Psychiatry and Clinical Neurosciences (2005), **59**, 229–239

Review Article

The management of bipolar disorder in primary care: A review of existing and emerging therapies

MICHAEL BERK, MBBCh, MMed (Psych), FF (Psych), FRANZCP, PhD,[1,2,3,4]
SEETAL DODD, BSc, DipEd, MSc, PhD, MRACI, CChem[1,2] AND
LESLEY BERK, BA (Hons), MA(Clin Psych)[1,2,5]
[1]*Department of Clinical and Biomedical Sciences – Barwon Health, University of Melbourne,* [2]*Community and Mental Health, Barwon Health, Geelong,* [3]*Orygen Youth Health, Parkville,* [4]*The Geelong Clinic, Healthscope, Geelong, and* [5]*Mental Health Research Institute, Parkville, Victoria, Australia*

Abstract Recent evidence suggests that the prevalence of bipolar disorder is as much as fivefold higher than previously believed, and may amount to nearly 5% of the population, making it almost as common as unipolar major depression. It is, therefore, not unrealistic to assume that primary care or family physicians will frequently encounter bipolar patients in their practice. Such patients may present with a depressive episode, for a variety of medical reasons, for longer-term maintenance after stabilization, and even with an acute manic episode. Whatever the reason, a working knowledge of current trends in the acute and longer-term management of bipolar disorder would be helpful to the primary care physician. In addition, an understanding of important side-effects and drug interactions that occur with drugs used to treat bipolar disorder, which may be encountered in the medical setting, are paramount. This paper will attempt to review existing and emerging therapies in bipolar disorder, as well as their common drug interactions and side-effects.

Key words adverse effects, anticonvulsants, atypical antipsychotics, bipolar disorder, drug interactions, lithium, mood stabilizers.

INTRODUCTION

Bipolar disorder has traditionally been viewed as having a prevalence of approximately 1%, however, there is emerging evidence that prevalence rates may actually be as high as 5%.[1] The disorder, characterized by mood fluctuations that include mania, hypomania, depression, and mixed episodes,[2,3] is devastating and chronic,[4,5] and a significant source of distress and disability.[6] The World Health Organization found bipolar disorder to be the world's sixth leading cause of disability-adjusted life years among people aged 15–44 years. There is also an increased risk of suicide associated with bipolar disorder; as many as 25–50% of patients with bipolar disorder attempt suicide during their lifetimes.[7,8]

RECOGNITION OF BIPOLAR DISORDER IN PRIMARY CARE

Patients suffering from bipolar disorder frequently present in the primary care setting, most commonly during the depressive phase of their illness. Up to 30% of depressed and/or anxious patients in primary care may have a primary diagnosis of bipolar disorder.[9] Bipolar disorder is distinguished from unipolar depression by identifying current or past symptoms of mania or hypomania in the bipolar disorder sufferer.[10] It needs to be stressed that most bipolar patients present with depressive symptoms rather than mania, and that active enquiry regarding past mania or hypomania is essential to establish the diagnosis. It may be difficult to make this distinction when a patient's history is unknown or unclear, however, there are several signs that may alert the general practitioner to the possibility

Correspondence address: Michael Berk, Department of Clinical and Biomedical Sciences, University of Melbourne, Swanston Centre, PO Box 281, Geelong, Victoria 3220, Australia.
Email: mikebe@barwonhealth.org.au

Received 31 August 2004; revised 1 December 2004; accepted 5 December 2004.

that a patient presenting with depression may suffer from bipolar illness. The patient may have a family history of bipolar illness, particularly if a first degree relative has a confirmed diagnosis of bipolar disorder. It is not uncommon to find three or more first degree relatives or three consecutive generations with identifiable mood disorders in the families of bipolar disorder sufferers.[11] A switch to mania or hypomania with antidepressant treatment will confirm a diagnosis of bipolar disorder, though more commonly, bipolar disorder suffers simply fail to respond to treatment using antidepressants. If a patient has failed to respond to three or more antidepressants, bipolar disorder should be suspected.[11] Rapid onset and offset of episodes, a seasonal pattern, and the presence of atypical depressive features may also alert clinicians to the possibility of a depressive episode having a bipolar basis. Another clue is that bipolar disorder has an earlier age of onset than unipolar depression. Bipolar disorder should be suspected in cases where depression appears prior to the age of 25.[11]

DIAGNOSIS OF BIPOLAR DISORDER IN PRIMARY CARE

In the spectrum of bipolar disorders, bipolar II disorder, characterized by symptoms of both depression and hypomania, is more common than bipolar I disorder in the primary care setting. In a study of 108 primary care patients diagnosed with depression or anxiety, three patients were found to have bipolar I disorder compared to 20 patients with bipolar II disorder. In the same study, an equal number of patients suffered from bipolar spectrum disorders and depressive disorders.[12] This presents a diagnostic challenge for the general practitioner. While a formal assignment to a subcategory of bipolar disorder may in some circumstances be too difficult to achieve within the context of primary care, it is vital that the depressive phase of bipolar disorder is not misdiagnosed for major depressive disorder, as this would be likely to lead to poor therapeutic outcomes predominantly through the use of antidepressants rather than mood stabilizers. Similarly, major depressions superimposed on cyclothymic oscillations may be confounded with borderline or other personality disorders.[1]

There is a high prevalence of comorbidities, including alcohol and substance abuse as well as anxiety states, among sufferers of bipolar disorder.[1] Indeed, comorbidity is probably more common than non-comorbid disorder. The general practitioner should be vigilant to identify and treat the comorbidities as well as the primary pathology. An instrument to determine alcohol usage, such as the Alcohol Use Disorders Identification Test, may be useful.[13]

TREATMENT OPTIONS IN BIPOLAR DISORDER

Mood stabilizers are the basis of therapy for bipolar disorder, and current guidelines recommend the use of a mood stabilizer in all phases of treatment.[14] A mood stabilizer is usually regarded as an agent that can effectively treat at least one acute phase of bipolar disorder (mania or depression) without increasing the risk of a 'switch', or conversion, to the other phase. Lithium is the most extensively studied of all the mood stabilizers, and has been used for both acute and prophylactic treatment of manic episodes of bipolar disorder. It has also traditionally been a first line choice for less severe bipolar depression.[14] Divalproex sodium and carbamazepine, initially marketed as anticonvulsants, have also been determined to have mood stabilizing properties. More recently, newer anticonvulsant mood stabilizers have emerged, such as lamotrigine. There are also new insights into the mood stabilizing effects in maintenance treatment of atypical antipsychotics, such as olanzapine and aripiprazole.

Antidepressants

Analysis of marketing data suggests that antidepressants may be more commonly prescribed for use in bipolar disorder than mood stabilizers in some areas.[15] However, their use may induce mania or rapid cycling,[16] as demonstrated in a naturalistic study of 500 bipolar patients where 37% reported a history of antidepressant-induced mania or hypomania.[17]

There is a paucity of controlled data for the use of antidepressants in bipolar disorder, especially with regard to long-term use. Studies have suggested that antidepressants may have a role in the acute treatment of the depressive phase of bipolar disorder. Antidepressants were shown to be useful as adjunctive therapy in patients whose Hamilton Rating Scale for Depression scores remain high 1–3 weeks after commencing treatment with a mood stabilizer.[18] A trial comparing paroxetine and venlafaxine treating 60 bipolar patients during depressive episodes, found both agents to be safe and effective.[19] In a 10-week acute phase and 1-year continuation phase, double-blinded trial of 64 depressed bipolar patients randomised to adjunctive therapy with bupropion, sertraline or venlafaxine, improved ratings in depression were demonstrated. However, switching to mania or hypomania occurred in 14% of acute phase patients and 33% of patients in the continuation phase.[20,21] This

suggests that switch into mania is potentially a longer-term risk than previously recognized. A retrospective cohort design study of 7607 elderly bipolar patients, found antidepressants use to be associated with a decreased rate of hospitalization.[22]

Curiously, in a study of mood patterns in 80 bipolar patients, 47 taking antidepressants and 33 not taking antidepressants, patients receiving antidepressants were measured as depressed twice as often as patients not receiving antidepressants and appeared to have a downshift in baseline mood.[23] These results may be due to subject selection biases where symptomatology is the criterion by which antidepressants are prescribed. However, the further finding that the frequency and size of mood changes was similar in both groups suggests that patients in this study did not benefit from antidepressant use.

In spite of antidepressants being available for over 40 years, no drug-company sponsored and controlled clinical trial of an antidepressant used to treat bipolar disorder has been published. In the absence of a body of controlled long-term maintenance data on the use of antidepressants, the use of the agents needs to be viewed with some caution.[24]

Lithium

Studies of lithium maintenance therapy for bipolar disorder[25–29] and treatment for acute manic episodes[27,30–32] have commonly demonstrated robust benefits. In spite of these findings, there has been increasing concern that lithium's efficacy has been overestimated in the past or that there has been subsequent increasing patient resistance to lithium.[29,33] However, a recent analysis which reviewed 11 controlled and 13 open, long-term trials of lithium in bipolar or mixed major affective disorders published between 1970 and 1996, found that the benefits of lithium prophylaxis have not been exaggerated, and that lithium's utility in maintenance therapy of bipolar disorder has not waned.[33] Results from other long-term longitudinal studies of lithium prophylaxis have similarly detected no reduction in lithium efficacy over the decades.[34,35]

Lithium has also been found to robustly reduce the risk of suicide by about 80% in certain patients – from about 30-fold to approximately 6.5-fold that of the general population. The benefit of other mood stabilizers in this arena has not been well established.[14] In a recent analysis of 22 studies, Tondo and Baldessarini found at least a sevenfold reduction in suicide rates for patients during long-term lithium treatment, compared with patients who were not receiving lithium, and patients after lithium discontinuation.[33]

In comparison with its efficacy in euphoric mania and prophylaxis, lithium may be less effective in patients with symptoms of mixed mania,[31] bipolar depression,[36] rapid-cycling features,[37–39] numerous previous mood episodes,[40] and more pretreatment hospitalizations.[41]

Three of the greatest concerns for patients receiving lithium therapy are regular monitoring of renal and thyroid function, and of lithium levels. Lithium therapy has been associated with an increased incidence of both goiter and hypothyroidism, and patients, therefore, require regular monitoring of thyroid function.[42] Lithium also reduces the kidney's ability to concentrate urine, although this is usually reversible. About 50–70% of patients on long-term lithium therapy develop polyuria, and about 10% develop frank diabetes insipidus.[43] Changes in tubular function may become irreversible in some patients.[44] Patients on ongoing lithium therapy should have their serum creatinine levels monitored at least yearly, and some experts recommend testing every 3 months.[44]

Lithium also interacts with a host of medications that are commonly used in medical practice, and physicians should use special caution in prescribing these drugs to patients on lithium therapy: diuretics, non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin II antagonists, xanthine preparations, and metronidazole, among others.[45,46]

Divalproex sodium

Divalproex sodium delayed-release tablets (Depakote–Abbott) were approved by the Food and Drug Administration (FDA) for the acute treatment of mania in the USA in 1995. In most expert consensus guidelines, divalproex is listed as the drug of choice for acute management of mixed manic states, and mania with a strong depressive component.[47] To date, no controlled studies have been conducted to determine the efficacy of divalproex sodium in bipolar depression.

While evidence for the efficacy of divalproex in the treatment of mania is convincing,[30,31,48,49] there is less evidence of its efficacy in bipolar disorder maintenance therapy, an indication for which it is not FDA-approved. Only one randomized controlled trial of divalproex as maintenance therapy has been conducted to date.[50] This randomized, double-blind, placebo-controlled, parallel-group study found that divalproex and lithium did not differ significantly from each other or placebo on the primary outcome of time to recurrence of any mood episode, though a trend favoring divalproex over lithium was observed.[50] Premature termination for any reason (development of

any mood episode, intolerance or non-compliance) tended to be lower in the divalproex group.[50] There are some reservations regarding the statistical power and methodology of this study, which reduced lithium–placebo differences.[50,51]

In spite of the paucity of research demonstrating its efficacy in maintenance therapy, divalproex is more commonly prescribed in the USA for bipolar disorder than lithium.[52] This may be, in part, due to its improved tolerability over lithium. In the above study by Bowden *et al*., divalproex was generally better tolerated than lithium, but both divalproex and lithium resulted in significantly higher rates of study termination than placebo due to intolerance or non-compliance.[50]

Divalproex carries a box warning for hepatotoxicity, teratogenesis and pancreatitis, and has been associated with blood dyscrasias. The risk of hepatotoxicity requires ongoing liver function monitoring.[53] Aside from sedation and gastrointestinal side-effects, divalproex has also been associated with significant weight gain,[53] which may result in non-compliance, and this should be closely monitored. There have also been reports of polycystic ovarian syndrome with the use of valproate in the epileptic population, although this has not been confirmed to date in patients with mood disorders.[54,55]

Drugs that should be used with caution in patients taking divalproex include those on other anticonvulsants, such as phenytoin, lamotrigine and carbamazepine, and those taking aspirin, rifampin and benzodiazepines, among others.[53]

Carbamazepine

Although carbamazepine has demonstrated acute antimanic effects in several controlled studies,[56,57] its efficacy in bipolar depression has not been well established.[58] It is not FDA-approved for treatment of bipolar disorder in the USA.

While carbamazepine is generally believed to be efficacious for prophylaxis of bipolar disorder, rigorous placebo-controlled trials are lacking. A combined analysis of 10 double-blind, randomized maintenance studies in bipolar disorder indicated slightly less efficacy with carbamazepine than lithium as evidenced by a non-significantly higher relapse rate with carbamazepine than lithium.[28] A second set of studies detected no statistically significant differences between carbamazepine and lithium in recurrence rate or hospitalization rate.[59–63] However, results were distinctly in favor of lithium when the definition of failure was broadened to include recurrences combined with co-medication ($P = 0.041$) and/or adverse effects.[62]

Carbamazepine's side-effect profile and pharmacokinetic interactions make its use difficult, and it has not achieved the same popularity in the USA as a mood stabilizer that it has in Europe. Adverse effects of carbamazepine include dizziness, nausea, vomiting, sedation, diplopia, clumsiness, cognitive impairment and, rarely, hepatotoxicity and agranulocytosis and aplastic anemia.[2]

Carbamazepine also interacts with the cytochrome P450 enzyme system, inducing its own metabolism and creating the potential for significant drug–drug interactions.[2] Carbamazepine levels can be increased by concomitant prescription of cimetidine, diltiazem, macrolides, erythromycin, clarithromycin, fluoxetine, loratadine, ketaconazole, itraconazole, verapamil and valproate, among others. Other drugs that should be used with caution, as carbamazepine reduces their serum blood levels, include acetaminophen, some benzodiazepines, doxycycline, contraceptives, warfarin and other mood stabilizers.[64]

Lamotrigine

Lamotrigine has been observed to improve mood, alertness and social interactions in some patients with epilepsy,[65] and these observations stimulated interest in lamotrigine's potential efficacy in bipolar disorder, and particularly depressive episodes in bipolar disorder.

Lamotrigine has subsequently been found to be efficacious in the acute management of bipolar depression[66] and long-term management of bipolar disorder, especially in delaying depressive recurrence,[67–72] either as monotherapy or as adjunctive therapy. This is in stark contrast with the predominantly antimanic activity seen with other mood stabilizers, and the fact that depression is the dominant phase of the disorder with regard to morbidity and time.[73] It is noteworthy that in acute studies, onset of antidepressant action of lamotrigine is similar to that noted for fluoxetine and imipramine in bipolar depression.[74,75] Lamotrigine has also been found effective in acute and long-term treatment of patients with rapid cycling,[76–79] and there is little evidence that it causes manic or hypomanic symptoms in patients with bipolar disorder.[66,69,80]

Lamotrigine is less likely than valproate and carbamazepine to cause fatigue, somnolence or weight gain.[81,82] However, of concern with lamotrigine use is the development of rash. In epilepsy trials, the incidence of serious rash, including Stevens–Johnson syndrome, is rare, occurring in approximately 1% of pediatric patients aged 16 or younger and 0.3% of adult patients.[83] Nevertheless, recent pooled data from randomized, controlled trials of lamotrigine in bipolar disorder and recurrent major depression show that no

cases of serious rash, including Stevens–Johnson syndrome or toxic epidermal necrolysis, were reported. Benign rash occurred in 9.0% of patients treated with lamotrigine.[16] Recent guidelines regarding slow dose titration may be contributing to the reduction in rash rates.

Lamotrigine should be used with caution together with valproate, as the combination increases lamotrigine levels, and hence, the risk of rash. Carbamazepine decreases lamotrigine levels by as much as 40%.[83] However, though controlled studies of efficacy are lacking, there are no known pharmacokinetic interactions between lamotrigine and lithium,[84] allowing for a combination that would conceivably protect against recurrence of both depressive and manic episodes. A recent case series found that oral contraceptives reduced lamotrigine plasma levels by 41–64% (mean 49%) in epileptic patients, and concluded that women with epilepsy who are treated with both lamotrigine and oral contraceptives should have their lamotrigine plasma levels monitored closely.[85] Further studies are needed in patients with bipolar disorder.

Topiramate

Case reports and open-label evaluations of topiramate used as adjunctive therapy in bipolar disorder I, demonstrate improvement in manic and mixed episodes[86–90] but little response in euthymic or depressed patients.[89] Controlled clinical trials in mania, as yet unpublished, are however negative.

Somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, nystagmus and paresthesia occur commonly in patients treated with topiramate for bipolar disorder, and it is the cognitive side-effects that are of particular concern in these patients. Topiramate is associated with weight loss, rather than weight gain,[91] and has been used as adjuvant therapy to control weight gain in adult patients with bipolar disorder.[90]

Caution should be exercised in prescribing other central nervous system depressants, and possibly digoxin, in patients taking topiramate. Topiramate may also reduce the efficacy of oral contraceptives. Carbonic anhydrase inhibitors should be avoided due to the risk of renal stone formation.[91]

Gabapentin

While uncontrolled and open studies pointed to gabapentin's possible efficacy as monotherapy or add-on therapy in acute treatment of manic or depressive symptoms,[92,93] both controlled studies conducted to date have shown negative results.[82,94] Gabapentin has a mild side-effect profile and has not been found to have any significant drug–drug interactions to date.[95]

Role of the atypical antipsychotics

Atypical antipsychotics like clozapine, risperidone, ziprasidone and olanzapine are frequently used to stabilize acutely manic patients and patients with bipolar disorder in whom frank psychotic symptoms are evident.[47] Due to the risk of induction of depression associated with the older antipsychotics,[96] and their side-effect profiles, atypical antipsychotics have largely replaced the older conventional antipsychotic medications.[96]

Olanzapine is the only atypical antipsychotic currently FDA-approved for treatment of acute mania, and a comparative study with lithium demonstrated similar efficacy between the two agents for this indication.[97]

Published data regarding efficacy of atypical antipsychotics for maintenance treatment of bipolar disorder is largely limited to small, open-label trials and case reports, and has not been well established.[98–100] A number of unpublished reports of the efficacy of olanzapine in bipolar disorder have been presented in trials comparing olanzapine against lithium, divalproex and placebo. These suggest that olanzapine may have efficacy in the maintenance phase of bipolar disorder.[101–106] Aripiprazole treatment has also demonstrated efficacy in maintenance in a 26-week placebo-controlled trial of 161 patients with Bipolar I Disorder.[107]

Additionally, there is evidence from double-blind, placebo controlled studies to support the use of olanzapine, aripiprazole, quetiapine, risperidone and ziprasidone in the treatment of acute mania. Clinical trial evidence also exists to support the efficacy of olanzapine and quetiapine in bipolar depression.[108]

Sedation is seen to varying degrees with atypical antipsychotic treatment, and while this may be beneficial during acute treatment for mania, longer-term sedation may result in patient non-compliance.

Weight gain, associated to varying degrees with the atypical antipsychotics, has been linked to the development of adverse lipid profiles and the possible induction of diabetes. Clozapine and olanzapine use appear to produce the most weight gain, while ziprasidone causes little, if any, weight gain.[109]

Psychosocial therapies

There is robust evidence suggesting a link between the number of previous episodes experienced by the indi-

vidual and his/her risk of future episodes.[110] The potential of medication to reduce relapse is not always realized in clinical settings.[111] This may be due at least, in part, to the problem of nonadherence to prescribed long-term medical treatment in bipolar disorder. Johnson and McFarland[112] followed over 1500 patients prescribed lithium over 5 years. They reported that the median duration of continuous lithium adherence after it was first prescribed, was 76 days. Jamison *et al*.[113] found that over a 2-year follow-up period, 50% of patients stopped and re-started their lithium against medical advice at least once and 30% at least twice. Lingam and Scott[111] in their review of the literature, suggest that adherence has not been improved by the introduction of newer pharmacological agents. Psychosocial interventions that improve medication adherence may serve as a useful adjunct to management in the primary care setting.

Cochran[114] conducted a small, randomised control trial using six sessions of Cognitive Behavioural Therapy (CBT) to improve medication adherence in patients with bipolar disorder. She found that at post-treatment and 6-months follow up, patients in the CBT group had significantly better adherence to medication and were 60% less likely to require hospitalization.

Recent studies of more comprehensive psychosocial interventions as an adjunct to pharmacological treatment also show positive outcomes for medication adherence, although meta-analysis suggests that medication adherence alone cannot account for the increase in time to relapse of bipolar outpatients in these studies.[115–118] In addition to problems in medication adherence, other psychosocial issues may impact on the course of illness. For example, despite medication compliance, Ellicott *et al*.[119] found a significant association between stressful life events and relapse over a 2-year period in a group of 61 outpatients with bipolar disorder. Negative life events have also been associated with a threefold increase in time to recovery from an episode of illness.[120] Life stressors that disrupt the sleep/wake cycle may influence the onset of mania.[121,122] Patients from families with high expressed emotion were found to have a higher risk of relapse.[123] Thus, management of stressful triggers of illness, family psychoeducation and reducing family conflict, interpersonal problem solving and establishing routines and regular sleep/wake cycles have also been targets of adjunctive interventions.

Different interventions, such as those based on CBT,[116,117,124,125] family therapy[115,126] or Interpersonal and Social Rhythm Therapy,[127] all involve a psychoeducation component and focus on relapse prevention through increased awareness of illness patterns and prodromes and coping skills to prevent full blown relapse. Enhancing suicide prevention has been considered as an important target.[128] In addition, there is a focus on the morbidity experienced in living with bipolar illness due to the disruption to relationships, personal status and quality of life as well as subsyndromal symptomatology and impaired functioning between episodes.[125,127,129] Keller *et al*.[130] suggests that substantial subsyndromal symptomatology, especially depressive symptomatology, remains in a large proportion of patients and that on maintenance lithium treatment, subsyndromal symptoms predicted a higher relapse within 2 years. The more episodes, especially depressive episodes, the patient has experienced, the worse the prognosis for functionality[131] and the higher the risk of recurrence.[132] Comorbid substance abuse has also been associated with poor prognosis and this has also been a target of psychosocial interventions.[125,133]

Recent research in the effectiveness of psychosocial interventions has shown positive outcomes. A handful of randomised control trials on the effectiveness of individual[116,124,134] and group[117] cognitive behavioral interventions for outpatients with bipolar disorder as an adjunct to medication, have shown improvements in time to relapse, fewer admissions, shorter affective episodes, affective symptomatology and social functioning. Most of these interventions utilize a number of different strategies, making it unclear what is the actual therapeutic agent involved in the positive outcomes and what phases of illness respond better to specific strategies.

The growing evidence for the effectiveness of CBT is supplemented by promising findings in other approaches, such as an integration of family and individual Interpersonal and Social Rhythm Therapy (IFIT) which showed an increase in time to relapse and a decrease in depressive symptomatology, and a study of family focused therapy (FFT)[115] which showed similar impact on depressive recurrence. In a meta-analysis of psychotherapy trials, add-on psychotherapy was associated with higher effect sizes than many trials of add-on pharmacotherapy.[135]

The psychosocial morbidity experienced by the individual with bipolar disorder and his/her family, and the potential importance of numerous psychosocial factors on the course of bipolar illness, highlight the need for psychosocial treatments as an adjunct to pharmacotherapy in primary care. Thus, when dealing with the real-life patient experiencing the impact of having to come to terms with living with bipolar disorder, its treatment, and the consequences of episodes, the possible advantages of adjunctive psychosocial interventions need to be considered.

DISCUSSION

The primary care physician is the 'first-line of defence' in detecting and managing a host of conditions, not the least among them being bipolar disorder. The increasing recognition that prevalence of bipolar disorder is higher than previously believed, points to the reality of considerable numbers of bipolar patients in the community remaining undiagnosed or incorrectly diagnosed. Patients with bipolar disorder will be encountered in the primary care setting, and care should be taken that their disorder not be missed or misdiagnosed. The National Depressive and Manic–Depressive Association survey of bipolar members,[136] showed an average of 8 years having elapsed between the first presentation of bipolar patients to a mental health professional and correct diagnosis. A recent survey of mental health professionals, indicated that the rate of screening for bipolar disorder is low, even in the mental health setting, and it is likely, therefore, that bipolar patients are missed even in this setting.[137] It is, therefore, conceivable that even more patients may be missed in the primary care setting.

The differentiation of unipolar and bipolar disorder is critical. The present danger to patients is that if they are misdiagnosed as suffering from unipolar major depression, there is a likelihood that primary treatment will be antidepressants, rather than mood stabilizers. It is established that antidepressants can induce both mania and rapid cycling and, as such, antidepressant monotherapy in bipolar disorder is strongly discouraged in most management guidelines.[138]

In addition, as patients with bipolar disorder will be encountered in primary care, even if their long-term management is to remain in the hands of the psychiatrist, it is important to acknowledge that many of the mood stabilizers used to treat and maintain this population will interact with drugs commonly used in the primary care setting. Lithium and divalproex, two of the drugs most commonly prescribed maintenance medications for bipolar disorder, interact with a host of commonly prescribed drugs. Because of the influence of many of the anticonvulsant mood stabilizers on cytochrome P450 and other enzyme systems, caution should be used in prescribing any drugs that have the possibility of interacting with them. In addition, it is important to keep in mind that patients chronically treated with lithium and anticonvulsant mood stabilizers are at risk of experiencing a host of side-effects, among them thyroid and renal dysfunction, and hepatotoxicity, all of which require ongoing monitoring to ensure normal functioning. It is also important to note, that as newer anticonvulsant mood stabilizers and atypical antipsychotics are thrust into the arena of bipolar disorder treatment, it is possible that new side-effects and drug interactions may emerge.

CONCLUSION

Although primary care physicians may not always be primarily responsible for the long-term medication management of bipolar patients, they are often the first clinicians to be in a position to screen for bipolar disorder and to manage its initial manifestations. There are increasing initiatives to integrate the primary care physician into the network of care for bipolar disorder. Primary care physicians, therefore, constitute a critical link in detecting and appropriately referring patients with bipolar disorder, and are vital for helping to manage a major component of the burden of illness in the community.

ACKNOWLEDGMENTS

This paper was supported by an unrestricted grant from GlaxoSmithKline Inc. The authors wish to thank Jaqui Brooks for her assistance with the manuscript.

REFERENCES

1. Akiskal HS, Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H, Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J. Affect. Disord.* 2000; **59** (Suppl. 1): S5–S30.
2. Griswold KS, Pessar LF. Management of bipolar disorder. *Am. Fam. Physician* 2000; **62**: 1343–1353, 1357–1358.
3. Botts SR, Raskind J. Gabapentin and lamotrigine in bipolar disorder. *Am. J. Health Syst. Pharm.* 1999; **56**: 1939–1944.
4. Goodwin GM. Prophylaxis of bipolar disorder: how and who should we treat in the long term? *Eur. Neuropsychopharmacol.* 1999; **9** (Suppl. 4): S125–S129.
5. Suppes T, Dennehy EB, Gibbons EW. The longitudinal course of bipolar disorder. *J. Clin. Psychiatry* 2000; **61** (Suppl. 9): 23–30.
6. Woods SW. The economic burden of bipolar disease. *J. Clin. Psychiatry* 2000; **61** (Suppl. 13): 38–41.
7. Jamison KR. Suicide and bipolar disorder. *J. Clin. Psychiatry* 2000; **61** (Suppl. 9): 47–51.
8. Simpson SG, Jamison KR. The risk of suicide in patients with bipolar disorders. *J. Clin. Psychiatry* 1999; **60** (Suppl. 2): 53–56; discussion 75–76, 113–116.
9. Piver A, Yatham LN, Lam RW. Bipolar spectrum disorders. New perspectives. *Can. Fam. Physician* 1999; **48**: 896–904.
10. Hinkle P. Bipolar illness in primary care: an overview. *Lippincotts Prim. Care Pract.* 2000; **4**: 163–173.

11. Manning JS. Bipolar disorder in primary care. *J. Fam. Pract.* 2003; Suppl: S6–S9.
12. Manning JS, Haykal RF, Akiskal HS. The role of bipolarity in depression in the family practice setting. *Psychiatr. Clin. North Am.* 1999; **22**: 689–703, x.
13. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption – II. *Addiction* 1993; **88**: 791–804.
14. Sachs GS, Yan LJ, Swann AC, Allen MH. Integration of suicide prevention into outpatient management of bipolar disorder. *J. Clin. Psychiatry* 2001; **62** (Suppl. 25): 3–11.
15. Ghaemi SN, Lenox MS, Baldessarini RJ. Effectiveness and safety of long-term antidepressant treatment in bipolar disorder. *J. Clin. Psychiatry* 2001; **62**: 565–569.
16. Calabrese JR, Sullivan JR, Bowden CL *et al.* Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. *J. Clin. Psychiatry* 2002; **63**: 1012–1019.
17. Baldassano CF, Goldberg JF, Wisniewski SR, Thase ME, Sachs G. *APA Annual Meeting NR29.* San Francisco, CA, 2003.
18. Fagiolini A, Frank E, Cherry CR *et al.* Clinical indicators for the use of antidepressants in the treatment of bipolar I depression. *Bipolar Disord.* 2002; **4**: 277–282.
19. Vieta E, Martinez-Aran A, Goikolea JM *et al.* A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. *J. Clin. Psychiatry* 2002; **63**: 508–512.
20. Kupka RW, Nolen WA, Altshuler LL *et al.* The Stanley Foundation Bipolar Network. 2. Preliminary summary of demographics, course of illness and response to novel treatments. *Br. J. Psychiatry Suppl.* 2001; **41**: s177–s183.
21. Post RM, Altshuler LL, Frye MA *et al.* Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers. *Bipolar Disord.* 2001; **3**: 259–265.
22. Schaffer A, Mamdani M, Levitt A, Herrmann N. Effect of antidepressant use on admissions to hospital among elderly bipolar patients. *Bipolar Disord.* 2003; **5**: 81.
23. Bauer M, Rasgon N, Grof P, Gyulai L, Glenn T, Whybrow PC. *43rd Annual NCDEU Conference 161.* Boca Raton, FL, 2003.
24. Berk M, Dodd S. Recent developments in the treatment of bipolar disorders. *Expert Opin. Investig. Drugs* 2003; **12**: 1621–1632.
25. Baastrup PC, Poulsen JC, Schou M, Thomsen K, Amdisen A. Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent-depressive disorders. *Lancet* 1970; **2**: 326–330.
26. Prien RF, Caffey EM Jr, Klett CJ. Prophylactic efficacy of lithium carbonate in manic-depressive illness. Report of the Veterans Administration and National Institute of Mental Health collaborative Study Group. *Arch. Gen. Psychiatry* 1973; **28**: 337–341.
27. Goodwin FK, Jamison KR. *Manic-depressive Illness.* Oxford University Press, New York, NY, 1990.
28. Davis JM, Janicak PG, Hogan DM. Mood stabilizers in the prevention of recurrent affective disorders: a meta-analysis. *Acta Psychiatr. Scand.* 1999; **100**: 406–417.
29. Bowden CL, Lecrubier Y, Bauer M *et al.* Maintenance therapies for classic and other forms of bipolar disorder. *J. Affect. Disord.* 2000; **59** (Suppl. 1): S57–S67.
30. Bowden CL, Brugger AM, Swann AC *et al.* Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. *JAMA* 1994; **271**: 918–924.
31. Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC. A double-blind comparison of valproate and lithium in the treatment of acute mania. *Am. J. Psychiatry* 1992; **149**: 108–111.
32. Ichim L, Berk M, Brook S. Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Ann. Clin. Psychiatry* 2000; **12**: 5–10.
33. Baldessarini RJ, Tondo L. Does lithium treatment still work? Evidence of stable responses over three decades. *Arch. Gen. Psychiatry* 2000; **57**: 187–190.
34. Rybakowski JK, Chlopocka-Wozniak M, Suwalska A. The prophylactic effect of long-term lithium administration in bipolar patients entering treatment in the 1970s and 1980s. *Bipolar Disord.* 2001; **3**: 63–67.
35. Berghofer A, Muller-Oerlinghausen B. Is there a loss of efficacy of lithium in patients treated for over 20 years? *Neuropsychobiology* 2000; **42** (Suppl. 1): 46–49.
36. Strakowski SM, McElroy SL, Keck PE. Clinical efficacy of valproate in bipolar illness: Comparisons and contrasts with lithium. In: Halbreich U, Montgomery SA (eds). *Pharmacotherapy for Mood, Anxiety and Cognitive Disorders.* American Psychiatric Press, Washington DC, 2000; 143–157.
37. Post RM, Ketter TA, Denicoff K *et al.* The place of anticonvulsant therapy in bipolar illness. *Psychopharmacology (Berl)* 1996; **128**: 115–129.
38. Post RM, Ketter TA, Pazzaglia PJ *et al.* Rational polypharmacy in the bipolar affective disorders. *Epilepsy Res. Suppl.* 1996; **11**: 153–180.
39. Baldessarini RJ, Tondo L, Floris G, Hennen J. Effects of rapid cycling on response to lithium maintenance treatment in 360 bipolar I and II disorder patients. *J. Affect. Disord.* 2000; **61**: 13–22.
40. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. *Am. J. Psychiatry* 1999; **156**: 1264–1266.
41. Maj M, Pirozzi R, Magliano L, Bartoli L. Long-term outcome of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients at a lithium clinic. *Am. J. Psychiatry* 1998; **155**: 30–35.
42. Leutgeb U. Overt hypothyroidism and goiter during prophylactic lithium treatment: the influence of ambient iodine supply. A critical review. *Neurol. Psychiatry Brain Res.* 1999; **7**: 121–130.

43. Arana GW, Rosenbaum J.F. *Handbook of Psychiatric Drug Therapy.* Lippincott Williams & Wilkins, Philadelphia, 2000.
44. Gitlin M. Lithium and the kidney: an updated review. *Drug Saf.* 1999; **20**: 231–243.
45. Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. *Clin. Pharmacokinet.* 1995; **29**: 172–191.
46. Eskalith CR Product information. In: *Physicians' Desk Reference Electronic Library*, 55th edn. Medical Economics Company Inc., Montvale, NJ, 2001.
47. Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP. The expert consensus guideline series: medication treatment of bipolar disorder 2000. *Postgrad. Med.* 2000; **Spec No**: 1–104.
48. Pope HG Jr, McElroy SL, Keck PE Jr, Hudson JI. Valproate in the treatment of acute mania. A placebo-controlled study. *Arch. Gen. Psychiatry* 1991; **48**: 62–68.
49. Swann AC, Bowden CL, Morris D *et al.* Depression during mania. Treatment response to lithium or divalproex. *Arch. Gen. Psychiatry* 1997; **54**: 37–42.
50. Bowden CL, Calabrese JR, McElroy SL *et al.* A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch. Gen. Psychiatry* 2000; **57**: 481–489.
51. Baldessarini RJ, Tohen M, Tondo L. Maintenance treatment in bipolar disorder. *Arch. Gen. Psychiatry* 2000; **57**: 490–492.
52. Bowden CL. Novel treatments for bipolar disorder. *Expert Opin. Investig. Drugs* 2000; **10**: 661–671.
53. Depakote product information. In: *Physicians' Desk Reference Electronic Library*, 55th edn. Medical Economics Company Inc., Montvale, NJ, 2001.
54. Herzog AG. Polycystic ovarian syndrome in women with epilepsy: epileptic or iatrogenic? *Ann. Neurol.* 1996; **39**: 559–560.
55. Garland EJ, Behr R. Hormonal effects of valproic acid? *J. Am. Acad. Child Adolesc. Psychiatry* 1996; **35**: 1424–1425.
56. Keck PE Jr, Mendlwicz J, Calabrese JR *et al.* A review of randomized, controlled clinical trials in acute mania. *J. Affect. Disord.* 2000; **59** (Suppl. 1): S31–S37.
57. McElroy SL, Keck PE Jr. Pharmacologic agents for the treatment of acute bipolar mania. *Biol. Psychiatry* 2000; **48**: 539–557.
58. Post R, Denicoff K, Frye M. Long-term outcome of anticonvulsants in affective disorders. In: Goldberg JF, Harrow M (eds). *Bipolar Disorders.* American Psychiatric Press, Washington DC, 1999; 85–114.
59. Greil W, Kleindienst N. Lithium versus carbamazepine in the maintenance treatment of bipolar II disorder and bipolar disorder not otherwise specified. *Int. Clin. Psychopharmacol.* 1999; **14**: 283–285.
60. Greil W, Kleindienst N. The comparative prophylactic efficacy of lithium and carbamazepine in patients with bipolar I disorder. *Int. Clin. Psychopharmacol.* 1999; **14**: 277–281.
61. Greil W, Kleindienst N, Erazo N, Muller-Oerlinghausen B. Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. *J. Clin. Psychopharmacol.* 1998; **18**: 455–460.
62. Greil W, Ludwig-Mayerhofer W, Erazo N *et al.* Lithium versus carbamazepine in the maintenance treatment of bipolar disorders – a randomised study. *J. Affect. Disord.* 1997; **43**: 151–161.
63. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology* 2000; **42** (Suppl. 1): 2–10.
64. Tegretol product information. In: *Physicians' Desk Reference Electronic Library*, 55th edn. Medical Economics Company Inc., Montvate, NJ, 2001.
65. Smith D, Chadwick D, Baker G, Davis G, Dewey M. Seizure severity and the quality of life. *Epilepsia* 1993; **34** (Suppl. 5): S31–S35.
66. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J. Clin. Psychiatry* 1999; **60**: 79–88.
67. Walden J, Hesslinger B, van Calker D, Berger M. Addition of lamotrigine to valproate may enhance efficacy in the treatment of bipolar affective disorder. *Pharmacopsychiatry* 1996; **29**: 193–195.
68. Fogelson DL, Sternbach H. Lamotrigine treatment of refractory bipolar disorder. *J. Clin. Psychiatry* 1997; **58**: 271–273.
69. Kusumakar V, Yatham LN. An open study of lamotrigine in refractory bipolar depression. *Psychiatry Res.* 1997; **72**: 145–148.
70. Sporn J, Sachs G. The anticonvulsant lamotrigine in treatment-resistant manic-depressive illness. *J. Clin. Psychopharmacol.* 1997; **17**: 185–189.
71. Corn T, Ascher J, Calabrese JR. *35th Annual Meeting of the American College of Neuropsychopharmacology 222.* San Juan, Puerto Rico, 1995.
72. Bowden CL, Calabrese JR, Sachs G *et al.* A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch. Gen. Psychiatry* 2003; **60**: 392–400.
73. Judd LL, Akiskal HS, Schettler PJ *et al.* The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? *J. Affect. Disord.* 2003; **73**: 19–32.
74. Cohn JB, Collins G, Ashbrook E, Wernicke JF. A comparison of fluoxetine imipramine and placebo in patients with bipolar depressive disorder. *Int. Clin. Psychopharmacol.* 1989; **4**: 313–322.
75. Himmelhoch JM, Thase ME, Mallinger AG, Houck P. Tranylcypromine versus imipramine in anergic bipolar depression. *Am. J. Psychiatry* 1991; **148**: 910–916.
76. Calabrese JR, Fatemi SH, Woyshville MJ. Antidepressant effects of lamotrigine in rapid cycling bipolar disorder. *Am. J. Psychiatry* 1996; **153**: 1236.

77. Fatemi SH, Rapport DJ, Calabrese JR, Thuras P. Lamotrigine in rapid-cycling bipolar disorder. *J. Clin. Psychiatry* 1997; **58**: 522–527.
78. Walden J, Schaerer L, Schloesser S, Grunze H. An open longitudinal study of patients with bipolar rapid cycling treated with lithium or lamotrigine for mood stabilization. *Bipolar Disord.* 2000; **2**: 336–339.
79. Calabrese JR, Suppes T, Bowden CL *et al.* A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *J. Clin. Psychiatry* 2000; **61**: 841–850.
80. Calabrese JR, Rapport DJ, Kimmel SE, Shelton MD. Controlled trials in bipolar I depression: focus on switch rates and efficacy. *Eur. Neuropsychopharmacol.* 1999; **9** (Suppl. 4): S109–S112.
81. Ketter TA, Post RM, Theodore WH. Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. *Neurology* 1999; **53**: S53–S67.
82. Frye MA, Ketter TA, Kimbrell TA *et al.* A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J. Clin. Psychopharmacol.* 2000; **20**: 607–614.
83. *GlaxoSmithKline. Lamictal (lamotrigine)* [Package Insert]. GlaxoSmithKline, Research Triangle Park, NC, 2001.
84. Veronese L, Chen C, Peck R. Lamotrigine does not cause clinically relevant changes in the pharmacokinetics of lithium. *Eur. Psychopharmacol.* 1998; **8**: S194–S195.
85. Sabers A, Buchholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Res.* 2001; **47**: 151–154.
86. Pecuch PW, Erfurth A. Topiramate in the treatment of acute mania. *J. Clin. Psychopharmacol.* 2001; **21**: 243–244.
87. Gordon A, Price LH. Mood stabilization and weight loss with topiramate. *Am. J. Psychiatry* 1999; **156**: 968–969.
88. Grunze HC, Normann C, Langosch J *et al.* Antimanic efficacy of topiramate in 11 patients in an open trial with an on-off-on design. *J. Clin. Psychiatry* 2001; **62**: 464–468.
89. McElroy SL, Suppes T, Keck PE *et al.* Open-label adjunctive topiramate in the treatment of bipolar disorders. *Biol. Psychiatry* 2000; **47**: 1025–1033.
90. Chengappa KN, Rathore D, Levine J *et al.* Topiramate as add-on treatment for patients with bipolar mania. *Bipolar Disord.* 1999; **1**: 42–53.
91. Topamax product information. In: *Physicians' Desk Reference Electronic Library*, 55th edn. Medical Economics Company Inc., Montvale, NJ, 2001.
92. Altshuler LL, Keck PE Jr, McElroy SL *et al.* Gabapentin in the acute treatment of refractory bipolar disorder. *Bipolar Disord.* 1999; **1**: 61–65.
93. Ghaemi SN, Goodwin FK. Gabapentin treatment of the non-refractory bipolar spectrum: an open case series. *J. Affect. Disord.* 2001; **65**: 167–171.
94. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. *Bipolar Disord.* 2000; **2**: 249–255.
95. Neurotin product information. In: *Physicians' Desk Reference Electronic Library*, 55th edn. Medical Economics Company Inc., Montvale, NJ, 2001.
96. Kukopulos A, Reginaldi D, Laddomada P, Floris G, Serra G, Tondo L. Course of the manic-depressive cycle and changes caused by treatment. *Pharmakopsychiatr. Neuropsychopharmakol.* 1980; **13**: 156–167.
97. Berk M, Ichim L, Brook S. Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *Int. Clin. Psychopharmacol.* 1999; **14**: 339–343.
98. Puri BK, Taylor DG, Alcock ME. Low-dose maintenance clozapine treatment in the prophylaxis of bipolar affective disorder. *Br. J. Clin. Pract.* 1995; **49**: 333–334.
99. Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush AJ. Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. *Am. J. Psychiatry* 1999; **156**: 1164–1169.
100. Ghaemi SN, Sachs GS. Long-term risperidone treatment in bipolar disorder: 6-month follow up. *Int. Clin. Psychopharmacol.* 1997; **12**: 333–338.
101. Tohen M, Baker RW, Altshuler LL *et al.* Olanzapine versus divalproex sodium for bipolar mania. *Eur. Psychiatry* 2002; **17**: 109.
102. Tohen M, Bowden CL, Calabrese JR *et al.* Olanzapine's efficacy for relapse prevention in bipolar disorder: a randomized double-blind, placebo-controlled 12-month clinical trial. *Bipolar Disord.* 2003; **5**: 89.
103. Tohen M, Chengappa KN, Suppes T *et al.* Olanzapine cotherapy in prevention of recurrence in bipolar disorder. *Eur. Psychiatry* 2002; **17**: 109.
104. Tohen M, Chengappa KN, Suppes T *et al.* Olanzapine combined with mood stabilizers in prevention of recurrence in bipolar disorder: an 18-month study. *Biol. Psychiatry* 2003; **53**: 134S.
105. Tohen M, Marneros A, Bowden CL *et al.* Olanzapine vs. lithium in relapse prevention in bipolar disorder: a randomized double-blind controlled 12-month clinical trial. *Bipolar Disord.* 2003; **5**: 89.
106. Tohen M, Marneros A, Bowden CL *et al. 43rd Annual NCDEU Conference 138.* Boca Raton, FL, 2003.
107. McQuade R, Sanchez R, Marcus R *et al.* Aripiprazole for relapse prevention in bipolar disorder in a 26-week trial [poster]. Presented at the XXIVth Collegium Internationale Neuro-Psycophamacologicum Congress Meeting, 20–24, June 2004, Paris, France.
108. Berk M, Dodd S. Atypical antipsychotics in bipolar disorder. *Drugs* 2005; **65**: 257–269.
109. Allison DB, Mentore JL, Heo M *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am. J. Psychiatry* 1999; **156**: 1686–1696.
110. Marneros A, Breiger P. Prognosis of bipolar disorder. In: Maj M, Akiskal H, Lopez-Ibor JJ, Sartorius N

(eds). *Bipolar Disorder.* John Wiley & Sons Ltd., UK, 2002.
111. Lingam R, Scott J. Treatment non-adherence in affective disorders. *Acta Psychiatr. Scand.* 2002; **105**: 164–172.
112. Johnson RE, McFarland BH. Lithium use and discontinuation in a health maintenance organization. *Am. J. Psychiatry* 1996; **153**: 993–1000.
113. Jamison KR, Gerner RH, Goodwin FK. Patient and physician attitudes toward lithium: relationship to compliance. *Arch. Gen. Psychiatry* 1979; **36**: 866–869.
114. Cochran SD. Preventing medical noncompliance in the outpatient treatment of bipolar affective disorders. *J. Consult. Clin. Psychol.* 1979; **52**: 873–878.
115. Miklowitz DJ, Simoneau TL, George EL *et al.* Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. *Biol. Psychiatry* 2000; **48**: 582–592.
116. Lam DH, Watkins ER, Hayward P *et al.* A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. *Arch. Gen. Psychiatry* 2003; **60**: 145–152.
117. Colom F, Vieta E, Martinez-Aran A *et al.* A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Arch. Gen. Psychiatry* 2003; **60**: 402–407.
118. Vieta E, Colom F. Combining medication and psychoeducation for the prevention of relapse in bipolar disorder. *Bipolar Disord.* 2003; **5**: 21.
119. Ellicott A, Hammen C, Gitlin M, Brown G, Jamison K. Life events and the course of bipolar disorder. *Am. J. Psychiatry* 1990; **147**: 1194–1198.
120. Johnson SL, Miller I. Negative life events and time to recovery from episodes of bipolar disorder. *J. Abnorm. Psychol.* 1997; **106**: 449–457.
121. Malkoff-Schwartz S, Frank E, Anderson B *et al.* Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes: a preliminary investigation. *Arch. Gen. Psychiatry* 1998; **55**: 702–707.
122. Wehr TA, Sack DA, Rosenthal NE. Sleep reduction as a final common pathway in the genesis of mania. *Am. J. Psychiatry* 1987; **144**: 201–204.
123. Miklowitz DJ, Goldstein MJ, Nuechterlein KH, Snyder KS, Mintz J. Family factors and the course of bipolar affective disorder. *Arch. Gen. Psychiatry* 1988; **45**: 225–231.
124. Scott J, Garland A, Moorhead S. A pilot study of cognitive therapy in bipolar disorders. *Psychol. Med.* 2001; **31**: 459–467.
125. Otto MW, Reilly-Harrington NA. Cognitive-behavioural therapy for the management of bipolar disorder. In: Hofmann SG, Tompson MC (eds). *Treating Chronic and Severe Mental Disorders: a Handbook of Empirically Supported Interventions.* The Guilford Press, NY, 2003.
126. Miklowitz DJ, Richards JA, George EL *et al.* Integrated family and individual therapy for bipolar disorder: results of a treatment development study. *J. Clin. Psychiatry* 2003; **64**: 182–191.
127. Frank E, Swartz HA, Kupfer DJ. Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder. *Biol. Psychiatry* 2000; **48**: 593–604.
128. Newman CF, Leahy RL, Beck AT, Reilly-Harrington NA, Gyulai L. *Bipolar Disorder. A cognitive therapy approach.* American Psychological Association, Washington DC, 2002.
129. Fava GA, Bartolucci G, Rafanelli C, Mangelli L. Cognitive-behavioral management of patients with bipolar disorder who relapsed while on lithium prophylaxis. *J. Clin. Psychiatry* 2001; **62**: 556–559.
130. Keller MB, Lavori PW, Kane JM *et al.* Subsyndromal symptoms in bipolar disorder. A comparison of standard and low serum levels of lithium. *Arch. Gen. Psychiatry* 1992; **49**: 371–376.
131. MacQueen GM, Young LT, Robb JC, Marriott M, Cooke RG, Joffe RT. Effect of number of episodes on wellbeing and functioning of patients with bipolar disorder. *Acta Psychiatr. Scand.* 2000; **101**: 374–381.
132. Kessing LV, Andersen PK. The effect of episodes on recurrence in affective disorder: a case register study. *J. Affect. Disord.* 1999; **53**: 225–231.
133. Weiss RD, Najavits LM, Greenfield SF. A relapse prevention group for patients with bipolar and substance use disorders. *J. Subst. Abuse Treat.* 1999; **16**: 47–54.
134. Perry A, Tarrier N, Morriss R, McCarthy E, Limb K. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *BMJ* 1999; **318**: 149–153.
135. Scott J. What is the role of psychotherapy in bipolar disorders? *Bipolar Disord.* 2003; **5**: 15–16.
136. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J. Affect. Disord.* 1994; **31**: 281–294.
137. Brickman AL, LoPiccolo CJ, Johnson SL. Screening for bipolar disorder. *Psychiatr. Serv.* 2002; **53**: 349.
138. Grunze H, Kasper S, Goodwin G *et al.* World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders. Part I: Treatment of bipolar depression. *World J. Biol. Psychiatry* 2002; **3**: 115–124.