CME

Treating bipolar disorder

Evidence-based guidelines for family medicine

Roger S. McIntyre, MD, FRCPC **Deborah A. Mancini,** MA, CCRC
Peter Lin, MD, CCFP **John Jordan,** MD, MCLSC, CCFP, FCFP

ABSTRACT

OBJECTIVE To provide an evidence-based summary of medications commonly used for bipolar disorders and a practical approach to managing bipolar disorders in the office.

QUALITY OF EVIDENCE Articles from 1990 to 2003 were selected from MEDLINE using the key words "bipolar disorder," "antiepileptics," "antipsychotics," "antidepressants," and "mood stabilizers." Good-quality evidence for many of these treatments comes from randomized trials. Lithium, divalproex, carbamazepine, lamotrigine, oxcarbazepine, and some novel antipsychotics all have level I evidence for treating various aspects of the disorder.

MAIN MESSAGE Treatment of bipolar disorder involves three therapeutic domains: acute mania, acute depression, and maintenance. Lithium has been a mainstay of treatment for some time, but antiepileptic drugs like divalproex, carbamazepine, and lamotrigine, along with novel antipsychotic drugs like olanzapine, risperidone, and quetiapine, alone or in combination, are increasingly being used successfully to treat acute mania and to maintain mood stability.

CONCLUSION Bipolar disorder is more common in family practice than previously believed. Drug treatments for this complex disorder have evolved rapidly over the past decade, radically changing its management. Treatment now tends to be very successful.

RÉSUMÉ

OBJECTIF Présenter une synthèse fondée sur des données scientifiques des médicaments habituellement utilisés pour les troubles bipolaires et d'une approche pratique à leur prise en charge au cabinet du médecin.

QUALITÉ DES DONNÉES SCIENTIFIQUES Des articles publiés entre 1990 et 2003 ont été sélectionnés dans MEDLINE à l'aide des mots clés «trouble bipolaire», «antiépileptique», «antipsychotique», «antidépresseur», «stabilisateur de l'humeur». De solides données scientifiques portant sur plusieurs de ces traitements sont tirées d'études randomisées. Le lithium, le divalproex, la carbamazépine, la lamotrigine, l'oxcarbazépine, et certains nouveaux antipsychotiques reçoivent tous une cote de niveau I pour le traitement de divers aspects du trouble.

PRINCIPAL MESSAGE Le traitement du trouble bipolaire comporte trois domaines thérapeutiques: la manie aiguë, la dépression aiguë et le maintien. Le lithium a été le traitement principal pendant un certain temps mais des médicaments antiépileptiques comme le divalproex, la carbamazépine et la lamotrigine, ainsi que de nouveaux médicaments antipsychotiques comme l'olanzapine, la rispéridone et la quetiapine, seuls ou en combinaison, sont de plus en plus utilisés pour traiter efficacement la manie aiguë et maintenir la stabilité de l'humeur.

CONCLUSION Le trouble bipolaire est plus courant en pratique familiale qu'on ne le croyait auparavant. Les pharmacothérapies pour ce trouble complexe ont évolué rapidement au cours de la dernière décennie, changeant radicalement sa prise en charge. Le traitement a maintenant tendance à très bien réussir.

This article has been peer reviewed.
Cet article a fait l'objet d'une évaluation externe.
Can Fam Physician 2004;50:388-394.

Bipolar spectrum disorders are increasingly recognized as prevalent in both community psychiatric and primary care populations.[1-3]

Bipolar disorder is a biphasic, chronic disorder. Therapeutic objectives include suppression of acute mania, treatment of acute depression, and protection from relapse (prophylaxis).[4] Available treatments for bipolar disorder vary in their effectiveness and in patients' tolerance while achieving these objectives. For example, some treatments for bipolar disorder are better at suppressing affective symptoms "above the baseline" of wellness (ie, bipolar hypomania or mania) while others are more effective in relieving symptoms of illness "below the baseline" (ie, bipolar depression). Unfortunately, no single medication is reliably effective at accomplishing all therapeutic objectives. This realization has revealed a need for safe and rational combination regimens for most patients with bipolar disorder.

Most people with bipolar disorder, however, remain undiagnosed or misdiagnosed in family practice.[1-3,5-11] Recently, a screening instrument has been validated and could assist family physicians in detecting bipolar disorder.[1-16] (See Piver et al[1] for a helpful review of diagnostic and screening devices in bipolar disorder for general practitioners.) This article is intended to review the quality of evidence of the efficacy of available medications for bipolar disorder. Practical suggestions for medication combinations are also presented.

Quality of evidence

Articles were selected from MEDLINE from 1990 to 2003 using the key words "bipolar disorder," "antiepileptics," "antipsychotics," "antidepressants," and "mood stabilizers." Treatment of bipolar disorder involves three domains: acute mania, acute depression, and prophylaxis. Level I evidence exists for lithium treatment in all three domains. Level I evidence exists for divalproex and carbamazepine treatment for acute mania, level II evidence for prophylaxis. Lamotrigine has level I evidence supporting its use for acute depression and prophylaxis and level II evidence supporting its use for acute mania. Level I evidence supports using oxcarbazepine for acute mania.

Level I evidence supports using some conventional antipsychotics (ie, haloperidol) for acute mania and level II evidence for prophylaxis. Level III evidence shows that conventional antipsychotics are ineffective for bipolar depression. Level I evidence supports using novel antipsychotics (eg, olanzapine, risperidone, and quetiapine) for acute mania; level I evidence supports using olanzapine for bipolar depression and maintenance.

Use of some antidepressants for acute bipolar depression is supported by level II evidence; however, the risk of an antidepressant mobilizing a patient into mania or rapid cycling is a serious liability (level I evidence).

Bipolar treatment

Table 1 shows current treatments for bipolar disorder and presents current levels of evidence for pharmacologic agents and clinical recommendations for their use.

Lithium. Isolated in the early 1800s, lithium remains a commonly prescribed mood stabilizer. Lithium's efficacy in the various phases of this disorder is unequivocally established. Moreover, emerging data indicate that lithium also bestows an antisuicide effect independent of its ability to offer symptom relief.[4,16-18] Lithium, however, is not a panacea. Naturalistic (or real-world) studies repeatedly have noted lower response rates with lithium. These lower rates might be due in part to enrolling patients who are less likely to respond to lithium (**Table 2**).[19,20] People likely to respond to lithium

Dr McIntyre *is an Assistant Professor in the Department of Psychiatry at the University of Toronto and is Head of the Mood Disorders Psychopharmacology Unit at the University Health Network in Toronto, Ont.* **Ms Mancini** *is a Clinical Research Coordinator in the Mood Disorders Psychopharmacology Unit at the University Health Network.* **Dr Lin** *is Director of the Health and Wellness Center at the Scarborough Clinic of the University of Toronto.* **Dr Jordan** *is an Associate Professor in the Department of Family Medicine at the University of Western Ontario in London.*

Table 1. Levels of evidence and clinical recommendations for treatment of bipolar disorder

TREATMENT	ACUTE MANIA LEVEL OF EVIDENCE (RECOMMENDATION)	ACUTE DEPRESSION LEVEL OF EVIDENCE (RECOMMENDATION)	PROPHYLAXIS LEVEL OF EVIDENCE (RECOMMENDATION)
Lithium	I (A for mania, B for mixed)*	I (A)	I (A)
ANTIEPILEPTIC AGENTS			
Divalproex	I (A for mania and mixed states)	III (B)	II (A)
Carbamazepine	I (C)	II (C)	II (C)
Lamotrigine	III (D)	I (A)	I (A)
Gabapentin	III (D)	III (D)	III (D)
Topiramate	III (D)	III (D)	III (D)
Oxcarbazepine	I (C)	III (D)	III (D)
NOVEL ANTIPSYCHOTIC DRUGS			
Olanzapine	I (A)	I (B)	I (A)
Risperidone	I (A)	III (C)	II (B)
Quetiapine	I (A)	III (C)	III (C)
NOVEL ANTIDEPRESSANTS (eg, SSRIs, SNRIs, NaSSAs)	(E)	I (B)†	III (D)

NaSSA—noradrenaline specific serotonin antagonist, SNRI—serotonin noradrenaline reuptake inhibitor, SSRI—selective serotonin reuptake inhibitors.
**Mixed state is the simultaneous presence of mania and depression.*
†*To be determined on an individual basis.*
A *Recommended first-line treatment;* B *Recommended second-line treatment;* C *Recommended third-line treatment;* D *No recommendation or proscription;* E *Not recommended*

Table 2. Predictors of acute nonresponse to lithium

Prominent depressive and anxious symptoms while manic (mixed states)
Rapid cycling
Comorbid medical disorder
Substance abuse
Negative family history
Frequent prior episodes

Table 3. Antiepileptic drugs

First generation*
• Phenytoin*
• Phenobarbital*
Second generation
• Divalproex (500-2000 mg)†
• Carbamazepine (800-1800 mg)
Third generation‡
• Lamotrigine (100-300 mg)
• Gabapentin(600-4000 mg)
• Topiramate (100-400 mg)
• Oxcarbazepine (600-2400 mg)

**Not routinely employed in bipolar disorder.*
†*Dosing to achieve plasma level of 350-700 mmol/L.*
‡*Routine hematologic, plasma level, and hepatic monitoring might be unnecessary.*

typically exhibit "classic bipolar disorder" in which recurrent mania and depression are uncomplicated by comorbidity or rapid cycling.

Antiepileptic drugs. Antiepileptic drugs (AEDs) are categorized as first, second, and third generation (**Table 3**). Divalproex and carbamazepine are unequivocally effective for acute mania. Their acute antidepressant and prophylactic efficacy, however, is modest and unreliable.[21] Both agents are often effective alone or in combination for many patients less likely to respond to lithium (ie, with prominent comorbidity). Second-generation AEDs are, however, limited by being poorly tolerated (eg, weight gain, somnolence) and by a need to monitor plasma levels as well as hematologic and hepatic indices. Numerous drug-drug interactions also complicate their use.

Lamotrigine, a novel third-generation AED, is established as effective for acute and prophylactic treatment of bipolar depression. When prescribing lamotrigine (and other third-generation AEDs), blood monitoring is unnecessary. Lamotrigine is

generally well tolerated but up to 10% of treated cases are complicated by cutaneous reactions, and 0.1% of patients with rash progress on to develop Stevens-Johnson syndrome. Risk of serious cutaneous syndrome is higher in preadolescent subjects, with rapid titration, and when lamotrigine is combined with other agents that interfere with its metabolism (eg, divalproex). Family physicians should consult the product monograph for dosing recommendations. The usual therapeutic dose of lamotrigine (without divalproex) is 200 to 300 mg daily. A lower dose (100 to 200 mg daily) is recommended when lamotrigine is coadministered with divalproex.

Gabapentin has not been established as a reliable treatment for any phase of bipolar disorder but has been effective for some anxiety and neuropathic pain syndromes.[24,25] Anxiety frequently complicates bipolar disorder, and gabapentin is often useful as an alternative to benzodiazepines to manage anxiety symptoms.[24]

Topiramate, a fructose derivative, is under active investigation for several medical disorders. A recent controlled study compared topiramate with an antidepressant for treatment of mild bipolar depression. Topiramate was effective and well tolerated. Subjects in this study lost a mean of 5.8 kg across 8 weeks of treatment. Topiramate has been associated with substantial weight loss and is effective for binge eating disorder and bulimia nervosa, which frequently complicate mood disorders. More rigorous data for using topiramate for depression are awaited.[27]

Oxcarbazepine, the keto-analog to carbamazepine, has been approved in several countries, including Canada, as an antiepileptic agent. Preclinical data suggest that this agent has some antidepressant effect. Oxcarbazepine is reported to be better tolerated than carbamazepine. Oxcarbazepine has a more favourable pharmacokinetic profile, as it does not appear to produce the 10-11 epoxide metabolite (which contributes to tolerance difficulties and not efficacy). Further, it has fewer side effects affecting the central nervous system than carbamazepine and fewer drug interactions.[28]

Preliminary evidence, largely from open trials, has suggested that oxcarbazepine suppresses symptoms among bipolar patients. Some data suggest an anti-manic and perhaps also an anti-mixed and antidepressant profile. Dosing for bipolar disorder requires further clarification (**Table 3**).

Conventional antipsychotics. Conventional antipsychotics (ie, haloperidol) have been used frequently to treat bipolar mania. As a class, however, these agents are without proven reliable antidepressant or prophylactic efficacy.[29,30] Moreover, patients often report dysphoria when taking these agents, and the risk of acute extrapyramidal syndrome and long-term risk of tardive dyskinesia are cause for concern.[29] Bipolar patients taking conventional antipsychotic agents are reported to be at greater risk of antipsychotic-associated extrapyramidal syndrome than patients with schizophrenia.[31]

Novel antipsychotics. Novel antipsychotics (NAPs) (eg, olanzapine, risperidone, and quetiapine) have supplanted conventional antipsychotics as recommended first-line pharmacologic treatment for schizophrenia. Available NAPs are both structurally and pharmacologically distinct from older conventional antipsychotics (and from each other), which could give these agents different profiles of efficacy and tolerance.

Although categorized as antipsychotic, some NAPs appear to offer a direct antidepressant effect in people with schizophrenia, bipolar disorder, and major depression.[32-36] Over the past several years, psychiatrists have been increasingly prescribing these agents as adjunct therapy or alternative strategies for people with nonpsychotic unipolar disorder. The role of NAPs in treatment-resistant depression has recently been elucidated in the Canadian Psychiatric Association's guidelines on treatment of depressive disorders.[37]

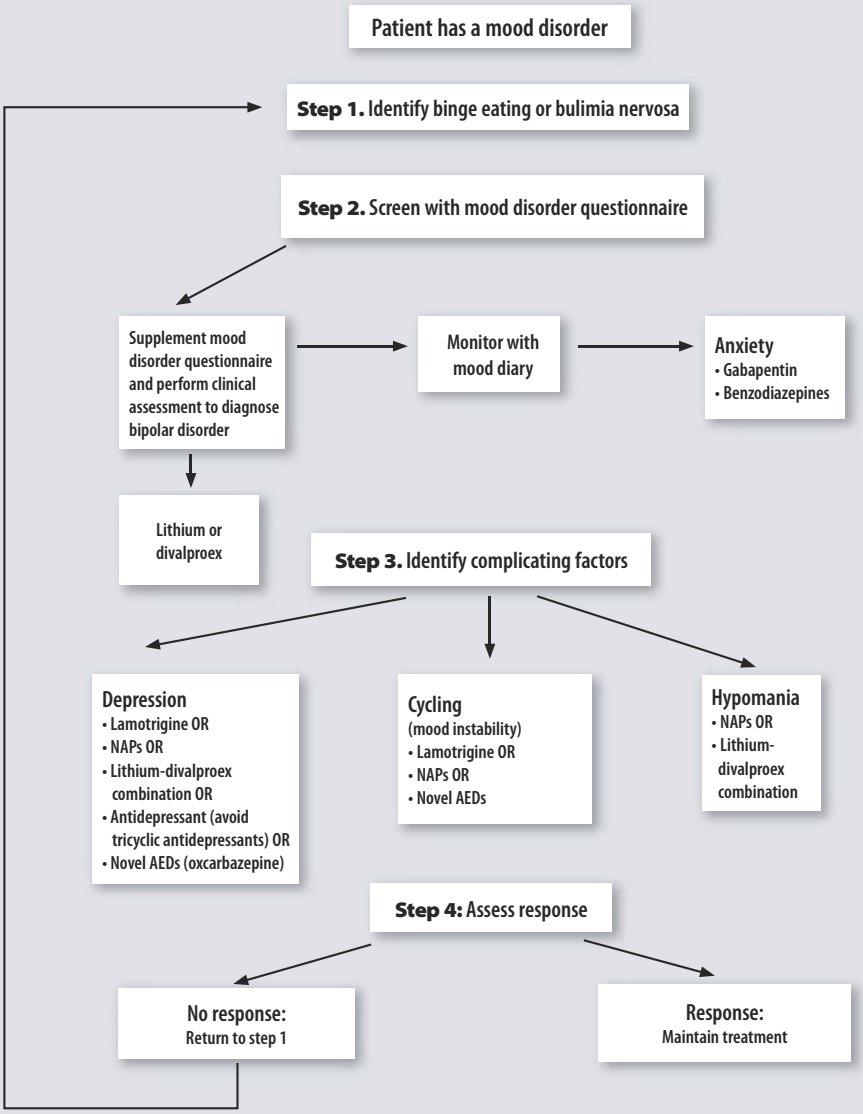
Several investigations confirmed the antimanic efficacy of each of the available NAPs in bipolar disorder (as monotherapy and as adjunct strategies).[14,38] It is noteworthy that the antimanic efficacy offered by these agents is independent of their antipsychotic effect. This response pattern suggests NAPs have a direct mood-stabilizing effect on patients with mood disorders. The effective dose of NAPs in

bipolar disorder overlaps with dosing in schizophrenia. Many bipolar patients might benefit from lower relative dosing (eg, olanzapine, 10-15 mg; risperidone, 2-4 mg; quetiapine, 400-800 mg).

Evidence of the antidepressant efficacy of NAPs in bipolar disorder is beginning to emerge.[39] A recent large placebo-controlled study (N = 833) noted the combination of olanzapine and fluoxetine (mean dose approximately 10 mg and 50 mg, respectively) offered a robust symptomatic benefit in acute bipolar depression. Evidence of antidepressant efficacy for the remaining NAPs is also beginning to surface.[39,40]

The optimal duration of adjunct NAP therapy for bipolar disorder is not empirically established. Some guidelines and bipolar experts recommend discontinuing the adjunct NAP after resolution of the acute episode (eg, approximately 1 to 2 months). In clinical practice, however, this is often impossible for many reasons

Figure 1. Sequence for combining and administering treatments



AEDs—antiepileptic agents, NAPs—novel antipsychotic drugs.

(eg, insufficient acute response on mood-stabilizer monotherapy, immediate symptom breakthrough after NAP discontinuation). Several uncontrolled investigations of naturalistic practice have noted that most people with bipolar disorder treated with antipsychotic agents use the antipsychotic for lengthy periods.[41]

Evidence from placebo-controlled trials currently supports use of olanzapine for maintenance treatment of bipolar depression. A recent study suggests that, when patients are maintained on adjunct olanzapine therapy (with lithium or divalproex) rather than mood-stabilizer monotherapy, relapse rates are significantly reduced.

There is no conclusive evidence that NAPs are associated with a greater risk of tardive dyskinesia. They are, however, associated with clinically significant weight gain. Weight and metabolic monitoring is recommended when prescribing these agents. Weight gain is greater with olanzapine than with risperidone and quetiapine. The risk of glucose dysregulation and lipid abnormalities suggests routine weight and metabolic monitoring in patients receiving these treatments.[43]

Novel antidepressants. Somewhat surprisingly, little evidence supports use of antidepressants as reliably effective in bipolar depression. Moreover, antidepressants can induce manic episodes or rapid cycling in predisposed patients. Of the available classes, tricyclic antidepressants are believed more likely to switch patients than novel agents (ie, selective serotonin reuptake inhibitors, venlafaxine, bupropion).[44,45] Short-term treatment with antidepressants, to be discontinued after 2 months of remission if possible, is promoted for treatment of many bipolar patients. Office counseling and psychoeducation is recommended for most patients with bipolar disorder. Formalized and structured education and lifestyle modification can beneficially influence the course of the illness. This review has focused on medical management. Patients with bipolar disorder often do not comply with treatment and often struggle with accepting being ill and coping. These concerns highlight the possible use of structured psychosocial interventions for some patients with bipolar disorder.[47]

EDITOR'S KEY POINTS

- Bipolar disorder is a chronic, biphasic disorder whose treatment objectives include managing acute mania, treating acute depression, and protecting patients from recurrence.
- Lithium is the most studied treatment, and it is effective for all three facets of the disease, but its use is hindered by side effects that often lead to discontinuation.
- Antiepileptic medications with proven antimanic efficacy are divalproex and carbamazepine, but they are less helpful for bipolar depression. They also have serious side effects. A newer medication, lamotrigine, appears to be more effective for bipolar depression and better tolerated.
- Novel antipsychotics, such as olanzapine, risperidone, or quetiapine, have been shown to be effective in several phases of bipolar disease and are recommended as first-line treatments. Currently more data support olanzapine for bipolar depression and prophylaxis.
- Treatment often requires two or more different medications with complementary effects tailored to patients' needs.

POINTS DE REPÈRE DU RÉDACTEUR

- Le trouble bipolaire est un trouble chronique, biphasique, dont les objectifs de traitement comportent la prise en charge de la manie aiguë, le traitement de la dépression aiguë et la protection des patients contre la récurrence.
- Le lithium est le traitement ayant fait l'objet de plus d'études et est efficace pour les trois facettes de la maladie, mais ses effets secondaires nuisent souvent à son utilisation, entraînant même souvent sa discontinuation.
- Les médicaments antiépileptiques ayant une efficacité éprouvée contre la manie sont le divalproex et la carbamazépine, mais ils sont moins utiles pour la dépression bipolaire. Un médicament plus récent, la lamotrigine, semble plus efficace pour la dépression bipolaire et est mieux toléré.
- Il a été démontré que les nouveaux antipsychotiques comme l'olanzapine, la risperidone ou la quetiapine ont été efficaces dans plusieurs phases du trouble bipolaire et sont recommandés comme traitements de première intention. À l'heure actuelle, on examine plus de données concernant le recours à l'olanzapine pour la dépression bipolaire et sa prévention.
- Le traitement exige souvent deux médicaments différents ou plus ayant des effets complémentaires adaptés aux besoins du patient.

Choosing a treatment regimen

The algorithm in **Figure 1** attempts to provide a rational sequence for administering and combining treatments for bipolar disorder. Monitoring

patient progress with a mood diary is further recommended as a careful, systematic, and quantifiable measure of patient progress.

Conclusion

An expanding array of treatments for bipolar disorder is changing the current standard of care for this condition. Some newer treatments are considered mood stabilizers and represent new therapeutic alternatives. Optimal treatment of this illness often requires a combination of both medications and psychosocial interventions. Current levels of evidence and clinical recommendations for treatment of bipolar disorder are changing based on new information from clinical trials. Several agents now being studied could further affect treatment.

Competing interests

Dr McIntyre *works as a consultant and member of the Speakers Bureau for Wyeth-Ayerst Canada, Organon, Lundbeck, Lilly, Oryx, AstraZeneca, Pfizer, Janssen-Ortho, and GlaxoSmithKline. He receives research support from GlaxoSmithKline, Merck Frosst Canada, Wyeth-Ayerst, and Servier.*

Correspondence to: **Dr Roger McIntyre,** *University Health Network, 399 Bathurst St, ECW-3D-008, Toronto, ON M5T 2S8; telephone (416) 603-5279; fax (416) 603-5368; e-mail* **rmcintyr@uhnres.utoronto.ca**

References

1. Piver A, Yatham LN, Lam RW. Bipolar spectrum disorders. New perspectives. *Can Fam Physician* 2002;48:896-904.
2. Hirschfeld RM, Holzer C, Calabrese JR, Weissman M, Reed M, Davies M, et al. Validity of the mood disorder questionnaire: a general population study. *Am J Psychiatry* 2003;160:178-80.
3. Hirschfeld RM, Calabrese JR, Weissamn MM, Reed M, Davies MA, Frye MA, et al. Screening for bipolar disorder in the community. *J Clin Psychiatry* 2003;64(1):53-9.
4. Tondo L, Baldessarini RJ. Reduced suicide risk during lithium maintenance treatment. *J Clin Psychiatry* 2000;61(Suppl 9):97-104.
5. Goodwin F, Jamison K. *Manic-depressive illness*. New York, NY: Oxford University Press; 1990.
6. 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.
7. Kessing LV, Andersen PK, Mortensen PB. Predictors of recurrence in affective disorder. A case register study. *J Affect Disord* 1998;49(2):101-8.
8. Lopez AD, Murray CC. The global burden of disease, 1990-2020. *Nat Med* 1998;4(11):1241-3.
9. Rothenberg A. Bipolar illness, creativity, and treatment. *Psychiatr Q* 2001;72(2):131-47.
10. Manning JS, Haykal RF, Connor PD, Akiskal HS. On the nature of depressive and anxious states in a family practice setting: the high prevalence of bipolar II and related disorders in a cohort followed longitudinally. *Compr Psychiatry* 1997;38(2):102-8.
11. Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin K. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *J Affect Disord* 1999;52(1-3):135-44.
12. Hirschfeld RM, Williams JB, Spitzer RL, Calabrese JR, Flynn L, Keck PE Jr, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry* 2000;157:1873-5.
13. American Psychiatric Association. *Diagnostic and statistical manual for mental disorders*. 4th edition. Washington, DC: American Psychiatric Association; 1994.
14. 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(4):281-94.
15. Tondo L, Hennen J, Baldessarini RJ. Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis. *Acta Psychiatr Scand* 2001;104(3):163-72.
16. Tondo L, Baldessarini RJ, Hennen J, Minnai GP, Salis P, Scamonatti L, et al. Suicide attempts in major affective disorder patients with comorbid substance use disorders. *J Clin Psychiatry* 1999;60(Suppl 2):63-9; discussion 75-6, 113-6.
17. Ghaemi SN. On defining 'mood stabilizer'. *Bipolar Disord* 2001;3:154-8.
18. Baldessarini RJ, Tondo L, Hennen J. Treating the suicidal patient with bipolar disorder. Reducing suicide risk with lithium. *Ann N Y Acad Sci* 2001;932:24-38; discussion 39-43.
19. Calabrese JR, Woyshville MJ. Lithium therapy: limitations and alternatives in the treatment of bipolar disorders. *Ann Clin Psychiatry* 1995;7(2):103-12.
20. Maj M, Pirozzi R, Magliano L. Nonresponse to reinstituted lithium prophylaxis in previously responsive bipolar patients: prevalence and predictors. *Am J Psychiatry* 1995;152:1810-1.
21. De Leon O. Antiepileptic drugs for the acute and maintenance treatment of bipolar disorder. *Harvard Rev Psychiatry* 2001;9(5):209-22.
22. Bowden CL. Novel treatments for bipolar disorder. *Expert Opin Investig Drugs* 2001;10(4):661-71.
23. Zerjav-Lacombe S, Tabarsi E. Lamotrigine: a review of clinical studies in bipolar disorders. *Can J Psychiatry* 2001;46(4):328-33.
24. 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(3 Pt 2):249-55.
25. Maidment ID. Gabapentin treatment for bipolar disorders. *Ann Pharmacother* 2001;35(10):1264-9.
26. McIntyre RS, Mancini DA, McCann S, Srinivasan J, Sagman D, Kennedy SH. Topiramate versus bupropion SR when added to mood stabilizer therapy for the depressive phase of bipolar disorder: a preliminary single-blind study. *Bipolar Disord* 2002;4:207-13.
27. VanKammen D. The efficacy of topiramate in acute bipolar mania. Montreal, Que: Collegium Internationale Neuro-Psychopharmacologicum; 2002.
28. Ramasubbu R. Dose-response relationship of selective serotonin reuptake inhibitors treatment-emergent hypomania in depressive disorders. *Acta Psychiatr Scand* 2001;104(3):236-8; discussion 238-9.
29. Siris SG. Depression in schizophrenia: perspective in the era of "atypical" antipsychotic agents. *Am J Psychiatry* 2000;157(9):1379-89.
30. Tollefson GD, Andersen SW. Should we consider mood disturbance in schizophrenia as an important determinant of quality of life? *J Clin Psychiatry* 1999;60(Suppl 5):23-9; discussion 30.
31. Yassa R, Ghadirian AM, Schwartz G. Prevalence of tardive dyskinesia in affective disorder patients. *J Clin Psychiatry* 1983;44:410-2.
32. Ghaemi SN, Cherry EL, Katzow JA, Goodwin FK. Does olanzapine have antidepressant properties? A retrospective preliminary study. *Bipolar Disord* 2000;2(3 Pt 1):196-9.
33. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 2001;158:765-74.
34. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. *J Clin Psychiatry* 1999;60:256-9.
35. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley C Jr, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol* 1997;17(5):407-18.
36. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, et al. A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry* 2001;158:131-4.
37. Kennedy SH, Lam RW, Cohen NL, Ravindran AV. Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological treatments. *Can J Psychiatry* 2001;46(Suppl 1):38S-58S.
38. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo controlled comparison of efficacy and safety. *Am J Psychiatry* 2002;159:1146-54.
39. McIntyre R, Mancini D, McCann S, Srinivasan J, Kennedy S. The antidepressant effects of risperidone and olanzapine in bipolar disorder. *Can J Clin Psychopharmacol*. In press.
40. Tohen M. The efficacy of olanzapine combination fluoxetine or their combination in bipolar depression. Philadelphia, Pa: American Psychiatric Association Annual Meeting. 2002.
41. Keck PE Jr, Wilson DR, Strakowski SM, McElroy SL, Kizer DL, Balistreri TM, et al. Clinical predictors of acute risperidone response in schizophrenia, schizoaffective disorder, and psychotic mood disorders. *J Clin Psychiatry* 1995;56:466-70.
42. Tohen M, Jacobs TG, Feldman PD. Onset of action of antipsychotics in the treatment of mania. *Bipolar Disord* 2000;2(3 Pt 2):261-8.
43. McIntyre R, McCann SM, Kennedy SH. Antipsychotic metabolic effects: weight gain, diabetes mellitus, and lipid abnormalities. *Can J Psychiatry* 2001;46(3):273-81.
44. Hummel B, Walden J, Stampfer R, Dittmann S, Amann B, Sterr A, et al. Acute antimanic efficacy and safety of oxcarbazepine in an open trial with an on-off-on design. *Bipolar Disord* 2002;4:412-7.
45. Howland RH. Induction of mania with serotonin reuptake inhibitors. *J Clin Psychopharmacol* 1996;16(6):425-7.
46. Gray SM, Otto MW. Psychosocial approaches to suicide prevention: applications to patients with bipolar disorder. *J Clin Psychiatry* 2001;62(Suppl 25):56-64.
47. Malkoff-Schwartz S, Frank E, Anderson BP, Hlastala SA, Luther JF, Sherrill JT, et al. Social rhythm disruption and stressful life events in the onset of bipolar and unipolar episodes. *Psychol Med* 2000;30(5):1005-16.