The Clinical Management of Bipolar Disorder: A Review of Evidence-Based Guidelines

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Objective: To discuss the criteria used to diagnose the mood episodes that constitute bipolar disorder, the approach to the differential diagnosis of these presentations, and the evidence-based treatments that are currently available.

Data Sources: A search for evidence-based guidelines for the diagnosis and treatment of adults with bipolar disorder was performed on May 5, 2010, using the National Guideline Clearinghouse database, the Agency for Healthcare Research and Quality Evidence Reports database, and the Cochrane Database of Systematic Reviews. In addition, a clinical query of the PubMed database (completed March 1, 2010) and searches of drug manufacturers' Web sites (for unpublished trials) were performed to identify randomized, controlled trials and meta-analyses evaluating strategies to treat resistant depression.

Study Selection: Guidelines were selected based on data from randomized, controlled trials; meta-analyses; and well-conducted naturalistic trials that were published since 2005.

Data Extraction: Four evidence-based treatment guidelines for bipolar disorder were included. Three were published in 2009: those put forth as part of an Australian project, those of the British Association for Psychopharmacology, and those produced by the International Society for Bipolar Disorders and the Canadian Network for Mood and Anxiety Treatments. The most recent US guidelines are that of the Texas Implementation of Medication Algorithms project, last updated in 2005.

Data Synthesis: Recommendations from all 4 guidelines were reviewed and are presented with a focus on using them to improve clinical care. The recommendations with the most agreement and highest level of clinical evidence were as follows: (1) mania should be treated first-line with lithium, divalproex, or an atypical antipsychotic medication; (2) mixed episodes should be treated first-line with divalproex or an atypical antipsychotic; (3) bipolar depression should be treated with quetiapine, olanzapine/fluoxetine combination, or lamotrigine; and (4) all patients should be offered group or individual psychoeducation. Additionally, recommendations for therapeutic drug monitoring are presented due to their importance for patient safety, particularly for the primary care physician, although these are based on consensus guidelines.

Conclusions: Bipolar disorder is a lifelong illness that is complicated by high comorbidity and risk of poor health outcomes, making the primary care physician's role vital in improving patient quality of life. The management of acute mood episodes should focus first on safety, should include psychiatric consultation as soon as possible, and should begin with an evidence-based treatment that may be continued into the maintenance phase. Long-term management focuses on maintenance of euthymia, requires ongoing medication, and may benefit from adjunctive psychotherapy.

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Bipolar disorder is a mental disorder characterized by dramatic shifts in mood, thinking, behavior, and energy that is seen in up to 5% of primary care patients.[1] In collaboration with a psychiatrist, the family physician plays a vital role in supporting the long-term stability and general health of these patients. In order to effectively treat such patients, it is important that the family physician have a good grasp of the disease, its long-term management, and its impact on overall health.

A search for evidence-based guidelines for the diagnosis and treatment of adults with bipolar disorder was performed on May 5, 2010, using the National Guideline Clearinghouse database, the Agency for Healthcare Research and Quality Evidence Reports database, and the Cochrane Database of Systematic Reviews. In addition, a clinical query of the PubMed database (completed March 1, 2010) and searches of drug manufacturers' Web sites (for unpublished trials) were performed to identify randomized, controlled trials and meta-analyses evaluating strategies to treat resistant depression.

Guidelines were selected based on data from randomized controlled trials, meta-analyses, and well-conducted naturalistic trials that were published since 2005. We present recommendations from 4 evidence-based treatment guidelines with a focus on using them to improve clinical care. Additionally, recommendations for therapeutic drug monitoring are presented due to their importance for patient safety, particularly for the primary care physician, although these are based on consensus guidelines.

Clinical Points

- Mania should be treated with lithium, divalproex, or an atypical antipsychotic medication.
- Bipolar depression should be treated with quetiapine, olanzapine/fluoxetine combination, or lamotrigine.
- Once mood episodes are successfully treated, effective acute phase medications should be continued for maintenance of euthymia with appropriate medication monitoring.
- All patients should be offered individual or group psychoeducation to prevent relapse and improve treatment adherence.

EPIDEMIOLOGY

Most frequently diagnosed before age 30 years, bipolar disorder includes bipolar I disorder, characterized by manic or mixed episodes (nearly always alternating with depressive episodes), and bipolar II disorder, marked by recurrent episodes of depression and less severe or briefer hypomanic episodes. Related are cyclothymia, characterized by hypomania and subthreshold depression, and bipolar disorder not otherwise specified, a "catch-all" diagnosis for conditions that do not fit neatly into bipolar disorder but that are felt to be properly classified with the bipolar spectrum.[2] Some experts argue that up to 50% of recurrent depressions might be so classified, but others have disagreed with this widening of the diagnosis.[3,4]

Lifetime prevalence of bipolar I disorder is 1% to 2% in both men and women; prevalence of bipolar II disorder is at least 2% and may be underestimated due to the likelihood of recall bias in reporting hypomania.[1,5] Estimates of the prevalence of bipolar disorder not otherwise specified vary widely, but the total lifetime prevalence of these 3 disorders is at least 2.4% to 6%.[1,5]

COMORBIDITY

Patients with bipolar disorder have high rates of medical, psychiatric, and substance abuse disorders, which contribute to reduced life expectancy and lower quality of life.[6] A majority meet criteria for at least 1 other mental disorder; anxiety and substance abuse disorders are most common, with a 40% to 60% lifetime prevalence.[7–10] Compared to the general population, patients with bipolar disorder have higher rates of diabetes mellitus and liver and cardiovascular disease and experience increased disability and mortality from these illnesses.[11,12] The family physician has a valuable opportunity to improve outcomes by aggressive screening for, and maintenance of, these comorbid conditions.

PRESENTATION AND DIAGNOSIS

As at least one-half of patients with bipolar I disorder and most patients with bipolar II disorder will initially present during a major depressive episode, a careful history to probe for past manic or hypomanic symptoms is vital to assure a correct diagnosis.[13] To screen for historical manic or hypomanic symptoms that might otherwise be overlooked, the self-report Mood Disorders Questionnaire is a validated and useful instrument[14,15] (Figure 1).

The initial evaluation should aim to collect historical and laboratory data that will help to rule out other disorders and provide essential information to assure a safe and effective medication treatment plan (Table 1 and 2).[16,17]

Manic Episode

Though classically in a euphoric state, manic patients may also display intense irritability and agitation and profound impairments in reality testing and judgment. About two-thirds of manic episodes are psychotic, with delusions and hallucinations. Mania usually requires psychiatric hospitalization (see appropriate diagnostic criteria in the *DSM-IV-TR*[18]).

Major Depressive Episode

The diagnostic criteria for a major depressive episode are the same for bipolar disorder as those used for so-called "unipolar" depression. Some clinical characteristics are more common in bipolar depressions, however, including "atypical" symptoms such as oversleeping and weight gain, delusions, an earlier age at first onset, and prominent mood lability[19] (see appropriate diagnostic criteria in the *DSM-IV-TR*[18]).

Hypomanic Episode

Hypomanic episodes are similar to mania but more limited in degree and duration. Hypomanias, by definition, are not psychotic and do not require hospitalization. Many patients will not seek medical attention during hypomanic episodes as they are often times of relative productivity and pleasant mood (see appropriate diagnostic criteria in the *DSM-IV-TR*[18]).

Mixed Episode

During a mixed episode, patients simultaneously meet full criteria for both mania and depression that co-occur

Figure 1. Mood Disorder Questionnaire[a]

Section 1: Has there ever been a period of time when you were not your usual self (while not on drugs or alcohol) and-		
1.	-you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	Yes/No
2.	-you were so irritable that you shouted at people or started fights or arguments?	Yes/No
3.	-you felt much more self confident than usual?	Yes/No
4.	-you got much less sleep than usual and found you didn't really miss it?	Yes/No
5.	-you were much more talkative or spoke faster than usual?	Yes/No
6.	-thoughts raced through your head or you couldn't slow your mind down?	Yes/No
7.	-you were so easily distracted by things around you that you had trouble concentrating or staying on track?	Yes/No
8.	-you had much more energy than usual?	Yes/No
9.	-you were much more active or did many more things than usual?	Yes/No
10.	-you were much more social or outgoing than usual? For example, you telephoned friends in the middle of the night.	Yes/No
11.	-you were much more interested in sex than usual?	Yes/No
12.	-you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	Yes/No
13.	-spending money got you or your family into trouble?	Yes/No
Section 2: If you checked YES to more than 1 of the above, have several of these ever happened during the *same period of time*?		Yes/No
Section 3: How much of a problem did any of these cause you—like being unable to work; having family, money, or legal troubles; or getting into arguments or fights?		No problem/ Minor Problem/ Moderate Problem/ Serious problem
Scoring: 7 "yes" answers to items in section 1 with "yes" in section 2 and at least a minor problem in section 3 constituted a positive screen for bipolar disorder and should lead to further investigation		

[a]Adapted with permission from Hirschfeld et al.[14]

for at least 1 week; women are more commonly affected than men.[20] The presence of mixed episodes is associated with poorer prognosis due to a greater risk of chronicity and a higher risk of suicide during the episode.[20]

Rapid Cycling

Patients who experience more than 4 episodes per year are diagnosed with the rapid-cycling subtype of bipolar disorder; this is associated with treatment resistance and overall poorer prognosis.[21] There is some evidence that iatrogenic factors (ie, an "on again-off again" pattern of antidepressant prescription or lithium-induced hypothyroidism) and nonadherence contribute to the risk of rapid cycling.

SPECIAL POPULATIONS

Children and Adolescents

Table 3 summarizes 2007 guidelines for the assessment of child and adolescent bipolar disorder published by the American Academy of Child and Adolescent Psychiatry.[22,23] Recommendations for treatment are similar to those of adults with the caveat that research is lacking in this area and that the US Food and Drug Administration (FDA)–approved agents for childhood bipolar disorder are more limited. Currently, the FDA-approved medications for child bipolar disorder include olanzapine (age 13+), lithium (age 12+ years), and, for children aged 10 years and above, quetiapine, risperidone, and aripiprazole (Table 3).

Pregnancy

The clinical lore that pregnancy is protective against mood episodes is most likely a myth; treatment to ensure mood stability during pregnancy is vital.[23,24] Careful discussion and collaboration between the family physician or obstetrician and psychiatrist are essential to balance maternal and fetal risks, however, given the teratogenicity of many medications used for bipolar disorder (Table 4).

Postpartum

Between 25% to 40% of mothers with bipolar disorder will experience a postpartum mood episode, and up to 30% may be affected by postpartum psychosis; thus, all new mothers should be screened for mood symptoms.[25,26] Postpartum psychosis is a psychiatric emergency with gross disturbances in mood, cognition, and behavior and frank hallucinations and delusions.[27] Hospitalization should be strongly considered for these indications.

The Elderly

While the course of bipolar disorder sometimes becomes less severe with advancing age, mood episodes may occur at any time. Recommendations for bipolar disorder in the elderly are similar to those in adults, with the caveat that lower doses of medications should be tried in order to minimize adverse effects. For this reason, electroconvulsive therapy may be used earlier in the treatment course, as it is often better tolerated in geriatric populations.[28]

URGENT AND EMERGENT CARE

Acute mania, depression, and mixed states may all include psychosis, poor insight, and high risks of

Table 1. Initial Evaluation of Suspected Bipolar Disorder[a]

Tests to aid diagnosis	Thyroid function test, rapid plasma reagin test for syphilis, urine drug screen, B_{12} level, and careful history to screen for other secondary causes of mood symptoms (see Table 2)	Consider neuroimaging for first episode, electroencephalogram if indicated, HIV test if applicable, and expanded toxicologic screen if suspicion of substance-induced episode is high
Tests to guide treatment and health maintenance	*General*: personal and family history of metabolic/cardiac disease; prior to lithium treatment: thyroid function test, complete blood count, urinalysis, electrocardiogram (≥ 40 y), electrolytes *Prior to treatment with anticonvulsants*: complete blood count, liver function, electrolytes, weight/body mass index *Prior to treatment with antipsychotics*: screen for extrapyramidal/ motor symptoms, metabolic syndrome (body mass index, waist circumference, blood pressure, lipid profile, fasting glucose)	Consider 24-hour urine creatinine for lithium treatment, evaluation for cataracts with quetiapine treatment, evaluation of menstrual irregularity with divalproex, initial screening for rash prior to lamotrigine treatment

[a]Based on Stern et al[16] and Malhi et al.[17]

Table 2. Differential Diagnosis of Bipolar Disorder[a]

Secondary mania	Substance induced	Intoxication or use: alcohol, LSD, amphetamines/sympathomimetics, benzodiazepines, corticosteroids, isoniazid, levodopa, thyroxine, zidovudine Withdrawal: alcohol, benzodiazepines, β-blockers
	Metabolic	Hemodialysis, postoperative state, thyrotoxicosis, B_{12} deficiency, Cushing's syndrome
	Infectious	Influenza, encephalitis, HIV, neurosyphilis
	Neurologic	Neoplasm, complex partial seizure, Wilson's disease, Huntington's disease, multiple sclerosis, stroke
Secondary depression	Substance induced	Intoxication or use: opiates, benzodiazepines, anticonvulsants, alcohol, reserpine Withdrawal: cocaine, amphetamines/sympathomimetics
	Metabolic	Uremia, niacin deficiency (pellagra), B_{12} deficiency, anemia, hypothyroidism, Cushing's syndrome, Addison's disease, sleep apnea, heavy metal toxicity, paraneoplastic syndromes
	Infectious	Lyme disease, neurosyphilis, HIV, Behçet's syndrome, meningitis
	Neurologic/ cerebrovascular	Ischemia, stroke (especially left-sided), neoplasm, complex partial seizures, postictal state, normal pressure hydrocephalus, Parkinson's disease

[a]Based on Stern et al.[16]

suicide and thus must be assessed urgently; psychiatric consultation should be sought as soon as possible, and the family should be recruited to help support the patient. Urgent evaluation should focus on safety, and inpatient hospitalization should be strongly considered except in mild cases with no risk to self or others and strong social support. Patients suffering from manic or mixed states may display agitated behavior and may require rapid-acting medication. Under these circumstances, the family practitioner should have a plan for transport of the patient to a nearby emergency center and be familiar with state laws concerning involuntary hospitalization.

PHARMACOLOGIC MANAGEMENT

A number of evidence-based treatment guidelines for bipolar disorder were published in 2009: those put forth in Mahli et al[17] as part of an Australian project, those of the British Association for Psychopharmacology,[29] and those produced by the International Society for Bipolar Disorders and the Canadian Network for Mood and Anxiety Treatments.[30] The most recent US guidelines are those of the Texas Implementation of Medication Algorithms project, which were last updated in 2005.[8] These guidelines are reflected in the recommendations below.

Table 3. American Academy of Child and Adolescent Psychiatry 2007 Recommendations for Screening and Assessment of Juvenile Bipolar Disorder[a]

Screening	*Recommendation 1.* Psychiatric assessments for children and adolescents should include screening questions for bipolar disorder
Assessment	*Recommendation 2.* The *DSM-IV-TR* criteria, including the duration criteria, should be followed when making a diagnosis of mania or hypomania in children and adolescents
	Recommendation 3. Bipolar disorder not otherwise specified should be used to describe youths with manic symptoms lasting hours to less than 4 days or for those with chronic manic-like symptoms representing their baseline level of functioning
	Recommendation 4. Youths with suspected bipolar disorder must also be carefully evaluated for other associated problems, including suicidality, comorbid disorders (including substance abuse), psychosocial stressors, and medical problems
	Recommendation 5. The diagnostic validity of bipolar disorder in young children has yet to be established; caution must be taken before applying this diagnosis in preschool children

[a]Adapted with permission from McClellan et al.[22]

Table 4. Medications for Bipolar Disorder in Pregnancy[a]

Agent	Characteristic Adverse Outcomes	US Food and Drug Administration Pregnancy Class	Rate of Major Congenital Malformations and Major Adverse Events With In Utero Exposure, %[b]
Antipsychotics	Haloperidol has not been associated with teratogenesis or poor outcomes; chlorpromazine is associated with infant respiratory distress syndrome; atypical antipsychotics have not been associated with fetal abnormalities, but have been associated with gestational diabetes, which may lead to poor outcomes	C (except clozapine, class B)	Limited data, no apparent increase
Lithium	Associated with floppy infant syndrome, thyroid toxicity, and rare cardiac defects (Ebstein's anomaly)	D	4–12
Valproate (includes divalproex and valproic acid)	Neural tube defects, fetal valproate syndrome	D	6–20
Carbamazepine	Neural tube defects, fetal carbamazepine syndrome	D	2–8
Lamotrigine	None reported	C	1–6

[a]Based on Cohen[23] and Nguyen et al.[24]
[b]Rate in general population is 2% to 4%.

Table 5. First-Line Agents for Acute Manic or Mixed Episode[a]

Class	Agent	Target Dose	Notable Adverse Effects	Notes
Mood stabilizers	Lithium[b]	Sufficient for blood level of 0.6–1.2 mEq/L, usual dose 900–1,800 mg	Sedation, dry mouth, polyuria; more rarely kidney or thyroid failure	May be slower to control mania than other options
	Divalproex	Titrate rapidly to a blood level of 85–125 μg/mL; up to 60 mg/kg	Sedation, nausea, weight gain; may cause menstrual irregularities; rare pancreatitis or liver failure	Very high risk of neural tube defects with fetal exposure; caution in women of childbearing age
Second-generation antipsychotics	Aripiprazole	15–30 mg/d	Akathisia and other EPS, sedation	Among the least likely second-generation antipsychotics to cause weight gain
	Asenapine	10 mg bid	EPS, sedation	…
	Olanzapine[c]	15–20 mg/d	Sedation, weight gain, less commonly EPS	Weight gain; lipid and glucose derangements may be particularly severe
	Quetiapine[b]	400–800 mg/d	Sedation, weight gain, less commonly EPS	Titrate immediate-release form over 6 days
	Risperidone	3–6 mg/d	EPS, sedation, hyperprolactinemia	…
	Ziprasidone	40–80 bid	EPS, sedation or agitation	Taken with meals to improve absorption; contraindicated if history of prolonged QTc interval or in combination with QTc-prolonging medications

[a]Based on Suppes et al,[8] Malhi et al,[17] Yatham et al,[29] Goodwin,[30] and Stoner and Dahmen.[32]
[b]Not recommended as first-line for mixed episodes.
[c]Olanzapine is not generally recommended as first-line due to metabolic adverse effects.
Abbreviation: EPS = extrapyramidal symptoms.
Symbol: … = no data.

Acute Manic or Mixed Episode

In the case of acute mania, discontinuation or tapering of antidepressant medication should be considered and optimization of any antimanic medication should be undertaken. In the case that the patient is naive to antimanic medication, a first-line antimanic agent such as lithium carbonate should be chosen (Table 5). In addition to lithium salts, divalproex, carbamazepine, and most of the second-generation antipsychotics (SGAs) are FDA-approved treatments for acute mania. While these agents are all effective as monotherapy, results of meta-analysis suggest that a combination of an SGA and either lithium or divalproex is the most effective treatment of acute mania or mixed states, though combination treatment significantly increases adverse effect burden.[31]

Among the antimanic agents, olanzapine may have a significantly higher liability to cause weight gain and glucose intolerance and so should likely not be used first.[8] Divalproex and carbamazepine are significantly associated with neural tube defects and should be used with care in women who may become pregnant; divalproex may additionally lead to menstrual abnormalities and hyperandrogenism in women.[33] Carbamazepine also leads to rare but potentially life-threatening blood dyscrasias and is a potent cytochrome P450 inducer.

Once efficacy has been weighed with tolerability and safety, reasonable first-line treatment for an acute manic episode should begin with lithium, divalproex, or SGA monotherapy, with the caveats that olanzapine should be reserved for later steps

Table 6. Medications for Acute Bipolar Depression[a]

	Agent	Target Dose	Notable Adverse Effects	Notes
First-line treatments	Quetiapine	300–600 mg/d	Sedation, weight gain, less commonly EPS	Titrate immediate-release form over 6 days
	Olanzapine/fluoxetine combination	Olanzapine 6–12 mg/fluoxetine 25–50 mg	Sedation, weight gain, less commonly EPS	…
	Lamotrigine[b]	200 mg/d	Stevens-Johnson syndrome, especially with enzyme-inhibiting medications (eg, divalproex)	Titrate to target dosage based on schedule appropriate for coadministered medications (see package information)
Second-line treatments	Lithium[b]	Sufficient for blood level of 0.6–1.2 mEq/L; usual dose 900–1,800 mg	Sedation, dry mouth, polyuria; more rarely kidney or thyroid failure	…
	Divalproex[b]	Titrate rapidly to a blood level of 85–125 μg /mL; up to 60 mg/kg	Sedation, nausea, weight gain; may cause menstrual irregularities; rare pancreatitis or liver failure	Very high risk of neural tube defects with fetal exposure; caution in women of childbearing age
	Combinations: SSRI or bupropion with SGA, lithium, or divalproex[b]	Antidepressants should be used only with an effective antimanic agent when treating bipolar depression	Those of constituent agents	While these combinations are a common practice, evidence of their efficacy is controversial

[a]Based on Suppes et al,[8] Malhi et al,[17] Yatham et al,[29] Goodwin.[30]
[b]Not approved by the US Food and Drug Administration for this indication.
Symbol: … = no data.

and that divalproex is not a good first choice in women when other options are available (Table 5).

Acute Depression

Recommendations differ among the most recent guidelines as to the best treatment for bipolar depression, highlighting the need for more research in this area.[8,17,29,30] FDA-approved treatments for acute bipolar depression include only quetiapine and olanzapine/fluoxetine combination. Lamotrigine is approved for the prevention of depressive episodes but has not been effective as a monotherapy for acute depression in clinical trials. A meta-analysis found, however, that overall, lamotrigine monotherapy improved the rate of clinical response in bipolar depression, and this agent is currently in widespread clinical use for this indication.[34] Lithium or divalproex, alone or in combination with SSRI antidepressants or bupropion, may be considered as second-line options, though the evidence supporting the efficacy of such combinations remains equivocal[17,35,36] (Table 6).

Maintenance

Maintenance of euthymia is the primary goal in the long-term treatment of bipolar disorder and is best achieved through the use of long-term medication.[30] Current evidence best supports the use of lithium as first-line treatment: it has been shown to prevent both manic and depressive relapse, as well as suicide in meta-analytic reviews of randomized controlled trials.[37,38] Divalproex has somewhat less evidence than lithium, but may also be considered a first-line treatment.[39] Lamotrigine has demonstrated efficacy in preventing depressive relapse and may be a good option for more depression-prone patients. Among the SGAs, olanzapine and aripiprazole have demonstrated efficacy in preventing relapse among acute responders, and quetiapine and ziprasidone have some evidence as adjuncts to divalproex or lithium.[40–45] Most recently, a long-acting injectable preparation of risperidone was approved by the FDA to prevent relapse on the basis of 2 positive, randomized trials.[46,47] For many patients, maintenance therapy will be the medication to which they responded acutely; this should be borne in mind when selecting an acute agent. Careful consideration of the adverse effects of these agents (discussed above) should be undertaken as well before embarking on long-term treatment. One important additional caveat pertains to the cessation of an effective medication: there is evidence that abrupt discontinuation of mood stabilizers may actually hasten relapses, even after sustained periods of remission. As such, patients should be cautioned to not stop their medications abruptly, and when a medication must be discontinued, if possible, it should be slowly tapered.

Table 7. Psychosocial Treatments for Bipolar Disorder[a]

Interpersonal and social rhythms therapy	Aims to regulate social routines and stabilize interpersonal relationships to improve depression and prevent relapse, includes psychoeducation
Family focused therapy	Aims to involve family to help improve communication and reduce negative expressed emotion and stressors that provoke episodes, includes psychoeducation
Cognitive behavioral therapy	Aims to correct negative thoughts and dysfunctional beliefs and improve problem solving and communication, includes psychoeducation

[a]Based on Miklowitz et al.[49]

Table 8. Long-Term Monitoring Parameters for Patients With Bipolar Disorder[a]

Patient Is Maintained On:	Check	Monitor For:
Lithium	Serum level: once therapeutic level is achieved, every 3–6 mo	Subtherapeutic or toxic level
	EUC: every 3–6 mo	Renal insufficiency, nephrogenic diabetes insipidus
	Calcium, TSH, weight: after 6 mo and then annually	Thyroid/parathyroid dysfunction
Divalproex	Serum level: during initial therapy and then as clinically indicated	Subtherapeutic or toxic level
	Weight, complete blood count, menstrual history, liver function tests every 3 mo for the first year and then annually	Weight gain, thrombocytopenia, dysmenorrhea, liver failure
	Blood pressure, fasting blood glucose, lipid profile, bone densitometry (if risk factors)	Metabolic syndrome, anticonvulsant-related osteopenia
Carbamazepine	Serum level: during initial therapy and then as clinically indicated	Subtherapeutic or toxic level
	Complete blood count, liver function tests, EUC monthly for 3 mo then annually	Blood dyscrasias, liver failure, hyponatremia
	Bone densitometry and evaluation of oral contraceptive efficacy when applicable	Anticonvulsant-related osteopenia, increased metabolism of oral contraceptives
	Monitor for rash	Stevens-Johnson Syndrome
Lamotrigine	Monitor for rash	Stevens-Johnson Syndrome
Second-generation antipsychotics	Weight monthly for 3 mo and then every 3 mo	Weight gain
	Blood pressure, fasting blood glucose, lipid profile every 3 mo and then annually	Metabolic syndrome
	Monitor for abnormal movements	Acute dystonias, drug-induced parkinsonism, tardive dyskinesia
	Electrocardiogram, prolactin as clinically indicated	QTc prolongation/dysrhythmias, hyperprolactinemia

[a]Based on Ng et al.[52]
Abbreviations: EUC = electrolytes, urea, creatinine; TSH = thyroid-stimulating hormone.

Table 9. Key Recommendations for the Management of Bipolar Disorder

Recommendations	Strength of Evidence	References	Notes
Mania should be treated first-line with lithium, divalproex, or an atypical antipsychotic medication	Strong	Gijsman et al,[35] Sachs et al,[36] Burgess et al,[37] Cipriani et al[38] (evidence-based guidelines)	Combination of lithium or divalproex with an antipsychotic is likely more effective than monotherapy; see discussion in text to guide agent choice
Mixed episodes should be treated first-line with divalproex or an atypical antipsychotic	Strong	Gijsman et al,[35] Sachs et al,[36] Burgess et al,[37] Cipriani et al[38] (evidence-based guidelines)	Quetiapine has not been well studied for treatment of mixed episodes
Bipolar depression should be treated with quetiapine, olanzapine/fluoxetine combination, or lamotrigine	Strong (moderate for lamotrigine)	Gijsman et al,[35] Sachs et al,[36] Burgess et al,[37] Cipriani et al[38] (evidence-based guidelines); Cipriani et al[42] (meta-analysis of 5 RCTs)	The meta-analysis of lamotrigine included 4 trials that showed no significant benefit for bipolar depression
All patients should be offered group or individual psychoeducation	Strong	Scott et al,[51] (meta-analysis of 6 RCTs)	…
All patients should have ongoing monitoring of appropriate health variables (see Table 8)	Moderate	Ng et al,[52] (consensus guideline)	Monitoring parameters provided in Table 8 should serve as a minimum standard

Abbreviation: RCT = randomized controlled trial.
Symbol: … = no data.

PSYCHOSOCIAL TREATMENT

Psychoeducation focusing on recognition of early warning signs of relapse is an effective adjunct to medication management and should be offered to all patients with bipolar disorder.[48] More intensive psychotherapies (cognitive-behavioral therapy, family focused therapy, interpersonal and social rhythm therapy) have also demonstrated benefit as adjuncts to improve both symptoms and function and should be considered when available and financially feasible[49–51] (Table 7).

MAINTENANCE OF GENERAL HEALTH

As discussed, bipolar disorder carries with it the burden of higher comorbidity and medication effects that may pose risks to the general health of the patient. The family physician plays a vital role

in mitigating these risks by careful monitoring of a number of health parameters (Table 8).[52]

KEY RECOMMENDATIONS

Bipolar disorder is a lifelong illness that is complicated by high comorbidity and risk of poor health outcomes. The family physician has a vital role in improving patient quality of life as the primary care provider. The management of acute mood episodes should focus first on safety, should include psychiatric consultation as soon as possible, and should begin with an evidence-based treatment that may be continued into the maintenance phase (Table 9). Long-term management focuses on maintenance of euthymia, requires ongoing medication, and may benefit from adjunctive psychotherapy. In the longitudinal management of these patients, the family physician may be particularly helpful in working to mitigate the unfortunate effects of the comorbidity that this disorder carries with it and the adverse effects inherent in even its best treatments.

Drug names: aripiprazole (Abilify), asenapine (Saphris), bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), quetiapine (Seroquel), risperidone (Risperdal and others), valproic acid (Depakene, Stavzor, and others), ziprasidone (Geodon).

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