Treatment of bipolar depression

Michael Berk
PhD, MB BCh, FRANZCP, Chair in Psychiatry at Barwon Health[1,2,3]

Lesley Berk
MA(Clin Psych), PhD Student[1,2]

Christopher G Davey
FRANZCP, Psychiatrist[3]

Steven Moylan
BM BS(Hons), MPH, BSc, Clinical Lecturer[1]

Francesco Giorlando
MB BS, BMedSc, Psychiatric Registrar[2]

Ajeet B Singh
MB BS, MPsych, FRANZCP, Psychiatrist and Clinical Senior Lecturer[1]

Harish Kalra
FRANZCP, Psychiatrist[1]

Seetal Dodd
BSc, MSc, PhD, Clinical Associate Professor,[1] and Senior Fellow[2]

Gin S Malhi
MB ChB, FRANZCP, MD, Executive and Clinical Director[4]

1 School of Medicine, Deakin University, Geelong, VIC.

2 Department of Psychiatry, University of Melbourne, Melbourne, VIC.

3 Orygen Youth Health Research Centre, Centre for Youth Mental Health, Melbourne, VIC.

4 Discipline of Psychiatry, Sydney Medical School, University of Sydney, Sydney, NSW.

seetald@barwonhealth.org.au

MJA Open 2012; 1 Suppl 4: 32–35
doi: 10.5694/mjao12.10611

Summary

- Depression is usually the predominant phase in bipolar disorder, causes the most psychosocial disability, and carries significant risk of suicide.
- The management of bipolar depression is relatively under-studied and poses significant challenges for clinicians.
- There is substantial dissent regarding optimal pharmacotherapy for bipolar depression, particularly around the role of antidepressants.
- Individual and combination pharmacotherapy should be integrated into a personalised psychosocial and lifestyle package of interventions that considers the person's clinical profile and preferences.
- The relative lack of evidence relating to optimal strategies, especially when bipolar depression occurs with common comorbidities, poses challenges and requires further research.
- A flexible approach and evidence-based combinations of treatments can provide effective strategies for improving quality of life and reducing morbidity and mortality.

Bipolar disorders (BDs) are chronic and progressive mood disorders characterised by manic, hypomanic or mixed episodes that typically occur in conjunction with depressive episodes.[1] Globally, BDs are a leading cause of disability, with consequences that include long-term unemployment, comorbid medical illness, and suicide.[2-5] Because of its recurrent pattern, people with BD are symptomatic for about half their lives, with the bulk of the psychosocial disability resulting from the depressive pole of the disorder.[1,6] Despite this, much of the research for BD focuses on the manic phase of the illness, while most depression-related research focuses on unipolar depression. However, BD — and therefore bipolar depression — is a distinct illness that requires a specific treatment approach, tailored to individual needs. Here, we outline the distinct features of bipolar depression and present evidence-based treatment options.

Features and management issues

BD is classically divided into bipolar I and II subtypes, but the bulk of the clinical data pertain to the bipolar I variant. It is a common disorder, with estimated lifetime prevalences of 0.6%–1.0% for the bipolar I subtype, 0.4%–1.1% for the bipolar II subtype, and 2.4%–5.1% for subthreshold (spectrum) forms of the disorder.[1]

The disorder characteristically begins in late adolescence, with the onset of subthreshold symptoms that are usually depressive in nature, followed by the later emergence of threshold depressive, manic or hypomanic episodes.[7] People with BD commonly spend three times as long in the depressive pole of the disorder as they do in the manic pole.[1] Bipolar depression, like its unipolar cousin, is undoubtedly heterogeneous, with biological, social, personality, trauma, lifestyle and substance misuse determinants. In contrast, mania appears to be more biologically grounded. This is of substantial relevance to treatment and should be considered when developing an individualised treatment package. Bipolar depression is particularly disabling, resulting in occupational and social impairment, and eroding quality of life. Depression and depressive mixed states are the illness phases that confer the greatest risk of suicide. The delay in the emergence of manic or hypomanic symptoms — the hallmark of the diagnosis — together with a high prevalence of comorbid disorders, typically leads to protracted delays in the correct diagnosis of BD and the initiation of appropriate management. Diagnostic delay can also result in patients receiving treatment that potentially worsens the core cyclicity of the disorder and its progression.[8]

The efficient management of bipolar depression is further hindered by a paucity of effective treatments, a problem that is compounded by a relative lack of clinical trial data. As there are few robust placebo-controlled studies of the treatment of bipolar depression, there is substantial dissent regarding optimal pharmacotherapy, particularly around the role of antidepressants.[9] Recent well designed, large-scale trials of conventional antidepressants (selective serotonin reuptake inhibitors [SSRIs]) in BD have essentially been negative.[10] There is also concern about the potential risk of inducing mania and worsening cycle frequency with antidepressant use in BD. Despite a limited evidence base for their effectiveness in this population, psychological treatments are often used in bipolar depression, based on extrapolation of data supporting the role of cognitive behaviour therapy (CBT) and related psychological therapies in unipolar depression and in maintenance treatment of BD.[11]

As a consequence, there is consensus that bipolar depression is the predominant unmet clinical need in patients with BD.[12,13] The management of bipolar depression has by necessity become broader, to take the diversity of putative aetiological factors into account. A multifaceted approach to treatment is gaining traction and, clinically, has face validity. This broadening of therapeutic approaches recognises the polymorphous nature of bipolar depression, but also reflects the intrinsic ceiling effect that is commonly observed with pharmacological or psychosocial monotherapy. In clinical practice, pharmacotherapy is only modestly efficacious, largely because the underlying pathophysiology of the disorder remains unknown and because the mechanisms of action of most medications are poorly understood. Further, nearly all medications that are currently used to treat bipolar depression have been adopted from other primary indications.

Balancing efficacy, safety and tolerability

There are three concurrent goals in the optimal management of bipolar depression: (i) to treat the acute

episode effectively; (ii) to consolidate the gains of acute treatment and prevent depressive relapse or switch to hypomania or mania; and (iii) to manage potentially reversible risk factors.[12] As BD is a chronic lifelong illness, it is essential to balance safety and tolerability of treatment against efficacy, and to build a long-term management plan based on informed, shared goals.

It is important to recognise that all interventions have the potential to cause harm. It is essential to weigh the risks and benefits of each treatment, taking into account a person's demographic and clinical profile, values and preferences. While the risks of pharmacotherapy have long received recognition, the risks of inappropriately applied psychosocial interventions are also now beginning to be appreciated.[14]

Approach to treatment

To limit disability and maximise the likelihood of recovering psychosocial functioning,[13] a suitable first-line treatment must be chosen.[15] The choice needs to be tailored to the individual's psychiatric history; in particular, comorbidities, pattern and severity of symptoms, prior illness course, history of response to and tolerability of treatments, family history of treatment response, and individual preference.[13,15] Intriguing new data suggest that this latter factor potently predicts both treatment response and the development of adverse events.[16] As treatments that are useful in acute treatment tend to be continued as maintenance therapy, treatments with maintenance efficacy should be prioritised over those without such an evidence base.[13] This also means that long-term risk factors, including metabolic disturbance, may weigh against the long-term use of agents with short-term efficacy.

Where there is a partial or inadequate response to treatment, drug dosage needs to be optimised. In addition, adherence-related issues, medical or substance misuse comorbidities, and psychosocial factors must be considered and appropriately managed. Examination of psychosocial factors includes the role of personality, prior trauma, persistent psychosocial stressors and the development of abnormal illness behaviour.[13,15,17]

In the face of continued non-response to treatment or the development of unmanageable adverse events, augmentation or switching strategies should be considered. Augmentation is more likely to be used in situations of partial response and tolerability, whereas switching is more appropriate for non-response and intolerance.[13,15] Assessment of the pattern of prior mood episodes to identify the predominant pole of illness (depression or mania) can often assist treatment choice, as predominant polarity tends to be relatively stable throughout the longitudinal course of the illness. Consequently, those agents with a documented profile of efficacy in the depressive phase (eg, lamotrigine or lithium) should be selected for treating bipolar depression.[18]

The natural history of the disorder is also informative. Depressive episodes can take many months to resolve, and the true effect of an agent on the long-term illness trajectory can only be determined over a prolonged period of observation. Therefore, any treatment trial needs to be of sufficient duration to ensure that potentially valuable therapies are not abandoned before they can demonstrate utility. Intensive psychoeducation regarding potential benefits and side effects of treatments can also help reduce non-adherence and early cessation of a potentially useful therapy.

Pharmacological and other biological therapies

First-line monotherapy options include lithium and the anticonvulsant lamotrigine (used as mood stabilisers), and the atypical antipsychotics quetiapine and olanzapine.[13,19-23] Lamotrigine has documented efficacy, but with small effect sizes in controlled trials.[24] However, this may reflect an underestimation of its true efficacy, resulting from its slow titration phase and subsequent sluggish onset of effect. Lithium, the benchmark pharmacological therapy in BD, also has a slow onset of action and has poorer evidence of effectiveness for acute depression than for mania. Similarly, the evidence for using valproate, another mood-stabilising anticonvulsant, in bipolar depression is less clear than the evidence for its role in mania.[25] Atypical antipsychotic agents, as a class, do not show efficacy in treating bipolar depression. Those that individually show efficacy (such as quetiapine and olanzapine) have clinically relevant pragmatic and tolerability limitations in some patients, not least weight gain and metabolic syndrome.[12]

In clinical practice, combination treatment is the norm in the management of acute bipolar depression. Practical treatment algorithms are given in the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.[18,26] Recommended first-line combinations include lamotrigine or valproate added to lithium.[13,24] Second-line pharmacotherapies include adjunctive therapies and medication combinations, such as lithium augmentation of antidepressants, atypical antipsychotic–mood stabiliser combinations, and olanzapine combined with fluoxetine.[13,24,27,28] In individuals not taking a mood stabiliser, the CANMAT guidelines recommend commencing either lamotrigine or lithium monotherapy, or a combination of lithium and valproate (to which an SSRI can be later added), or the combination of an atypical antipsychotic agent with fluoxetine. In patients already taking valproate or an atypical antipsychotic agent, an SSRI, bupropion, lamotrigine or lithium can be added. A caveat here is that other guidelines, examining the same patchy literature base, give substantially different recommendations.

Despite the absence of clear evidence for their effectiveness, antidepressants are widely prescribed for BD and are the most widely used medication class for the depressive phase of the illness.[29] A meta-analysis of the most recent, large-scale and rigorous trials found that they were discouragingly negative.[30] The use of antidepressants in BD is therefore controversial, especially in the context of evidence that they can on occasion induce switching to mania or hypomania, aggravate the inherent cyclicity of the disorder, and trigger or worsen rapid cycling.[31,32] These adverse events appear more common with noradrenergic antidepressants (such as tricyclics) and dual-acting agents (such as venlafaxine) compared with SSRIs.[31-33] While the risks appear clearer when antidepressants are used as monotherapy,[34] they are less clear when they are combined

with a mood stabiliser or an antipsychotic.[30,33] The threshold used in trials for switching to mania (ie, induction of full mania) ignores both the precipitation of the considerably more common subthreshold mixed states and any impact on the cyclical pattern of the illness. Until more definitive data emerge, the precautionary principle should guide treatment, and use of prescribed antidepressants should be limited. Some clinical features, such as mixed states and rapid cycling, predict greater risk with antidepressant therapy.

Other biological therapies include electroconvulsive therapy and transcranial magnetic stimulation (see Fitzgerald, *page 48*);[35] however, these have not been extensively studied in BD.[36]

Psychosocial and lifestyle therapies

The mixed aetiology of bipolar depression, with a combination of biological, social, personality, trauma, lifestyle and substance misuse determinants, should guide the development of personalised treatment packages. Evidence-based psychosocial therapies should be integrated into a management plan that is tailored to the individual's profile.[37] Long-term adjunctive psychosocial interventions with an interpersonal or cognitive focus, such as CBT, family-focused therapy (FFT) and interpersonal and social rhythm therapy (IPSRT), have been found to help people with BD recover more quickly from acute depressive episodes and to improve social functioning.[38] FFT and CBT have also shown positive results in preventing depressive relapse.[39] These therapies include psychoeducation about the illness and treatment, training in phase-specific illness management strategies, lifestyle regulation and problem solving that can be tailored to the needs of the patient and his or her family. As well as having elements in common, psychosocial approaches emphasise different aspects.[40] For example, CBT focuses on helping the person to restructure negative thinking patterns. IPSRT assists people to come to terms with the losses and changes connected with having BD and to regulate their activity and sleep. These disparate elements can effectively be brought together in a comprehensive care model.[41]

Family therapy or psychoeducation groups for caregivers may help family members adjust to the illness and learn communication skills and ways to provide informal support.[40] Improved family relationships and social support can have a positive effect on depressive symptoms.[37] Group therapy approaches also have social support benefits. Group psychoeducation was found to reduce bipolar relapse and depressive symptoms during 5 years of follow-up, especially for people with 14 or fewer previous episodes.[42]

In terms of their effect on bipolar depression, some psychotherapeutic approaches may be more helpful for those with less chronic patterns of illness and comorbidity.[43] Due to neurocognitive difficulties, people with more severe and frequent bipolar episodes may respond better to less cognitively taxing interventions.[42] New psychosocial treatments are currently being explored, such as combining elements of CBT with cognitive remediation treatment, or more experiential types of therapy, such as mindfulness-based cognitive therapy. This latter treatment shows promising results in improving cognitive functioning and reducing depressive symptoms.[44]

There is also a considerable body of evidence that lifestyle factors such as substance use, diet, smoking and exercise influence the development of depression in BD, and these factors should be the target of individualised interventions. For example, more specialised psychosocial treatments that address both the BD and a substance use disorder may be preferable.[45] Supplementation with omega-3 fatty acids has shown effectiveness in reducing depressive symptoms in patients with bipolar depression.[46] An integrated approach to psychosocial treatment focusing on nutrition, weight loss, exercise and wellness treatment has recently shown benefits in reducing depressive symptoms in a small number of patients with BD.[47] This type of approach is the next logical step in the implementation of evidence-based interventions.

Special populations

Although BD is inherently complex,[13] clinical trials frequently have extensive inclusion and exclusion criteria that limit their generalisability. There is therefore little evidence for effective treatments for complex presentations, including treatment-resistant BD; comorbidity with anxiety or substance misuse; bipolar depression in younger people, pregnant women and older people; and the needs of those at different illness stages.

Conclusions

Bipolar depression is the most common and difficult-to-treat phase of BD. There is a high incidence of subsyndromal symptoms in the disorder, which result in residual functional impairment and erosion of quality of life. Barriers due to stigma, acceptance, availability of treatment and psychoeducation need to be overcome to limit non-adherence to treatment and risk of relapse.[48]

The therapeutic benefits of any treatment choice need to be balanced against risk,[49] and a long-term outlook is essential. In the context of a collaborative alliance between the patient and clinicians, continuous monitoring is also crucial. Pharmacotherapy should be integrated into a personalised psychosocial and lifestyle package of interventions that considers the person's clinical profile and preferences.[50] The treatment recommendations offered here are based on an evolving and incomplete evidence base, and should be used in conjunction with clinical judgement. Given that it is the predominant illness phase of BD, and the extant literature is patchy, high-quality trials of bipolar depression should be a priority.

Acknowledgements: Lesley Berk acknowledges the National Health and Medical Research Council (NHMRC) for funding her PhD scholarship.

Competing interests: Michael Berk has received grant or research support from Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma and Servier; has been a speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck, Pfizer, Sanofi-Synthelabo, Servier, Solvay and Wyeth; and served as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck and Servier. Francesco Giorlando has received grant or research support from AstraZeneca and Pfizer. Ajeet Singh has received grant or research support from Healthscope Molecular and Pfizer; and has been a speaker for AstraZeneca, Eli Lilly, Lundbeck and Pfizer. Harish Kalra has been a speaker for Eli Lilly and Pfizer. Seetal Dodd has received grant or research support from Bristol-Myers Squibb, Eli Lilly, Novartis, Mayne Pharma and Servier; and has been a speaker and served as a consultant for Eli Lilly.

Provenance: Commissioned by supplement editors; externally peer reviewed.

1 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.

2 Zimmerman M, Galione JN, Chelminski I, et al. Sustained unemployment in psychiatric outpatients with bipolar disorder: frequency and association with demographic variables and comorbid disorders. *Bipolar Disord* 2010; 12: 720-726.

3 Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. *Biol Psychiatry* 1996; 39: 896-899.

4 Dalton EJ, Cate-Carter TD, Mundo E, et al. Suicide risk in bipolar patients: the role of co-morbid substance use disorders. *Bipolar Disord* 2003; 5: 58-61.

5 Leverich GS, Altshuler LL, Frye MA, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry* 2003; 64: 506-515.

6 Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord* 2003; 73: 123-131.

7 Perugi G, Micheli C, Akiskal HS, et al. Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar I patients. *Compr Psychiatry* 2000; 41: 13-18.

8 Matza LS, Rajagopalan KS, Thompson CL, de Lissovoy G. Misdiagnosed patients with bipolar disorder: comorbidities, treatment patterns, and direct treatment costs. *J Clin Psychiatry* 2005; 66: 1432-1440.

9 Ghaemi SN. Why antidepressants are not antidepressants: STEP-BD, STAR*D, and the return of neurotic depression. *Bipolar Disord* 2008; 10: 957-968.

10 Ghaemi SN, Ostacher MM, El-Mallakh RS, et al. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. *J Clin Psychiatry* 2010; 71: 372-380.

11 Scott J, Colom F. Psychosocial treatments for bipolar disorders. *Psychiatr Clin North Am* 2005; 28: 371-384.

12 Malhi GS, Berk M. Pharmacotherapy of bipolar disorder: the role of atypical antipsychotics and experimental strategies. *Hum Psychopharmacol* 2002; 17: 407-412.

13 Malhi GS, Adams D, Cahill CM, et al. The management of individuals with bipolar disorder: a review of the evidence and its integration into clinical practice. *Drugs* 2009; 69: 2063-2101.

14 Berk M, Parker G. The elephant on the couch: side-effects of psychotherapy. *Aust N Z J Psychiatry* 2009; 43: 787-794.

15 Nivoli AM, Colom F, Murru A, et al. New treatment guidelines for acute bipolar depression: a systematic review. *J Affect Disord* 2011; 129: 14-26.

16 Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. *Psychosom Med* 2011; 73: 598-603.

17 Berk M, Berk L, Dodd S, et al. Psychometric properties of a scale to measure investment in the sick role: the Illness Cognitions Scale. *J Eval Clin Pract* 2012; 18: 360-364.

18 Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disord* 2009; 11: 225-255.

19 Vieta E, Calabrese JR, Goikolea JM, et al. Quetiapine monotherapy in the treatment of patients with bipolar I or II depression and a rapid-cycling disease course: a randomized, double-blind, placebo-controlled study. *Bipolar Disord* 2007; 9: 413-425.

20 Nierenberg AA, Ostacher MJ, Calabrese JR, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry* 2006; 163: 210-216.

21 Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. *J Affect Disord* 2010; 124: 228-234.

22 Bowden CL, Grunze H, Mullen J, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 2005; 66: 111-121.

23 Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry* 2009; 194: 4-9.

24 van der Loos ML, Mulder PG, Hartong EG, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; 70: 223-231.

25 Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. *J Affect Disord* 2010; 124: 228-234.

26 Yatham LN, Kennedy SH, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. *Bipolar Disord* 2005; 7 Suppl 3: 5-69.

27 Ghaemi SN, Gilmer WS, Goldberg JF, et al. Divalproex in the treatment of acute bipolar depression: a preliminary double-blind, randomized, placebo-controlled pilot study. *J Clin Psychiatry* 2007; 68: 1840-1844.

28 Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. [Erratum in *Arch Gen Psychiatry* 2004; 61: 176.] *Arch Gen Psychiatry* 2003; 60: 1079-1088.

29 Yerevanian BI. The role of antidepressants in bipolar disorder. In: Akiskal HS, Tohen M, editors. Bipolar psychopharmacotherapy: caring for the patient. 2nd ed. Hoboken, NJ: Wiley, 2011: 299-316.

30 Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry* 2011; 72: 156-167.

31 Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry* 2006; 163: 232-239.

32 Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry* 2006; 189: 124-131.

33 Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 2004; 161: 1537-1547.

34 Baldessarini RJ, Leahy L, Arcona S, et al. Patterns of psychotropic drug prescription for US patients with diagnoses of bipolar disorders. *Psychiatr Serv* 2007; 58: 85-91.

35 Fitzgerald PB. Non-pharmacological biological treatment approaches to difficult-to-treat depression. *MJA Open* 2012; 1 Suppl 4: 48-51.

36 Loo C, Katalinic N, Mitchell PB, Greenberg B. Physical treatments for bipolar disorder: a review of electroconvulsive therapy, stereotactic surgery and other brain stimulation techniques. *J Affect Disord* 2011; 132: 1-13.

37 Lauder SD, Berk M, Castle DJ, et al. The role of psychotherapy in bipolar disorder. *Med J Aust* 2010; 193 (4 Suppl): S31-S35.

38 Parikh SV, LeBlanc SR, Ovanessian MM. Advancing bipolar disorder: key lessons from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Can J Psychiatry* 2010; 55: 136-143.

39 Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: state of the evidence. *Am J Psychiatry* 2008; 165: 1408-1419.

40 Miklowitz DJ, Goodwin GM, Bauer MS, Geddes JR. Common and specific elements of psychosocial treatments for bipolar disorder: a survey of clinicians participating in randomized trials. *J Psychiatr Pract* 2008; 14: 77-85.

41 Castle D, White C, Chamberlain J, et al. Group-based psychosocial intervention for bipolar disorder: randomised controlled trial. *Br J Psychiatry* 2010; 196: 383-388.

42 Colom F, Reinares M, Pacchiarotti I, et al. Has number of previous episodes any effect on response to group psychoeducation in bipolar patients? A 5-year follow-up post hoc analysis. *Acta Neuropsychiatr* 2010; 22: 50-53.

43 Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry* 2006; 188: 313-320.

44 Stange JP, Eisner LR, Holzel BK, et al. Mindfulness-based cognitive therapy for bipolar disorder: effects on cognitive functioning. *J Psychiatr Pract* 2011; 17: 410-419.

45 Weiss RD, Griffin ML, Jaffee WB, et al. A "community-friendly" version of integrated group therapy for patients with bipolar disorder and substance dependence: a randomized controlled trial. *Drug Alcohol Depend* 2009; 104: 212-219.

46 Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br J Psychiatry* 2006; 188: 46-50.

47 Ng F, Dodd S, Berk M. The effects of physical activity in the acute treatment of bipolar disorder: a pilot study. *J Affect Disord* 2007; 101: 259-262.

48 Gaudiano BA, Weinstock LM, Miller IW. Improving treatment adherence in bipolar disorder: a review of current psychosocial treatment efficacy and recommendations for future treatment development. *Behav Modif* 2008; 32: 267-301.

49 Ketter TA. Monotherapy versus combined treatment with second-generation antipsychotics in bipolar disorder. *J Clin Psychiatry* 2008; 69 Suppl 5: 9-15.

50 Gillhoff K, Gaab J, Emini L, et al. Effects of a multimodal lifestyle intervention on body mass index in patients with bipolar disorder: a randomized controlled trial. *Prim Care Companion J Clin Psychiatry* 2010; 12: pii: PCC.09m00906. ❑