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Beyond evidence-based treatment of bipolar disorder: Rational pragmatic approaches to management

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Abstract

The evidence for efficacy of many currently available treatments for bipolar disorder is based on studies of nonrefractory patients with bipolar disorder. Therefore, not surprisingly, most treatment recommendations and guidelines for the treatment of bipolar disorder and its many comorbidities depend heavily on data from placebo controlled randomized clinical trials (RCTs), but these RCTs provide little direction for the clinician as to what next steps might be optimal in non- or partial-responders and in those with ongoing medical and psychiatric comorbidities. Given this and the paucity of RCTs at later treatment junctures, we thought it appropriate to begin a discussion of the quality of the data that some experts in the field might consider using in choosing and sequencing drugs and their combination. We acknowledge that many other clinical investigators may prefer very different sequences, but thought the suggestions offered here might be useful to some clinicians in the field, might start discussions of other options in the literature, and, at the same time, provide a preliminary outline for a new round of much-needed clinical trials to better inform clinical practice. Given the very wide range of the quality of the data and clinical principles on which the current suggestions are based, only minimal references are included and a comprehensive review of the literature supporting each option would be outside the scope of this manuscript.

KEYWORDS
anticonvulsants, anxiety comorbidity, atypical antipsychotics, childhood onset bipolar disorders, disruptive behavioral disorders, lithium, stimulants, substance abuse

1 | INTRODUCTION

Evidence-based medicine ultimately must proceed on the basis of what works for an individual patient. Data from randomized placebo controlled clinical trials (RCTs) are considered the gold standard for making clinical judgments. However, there are many pitfalls to this assumption. Patients are highly selected for homogeneity for the RCTs and typically do not represent the range and complexity of patients in the general population. There is little room for generating clinical predictors of response, as only half the patients receive the

active medication, real responders cannot be readily separated from placebo responders, and secondary analyses of possible predictors and subgroups have methodological limitations that are frowned upon by the FDA and many journal editors and referees.

However, the most egregious deficit is that there are rarely sufficient RCTs in patients with bipolar disorder to cover the whole range of first-, second-, or third-line treatments and even when an RCT does exist in a given area, it often provides no guidance for the clinician interested in knowing what might be the next best option for nonresponders. Another problem is that most current treatment guidelines take the perspective that most patients are responsive to initial treatment, while in reality, many patients (perhaps the majority in some settings) present with complex late stage illness that shows considerable treatment refractoriness that is rarely addressed in RCTs. These treatment refractory patients are often excluded from industry-sponsored RCTs, as relatively early stage and treatment naive patients are more likely to show responsiveness and thus help obtain FDA approval for a given drug. An additional gap in RCTs is the unfortunate exclusion of people with serious suicidal ideation, personality disorder, and medical, behavioral, and substance abuse comorbidities.

In this manuscript, we review potential treatment options for these more difficult patients, and focus on the most sought after goal of achieving and maintaining remission. We thought it appropriate to take a clinician's perspective in thinking about other types of evidence which clinicians might use. Here we include data: from nonrandomized studies; comparative studies without a placebo; studies of effectiveness, safety, and utility of a drug in related but nonbipolar populations; preliminary and pilot studies; and even those based on minimal treatment effectiveness, but having a strong theoretical foundation and/or a record of safety.

2 | APPROACHES TO PATIENTS AND FAMILIES

There are also a number of principles of optimal patient treatment that need to be considered, including: safety and tolerability; willingness to tolerate and report side effects, willingness to try treatments supported by progressively less evidence after more promising and better validated treatments have failed; and to take medicines for the long term. If a patient or family member is able to provide a consistent longitudinal numerical or graphic depiction of mood, behavior, sleep, side effects, and ancillary or comorbid syndromes such as anxiety and substance abuse disorders, the evaluation of treatment effectiveness or nonresponsiveness for that individual patient becomes vastly more efficient, reliable, and valid. We thus strongly encourage the systematic use of such a mood chart in the context of other psycho-educational and psychotherapeutic approaches to the illness to augment pharmacotherapy. Ultimately, the goal is to construct a learning healthcare system consortium with clinicians, patients, researchers, administrators, and to provide data on the outcomes of these treatments.[1] Such an approach is also essential in bringing the patient into the therapeutic alliance and providing comprehensive informed consent.

Especially when revealed by longitudinal mood charting, we consider that an individual patient's responsiveness, nonresponsiveness, or intolerance of a given drug trumps any FDA approval status or treatment guideline. Guidelines make the assumption of pristine diagnostic clarity, whereas real-world patients have extensive comorbidity, diagnostic uncertainty and shifting diagnostic classifications. Given the many major differences of recommendations in this manuscript to those generated in most treatment guidelines constructed on the basis of a strong reliance on RCTs, we acknowledge that many recommendations in this manuscript will be debated by many clinicians and investigators who may differ with rankings or sequences of drugs suggested. The suggestions offered should thus be considered highly preliminary.

In fact it is hoped that the long list of basic unanswered questions about the optimal treatment of bipolar disorder in virtually every stage of illness evolution will help engender new research efforts, and that the suggestions generated here can rapidly be modified as new data become available. Since this is not likely to occur rapidly, the authors also hope that many of controversial recommendations would generate further discussion and critiques in the published literature.

Another caveat about this manuscript is that direct and indirect references supporting the recommendations given will only be sparsely cited. We will attempt to allude to the reasoning behind the recommendations, but a comprehensive discussion, rationale, and justification of each choice, sequence, and preference is not possible within the scope of this manuscript. The wealth of references in publications and text books[2-5] provide a much more comprehensive review of the literature.

3 | COMPREHENSIVE PROPHYLACTIC TREATMENT AFTER A FIRST MANIC EPISODE

The data of Kessing et al 2013[6] validate the widely held (but rarely followed) proposition that early comprehensive treatment can mitigate illness severity and moderate the course of illness in the long term. Kessing et al randomized a cohort of patients hospitalized for an early manic episode to expert clinic treatment (expert treatment) or treatment as usual (TAU) for 2 years. Not only did the patients given expert treatment have fewer relapses over this time frame, but also after the next 4 years, even though all patients had returned to TAU after 2 years. Expert treatment included: counseling about the transition from the hospital; illness education (including symptom recognition and life charting); pharmacotherapy; and psychotherapy. Kessing's findings are supported by a considerable literature suggesting better response to treatment in the early stages of illness, and this has been validated for naturalistic treatment, lithium, atypical antipsychotics, and even psychotherapy.[7] The approach contrasts with previous recommendations that initiation of definitive

mood stabilizer therapy could be delayed until a few episodes had manifested, and our belief is that the watch and wait approach after a first episode is no longer supported by evidence.

Thus, we recommend that all first manic patients receive this type of consistent and comprehensive treatment just in the same way that a new onset youngster with diabetes receives information and support from a large team of clinicians including: MDs, nurses, case workers, dieticians, social workers, and the like. The youngster still may then go off track, but this is usually rapidly recognized and ameliorated. It also is noteworthy, that even earlier intervention in the prodrome for psychosis or schizophrenia has been well studied and well funded for several decades, while there have been few initiatives and little funding for this approach in bipolar disorder.

This recommendation for intensive treatment after a first episode is further supported by data in a first episode mania cohort, where early intervention has also been shown to reverse cognitive deficits and prevent structural brain changes, but only under the circumstance that relapses can be prevented over the course of the first year.[8-10] The only problem is that such an extended remission is not easily or readily achievable, and a very substantial percentage of patients relapse in the first year despite expert treatment.

Furthermore in a randomized study of patients with a first mania, the high response rates to lithium compared to quetiapine contrast greatly to the poorer responses in a cohort of more chronic individuals.

We also know from long-term studies in US patients, that monotherapy is rarely sufficient to achieve and maintain a long-term remission, but is nonetheless a traditional and typical recommendation. We believe that in the absence of side effects or if adverse events are tolerable and judged worth the price of admission, patients should be continued on the combination treatment used to achieve acute remission in the hospital if they have stabilized on that regimen. However, an ideal complex combination regimen should be iteratively constructed for each patient and revised as necessary during prophylactic treatment at the first signs of the emergence of symptoms that herald an impending new episode.

A caveat is necessary; if medications are added serially in reaction to observed partial response, as opposed to multiple medications being started simultaneously, one can have slightly greater confidence in the value of polypharmacy and the assumption that they are all partially contributing to response. A further caveat is that because of extensive comorbidity (e.g. anxiety disorders, substance abuse, personality disorder) and the intrusion of primary or secondary life events, not all symptoms in a person with bipolar disorder are due to bipolar disorder and require major mood stabilizer revision. A formulation-based understanding of the person's broader issues is necessary to see bipolar disorder and its treatment in a broader context.

4 | FREQUENT NEED FOR COMPLEX COMBINATION THERAPY

4.1 | A new look at lithium

Guidance about how this is done is generally not available based on an inadequate treatment literature or spelled out in traditional

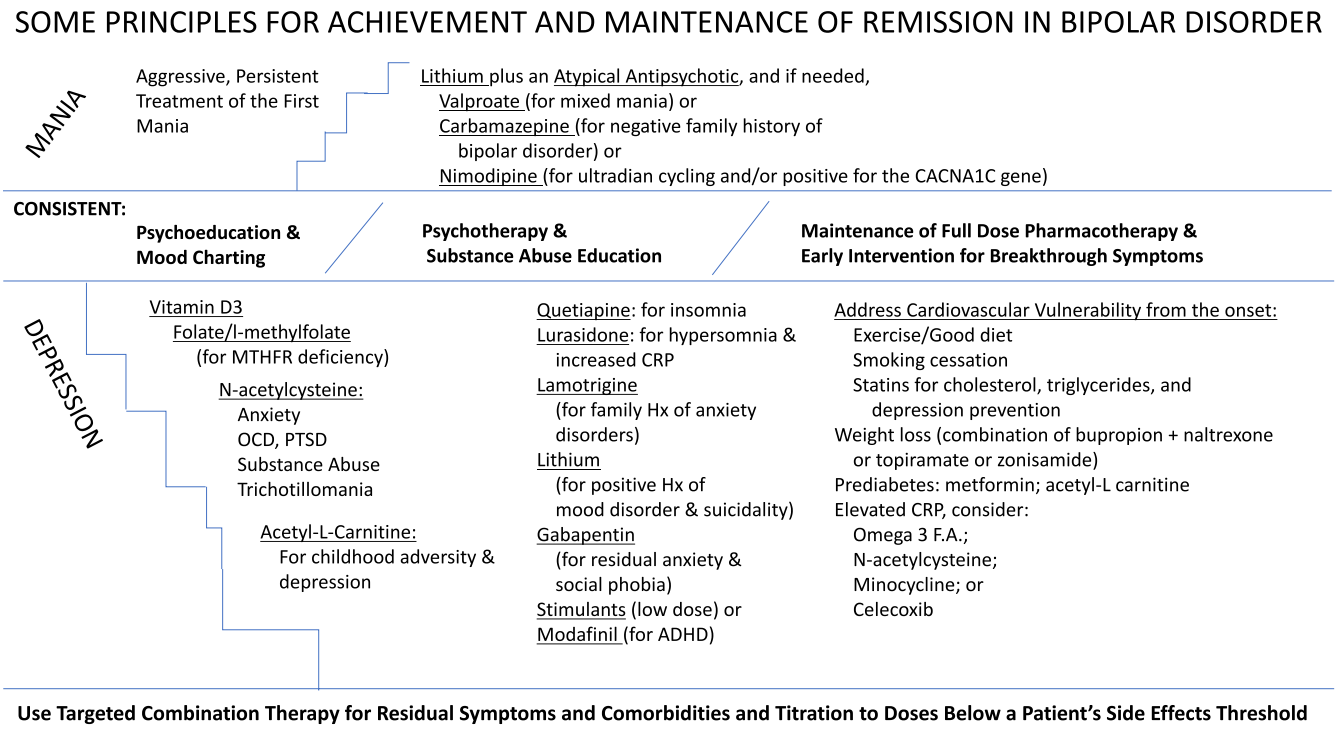

FIGURE 1 Some principles for achievement and maintenance of remission in bipolar disorder

guidelines, so we present here some preliminary suggestions as to how this might be pursued. Berk et al 2017[8] reported that a year of randomized treatment with lithium of first episode manic patients was superior to that of quetiapine on virtually every measure assessed, including: mania, depression, functioning, cognition, and changes on brain imaging. Particularly if the patient has other characteristics predictive of lithium responsiveness, such as: a positive family history of bipolar disorder (and especially a family history of responsivity to lithium); euphoric mania; discrete episodes with well intervals; lack of anxiety and substance abuse comorbidity; and a sequence of mania-depression-well interval as opposed to DMI,[3] one should strongly consider putting the patient on lithium or keeping it in the mix if it has already been used, but found not sufficiently effective.[9] For the very large group without these characteristics such as those with an anxiety or substance abuse comorbidity, a mood stabilizing anticonvulsant such as valproate, lamotrigine, or carbamazepine or an atypical antipsychotic could be used in augmentation.

In the face of psychosis, residual manic or mixed symptoms, a well-tolerated atypical antipsychotic in addition to lithium and an anticonvulsant might also be necessary. However, in people with psychotic symptoms, lithium has clear antipsychotic efficacy, suggesting the primacy of mood over psychosis in people with bipolar disorder. If the patient had had multiple depressive episodes prior to the first mania, lamotrigine or an atypical antipsychotic with efficacy in depression, such as quetiapine, lurasidone, or cariprazine might be preferred. It is noteworthy that the olanzapine-fluoxetine combination (OFC) is not on our or many guideline's first-line list as it can be associated with considerable weight gain and metabolic difficulties. There is evidence that weight gain is associated with poorer course and clinical outcomes and more pronounced brain structural and chemical changes in bipolar disorder. Further, it is also unlikely that OFC is a uniquely synergistic combination over and above that of other SSRI's or atypical antipsychotics, absence of data notwithstanding.

In patients relapsing on dual therapy, the combination of lithium, an anticonvulsant, and an atypical, such as the combination of lithium, lamotrigine and lurasidone, would appear to offer a good chance of prophylaxis against both manic and depressive phases of illness and good tolerability. Each of these three agents has nonoverlapping greater or lesser protection against manias and depressions. Multiple other approaches may be necessary to add as well, as discussed in several of the sections below.

Among lithium, the anticonvulsant mood stabilizers, and the atypical antipsychotics, combinations of two of these agents are usually superior to a single drug alone as repeatedly demonstrated in multiple RCTs. To what extent double and triple combination treatment from the outset is superior to attempts at monotherapy followed by augmentation as symptom emergence dictates, remains poorly delineated, but the data on relapses hurting cognitive recovery and episode occurrence sensitizing to further recurrences and driving treatment resistance, suggest that such an approach should be considered. One cannot lower viral load adequately without triple antiviral treatment in AIDS or triple antibiotic treatment in tuberculosis, or three or four drugs in cancer chemotherapy,[10] suggesting that in some instances aggressive treatment from the outset may be preferable and more effective than gradual, but unsuccessful attempts at prophylaxis. Curiously, there is preliminary preclinical evidence that combinations of mood stabilizers have substantive neurobiological effects not shared by the individual constituents.[11] These data provide a heuristic framework for conceptualizing the clinical observations about combinations.

5 | GENETIC TESTING: DOES IT HAVE UTILITY?

If one has used genetic testing and it reveals that the patient has the CACNA1C allele allowing too much intracellular calcium influx, one might consider the addition of the dihydropyridine calcium channel blocker nimodipine (which may be effective in ultra-rapid and ultradian cyclers).[3] When lithium and nimodipine are used in combination, there are tentative signals that they may be more effective than either drug alone.[12] The empirical data for the efficacy of nimodipine or isradipine do not meet the usual standards of being based on multiple RCTs or large numbers of patients; trials of the calcium channel blocker verapamil have been negative and hoped for rationale of seeing more efficacy of nimodipine in those with the CACNA1C allele (which is a dihydropyridine subunit of the voltage gated calcium channel) than in those without this allele has not yet been specifically tested. However, nimodipine can work in nongeneotyped patients when other agents do not and it has an excellent safety profile. Placebo controlled on-off-on-off designs have demonstrated efficacy in some lithium refractory ultra-rapid and ultradian cyclers.[13,14] It may preliminarily be considered a lithium-like mood stabilizer without lithium's common side effects of tremor, weight gain, or GI distress in those individuals who have failed the usual options. Thus nimodipine can be used as an adjunct to try to obtain more maximal effects of lithium when dose increases are limited by side effects or in instances of only partial responsiveness to lithium and other agents has been obtained.

New data on knockout animals of ANK3 are striking in animals that show increases in both manic-like and depressive-like behavior in response to defeat stress and these alterations respond to lithium and valproate.[15] Whether the deficits in sodium channels involved in the ANK3 can be used as a predictor of clinical response or a target of new therapy remains for further study.

Another actionable genetic finding would be evidence of a deficiency in methyl-tetrahydroreductase (MTHFR) which would indicate the need for augmentation with l-methylfolate rather than folic acid itself. Whether the presence of the short form of the serotonin transporter increases the risk for switching into mania on antidepressants remains to be further documented, as do many other promising genetic findings. While delineating vulnerability to bipolar disorder with genetic markers would appear to be a long way off, linking them to prediction of treatment response would be more promising for enhancing immediate clinical utility.

6 | SERUM LEVELS: BALANCING "THERAPEUTIC" LEVELS AND ADVERSE EVENT RISK

Parenthetically, the authors would endorse the use of lithium below what a patient would consider their "bothersome or discomforting" side effects threshold, even though this might yield blood levels at or below those (0.6 to 1.0 meq/L) usually recommended in the literature. Pragmatically, low lithium may be better than no lithium. Willingness to consistently take the drug trumps other considerations, and one can hope that some of lithium's many other assets would occur at these lower levels, including its anti-suicide effects, increases in hippocampal and cortical volume, prevention of cognitive deterioration, increasing the length of telomeres, and increasing production of stem cells.[16]

Lower than usual lithium levels also can have a role at a first or second episode or in a well interval. Gradual dose titration when the agent is first started is can be valuable, as people tend to generalize and extrapolate their experiences, and the first exposure influences people to believe that they do or do not tolerate medicines in general.[17] This has major implications for long-term adherence and willingness to try therapies, as well as the risk for the development of nocebo phenomena in people who are sensitized to believe that they are sensitive to medications.[17]

Similarly, the emergence of side effects should trump any attempts to titrate doses of carbamazepine based on blood levels, especially since there is very wide individual variation in blood levels at which patients begin to experience side effects and there are no data that blood levels correlate with clinical response. Thus, routine repeated blood level measurements of carbamazepine are not needed.

To a lesser degree, side effects of valproate can vary independently of blood levels, but there is the critical caution about using valproate in women of childbearing age, as exposure to valproate in women with epilepsy is associated with major problems for the fetus, including: a 2%–5% incidence of spina bifida; a higher percent of cardiac and other malformations; and a development delay averaging about nine IQ points. Mitigating against these cautions are the recent observations that each of the abnormalities noted above for valproate use in women with epilepsy are very much reduced in incidence in women with psychiatric disorders. Neurologists advise counseling about the careful use of birth control measures and augmenting with folate, vitamin B6, and B12 in case women of childbearing age should have an unanticipated pregnancy while taking valproate.

7 | LIFETIME PROPHYLACTIC TREATMENT

The proposition about tolerability noted above is reinforced by the data that bipolar disorder at least in some people may be a neuroprogressive illness with multiple difficulties emerging as a function of episode recurrence, such that one is almost invariably considering a regimen suitable for lifelong treatment.[18] The number of episodes or duration of illness an individual experiences is associated with many adverse consequences. These include disruption of key academic, occupational, social, and interpersonal developmental milestones, given the large proportion of onset in childhood and adolescence. Illness related consequences include cycle acceleration (episode sensitization); increasing stressors, but increasing autonomy of episodes necessarily being precipitated by stressors (stressor sensitization); substance use (and its sensitization); dysfunction; disability; cognitive dysfunction; medical comorbidities; deficits in brain structure and function; and a loss of many years of life expectancy particularly from cardiovascular disease. Many of these types of sensitization that drive illness progression are based on epigenetic changes in one's DNA, histones, or mRNA, such that avoiding and mitigating the environment factors that produce these fundamental changes in gene expression is of great importance.[18]

Therefore, long-term prevention of episodes is of paramount importance and should be the focus of ongoing educational efforts about the need for continual prophylaxis. Heading off or minimizing comorbidities and medical risk factors from the start is also a crucial strategy and goal, given the high incidence of the metabolic syndrome and its auguring of poor health and longevity.

8 | MEDICAL COMORBIDITIES AND REDUCING CARDIOVASCULAR RISK

In patients with pre- or borderline diabetes, one might consider the use of metformin or acetyl-L-carnitine (ALC) which appears to have antidepressant properties and reverses components of diabetes by sensitizing insulin receptors.[19] Pioglitazone also has antidepressant effects and anti-diabetes effects.[20]

Weight loss strategies based on a good diet and exercise, are supported by two clinical trials in depression, showing effects of diet in depression and a large evidence base of antidepressant effects of exercise.[21] Weight loss can be supplemented by the combination of bupropion sr (150-300 mg/day) plus naltrexone (50 mg/day). The potentially weight losing anticonvulsants, topiramate and zonisamide, can also be helpful. High cholesterol or triglycerides should be actively treated with statins to reduce cardiovascular risk and new data suggest that they may also help prevent depressive episode occurrence.[22] Blood pressure requires careful monitoring and treatment, as it adds to cardiovascular and renal damage risk. In this regard, angiotensin agents are to be preferred over diuretics, beta-blockers, and nondihydropyridine calcium channel blockers based on a growing evidence base of potential antidepressant effects of angiotensin based drugs.

Likewise smoking cessation should be encouraged as patients with bipolar disorder smoke at a higher rate than the general population and this adds another cardiovascular risk factor. There is a meta-analytic level of evidence that smoking cessation is associated with improved mental health.[23] Cessation should be a long-term goal in all patients who smoke.

9 | APPROACHES TO ANXIETY AND SUBSTANCE ABUSE COMORBIDITIES

Medical and psychiatric comorbidities are extremely common in patients with bipolar disorder. Therefore, as a general strategy, we would recommend treatments for bipolar disorder that minimize the emergence of new comorbidities such as weight gain or the metabolic syndrome and actively treat psychiatric comorbidities such as anxiety disorders. While not optimal for anxiety and substance abuse comorbidity, lithium helps prevent episode sensitization by inhibiting the recurrence of both manic and depressive episodes, protects against the progression of cognitive dysfunction and may slow or prevent cortical volume decrements. Comorbid anxiety disorders, which convey a poor prognosis, appear best treated with mood stabilizing anticonvulsants (lamotrigine, valproate, carbamazepine) as well as atypical antipsychotics, rather than antidepressants which have a low rate of effectiveness in patients with bipolar disorder, and an even lower rate in those with anxiety disorders.[24] Lamotrigine appears more effective in those with a personal or family history of anxiety disorders[25,26] reported a trend for superior effectiveness of carbamazepine compared to lithium in those with BP II and anxiety and substance abuse comorbidities. Marked antianxiety effects were reported for valproate in the treatment of bipolar depression.[27] Gabapentin, which does not have antimanic effectiveness, may nonetheless help treat a variety of anxiety syndromes, including panic and social phobia,[28] as well as help with alcohol avoidance at doses of 900 to 1200 mg/day.[29] Likewise, topiramate possesses no anti-manic efficacy, but can help multiple comorbidities including alcohol and cocaine addiction, bulimia, and anger attacks. Use of off-label agents to address anxiety and related comorbidities is thus to be encouraged rather than avoided, and as a consequence leaving the patient inadequately treated.

Multiple drugs are now FDA-approved treatments for alcohol abuse, although all have been studied and approved for those with primary abuse disorders and not bipolar disorder. Most of these drugs, perhaps with the exception of disulfiram, which is a dopamine beta hydroxylase inhibitor, would likely be safe in patients with bipolar disorder. Baclofen which has beneficial effects in alcohol abuse, should also be avoided as it can exacerbate depression.[30]

In patients experiencing difficulties with a variety of anxiety and/or substance abuse syndromes, N-acetylcysteine (NAC) may offer actions against both.[31,32] NAC helps reduce depression, OCD, and PTSD and the use of substances, including nicotine, alcohol, cocaine, as well as marijuana in youngsters. Inconsistent data in bipolar disorder notwithstanding,[33] the authors endorse the use of NAC, typically 500 mg bid for 1 week increasing to 1000 mg bid thereafter in most individuals with difficult-to-treat depression and anxiety, especially if there is complicating substance use,

Folic acid has a long record of effectiveness in supplementing the efficacy of antidepressants in unipolar disorder[32] and one small study by Alec Coppen[34] in augmenting lithium, so it might be useful to add. However, this is countered by the data that in patients where lamotrigine was added to quetiapine that the addition of folate was detrimental to the lamotrigine effect.[35] If the patient has a MTHFR deficiency, l-methylfolate becomes necessary rather than folate.[36] There are trials of omega 3 supplementation that are positive, augmented pragmatically by the safety and tolerability of this option.

Vitamin D3 levels are low in a high percent of those with major psychiatric illness,[37] and while the data are skimpy and mixed for added improvement in those with mood disorders, it would appear a potentially useful augment strategy. One study in normal volunteers indicated that 4000 IU/day had better effects on cognition than lower (400 IU/day) doses. A caveat is that low levels of vitamin D are found in many medical disorders, and quality trials to treat these have almost universally been disappointing.[38,39]

10 | INFLAMMATION AS A POTENTIAL TARGET

About one-third of the patients with bipolar disorder show some evidence of inflammation, most commonly in increased blood levels of Il-1, Il-6, TNF alpha, or CRP. When one of these is elevated, a patient's depression often remains refractory to multiple treatments, and consideration of an anti-inflammatory agent may be warranted. Minocycline 100 mg bid,[40] or if response is not forth coming, celecoxib 200 mg bid could be used as a further adjunct.[41] It is theoretically possible that those with low values at baseline, may show exacerbation of depression if anti-inflammatory agents are added,[42] so in the absence of good data to guide therapy, one might want to test for evidence of inflammation prior to use of these type of agents. A CRP level of above, say 3 mg/L, might be indicative, but these data are highly speculative.

11 | SOMATIC TREATMENTS

While rTMS is not approved for use in bipolar depression in the US, considerable clinical evidence and a preliminary meta-analysis[43] suggest effectiveness equal to that seen in unipolar depression.

If rTMS is used, one of the authors suggests the potential utility of engaging the patient in positive cognitive therapy or having them self-induce positive autobiographical memories which active the anterior cingulate gyrus during the time of brain stimulation. rTMS releases glutamate and BDNF and appears, like with LTP, to induce experience-dependent neuroplasticity, that is, there is enhancement of synaptic function in only those synapses specifically activated. Potentiation of positive synaptic engrams would appear superior to enhancement of a patients usual depressive ruminations occurring while the patient is “at rest” or undirected. New data suggest theta burst rTMS stimulation works as well as the regular stimulation, and only requires 5 minutes/session rather than the usual 25 minutes.[44]

ECT remains the most effective treatment for refractory depressed patients, particularly those with high suicidal risk or medical compromise. The older concerns about memory loss with bilateral

ECT are less pressing when one uses right unilateral ultra-brief pulse ECT, and this modality has the advantage that it can be readily used in concentrated continuation and then prophylactic phases for good responders.[45]

Vagal nerve stimulation is an FDA-approved treatment for major depression, and recent 5 year follow-up data of patients with both unipolar and bipolar depression reveal a greater than 50% response rate, remarkably even in those who were previous nonresponders to ECT.[46]

12 | RAPID ONSET ANTIDEPRESSANT TREATMENTS

Multiple RCTs, even some with an active sham comparator treatment, have demonstrated the rapid onset of antidepressant effects of intravenous (iv) ketamine (0.5 mg/kg infused over 40 minutes) in highly treatment refractory unipolar and bipolar depressed patients. Effects on both depression and suicidality can be seen within several hours and are typically maximum at 24 hours, but response usually lasts only 3–5 days and continuation treatment is required to maintain a good response.

When repeated treatments are given, many investigative groups have shown a diminution of the acute transient unpleasant dissociative side effects and no loss of ketamine's effectiveness. In patients who were treated in academic centers in Toronto and New Haven, maintenance of response to ketamine has been seen in some patients for more than 2 years. The data on intranasal (i.n.) esketamine appear positive in the short and long term (1 year follow-up) so one might look forward to this becoming an FDA-approved treatment for refractory depressed patients in the future, although these studies included only unipolar patients. However, extrapolating from the data with iv ketamine in bipolar depression, one might reasonably expect to see responsiveness to i.n. esketamine in this group as well.

However, caution is indicated given that ketamine is a street drug of known addictive and abuse liability, and most trials of ketamine were not optimized to explore this risk, which is likely much greater in clinical use than in the highly regulated environment of clinical trials.[47] Long-term experience with agents such as alprazolam for depression and opiates for chronic pain—where clear signals in pivotal trials heralding future problems were not rigorously sought or detected—would suggest considerable caution may be required in general clinical use of ketamine.[48]

Ketamine's actions appear to involve blockade of the glutamate NMDA receptor and this raises the issue of the utility of blocking by other mechanisms excess synaptic glutamate which appears associated with fast firing neurons and increases in depression and anxiety. In this regard it is of interest that memantine, although more weakly, also blocks the glutamate NMDA receptors and its addition to treatment refractory patients with rapid cycling bipolar disorder is reported to result in a very high rate of remission.[49] Other approaches already mentioned also reduce glutamateric tone. These include blocking glutamate release with lamotrigine or carbamazepine, and increasing glial glutamate transports to increase clearance of synaptic glutamate with NAC. ALC rapidly increases the production of the inhibitory metabotropic glutamate receptor mGluR-2, which decreases glutamate release by another mechanism[19,50] and appears to have rapid onset antidepressant effects in animal models of depression by this epigenetic mechanism.[51]

13 | PSYCHOSOCIAL TREATMENTS AND THE THERAPEUTIC ALLIANCE

Because of the manifold psychosocial triggers and consequences of bipolar disorder, psychological therapies should be considered normative in management. There are many models of psychosocial care, including psychoeducation, CBT, IPSRT, and Family focused therapy, available as individual or group based approaches, and some have been adapted to the internet. Support resources for caregivers such as bipolarcaregivers.org are valuable. Because comorbidity can often drive outcomes as powerfully as the primary disorder, psychosocial therapies aimed at, for example, anxiety or substance abuse are invaluable. Given the fact that a proportion of patients with bipolar disorder have cognitive impairment, cognitive and functional remediation may be necessary as well.[52] Lastly, because of extensive comorbidity with personality disorders, approaches such as dialectical behavior therapy may be valuable for individual patients.[53]

A critical, if neglected element is the value of the therapeutic alliance and long term stable clinical care. Engagement and alliance may be most critical at the formative first episode and early stages, but remain cornerstone elements of quality care. Consistency of care with a stable clinical relationship greatly enhances illness acceptance, adaptive health behaviors and adherence.[54]

14 | CONCEPTUAL OVERVIEW AND CONCLUSIONS

As bipolar disorder is currently treated, especially in the US, functional recovery over 1 year remains low and relapses high, yielding a very large group of patients with relatively treatment refractory illness. Given these data, we believe a new set of principles of treatment are in order. As shown by Kessing et al 2013,[6] intense comprehensive specialty clinic treatment is superior to TAU, but even with specialty treatment, relapses do occur over the next 6 years. Greater use of complex combination treatment from the start may make further in-roads in achieving and maintaining remission and reducing relapse rates.

For some this may involve a combination of lithium, an anticonvulsant mood stabilizer, and a well-tolerated atypical antipsychotic as supplemented by a variety of adjunctive treatments according to a patient's needs and symptom profile. Ready embrace of lifestyle interventions such as diet, physical activity and smoking cessation which have the benefit of trivial or no risk and great benefit in diverse comorbidities is endorsed as is the use of safe nutraceutical

interventions on the same basis, albeit with a smaller evidence base. Options include vitamin D3 (which is low in a high proportion of patients with the illness); folate or l-methylfolate, NAC, and ALC may be indicated along with a variety of other adjuncts added sequentially aimed at patients' medical and psychiatric comorbidities (Figure 1).

Medical comorbidity such as diabetes, hyperlipidemia and hypertension should be aggressively treated with agents that have potential dual benefits such as metformin, statins, and angiotensin agents, respectively. Treatment of anxiety and substance abuse comorbidities is a must, as repeated studies reveal their presence to be associated with a poor outcome. As almost all of these treatments are off label, one must make indirect inferences about their potential utility in bipolar disorder based on effectiveness data in other populations, and then estimate their likely advantages or disadvantages for mood stabilization in patients with bipolar disorder. Preliminary attempts at codifying or grading the: (a) effectiveness of these agents in non-bipolar patients; (b) their safety and tolerability; and then integrating these two into (c) a utility rating for patients with bipolar illness have been outlined.[55,56]

When complex combination treatment is employed with careful, sequential addition of major medicines to the regimen, this can result in both excellent effectiveness and even a lower total side effects burden than that achieved by trying to obtain maximal efficacy from one or two agents pushed to their limits. Most of the reports that combinations are associated with more side effects are based on studies of combinations of medicines at traditional doses or those mandated in the study methods, and are without careful dose titration against side effects. When combinations are instituted in this fashion, side effects can be minimized.[1,3,5,53,57] Lower doses are often possible in combination than monotherapy.

Very complex combination therapies are used in many other medical syndromes, and highly refractory bipolar disorder will likely be no exception. The authors are aware that this approach is counter to many texts and guidelines, but the recommendations for monotherapy are somewhat mistakenly derived from FDA-mandated RCTs where only superiority to placebo is required and is typically calculated with clinical response or 50% reductions in conventional scales and not the desired achievement of remission. Therefore FDA approval indicates significant improvement over placebo, but usually carries little weight about what it takes to achieve remission. Thus, one should recognize that reluctance to go beyond FDA-approved agents for a patient in the absence of a complete response is more likely a sign of inadequate treatment than an indicator of good medicine.

The achievement and maintenance of remission is the major goal of therapeutics of bipolar disorder. Since guidance from the literature is so poor as to how to achieve this goal, careful longitudinal assessment of an individual patient's degree of response and tolerability to a drug is a crucial determination. More medications (of different mechanisms of action) and multiple types of therapeutic approaches including psychotherapeutic and lifestyle may be necessary to initially achieve remission, and additional treatment revisions will likely also be required as symptoms emerge with the hope that prompt attention to these will abort the development of full-blown relapses. When this comprehensive approach is taken, recurrence of and sensitization to mood episodes, stressors, and bouts of substance abuse, and their epigenetic underpinnings,[18] may be headed-off or minimized.

Yet, it is our experience that even patients with late stage, apparently treatment refractory illness, can achieve considerable improvement, if not remission, if unconventional approaches are utilized that involve multiple medications with different neurotransmitter targets, multiple off label adjuncts, lifestyle modification, psychosocial approaches and neutraceuticals.[3] Obviously, it would be highly preferable to have a systematic treatment literature upon which to make clinical decisions rather than those based on indirect evidence and clinician's suppositions, but in the absence of such a literature the clinician must enjoin patients and family members in constructing and revising treatment regimens until good results are achieved. The philosophy that is foreign to many patients and requiring ongoing educational and psychotherapeutic efforts is that maintaining remission may require a large number of medications carefully given together with adjunctive psychosocial and lifestyle approaches, hopefully yielding both more effectiveness on primary symptoms and comorbidities with fewer side effects.

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