits policy, as it sets the stage for a faster knowledge to translation process. We provide examples of several exemplary programs, and we suggest a number of pathways to stronger engagement for those with lived experience, including the development of community advisory groups, the use of community engagement events, the involvement of experts by experience as 'peer-researchers' and effectively harnessing social media. We will also touch on some of the limitations and challenges of CBPR, and methods for mitigating these.

## Thyroid abnormalities in lithium treated bipolar patients: a crosssectional study with healthy controls

F Akdeniz<sup>a</sup>, O Kuman<sup>b</sup>, S Ozbek<sup>c</sup>

<sup>a</sup>Psychiatry, Ege University School of Medicine, Izmir, Turkey,

<sup>b</sup>Psychiatry, Katip Celebi University, Izmir, Turkey, <sup>c</sup>Radiology, Ege University School of Medicine, Izmir, Turkey

Lithium's effect on thyroid has been known for a long time; however data of detailed ultrasonography of thyroid gland are lacking. This study aimed to investigate thyroid morphology, hormone levels and antibodies in lithium treated patients. This is a cross-sectional study of 84 lithium-treated patients and 65 healthy controls. 30 controls and all of the patients referred detailed ultrasonography. The median level for TSH was significantly higher in lithium group (2.11  $\mu$ IU/l vs 1.66  $\mu$ IU/l). In lithium group 14 (16.7%) hypothyroidism, seven (8.3%) subclinical hypothyroidism, one (1.2%) subclinical hyperthyroidism; in control group seven (10.8%) hypothyroidism and two (3.1%) subclinical hyperthyroidism were defined. Thus thyroid dysfunction was significantly more prevalent in lithium group ( $p = 0.049$ ). There was no statistical significant difference for anti-Tg positivity and autoimmunity presence between groups, but Anti TPO positivity was significantly more prevalent in the control group ( $p = 0.040$ ). When we compared the lithium treated patients who have thyroid dysfunction with the other lithium treated patients (without thyroid dysfunction); there were no significant difference for familial thyroid disease, current age, serum lithium level, duration of lithium treatment, the age onset for lithium treatment ( $p = 0.115$ ), autoim-

munity presence and smoking. Females were significantly more prevalent in thyroid dysfunction group (77.3% vs. 45.2%,  $p = 0.009$ ) among lithium treated group; whereas there was no gender difference in control group ( $p = 0.500$ ). Goiter, parenchymal abnormality and ultrasonographic thyroid pathology were significantly more prevalent in lithium group. As a summary goiter, parenchymal abnormality, ultrasonographically defined thyroid abnormality, thyroid dysfunction and thyroid disorder were found to be more prevalent in lithium group. To prevent a bias that can be related to the participants who had already known thyroid disease before the study, the statistical analysis was repeated after exclusion of this group. In this case, again goiter (57.4% vs. 6.7%,  $p = 0.0001$ ), ultrasonographic pathology (83.8% vs. 46.7%,  $p = 0.0001$ ) and thyroid disorder (86.8% vs. 44.1%,  $p = 0.0001$ ) were more prevalent in the lithium group. In conclusion, our study is the first study using such a detailed sonographic scan. The prevalence rates of 47.6% for goiter and 83.3% for an ultrasonographic pathology emphasize the need for ultrasonographic examination in lithium treated patients.

## Roles of metabotropic glutamate receptors (mGluRs) in bipolar disorder: a systematic review

CJ Blacker, CP Lewis, MA Frye, M Veldic

Department of Psychiatry and Psychology, Mayo Clinic Depression Center, Rochester, USA

**Objective:** Describe the current understanding of the function of metabotropic glutamate receptors (mGluRs) in the pathophysiology of bipolar disorder (BD).

**Background:** Existing research demonstrates the role of mGluRs in the etiology of many neuro-psychiatric disorders. BD is a mood disorder which may be associated with psychotic features, and hence, many investigations have included results with those from other affective or psychotic conditions. Extrapolation of the role of mGluRs in BD has been based on these pooled results. This review sought literature describing mGluR activity in discrete BD populations.

**Methods:** A comprehensive literature search of mGluRs in studies of bipolar disorder was performed. Full-text literature published between January 1992 and January 2015 was searched via PubMed, Web of Science, and Scopus, including pre-publication literature available on 13 January 2015. Full-text screening, data abstraction and quality appraisal were conducted in duplicate. Literature was chosen using strict inclusion and exclusion criteria. A subset of literature describing function, genetics, and pharmacology of mGluRs in BD was collated.

**Results:** The initial comprehensive literature search for mGluRs retrieved 7,872 articles. 32 articles were selected for keywords relating to BD, and 16 articles met inclusion criteria. Three additional articles were found via citations. Studies demonstrated mGluR3 gene (*GRM3*) upregulation in dorsolateral prefrontal and anterior cingulate cortices of bipolar patients. A specific *GRM3* SNP was associated with a greater likelihood of psychosis. Multiple intracellular proteins were described as interacting with mGluRs and each other. The mRNA binding protein Fragile X Mental Retardation Protein (FMRP) is associated with altered mGluR1/5 activity in BD populations. The scaffolding proteins Homer and Shank interact with each other and mGluRs. The expression of these scaffolding proteins is downregulated by medications used in BD, including the mood stabilizers lithium and valproate, and the antipsychotic quetiapine, suggesting a possible mechanism of action in the treatment of BD. Lithium additionally has effects on glutamate-mediated intracellular calcium response and decreases mGluR5 expression. No literature was found on epigenetic regulation of mGluRs in BD.

**Conclusions:** Literature describing mGluRs in BD is limited. *GRM* polymorphisms, epigenetic regulation, intracellular proteins, and pharmacologic mechanisms are targets for future research.

### First bipolar episodes and functionality. Relation with depressive symptoms and inflammation

A Gonzalez-Pinto<sup>a,b,c</sup>, M Martinez<sup>a,b,d</sup>, A Garcia-Alcena<sup>a</sup>, C Bermudez<sup>a,b</sup>, P Lopez<sup>a,b,c</sup>

<sup>a</sup>University Hospital of Alava, Vitoria, Spain, <sup>b</sup>CIBERSAM, Instituto de Salud Carlos III, Spain, <sup>c</sup>University of the Basque Country, <sup>d</sup>National Distance Education University

It is important to make an early and effective intervention from the first bipolar episode in order to prevent the deleterious effects of the disease. The presence of depressive symptoms in the course of a manic episode and during the early stage of the disease could influence negatively the evolution and the prognosis of the patient. In addition, cognitive symptoms are associated also with lower functioning. At a biological level there are some biomarkers related with cognition and functioning, such as inflammatory parameters, oxidative stress data and myelin basic protein. Inflammation and oxidative stress are also related with functionality. In this presentation we will review some now therapeutical approaches to improve prognosis presenting results of our cohort of patients with a first episode of mania.

### 5-HTTLPR genotype associated with inattention in childhood of the subjects with bipolar disorder

E Joo<sup>a</sup>, K Lee<sup>a</sup>, S Kim<sup>b</sup>, Y Ahn<sup>c</sup>, Y Kim<sup>b</sup>

<sup>a</sup>Psychiatry, Eulji University, Seoul, Korea, <sup>b</sup>Psychiatry, Dongguk University, Goyang, Korea, <sup>c</sup>Psychiatry, Seoul National University, Seoul, Korea

A significant diagnostic overlap has been reported between childhood bipolar disorder and ADHD. It is also suggested that childhood ADHD feature is consistently associated with mood disorders. Common genetic factors for both ADHD feature and mood disorders would work on this association. For example, a strong candidate gene for ADHD, dopamine transporter gene has been reported to have association with mood instability in bipolar patients. 5-HTTLPR is a well-known polymorphic site of serotonin transporter gene consistently associated with mood disorders. In this study we tried to find possible genetic role of 5-HTTLPR in the childhood ADHD features. We included 232 patients with major depressive disorder, 103 patients with bipolar disorder, and 1297 normal controls. Childhood ADHD features were measured by WURS (Wender Utah Rating Scale). Our previous factor analysis found three factors: Impulsivity, Inattention, Mood instability. Among three factors, inattention factor is significantly associated with 5-HTTLPR genotype only in the group of patients with bipolar disorder ( $p = 0.038$ ). The association was more significant in the female subgroup of bipolar patients ( $p = 0.025$ ). Other factors did not show any association with 5-HTTLPR. No association between childhood ADHD feature and 5-HTTLPR genotype was found in the group of major depression and normal controls. This finding suggests that 5-HTTLPR genotype may play a role in the inattention of childhood in the subjects with bipolar disorder. Further studies on other genes are warranted in order to find common genetic factors for both ADHD features of childhood and mood disorders in adulthood. In the future study, sample size of bipolar patients should be increased and it would be more interesting if bipolar I disorder and bipolar II disorder analyzed separately.

### How childhood maltreatment is related to bipolarity and central serotonergic activity in patients with major depressive disorder: a cross-sectional pilot study

Y Park<sup>a</sup>, B Lee<sup>b</sup>

<sup>a</sup>Psychiatry, Ilsan Paik Hospital, Goyang, Korea, <sup>b</sup>Psychiatry, Gangnam Eulji Hospital, Seoul, Korea

**Background:** The aims of this study were to determine whether childhood maltreatment contributes to the occurrence of major depressive disorder (MDD) with bipolarity, and whether there is a relationship between central serotonergic activity, as assessed using loudness dependence of auditory evoked potentials (LDAEP), and childhood maltreatment.

**Methods:** Thirty-five MDD patients were stratified according to the presence or absence of childhood trauma into two subgroups, childhood trauma (CT) and no childhood trauma (NCT), using the Korean version of the Childhood Trauma Questionnaire (K-CTQ). The CT group was subjected to further analysis. Several psychometric ratings were also applied. In addition, auditory processing for the loudness dependence of auditory evoked potentials (LDAEP), which was used as a marker of serotonergic activity, was measured before beginning medication.

**Results:** There was a significant difference in total Korean Bipolar Spectrum Disorder Scale score between the CT and NCT groups ( $t = -2.14$ ,  $p = 0.04$ ). The total K-CTQ score was positively correlated with the total Beck Scale for Suicidal Ideation (BSS) score ( $r = 0.36$ ,  $p = 0.036$ ). In particular, emotional abuse was positively correlated with the total Barratt Impulsiveness Scale ( $r = 0.38$ ,  $p = 0.026$ ), BSS ( $r = 0.38$ ,  $p = 0.025$ ), and Hamilton Depression Rating Scale (HAMD) ( $r = 0.36$ ,  $p = 0.035$ ) scores. There was also a positive correlation between LDAEP and total Hypomania Personality Scale ( $r = 0.49$ ,  $p = 0.02$ ) and HAMD ( $r = 0.58$ ,  $p = 0.004$ ) scores within CT group.

**Limitations:** The small sample in the present study can limit the generalizability of the results.

**Conclusions:** The findings of this study support that there is a relationship between childhood maltreatment and bipolarity in patients with MDD.

### Steeper slope of age-related white matter changes in bipolar disorder: a diffusion tensor imaging study

S Dev<sup>a</sup>, BS McKenna<sup>b</sup>, AN Sutherland<sup>c</sup>, H Bartsch<sup>d</sup>, RJ Theilmann<sup>d</sup>, LT Eyler<sup>a</sup>

<sup>a</sup>Clinical Psychology, SDSU/UCSD Joint Doctoral Program, San Diego, USA, <sup>b</sup>Psychiatry, University of California, San Diego, USA, <sup>c</sup>Research, Veterans Medical Research Foundation, San Diego, USA, <sup>d</sup>Multi-Modal Imaging Laboratory, University of California, San Diego, USA, <sup>e</sup>Department of Psychiatry, University of California, San Diego, USA

**Aims:** Recent evidence has suggested the possibility of premature or more rapid aging in the domains of cognition and cardiovascular health in bipolar disorder (BD). While several diffusion tensor imaging (DTI) studies have demonstrated altered white matter (WM) microstructure in adult patients with BD, less is known about relationships between age and WM integrity within this population and whether these relationships differ from those without BD. Thus, we examined whether associations between age and measures of WM microstructure differ between euthymic BD and healthy comparison (HC) participants.

**Methods:** DTI data were collected from 40 euthymic BD (mean age: 45, range: 30–69) and 52 demographically-comparable HC (mean age: 48, range: 30–68) participants. Raw images were screened for artifacts and corrected for motion, image distortions,

and scaling differences. Fractional anisotropy (FA) was calculated using standard formulas, and whole brain FA maps were converted into standard Talairach space. A voxel-wise regression analysis with FA as the dependent variable was performed to test group, age, and group-by-age interaction terms. Regions of significant effects were identified as clusters of 7 contiguous voxels that were significant at a per voxel threshold of  $p = 0.05$ . Within identified regions of interactions that were significant at  $p = 0.01$ , groupwise age correlations were examined to further explore the nature of the result.

**Results:** Voxel-wise whole brain regression analysis revealed a significant group-by-age interaction in the frontal portion of the left uncinate fasciculus. Further analysis indicated a significantly negative correlation between age and FA ( $r = -0.42$ ;  $p = 0.01$ ) in the BD sample and a non-significant negative correlation ( $r = -0.23$ ;  $p = 0.11$ ) in the HC sample. There were no group differences in mean FA in this region.

**Conclusions:** Results indicate a steeper negative slope of apparent age-related loss of FA in the BD group in a tract important for emotionally relevant memories and decision-making, suggesting that WM microstructure may be more sensitive to the effects of age in BD than in those without the disorder. Future studies will examine whether clinical or demographic subgroups may be driving the steeper age-related slope in the BD group.

### Differences in resting state connectivity between follicular and luteal menstrual cycle phases in euthymic women with bipolar disorder

SK Syan<sup>a</sup>, L Minuzzi<sup>b</sup>, M Smith<sup>b</sup>, N Snelgrove<sup>b</sup>, OR Allega<sup>a</sup>, A Hall<sup>a</sup>, BN Frey<sup>b</sup>

<sup>a</sup>MiNDS Neuroscience Graduate Program, McMaster University, Hamilton, Canada, <sup>b</sup>Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, Canada

**Aims:** Previous studies investigating differences in resting state connectivity in healthy controls found conflicting results between the follicular and luteal menstrual phases. There is no study to date that examines resting state connectivity in women with bipolar disorder (BD) between menstrual phases. Further, women with BD display heightened sensitivity to the development of mood episodes in the premenstrual phase. Here we examine resting state functional connectivity in bipolar women at two points of the menstrual cycle as compared to healthy controls.

**Methods:** 19 right-handed bipolar women and 20 healthy controls, between 18–45 years of age (BD mean age =  $32.7 \pm 8.5$ , CTRL mean age =  $28.3 \pm 8.3$ ), not using any form of hormonal contraception were studied. Psychiatric diagnoses were assessed with the SCID-IV. All BD subjects were euthymic for at least two months. Resting state fMRI was measured using a 3T MRI at two points of the menstrual cycle: mid-follicular phase (day 5–10) and late luteal phase (within 5 days of anticipated menses). Menstrual cycle phase was confirmed with hormonal assay.

**Results:** In bipolar women only, the right premotor cortex displayed significant positively correlated activation with the right anterior cingulate cortex ( $p = 0.03$ ) and left dorsal frontal cortex ( $p = 0.03$ ) in the luteal phase. This pattern of activity was negatively correlated in the follicular phase. Results were corrected for multiple comparisons (FDR-corrected,  $p < 0.05$ ). No significant differences in resting state connectivity between menstrual phases were found among healthy controls.

**Conclusions:** These preliminary results suggest that resting state connectivity in the frontal cortex in euthymic bipolar women may be affected by changes associated with menstrual phases.

### Metabolites and volumes of the hippocampi in bipolar disorder

BCM Haarman<sup>a</sup>, RF Riemersma-Van der Lek<sup>a</sup>, H Burger<sup>b</sup>, R Renken<sup>c</sup>, AJ Sijbeijn-Kuiper<sup>c</sup>, JBC Marsman<sup>c</sup>, JC de Groot<sup>d</sup>, WA Nolen<sup>a</sup>

<sup>a</sup>UMCG Department of Psychiatry, University of Groningen, Groningen, Netherlands, <sup>b</sup>UMCG Department of General Practice, University of Groningen, Groningen, Netherlands, <sup>c</sup>Neuroimaging Center, University of Groningen, Groningen, Netherlands, <sup>d</sup>UMCG Department of Radiology, University of Groningen, Groningen, Netherlands

**Aims:** Bipolar disorder (BD) has been reported to be associated with alterations in the prefrontal and limbic brain regions and the connectivity between these areas. The hippocampi, part of the limbic system, are thought to play a role in the inhibition of stress responses and in emotion and behavior regulation, leading to contextually appropriate emotional responses. We aimed to investigate metabolite concentrations and volumes of the hippocampi in BD patients compared to healthy controls (HC). Furthermore, we investigated the relation between these properties and illness characteristics, such as duration of illness and medication use.

**Methods:** Using 3 Tesla MRI, a T1 weighed anatomical image and two PRESS <sup>1</sup>H magnetic resonance spectroscopy (MRS) scans of 3.375 cm<sup>3</sup> cubic voxels containing the two hippocampus heads were acquired in 22 adult patients with a BD I and in 24 HC. Patient demographic and illness characteristics were gathered with questionnaires and interviews. MRS quantification using water scaling was performed using LCModel. For each voxel the gray matter fraction was determined using an in-house developed script. Statistical analysis of the choline (GPC+PCh), creatine (Cr+PCr) and N-acetylaspartate (NAA+NAAG) metabolite differences were performed between patients and controls using MANCOVA while correcting for gray matter fraction, age and gender. The left and right hippocampus volumes were determined using Freesurfer. Statistical analyses of the volume differences of the hippocampi between patients and controls were performed using MANCOVA while correcting for whole brain volume, age and gender.

**Results:**

**Metabolites:** In the left hippocampus the NAA+NAAG and Cr+PCr corrected concentrations were reduced in BD patients when compared to controls. In the right hippocampus these differences were not found to be statistically significant.

**Volume:** There was no significant corrected volume difference in the left hippocampus as well as the right hippocampus when comparing patients to controls.

**Association with patient characteristics:** Further results of the patient characteristics analyses will be presented at the conference.

**Conclusion:** This study shows reduced NAA+NAAG and Cr+PCr concentrations in the left hippocampus of BD patients when compared to HC. Metabolite differences in the right hippocampus as well as volume differences between patients and controls could not be demonstrated.

### Cortical thickness in bipolar disorder: a systematic review

L Hanford<sup>a</sup>, A Nazarov<sup>a</sup>, GB Hall<sup>b</sup>, RB Sassi<sup>c</sup>

<sup>a</sup>Neuroscience Program, McMaster University, Hamilton, Canada, <sup>b</sup>Psychology Neuroscience & Behaviour, McMaster University, Hamilton, Canada, <sup>c</sup>Psychiatry & Behavioural Neuroscience, McMaster University, Hamilton, Canada

**Aims:** Bipolar Disorder (BD) is a debilitating illness whose psychopathology is associated with aberrant structural and functional differences in the brain. Despite the many advances in psychiatry research, our understanding of the complex neurobiological underpinnings of BD remains incomplete. The aim of this review was to

critically examine all available published MRI research reporting cortical thickness in bipolar disorder with respect to a healthy population and/or other psychiatric disorders.

**Methods:** Our systematic review was conducted in November 2014. Relevant papers were identified through an online search of select databases (MEDLINE and EMBASE) using key terms ‘bipolar disorder’ or ‘mania’, and ‘cortical thickness’. A manual search of reference lists from included papers. Two independent raters determined the eligibility of papers and performed separate data extraction to ensure quality and accuracy of reporting.

**Results:** A total of 23 papers met criteria and were included. Compared to a healthy population, most reports showed decreased cortical thickness in left anterior cingulate/paracingulate, several temporal regions bilaterally, as well as the superior frontal gyrus and orbital frontal cortex bilaterally in bipolar disorder. Studies also show consistency of cortical thinning in individuals with bipolar disorder and schizophrenia in frontal and temporal regions, suggesting some common neuropathology.

**Conclusions:** This systematic review further supports of the link between specific structural brain abnormalities and bipolar disorder. Future studies should investigate cortical thickness with respect to at-risk populations to determine whether these neuropathologies develop before or after the onset of bipolar disorder.

### Lithium treatment and hippocampal subfields and amygdala volumes in bipolar disorder

C Hartberg<sup>a</sup>, KN Jørgensen<sup>a</sup>, UK Haukvik<sup>b</sup>, LT Westlye<sup>c</sup>, I Melle<sup>b</sup>, OA Andreassen<sup>b</sup>, I Agartz<sup>a</sup>

<sup>a</sup>Department of Psychiatry, Diakonhjemmet Hospital, Oslo, Norway, <sup>b</sup>Institute of Clinical Medicine University of Oslo & Oslo University Hospital, NORMENT/K.G. Jebsen Centre for Psychosis Research, Oslo, Norway, <sup>c</sup>Department of Psychology, University of Oslo, Oslo, Norway

**Objectives:** Results from MRI studies are heterogeneous with regard to hippocampal and amygdala volume alterations in bipolar disorder (BD). Lithium treatment may influence both structures. It is unknown if Lithium treatment has distinct effects on hippocampal subfield volumes and if subfield volumes change over the course of illness in BD.

**Methods:** MRI scans were obtained for 34 Lithium-treated BD patients (Li+) and 147 BD patients with no Lithium treatment (Non-Li) and 300 healthy controls. Hippocampal total and subfield volumes and amygdala volumes were automatically estimated using Freesurfer. General linear models were used to investigate structure volume differences between groups and effects of illness course and Lithium treatment.

**Results:** The Non-Li BD group displayed smaller volumes for the bilateral CA2/3 and CA4/DG subfields, bilateral total hippocampus volumes, the right CA1 and right subiculum subfields, and the left amygdala when compared to healthy controls. There were no significant differences between Li+ BD and Non-Li BD or the healthy controls. In patients with numerous affective episodes, Non-Li BD patients had smaller left CA1 and CA2/3 volumes compared to both the Li+ BD group and healthy controls. There were significant positive associations between Lithium treatment duration and left amygdala volume.

**Conclusions:** We found smaller hippocampal subfield and amygdala volumes in Non-Li BD compared to healthy controls, while the volumes in the Li+ BD group were not significantly different from either the Non-Li group or healthy controls. Over the course of illness Lithium treatment might counteract reductions specifically in the left CA1 and CA2/3 hippocampal subfield and amygdala volumes in BD, in accordance with the suggested neuroprotective effects of Lithium.

### Brain volumetric changes in high-risk and ultra-high-risk offspring of bipolar proband

G Xu<sup>a</sup>, W Lu<sup>a</sup>, H Wu<sup>b</sup>, G Miao<sup>a</sup>, T Li<sup>a</sup>, K Chen<sup>a</sup>, B Lai<sup>a</sup>, X Chen<sup>a</sup>, K Lin<sup>c</sup>  
<sup>a</sup>Affective Disorders, Guangzhou Psychiatric Hospital, Guangzhou, China, <sup>b</sup>Radiology, Guangzhou Psychiatric Hospital, Guangzhou, China, <sup>c</sup>Psychology, The University of Hong Kong, Hong Kong, Hong Kong China

**Background:** Recently the clinical staging models of bipolar disorder (BP) have been proposed that there exist prodromal stages preceding the official onset of BP, raising the possibilities for secondary or primary prevention. It is little known about gray matter volume changes in these stages.

**Objective:** We aimed to delineate the volumetric changes in offspring with parents with BP for in two stages—high-risk stage that shows no or mild symptoms and ultra-high-risk (UHR) stage that displays subthreshold syndromes.

**Method:** Offspring were identified through their parents who received psychiatric services in Guangzhou psychiatric hospital and form the communities from March 2013 to January, 2015. By a putatively operational criteria for UHR, these offspring were assigned into HR group and UHR group. Voxel-based morphometry (VBM) analysis was applied to investigate volumetric changes.

**Result:** In the HR offspring versus healthy controls contrast, HR offspring showed significantly decreased gray matter volume in the right orbitofrontal gyrus and the right cerebellum (p<sub>FWE-corrected</sub> < 0.05). Compared with HR offspring, UHR offspring showed increased GM in four regions, including superior frontal gyrus, posterior cingulate, left parietal cortex, and the right inferior and middle occipital gyrus (p<sub>FWE-corrected</sub> < 0.05).

**Conclusion:** Our data suggest that orbitofrontal cortex and right cerebellum may represent the genetic vulnerabilities for BP while some regions locating in parietal and occipital may be related to stage-specific changes.

### Differences in emotion regulation between unmedicated bipolar and major depressive disorder interact with mood state

H Ruhe<sup>a</sup>, M Rive<sup>b</sup>, R Mocking<sup>b</sup>, M Koeter<sup>b</sup>, G van Wingen<sup>c</sup>, S de Wit<sup>d</sup>, O van den Heuvel<sup>d</sup>, D Veltman<sup>d</sup>, A Schene<sup>e</sup>

<sup>a</sup>Department of Psychiatry (UCP) Program for Mood and Anxiety Disorders, University Medical Center Groningen (UMCG), Groningen, Netherlands, <sup>b</sup>Department of Psychiatry Program for Mood Disorders, Academic Medical Center (AMC) University of Amsterdam, Amsterdam, Netherlands, <sup>c</sup>Department of Psychiatry, Academic Medical Center (AMC) University of Amsterdam, Amsterdam, Netherlands, <sup>d</sup>Department of Anatomy and Neurosciences, VU Medical Center (VUMC) Vrije Universiteit Amsterdam, Amsterdam, Netherlands, <sup>e</sup>Department of Psychiatry, Radboud University Medical Center Nijmegen, Nijmegen, Netherlands

**Background:** Major depressive disorder (MDD) and bipolar disorder (BD) are difficult to distinguish clinically during the depressed or remitted state. Both mood disorders are characterized by emotion regulation disturbances, but little is known about emotion regulation differences between MDD and BD. Better insight in these differences would be helpful for differentiation based on disorder-specific underlying pathophysiological mechanisms. Previous studies comparing these disorders often allowed medication use, limiting generalizability and validity. Moreover, MDD and BD subjects were mostly compared during the depressed, but not the remitted state, while state might potentially modulate differences between MDD and BD.

**Aim:** To investigate positive and negative emotion regulation in medication-free MDD and BD subjects in two mood states: depressed or remitted.



**Methods:** A cross sectional study comparing behavioral and functional magnetic imaging (fMRI) emotion regulation data of 42 MDD, 35 BD and 36 healthy control (HC) subjects, free of psychotropic medication. Subjects underwent a voluntary emotion regulation fMRI-task using positive and negative pictures. *Main outcomes* were behavioral and fMRI BOLD responses during emotion regulation. This study was approved by the local institutional ethical review board and all participants provided written informed consent.

**Results:** In the remitted state, only BD subjects showed impaired emotion regulation, irrespective of emotion type and associated with increased dorsolateral prefrontal cortex activity compared to MDD and HC. In the depressed state, MDD and BD subjects differed with regard to happy versus sad emotion regulation, associated with differences in rostral anterior cingulate activity. MDD subjects regulated sad and happy emotions poorly compared to BD and HC, while they demonstrated no rostral anterior cingulate difference between happy and sad emotion regulation. In contrast, BD subjects performed worse than MDD on sad emotion regulation, but normal on happy emotion regulation and demonstrated significantly less rostral anterior cingulate activity while regulating happy compared to sad emotions.

**Conclusion:** Medication-free MDD versus BD patients appear to differ in brain activations during emotion regulation, both while depressed as well as in remission, but differences vary with mood state. These different neuropathophysiological mechanisms between MDD and BD may be useful for further development of additional diagnostic tools.

## A multi-relational model for depression relapse in patients with bipolar disorder by means of a machine learning approach

R Dias<sup>a</sup>, R Salvini<sup>b</sup>, I Dutra<sup>c</sup>, B Lafer<sup>d</sup>

<sup>a</sup>Psychiatry Bipolar Disorder Research Group, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil,

<sup>b</sup>Instituto de Informática, Universidade Federal de Goiás, Goiania, Brazil, <sup>c</sup>CRACS & INESC TEC-PORTO, Universidade do Porto, Porto, Portugal, <sup>d</sup>Psychiatry Bipolar Disorder Research Group, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

**Aims:** Relapse prevention is the main target in Bipolar Disorder (BD) treatment, since the relapse rate are around 50% at one year and 70% at four years treatment. As BD presents multi-factorial and multidimensional characteristics, there appears an urgent necessity of new techniques to investigate patterns associated to the outcome Machine learning and data mining bring the possibility to explore that. We investigate the use of Inductive Logic Programming (ILP), which combines inductive machine learning, logic programming and expert's knowledge encoded as background knowledge, to generate multi-relational classifiers models for depressive relapse in patients with BD.

**Methods:** We explored a cohort of 108 patients with BD followed by periods of 6 months to 10 years from the Brazilian Bipolar Research Group from the Institute of Psychiatry – São Paulo State University Outpatient Clinic. These data are associated 211 variables covering psychiatric and medical comorbidity, BD history, medication and mood assessed by HAMD and YMRS at baseline and during follow-up. The ILP was settled with clause length of 10, 2 minpos, 0 noise and 2,000,000 nodes to be exploited. The results were evaluated using stratified 10-fold cross-validation. Metrics presented are averaged across all folds related to the test sets.

**Results:** Mean age was 40.23 y.o. (SD 11.50), 72 (66.7%) were female, 84 (77.8%) were Caucasian, 47 (43.5%) were single and mean years of education was 11.78 (SD 3.25). Compared with No Relapse (NRG) the Relapse Group RG had earlier BD onset (RG:

median (MD) 18.5, inter quartile range (IQR) 15.0–26.0 vs. NRG: MD-27, IQR- 17.0–32.0) and more years with BD (RG: MD 15.5, IQR 10.0–23.75 vs. NRG: 10.0) 6.0–16.0). The ILP generated one theory composed by four rules for RG (sensitivity 0.92; specificity 0.59) and by two for NRG (sensitivity 0.73; specificity 0.95).

**Conclusions:** The generated rules were easy to interpret and selected clinical features associated with outcome in BD already described in the scientific literature and correlate many variables, contrary to most studies, avoiding the 'black-box' phenomenon. The ILP could be especially useful in exploratory studies with a multifactorial approach, as translational research, and the possibility to find patterns with a impressive precision.

## Discussion board utilization within an online self-help program for bipolar disorder (MoodSwings 2.0)

E Gliddon<sup>a</sup>, S Lauder<sup>b</sup>, L Berk<sup>c</sup>, V Cosgrove<sup>d</sup>, D Grimm<sup>d</sup>, S Dodd<sup>a</sup>, T Suppes<sup>d</sup>, M Berk<sup>a</sup>

<sup>a</sup>IMPACT Strategic Research Centre, Deakin University, Geelong, Australia, <sup>b</sup>Department of Psychiatry, University of Melbourne, Parkville, Australia, <sup>c</sup>School of Psychology, Deakin University, Burwood, Australia, <sup>d</sup>Bipolar and Depression Research Program, VA Palo Alto Health Care System, Palo Alto, USA

**Aims:** Online discussion boards are commonly included in online self-help programs for mental illness; however few studies have evaluated their utilization. This poster discusses the frequency of discussion utilization across the three discussion boards included within the MoodSwings online self-help program for bipolar disorder.

**Method:** This project involves a three-arm randomised controlled trial, comparing discussion board only (arm 1), discussion board plus psychoeducation (arm 2), and discussion board, psychoeducation, and interactive tools (arm 3). Participants are aged 21 to 65, and diagnosed with bipolar disorder. Recruitment is ongoing, with an international sample target of 300. All participants have access to one of three moderated discussion boards with 100 participants allocated to each. This project has received approval from the Barwon Health Human Research Ethics Committee and the Department of Veterans Affairs Institutional Review Board. All participants complete consent prior to randomization.

**Results:** As of January 1st 2015, participants have created over 1700 discussion posts and over 200 discussion topics. Discussion board utilization across the three intervention arms is lowest in arm 1 and highest in arm 3, suggesting discussion boards are utilized most when they are offered in conjunction with other program material.

**Conclusion:** Preliminary results suggest discussion boards are a valuable inclusion within online interventions. This research is supported by the National Institute of Mental Health (R34MH091384 and R34MH091284).

## The simple project: self-monitoring and psychoeducation with a smartphone application

D Hidalgo-Mazzei, M Reinares, CM Bonnin, A Murru, F Colom, E Vieta  
Bipolar disorders Program Psychiatry and Psychology, Institute of Neurosciences Hospital Clinic de Barcelona University of Barcelona IDIBAPS CIBERSAM, Barcelona, Spain

**Introduction:** Bipolar disorder is a frequent condition in the general population with a high morbimortality, which consists in dysfunctional temporal fluctuations between different mood phases during which frequently there is a lack of insight. Besides the pharmacological treatment, psychoeducational programs have proved to be a cost-effective approach to help patients recognize early signs and

symptoms in order to prevent full-blown episodes, although its broad implementation is still difficult and costly [1].

**Objectives and Aims:** The main aim of this study is to develop and clinically validate a smartphone application to monitor symptoms and signs in stable bipolar patients along with customized embedded psycho-education contents and empower the self-management of their disorder to avoid relapses and hospitalizations.

**Methods:** The study will be carried out in three different but complementary phases in order to fully include patients and therapist's preferences: 1. Feasibility study using SIMPLE 1.0 app (subjective information only). 2. Feedback-based improvement process which will incorporate the objective information. 3. Randomized controlled trial with two arms of 74 patients each (SIMPLE 2.0 + TAU vs. TAU).

**Results:** After the collaborative development of clinical algorithms to ensure adequate sensibility and specificity to detect relapses and personalize psychoeducational messages, a technical pilot test of SIMPLE 1.0 app is underway and the first patients are being recruited to start the 1st phase of the study in the first quarter of 2015.

**Conclusions:** The possibility to deliver personalized psychoeducation contents based on monitoring signs and symptoms through a smartphone seems a promising cost-effective method, although a clinical validation is necessary.[1] Colom F. Keeping therapies simple: psychoeducation in the prevention of relapse in affective disorders. *Br J Psychiatry* 2011;198:338–40.

## Mental health telemetry for mapping mood dynamics in bipolar disorder and affective illness

**D. Kreindler**

*Sunnybrook College Health Sciences Centre, Toronto, Ontario*

To address a lack of high-quality longitudinal data on mood variability in health and illness, our group developed a system for mobile monitoring of self-report mood symptoms using wirelessly networked hand-held computers in 2000, which we refer to as “Mental Health Telemetry (MHT)”. Our core MHT platform has been used in several studies to explore mood dynamics in bipolar disorder, women of reproductive age, and teens with self-reported severe mood swings. We have collected visual analog scale (VAS) ratings of multiple symptoms of mood and anxiety, multiple-choice answers to standard mood questionnaires, and life event data from patients and healthy controls over intervals of 6 to 18 months. Our studies to-date have consistently demonstrated that 75–80% of patients and healthy controls who responded to recruiting advertisements and began MHT continued reporting beyond three months with very low attrition rates subsequently and 75–80% rates of adherence to daily reporting protocols. Time series analysis of MHT VAS data revealed that mood periodicity is power-law distributed in both bipolar disorder and health with no evidence of spectral peaks. A similar analysis in women of reproductive age revealed no evidence to support a linkage between mood changes and the menstrual cycle. Analysis of life event reporting revealed individualized censoring of low-significance events, consistent with variability in the number of events reported. Small pragmatic trials are currently underway using an enhanced customizable, platform-independent version of MHT exploring whether sharing MHT data with clinicians and patients favourably impacts outcome in recurrent mood disorder and major depression.

## Systematic assessment of mobile apps for bipolar disorder: features and content

**J Nicholas<sup>a</sup>, ME Larsen<sup>b</sup>, H Christensen<sup>b</sup>, J Proudfoot<sup>a</sup>**

*<sup>a</sup>School of Psychiatry, Black Dog Institute – University of New South Wales, Sydney, Australia, <sup>b</sup>Black Dog Institute, University of New South Wales, Sydney, Australia*

**Aims:** The ability to monitor symptoms using mobile phones has the potential to assist people with the management their bipolar disorder (BD). Mobile phones might also be useful for intervention delivery, supplementing treatment and enhancing therapeutic reach, as mobile applications (apps) are cost-effective, accessible, anonymous, and convenient. However, while evidence-based development of apps for BD is in its infancy, there has been an explosion of publicly available apps unsupported by research data. The aim of the current study was to identify the types of self-management apps available and assess the comprehensiveness and quality of their content, with reference to evidence-based practice.

**Methods:** A systematic review framework was applied to the assessment of apps. Searches of the Australian iOS and Android app stores identified English-language apps developed for BD. The comprehensiveness and quality of information, and the degree monitoring tools paralleled current resources developed for the disorder were assessed. A list of evidence-based practice activities was compiled, based on current treatment guidelines for BD, established monitoring resources, and psychotherapy manuals for BD.

**Results:** Of the 83 functioning BD apps identified, the majority (59) were available on the Android platform, with 10 available on both. Thirty-five apps were exclusively monitoring tools, 31 provided psychoeducation about the disorder, 10 delivered self-assessment tests, five provided capability for community support or awareness, and two provided treatment. No apps provided multiple functions. Overall, apps providing psychoeducation were neither comprehensive nor in line with best-practice guidelines. Approximately half of the mood monitoring apps failed to monitor additional critical information such as medication (57%) and sleep (49%), while none had duty-of-care notifications for severe depressed or manic mood, or suicidality. Finally, most apps were commercially developed, and few addressed privacy.

**Conclusions:** This assessment of apps developed for BD indicates that currently available apps are not generally developed with reference to practice guidelines, proven therapeutic techniques, or established self-management tools. Physicians looking to recommend apps to supplement treatment should exercise caution with app selection. New frameworks for mobile mental health research are needed to prevent lag in availability and ensure that evidence-based apps are available to the public.

## Daily and weekly mood ratings: relative contributions to the differentiation of bipolar disorder and borderline personality disorder

**AC Bilderbeck<sup>a</sup>, KEA Saunders<sup>a</sup>, GD Clifford<sup>b</sup>, A Tsanas<sup>b</sup>, M Ospio<sup>b</sup>, PJ Harrison<sup>a</sup>, CJ Harmer<sup>a</sup>, AC Nobre<sup>a</sup>, JR Geddes<sup>a</sup>, GM Goodwin<sup>a</sup>**

*<sup>a</sup>Department of Psychiatry, University of Oxford, Oxford, United Kingdom, <sup>b</sup>Institute of Biomedical Engineering, University of Oxford, Oxford, United Kingdom*

Mood instability is a characteristic feature of both Bipolar disorder (BD) and Borderline Personality disorder (BPD). The context and temporal pattern of mood change may differ between BD and BPD, and inter-episode mood stability in BD may be critical to function and prognosis. However, retrospective accounts of mood are inherently unreliable, lacking sensitivity to recall mood instability that is mild but functionally significant. Remote monitoring technologies offer promising methodological approaches to the monitoring of mood instability.

**Aims:** To use internet and mobile phone technology to record longitudinal mood ratings on different time-scales, in BD and BPD patients, and healthy controls (HC).

**Methods:** We collected weekly, daily, and (for one week) 10× day mood ratings for individuals with BD (N = 32), BPD (N = 9) and HCs (N = 22) (recruitment ongoing) for a period of 4–48 weeks. Using standardised questionnaires, weekly ratings of depression (QIDS), mania/hypomania (Altman), and anxiety (GAD-7) were collected via the TrueColours system ([www.truecolours.nhs.uk](http://www.truecolours.nhs.uk)). Daily and 10× daily ratings were made for 6 mood descriptors (Anxious, Elated, Sad, Angry, Irritable, Energetic) via a smart-phone app.

**Results:** In preliminary analyses, BPD participants reported higher levels of depression and anxiety than BD participants, as rated weekly ( $F_{(1,37)} > 4.8$ ,  $p$ 's < 0.04). BD and BPD participant groups did not differ in variability of weekly ratings ( $F_{(1,37)} < 1.2$ ;  $p$ 's > 0.25). In daily ratings, BPD participants reported greater anxiety, sadness and irritability compared to BD ( $F_{(1,37)} > 4.5$ ;  $p$ 's < 0.04). However, variability for all daily ratings were higher for the BPD compared to BD group ( $F_{(1,37)} > 5.3$ ;  $p$ 's < 0.03). This difference appeared most pronounced in the 10× day ratings of mood. As expected, both patient groups showed elevated depressive and manic symptoms compared to HCs, and greater variability than HC in daily and weekly ratings.

**Discussion:** BPD participants reported more negative mood symptoms, longitudinally, compared to BD participants. BPD participants also demonstrated more changeable mood in higher frequency monitoring compared to BD participants. Further analyses will explore the relationship between weekly symptom ratings and daily mood descriptors. These findings support clinical observations of more labile mood among BPD participants, and highlight the potential of novel technologies to track symptoms at different temporal resolutions.

## Effects of a multimodal intervention program in patients with bipolar disorder and schizophrenia

C López-Jaramillo, JD Palacio, C Vargas

Antioquia, Universidad de Antioquia, Medellin, Colombia

**Background:** Patients with bipolar disorder and schizophrenia represent a high social and economic burden to their families and health system. A multimodal approach to this condition needs to be studied to identify potential benefits

**Objective:** Analyze the clinical, neurocognitive, neurofunctional, psychological, occupational and social effect in short-mid-long term of a multimodal approach in bipolar and schizophrenic patients and to determine its effect in clinical functionality, brain activation and specific biomarkers.

**Methods:** 301 bipolar and schizophrenic patients, aged 18 to 65, were randomized to control or intervention group. All subjects were assessed using psychiatric (DIGS, HRSD, YMRS), psychological (AQ-12, TEMPS-A, FAST, BIS-11, SAI-E), neuropsychological (WCST, CVLT-II, WAIS III, TMT, WMS III, Rey-Osterrieth complex figure), occupational (SSI, EMES-M, EMES-C, assertiveness test, SAD scale), familiar (FEICS, FACES-III, ECF) and general practitioner (BRIAN, MMSE) evaluations. Samples for biomarkers (NT-3, IL6, 10, 17, BDNF, NT-3, TNF-alpha, carbonylation of proteins, nitration of proteins and TBARS) were obtained and fMRI studies (3 tesla scanner) were made in 150 patients defined randomly. Intervention comprises 12–18 specific interventions and 10 psychoeducation sessions compared to control group, which were evaluated only by psychiatry and general practitioner. All instruments were applied before and after the interventions.

**Results:** 150 patients were in the multimodal group, 100 bipolar patients and 50 schizophrenic patients. 151 patients were in the control group, 98 bipolar patients and 53 schizophrenic patients. Preliminary results of the basal features show that the bipolar patients in multimodal group vs bipolar patients in control group were 67% vs 69% women, 58% vs 57% single, 47% vs 28% were technologist or professional, 5% vs 4% had had hospitalizations, 38% vs 41% had thyroid disease and 19% vs 14% had alcohol abuse. The schizophrenic patients in multimodal group vs control group were 14% vs 22% women, 95% vs 96% single, 28% vs 24% were technologist or professional, 3% vs 4% had had hospitalizations, 16% vs 11% had thyroid disease and 8% in both groups had alcohol abuse.

**Conclusions:** Our final results will show if comprehensive rehabilitation programs affect multiple features in bipolar and schizophrenic patients as compared with standard intervention.

## Impact of online continuing medical education on improving treatment of depression in bipolar I disorder

J Lubarda<sup>a</sup>, P Chatterjee<sup>a</sup>, J Calabrese<sup>b</sup>

<sup>a</sup>Medical Education, Medscape Education, New York City, USA,

<sup>b</sup>Mood Disorders, Case Western Reserve University School of Medicine, Cleveland, USA

**Aims:** The objective of this study was to determine if an online continuing medical education (CME) activity designed to address gaps in care could improve the knowledge and performance of psychiatrists and PCPs in management of depression in bipolar I disorder (BP-I).

**Methods:** A CME activity was developed and administered as an online text-based article on diagnosis of BP-I depression and selection of appropriate treatments. To measure effectiveness of education on clinical practice of psychiatrists and PCPs, linked individual participant responses to a case-based online survey were captured before (pre-CME), immediately after (post-CME), and again 30–60 days post-CME (follow-up). McNemar's chi-squared test was used to compare linked learners' responses across the 3 time-points, and effect size of the education (ie. performance change from pre- to post-CME) was calculated using Cramer's V. The CME activity launched 9/17/14 and data were collected for 64 days.

**Results:** The survey on BP-I showed a significant improvement in knowledge and performance for both psychiatrists (n = 1259) and PCPs (n = 329):

- Percentage of psychiatrists who answered all 3 clinical performance questions correctly increased from 27% pre-CME to 47% post-CME ( $p < 0.001$ ; moderate effect size,  $V = 0.52$ ), and was retained on follow-up at 46% (n = 134).
- Percentage of PCPs who answered all 3 clinical performance questions correctly increased from 3% pre-CME to 31% post-CME ( $p < 0.001$ ; moderate effect size,  $V = 0.4$ ), and increased on follow-up to 33% (n = 36).

Immediately post-CME, 17% more psychiatrists and 31% more PCPs selected atypical antipsychotics as first-line therapies for BP-I depression, with 20% more psychiatrists and 33% more PCPs correctly identifying that lurasidone reduces symptoms with few changes in metabolic parameters. Although improvements were significant, 30–35% of psychiatrists and 44–46% of PCPs would benefit from additional education on use of atypical antipsychotics versus mood stabilizers in management of acute depressive episodes in patients with BP-I.

**Conclusions:** Statistically significant improvements show that the online CME activity was successful in improving performance amongst psychiatrists and PCPs who manage BP-I with depression. Text-based or video-based expert commentaries would serve

as an effective format to deliver future education to drive knowledge retention and improve clinical performance in this area.

## Success of online educational intervention on the management of depression in bipolar I disorder

**J Lubarda, M Krawczyk, P Chatterjee**

*Medical Education, Medscape Education, New York City, USA*

**Aims:** Multiple treatment options exist for depression in bipolar I disorder (BP-I), however clinicians still have difficulty in decision-making on optimal management and pharmacologic treatment selection for patients. A study was conducted to determine if online continuing medical education (CME) could improve performance of psychiatrists who manage BP-I with depression.

**Methods:** An online CME activity on treatment options for managing depression in BP-I was developed as an expert-guided text-based commentary. A survey was administered to linked participants to measure performance via 3 case-based, multiple-choice questions before (baseline), immediately after CME, and again 30–60 days post-CME (follow-up). Overall mean scores for answers at the different time points and McNemar's chi-squared tests were used to determine statistical significance. Cramer's V was used to calculate the effect size of education, based on strength of association between baseline and immediate post-CME answers. The study launched on December 18, 2013, and data were collected for 82 days.

**Results:** In total, 2013 psychiatrists participated in the CME outcomes survey. Compared with baseline assessment, statistically significant improvements in management of depression in BP-I were demonstrated as a result of participation in CME, with an effect size of  $V = 0.32$  (moderate impact,  $p < 0.000001$ ). Specific areas of improvements included:

- Psychiatrists' ability to select appropriate adjunctive therapy for patients with partial response and continued depressive symptoms improved by 30% from baseline to immediately post-CME ( $p < 0.000001$ ). However, 50% still need additional intervention.
- 14% of psychiatrists improved ability to select appropriate first-line treatments for BP-I with depression ( $p < 0.000001$ ). However, 59% still need additional intervention.
- Follow-up assessment was performed 30–60 days after the CME on a smaller sample of linked participants ( $n = 82$ ), and 77% answered 2 out of 3 survey questions correctly on follow-up, an increase from 35% in post-CME assessment, indicating large retention and improved decision-making skills.

**Conclusions:** This study demonstrated the success of targeted, text-based, online CME on improving practice patterns of psychiatrists managing depression in BP-I. Psychiatrists would benefit from additional in-depth case-based education to raise awareness and improve decision-making, and to stimulate appropriate use of pharmacologic therapy for depression in BP-I.

## Perception of stigma among patients with humor disorders

**L Santos, G Antunes, A Carneiro, D Bio, R Moreno**

*CEAPESQ Mood Disorders Unit (GRUDA), Institute of Psychiatry School of Medicine University of Sao Paulo, São Paulo, Brazil*

**Introduction:** Some decades ago, people diagnosed with mental illnesses were perceived as dangerous and crazy. Unfortunately, these people are still viewed this way in the 21st century. Patients feel like they do not belong in this society, which can result into various outcomes. Objectives: this study aims to describe the results of a previous investigation of experiences with stigma that euthimic patients suffered during their treatment. Method: A total of 43

patients from a Mood Disorders Unity – GRUDA, previously diagnosed and treated for Bipolar Disorder II and Major Depressive Disorder were selected. The mean age was 34.09 (SD = 11.43), and 72.1% ( $n = 31$ ) were females. The Inventory of Stigma Experiences was applied when patients met criteria for euthimic (Hamilton Rating Scale and Young Mania Rating Scale  $< 7$ ). Results: data indicated that participants avoid talking about their disorder with friends and parents, believing it can lead to a stigma of their disorder. Moreover, it was reported that patients between the ages of 25 to 35 were more apt to avoid talks about their symptoms and disorder. Conclusion: this study increases public knowledge about mental disorders and the difference it makes in recovery when an adequate family support is present. Also, the results may help to improve the steps of a recovery treatment.

## Psychiatric polypharmacy and implications for obesity

**N Bareis, B Mezuk**

*Family Medicine and Population Health Division of Epidemiology, Virginia Commonwealth University, Richmond, USA*

**Introduction:** Individuals with serious mood disorders (e.g., Bipolar and Major Depressive disorders) are often prescribed multiple psychiatric medications to manage their condition. The long-term impact of this polypharmacy on physical health for those with these conditions is unknown. Obesity contributes to poor health, and some psychiatric medications are associated with weight gain. This study examines the relationship between psychiatric polypharmacy and weight among individuals with lifetime Bipolar spectrum disorders (BSD) and Depression spectrum disorders (DSD).

**Methods:** Data come from the National Comorbidity Survey – Replication (2001–2003) and are limited to respondents with body mass index (BMI) data ( $N = 5,692$ ). Psychiatric diagnoses were based on the CIDI, which operationalizes DSM-IV diagnostic criteria. Medications were self-reported, and then categorized into yes or no psychiatric medications for this analysis. Polypharmacy was defined as four or more different medications taken daily, with psychiatric polypharmacy specifying psychiatric medications. Logistic regression assessed the relationship between the polypharmacy groups and overweight/obese (defined as  $BMI \geq 25 \text{ kg/m}^2$ ) among: (1) respondents who never met criteria for DSM disorder; (2) BSD (Bipolar I, II, Subthreshold, Mania and Hypomania), and (3) DSD (Major Depressive Disorder, Episode, and Dysthymia). Survey weights were used because of the complex sampling design.

**Results:** BSD criteria were met by 4% of the sample ( $n = 406$ ) and 20% met DSD criteria ( $n = 1,825$ ). BSD respondents took 3.57 (SE = 0.35) different psychiatric medications daily with over 80% ( $n = 58$ ) of those taking polypharmacy meeting criteria for psychiatric polypharmacy. Regression analysis revealed crude odds ratio (COR) differences in obese/overweight for BSD and DSD polypharmacy groups when compared with numbers of different medications taken daily (BSD polypharmacy COR = 1.64; 95% CI (1.04–2.59) versus different medications COR = 1.08; 95% CI (0.97–1.20)). BSD COR in psychiatric versus general polypharmacy showed a difference not seen in DSD (COR = 2.48; 95% CI (1.20–5.11) versus 1.64; 95% CI (1.04–2.59)). Adjusting for age, sex, race and education removed significance for all but the DSD polypharmacy groups.

**Conclusions:** This study shows psychiatric diagnoses are associated with elevated odds of overweight/obese as evidenced in BSD and DSD. Psychiatric polypharmacy is related to overweight/obese in the BSD group. Management of these illnesses should integrate metabolic monitoring during routine appointments.

# Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo-controlled 6 week trial

T Suppes<sup>a</sup>, R Silva<sup>b</sup>, Y Mao<sup>b</sup>, J Cucchiaro<sup>b</sup>, C Streicher<sup>b</sup>, A Loebel<sup>c</sup>

<sup>a</sup>Psychiatry and Behavioral Sciences, Stanford School of Medicine and the VA Palo Alto Health Care System, Palo Alto, USA,

<sup>b</sup>Clinical Development, Sunovion Pharmaceuticals Inc, Fort Lee, USA,

<sup>c</sup>Clinical Development and Medical Affairs, Sunovion Pharmaceuticals Inc, Fort Lee, USA

**Aims:** To evaluate the efficacy and safety of lurasidone in patients with major depressive disorder (MDD) presenting with mixed (sub-threshold hypomanic) features.

**Methods:** In this multi-regional study, conducted in the US and Europe, patients were required to meet DSM-IV-TR criteria for MDD, with a Montgomery-Asberg Depression Rating Scale (MADRS) total score  $\geq 26$ , and to have 2 or 3 DSM-5 mixed features criteria manic symptoms on most days over  $\geq 2$  weeks prior to screening. Patients with any lifetime history of bipolar I manic episodes, or any mixed manic episodes, were excluded. Eligible patients were randomized to 6 weeks of double-blind treatment with either lurasidone 20–60 mg/d or placebo. Changes from baseline in MADRS total score (primary assessment) and Clinical Global Impression, Severity (CGI-S) scale (key secondary) were analyzed using a mixed model for repeated measures (MMRM) analysis. A sequential testing procedure was used to control overall Type I error. Responder rates ( $\geq 50\%$  reduction from baseline in MADRS total) were analyzed using logistic regression.

**Results:** Patients were randomized to lurasidone (N = 109; baseline MADRS, 33.2), or placebo (N = 100; baseline MADRS, 33.3). Treatment with lurasidone was associated with significantly greater improvement compared with placebo from Weeks 2 through 6 on both the MADRS total score and CGI-S score. At Week 6, LS mean change for lurasidone vs placebo on the MADRS total score was (-20.5 vs -13.0;  $P < .001$ ; effect size, 0.80), and on the CGI-S score was (-1.83 vs -1.18;  $P < .001$ ; effect size, 0.60). Week 6 responder rates, for lurasidone vs placebo, were 67.6% vs 33.0% ( $P < .001$ ; NNT = 3). The incidence of adverse events (AEs) resulting in discontinuation was 2.8% and 5.0%, respectively on lurasidone and placebo. Nausea was the only AE that occurred with an incidence  $\geq 5\%$  (and greater than placebo) on lurasidone (6.4% vs 2.0%). Minimal changes in weight, lipids and measures of glycemic control were observed on lurasidone.

**Conclusions:** In this study, the first ever placebo-controlled trial we are aware of in an MDD with mixed features population, lurasidone demonstrated significant efficacy on multiple efficacy endpoints. Lurasidone was well-tolerated, with an overall discontinuation rate due to AEs that was lower than placebo.

# Efficacy and safety of long-term treatment with lurasidone in older adults with bipolar depression: results of a 6 month open-label study

B Forester<sup>a</sup>, M Sajatovic<sup>b</sup>, J Tsai<sup>c</sup>, H Kroger<sup>d</sup>, A Pikalov<sup>e</sup>, J Cucchiaro<sup>f</sup>, A Loebel<sup>e</sup>

<sup>a</sup>Psychiatry, Harvard Medical School and McLean Hospital, Belmont, USA, <sup>b</sup>Psychiatry, Case Western Reserve University School of Medicine, Cleveland, USA, <sup>c</sup>Medical Affairs, Sunovion Pharmaceuticals Inc, Marlborough, USA, <sup>d</sup>Clinical Development, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>e</sup>Clinical Development and Medical Affairs, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>f</sup>Clinical Development, Sunovion Pharmaceuticals Inc, Fort Lee, USA

**Aims:** To evaluate the safety and efficacy of 6 months of treatment with lurasidone in patients over 55 years with bipolar depression.

**Methods:** Older adults (age  $\geq 55$  years) who completed one of three 6 week, double-blind, placebo-controlled trials of lurasidone were enrolled in a 6 month, open-label, extension study. One acute study evaluated monotherapy with lurasidone; two studies evaluated lurasidone adjunctive with lithium (Li) or valproate (VPA). Patients with bipolar I depression, with a Montgomery-Asberg Depression Rating Scale (MADRS) score  $\geq 20$ , entered the acute double-blind studies. All patients who completed 6 weeks of double-blind treatment, and who consented to participate in the extension study, started open-label treatment with lurasidone on a dose of 60 mg for one week, regardless of double-blind treatment assignment. After one week, dosing was flexible at 20–120 mg/d.

**Results:** The proportion of older adults who entered the extension study (safety sample) was 55/316 (17.4%) on lurasidone monotherapy, and 86/497 (17.3%) on lurasidone adjunctive therapy. At the end of 6 months of treatment with lurasidone, monotherapy and adjunctive therapy, respectively, minimal changes were observed in mean weight (-1.0 kg; -0.4 kg); and median total cholesterol (-2.0 mg/dL; +6.0 mg/dL), triglycerides (+2.5 mg/dL; +6.0 mg/dL), and HbA1c (0.0%; -0.1%). Adverse events ( $\geq 10\%$ ) reported in patients receiving continued monotherapy with lurasidone were: fatigue (18.4%), insomnia (18.4%), headache (15.8%), somnolence (15.8%), dizziness (13.2%), nasopharyngitis (13.2%), nausea (13.2%), depression (10.5%), and dry mouth (10.5%); and in patients receiving continued adjunctive therapy with lurasidone were: akathisia (31.7%), insomnia (22.0%), tremor (19.5%), nausea (12.2%), somnolence (12.2%). Mean change in the MADRS was -15.7 for the monotherapy group, and -17.8 for the adjunctive therapy group, and in the Clinical Global Impressions Bipolar Version, Severity of Illness score was -2.0 for the monotherapy group, and -2.2 for the adjunctive therapy group.

**Conclusions:** Results of these secondary analyses suggest that 6 months of treatment with lurasidone, as monotherapy, or adjunctive to Li or VPA, was safe and efficacious in older adults with bipolar depression. Minimal changes were observed in weight and metabolic parameters. The antidepressant efficacy of lurasidone was maintained over the 6 month treatment period.

## Efficacy and safety of lurasidone in older adults with bipolar depression: analysis of two double-blind, placebo-controlled studies

M Sajatovic<sup>a</sup>, B Forester<sup>b</sup>, J Tsai<sup>c</sup>, H Kroger<sup>d</sup>, A Pikalov<sup>e</sup>, J Cucchiaro<sup>f</sup>, A Loebe<sup>g</sup>

<sup>a</sup>Psychiatry, Case Western Reserve University School of Medicine, Cleveland, USA, <sup>b</sup>Psychiatry, Harvard Medical School and McLean Hospital, Belmont, USA, <sup>c</sup>Medical Affairs, Sunovion Pharmaceuticals Inc, Marlborough, USA, <sup>d</sup>Clinical Development, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>e</sup>Clinical Development and Medical Affairs, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>f</sup>Clinical Development, Sunovion Pharmaceuticals Inc., Fort Lee, USA

**Aims:** To evaluate the efficacy of lurasidone in patients aged 55 years and older with bipolar depression.

**Methods:** Patients meeting DSM-IV-TR criteria for bipolar I depression with a Montgomery-Asberg Depression Rating Scale (MADRS) score  $\geq 20$  were randomized to 6 weeks of once-daily, double-blind treatment with lurasidone 20–60 mg/d or 80–120 mg/d, or placebo in a monotherapy study; or lurasidone 20–120 mg/d or placebo in an adjunctive therapy study with either lithium or valproate. The primary endpoint was LS mean change from baseline to Week 6 in the MADRS total score. The criterion for response was  $\geq 50\%$  reduction in MADRS score at last observation carried forward (LOCF) endpoint.

**Results:** The proportion of older adults was 83/485 (17.1%) in the monotherapy study, and 53/340 (15.6%) in the adjunctive therapy study. At Week 6 in the monotherapy study, mean change in the MADRS was significantly greater for the lurasidone 20–60 mg ( $-15.4$ ;  $P = 0.054$ ; NNT = 4). At Week 6 in the adjunctive therapy study, mean change was numerically greater for lurasidone vs placebo on the MADRS ( $-13.9$  vs  $-11.1$ ; ns), and the CGI-BP-S score ( $-1.4$  vs  $-0.9$ ; ns); responder rates were numerically greater for lurasidone vs placebo (46.2% vs 37.0%; ns; NNT=11). In the monotherapy study, discontinuation due to adverse events occurred in 7.7% of patients on lurasidone 20–60 mg, 6.7% on lurasidone 80–120 mg, and 3.7% on placebo; and in the adjunctive therapy study, discontinuation due to adverse events occurred in 3.8% of patients on lurasidone, and 7.4% on placebo.

**Conclusions:** Lurasidone monotherapy has significantly greater efficacy than placebo in the treatment of older adults with bipolar depression; efficacy was numerically greater on adjunctive therapy with lurasidone. Lurasidone was well-tolerated in the short-term treatment of older adults with bipolar depression.

## Lurasidone in bipolar depression studies: dose utilization frequencies

M Frye<sup>a</sup>, J Tsai<sup>b</sup>, H Kroger<sup>c</sup>, A Pikalov<sup>d</sup>, J Cucchiaro<sup>e</sup>, A Loebe<sup>f</sup>

<sup>a</sup>Psychiatry, Mayo Clinic, Rochester, USA, <sup>b</sup>Medical Affairs, Sunovion Pharmaceuticals Inc, Marlborough, USA, <sup>c</sup>Clinical Development, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>d</sup>Clinical Development and Medical Affairs, Sunovion Pharmaceuticals Inc, Fort Lee, USA, <sup>e</sup>Clinical Development, Sunovion Pharmaceuticals Inc., Fort Lee, USA

**Aims:** To examine patterns of dose utilization, tolerability, and patient factors associated with dose escalation.

**Methods:** Patients with bipolar I depression were randomized to 6 weeks of double-blind treatment with once-daily, fixed-flexible doses of lurasidone 20–60 mg or 80–120 mg, or placebo in a monotherapy study; or flexible doses of lurasidone 20–120 mg or placebo in an adjunctive therapy study with either lithium or valproate. The starting dose was 20 mg/d for each lurasidone arm. Acute study completers continued in an open-label, 6 month extension study; patients received flexible doses of lurasidone 20–

120 mg/d starting at 60 mg/d, either as monotherapy or adjunctive therapy.

**Results:** In the monotherapy study, the distribution of modal doses was skewed toward use of lower doses of lurasidone: 49% of patients had a modal dose of 20 mg (in the 20–60 mg group) and 49% had a modal dose of 80 mg (80–120 mg group). In the adjunctive study, 38% of patients had a modal dose of 60 mg, and smaller proportions of patients had modal doses of 80 mg (28%), 100 mg (17%), and 120 mg (10%); very few patients had modal doses of 20 mg (3%) or 40 mg (5%). There were no significant differences in baseline demographic or clinical characteristics of patients who stayed at the starting dose, and patients who escalated their dose. Among patients switching abruptly from placebo in the acute study to lurasidone 60 mg in the extension study, the incidence of adverse events was comparable to that seen during acute lurasidone treatment.

**Conclusions:** This analysis found that patients treated with lurasidone in a monotherapy or adjunctive therapy study under-utilized the higher permissible doses. The reason for this is uncertain, but warrants further evaluation, especially in light of a previous exposure-response modeling analysis which found that higher doses of lurasidone are associated with greater efficacy. The current results illustrate the potential methodological trade-offs that occur when choosing a flexible-dose study design, which has a high degree of external validity and generalizability, and a fixed-dose study design, which has less clinical generalizability, but provides a better understanding of dose-response effects.

## Providing further details on the experience of somnolence for patients with acute depressive episodes treated with quetiapine XR

C Datto<sup>a</sup>, O Meléndez Nesbitt<sup>b</sup>, W Pottorf<sup>c</sup>, S LaPorte<sup>c</sup>, C Liss<sup>c</sup>

<sup>a</sup>US Medical Affairs, AstraZeneca Pharmaceuticals, Wilmington, USA, <sup>b</sup>Medical Information, AstraZeneca Pharmaceuticals, Wilmington, USA, <sup>c</sup>Biometrics and Information Sciences, AstraZeneca Pharmaceuticals, Wilmington, USA

**Aims:** This analysis describes the experience of somnolence (the most common adverse event [AE] with quetiapine) in patients taking quetiapine extended release (QXR) for acute depressive episodes in studies of bipolar disorder (BD) and adjunct treatment of major depressive disorder (MDD).

**Methods:** For this analysis, somnolence is the expression of 1 of 2 AE-preferred terms according to MedDRA: somnolence or sedation. Acutely depressed patients with MDD in 2 studies were randomized to adjunct treatment with QXR 150 mg ( $n = 315$ ) or 300 mg ( $n = 312$ ) or placebo ( $n = 309$ ) [1]. In a separate study, acutely depressed patients with BDI or II were randomized to QXR 300 mg ( $n = 137$ ) or placebo ( $n = 140$ ) [2]. The timing of AEs, severity, duration, rates of discontinuation, and influence on the Montgomery-Åsberg Depression Rating Scale (MADRS) efficacy scale were evaluated.

**Results:** The combined proportions of patients with somnolence in the adjunct MDD studies were 35.6%, 42.3% (QXR 150 mg and 300 mg, respectively), and 7.8% (placebo). In the BD study, somnolence rates were 51.8% for QXR 300 mg and 12.9% for placebo. Most patients on QXR reported the AE as mild-to-moderate severity (MDD studies: 84.8% and 83.3% for QXR 150 and 300 mg; BD study: 88.7% for QXR 300 mg). Proportions of patients who discontinued due to somnolence in the MDD studies were 4.8%, 8.0%, and 0.3%, for QXR 150 mg, 300 mg, and placebo, respectively. For the BD study these discontinuation rates were 10.2% for QXR 300 mg and 0.0% for placebo. In both MDD and BD studies, patients with and without experience of somnolence saw important improvements in their MADRS total scores when treated with QXR versus placebo.

**Conclusion:** The somnolence associated with QXR is typically mild to moderate, often resolves with continued treatment, but can result in treatment discontinuation. Acutely depressed patients treated with adjunct QXR for MDD or monotherapy for BD have similar improvements in mean MADRS score with or without the presence of somnolence. Providing prescribers/patients with tolerability details can facilitate treatment decision-making. Sponsored by AstraZeneca.

**References:** [1] Bauer M, J Affect Disord. 2010;127:19–30; [2] Suppes T, J Affect Disord. 2010;121:106–15.

## Antidepressants in bipolar disorder why does the controversy continue?

A Eppel, R Wilson

*Psychiatry and Behavioural Neurosciences, McMaster University, HAMILTON, Canada*

**Aims:** For over three decades a debate has raged within psychiatry regarding the role of antidepressants alone and adjunctively with mood stabilizers in the treatment of bipolar disorder. Physician opinion is divided between a minimalist and maximalist position. Although recent reviews tend to support the minimalist view antidepressants continue to be prescribed with high frequency.

**The aims of this paper are::** (1) To identify key methodological parameters that must be in place in order to eventually arrive at a definitive answer to this question. (2) To describe the application of clinical decision analysis to determine the potential for benefit versus harm with the use of antidepressants in bipolar disorder. Clinical decision analysis assigns probabilities to the likelihood of benefit and likelihood of harm with any specific treatment intervention.

**Methods:** Search of PubMed, Ovid Medline, PsycInfo, EMBASE and LILACS data bases using search terms “bipolar disorder and antidepressants” and “bipolar maintenance” for the period 2011 to 2014.

**Results:** Thirty eight articles consisting of key meta-analyses, longitudinal studies and randomized control trials were reviewed. Studies reporting evidence of benefit with the use of antidepressants are more likely to be short-term and randomized lasting 8 to 12 weeks. Studies identifying harms such as cycle acceleration and mood switching, are more likely to last longer, from six months to three years and include measures of subsyndromal hypomania. However they are less likely to be randomized.

**Conclusions:** The following are prerequisite parameters for studies attempting to determine conclusively whether antidepressants alone or with mood stabilizers should be used in bipolar disorder: 1. Sample characteristics: clear separation of diagnosis of bipolar 1 and 2. Exclusion of unipolar or monopolar depression. No exclusions for severity or suicidal ideation. 2. Duration of follow up 1 to 3 years. 3. Adequate sensitivity of measures to capture cycle acceleration and subthreshold hypomania. The application of clinical decision analysis could assist clinicians in making more objective decisions about medication interventions.

## Adjunctive asenapine in the treatment of mania in clinical practice: results from the MANACOR study

I Grande<sup>a</sup>, D Hidalgo-Mazzei<sup>a</sup>, E Nieto<sup>b</sup>, M Mur<sup>c</sup>, C Saez<sup>d</sup>, I Forcada<sup>c</sup>, E Vieta<sup>a</sup>

<sup>a</sup>Bipolar Disorders Unit, Clinical Institute of Neurosciences Hospital Clinic University of Barcelona IDIBAPS CIBERSAM, Barcelona, Spain, <sup>b</sup>Mental Health Division of Althaia, Xarxa Assistencial Universitaria de Manresa, Manresa, Spain, <sup>c</sup>Psychiatric Service, Santa Maria Hospital IRB Lleida (Biomedicine Research Institute) University of Lleida, Lleida, Spain, <sup>d</sup>University Psychiatric Hospital, Institut Pere Mata CIBERSAM Reus, Reus, Spain

**Background:** Asenapine is the most recent compound that has been FDA- and EMA-approved for treatment of mania. Its efficacy and safety have been assessed in placebo-controlled trials, but little is known about its performance in routine clinical conditions. In this study, we compared features of patients treated with adjunctive asenapine or other adjunctive antipsychotics and the costs of the treatment.

**Methods:** A combined prospective and retrospective data collection and analysis was conducted from January 2011 to December 2013 following a clinical interview and assessment of manic and depressive symptoms (YMRS, HDRS-17), clinical state (CGI-BP-M), psychosocial functioning (FAST), sexual dysfunction (PRSexDQ) and health resource costs associated with treatment with adjunctive asenapine versus other adjunctive antipsychotics.

**Results:** 152 patients from different university hospitals were included. 53 patients received adjunctive asenapine and 99 received other adjunctive antipsychotics concomitantly to mood stabilizers. Considering inpatients, those treated with adjunctive asenapine presented a significantly less severe manic episode ( $p = 0.001$ ), less psychotic symptoms ( $p = 0.030$ ) and, more comorbid personality disorder ( $p = 0.002$ ). Regarding outpatients, those treated with adjunctive asenapine showed significantly less severe manic episode ( $p = 0.046$ ), more previous mixed episodes ( $p = 0.013$ ) and, more sexual dysfunction at baseline ( $p = 0.036$ ). No significant differences were found in mean total costs per day.

**Conclusion:** Clinicians tended to use adjunctive asenapine in patients with less severe manic symptoms but more complex clinical profile, including more mixed episodes in the past, concomitant personality disorder, and sexual problems. Treatment with adjunctive asenapine was not associated with higher costs when compared to other options.

## Protective and risk factors for medication related cognitive impairment in individuals with bipolar disorder

A Hayek<sup>a</sup>, K Hinrichs<sup>a</sup>, K Angers<sup>a</sup>, B Pester<sup>a</sup>, D Marshall<sup>a</sup>, S Langenecker<sup>b</sup>, M Kamali<sup>c</sup>, M McInnis<sup>c</sup>, K Ryan<sup>a</sup>

<sup>a</sup>Neuropsychology, University of Michigan, Ann Arbor, USA, <sup>b</sup>Psychiatry, UIC, Chicago, USA, <sup>c</sup>Psychiatry, University of Michigan, Ann Arbor, USA

**Aims:** Medications used to treat bipolar disorder (BD) are related to impairment in several areas of cognitive functioning. Cognitive side effects are one of the primary reasons for poor treatment adherence. As such, examining different protective/risk factors regarding medication related cognitive impairment may help guide treatment. The purpose of this study is twofold: First, to examine how medication load, a novel approach in examining cumulative psychotropic medication effects (Almeida et al., 2009; Hassel et al., 2008; Sackeim, 2001), is related to impairment in different cognitive domains, and second, to examine how different protective/risk factors (age, IQ, and education), may moderate the relationship between medication load and cognitive impairment.

**Methods:** 278 individuals diagnosed with BD (I, II, NOS) were recruited as part of the Prechter Longitudinal Study of Bipolar Disorder at the University of Michigan. During the clinical/diagnostic evaluation, information about current medications was collected. Participants also were administered a battery of neuropsychological tests that were used to calculate eight cognitive factor scores.

**Results:** Bivariate correlations between medication load and cognitive scores revealed that individuals with a higher medication load performed worse on fine motor dexterity (FM),  $r = -0.19$ , visual memory (VM),  $r = -0.13$ , and verbal fluency with processing speed (VFPS),  $r = -0.16$ . A regression analysis demonstrated an interaction between medication load and age, such that medication load had a greater negative relationship with VFPS,  $\beta = -0.24$   $p < 0.01$ , and FM,  $\beta = -0.12$   $p = 0.042$ , as age increased. An interaction between medication load and education was also demonstrated, with a greater negative relationship with VFPS as education increased,  $\beta = -0.12$   $p = 0.049$ . No significant interactions were found between medication load and IQ.

**Conclusions:** Higher medication burden is related to poorer performance in several cognitive domains. Moreover, this relationship is especially important in older individuals, such that older age may constitute as a risk factor to cognitive impairment for individuals with a large medication burden. Also, while individuals with high education perform worse as medication burden increases, low education individuals perform about the same on cognitive measures, independent of medication burden.

### Lithium nephropathy: a long-term complication of chronic lithium therapy

A Hercegovac<sup>a</sup>, R Hoekstra<sup>b</sup>, TM Bosch<sup>c</sup>, AM Alphen<sup>a</sup>

<sup>a</sup>Department of Nephrology, Maastad Hospital, Rotterdam, Netherlands, <sup>b</sup>Department of Psychiatry, Delta Center for Mental Health Care, Rotterdam, Netherlands, <sup>c</sup>Department of Hospital Pharmacy, Maastad Hospital, Rotterdam, Netherlands

**Aims:** Lithium is the treatment for bipolar disorder. Lithium-induced nephropathy is a known complication limiting its use. The aim of this study is to establish the prevalence of renal failure in our population and to relate its occurrence to lithium serum concentration, number of intoxications and duration of lithium therapy.

**Methods:** We selected 1751 patients on lithium therapy from the laboratory database of the Delta Center for Mental Health Care, Rotterdam. The database contains measurements of lithium and creatinine concentration over a period from 2000 to 2011. eGFR was calculated using the 4-variable MDRD formula. Renal failure was defined as having GFR  $< 60$  mL/min on at least 2 measurements 6 weeks apart. A comparison was made between patients with and without renal insufficiency regarding the number of lithium intoxications, mean lithium concentration in serum, duration of therapy, cardiovascular disease, hypertension and diabetes mellitus.

**Results:** 305 out of 1751 (17.4%) patients were developed renal failure. Renal failure was positively correlated with duration of lithium therapy ( $p < 0.0001$ ). Mean lithium serum concentration and a history of lithium intoxication did not prove different between groups. Significant correlation was observed between renal insufficiency and cardiovascular disease, hypertension and diabetes mellitus.

**Conclusions:** The incidence of renal insufficiency in our cohort is comparable to other reports. Longer duration of lithium therapy was found to be associated with an increased risk of renal insufficiency. Contrary to our expectation the frequency of toxic lithium serum concentration was not clearly associated with an increased risk of renal failure.

### Bipolar patients treated by long-acting injectable risperidone in Taiwan: a one-year mirror-image study using a national claim-based database

P Chuang<sup>a</sup>, C Tang<sup>a</sup>, C Wu<sup>b</sup>, C Chang<sup>c</sup>, M Hsieh<sup>b</sup>

<sup>a</sup>School of Health Care Administration, Taipei Medical University, Taipei, Taiwan, <sup>b</sup>Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan, <sup>c</sup>Department of Psychiatry, Cathay General Hospital, Taipei, Taiwan

**Objectives:** Long-acting injectable risperidone (RLAI) is the first depot antipsychotics indicated for treatment of bipolar disorder. This study examined the Taiwan National Health Insurance Research Database with bipolar disorder and RLAI, while our analyses focusing on health utilization and cost.

**Methods:** The 2007–2012 National Health Insurance Research Database was used for an one-year mirror-image design comparing the pre-RLAI period and the post-RLAI period among patients who initiate RLAI. Patients who had both a diagnosis of bipolar disorder (ICD-9-CM) at the index visit/hospitalization and received at least 25-mg RLAI every 3 months in one year after the index visit/hospitalization were included. In addition, they were further classified into rapid cycling patients and non-rapid cycling patients based on the number of mood episode change in one year before the index date. In order to adjusted for skewed data, non-parametric bootstrapping with resampling with 1000 replications was used.

**Results:** From 2007 to 2012, 3115 bipolar disorder patients at the index visit/hospitalization had received at least one shot of RLAI, while among them only 287 patients received at least 25-mg RLAI every 3 months for one year. RLAI revealed significant decrease of the number of ER visit, number of admission, length of stay and non-medication costs. In comparison with non-rapid cycling subjects ( $n = 251$ ), rapid cycling patients ( $n = 36$ ) revealed more prominent RLAI improvement of the above outcome.

**Conclusion:** RLAI reduces the health utilization and non-medication cost in patients with bipolar disorder. Furthermore, RLAI lowers the numbers of mood episode change in patients with rapid cycling bipolar disorder. Besides better medical adherence, long-acting injectable risperidone should be considered in bipolar disorder patients, especially in rapid-cycling bipolar disorder.

### Bipolar patients treated by long-acting injectable risperidone in Taiwan: a one-year mirror-image study using a national claims database

MH Hsieh<sup>a</sup>, PY Chuang<sup>b</sup>, CS Wu<sup>a</sup>, CJ Chang<sup>c</sup>, PF Chung<sup>d</sup>, CH Tang<sup>b</sup>

<sup>a</sup>Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan, <sup>b</sup>School of Health Care Administration, Taipei Medical University, Taipei, Taiwan, <sup>c</sup>Department of Psychiatry, Cathay General Hospital, Taipei, Taiwan, <sup>d</sup>Assistant Medical Science Liaison Manager, Janssen Taiwan, Taipei, Taiwan

**Objectives:** Long-acting injectable risperidone (RLAI) is the first depot antipsychotic indicated for treatment of bipolar disorder. This study examined the health utilization and cost related to RLAI on bipolar disorder using the Taiwan National Health Insurance Research Database.

**Method:** The 2007–2012 Taiwan's National Health Insurance Research Database was used for a one-year mirror-image design comparing the pre- and post-RLAI period among patients who initiate RLAI. Patients who had both a diagnosis of bipolar disorder (ICD-9-CM) at the index visit/hospitalization and received at least one injection every 3 months within one year after the index visit/hospitalization were included. In addition, they were further classified into rapid cycling patients and non-rapid cycling patients based on an estimate of the number of mood episode changes



derived from prescription patterns in one year before the index date. In order to adjust for skewed data, non-parametric bootstrapping with resampling with 1000 replications was used.

**Results:** From 2007 to 2012, 3115 bipolar disorder patients at the index visit/ hospitalization had received at least one injection of RLAI. Among them, only 287 patients were eligible for analysis. Use of RLAI was associated with a decrease in the number of ER visits ( $p = 0.0003$ ), number of admissions ( $p < 0.0001$ ), length of stay ( $p < 0.0001$ ) and non-medication costs ( $p = 0.1686$ ). In comparison with non-rapid cycling subjects ( $n = 251$ ), rapid cycling patients ( $n = 36$ ) revealed greater improvement on RLAI. For concomitant usage, the doses in both typical and atypical antipsychotics and anti-epileptics were significantly decreased, while the doses in anti-depressants and lithium were not significantly different in the post-RLAI treatment.

**Conclusion:** Our findings suggest that patients with bipolar disorder treated with RLAI might have a lower health utilization and non-medication cost in Taiwan healthcare settings. The limitation of national claims database is not available for certain information such as disease severity, or the actual drug compliance. Further research is required to clarify the underlying findings.

### Minocycline as an adjunct for the treatment of depressive symptoms: pilot randomised controlled trial

MI Husain<sup>a</sup>, IB Chaudhry<sup>b</sup>, RR Rahman<sup>c</sup>, MM Hamirani<sup>d</sup>, I Qurashi<sup>e</sup>, AB Khoso<sup>f</sup>, N Husain<sup>b</sup>, AH Young<sup>a</sup>

<sup>a</sup>Centre for Affective Disorders, Institute of Psychiatry Psychology and Neuroscience, London, United Kingdom, <sup>b</sup>Department of Psychiatry, University of Manchester, Manchester, United Kingdom, <sup>c</sup>Department of Psychiatry, Dow Institute of Health Sciences, Karachi, Pakistan, <sup>d</sup>Department of Psychiatry, Abbasi Shaheed Hospital, Karachi, Pakistan, <sup>e</sup>Ashworth Hospital, Mersey Care NHS Foundation Trust, Maghull, United Kingdom, <sup>f</sup>Psychological Research, Pakistan Institute of Learning and Living, Karachi, Pakistan

**Background:** Depression is one of the leading causes of disability worldwide. A high proportion of patients do not respond to standard drug treatments. Recent evidence has shown that anti-inflammatory treatment may have beneficial effects in major depression. Minocycline is a pleiotropic agent that exerts effects on multiple interacting symptoms (i.e. anti-inflammatory, anti-oxidant, anti-apoptotic, anti-gutamatergic, monaminergic) implicated in the pathophysiology of mood disorders. Open label studies have suggested that minocycline is effective as an adjunct drug in improving depressive symptoms.

**Aim:** To establish whether the addition of minocycline to treatment as usual is effective and tolerable in the treatment of depressive symptoms.

**Methods:** This is a multi centre, three-month, double blind placebo controlled, pilot trial of minocycline added to treatment as usual for patients suffering from DSM IV major depressive disorder. This will be a two-arm design with 20 participants in each arm, giving a total of 40 participants. There will be a screening, a randomization and four follow-up visits. Full clinical assessments using the Hamilton Depression Rating Scale (HAMD), Clinical Global Impression scale (CGI), Patient Health Questionnaire-9 (PHQ-9), and the Generalised Anxiety Disorder scale (GAD-7) will be carried out at every visit. Side effects checklists will also be undertaken at every visit. Minocycline will be started at 100 mg once daily (OD), this will be increased to 200 mg after two weeks.

**Results:** Thus far, 10 participants have been recruited and randomised. We aim to present preliminary data for these participants during the conference.

**Trial Registration:** ClinicalTrials.gov NCT02263872.

### Effectiveness of medication in preventing hospitalization of bipolar patients – a register based study of mood stabilizing medication with lithium and anticonvulsants in Sweden

E Joas<sup>a</sup>, A Karanti<sup>a</sup>, P Lichtenstein<sup>b</sup>, M Landén<sup>a</sup>

<sup>a</sup>Psychiatry and Neurochemistry Affective disorders, University of Gothenburg, Gothenburg, Sweden, <sup>b</sup>Medical Epidemiology and Biostatistics, Karolinska Institutet, Gothenburg, Sweden

**Aims:** It has been known since the 1960s that treatment with mood stabilizing drugs can prevent recurrences of new mood episodes. Even though randomized controlled trials (RCTs) have demonstrated efficacy for several drugs, head-to-head comparisons are scarce and their relative efficacy disputed. Moreover, effectiveness of the drugs in a naturalistic setting cannot be inferred from RCTs since they typically exclude patients with for example comorbidities. The aim of this study was to assess the effectiveness of lithium and three anticonvulsant drugs in preventing any psychiatric hospitalization among patients with bipolar disorder. As secondary outcomes we used hospitalizations due to manic-, depression- and mixed episodes.

**Methods:** Through a linkage of Swedish national registries we identified 35,182 people with bipolar disorder and their medication between 2006 and 2009. Psychiatric hospitalizations were captured in the patient register. The effectiveness of lithium, valproate, lamotrigine and carbamazepine was assessed using cox regressions in both within- and between-individual models.

**Results:** Our within-individual analyses demonstrated a protective effect of lithium (HR: 0.62, 95% CI: 0.59; 0.66), valproate (HR: 0.67, 95% CI: 0.62; 0.73), and lamotrigine (HR: 0.77, 95% CI: 0.72; 0.83) for any psychiatric hospitalization. Lithium (HR: 0.53, 95% CI: 0.45; 0.61), valproate (HR: 0.43, 95% CI: 0.34; 0.54), and carbamazepine (HR: 0.50, 95% CI: 0.30; 0.85) demonstrated protective effects against manic episodes. Lithium (HR: 0.58, 95% CI: 0.51; 0.66), valproate (HR: 0.64, 95% CI: 0.52; 0.78) and lamotrigine (HR: 0.66, 95% CI: 0.58; 0.77) showed protective effects against depression. The between-individual analyses showed potential confounding-by-indication where for example valproate, carbamazepine, and lamotrigine were associated with higher risk of psychiatric hospitalization.

**Conclusions:** Our findings show that valproate and lithium have a protective effect against any psychiatric hospitalization for patients with bipolar disorder in a real world setting. The effect of lamotrigine and carbamazepine were unidirectional with regards to polarity of episode, with protective effects solely against depressive and manic episodes, respectively. Our study underlines the importance of controlling for confounding-by-indication in pharmacoepidemiological studies. Finally, our study corroborates findings from meta-analyses of RCTs on mood stabilizing medication, which is reassuring both for patients and clinicians.

### Dosing patterns among patients initiating lurasidone for the treatment of bipolar disorder: a real-world claims database analysis

D Ng-Mak<sup>a</sup>, K Rajagopalan<sup>a</sup>, A Loebe<sup>b</sup>

<sup>a</sup>Health Economics and Outcomes Research, Sunovion Pharmaceuticals Inc., Marlborough, USA, <sup>b</sup>Research & Development, Sunovion Pharmaceuticals Inc., Fort Lee, USA

**Aims:** Lurasidone received FDA approval for treatment of bipolar depression in June 2013. Given that real-world lurasidone dosing patterns can provide insight about its use in clinical practice, this study examined dosing patterns among adults initiating lurasidone treatment for bipolar disorders.

**Methods:** Claims data from Optum Research Database from 6/28/2013 to 1/31/2014 were analyzed among patients  $\geq 18$  years old

with bipolar I or II disorders (ICD-9-CM codes 296.0X-296.1X, 296.4X-296.81, 296.89) with  $\geq 180$  days continuous enrollment before and after lurasidone initiation. Mean daily dose ((dose strength  $\times$  drug quantity)/days supply) was calculated for each filled prescription (Rx). Outcome measures included average daily starting and maintenance (i.e., 6-month-follow-up) doses, average Rx number, average daily dose escalation or reduction (defined as  $\geq 20$  mg escalation or reduction between Rx's), and mean time to average daily dose escalation or reduction.

**Results:** Of 339 patients initiating lurasidone, 72.6% were female; mean age  $39.0 \pm 12.6$  years; 32.7% with bipolar I or II depression; 10.9% bipolar mania; 13.6% bipolar mixed; and 42.8% unspecified/others. Overall, mean lurasidone starting and maintenance daily doses were 45.1 and 54.9 mg, respectively (46.8/55.6, 50.0/58.2, and 47.8/61.3 mg for patients with bipolar I or II depression, bipolar mania and bipolar mixed, respectively). Starting doses were 20 mg for 30.7% of patients, 40 mg/40.4%, 60 mg/ 3.5%, 80 mg/20.7%, 120 mg/2.6%, 160 mg/0.3%, and other doses/1.8%. On average, patients had  $3.2 \pm 2.1$  lurasidone fills. Overall, 64% of patients stayed at starting dose. While 26% reported dose escalation with 65 days mean time-to-escalation, 3% had dose-reduction with 88 days mean time-to-reduction. Patients starting on 20 mg/d were more likely to have mean daily dose-escalation than patients starting on doses  $>20$  mg/d (47.1% versus 27.1%;  $p < 0.001$ ). Furthermore, patients starting on 20 mg/d had shorter mean time-to-first-dose-escalation compared to those starting on doses  $>20$  mg/d (52.3 days versus 76.6 days;  $p < 0.01$ ).

**Conclusion:** This real-world analysis showed majority of bipolar disorder patients initiated lurasidone at 20 or 40 mg/d and about two-thirds stayed on their initial dose. Consistent with the clinical trial for bipolar depression, mean lurasidone initiation and maintenance doses were lower for bipolar depression compared to those with bipolar mixed and mania patients.

### Paliperidone palmitate vs. oral atypical antipsychotics in schizoaffective disorders

S Sánchez-Alonso<sup>a</sup>, L Mata<sup>a</sup>, R Álvarez<sup>b</sup>, M Iza<sup>c</sup>, S Ovejero<sup>c</sup>

<sup>a</sup>Psychiatry Outpatient Unit, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, <sup>b</sup>Psychiatry Inpatient Unit, Hospital Rey Juan Carlos, Mostoles, Spain, <sup>c</sup>Psychiatry Inpatient Unit, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

**Objectives:** The aim of this study is to assess the differences between paliperidone palmitate and oral atypical antipsychotics on the use of adjuvant drug therapy in patients diagnosed with schizoaffective disorder in an outpatient setting.

**Methods:** We gathered data of 23 schizoaffective patients in clinical remission status ( $n = 23$ ) on antipsychotic treatment. 2 treatment groups were analyzed: patients on paliperidone palmitate (PALM,  $n = 12$ ) and oral atypical antipsychotics (OAA,  $n = 11$ ). Percentages of absolute monotherapy, antipsychotic monotherapy, use of mood stabilizers, use of antidepressants, use of biperiden and rates of polypharmacy are examined.

**Results:** The percentage of absolute monotherapy is higher in the PALM group (33.3%) compared to the OAA group (0%) with statistical significance (Student  $T$ :  $p = 0.039$ ). Percentages of antipsychotic monotherapy show differences in PALM and OAA groups (83.3 and 54.5%, respectively), but did not reach statistical significance (Student  $T$ :  $p = 0.154$ ). We have not found differences in the use of mood stabilizers between groups (66.7% and 63.6% respectively). There were no statistical differences between the groups about the use of biperiden, with percentages of 0% in the PALM group versus 18.2% in the oral group. There were differences in the use of antidepressants between the groups. In the PALM group, none of the patients needed antidepressants, while in the OAA group, the 36.4% if needed them. This difference show statistical significance ( $t$  Student test;  $p = 0.038$ ). The use of polypharmacy is

significantly lower in the PALM group (41.7%) versus 81.8% of the OAA group. Differences between groups were statistically significant ( $t$  Student test;  $p = 0.049$ ).

**Conclusions:** Treatment with paliperidone palmitate provides a higher percentage of absolute monotherapy over oral atypical antipsychotics in the patients of the study. The results show a higher percentage of antipsychotic monotherapy in the PALM group too despite the statistical difference were not reached. The risk of using polypharmacy is lower in the PALM group. As well as the use of antidepressants use. The use of paliperidone palmitate in schizoaffective disorders may open a new way to reach the clinical remission using less adjuvant drug therapy.

### Aripiprazole impact in defenses modulation and reality testing. Efficacy in manic episodes

EG Carp<sup>a</sup>, S Trifu<sup>b</sup>, D Braileanu<sup>c</sup>, J Voicu<sup>c</sup>, M Hamalgeanu<sup>c</sup>

<sup>a</sup>Psychiatry, Sapunari Psychiatric Hospital, Calarasi, Romania,

<sup>b</sup>Psychiatry, UMF Carol Davila, Bucharest, Romania, <sup>c</sup>Psychology, Sapunari Psychiatric Hospital, Calarasi, Romania

**Motivation of topic:** Bipolar disorder is a complex disease, whose explanatory theories ranging from bio-genetic to the biochemical disturbances in the neuromediators, not be neglected the psychodynamic psychiatry explanations on pathology of defense mechanisms.

**Objective:** Present paper aims to study 20 patients hospitalized in the Sapunari Psychiatric Hospital, diagnosed with bipolar disorder, severe manic episodes with psychotic features, treated with a combination of Aripiprazole (doses ranging from 20 to 30 mg) and Valproate (doses ranging from 1000 to 2000 mg).

**Hypothesis:** Aripiprazole, by acting antipsychotic and antimanic subsidiary, acts in psychiatric sense on triple level: ideatic cognitive, affective (modulating the hostile irritable dysphoric disposal) and behavioral attitudes (reducing maniacal agitation). In psychodynamic meaning, long term administration of Aripiprazole modulates defenses used by patients in question, significantly acting on the concept of *reality testing*.

**Results:** The present study is a longitudinal type, following patients both during hospitalization, as well as for a period of at least one year post manic episode. Long-term action of Aripiprazole produces: thinking organization into planning dimension, sequencing, operational and increase coefficient of involvement in actions and activities; modulating the pathological mood through euthymia and stopping acting-out and irritable type discharges. In terms of psychodynamic, long-term treated patients with aripiprazole will replace the primitive defense mechanisms of the projection type, conversion in to the contrary, psychotic denial with mechanisms of repressive type, suppress and the ability to shape partial isolation.

**Conclusions:** Mania patients followed up in the long term study with aripiprazole showed quasi normal social functioning alongside adequate defenses both situational, as well reported to endogenous dynamics compulsion.

### Strategic algorithms of pharmacotherapy of bipolar affective disorder

I Zrazhevskaya<sup>a</sup>, B Tsygankov<sup>b</sup>, A Berezkin<sup>a</sup>, E Korovyakova<sup>c</sup>, A Ter-Israelyan<sup>a</sup>, E Topka<sup>a</sup>

<sup>a</sup>Department of Psychiatry Narcology & Psychotherapy, Peoples' Friendship University of Russia, Moscow, Russia, <sup>b</sup>Department of Psychiatry Narcology & Psychotherapy, Moscow State Medical Stomatological University, Moscow, Russia, <sup>c</sup>Department of General and Clinical Pharmacology Medical Faculty, Peoples' Friendship University of Russia, Moscow, Russia

**Aim:** The development of individualized, flexible strategic algorithms of effective and safe pharmacotherapy of BD, designed for use in departments as inpatient and outpatient types.

**Methods:** Clinical (anamnesic, psychopathological, dynamic, cat-anamnesic), statistical, selectively – paraclinical (including experimental-psychological survey, psychometric, pathopsychological; instrumental; laboratory, etc.).

**Results:** As a result of the research were determined the characteristic types of:- *premorbid personality traits of patients of BD* (paranoid, schizoid, dissociative, emotionally unstable, hysterical, anankastic, anxious, dependent, mixed);- *the initial period of the disease* (dissomnic, dyspeptic, psychovegetative, anergic, affective, algic, hypohedonic, hyperhedonic, addictive, polypragmatic);- *the disease onset* (suddenly, acute, subacute, gradual);- *syndromal variant of the current affective episode* (simple, adynamic, anesthetic, anankastic, hypochondriac, anxious, dysphoric, delusional or atypical depression, and also simple, delusional or atypical mania, either mixed depression/mania). Among them are revealed the most frequently encountered in BD and more typical for BD, then for recurrent depressive disorder or depressive episode. Next in patients with BD were selected 7 main options of combination of certain premorbid personality traits, types of the disease onset, syndromal variants of the initial period of the disease and of the current affective episode. For each variant there was developed the algorithm of pharmacotherapy. The algorithms are the systematic and structured multivariable step-by-step recommendations for prescribing therapy for stop acute and anti-relapse treatment. In the structure of each algorithm, the decision about the choice of drug is determined by 3 elements: efficiency, tolerability and safety. In all strategic algorithms at each stage also provides the possibility of solving tactical problems (for example, in the form of a correction dose of medication or dosing regimen, adding psychotherapy and/or psychoeducation, rehabilitation measures, and etc.).

**Conclusions:** Strategic algorithms of pharmacotherapy of BD are individualized, balanced approach to the treatment of bipolar patients on the basis of preliminary subtle clinical differentiation of the patient's condition at the moment of prescribing therapy. They are built using modern diagnostic criteria. These algorithms are reliable, because in the process of their development took into account the latest evidence, the results of the latest international research on the effectiveness, tolerability and safety of the medicines, which were included in algorithms.

## Economic burden of bipolar disorder in the United Kingdom: a patient-level exploratory analysis

A Abdul Pari<sup>a</sup>, J Simon<sup>b</sup>, J Wolstenholme<sup>a</sup>, J Geddes<sup>c</sup>, G Goodwin<sup>c</sup>

<sup>a</sup>Nuffield Department of Population Health Health Economics Research Centre, University of Oxford, Oxford, United Kingdom,

<sup>b</sup>Centre for Public Health, Medical University of Vienna, Vienna, Austria, <sup>c</sup>Department of Psychiatry, University of Oxford, Oxford, United Kingdom

**Background:** Bipolar disorder (BD) is a severe mental illness and one of the leading causes of disability worldwide. However, up-to-date evidence assessing the societal costs of BD using patient-level data in the UK is deficient.

**Aim:** Comprehensively estimate the societal costs of BD in the UK and explore clinical and socio-demographic factors driving the variations in the cost of BD.

**Method:** Health and non-health care resource use data were collected at baseline and four consecutive, prospective three monthly follow-up points up to 12 months for a cohort of 91 BD patients. Annual costs per patient were calculated and Generalised Estimating Equation framework was used to investigate factors influencing total cost. Cost-of-illness of BD was derived by multiplying the average annual costs per patient with the pooled prevalence rate derived from meta-analysis of the best available estimates of BD prevalence.

**Results:** The average annual cost of BD per patient was £12,617 (SE: ±£1085) with 68.1% of the total costs attributed to indirect costs, 30.6% to healthcare costs, 0.9% to private out-of-pocket expenses, and 0.5% to social care costs. Increased severity of depression by one unit on the Quick Inventory of Depressive Symptomatology-self reported scale was associated with 7.6% ( $p = 0.012$ ) increase in the total societal cost. The annual societal cost for BD in the UK was estimated to be £5.14 billion in 2010/11.

**Conclusion:** The cost of BD remains under-appreciated; policy makers need to be aware of the real economic burden that BD places on the society and take this information into consideration while making decisions on relevant patient care. Average change in severity of depression resulted in increased societal costs. Average symptom levels are largely determined by the clinical state between episodes and are not usually regarded as a serious target for management. Our results generate the hypothesis that significant cost savings could result from improved monitoring and control of symptoms between episodes. With indirect costs including productivity losses and informal care amounting to £3.5 billion, better treatment and care options may also mean substantial savings to the UK tax payer over and above the potential health gains.

## Mental health population study: a retrospective review of the incidence of prescribed antipsychotic medications and other substances detected in urine

R Millet<sup>a</sup>, M Ko<sup>b</sup>, P Woster<sup>b</sup>, M DeGeorge<sup>b</sup>, T Smith<sup>b</sup>

<sup>a</sup>NA, Carolina Behavioral Care, Durham, USA, <sup>b</sup>Medical Affairs, Ingenuity Health, Baltimore, USA

**Aims:** The purpose of this study was to identify potential non-adherence rates among patients on antipsychotic drug (APD) therapy and to determine if differences in urine drug testing (UDT) results exist between APD-positive and APD-negative patients.

**Methods:** Between April 15, 2013, to July 3, 2014, 7700 urine samples were obtained from patients prescribed APD. Samples were classified as APD positive (a positive LC/MS/MS result for APD parent and/or metabolite) or APD negative (negative LC/MS/MS). Samples were also classified as positive or negative for the following: non-prescribed opiate medications, non-prescribed synthetic opioids, cocaine, and THC.

**Results:** The study population was 45.6% male and had a mean age of  $42.9 \pm 13.3$  years. The geographic distribution was 83.1% South, 10.3% Midwest, 5.2% North, and 1.5% West. UDT was positive for APD in 75.2% of samples and negative in 24.8%. APD-negative individuals were more likely than APD positive to have a non-prescribed opiate found (16.6% vs 12.8%; OR, 1.36; 95% CI, 1.18–1.57), a non-prescribed synthetic opiate found (5.5% vs 3.2%; OR, 1.78; 95% CI, 1.39–2.27), have THC found (20.9% vs 18.5%; OR, 1.17; 95% CI, 1.02–1.33), and/or cocaine found (6.1% vs 3.7%; OR, 1.70; 95% CI, 1.35–2.14). Approximately 6% of all the samples had a non-prescribed APD (either parent or metabolite) found. In this group, 6% had both the prescribed APD present and an additional non-prescribed APD, and 6% of the samples were missing the prescribed APD with a different APD found.

**Conclusions:** These data suggest that UDT in patients who are prescribed APD can be of value in both monitoring adherence to APD therapy and in identifying the use of inappropriate prescription and non-prescription substances. The data also suggest that non-adherence to prescribed APD therapy is associated with use of non-prescribed opioids, marijuana, and cocaine.

## A prospective naturalistic multisite follow-up of survival times for patients with bipolar disorder treated under CANMAT guidelines

E Morton<sup>a</sup>, G Murray<sup>a</sup>, E Michalak<sup>b</sup>, R Lam<sup>c</sup>, S Beaulieu<sup>d</sup>, V Sharma<sup>e</sup>, P Cervantes<sup>f</sup>, S Parikh<sup>g</sup>, L Yatham<sup>b</sup>

<sup>a</sup>Faculty of Health Arts and Design, Swinburne University of Technology, Ashburton, Australia, <sup>b</sup>Department of Psychiatry, University of British Columbia, Vancouver, Canada, <sup>c</sup>Department of Clinical Neuroscience, University of British Columbia, Vancouver, Canada, <sup>d</sup>Bipolar Disorders Program, Douglas Hospital, Verdun, Canada, <sup>e</sup>Regional Mental Health Care, St. Joseph's Health Care, London, Canada, <sup>f</sup>Department of Psychiatry, McGill University, Montreal, Canada, <sup>g</sup>Department of Psychiatry, Toronto Western Hospital, Toronto, Canada

**Background:** Randomised trials do not reflect the reality of bipolar disorder (BD) treatment in clinical practice. Naturalistic data can illuminate real-world outcomes in BD. The aim of this study was to investigate time to relapse, remission and medical intervention for patients receiving CANMAT guideline-driven treatment for BD.

**Methods:** A total of 429 participants (62.1% female) aged 18 to 72 ( $M = 41.9$ ,  $SD = 12.3$ ) were recruited from 12 sites across Canada. Participants were diagnosed with BD (239 BD I, 151 BD I, 39 BD NOS). At baseline, participants met, or had recently met criteria for an episode of BD, or required a medication change. Data was collected at scheduled 3 monthly visits and unscheduled treatment-driven visits for between 1 and 4.5 years. Relapse and remission were operationalised according to accepted cutoffs for depression (HamD-17) and mania (YMRS). Survival curves for time to relapse, remission and medication change were plotted with the Kaplan Meier method.

**Results:** Polypharmacy was observed in 243 participants (56.6%), with approximately equal numbers prescribed antipsychotics (33.1%), anticonvulsants (37.5%), lithium (32.2%) and antidepressants (28.7%). A total of 337 participants achieved remission during the study (78.6%), with a mean of 356.61 ( $SD = 19.1$ ) days to first remission. Shorter time to remission was associated with (i) diagnosis of BD I ( $M = 322.9$  days,  $SD = 22.1$ ) versus BD II ( $M = 412.3$ ,  $SD = 35.6$ ,  $p < 0.05$ ), and (ii), polypharmacy ( $M = 402.9$ ,  $SD = 38.8$ ) versus monotherapy ( $M = 300.3$ ,  $SD = 38.8$ ) at baseline ( $p < 0.05$ ). At least one relapse was reported in 229 participants (53.3%,  $M = 653.4$  days to first relapse,  $SD = 39.2$ ). A total of 61 (14.2%) did not meet criteria for either relapse or remission. At least one medication change was recorded for 386 participants (90%,  $M = 120.6$  days to first change,  $SD = 9.8$ ).

**Conclusion:** Naturalistic investigation across an extended time period underscores the significant morbidity associated with BD, and the consequent complexity of its medication management: 90% of patients treated under consensus guidelines changed medications at some point. While the majority of patients experienced remission, approximately half relapsed within the study window.

## Insomnia and hypersomnia in bipolar disorder

MK Steinan<sup>a</sup>, J Scott<sup>b</sup>, TV Lagerberg<sup>c</sup>, I Melle<sup>c</sup>, OA Andreassen<sup>c</sup>, AE Vaaler<sup>a</sup>, G Morken<sup>a</sup>

<sup>a</sup>Department of Psychiatry, St. Olavs University Hospital, Trondheim, Norway, <sup>b</sup>Institute of Neuroscience, Newcastle University, Newcastle, United Kingdom, <sup>c</sup>KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, Norway

Sleep problems in Bipolar Disorder (BD) are common during and between episodes. However, rates vary from 10 to 80% depending on definitions of the sleep problems and the included patients. This study compares associations between current mental state and BD

subtype in groups with Insomnia, Hypersomnia and No Sleep Problems, and explores potential confounders such as age, gender, body mass index (BMI), and/or prescribed medications.

**Methods:** A cross-sectional study of 563 individuals with BD I or II who participated in a structured clinical assessment of demographic, clinical, illness history and treatment variables performed by trained researchers.

**Results:** Over 40% cases met criteria for Insomnia and 29% for Hypersomnia. In univariate analysis, Insomnia was associated with BD II depression; whilst Hypersomnia was associated with BD I depression or euthymia. Logistic regression analyses demonstrated that Insomnia and Hypersomnia showed different patterns for mood state compared with the No Sleep Problems group; both groups were significantly more likely to be depressed or in a mixed state. Furthermore, Hypersomnia cases were significantly more likely to be younger, BD I and prescribed antidepressants.

**Conclusions:** Whilst Insomnia symptoms are common in BD, Hypersomnia is a significant, frequently under-explored problem. Previous studies either failed to differentiate between the diverse sleep profiles associated with BD or had inadequate statistical power to examine sub-group difference in sufficient detail. More sophisticated studies with prospective follow-up are needed to ensure that future treatment protocols target different sleep problems in a systematic manner.

## A study of emotional intelligence in patients with bipolar disorder

I Arowolo, E Sundin, S Walker, P Premkumar

Psychology, Nottingham Trent University, Nottingham, United Kingdom

Emotions play a major role in an individual's life; people, irrespective of their status and age, tend to react in different ways to life events. Emotional intelligence (EI) is important in people's everyday life as it is considered as a basic skill for successful social interaction. In this study, we investigate if (1) people with bipolar disorder (BD) differ in their emotional intelligence from people in the general population and (2) people with BD have better abilities to identify and relate positive as compared to negative emotions. Gender differences in the emotional intelligence of people with BD and control group is also examined. To investigate these research questions, participants were ( $n = 100$  (50 females and 50 males). Half of the participants ( $n = 50$ ) are adults with BD recruited through BD support groups in the UK, and the other half ( $n = 50$ ) are adults in the general population (controls). Participants completed the Wong and Law EI Scale (WLEIS) Sense of Emotional Control Questionnaire (SEC) and Toronto Alexithymia scale (TAS-20). The controls were matched with the BD participants for age and gender. Current symptoms of BD participants are ascertained using Centre for Epidemiological Studies Depression scale and Young Mania Rating Scale (YMRS). The results from an initial, questionnaire study are presented. Results showed individuals with BD differ in their EI to the controls. Results of the ANOVA analysis also showed no gender differences between groups. Based on our result, we concluded that individuals with BD have a better ability to describe than to identify their feelings when compared to the control group. Discussion focuses on implication of the results for treatment and maintenance of BD. Further studies should clarify whether emotion recognition deficits influences ability to describe emotions in individuals with BD.

## The integrated intervention for patients with bipolar disorder in the Italian mental health services: a possible and effective choice

V Candini<sup>a</sup>, C Buizza<sup>b</sup>, C Ferrari<sup>a</sup>, A Ghilardi<sup>b</sup>, R Pioli<sup>c</sup>, E Sacchetti<sup>d</sup>, F Saviotti<sup>e</sup>, G de Girolamo<sup>f</sup>

<sup>a</sup>Epidemiological and Evaluative Psychiatry Unit, IRCCS St. John of God Fatebenefratelli, Brescia, Italy, <sup>b</sup>Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy,

<sup>c</sup>Psychiatric Unit, IRCCS St. John of God Fatebenefratelli, Brescia, Italy, <sup>d</sup>Department of Mental Health, Azienda Ospedaliera Spedali Civili, Brescia, Italy, <sup>e</sup>Department of Mental Health, Azienda Ospedaliera Desenzano s/G, Brescia, Italy, <sup>f</sup>Epidemiological and Evaluative Psychiatry Unit, IRCCS St. John of God Fatebenefratelli, Brescia, Italy

**Aims of the study:** (a) To implement structured psychoeducational interventions, according to the Colom and Vieta model, within the routine of the Italian Mental Health Services; (b) to assess their effectiveness in terms of reducing the number of hospitalizations (primary outcome); (c) to assess their effectiveness in terms of improving the awareness of the disease and reduction of self stigma (secondary outcomes).

**Methods:** The study involved 102 outpatients with diagnosis of BD type I and II. All patients received the standard treatment provided by the service (drug therapy) and in addition the experimental group also received psychoeducation (21 weekly sessions). The topics are: awareness of the disease, treatment adherence, early identification of warning signs, regularization of lifestyle. Psychoeducation was conducted by two psychologists specifically trained. Each group consisted of 8–12 people.

**Results:** The experimental group was composed of 57 patients, while the control group of 45. The average age was 41.5 years (SD = 9.1) for the experimental group and 44.8 (SD = 8.8) for the control group. The two groups are homogeneous for socio-demographic and clinics characteristics. In the group of people who have followed the psychoeducation, 46 patients (80.7%) completed the entire treatment program. During the year of follow-up, patients who attended psychoeducation have an average of 0.11 (SD = 0.36) hospitalizations, compared to an average of 0.47 (SD = 0.69) in the control group ( $U = 934$ ,  $p = 0.001$ ); patients in the experimental group spent an average of 1.75 days of hospitalization (SD = 7.0) compared to 10.16 days (SD = 16.8) recorded in the control group ( $U = 924$ ,  $p = 0.001$ ). During the Congress will be also presented data on the three years follow-up.

**Conclusions:** The present study has shown that psychoeducation, according to the Colom and Vieta model, is an effective intervention for the relapses prevention in patients with BD, also applicable in routine settings. This data confirm that the integrated treatment (drugs therapy plus psychoeducation) for bipolar patients is necessary in order to allow a better course of the disease.

## Ethical dilemmas of participant safety monitoring in online clinical research

V Cosgrove<sup>a</sup>, D Grimm<sup>b</sup>, E Gliddon<sup>c</sup>, S Lauder<sup>d</sup>, S Dodd<sup>c</sup>, M Berk<sup>c</sup>, T Suppes<sup>b</sup>

<sup>a</sup>Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, USA, <sup>b</sup>Bipolar and Depression Research Program, VA Palo Alto Health Care System, Palo Alto, USA,

<sup>c</sup>IMPACT Strategic Research Centre, Deakin University, Geelong Victoria, Australia, <sup>d</sup>Department of Psychiatry, The University of Melbourne, Parkville Victoria, Australia

**Aims:** Creating internet-based mental health assessment and intervention not only changes landscape of service provision, but also warrants ethical considerations that differ greatly from traditional treatment settings. Conducting clinical research with online plat-

forms for mental health intervention necessitates sailing even farther into ethically uncharted waters. This poster will consider the potential ethical concerns arising from participant monitoring in online technologies for mental health, citing experiences from the MoodSwings 2.0 self-help program for bipolar disorder.

**Methods:** In clinical research studies with high-risk populations, protecting participants and minimizing their clinical risk are paramount to most other concerns. While this remains true for online clinical trials, the conceptualization of risk must be broadened to include things such as confidentiality in online communications, data privacy and security. In a randomized controlled trial involving the MoodSwings 2.0 self-help intervention for individuals with bipolar disorder, a “Red Flag Monitoring System” is utilized. This system notifies researchers of users responding to self-administered assessments with high-risk answers (for example, expressions of suicidal ideation). Participants are assessed using self-report measures for depression (MADRS-S), mania (ASRM) and suicide (MADRS-S question 9 and HAM-D question 3).

**Results:** Specific safety monitoring data will be presented. Ethical concerns arising from this monitoring system, including participant follow up, will also be discussed.

**Conclusions:** Participant safety monitoring is vital in online clinical research, particularly when working with internet-based interventions targeting high-risk groups. It is crucial that researchers consider the many ethical dilemmas that can arise as a result of safety monitoring systems and the follow up required.

## Fast psychoeducational intervention in patients with affective disorders in a general hospital

LFO Costa<sup>a</sup>, APS Guimaraes<sup>b</sup>, LP Fascina<sup>c</sup>

<sup>a</sup>Psychiatry Coordinator, Hospital Sepaco, Sao Paulo, Brazil,

<sup>b</sup>Coordinator – General Practice, Hospital Sepaco, Sao Paulo, Brazil, <sup>c</sup>Hospital Board Director, Hospital Sepaco, Sao Paulo, Brazil

**Aims:** Estimate the prevalence of bipolar disorder and unipolar depression in a general hospital with psychiatric care and propose a fast psychoeducational manual for families and patients.

**Methods:** During 17 months was performed a screening of possible psychiatric patients admitted for other specialties at the Sepaco Hospital in Sao Paulo, Brazil, using an active search for patients and receiving query requests from other medical specialties. The active search consisted of seeking patients who had psychiatric history or were using psychotropic drugs. It was made according to the internal protocol of Psychiatry Service approved by the Ethics Committee and Hospital Board. Then we intended to establish the prevalence of psychiatric disorders in our hospital, especially affective disorders. The psychoeducational manual proposed took into account the most prevalent psychiatric disorders, the main questions of family members and patients and listed the main symptoms and their warning signs of symptomatic worsening.

**Results:** The data of 108 patients were collected over a period of 17 months with the following prevalence of psychiatric disorders: 37 patients (34%) had unipolar depressive disorder, 14 patients (13%) had personality disorders, 12 patients (11%) had anxiety disorders, 9 patients (8%) had dementia, 8 patients (7%) had bipolar disorder (including bipolar spectrum), 5 patients (5%) had drug dependence and 2 patients (2%) had schizophrenia.

**Conclusion:** Affective disorders (both unipolar depression and bipolar disorder) have high prevalence rates in hospitalized patients in a general hospital. From previous experience of care, it was found that most of the families and patients had little knowledge about depression and bipolar disorder and that this could encourage a greater number of readmissions for the same previous psychiatric conditions. The proposal to create a psychoeducational

manual of quick reference may assist in the early detection of symptoms and better clinical outcomes.

## Meditation, mindfulness and Naikan: are they for me?

**A Lamden**

*MS, LPC, Anna, Locus Therapy Center, US*

Meditation, Mindfulness and Naikan: Are they for me? Moderator: Manuel S Silverman This session will explore the use of meditation, mindfulness-training and the Naikan method. Participants will share opinions regarding the use of these methods. Topics will include: definition of terms, process, time management, practicality and resources for patient support. Participants will share insights regarding the use of these methods. Meditation relates to relaxation, with conscious attention on the “here and now.” Attention is focused on a sound, an object, a visualization, breath or even a word. Mindfulness-based methods also involve attention to the here and now, with emphasis on awareness of one’s senses, thoughts, feelings and attitudes, applied non-judgementally. The Naikan process emphasizes forgiveness grace and self-reflection. Naikan poses 3 questions. Meditation on each of the questions asks for information as specific as possible. The questions are: 1) What gifts have I received from other (s)? 2) What gifts have I given to other(s)? 3) What trouble have I caused to other(s)? Meditation on each of the 3 questions asks for answers that are as specific as possible. Naikan practitioners claim that this process enhances self-reflection and self-understanding with a decrease in symptomatic behavior and better relationships with others. Our brainstorming will examine and assess the uses and abuses of these three processes.

## Negative familiar environment and child trauma can be associated with bipolar disorder

**R Moreno<sup>a</sup>, R Orselli Monteiro<sup>b</sup>, D Soares Bio<sup>a</sup>, M Soerio-de-Souza<sup>a</sup>, G Missio<sup>a</sup>, A Osório<sup>c</sup>, G Antunes<sup>a</sup>**

<sup>a</sup>Bipolar Disorder, Department & Institute of Psychiatry University of Sao Paulo, Sao Paulo, Brazil, <sup>b</sup>Student, Universidade Presbiteriana Mackenzie, Sao Paulo, Brazil, <sup>c</sup>Neuropsychology, Universidade Presbiteriana Mackenzie, Sao Paulo, Brazil

**Background:** Bipolar disorder can be characterized by high levels of childhood trauma as well as of negative familiar environment. Our aim is to investigate the association between these two factors in bipolar patients and in healthy controls.

**Materials and methods:** A total of 80 patients with bipolar disorders in euthymia, aged between 18 and 40 years old, were recruited at Hospital das Clinicas in São Paulo, Brazil. Ninety four healthy volunteers (predominantly medical students) aged between 18 and 35 years old, with no current or past history of psychiatric disorder, were recruited from the University of São Paulo. Information about early life stress was obtained using the Childhood Trauma Questionnaire (CTQ) and environment was obtained using the Family Environment Scale (FES).

**Results:** In the bipolar group were observed that Physical abuse, emotional neglect and emotional abuse were significantly associated with reduced scores on independence ( $p < 0.001$ ,  $p = 0.002$  and  $p < 0.001$ ) and conflict ( $p = 0.006$ ,  $p < 0.001$  and  $p < 0.001$ ). Emotional Neglect and Emotional abuse were associated with intellectual cultural ( $p = 0.002$  to  $p = 0.001$ ) and active recreation ( $p < 0.001$  to  $p = 0.006$ ). Abuse was associated with reduced scores on Moral Religious ( $p < 0.001$ ). the correlation made between control group with the bipolar group, could observe the healthy group only has higher values in the Family Environment Scale in the following items, Expressiveness ( $p < 0.001$ ), Independence

( $p < 0.001$ ), Intellectual Cultural ( $p = 0.005$ ), Active- recreation ( $p < 0.001$ ).

**Conclusion:** Our results indicate that childhood trauma is associated with a negative familiar environment on Bipolar Disorder Type I. In accordance with the results we can blurt the importance of a child grow up of a healthy family environment so that traumas can be smaller or nonexistent.

## Young-adult family members as participants, recipients and agents in psychosocial interventions for mental health promotion in Germany and Canada

**M Schnute**

*Pedagogy & Organizational Studies, Social Sciences, Hildesheim, Germany*

**Background:** Networks of collaborative healthcare between consumers, family members, communities, healthcare-, and social service providers play an increasing role for mental health promotion and psychosocial intervention. At the same time, more research is needed on the effects, barriers and potentials of family member (FM) participation in psychosocial interventions in general, and the special implications of involving young-adult family members in particular.

**Objectives:** To generate a grounded theory on the coping strategies and support needs and experiences of young Germans and Canadians during their transitions to adulthood in the context of current healthcare and welfare reforms.

**Methods:** Art-based social network visualizations and biographic-narrative interviews were collected with 49 young Germans and Canadians and analyzed in accordance with the grounded theory methodology.

**Results:** Outcomes suggest the close intertwinement between personal, professional and contextual factors in regard to barriers, effects and potentials for FM participation in mental health promotion. On the personal level, FMs’ shared concern to ensure the well-being of their affected parent, sibling or spouse is embedded in an inverse relationship with the developmental demands of being a young agent negotiating the transition to adulthood. At the professional level of healthcare provision, exclusionary practices and a perceived lack of confidence towards working with FMs, shapes FMs’ roles as participants and potential recipients of care and support. The contextual level goes beyond the realm of health and includes employment and social services. Cumulative effects between support gaps in the healthcare and social service system create FMs’ experiences of mutual exclusivity with regards to intervention-participation and life organization.

**Conclusion:** FM participation and effects in psychosocial intervention are not only the outcome of personal choices, but also grounded and re-enforced by professional and contextual structures, preconceptions of health and gaps in inter-sectoral collaboration. Therefore it is important to understand the complex interplay of personal, professional and contextual factors that inform young-adults’ roles as participants, recipients and agents in collaborative mental healthcare settings in order to plan and deliver inclusive and effective healthcare interventions for this young population and their affected loved ones.

## Meditation, mindfulness and Naikan: are they for me?

**M Silverman**

*Psychological Services Locus Therapy Center, Chicago, USA*

Meditation, Mindfulness and Naikan: Are they for me? Moderator: Manuel S Silverman This session will explore the use of medi-

tation, mindfulness-training and the Naikan method. Participants will share opinions regarding the use of these methods. Topics will include: definition of terms, process, time management, practicality and resources for patient support. Participants will share insights regarding the use of these methods. Meditation relates to relaxation, with conscious attention on the "here and now." Attention is focused on a sound, an object, a visualization, breath or even a word. Mindfulness-based methods also involve attention to the here and now, with emphasis on awareness of one's senses, thoughts, feelings and attitudes, applied non-judgementally. The Naikan process emphasizes forgiveness grace and self-reflection. Naikan poses 3 questions. Meditation on each of the questions asks for information as specific as possible. The questions are: 1) What gifts have I received from other (s)? 2) What gifts have I given to other(s)? 3) What trouble have I caused to other(s)? Meditation on each of the 3 questions asks for answers that are as specific as possible. Naikan practitioners claim that this process enhances self-reflection and self-understanding with a decrease in symptomatic behavior and better relationships with others. Our brainstorming will examine and assess the uses and abuses of these three processes.

### Naikan process: wellness through introspection

**M Silverman**

*Psychological Services Locus Therapy Center, Chicago, USA*

Dr. Silverman has a PhD in counseling psychology from Northwestern University and is a Licensed Clinical Psychologist. He is an expert on the diagnosis and treatment of social anxiety, depression, and bipolar disorder. In addition to having treated adolescents, adults, and families with mood disorders and/or chronic illnesses for more than 40 years, Dr. Silverman also taught in the counseling psychology department at Loyola University Chicago. He has written over 75 articles and has published two books, *Stormy Weather* and *Counseling the Opiate Addict*. His experience also extends to counseling and public speaking engagements in the United States, Canada, Mexico, the Philippines, and Singapore. He has served on both the local and national boards of the Depression and Bipolar Support Alliance and is an executive member of the national Depression and Bipolar Support Alliance. He is also active in the International Society for Bipolar Disorder, serving on their advocacy board.

### Influence of depressive symptoms on the functionality in a early onset sample of first manic episode patients

**M Martínez-Cengotitabengoa<sup>a</sup>, C Bermúdez-Ampudia<sup>b</sup>, A García-Alocén<sup>b</sup>, I González-Ortega<sup>a</sup>, S Alberich<sup>b</sup>, P López<sup>b</sup>, A González-Pinto<sup>c</sup>**

<sup>a</sup>Psychiatry, University Hospital of Alava-Santiago. National Distance Education University, Vitoria-Gasteiz, Spain, <sup>b</sup>Psychiatry, University Hospital of Alava-Santiago, Vitoria-Gasteiz, Spain,

<sup>c</sup>Psychiatry, University Hospital of Alava-Santiago. University of Basque Country, Vitoria-Gasteiz, Spain

**Aims:** The early appearance of depressive symptoms during a first manic episode, is very important and could influence negatively the evolution and prognosis of the patient. In general, patients with an early onset of the disease have a poor prognosis than those with a later onset (Lopez et al 2001). For this reason the objective of this study is to evaluate the presence of depressive symptoms in a group of manic patients under 40 years old and assess their influence in the functionality of patients after one year of follow-up.

**Methods:** The sample included 75 patients with a first manic episode started before the age of 40. All of them were inpatients of the Psychiatric Unit of the University Hospital of Alava and diagnosed according to DSM-IV criteria. Patient's functionality was assessed by Functioning Assessment Short Test (FAST) and depressive symptoms by Hamilton Rating Scale for Depression (HRSD), both of them administered to patient one year after the illness onset. In order to assess the influence of depressive symptoms into the functionality we used a logistic regression model. We chose FAST score as dependant variable in a dicotomic manner (cut point 18) and HRSD score as independent one.

**Results:** The sample has an age mean of  $28.0 \pm 7.6$ , from which 34 patients show a good functionality versus 41 with bad and is composed of 61 men and 30 women. For the whole sample we found significant outcomes in the influence of the depressive symptoms into the functionality, in such a way that it is more likely to present a bad functionality one year after the illness onset when there is a higher depressive symptomatology at the same time (OR = 1.505;  $p = 0.001$ ).

**Conclusions:** In this study we observed that patients with a first episode of mania with a higher presence of depressive symptoms 1 year after the illness onset are more likely to show a bad functionality too. These results highlight the importance of early and effective interventions from the first appearance of a manic episode in order to prevent the deleterious effects of the disease in the long term.

# Author Index

- Aas, M., 72, 73, 80, 98  
 Abdel-Malek, A., 111  
 Abdul Pari, A., 138  
 Abramowicz, M., 51  
 Abramson, L.Y., 119  
 Abreu, L.N., 114  
 Agartz, I., 127  
 Agrawal, S., 35  
 Ahmed, S., 95  
 Ahn, S., 70  
 Ahn, Y., 125  
 Akdeniz, F., 124  
 Akers, B., 58  
 Al Jurdi, R.K., 28  
 Alarcon, R., 17  
 Alberich, S., 142  
 Albuquerque, M., 79  
 Alda, M., 32, 49  
 Alexandra, S., 123  
 Ali, S.B., 86  
 Allega, O.R., 120, 126  
 Allen, N., 54  
 Alloy, L.B., 119  
 Almeida, J.G., 78, 120  
 Almeida, K.M., 77  
 Alphen, A.M., 135  
 Altamura, A.C., 108  
 Altshuler, L., 31, 106  
 Alvarado, P., 51  
 Álvarez, R., 92, 137  
 Alves Pereira, V., 54  
 Amann, B., 74  
 Aminoff, S.R., 72, 77  
 Anderson, J., 62  
 Andreassen, O.A., 68, 72, 73, 77, 80, 94, 98, 127, 139  
 Andreatza, A.C., 11, 13, 49, 59, 59, 63  
 Andruskevicius, S., 66  
 Angers, K., 69, 97, 122, 134  
 Ansari, S.H., 95  
 Antony, A., 123  
 Antunes, G., 131, 141  
 Arahamian, I., 70, 78, 120  
 Arat, E., 100  
 Arbour-Nicitopoulos, K., 65  
 Arciszewska, A., 71, 79, 113  
 Arnold, L.E., 62, 118  
 Arowolo, I., 139  
 Arvilommi, P., 93  
 Ashraf, M., 117  
 Assuncao, F., 119  
 Atkinson, L., 111  
 Atriano, C., 51  
 Attenburrow, M.J., 25, 50, 110  
 Aubin, V., 52  
 Aubry, J.M., 30  
 Auer, D.P., 83  
 Austin, D., 94  
 Azorin, J.M., 52  
 Babadi, B., 85  
 Badcock, J., 76  
 Baek, J.H., 81, 85  
 Bahk, W.M., 31  
 Baker, A., 12  
 Baldessarini, R.J., 91  
 Balzafiore, D., 114  
 Bani-Fatemi, A., 58  
 Barbieri, S., 77  
 Barbosa, I., 81  
 Bardram, J., 85  
 Bareis, N., 131  
 Barendregt, J., 52  
 Barichello, T., 58  
 Bartsch, H., 125  
 Basu, S., 77, 86  
 Batzler, A., 54  
 Bauer, I.E., 96  
 Bauer, M., 12, 31  
 Beaglehole, B., 87  
 Beaulieu, S., 81, 111, 139  
 Bellivier, F., 19, 52, 72, 73, 80  
 Bellvior, F., 56  
 Belzeaux, R., 56  
 Benizr, C., 19  
 Berezkin, A., 137  
 Bergen, S., 94  
 Bergink, V., 34  
 Berk, L., 21, 54, 94, 128  
 Berk, M., 14, 15, 15, 16, 18, 21, 52, 54, 57, 68, 85, 91, 94, 99, 109, 113, 128, 140  
 Berlanga-Flores, C., 51  
 Bermudez, C., 125  
 Bermúdez-Ampudia, C., 142  
 Bernal, G., 97  
 Bernstein, E., 23, 75  
 Berutti, M., 54  
 Besche-Richard, C., 71, 113  
 Bettella, F., 98  
 Biernacka, J., 54, 59, 61, 72, 78, 100, 102, 116  
 Bilderbeck, A.C., 86, 110, 111, 129  
 Bio, D., 131  
 Birmaher, B., 8, 118  
 Bissierbe, J.C., 118  
 Bjella, T., 72  
 Bjella, T.D., 73  
 Bjørngaard, J.H., 95  
 Black, C.L., 119  
 Blacker, C.J., 124  
 Blackwell, S., 37  
 Blixen, C., 117  
 Bobo, W.V., 23, 45, 46, 53, 78, 102, 116  
 Bohus, M.R.M., 18  
 Bolton, J., 93  
 Bond, D.J., 14, 49, 55, 59, 116  
 Bonnín, C.M., 97, 128  
 Bosch, T.M., 135  
 Bostock, E.C.S., 79  
 Boudebessé, C., 19, 52  
 Bouteloux, M., 37  
 Bowden, C.L., 23  
 Bowe, S., 81  
 Bowersox, N., 87  
 Bowie, C., 87  
 Boyce, P., 35  
 Bozaoglu, K., 84  
 Bradler, K., 49  
 Braileanu, D., 123, 137  
 Brambilla, P., 17  
 Breakspear, M.L.R., 11, 51  
 Bressan, R., 103  
 Brett, D., 86  
 Brietzke, E., 103, 119  
 Brody, B., 23  
 Brown, R.D., 53  
 de Bruin, C., 109  
 Buizza, C., 140  
 Burger, H., 126  
 Burghardt, K., 115  
 Burke, A., 114  
 Caillies, S., 113  
 Cairney, J., 93  
 Calabrese, J.R., 15, 25, 130  
 Can, G., 100  
 Canale, F., 75, 115  
 Candini, V., 140  
 Capponi, P., 32, 33  
 Carneiro, A., 131  
 Carp, E.G., 137  
 Carrillo, R., 51  
 Carter, R., 52



## Author Index

- Cassidy, K., 117  
 Castelao, E., 30  
 Castle, D., 76  
 Castro, V., 12  
 Casuto, L., 61  
 Ceglowski, J., 21  
 Cercy, K., 61  
 Cervantes, P., 81, 139  
 Ceylan, D., 100  
 Cha, B., 121  
 Chaimani, A., 56  
 Chamberlain, A.M., 53  
 Chang, C., 135, 135  
 Chang, K., 36  
 Chang, K.D., 106  
 Chatterjee, P., 130, 131  
 Chatterton, M.L., 52  
 Chaudhry, I.B., 95, 136  
 Chen, K., 112, 127  
 Chen, M.L., 78  
 Chen, P.H., 78  
 Chen, X., 127  
 Chengappa, K.N.R., 33  
 Cheung, A., 93  
 Chlopocka-Wozniak, M., 51  
 Cho, C., 66  
 Cho, E., 81  
 Cho, Y., 87  
 Choi, D., 102  
 Choi, J.W., 121  
 Choi, M., 87  
 Choudhury, T., 10  
 Christensen, E.M., 85  
 Christensen, H., 129  
 Chrobak, A.A., 71, 79, 113  
 Chuang, P.Y., 135, 135  
 Chung, K.H., 78  
 Chung, P.F., 135  
 Chung, T., 60, 67, 80, 109, 111  
 Cichon, S., 18  
 Cigliobianco, M., 108  
 Cipriani, A., 56, 110  
 Clifford, G.D., 86, 129  
 Coelho, L.P., 70  
 Cohen, B., 13, 84, 101  
 Collins, J., 105, 107  
 Colom, F., 38, 96, 97, 128  
 Comes, M., 97  
 Cooke, C., 32  
 Cordeiro, Q., 119  
 Corrêa, H., 79, 116  
 Cosgrove, V., 36, 36, 68, 85, 94, 128, 140  
 Costa, L.F.O., 140  
 Cotton, S.M., 18  
 Courtet, P., 52, 56  
 Courtin, C., 19  
 Craddock, N., 73, 90, 120  
 Cremaschi, L., 108  
 Croarkin, P., 59, 61, 102  
 Crow, S., 116  
 Crowe, M., 87  
 Cucchiaro, J., 88, 88, 88, 92, 132, 132, 133, 133  
 Cuellar-Barboza, A.B., 54, 61, 75, 78, 115  
 Cui, L., 30  
 Cullen, K., 59  
 Cunha, G., 103  
 Cussac, I., 56  
 Cuthbert, B., 8  
 Czechor, J., 99  
 Daglas, R., 18, 109  
 Dahmen, N., 18  
 Daigneault, A., 111  
 Dandash, O., 109  
 Darggoél, A.A., 52  
 D'Souza, I., 89  
 Datto, C., 89, 90, 133  
 Dawson, N.V., 117  
 De Luca, V., 58, 121  
 De Quevedo, J., 58  
 Dean, O., 91  
 Debelle, M., 89  
 Deckersbach, T., 15, 15, 16, 23, 47, 47, 57, 75, 94, 110, 113  
 Degenhardt, F., 18  
 DeGeorge, M., 138  
 DelBello, M.P., 59, 106  
 Dell'Osso, B., 108  
 Dembinska-Krajewska, D., 76  
 Demirer, R.M., 82  
 Demmo, C., 68, 77  
 Depp, C.A., 21, 97  
 Desage, A., 37, 96  
 Dev, S., 125  
 Dhaliwal, D., 120  
 Dhanoa, T., 49, 59  
 Di Florio, A., 90, 120  
 Dias, R., 56, 128  
 Díaz, A.M., 63  
 Dietch, D., 46  
 Dietl, L., 18  
 Dizdaro lu, M., 100  
 Djouini, A., 111  
 Djurovic, S., 98  
 Dobrea, C., 108  
 Dodd, S., 68, 85, 91, 128, 140  
 Doederlein, A., 24, 33, 37, 110  
 Dolinoy, D., 115  
 Dols, A., 66  
 Domingui, D., 58  
 Dora, B., 84  
 Doucette, S., 11  
 Dougherty, D.D., 15, 15, 16, 47, 47  
 Douglas, K., 87  
 Douglas, S., 101  
 Drevets, W., 13  
 Du, F., 13, 84  
 Duarte, D., 79  
 Dudek, D., 71, 79, 113  
 Duffy, A., 11  
 Duncan, M., 65  
 Durgam, S., 89, 90  
 Dutra, I., 128  
 Earley, W., 90  
 Edenberg, H., 11  
 Edgman-Levitan, S., 110  
 Eftekhari, P., 99  
 Einstadter, D., 117  
 Elie, D., 116  
 Ellingrod, V., 115  
 El-Mallakh, R., 58, 82  
 Eppel, A., 134  
 Epstein-Lubow, G., 117  
 Erol, A., 78  
 Escamilla, M., 60  
 Eschbach, J., 99  
 Etain, B., 19, 20, 24, 52, 56, 72, 73, 80, 96  
 Evans, J., 100  
 Eyler, L.T., 83, 125  
 Fang, F., 91  
 Fang, Y.R., 75  
 Farahbakhsh, M., 110  
 Faraone, S., 23  
 Farb, D., 13, 32  
 Fascina, L.P., 140  
 Fasmer, O.B., 86  
 Faulkner, G., 65  
 Faurholt-Jepsen, M., 85  
 Favila, R., 51  
 Feeder, S., 102  
 Fernandes, B., 91  
 Fernandes, J.N., 112  
 Ferrari, C., 140  
 Findling, R.L., 64, 65, 76, 104, 106, 118  
 Fischer, H.D., 74  
 Flores, D., 60  
 Follenfant, A., 96  
 Forcada, I., 134  
 Forester, B., 132, 133  
 Forlenza, O.V., 70, 78, 120  
 Fornito, A., 109  
 Foroud, T., 11  
 Forstner, A., 18  
 Forty, L., 73, 90, 120

- Frank, E., 15, 16, 17  
Frank, F., 19  
Frankland, A., 11, 51  
Frazier, T.W., 118  
Frey, B., 24  
Frey, B.N., 48, 100, 108, 120, 126  
Friedman, E., 23  
Fristad, M.A., 62, 118  
Frost, M., 85  
Frye, M.A., 17, 31, 31, 33, 53, 54, 57, 59, 61, 67, 72, 78, 100, 102, 106, 116, 124, 133  
Fullerton, J., 11  
Fung, K., 74
- Gadelha, A., 103  
Gallardo, M., 61, 103  
Ganeshan, D., 50  
Gao, K., 91  
Gao, Y., 58, 82  
García-Alocén, A., 125, 142  
Gard, S., 37, 56, 96  
Gardiner, A., 23, 50  
Gardner, W.P., 62  
Garnham, J., 49  
Garry, M.I., 79  
Gaudiano, B.A., 117  
Geddes, J.R., 12, 23, 50, 56, 86, 110, 111, 129, 138  
Geerling, B., 45, 46  
Generoso, J.S., 58  
van Gent, E., 109  
Geoffroy, P.A., 19  
Geske, J., 59, 61, 72, 78  
Ghaziuddin, N., 11  
Ghilardi, A., 140  
Gholam-Rezaee, M., 30  
Gierski, F., 113  
Gigler, M.E., 75  
Gildengers, A., 25  
de Girolamo, G., 140  
Gliddon, E., 68, 85, 94, 128, 140  
Glowinsky, A., 11  
Gobin, P., 71  
Godin, O., 52  
Goffin, K.C., 76, 114, 118, 122  
Goldbach, J., 84  
Goldstein, B., 21, 63, 64, 65, 65, 84, 102, 104, 105, 105, 105, 107, 112  
Gómez, A., 61, 103  
Gonzalez, R., 60  
Gonzalez, S.D., 60  
González-Ortega, I., 142  
Gonzalez-Pinto, A., 125, 142  
Goodale, L., 22  
Goodman, D., 110  
Goodrich, J., 115
- Goodwin, G.M., 17, 23, 29, 37, 50, 86, 110, 111, 129, 138  
Gordon-Smith, K., 73, 90, 120  
Gossink, F.T., 66  
Grande, I., 14, 134  
Granholm, E.L., 21  
Grassi-Oliveira, R., 103  
Green, M.A., 50  
Green, M.J., 11, 51  
Greenberg, R., 62  
Grigoriadis, S., 93  
Grimm, D., 68, 85, 94, 128, 140  
Grof, P., 11  
de Groot, J.C., 126  
Gruber, J., 81  
Gruber, S., 84  
Gründer, G., 68  
Grunebaum, M.F., 114  
Gruneir, A., 74  
Grunze, H., 9, 31  
Grzenda, A., 72  
Guadamuz, A., 51  
Guimaraes, A.P.S., 140  
Guimaraes, F.T.L., 81  
Gulei Gradinaru, B.M., 123  
Gülşen Küçüksabas, Y.B., 108  
Gunnar, M., 24  
Gunzler, D., 117  
Guo, H., 90  
Gusenbauer, K., 120  
Gutt, A., 123
- Ha, K., 31, 60, 67, 80, 81, 87, 109, 111  
Ha, T., 60, 67, 109, 111  
Ha, T.H., 80  
Haarman, B.C.M., 126  
Haddad, P., 95  
Hagan, G.O., 64  
Hajek, T., 32  
Hales, S., 37  
Hall, A., 126  
Hall, G.B., 126  
Hall, M.H., 101  
Hallmayer, J., 36  
Halverson, T.F., 64, 65, 104  
Hamalgeanu, M., 137  
Hamdani, N., 20  
Hamirani, M.M., 95, 136  
Hanford, L., 126  
Hansen, N.S., 15, 15, 16  
Hanstock, T.L., 53, 63  
Harel, Z., 74  
Harmer, C.J., 12, 86, 110, 111, 129  
Harrison, P.J., 12, 50, 86, 110, 129  
Hartberg, C., 127  
Hatch, J., 63
- Haukvik, U.K., 127  
Hautzinger, M., 96  
Hawke, L., 35, 36, 73  
Hayek, A., 69, 97, 122, 134  
Hazell, P.L., 53, 63  
Hearing, C., 110  
Heilmann, S., 18  
Hellemann, G., 31  
Hellvin, T., 77  
Henriksen, T.E.G., 86  
Henry, C., 32, 37, 52, 72, 73, 80, 96  
Herbert, A.M., 107  
Hercegovic, A., 135  
Herrmann, N., 74  
van den Heuvel, O., 127  
Hickie, I., 30  
Hidalgo, M.P., 108  
Hidalgo-Mazzei, D., 97, 128, 134  
Hidiroğlu, C., 70  
Highsmith, W., 100  
Hinds, C., 23, 50  
Hinrichs, K., 69, 97, 122, 134  
Hirneith, S.J., 53, 63  
Hoekstra, R., 135  
Holcroft, C., 116  
Holmes, E.A., 37  
Holtzman, J.N., 76, 91, 118, 122  
Hong, K., 81, 87  
Hong, W., 75  
Hooshmand, F., 76, 118, 122  
Hornbacher, M., 25  
Horrocks, J., 11  
Horwitz, S.M., 118  
Hoschl, C., 32  
Houenou, J., 32  
Hsieh, M., 135, 135  
Hu, S., 69  
Huang, S.H., 78  
Huber, R., 55  
Hughes, J., 49, 59  
Huh, I., 81  
Hulvershorn, L., 11  
Hundt, C., 92  
Huryk, K., 57  
Husain, M.I., 95, 136  
Husain, M.O., 95  
Husain, N., 95, 136
- Iacoviello, B., 57  
Ibañez, I., 61, 103  
Icick, R., 73  
Inder, M., 87  
Iosifescu, D.V., 57, 88  
Iskric, A., 104, 105, 105  
Isometsa, E., 26, 93  
Iwabuchi, S.J., 83  
Iza, M., 92, 137

## Author Index

- Jacoby, A., 67  
 Jain, S., 123  
 Jang, J., 121  
 Jang, S., 67, 80, 109, 111  
 Janney, C., 87  
 Jaramillo, C.L., 63  
 Jelihovschi, A.P.G., 112  
 Jenkins, G., 100  
 Jenkins, G.D., 54, 102  
 Jensen, P., 61  
 Jerez, A., 60  
 Jewell, L., 110  
 Jeziorko, S., 71, 79, 113  
 Jiménez, E., 97  
 Joas, E., 136  
 Joffe, H., 56  
 John, J.P., 123  
 Johnson, E.M.S., 124  
 Johnson, S., 49, 54  
 Jones, I., 35, 73, 90, 120  
 Jones, L., 73, 90, 120  
 Jones, S., 54  
 Joo, E., 125  
 Jordan, J., 87  
 Jørgensen, K.N., 127  
 Joshi, P., 61  
 Jungkunz, M., 18  
 Juruena, M.F., 46  
 Jutant, A., 37
- Kahn, J.P., 56  
 Kaladjian, A., 113  
 Kale, R., 57, 99  
 Kallestad, H., 95  
 Kamali, M., 11, 23, 69, 97, 122, 134  
 Kang, S., 66  
 Kanske, P., 83  
 Kanuch, S., 117  
 Kapczinski, F., 20  
 Karanti, A., 136  
 Kauer-Sant'Anna, M., 103  
 Kaymak Koca, E., 70  
 Keating, C., 49  
 Keck Jr, P., 106  
 Keck, P., 31  
 Kelly, L., 92  
 Kemp, D., 23  
 Kennedy, J., 64  
 Kennedy, S.H., 103  
 Keown-Stoneman, D., 11  
 Kesebir, S., 69, 70, 72, 82, 108, 112, 122  
 Kessing, L.V., 26, 28, 60, 67, 85, 101, 104  
 Ketter, T.A., 23, 76, 91, 92, 108, 114, 118, 122  
 Khan, M., 79
- Khoo, J., 52  
 Khoso, A.B., 136  
 Kilbourne, A., 87  
 Kim, B.J., 121  
 Kim, E., 60, 67  
 Kim, E.J., 80  
 Kim, H., 66, 76, 114, 118  
 Kim, J., 60, 67, 80, 87, 87, 109, 111  
 Kim, L., 66  
 Kim, S., 125  
 Kim, W., 76, 118  
 Kim, Y., 99, 125  
 Kinrysm, G., 23  
 Kiran, T., 95  
 Kırkalı, G., 100  
 Kirkby, K.C., 79  
 Kirner, A., 68  
 Klaas, J.P., 53  
 Kleiman, E.M., 113  
 Kleindienst, N., 18  
 Knott, S., 73  
 Ko, M., 138  
 Kocsis, J.H., 23  
 Koeter, M., 127  
 Kolbe, M., 15, 55  
 Koller, D., 11  
 Kollmann, B., 71  
 Kondo, D., 55  
 König, B., 74  
 Kopecek, M., 32  
 Korczak, D., 64, 65  
 Korovyakova, E., 137  
 Kouzani, A., 57, 99  
 Kovacevic, S., 83  
 Kozicky, J.M., 49, 59  
 Krane-Gartiser, K., 86  
 Kraszewska, A., 51  
 Krawczak, E., 108  
 Krawczyk, M., 131  
 Kreindler, D., 80, 129  
 Krishnamoorthy, R., 20  
 Kroger, H., 88, 88, 132, 133, 133  
 Krumm, B., 18  
 Krupp, S., 58  
 Kruse, J.L., 53  
 Kuman, O., 124  
 Kung, S., 17, 102  
 Kupfer, D., 8  
 Kupka, R., 31, 106  
 Kurdyak, P., 93  
 Kvitland, L., 68, 77  
 Kyrios, M., 54
- Laber, E., 93  
 Lacey, C., 87  
 Ladeira, R.B., 70, 78
- Lafer, B., 31, 54, 56, 70, 77, 78, 114, 120, 128  
 Lagerberg, T.V., 72, 73, 77, 94, 139  
 Lai, B., 112, 127  
 Lai, J., 69  
 Lai, Z., 69  
 Lam, R.W., 49, 55, 59, 81, 139  
 Lamden, A., 141  
 Lameira, D., 30  
 Lamers, F., 30  
 Landbloom, R., 92  
 Landén, M., 94, 136  
 Langenecker, S., 69, 97, 134  
 Lankappa, S., 83  
 LaPorte, S., 89, 90, 133  
 Larsen, M.E., 129  
 Larsson, H., 94  
 Laszlovszky, I., 90  
 Lauder, S., 68, 85, 94, 128, 140  
 Lau-Zhu, A., 37  
 Lavebratt, C., 61  
 Le Couteur, A.S., 117  
 Leach, R.J., 60  
 Leboyer, M., 20, 52, 72  
 Leclerc, E., 119  
 Lee, A., 87  
 Lee, B., 125  
 Lee, C.S., 121  
 Lee, D., 121  
 Lee, E., 66  
 Lee, H., 60, 66, 67, 109  
 Lee, H.J., 80  
 Lee, K., 81, 125  
 Lee, S., 60, 66, 67, 80, 109, 111  
 Lee, S.J., 121  
 Lee, T., 112  
 Leffler, J., 59  
 Lei, Z., 82  
 Leitan, N., 21, 49, 54  
 Lenroot, R., 51  
 Leon, A.C., 23  
 Leppämäki, S., 93  
 Leverich, G., 31  
 Levy, D., 101  
 Levy, F., 51  
 Lewin, T.J., 53, 63  
 Lewis, A., 94  
 Lewis, C.P., 124  
 Li, M., 103  
 Li, T., 127  
 Lichtenstein, P., 94, 136  
 Lieb, K., 18  
 Lima, I., 112  
 Lin, K., 112, 127  
 Lin, P., 84  
 Linke, J., 71, 83  
 Lipkovich, I., 93

- Lipschitz, A., 90  
Liss, C., 89, 133  
Liu, T.T., 83  
Loebel, A., 88, 88, 88, 92, 132, 132, 133, 133, 136  
Loftus, J., 56  
Lolich, M., 91  
Looper, K.J., 116  
López, P., 125, 142  
López-Jaramillo, C., 130  
Lord, A., 11  
Losey, J., 20  
Low, N.C.P., 116  
Lu, C., 82  
Lu, K., 83, 89  
Lu, W., 112, 127  
Lubarda, J., 130, 131  
Luby, J., 61  
Luty, L., 113
- M'Bailara, K., 37, 52, 96  
McAndrews, M.P., 103  
McCormick, R., 117  
McCoy, T., 12  
McCurdy, R.D., 50  
McElroy, S., 23, 31, 61, 72, 78, 100, 106  
McGee, S., 99  
McGorry, P., 109  
McInnis, M., 9, 23, 69, 97, 122, 134  
MacIntosh, B., 64, 65, 84  
McIntyre, R.S., 28, 36, 92, 103  
Mackala, S., 70  
Mackay, D., 62  
McKenna, B., 83, 125  
Mackle, M., 92  
McMahon, H., 56, 111  
McNamara, R., 59  
Magalhães, P.V., 113  
Magrini, C., 25  
Mahableshwarkar, A., 45  
Malhi, G.S., 19, 27, 49  
Malloy-Diniz, L.F., 112  
Mallya, S., 101  
Mangin, J.F., 32  
Mann, J.J., 114  
Mansur, R., 103  
Mantere, O., 93  
Mao, Y., 88, 132  
Marie-Claire, C., 19  
Marin, A., 74  
Marinescu, V., 114  
Marquet, P., 30  
Marrufo, O., 51  
Marsh, W., 48  
Marshall, D., 69, 97, 122, 134  
Marsman, J.B.C., 126
- Martin, K., 105  
Martinez, D., 51  
Martinez, M., 125  
Martínez-Arán, A., 97  
Martínez-Cengotitabengoa, M., 142  
Mata, L., 92, 137  
Mathews, M., 92  
Mathey, S., 71  
Mausbach, B.T., 21  
Mcelroy, S., 116  
Medeiros, G.C., 77  
Mehmood, N., 95  
Meiner, V., 66  
Meinhard, N., 101  
Meléndez Nesbit, O., 133  
Melle, I., 68, 72, 73, 77, 80, 94, 98, 127, 139  
Melo, G.B., 81  
Meluken, I., 101  
Mendonça, V.A., 81  
Merikangas, K., 30, 30  
Metcalf, A.W.S., 84  
Meyer, T.D., 62, 74, 96  
Mezuk, B., 131  
Miao, G., 112, 127  
Michalak, E., 20, 21, 54, 70, 81, 139  
Miclutia, I., 114  
Mihalopoulos, C., 52  
Miklowitz, D.J., 13, 15, 15, 16, 23, 34, 34, 47, 47, 56, 106  
Miller, I.W., 74, 81, 117  
Miller, S., 31, 76, 118, 122  
Millet, R., 138  
Minois, I., 37, 96  
Mintz, J., 31  
Minuzzi, L., 108, 120, 126  
Mishra, R.K., 100  
Miskowiak, K.W., 101, 104  
Missio, G., 141  
Mitchell, H., 37  
Mitchell, P.B., 11, 51, 52  
Mitchell, R.H.B., 105  
Mocking, R., 127  
Montana, R., 110  
Moody, A., 63  
Moon, J., 66  
Moore, K., 102  
Moreira, J., 19  
Moreno, R., 131, 141  
Morgan, R., 67  
Mori, N., 78, 116  
Morken, G., 86, 94, 95, 121, 139  
Morozova, Y., 60, 101  
Morton, E., 81, 139  
Mucsi, I., 116  
Mühleisen, T., 18  
Mulder, R., 87
- Mullen, J., 89, 90  
Muller, S., 99  
Munkholm, K., 60, 67  
Munoz, D., 74  
Munshi, A., 80  
Mur, M., 134  
Murray, G., 20, 21, 49, 54, 81, 139  
Murrough, J.W., 57  
Murru, A., 128  
Muskin, A., 110
- Naeem, F., 95  
Naiberg, M., 102, 112  
Nassan, M., 61, 100, 102  
Nazarov, A., 126  
Nelissen, N., 12  
Németh, G., 90  
Nery, F.G., 54  
Netemeyer, T., 83  
Neves, F.S., 79, 112, 116, 119  
Neves, M., 79  
Newcomer, J.W., 88  
Newton, D., 102, 112  
Ng, T.H., 119  
Ng-Mak, D., 136  
Nguyen, V.T., 51  
Nicholas, J., 129  
Nicolini, H., 60  
Nierenberg, A.A., 15, 15, 16, 23, 45, 47, 47, 56, 57, 75, 85, 110, 113  
Nieto, E., 61, 103, 134  
Nobre, A.C., 12, 86, 110, 129  
Nolen, W.A., 31, 106, 126  
Nordahl, T.E., 123  
Nöthen, M.M., 18  
Noto, C., 119  
Novak, T., 32  
Nunes, P., 70, 78, 120  
Nunes, S., 116  
Nurnberger, J.I., 11
- O'Shea, S., 9  
Oliveira, J., 20  
Olowoyeye, O., 63  
Omrin, D., 105  
Ong, M., 64, 65, 104  
Öngür, D., 13, 84, 101  
Ontiveros, A., 60  
Oquendo, M.A., 114  
Orselli Monteiro, R., 141  
Ortiz, A., 49  
Osório, A., 141  
Ospiov, M., 129  
Ostacher, M., 12  
Otto, M.W., 15, 15, 16, 47, 47  
Ou, X., 64, 84  
Ovejero, S., 92, 137

## Author Index

- Owen, R., 87  
 Ozbek, S., 124  
 Özerdem, A., 34, 82, 100
- Palacio, J.D., 63, 130  
 Palaniyappan, L., 83  
 Palmer, B., 17, 102  
 Pan, P.M., 103  
 Panchal, P., 86  
 Pantelis, C., 109  
 Parikh, S., 38, 73, 139  
 Park, C.S., 121  
 Park, D.Y., 122  
 Park, T., 81  
 Park, Y., 60, 66, 67, 80, 109, 111, 125  
 Passerieux, C., 52, 56, 56  
 Paterniti, S., 118  
 Pathak, J., 54  
 Paulzen, M., 68  
 Pearlstein, J., 36  
 Peckham, A., 47  
 Peijs, L., 60  
 Pell, J., 62  
 Pelz, J.B., 107  
 Peña, C., 63  
 Perez Algorta, G., 65  
 Perlis, R.Y., 12  
 Perugi, G., 31  
 Perzynski, A.T., 117  
 Pester, B., 69, 97, 122, 134  
 Peter, J., 99  
 Peters, A., 15, 16, 47, 47  
 Peterson, B.S., 69  
 Phillips, M., 9, 16, 27, 32  
 Piersaint, T., 106  
 Pietrobon, R., 114  
 Pijnenburg, Y.A.L., 66  
 Pikalov, A., 88, 88, 88, 92, 132, 133, 133  
 Pioli, R., 140  
 Pizzagalli, D., 101  
 Plans, L., 61, 103  
 Porter, R., 87  
 Post, R., 31, 61, 106  
 Pottorf, W., 89, 90, 133  
 Potvin, S., 111  
 Poupon, C., 83  
 Preisig, M., 30  
 Premkumar, P., 139  
 Prescott, A., 55  
 Price, J., 111  
 Prieto, M.L., 31, 53, 54, 78  
 Pring-Mill, K., 96  
 Prisciandaro, J.J., 110  
 Proudfoot, J., 129  
 Provencher, M.D., 73
- Qi, H., 69  
 Quevedo, J., 99  
 Qurashi, I., 136
- Rabideau, D.J., 23  
 Radua, J., 74  
 Rahman, R.R., 95, 136  
 Rajagopalan, K., 92, 136  
 Rakesh, J., 22  
 Ralat, S.I., 97  
 Ramirez-Bermudez, J., 51  
 Raschke, F., 83  
 Rasgon, N., 114  
 Ratz, D., 87  
 Raucher-Chéné, D., 113  
 Raventós, H., 60  
 Ravichandran, C., 84  
 Reddy, M.K., 74  
 Reddy, Y.C.J., 123  
 Reed, Z.E., 111  
 Reilly-Harrington, N.A., 23  
 Reinares, M., 97, 128  
 Rej, S., 74, 116  
 REI-Mallakh, S., 99  
 Remlinger-Molenda, A., 20  
 Renaud, S., 111  
 Rendell, J., 23, 50, 110  
 Renken, R., 126  
 Renshaw, P., 55  
 Rhodes, A., 93  
 Richardson, C., 87  
 Riemersma-Van der Lek, R.F., 126  
 Ringen, P.A., 73, 77  
 Rive, M., 50, 127  
 Roberts, G., 11, 51  
 Roberts, M., 58  
 Rocca, W.A., 53  
 Rocha, N.P., 81  
 Rocha, P.M.B., 116  
 Roepke, S., 18  
 Roger, V.L., 53  
 Rogers, R., 17  
 Roisen, F., 82  
 Rossell, S., 49, 76, 84  
 Rouan, E., 96  
 Rowe, M., 106  
 Ruhe, H., 50, 127  
 Rujescu, D., 18  
 Ruth, A., 89  
 Ryan, K., 69, 97, 122, 134  
 Rybakowski, J., 20, 51, 76  
 Ryu, E., 54, 100  
 Ryu, S., 81
- Sacchetti, E., 140  
 Sachs, G.S., 56  
 Saez, C., 134
- Sajatovic, M., 27, 117, 132, 133  
 Salanti, G., 56  
 Salcedo, S., 64, 65, 104  
 Salloum, I., 34  
 Sallum, G., 103  
 Salvini, R., 128  
 Sanchez de Carmona, M., 15  
 Sánchez-Alonso, S., 92, 137  
 Sánchez-Moreno, J., 97  
 Santos, G.D., 78, 120  
 Santos, L., 131  
 Sareen, J., 93  
 Sarrazin, S., 32  
 Sassi, R.B., 126  
 Saunders, K.E.A., 17, 86, 110, 129  
 Saury, S., 111  
 Saviotti, F., 140  
 Şayakçı Gürdal, S., 112  
 Scavone, A., 64, 64, 65, 65, 84, 104, 105, 105, 105, 107  
 Schaffer, A., 26, 29, 93  
 Schaffer, C.B., 123  
 Schaffer, L.C., 123  
 Schak, K., 17  
 Schalling, M., 61  
 Schenck, L.A., 53  
 Schene, A., 50, 127  
 Schenkel, L.S., 107  
 Schmaal, L., 50  
 Schmah, C., 18  
 Schneck, C.D., 106  
 Schnute, M., 141  
 Schoenfeld, D., 23  
 Schoeyen, H.K., 121  
 Scholz, V., 71  
 Schott, B., 18  
 Schwarze, C.E., 18  
 Scola, G., 13, 63  
 Scott, J., 19, 31, 38, 94, 96, 139  
 Segal, M., 116  
 Sehmbi, M., 100  
 Seidenfeld, A., 62  
 Selo, M., 55  
 Severus, E., 93  
 Seymour, L., 116  
 Sharma, A.N., 34, 117  
 Sharma, V., 79, 81, 139  
 Shelton, R.C., 23  
 Sher, L., 114  
 Shesler, L.W., 23  
 Shi, X., 55  
 Shulman, K.I., 116  
 Shuman, K.I., 74  
 Sibeijn-Kuiper, A.J., 126  
 Siddiqui, A., 100  
 da Silva Magalhaes, P.V., 16, 17  
 Silva, R., 132



- Silverman, M., 141, 142  
Simhandl, C., 74  
Simoes, L.R., 58  
Simon, G., 29  
Simon, J., 138  
Simonsen, C., 68  
Simplicio, M.Di., 37  
Simpson, W., 108  
Singh, M.K., 106, 117  
Singh, V., 23  
Sinyor, M., 93  
Siu, C., 92  
Siuda-Krzywicka, K., 71, 79, 113  
Siwek, G., 71, 79, 113  
Siwek, M., 71, 79, 113  
Sjölander, A., 94  
Slaney, C., 49  
Smith, D., 46, 62  
Smith, M., 126  
Smith, T., 138  
Smoller, J., 101  
Snelgrove, N., 126  
Snow-Adami, L., 92  
So, K., 112  
Soares Bio, D., 141  
Soares, J.C., 16, 74  
Soczynska, J.K., 103  
Soerio-de-Souza, M., 141  
Solé, B., 97  
Soncin, S., 74  
Song, H., 66  
Song, J., 94  
Soraggi, C., 112  
Specht, C., 29  
Spencer, K., 101  
Stange, J.P., 15, 47, 47, 113, 119  
Stark, N.M., 123  
Steinan, M.K., 94, 139  
Stek, M.L., 66  
Stevens, A., 45, 46  
Stiles, T.C., 95  
Stockton, S., 56  
Streicher, C., 132  
Strejilevich, S., 24  
Strippoli, M.P.F., 30  
Sublette, M.E., 114  
Subramaniapillai, M., 65  
Sullivan, G.M., 114  
Sun, J., 32  
Sundin, E., 139  
Sung, Y., 55  
Suominen, K., 93  
Suppes, T., 31, 31, 36, 68, 85, 94, 106, 128, 132, 140  
Sutherland, A.N., 125  
Sutor, S., 99, 102  
Swaden Lewis, K.J., 120  
Swampillai, B., 65  
Swann, A.C., 31  
Swendsen, J., 30  
Syan, S.K., 126  
Sylvia, L.G., 15, 15, 16, 23, 47, 47, 75, 110, 113  
Taboada, J., 51  
Tadic, A., 18  
Talasman, A., 114  
Tamerin, J.S., 25  
Tamouza, R., 20  
Tang, C.H., 135, 135  
Taylor, B.V., 79  
Teixeira, A.L., 81, 103  
Tereszko, A., 71, 79, 113  
Ter-Israelyan, A., 137  
Termansen, P., 96  
Terpstra, K., 100  
Terrien, S., 71, 113  
Tesli, M., 98  
Thase, M.E., 23  
Theilmann, R.J., 125  
Thida, T., 84  
Thomas, C., 117  
Thomas, N., 54, 76  
Thompson, W.K., 21  
Thusius, N., 67  
Timmins, V., 64, 65, 104, 105, 105, 105, 107  
Ting, L., 112  
Toh, W., 76  
Tohen, M., 10, 23  
Tolliver, B.K., 110  
Topka, E., 137  
Torrent, C., 97  
Torres, I.J., 49, 55, 59, 70  
Tourjman, V., 111  
Tovey, R., 110  
Towne, T.L., 107  
Treutlein, J., 18  
Trifu, S., 123, 137  
Trudeau, M., 8  
Tsai, J., 88, 88, 88, 132, 133, 133  
Tsai, S.Y., 25, 78  
Tsanias, A., 129  
Tseng, M., 50  
Tsygankov, B., 137  
Tuna, G., 100  
Tunbridge, E., 50  
Tunca, Z., 100  
Turecki, G., 10  
Tye, S., 57, 67, 99, 102  
Ueland, T., 68  
Uher, R., 32  
Vaaler, A., 86, 94, 139  
Valtonen, H., 93  
Valvassori, S.S., 58  
Van Meter, A., 21, 64, 76, 104, 118  
Van Rheenen, T., 26, 84  
Vandeleur, C.L., 30  
Vargas Castro, J.A., 107  
Vargas, C., 130  
Vazquez, G.H., 91  
Veldic, M., 61, 72, 102, 124  
Veltman, D., 50, 127  
Verma, S., 77, 86  
Vesco, A.T., 62  
Veselinovic, T., 68  
Vieta, E., 18, 28, 97, 128, 134  
Vigod, S., 93  
Vik Lagerberg, T., 68  
Villa, E., 60  
Vinberg, M., 60, 67, 85, 101, 104  
Vindasiene, G., 66  
Vinther, O., 85  
Vissoci, J.R., 114  
Voicu, J., 137  
Voysey, M., 23, 50  
Vrabie, M., 114  
WA, K., 66  
Waghmare, A., 123  
Wagner, K., 61  
Walder, K., 57, 99  
Walker, A., 99  
Walker, M., 12, 55, 110  
Walker, S., 139  
Walkup, J., 61  
Wang, J.H., 121  
Wang, P.W., 76, 118, 122  
Wang, V.C., 21  
Warsh, J., 50  
Watson, S., 47  
Wedge Árdal, E., 35  
Weikop, P., 104  
Weinstock, L.M., 74, 81, 117  
Weiss, R.B., 119  
Wen, W., 11  
Wenze, S.J., 117  
Wessa, M., 32, 37, 71, 83  
Westlye, L.T., 127  
Whitton, A., 101  
Wilcox, H., 11  
Wilma, K., 29  
Wilson, R., 134  
van Wingen, G., 127  
Winham, S., 78, 116  
Winstead, W., 82  
Wiste, A., 12  
de Wit, S., 127  
Witt, S.H., 18

## Author Index

Witterick, I.J., 50  
Wolfson, H., 62  
Wolstenholme, J., 138  
Woo, J., 105  
Woolrich, M., 12  
Woster, P., 138  
Wu, C.S., 135, 135  
Wu, F., 93  
Wu, H., 127  
Wu, X., 92  
Wullum, E., 95  
  
Xu, D., 69  
Xu, G., 112, 127  
Xu, Y., 69

Yaghouti, F., 21  
Yatham, L.N., 18, 49, 55, 59, 70,  
81, 90, 139  
Yeni Elbay, R., 69  
Yıldırım, G., 122  
Yoon, H., 66  
Yoon, S., 87  
Young Ryan, A.S., 62  
Young, A.H., 136  
Young, K., 37  
Young, L.T., 13, 49, 59  
Young, T., 11  
Youngstrom, E.A., 21, 31, 64, 65,  
76, 104, 118  
Youngstrom, J., 64

Yu, C., 74  
Yucel, M., 18, 109  
Yuen, L., 76, 118, 122  
Yuksel, C., 13, 84  
  
Zammit, S., 62  
Zanouy, L., 37  
Zarate, P., 75, 115  
Zeni, C.P., 22  
Zhong, L., 112  
Zipunnikov, V., 30  
Zrazhevskaya, I., 137  
Zukin, S., 89