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Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies

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Since the previous publication of Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines in 1997, there has been a substantial increase in evidence-based treatment options for bipolar disorder. The present guidelines review the new evidence and use criteria to rate strength of evidence and incorporate effectiveness, safety, and tolerability data to determine global clinical recommendations for treatment of various phases of bipolar disorder. The guidelines suggest that although pharmacotherapy forms the cornerstone of management, utilization of adjunctive psychosocial treatments and incorporation of chronic disease management model involving a healthcare team are required in providing optimal management for patients with bipolar disorder. Lithium, valproate and several atypical antipsychotics are first-line treatments for acute mania. Bipolar depression and mixed states are frequently associated with suicidal acts; therefore assessment for suicide should always be an integral part of managing any bipolar patient. Lithium, lamotrigine or various combinations of antidepressant and mood-stabilizing agents are first-line treatments for bipolar depression. First-line options in the maintenance treatment of bipolar disorder are lithium, lamotrigine, valproate and olanzapine. Historical and symptom profiles help with treatment selection. With the growing recognition of bipolar II disorders, it is anticipated that a larger body of evidence will become available to guide treatment of this common and disabling condition. These guidelines also discuss issues related to bipolar disorder in women and those with comorbidity and include a section on safety and monitoring.

Co-Chairs: Lakshmi N Yatham[a], Sidney H Kennedy[b]

Section Leaders: Claire O'Donovan[c], Sagar Parikh[b], Glenda MacQueen[d], Roger McIntyre[b], Verinder Sharma[e], Peter Silverstone[f]

Guidelines Committee: Martin Alda[c], Philippe Baruch[g], Serge Beaulieu[h], Andree Daigneault[i], Roumen Milev[j], L. Trevor Young[b], Arun Ravindran[b], Ayal Schaffer[b], Mary Connolly[k] & Chris P Gorman[l]

[a]Department of Psychiatry, University of British Columbia, Vancouver, BC, [b]Department of Psychiatry, University of Toronto, Toronto, ON, [c]Department of Psychiatry, Dalhousie University, Halifax, NS, [d]McMaster University, Hamilton, ON, [e]Department of Psychiatry, University of Western Ontario, ON, [f]Departments of Psychiatry and Neuroscience, Alberta, Edmonton, AB, [g]Department of Psychiatry, Laval University, Quebec City, QC, [h]Department of Psychiatry, McGill University, Montreal, [i]Department of Psychiatry, University of Montreal, [j]Department of Psychiatry, Queen's University, Kingston, ON, [k]Mood Disorders Service, Victoria, BC, [l]University of Calgary, Calgary, AB, Canada

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Section 1: Introduction

There has been an explosion of research into treatment of bipolar disorder since the publication of the first guidelines for the treatment of bipolar disorder by the American Psychiatric Association in 1994 (1). Over the past decade, novel anti-convulsants (2), atypical antipsychotics (3), and

psychosocial treatments (4, 5) have been widely studied for their efficacy in bipolar disorder. In order to capture and distil these advances in treatment to clinicians, several regional (6), national (7–10) and expert groups (11–15) have published treatment guidelines for bipolar disorder over the past 10 years. Some of these guidelines have already gone through a second revision (16, 17) while others will probably be revised in the near future.

This publication represents a timely update to the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines published in 1997 (7). The previous guidelines used periodic health examination guidelines for rating strength of evidence and clinical recommendations. In order to make these more clinician friendly, we have modified the criteria for rating strength of evidence for intervention and a clinical recommendation is made for each intervention based on global impression of efficacy, effectiveness, and side effects. The new criteria for rating strength of evidence and clinical recommendations are outlined below (Tables 1.1 and 1.2).

These guidelines are divided into eight sections, including this introductory section. In Section 2, the basic principles of management are discussed. These include early and accurate diagnosis, educating the patients and significant others about the disorder and its treatment, and incorporation of psychosocial strategies and a chronic disease management model into patient care. The treatment of acute mania, acute bipolar depression and maintenance treatment are, respectively, reviewed in Sections 3, 4 and 5. The section on acute mania not only includes emergency management but also a treatment algorithm that provides options at various steps, depending upon the previous medication status of the patient and level of response. Similarly, in Section 4, a treatment algorithm provides management options for patients with acute bipolar depression while Section 5 addresses long-term treatment, emphasizing the importance of treatment adherence in achieving mood stability as well as current evidence-based pharmacotherapies. Clinical features that might help clinicians to make choices between those options are also reviewed.

Table 1.1. Evidence criteria

1.	Meta-analysis or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo condition
2.	At least one DB-RCT with placebo or active comparison condition
3.	Prospective uncontrolled trial with 10 or more subjects
4.	Anecdotal reports or expert opinion

Table 1.2. Treatment recommendation

First line	Level 1 or level 2 evidence plus clinical support for efficacy and safety
Second line	Level 3 evidence or higher plus clinical support for efficacy and safety
Third line	Level 4 evidence or higher plus clinical support for efficacy and safety
Not recommended	Level 1 or level 2 evidence for lack of efficacy

Treatment of bipolar disorder in women who are contemplating pregnancy, during pregnancy or in the postpartum period poses unique challenges, as clinicians have to carefully balance risks and benefits. As well, management of bipolar disorder in children and adolescents and those with comorbidity can be equally challenging and these issues are covered in Section 6. Although bipolar II disorder is very common, it has been neglected as an area of research, and until now few, if any, guidelines have specifically addressed treatment of this condition. Section 7 of these guidelines reviews the limited data available on evidence-based treatments for bipolar II disorder, and provides treatment recommendations while acknowledging the limitations of such recommendations. Treatment adherence is a substantial challenge in the management of bipolar disorder and one of the major reasons for non-adherence is adverse events. Hence, the monitoring of patients for adverse effects is of paramount importance. This is discussed in Section 8, in addition to the principles of medical monitoring.

A clinical case is interwoven throughout these guidelines to illustrate how treatment evidence can be incorporated into the management of a patient with bipolar disorder and controversial topics are raised at the end of different sections.

Although these guidelines were developed by Canadian experts on bipolar disorder, we have attempted to make them applicable to physicians and other health professionals elsewhere in the world and are pleased that they will be published in the *Bipolar Disorders* journal. To add to their international relevance, we have invited experts from North America, Europe, Australasia, South America, and Africa to provide complementary written commentaries in this supplement on these 2005 CANMAT guidelines for bipolar disorder. We hope that this initiative might contribute to future development of international guidelines for treatment of bipolar disorder.

Section 2: Foundations of management

Epidemiology

Prevalence. Bipolar disorder is a relatively common and highly disabling mood disorder. Bipolar disorder has been sub-categorized into bipolar I, bipolar II, and bipolar disorder not otherwise specified (NOS). According to the DSM-IV, individuals may also experience bipolar symptoms as part of cyclothymia, substance-induced mood disorders, secondary to a medical disorder, and schizoaffective disorder-bipolar subtype (18). The term bipolar spectrum disorder captures a variety of clinical conditions that are thought to be closely related to bipolar disorder and are discussed below.

In the general population, the prevalence of bipolar I disorder is estimated at approximately 0.5–2.4% (19–26), and the prevalence of bipolar II disorder at 0.2–5.0% (20, 27, 28). Higher prevalence rates are reported for bipolar spectrum disorder as defined by subsyndromal manic symptoms (3.0–6.5%) (27, 29, 30). However, determining the true prevalence of bipolar disorder is hampered by serious deficits in virtually all population-based surveys, due primarily to the lack of a reliable instrument for diagnosis of the disorder (31). The prevalence of bipolar I disorder is similar in both men and women (32–34). Comorbid anxiety disorders and substance abuse are reported in almost half of patients with bipolar disorder (35).

Age of onset. The mean age of onset is between 17 and 21 years (36, 37). Functional impairment may be more pronounced in individuals who develop the illness prior to age 19, as early onset frequently disrupts subsequent education, career, and social development (38).

Burden of illness. Bipolar disorder results in significant disability and negative impact on quality of life (23, 29, 39–42). Compared with healthy subjects, patients with bipolar disorder report significantly more difficulties with work-related performance, leisure activities, as well as social and family interactions (29, 39); however, treatment can improve many of these difficulties. In 1990, the World Health Organization identified bipolar disorder as the world's sixth leading cause of disability-adjusted life years among people aged 15–44 years (41). Individuals with bipolar disorder also demonstrate significant increases in lifetime health service utilization and the need for welfare and disability benefits, compared to populations with no mental disorder (29). The lifetime cost for all individuals in the United States with onset of bipolar disorder in 1998 has been estimated at US$24 billion (43).

Suicide risk. There is an increased lifetime risk of suicide among patients with bipolar disorder, estimated at 17–19%, or 15–20 times more than that of the general population (44–51). As many as 25–50% of patients with bipolar disorder attempt suicide at least once during their lifetime (45, 49–54). While some controversies exist over the research methods used to make these estimates, the high risk of suicidality is undeniable.

Several risk factors for suicidal behaviour have been identified, and many of these are additive (Table 2.1) (51, 53, 55–58). Therefore, in addition to obtaining a history of personal and family suicidal behaviour, it is important to assess a patient's history of depression, current level of pessimism, aggressive/impulsive traits, and comorbidity with substance use disorders, to help identify patients at risk for suicidal behaviour (55, 57, 59).

A treatment programme in a maximally supportive clinical environment can reduce suicidal behaviour in high-risk patients. Long-term maintenance pharmacotherapy with lithium may substantially reduce the risk of suicide in these patients (60–64), however, this must be balanced against its risk of toxicity and high lethality in overdose.

Diagnostic assessment

DSM-IV diagnostic criteria. Bipolar I disorder is characterized by the occurrence of one or more manic (Table 2.2) or mixed episodes. Although the occurrence of a depressive episode is not required for a diagnosis of bipolar I disorder, almost all patients experience depressive episodes, which in fact are more common than manic episodes. Bipolar II disorder is characterized by the occurrence of one or more major depressive episodes accompanied by at least one hypomanic episode (Table 2.2). To meet criteria, mood symptoms must cause clinically significant distress or impair-

Table 2.1. Risk factors for suicidal behaviour in patients with bipolar disorder (51, 53, 55–58)

History of suicide attempt
Family history of suicidal behaviour
Severity/number of depressive episodes
Alcohol/substance abuse
Level of pessimism
Level of aggression/impulsivity
Younger age of onset

Table 2.2. Bipolar disorder – diagnostic features (DSM-IV) (18)

Mania

A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (any duration if hospitalization is necessary)

Persistence of three or more of the following symptoms to a significant degree:

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep (e.g. feels rested after only 3 h of sleep)
3. More talkative than usual or pressure to keep talking
4. Flight of ideas or subjective experience that thoughts are racing
5. Distractibility
6. Increase in goal-directed activity or psychomotor agitation
7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained buying sprees, sexual indiscretions or foolish business investments)

Hypomania

A distinct period of persistently elevated, expansive or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual non-depressed mood

Persistence of three or more of the symptoms necessary for a manic episode

Cyclothymic disorder

The presence of numerous periods with hypomanic symptoms and numerous periods with depressive symptoms that do not meet criteria for a major depressive episode, for at least 2 years

During the above 2-year period, the person has not been without the symptoms for more than 2 months at a time

No major depressive episode, manic episode, or mixed episode has been present during the first 2 years of the disturbance

Bipolar disorder not otherwise specified

1. Very rapid alternation (days) between manic and depressive symptoms that do not meet duration criteria
2. Recurrent hypomania without intercurrent depressive symptoms
3. Manic or mixed episode superimposed on delusional or psychotic disorder
4. Unable to determine if bipolar disorder is primary, substance-induced or related to a medical condition

ment in social, occupational, or other important areas of functioning.

The bipolar spectrum. There is a broad range of clinical presentations between the extremes of classic manic-depressive disorder (bipolar I disorder) and strictly defined unipolar depression [major depressive disorder (MDD)] (65). To more precisely characterize the varied clinical presentations, a number of authors have proposed classification systems that identify other purported subtypes of bipolar disorder or invoke a relationship conveyed by the term 'bipolar spectrum disorder' (65–68). However, as noted in Table 2.2, the DSM-IV only formally recognizes a few categories of bipolar disorder, while also allowing for the expression of bipolar symptoms resulting from substance use or other medical disorder. As the majority of clinical trials have been conducted in patients with bipolar I disorder, most of the recommendations made in this document apply to that patient group. Where data are available from patients with bipolar II disorder, they are reviewed and recommendations are made. However, although few data are available, biphasic mood dysregulation, that may not meet the full threshold criteria for a bipolar disorder as per DSM-IV (Table 2.2), may benefit from mood-stabilizing therapies in conjunction with other treatments (69). None the less, clinicians should be cautious in interpreting literature citing 'bipolar spectrum disorder' because of the lack of agreement around its definition and the absence of specific treatment studies for these conditions.

Screening for and diagnosing bipolar disorder. Diagnosing bipolar disorder can be a challenge. Delays from the onset of symptoms to the time of initial treatment for bipolar disorder of up to 20 years have been reported (40, 70, 71). An estimated 35–45% of patients with bipolar I disorder are misdiagnosed with unipolar depression (70, 72–74). One of the reasons for this is the fact that patients with bipolar disorder seek treatment in the depressive state two to three times more often than in the manic state (75).

The strategies shown in Table 2.3 can help to screen for bipolar disorder, which can then be diagnosed according to DSM-IV criteria (Table 2.2). Currently there is no ideal screening tool or diagnostic test for bipolar disorder; however, the Mood Disorder Questionnaire (MDQ) (Table 2.4) may be a useful screening instrument. Endorsement of two or more symptoms by an individual should alert the physician to further explore potential manic/hypomanic symptoms in more detail. Patients seldom recognize hypomania as a problem, particularly when being questioned in an acute depression, as they may have concentration and memory difficulties that make it difficult to recall either hypomanic or even manic episodes. As such, several screening questions for both mania and hypomania should be asked, and if available, collateral history from family or friends should be obtained. In uncertain cases, prospective use of a mood diary can be very useful in identifying symptoms of a manic or hypomanic episode. The best way to confirm the diagnosis may be to assess the patient on those days when the patient rates symptoms in the mood diary in the hypomanic/manic range.

Screening for a family history of bipolar disorder is critical. A positive family history among first-degree relatives increases the likelihood of bipolar

Table 2.3. Interviewing for the potential for bipolar disorder

Who to screen?
Screen patients who present with depressive symptoms for a history of hypomanic or manic symptoms
Consider an underlying mood disorder in patients presenting with unexplained vague/non-specific somatic symptoms or reverse vegetative symptoms (e.g. hypersomnia and hyperphagia)
How to screen?
Listen to the patient's unprompted presenting complaints
Ask open-ended and non-leading general questions about the common symptoms of depression and mania
Ask questions about specific symptoms of depression and mania, including how long the symptoms have been present during the current episode, how long they lasted during prior episodes (if applicable), and whether they have caused problems in social relationships or work
Always ask about suicidal ideation
Ask about psychotic symptoms
Consider asking the patient to complete the Mood Disorder Questionnaire
Ask about a family history of bipolar disorder
Interview family or friends regarding prior episodes of mania or hypomania
If unclear, ask patients to do prospective mood ratings and assess when patients are rating symptoms in manic or hypomanic range
Consider alternative diagnoses
General medical conditions that may produce similar symptoms
Alcohol and other substance abuse
Medications that may produce similar symptoms

II disorder by 8–18 times compared to those with no family history (76).

Comorbidities and mimics. Bipolar disorder is associated with an increased incidence of comorbidity with substance abuse, anxiety disorders, and personality disorders (35, 78–80). Axis I or Axis II comorbidity may be associated with an earlier age at onset and a worse course of bipolar illness (35, 59).

Alternative causes of mood disorders, including general medical conditions, alcohol and substance abuse, medications that may produce similar symptoms and psychiatric disorders including schizophrenia and other psychoses, must be considered in the differential diagnosis of depressive and manic syndromes (Table 2.5).

Chronic Disease Management: an integrated patient, provider, and systems model

Bipolar disorder is a chronic illness characterized by episodes of relapse/recurrence and periods of remission. As patients require a long-term, multidisciplinary management plan, the Chronic Disease Management Model should be applied (81, 82). The model, first proposed by Wagner (82), identifies the essential elements of a healthcare system for high-quality management of patients with chronic diseases (Table 2.6).

In patients with bipolar disorder, before addressing long-term strategies, stabilization of the acute episode, particularly those in the manic/hypomanic phase, is the first step in management. The first priority is to determine if patients are a danger to themselves or others, and whether they require hospitalization. For a patient who is no longer severely ill, the psychosocial approach should be modified to facilitate enhanced discussion and review of treatment options as a way of building patient confidence and responsibility in managing his or her own care.

The Chronic Disease Management Model, along with other models, has been integrated into a stepped care model specifically for bipolar disorder by Parikh and Kennedy (83). After initial pharmacotherapy and related clinical management as the first step, care should ideally be provided with a healthcare team that includes at least one other health professional in addition to the physician, typically a nurse who may provide detailed psychoeducation, additional monitoring, and support. One key example of monitoring would involve active outreach and follow up of patients known to be more severely ill, to ensure such individuals attend appointments and follow recommendations. The third step involves the provision of robust psychoeducation, whose elements would include preparing the patient to become actively involved in self-management, identifying ways to collaborate most effectively with health providers, teaching key facts about bipolar disorder, teaching recognition of early signs of relapse, identifying a relapse drill, and learning a variety of key stress management techniques, including careful attention to sleep regulation and avoidance of substance misuse. Involvement of family or key friends in part of the psychoeducation can be invaluable, particularly in creating a relapse drill. Effective relapse drills feature creating a document that lists early warning symptoms of relapse and specifies usual treatment responses, including self-management manoeuvres. This relapse drill document has the additional benefit of speeding and simplifying medical decision-making and reducing patient ambivalence about treatment, as the patient is the principal author of the document.

Under the stepped care approach, after initiating pharmacotherapy, identifying a treatment

Table 2.4. Mood Disorder Questionnaire (MDQ) (77).

1.	Has there ever been a period of time when you were not your usual self and...	YES	NO
	...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?	☐	☐
	...you were so irritable that you shouted at people or started fights or arguments?	☐	☐
	...you felt much more self-confident than usual?	☐	☐
	...you got much less sleep than usual and found you didn't really miss it?	☐	☐
	...you were much more talkative or spoke faster than usual?	☐	☐
	...thoughts raced through your head or you couldn't slow your mind down?	☐	☐
	...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	☐	☐
	...you had much more energy than usual?	☐	☐
	...you were much more active or did many more things than usual?	☐	☐
	...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	☐	☐
	...you were much more interested in sex than usual?	☐	☐
	...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	☐	☐
	...spending money got you or your family into trouble?	☐	☐
2.	If you checked YES to more than one of the above, have several of these ever happened during the same period of time? *Please circle one response only.* YES NO		
3.	How much of a problem did any of these cause you—like being unable to work: having family,money, or legal troubles: getting into arguments or fights? *Please circle one response only.* No problem Minor problem Moderate problem Serious problem		

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team (where available), and providing psychoeducation, the next steps involve tailoring the psychosocial treatments to the specific needs of the patient, as reviewed in detail below. However, implicit in the first few steps of the stepped care model is that the physician should base treatment decisions on evidence-based guidelines, and that these guidelines should be explicitly revealed to the patient to enhance shared decision-making. Other key recommendations for care drawn from the broader chronic care model include connecting the patient to other community resources to enhance support and autonomy. Community resources for bipolar disorder, as well as information on key treatment centres, reference texts, and websites, are listed at the end of this document.

Psychosocial interventions

Beyond regular monitoring and supportive care, there is evidence that psychoeducation and more formal psychotherapy can improve outcome when used in conjunction with maintenance pharmacotherapy. Adjunctive psychosocial therapies should be considered early in the course of illness to improve medication adherence, identify prodromes of relapse, decrease residual symptoms (particularly depressive) and suicidal behaviour, and help move patients towards a comprehensive functional recovery (84–90). A list of useful manuals describing various methodologies can be found in Appendix 2. For consistency of scientific review, the major modalities are discussed in the context of available studies below; however, it is recommen-

Table 2.5 Differential diagnosis of bipolar disorder

Diagnosis[a]	Distinguishing features
Major depressive disorder or dysthymic disorder	Manic or hypomanic episodes probed for and not present
Mood disorder due to a general medical condition	Episodes are judged to be a consequence of a medical condition such as multiple sclerosis, stroke or hyperthyroidism. Onset or exacerbation of mood coincides with that of medical condition
Substance-induced mood disorder	Episodes are judged to be a consequence of a substance such as an illicit drug, a medication (stimulants, steroids, L-dopa, antidepressants), or toxin exposure. Episodes may be related to intoxication or withdrawal
Cyclothymic disorder	Hypomanic symptoms do not meet the criteria for a manic episode, and depressive symptoms do not meet the criteria for a major depressive episode
Psychotic disorders (schizoaffective disorder, schizophrenia, delusional disorder)	Periods of psychotic symptoms in the absence of prominent mood symptoms. Consider onset, accompanying symptoms, previous course and family history
Borderline personality disorder	Instability of interpersonal relationships, self-image and mood, with marked impulsivity, and a central theme of intense abandonment fears. Early onset and a long-standing course. True euphoria and prolonged well-functioning intervals are extremely rare
Narcissistic personality disorder	Grandiosity, need for admiration and lack of empathy of early onset. Grandiosity not associated with mood changes or functional impairments
Antisocial personality disorder	Early onset of disregard for, and violation of, the rights of others, which does not occur only in the context of a manic episode

[a]Note many of these diagnoses frequently occur comorbidly with bipolar disorder.

Table 2.6. The Chronic Disease Management Model: elements of a healthcare system for effective care of patients with chronic disorders

Self-management support
Empower and prepare patients to manage their health and health care
Use effective self-management support strategies that include assessment, goal-setting, action planning, problem-solving and follow up
Decision support
Promote clinical care that is consistent with scientific evidence and patient preferences
Embed evidence-based guidelines into daily clinical practice and share this and other information with patients to encourage their participation
Use proven provider education methods
Community
Encourage patients to participate in effective community programmes
Form partnerships with community organizations
Delivery system design
Provide clinical care and self-management support that patients understand and that fits with their cultural background
Ensure regular follow up by the care team, with defined tasks for different team members
Provide clinical case management services for complex patients
Clinical information systems
Provide timely reminders for providers and patients
Facilitate individual patient care planning
Share information with patients and providers to coordinate care
Health system
Measure outcomes and use information to promote effective improvement strategies aimed at comprehensive system change
Develop agreements that facilitate care coordination within and across organizations

ded that all patients first receive psychoeducation. Subsequently, only selected individuals would be recommended to pursue additional therapy such as cognitive-behavioural therapy (CBT) or interpersonal therapy (IPT) based on specific clinical problems or characteristics, such as persistent symptoms, pervasive pessimism, or interpersonal deficits. Evidence for such a sequential approach has been provided by one randomized clinical trial (RCT) that has been submitted for publication (S. Parikh, personal communication).

Psychoeducation. Psychoeducation is focused on providing information on the disorder, its treatment, and the social and family consequences of the disorder. When added to pharmacotherapy, RCTs have shown that group psychoeducation significantly increased the time to depressive, manic, hypomanic, and mixed recurrences and reduced relapse rates (88, 91). Psychoeducation aimed at teaching patients to recognize prodromal symptoms of relapse was associated with improvements in time to first manic relapse, social func-

tioning, and employment but had no effect on depressive relapse (92).

Cognitive-behavioural therapy. Here the focus is on cognitive restructuring and includes self-monitoring, strategies to deal with dysfunctional thoughts, and behavioural techniques to promote social functioning. Controlled trials comparing CBT to treatment as usual or wait-listed controls in bipolar patients have demonstrated increased functioning and adherence, and decreased relapses, mood fluctuations, need for medications, and hospitalizations (93–95).

Interpersonal and social rhythm therapy (IPSRT). Interpersonal and social rhythm therapy includes the traditional IPT focus on one of four problem areas (grief, interpersonal role transition, role dispute and interpersonal deficits) but extends into meticulous regulation of social and sleep rhythms. A large controlled trial demonstrated that therapy did not alter time to relapse but did have a significant impact on subsyndromal symptoms; patients spent more time euthymic and less time depressed relative to intensive clinical management (96, 97).

Family interventions. Family psychoeducational therapy is based on the premise that a hostile, critical or over-involved family atmosphere has a negative impact on relapse of bipolar disorder (98, 99). In RCTs, family-focused treatment was associated with fewer relapses and hospitalizations, and improvements in depressive symptoms and medication adherence compared with individual therapy or a family crisis management intervention (100–102). However, a recommendation that there should be 21 sessions of family therapy is somewhat impractical for most patients.

Putting recommendations into practice

A clinical case will be introduced in this section and the patient will be followed throughout these guidelines. The case will help demonstrate the evidence-based approach to case management throughout various phases of bipolar disorder.

Case study

Sara, 20 years old, is referred to you by her family practitioner for persistent symptoms of depression over the past several years, for which she has been taking an antidepressant 'on-and-off.' She explains that when she takes the antidepressant for a few weeks, she feels great, being so productive at work, doing projects at home, and socializing with friends and family. When this happens she discontinues the antidepressant, but inevitably she slips back into depression and restarts the medication.

- What questions should you ask?
- What is your diagnosis?
- What is your treatment plan?

Clinical management. Patients who present with depressive symptoms should be thoroughly questioned about their medical and psychiatric history including a history of substance abuse. In particular, all patients with depression should be specifically probed for prior episodes of mania or hypomania. In Sara's case, her bouts of 'feeling great' triggered by antidepressant use suggest a hypomanic/manic switch, and a possible diagnosis of bipolar I or bipolar II disorder. On questioning, you learn that her 'high' periods have not been all positive. During these periods, she has an incredible amount of energy, gets very little sleep and her thoughts race; she often feels jumpy and cannot sit still at work. When things get too 'out of control' she usually calls in sick to work so she can do something physically active or go shopping. She has substantial debt from impulse purchases of things she admits she does not need. Her family and friends worry about her thrill-seeking behaviours. She has lost a few friends because of her irritability and 'obnoxious behaviour'; she has engaged in sexual relationships with strangers during these periods, which she regrets. These episodes usually occur once or twice a year, lasting from a few days to a few weeks, and have occurred both on and off antidepressants. She denies using cocaine, but says she likes marijuana and occasionally 'lets guys talk her into taking Ecstasy' at parties because the 'sex is more intense'. However, during her depression she feels 'incredibly guilty and stupid' about this.

You diagnose bipolar I disorder and recommend that she discontinue the antidepressant. You discuss with Sara the need to first stabilize her condition and then put in place a long-term chronic disease management plan. The first steps are for her to understand the chronic nature of the disease and to recognize the negative impact of manic episodes both in terms of immediate and long-term consequences. You use an evidence-based approach to explain that relapse can become more frequent over time if the condition is left untreated and that there can be long-term changes in the brain. When viewing the overall picture, Sara agrees that she is having manic and depressive episodes and she accepts the diagnosis of bipolar disorder and agrees that long-term therapy is

necessary. After you explain the benefits and risks of the various mood-stabilizers, Sara agrees to take lithium.

You discuss with Sara the importance of self-management, and together you set a goal for the next 2 weeks for Sara to make a list of the signs of her manic and depressive relapses and she agrees to discontinue use of caffeine, alcohol and illicit substances. She agrees that together you will develop a written management contract, and she identifies her mother as the best person to help her monitor her mood. You ask her to bring her mother to the next visit and encourage her to participate in a bipolar support programme. You provide her with information on the disorder and tell her that at her next visit you will introduce her to the other members of the healthcare team who will participate in her care.

Section 3: Acute management of bipolar mania

Presentations of mania

Presentations can be either manic or mixed (dysphoric) with or without psychotic features. Prior to initiating algorithmic treatment for mania, manic episode secondary to a general medical condition or substance use disorder (including antidepressant-associated mania) should be ruled out (103).

Mania. For a diagnosis of a manic episode, symptoms must be present for at least 1 week (or any time if hospitalization is required). Symptoms include a primary mood disturbance of persistently elevated, expansive, or irritable mood along with at least three of the following: inflated self-esteem or grandiosity, decreased need for sleep, pressure of speech, flight of ideas, distractibility, increased goal-directed activity or psychomotor agitation, and excessive involvement in pleasurable activities with a high potential for painful consequences (Table 2.2) (18). In patients with irritable mood as the primary mood disturbance, at least four of the above symptoms must be present to diagnose a manic episode.

Mania with psychotic features. If possible, specify if the psychotic features are mood-congruent (delusions/hallucinations where content is entirely consistent with typical manic themes) or mood-incongruent (delusions/hallucinations where content does not involve typical manic themes, e.g. persecutory delusions, delusions of being controlled or thought insertion) (18). The presence of psychotic features and their congruency with the mood state may have prognostic implications.

Mixed states are a common presentation in an acutely manic patient and remain a significant treatment challenge. The criteria for both a manic and a major depressive episode (except for duration) are met nearly every day for at least 1 week or for any duration if hospitalized (18).

Rapid cycling. About 20% of patients with bipolar disorder have a rapid cycling course with four or more mood episodes within 1 year (18). Episodes are demarcated by either partial or full remission for at least 2 months or a switch to an episode of opposite polarity (e.g. depressive to manic episode).

Terminology for pharmacotherapy

Although the term 'mood-stabilizer' is used frequently in the literature, there is no consensus on its definition. Several overlapping definitions and criteria have been proposed that include some combination of: proven efficacy for the treatment of acute mania and depression, no propensity to induce an episode of opposite polarity or to destabilize the long-term course of the illness, and prophylactic efficacy (8, 17, 104, 105). To avoid confusion in these guidelines, generally accepted descriptive terms for medications according to their therapeutic class (e.g. antidepressants, anticonvulsants, antipsychotics) or the name of specific agents (e.g. lithium) will be used. For the sake of convenience we have used divalproex to refer to valproate, valpromide, valproic acid and divalproex sodium. In the case of 'antipsychotic agents' the term has been used to describe a group of medications that act across a broader therapeutic target, than just psychoses.

Emergency management of agitation

The acutely manic bipolar patient may present in an agitated state that acts as a barrier to therapy, interrupts the physician–patient alliance, and creates a disruptive, even hazardous, environment. For all manic patients, the general principles of management of acute mania described in step 1 (see below) should be applied in combination with rapid effective pharmacotherapy.

Benzodiazepines, atypical antipsychotics, and conventional antipsychotics are the most commonly prescribed medications in emergency settings. The choice of a single medication or a combination of medications is based on current and prior medication history, but the need for rapid control of agitation and aggressive behaviour, as well as a patient's willingness or refusal to take medication may influence the choice of drug delivery system (106, 107). This may include the use of

drugs that are available in intramuscular formulations. Whenever possible, oral therapy should be offered first, as evidence suggests that oral agents can be as effective as intramuscular agents (108, 109). Intramuscular injections offer an alternative when oral therapy cannot be reliably administered.

Based on current efficacy and safety data, the atypical antipsychotics risperidone (level 2) (109), olanzapine (level 2) (110, 111), and quetiapine (level 3) (112) should be considered as a first choice in the treatment of acute agitation. In patients who refuse oral atypical antipsychotics, intramuscular olanzapine, ziprasidone (113, 114) or a combination of an injectable typical antipsychotic and a benzodiazepine should be considered (level 2) (115–117). In general, benzodiazepines should not be used as monotherapy in patients with bipolar disorder. Benzodiazepines are useful adjuncts to sedate the acutely agitated manic patient with faster onset than anticonvulsants or lithium.

Pharmacological treatment of manic episodes

Lithium, divalproex sodium, atypical antipsychotics, carbamazepine, conventional antipsychotics and other agents, including benzodiazepines alone or in combination, have all been examined for their efficacy in the treatment of acute mania. These treatments have been evaluated using the criteria for strength of evidence (Tables 1.1 and 1.2) for their use and these are summarized in Tables 3.1 and 3.2.

Step 1: Review general principles and assess medication status. When a patient presents in a manic state, certain general principles should be followed. The patient should be immediately assessed for risk of aggressive behaviour/violence to others, suicide, degree of insight and the ability to adhere to treatment. A physical examination with appropriate lab investigations should be conducted (see Section 8), but may be deferred until the patient is more cooperative. Based on the overall assessment the type of treatment setting (e.g. ambulatory or inpatient) should be established.

Antidepressants should be discontinued and steps taken to rule out factors that may be perpetuating manic symptoms, such as prescribed medication, illicit-drug use/abuse or an endocrine disorder. Substance abuse should be identified and treated. Patients should also be strongly encouraged to discontinue using stimulants such as caffeine and alcohol and gradually discontinue nicotine. When patients are stabilized, behavioural and educational strategies should be applied (see Section 2). In order to direct subsequent therapeutic choices, current therapy should be assessed, including what medications the patient is taking and at what dose.

Table 3.1. Strength of evidence for monotherapy treatments of acute bipolar mania

Agent	Level of evidence
Lithium	1
Anticonvulsants	
Divalproex	1
Carbamazepine	1
Oxcarbazepine	2
Lamotrigine	1 (−ve)
Topiramate	1 (−ve)
Gabapentin	2 (−ve)
Tiagabine	3 (−ve)
Atypical antipsychotics	
Olanzapine	1
Risperidone	1
Quetiapine	1
Ziprasidone	1
Aripiprazole	1
Clozapine	3
Other treatments	
Haloperidol	1
Chlorpromazine	1
Clonazepam	2
Verapamil	2 (−ve)
ECT	3

ECT = electroconvulsive therapy.

Table 3.2. Strength of evidence for combination treatments of acute bipolar mania

Agent	Level of evidence
Lithium/divalproex + risperidone	1
Lithium/divalproex + olanzapine	2
Lithium/divalproex + quetiapine	1
Lithium/divalproex + ziprasidone	2 (−ve)
Lithium/divalproex + aripiprazole	No data
Lithium/divalproex + haloperidol	1
Lithium + divalproex	3
Lithium + carbamazepine	2
Divalproex + carbamazepine	3
Risperidone + carbamazepine	3
Adjunctive gabapentin	2 (−ve)
Adjunctive lamotrigine	2 (−ve)
Adjunctive rTMS	3 (−ve)

rTMS = repetitive transcranial magnetic stimulation.

Step 2: Initiate or optimize therapy and check adherence. In managing an acute manic episode, the decision to treat with monotherapy or a combination of medications is influenced by current and prior medication use (Fig. 3.1), as well as patient factors that may influence prognosis or safety (106, 107). For untreated manic patients or those receiving a medication other than a first-line agent, therapy should be initiated with one or more of the first-line agents: lithium, divalproex or an atypical antipsychotic (Table 3.3) (level 1). For patients who are uncontrolled on monotherapy with a first-line

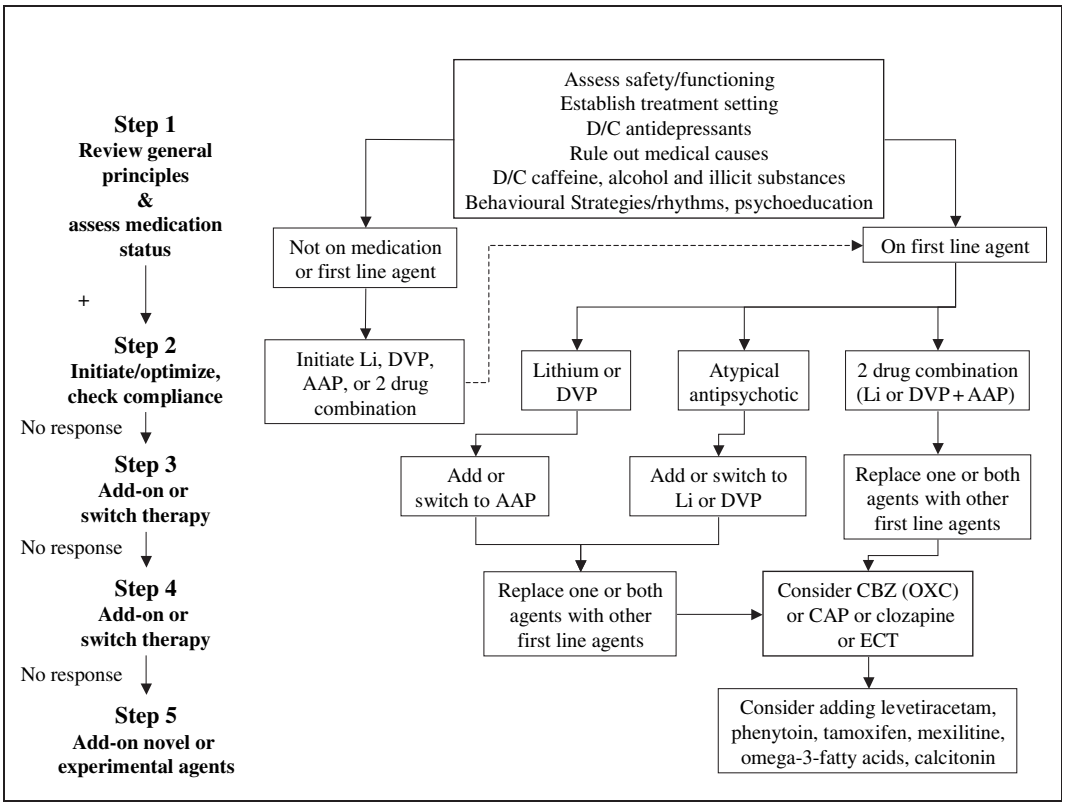

Fig. 3.1. Treatment algorithm for acute mania. AAP = atypical antipsychotic; CBZ = carbamazepine; CAP = conventional antipsychotic; DVP = divalproex; ECT = electroconvulsive therapy; Li = lithium; OXC = oxcarbazepine.

Table 3.3. Recommendations for pharmacological treatment of acute bipolar mania

First line	Lithium, divalproex, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, lithium or divalproex + risperidone, lithium or divalproex + quetiapine, lithium or divalproex + olanzapine
Second line	Carbamazepine, oxcarbazepine, ECT, lithium + divalproex
Third line	Haloperidol, chlorpromazine, lithium or divalproex + haloperidol, lithium + carbamazepine, clozapine
Not recommended	Monotherapy with gabapentin, topiramate, lamotrigine, verapamil, tiagabine, risperidone + carbamazepine

ECT = electroconvulsive therapy.

medication, the first option before adding or switching therapies is to optimize the dose of current medication and to identify issues of non-adherence. Non-adherence to therapy is a frequent cause of recurrence of bipolar disorder, which is often associated with hospitalization or suicide (118).

Lithium. As in previous guidelines (103), lithium continues to be recommended as a first-line acute pharmacological treatment (level 1). Lithium is superior to placebo and comparable in efficacy to conventional antipsychotics and anticonvulsant agents, with significant improvements occurring in about 50–70% of patients (103). Lithium has also been shown to be as effective as the atypical antipsychotics, olanzapine (119), risperidone (120) and quetiapine (121), and the conventional antipsychotic, haloperidol (120).

Divalproex. In a meta-analysis, the efficacy of divalproex was superior to placebo and equivalent to lithium and carbamazepine in the treatment of mania (level 1) (122, 123). Clinically, divalproex sodium is preferred because it has fewer gastrointestinal side effects compared with divalproex and valproic acid (103). In two studies examining the efficacy of divalproex compared with olanzapine in acute mania, one showed similar efficacy while the other showed statistically significant superiority of olanzapine (124, 125). A pooled analysis comparing an oral loading of divalproex to lithium or olanzapine showed no differences in early efficacy between these agents (126).

Atypical antipsychotics. Since 1997, substantial RCT data have emerged to support the efficacy of atypical antipsychotic monotherapy with olanzapine, risperidone, quetiapine, ziprasidone and ari-

piprazole for the treatment of acute mania (level 1). Olanzapine monotherapy was more effective than placebo (127, 128) and at least comparable to divalproex (124, 125), lithium (119) and haloperidol (level 1) (129, 130). Risperidone monotherapy was more effective than placebo (131, 132) and as effective as lithium or haloperidol (level 1) (120, 131). Quetiapine monotherapy has demonstrated efficacy in two randomized placebo-controlled trials in patients with acute mania (level 1) (121, 133) and appears to have comparable efficacy to lithium (121) and haloperidol (133).

Both ziprasidone (level 1) (134, 135) and aripiprazole (level 1) were more effective than placebo (136, 137), and aripiprazole was as effective as haloperidol in the treatment of acute mania (138). When ziprasidone was used as an adjunct to lithium therapy, there were early benefits over placebo but these were not sustained over the 3 weeks of the study (139). As aripiprazole and ziprasidone are not currently available in Canada, recommendations for their use in mania are based largely on the reported efficacy data and adverse event profile of these agents.

Combination therapy. The combinations of lithium or divalproex with various atypical antipsychotics [risperidone (140, 141), quetiapine (level 1) (142–144) or olanzapine (level 2) (145)] have demonstrated significant beneficial effects compared with lithium or divalproex monotherapy. These studies have shown that, on average, about 20% more patients will respond to combination therapy compared with mood-stabilizer monotherapy; hence, combination therapy could be considered as a first-line option for some patients. To date, the efficacy of such combination therapies compared with atypical antipsychotic monotherapies has not been reported.

Step 3: Add-on or switch therapy (alternate first-line therapies). If therapy with one of the first-line agents (lithium, divalproex or an atypical antipsychotic) at optimal doses is inadequate or not tolerated, the next step should involve switching to or adding-on an alternate first-line agent. Based on the efficacy and relative safety of first-line agents, the use of second- and third-line agents is only recommended after these classes of agents have been tried alone or in combination.

Step 4: Add-on or switch therapy (second- and third-line therapies)

Second-line options. In patients who are inadequately responsive to first-line agents, second-line choices would include other anticonvulsants such as carbamazepine and oxcarbazepine, the combination of lithium plus divalproex, or electroconvulsive therapy (ECT). Although there are substantial data [reviewed by Kusumakar et al. (103)] demonstrating that carbamazepine has efficacy similar to lithium and divalproex (level 1), safety and tolerability relegate it to a second-line option. Oxcarbazepine is a derivative of carbamazepine that is reported to be better tolerated and has demonstrated efficacy in acute mania (level 2). However, trials were very small and likely underpowered to show differences between active comparators [reviewed by Yatham (2)].

The combination of lithium and divalproex has demonstrated efficacy and safety in uncontrolled trials (146–149). It is a widely used and reasonable option to treat acute mania based on the strong evidence of each agent as monotherapy (level 3).

It has been suggested that up to 80% of patients with acute mania will show marked clinical improvement with ECT (150). Unfortunately, there has been minimal research since the publication of the previous guidelines by this group in 1997 (103) to provide additional data on ECT in the treatment of mania. Therefore, it continues to be recommended as a second-line therapy (level 3).

Third-line options. A variety of agents including the conventional antipsychotics, haloperidol, chlorpromazine or perphenazine in combination with lithium or divalproex (level 1), lithium plus carbamazepine (level 2) and clozapine (level 3) are recommended as third-line options for therapy.

In RCTs, the conventional antipsychotic, haloperidol has demonstrated efficacy that is superior to placebo and comparable to divalproex (151), lithium (120) and atypical antipsychotics such as olanzapine, risperidone, quetiapine and aripiprazole (level 1) (120, 129, 138, 152). Haloperidol has also demonstrated efficacy in combination with lithium or divalproex for the treatment of acute mania (level 1) (140, 153–155). However, side effects including extrapyramidal symptoms (EPS), acute dystonia and tardive dyskinesia limit the use of haloperidol (103). The combination of lithium and carbamazepine has demonstrated efficacy comparable to lithium plus haloperidol (level 2) (154); however, the limited data available, and the side effect profile of carbamazepine lead to a recommendation of the combination as a third-line option.

Although clozapine may have efficacy for acute mania, it should be reserved for treatment-resistant patients, based on the absence of double-blind RCTs in acute mania (156, 157) and concerns regarding its safety (level 3).

Step 5: Add-on novel or experimental agents. Phenytoin (level 2) (158) and levetiracetam (level 3) (159–161) show some antimanic efficacy but should preferably only be used as add-on therapies in those patients who have shown partial refractoriness to all the standard treatments reviewed above. Similarly, there are reports of potential antimanic efficacy for tamoxifen (162, 163), mexiletine (164, 165), omega-3-fatty acids (166) and calcitonin (167, 168) but given the very limited data, these can only be recommended as add-on therapies after failure of all standard therapies.

Agents not recommended for the treatment of acute mania. In randomized controlled trials, gabapentin (level 2, negative) and topiramate (level 1, negative) failed to demonstrate antimanic efficacy (169–171). However, gabapentin may be useful in the treatment of patients with comorbid panic disorder or alcohol abuse (172), while topiramate may be useful in attenuating or reversing atypical antipsychotic-induced weight gain (171, 173). In open trials and case reports, tiagabine did not have antimanic efficacy and was associated with seizures and other side effects (level 3, negative) (174–176). Lamotrigine monotherapy or add-on therapy has not consistently shown antimanic effects that are superior to placebo in RCTs (level 1, negative) (2, 170, 177, 178), although it does play a role in the acute and maintenance treatment of bipolar depression (see Sections 4 and 5). There is little evidence of antimanic efficacy, and in some cases evidence of inefficacy, for repetitive transcranial magnetic stimulation (rTMS) (level 2, negative) (179–181) and verapamil (level 2, negative) (182).

A meta-analysis concluded that the benzodiazepine clonazepam is effective and safe in the treatment of acute mania, but results were inconclusive for lorazepam (level 1) (183). However, because of concerns about benzodiazepine dependence, they are recommended as adjunctive therapy rather than as primary antimanic agents (103).

The combination of risperidone and carbamazepine should be avoided, as carbamazepine reduces the plasma concentration of risperidone by 40% resulting in decreased efficacy (141).

Clinical features that can help direct treatment choices

Lithium, divalproex and atypical antipsychotics, alone or in combination, are first-line treatments, but certain clinical features assist in making treatment choices for individual patients (see Table 3.4). Classical mania, elated mood in the absence of depressive symptoms or psychotic features, and a previous positive response to lithium are all predictors of a positive response to lithium treatment (103, 184, 185). Patients who display prominent depressive symptoms during mania and those with multiple prior mood episodes may respond better to divalproex (186–188). Rapid cycling and mixed mania are positive predictors of response to divalproex (103, 186, 187, 189), but generally predict poorer response to lithium (8,

Table 3.4. Predictors of response

Agent	Predictors of response	Predictors of non-response
Lithium	Elated mania (184, 185)	Mixed state (8, 103, 186, 194)
	Previous response to lithium (184, 185)	Rapid cycling (8, 103)
	Mania–depression–euthymia course (103)	Depression–mania–euthymia course (8, 103)
	No neurological impairment (184, 185)	Presence of depressive symptoms (184, 187)
	No psychotic symptoms (184, 185)	Multiple episodes (8)
	No substance abuse (8, 184, 185)	No family history (8)
	Few episodes of illness (103, 184, 185)	
Divalproex	Rapid cycling (103, 187, 189, 195)	Comorbid personality disorders (189)
	Mixed state (103, 186, 187, 189)	More severe mania (189)
	Multiple prior mood episodes (187, 188)	
	Irritable-dysphonic subtype (196)	
	Secondary mania (103)	
	Comorbid substance abuse (189)	
Carbamazepine	Mixed state (103, 189)	Rapid cycling (103, 197)
	Increased severity of acute mania (189)	>10 year history of illness (197)
	No family history of mood disorders (189)	
	Early age of onset (189)	
	Course dominated by manic episodes (189)	
Atypical antipsychotics	Early age of onset (190)	
	No prior substance abuse (190)	
	No prior antipsychotic treatment (190)	
	Rapid cycling (3, 127, 191)	

103). Patients with no family history and those with non-classical bipolar disorder, head injury or other neurological problems may respond to carbamazepine (103, 189).

Predictors of a positive response to olanzapine include younger age at illness onset, no history of substance abuse and absence of prior antipsychotic exposure (190). There is some evidence to suggest that olanzapine may be effective in patients with rapid cycling as well as those with mixed states (3, 127, 185, 190–193). Atypical antipsychotics in general appear to be equally effective in patients with or without psychotic symptoms (3, 127, 128, 131, 132, 140, 141, 145, 190).

Combination therapy should be considered the treatment of choice for those with severe manic or mixed episodes which result in impairment in functioning, while monotherapy may be sufficient for those patients with less severe symptomatology.

Mania with psychotic features

About half of manic episodes are characterized by the presence of psychotic features (198). Psychotic symptoms in mania are frequently misdiagnosed as schizophrenia, especially during early episodes (199, 200). The idea that psychotic symptoms correlate with a more severe course of illness, worse prognosis and a greater risk of suicide remains largely unsupported by the evidence, and the absence of psychotic symptoms should not be viewed as a less severe mood state. However, mood-incongruent psychotic features do appear to be associated with more severe illness (201) and a poorer long-term prognosis than mood-congruent psychotic features (199, 202–204). Whether this influences response to specific treatments is not currently known.

Despite clinical impressions to the contrary, there is limited evidence to suggest that psychosis predicts a poorer response to monotherapy with a mood-stabilizer or an atypical antipsychotic therapy. One study reported a poorer response to lithium in patients with psychotic symptoms, unless it was given in combination with antipsychotics (205), but this is not a consistent finding. In a review of RCTs, psychotic and classic mania responded similarly to lithium and divalproex (196). Similarly, treatment with an atypical antipsychotic alone or in combination with lithium/divalproex was equally effective in both patients with and without psychotic features (3, 127, 128, 131, 132, 140, 141, 145, 190). The efficacy of ECT in patients with mania was not influenced by the presence of delusions (206). There were no differences in the efficacy of olanzapine in patients with or without psychotic features, and olanzapine was as effective as divalproex in patients with psychotic features (124). It is likely that psychosis is a non-specific manifestation of mania that improves if the underlying mania improves (199).

Mixed states

The simultaneous presentation of manic and depressive symptoms presents significant treatment challenges. Data suggest that patients who are in a mixed state or rapid cycling are less likely to achieve remission and take longer to do so (207, 208). Suicide risk also appears to be higher in mixed mania compared with classic mania (209, 210).

Data also suggest that lithium is not as effective in mixed states as it is in classic mania (103, 186, 194, 207), while divalproex appears to be equally effective in both mixed episodes and pure mania (186, 211). Atypical antipsychotics alone or in combination with lithium or divalproex have shown conflicting results, but for the most part, appear to be as effective in patients with mixed episodes as in those with classic mania (3, 142, 185, 190, 193). Analysis of two RCTs showed that olanzapine had a significant effect on both manic and depressive symptoms in patients with mixed episodes (192). Carbamazepine also reduced depressive symptoms in patients with mixed episodes (103, 212). Evidence also exists supporting the use of ECT in patients with mixed episodes (206, 213, 214).

Rapid cycling

Rapid cycling is reported in about 13–20% of patients with bipolar disorder, and more often in women than in men (195, 215, 216). The definition of four or more episodes per year is largely an arbitrary cut-off, and it is hypothesized that rapid cycling exists on a continuum of cycle lengths (195).

Hypothyroidism, antidepressants and substance abuse may contribute to rapid cycling (195, 215, 216). Thus, it is important to assess thyroid function, and reduce or stop antidepressants, as well as caffeine, nicotine, alcohol and illicit drugs in the presence of rapid cycling (103). Psychotropic agents should be discontinued gradually (103).

There are few controlled treatment trials in patients with rapid cycling. Acute manic episodes should not be treated in isolation in any patient with bipolar disorder, especially in those with rapid cycling. Therefore, appropriate pharmacotherapy should be selected primarily as a maintenance strategy (see Section 5). Lithium and carbamaze-

pine monotherapy appear to be less effective in patients with rapid cycling compared to those without (215, 217, 218). Monotherapy with divalproex (195, 215) or olanzapine (128, 191) appears to be equally effective in patients with and without rapid cycling. The combination of lithium and divalproex has been shown to improve response rates (148, 195, 219). ECT may also prove efficacious in selected cases (215).

Clinical questions and controversies

How long should a medication be tried before adding or switching therapies? Most (122, 128, 131, 132, 141, 142, 153, 220) but not all (127, 152) clinical trials in acute mania have demonstrated superior effects of the active treatment compared with placebo within the first 1–2 weeks. In studies where this did not occur (127, 152, 177), the starting dose of the medication was lower and/or dose titration was slower, so that it took a few days to reach adequate target doses. Given these observations, it is recommended that a pharmacotherapeutic regimen be tried for at least 2 weeks at adequate doses before concluding that the patient is unlikely to respond ($\geq$30% reduction in symptoms).

What is the role of psychosocial treatments in the acute management of mania? Pharmacotherapy is the foundation of treatment for an acute manic episode. However, all patients require some psychoeducation, which should be undertaken once the patient–physician therapeutic alliance is established as discussed in step 1. Evidence suggests that a range of adjunctive psychological approaches offer some benefit during maintenance therapy (84, 86).

In patients successfully treated with a combination of a mood-stabilizer and an atypical antipsychotic, should one be discontinued and if so when? The prophylactic efficacy of lithium (221–229) is well established and there are some research data and a wealth of clinical experience supporting the utility of divalproex (219, 230, 231), however, this is not the case with atypical antipsychotics other than olanzapine (228, 231, 232). In an effort to minimize the side effect burden, it is prudent to minimize the number of medications whenever possible. However, it is also important to recognize that monotherapy may be insufficient to prevent relapses in many patients with bipolar I disorder. A patient's prior history of mood stability on lithium or divalproex monotherapy should serve as a clinical guide as to whether monotherapy is adequate for that individual or combination therapy is required.

Case study

Two years after being diagnosed with bipolar disorder, Sara, now 22 years old, is brought to the emergency department (ED) in an acutely agitated state. During the past week, she has been out every night partying, coming home in the early hours of the morning and sleeping for just 2 or 3 h a night. She was well controlled on lithium for over a year but all of a sudden, she has become increasingly unstable. Sara's mother asked her to see a doctor; she refused and she has become increasingly angry and physically aggressive towards her mother. When assessed in the ED she is fast talking and irritable, but denies having delusions or hallucinations.

- What is your immediate course of action?
- What questions should you ask?
- What is your treatment plan?

Clinical management. You administer an atypical antipsychotic on an as needed basis in order to reduce her acute agitation, and after assessing the degree of danger to herself and others, she is admitted to hospital. When she becomes calmer, you attempt to interview her, asking in particular about adherence to her medication. She denies non-adherence to lithium, claiming that she has been taking her medication everyday. She also vehemently denies drug and alcohol use. Discussion with Sara's mother belies this latter claim, and she says that although the number of pills in the bottle is decreasing she does not know whether Sara is actually taking them.

Assessments of thyroid status and lithium levels reveal no thyroid abnormalities and a lithium level of 0.2 mEq/L. Because she previously had a good response to lithium, you reinstate lithium. Over the course of the next 2 weeks, you see no improvement in her manic symptoms despite treatment adherence to lithium and serum lithium levels around 0.9 mEq/L. You decide to add an atypical antipsychotic at this stage and over the next few days, Sara becomes increasingly more rational and is able to discuss long-term management. She continues to insist that she had been taking lithium until confronted with the laboratory test results. She denies adverse effects but explains that she has read a lot of 'bad things' about lithium and because she had been well for more than a year she thought it would not be necessary for her to continue taking lithium on a regular basis.

You explain the proven benefits of lithium in preventing both depression and mania and preventing suicidal behaviour and hospitalizations. As she had a relapse of a manic episode because of her

poor adherence to lithium, you suggest that lithium remains a good choice to prevent her mood episodes. You also explain to her that continuing the atypical antipsychotic might provide additional benefit in preventing mood episodes. After discussing the risks and benefits of combination therapy, she agrees to continue both drugs. You emphasize the need for her to take lithium even when she feels well and to see her psychiatrist regularly for follow up, and she agrees to do so.

Section 4: Acute management of bipolar depression

Epidemiology of bipolar depression

Although diagnosis of bipolar disorder is based on the presence of hypomania or mania, depressive symptoms and episodes are more frequent over the course of bipolar I disorder. Furthermore, bipolar I patients in treatment experience syndromal/subsyndromal depressive symptoms up to three times more commonly than that of syndromal/subsyndromal manic symptoms (233, 234). Depressive symptoms are even more problematic for bipolar II patients who spend up to 37 times more days experiencing depressive symptoms than hypomanic symptoms (235). More than 50% of bipolar patients experience depression as their index mood episode (236) and patients seek treatment in the depressive state two to three times more often than in the manic state (75).

The depressive phase of bipolar disorder is chronic in 20% of patients (208) and causes more disability and decreased quality of life than any other phase of the illness (42, 234, 235, 237). Even subsyndromal depressive symptoms are associated with functional impairment (42, 238, 239). In rapid cycling bipolar patients, depressive episodes have been found to be more refractory to treatment than hypomanic or manic episodes (240).

Suicidal acts are a major concern in patients with bipolar disorder (48, 52–54), and are associated with severe depressive and mixed phases of illness, higher depression scores, and a greater number of severe depressive episodes (48, 51).

Psychosocial interventions

Although pharmacotherapy is the cornerstone of management of bipolar disorder, there is an important role for psychotherapy and psychoeducation. There are no large controlled trials examining the efficacy of psychosocial interventions in acute bipolar depression either alone or in combination with pharmacotherapy. The evidence to support psychosocial interventions has mainly come from maintenance trials, and most trials enrolled patients in a euthymic or subsyndromal state. However, IPSRT and CBT have demonstrated efficacy in acute unipolar depression, and a pilot trial has shown that CBT had similar efficacy in acute bipolar and unipolar depression (241). Thus, there is some evidence that psychosocial interventions, in combination with pharmacological treatments, can have a positive impact on depressive symptoms and reduce time spent depressed (84–89). Adjunctive psychosocial therapies should be considered early in the course of illness to improve medication adherence, identify prodromes of relapse, potentially decrease residual symptoms (particularly depressive) and help move patients towards a more comprehensive functional recovery (84). In addition, the use of psychotherapy that was tailored to bipolar disorder or intensive clinical management as adjuncts to lithium therapy were associated with significant reductions in suicidal behaviour in high-risk depressed patients with bipolar I disorder compared to prior treatment with lithium alone (90).

Pharmacological treatment of depressive episodes

Lithium, lamotrigine, atypical antipsychotics, divalproex sodium, carbamazepine and other agents, including antidepressants in combination, have been examined for their efficacy in the treatment of acute bipolar depression. These treatments have been evaluated using the criteria for strength of evidence (Tables 1.1 and 1.2) for their use and these are summarized in Tables 4.1 and 4.2.

Step 1: Review general principles and assess medication status. When a patient presents in a depressed state, certain general principles should

Table 4.1. Strength of evidence for monotherapy treatments of acute bipolar depression

Agent	Level of evidence
Lithium	1
Anticonvulsants	
Divalproex	3
Carbamazepine	2
Lamotrigine	1
Gabapentin	2 (−ve)
Atypical antipsychotics	
Olanzapine	2
Quetiapine	2
Risperidone	3
Aripiprazole	–
Ziprasidone	–
Clozapine	3
Other therapies	
ECT	3
Tranylcypromine	2

ECT = electroconvulsive therapy.

Table 4.2. Strength of evidence for combination treatments of acute bipolar depression

Agent	Level of evidence
Lithium + divalproex	2
Lithium + lamotrigine	3
Lithium + carbamazepine	3
Lithium or divalproex + SSRI	2
Lithium + tricyclic antidepressant	2
Lithium or divalproex + bupropion	2
Lithium + MAOI	2
Olanzapine + SSRI	2
Risperidone or quetiapine + SSRI	3
Divalproex + lamotrigine	3
Lithium or divalproex + venlafaxine	2
Adjunctive pramipexole	2
Adjunctive inositol	3
Adjunctive light therapy	3
Adjunctive omega-3-fatty acids	2

MAOI = monoamine oxidase inhibitor; SSRI = selective-serotonin reuptake inhibitor.

be followed (Fig. 4.1). The patient should be assessed for a risk of suicide/self-harm behaviour, ability to adhere to treatment plan, psychosocial support network and the ability to function. Based on these factors, a decision can be made as to whether the patient requires admission to hospital or can be safely managed in an outpatient setting. Behavioural and educational strategies are important to improve symptoms and prevent relapse (see Section 2). In order to direct subsequent therapeutic choices, current therapy should be assessed, including what medications the patient is taking and at what dose.

Step 2: Initiate or optimize therapy and check adherence. In managing an acute depressive episode, the decision to choose monotherapy or combination therapy is based on current and prior medication use (Fig. 4.1), as well as patient factors that may influence prognosis or safety.

In the drug-free patient, therapy should be initiated with one or more of the first-line agents: lithium (level 1), lamotrigine (level 1), lithium or divalproex, plus a selective-serotonin reuptake inhibitor (SSRI) or bupropion (level 2), olanzapine plus an SSRI (level 2), or lithium plus divalproex (level 2) (Table 4.3). Given that quetiapine monotherapy has also shown efficacy in acute bipolar depression, it is possible that quetiapine plus an SSRI will be as effective as olanzapine plus an SSRI (level 3).

For patients who relapse into a depressive episode while on divalproex or atypical antipsychotic monotherapy, addition of an SSRI, bupropion, lamotrigine or lithium, or a switch to lamotrigine or lithium would be appropriate.

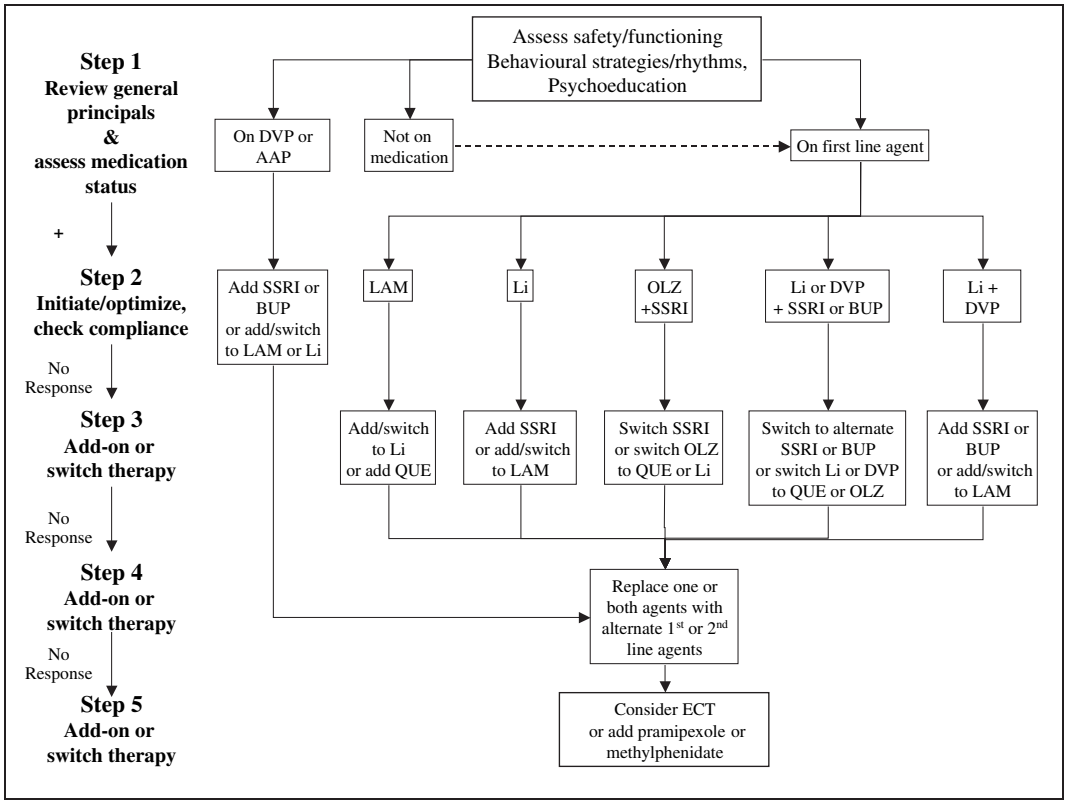

Fig. 4.1. Treatment algorithm for the management of bipolar depression. AAP = atypical antipsychotic; BUP = bupropion; DVP = divalproex; ECT = electroconvulsive therapy; LAM = lamotrigine; Li = lithium; OLZ = olanzapine; QUE = quetiapine; SSRI = selective-serotonin reuptake inhibitor.

Table 4.3. Recommendations for pharmacological treatment of acute bipolar depression

First line	Lithium, lamotrigine, lithium or divalproex + SSRI, olanzapine + SSRI, lithium + divalproex, lithium or divalproex + bupropion
Second line	Quetiapine, quetiapine + SSRI
Third line	Carbamazepine, olanzapine, divalproex, lithium + carbamazepine, lithium + pramipexole, lithium or divalproex + venlafaxine, lithium + MAOI, ECT, lithium or divalproex or AAP + TCA
Not recommended	Monotherapy with gabapentin

AAP = atypical antipsychotic; ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; SSRI = selective-serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

For patients on lithium or lamotrigine, which have established antidepressant efficacy, the first option before adding or switching therapies is to optimize the dose of these medications.

Lithium. As in the previous Canadian guidelines (1997), lithium remains a recommended first-line therapy for acute bipolar depression, with response rates ranging from 64 to 100% (level 1) (87). In one RCT, there were no significant differences between treatments when lithium was used in combination with placebo, imipramine or paroxetine (242). The superiority of antidepressant add-on was only apparent in those that had serum levels below 0.8 mEq/L thus confirming that when lithium is dosed adequately, it has antidepressant efficacy in monotherapy.

Lamotrigine. Two RCTs have demonstrated the efficacy of lamotrigine for the acute treatment of bipolar depression (level 1) (170, 243). About 40–50% of patients responded, which was twice that seen in the placebo group. Further, lamotrigine therapy was not associated with increased risk of manic switch in bipolar depressed patients.

Atypical antipsychotics + SSRIs. In a large RCT, the combination of olanzapine plus fluoxetine was more effective than olanzapine alone or placebo, and olanzapine alone was more effective than placebo in the treatment of bipolar depression without an increase in the development of manic symptoms (level 2) (244). Unfortunately, this trial did not include a fluoxetine-alone treatment regimen, which raises the possibility that the olanzapine plus fluoxetine combination may be no more effective than fluoxetine alone. In a comparison of risperidone and paroxetine combined, risperidone alone and paroxetine alone, there were similar improvements in depressive symptoms in all treatment groups, with no added benefit to the combination (level 2) (245). However, this trial was small, and the dose of paroxetine in the combination group was lower than that in the monotherapy group. Both trials suggest that atypical antipsychotics might have antidepressant effects, but it is possible that clinically they are not robust; therefore, until further data are available, these agents are not recommended as first-line monotherapy for the treatment of acute bipolar depression. Quetiapine has not been assessed in combination, but with evidence of efficacy as monotherapy; it is a recommended second-line choice (see below).

Lithium + SSRIs. The addition of an SSRI (paroxetine) to lithium or divalproex was as effective as combining lithium and divalproex in improving depressive symptoms, in a small RCT (level 2) (246). However, significantly more patients receiving lithium plus divalproex discontinued therapy compared with those receiving either lithium or divalproex plus paroxetine. In a double-blind RCT of imipramine, paroxetine and placebo as adjunct to lithium, antidepressant response did not significantly differ from placebo for patients with high lithium levels, but both paroxetine and imipramine were superior to placebo for patients with low serum lithium levels (242). Thus, antidepressants may be useful as adjunctive therapy for bipolar depressed patients who cannot tolerate high serum lithium levels or who have depressive symptoms that are refractory to lithium (242).

Lithium + divalproex. The combination of lithium plus divalproex was as effective as lithium or divalproex plus an SSRI in improving depressive symptoms in a small RCT (level 2) (246).

Lithium or divalproex + bupropion. In a small RCT, bupropion and desipramine were equally effective when combined with lithium or divalproex in acute and maintenance treatment of bipolar disorder, but bupropion had a much lower manic switch rate (level 2) (247). Bupropion was also as effective as sertraline or venlafaxine when used as add-on therapy in acute and maintenance treatment of bipolar depression, but in this case, manic switch rates were significantly greater in the venlafaxine group (level 2) (248). There is additional uncontrolled evidence to support the role of bupropion in acute bipolar depression (249, 250).

Step 3: Add-on or switch therapy. If optimizing therapy or adding an SSRI, bupropion, lithium, or lamotrigine to an atypical antipsychotic or divalproex therapy is inadequate, therapeutic choices are governed largely by the medication the patient is currently taking (Fig. 4.1). These include adding or

switching to alternate first-line agents or considering second-line options. Quetiapine with or without an SSRI is recommended as an alternate or as add-on to first-line therapies.

Quetiapine. In a large RCT, quetiapine monotherapy was significantly more effective than placebo for the treatment of bipolar depression (level 2) (251). The magnitude of antidepressant effect observed for both quetiapine doses used in the trial was similar to or greater than that reported with lamotrigine (170, 243) or antidepressants (252, 253) in other trials. However, given that this is the only trial available showing antidepressant efficacy of quetiapine, it is premature to recommend it as a first-line monotherapy until the findings are replicated. Quetiapine can be considered a second-line treatment as monotherapy or in combination with an SSRI.

Step 4: Add-on or switch therapy (alternate first- or second-line therapies). Where necessary, steps 2 and 3 should be repeated with further therapeutic choices being based on current medication. Because of the efficacy and relative safety of first- and second-line agents, the use of third-line agents is not recommended until these classes of agents have been tried alone or in combination.

Step 5: Add-on or switch therapy (third-line therapies). In patients who failed to respond to first- and second-line agents, third-line choices would include monotherapy or add-on therapy with olanzapine, divalproex or carbamazepine; combination therapy with lithium or divalproex plus pramipexole or venlafaxine, lithium plus a monoamine oxidase inhibitor (MAOI) or carbamazepine and lithium, divalproex or an atypical antipsychotic plus a TCA, as well as ECT.

Olanzapine monotherapy. Olanzapine monotherapy demonstrated statistically significant, but clinically modest antidepressant effects (level 2) (244) and therefore, is a recommended third-line treatment.

Divalproex monotherapy. In two uncontrolled trials divalproex showed positive results, one in patients with rapid cycling (254), and the other in patients with bipolar II depression (255). At this time, more data are needed to support the use of divalproex in acute bipolar depression (level 3).

Carbamazepine monotherapy. Early, small double-blind trials showed that carbamazepine was more effective than placebo in depressed bipolar patients (level 2) (256, 257).

Lithium or divalproex + pramipexole. In two small RCTs, 60–70% of patients with bipolar I or II depression were responders to pramipexole when used as add-on to lithium or divalproex compared with 9–20% of patients treated with placebo (level 2) (258, 259).

Lithium or divalproex + venlafaxine. In a randomized controlled trial, venlfaxine plus a mood stabilizer was as effective as a mood stabilizer plus paroxetine (253). In a double-blind trial, there were no differences in efficacy between venlafaxine, sertraline or bupropion when added to a mood stabilizer in treating bipolar depression but manic switches were more common in the venlafaxine group (248).

Lithium + MAOI. In two RCTs, tranylcypromine was more effective than placebo or imipramine in the treatment of bipolar depression (level 2) (260–262). However, because of concerns regarding manic switch, MAOIs are recommended in combination with lithium. These agents are generally held in reserve because of the recognized concerns about food and drug interactions. Two RCTs, one in a mixed population of bipolar and unipolar depression (263), and the other in bipolar depression (264), demonstrated that the efficacy of the reversible inhibitor of MAO-A (RIMA), moclobemide was similar to the tricyclic antidepressant (TCA), imipramine (level 2).

Lithium + carbamazepine. This combination is recommended as a third-line option based on evidence for each of the medications as monotherapy and case reports suggesting that carbamazepine plus lithium may be effective in lithium-resistant bipolar depressed patients (level 3) (87).

Lithium, divalproex or atypical antipsychotics + TCA. Imipramine was more effective than placebo, but less effective than fluoxetine for bipolar depression (252). When added to lithium therapy, imipramine was as effective as paroxetine and was superior to placebo for patients with low serum lithium levels (242) but not for those with high levels (level 2). Although specific data are not available, the combinations of divalproex or an atypical antipsychotic with a TCA may also be effective (level 4). However, adverse event rates and rates of switch into mania have been reported to be substantially greater with TCAs compared with SSRIs, suggesting these agents be reserved for only those patients who are not responsive to first-, second- and other third-line options with lower switch rates (265–267).

ECT. Although controlled data are lacking, open studies and clinical experience suggest that ECT is a very effective treatment for acute bipolar depression. In open-label and retrospective studies, response rates ranged from 43 to 100%, and ECT was more effective than antidepressant therapy (level 3) (268). Given this, ECT can be considered earlier in patients with severe psychotic bipolar depression, those at risk of significant medical complications because of non-eating and drinking, and those with a past history of non-response to antidepressants or antidepressant-induced rapid cycling.

Agents not recommended for the treatment of acute bipolar depression. Gabapentin (level 2, negative) and clozapine (level 3) have insufficient data to be recommended as monotherapy for the treatment of bipolar depression. The efficacy of gabapentin suggested by open trials was not borne out in a placebo-controlled RCT in a mixed population of patients with bipolar and unipolar depression (level 2) (170). Clozapine is not recommended for the treatment of acute bipolar depression, because of lack of data supporting antidepressant efficacy (269) and safety concerns (level 3).

Clinical features that can help direct treatment choices

No studies have systematically examined predictors of response to treatment in patients with bipolar depression. However, clinically there are some factors that can help direct treatment choices (87). It is important to consider a patient's history of manic and depressive episodes. For patients with a history of rapid cycling or severe mania, strategies that do not include an antidepressant should be tried first, while for those with severe bipolar depression and a history of mild mania, the use of a combination that includes an antidepressant would be appropriate. When antidepressants are used, SSRIs and bupropion are preferred over TCAs and MAOIs. In patients with mild bipolar depression on maintenance therapy, CBT or psychosocial strategies may be considered before adding adjunctive medications. For patients with bipolar depression and psychotic features, ECT or a combination of an atypical antipsychotic plus an SSRI should be considered early in therapy.

Clinical questions and controversies

In patients successfully treated for a depressive episode with a mood-stabilizer plus an antidepressant, how long should the antidepressant be continued? The risk-to-benefit ratio of the use of antidepressants as adjuncts to mood-stabilizers continues to be an area of controversy. In a meta-analysis of 12 trials, antidepressants were more effective and overall did not induce more switching to mania than placebo (3.8% versus 4.7% with placebo) (267). However, the rate of switching for TCAs was 10% compared with 3.2% for all other antidepressants combined. Other reviews have also reported a higher switch rate with TCAs (265, 266).

An RCT including only the episodes of mania with some dysfunction reported a 12.6% rate of switching in the acute phase and a 17.9% rate over 1 year (270). In a double-controlled trial, hypomanic/manic switch rates were 14% during the first 10 weeks of the trial, and 33% over a 1-year maintenance phase (271). These data suggest that the longer the antidepressant is continued, the greater the risk of switch. However, it has also been reported that the rate of relapse into depression in patients who respond to and continue antidepressants was 35% compared with almost 70% in those who discontinued, with no increase in the rate of switching to mania in the group who continued (272). Data from double-blind, placebo-controlled trials in a large sample of patients for various antidepressant treatments are urgently needed to resolve this issue. In the meantime, for all bipolar I patients with the exception of those with highly recurrent bipolar I depressive episodes, we recommend that clinicians attempt to taper antidepressants within 6–8 weeks of remission of depressive symptoms and discontinue whenever possible.

Are there differences in manic switch rates between newer antidepressants? Results from two trials suggest a higher switch rate for venlafaxine compared with SSRIs and bupropion when used as add-on therapy in RCTs (253). In the first, the rate of switch was 13% with venlafaxine and 3% with paroxetine (253), and in the second a higher risk of manic switch was reported with venlafaxine (38%) compared with sertraline (10%) and bupropion (9%) (248, 270).

Case study

Sara, 25 years old, presents to her family physician (FP) with depression of 2 weeks duration. She moved to the city 3 months ago for a new job, and has felt lonely without her family and friends. During the interview, the FP discovers that she has at least a 5-year history of bipolar disorder and, up until now, had been stable on lithium for the past 3 years.

- Should he refer her to a specialist?

Clinical management. It is important to get Sara's depression under control, but the FP is concerned

about prescribing antidepressants to a patient with bipolar disorder. Worried about manic switch, the FP decides to refer her to a psychiatrist in the new city for further management.

You are her new psychiatrist, and your assessment of Sara indicates that she is moderately depressed but has no psychotic features. Although Sara has suicidal thoughts, she has no plans to kill herself and is willing to enter into a contract regarding self-harm. She has no financial or other concerns, is not abusing any street drugs, and she has a good job, but she has little psychosocial support. She describes her past history of depressive episodes, her diagnosis of bipolar disorder at age 20, and her most recent manic episode 3 years ago. At that time she was treated with lithium and an atypical antipsychotic. She continued the atypical antipsychotic for 6 months but gained a lot of weight. As non-adherence to lithium probably played a role in her manic episode, she and her doctor decided that the atypical antipsychotic may not be necessary for maintenance if she adhered to the lithium regimen, which she says she has been doing faithfully.

You discuss with her a management plan that includes optimizing lithium therapy and helping her learn cognitive behavioural therapy (CBT) strategies to cope with her depression. Over the next 4 weeks, despite adequate serum lithium levels (0.9 mEq/L) and ongoing CBT, she shows little improvement in her symptoms.

You and Sara discuss possible next steps, including (i) adding or switching to lamotrigine, (ii) adding an SSRI antidepressant or bupropion, or (iii) adding divalproex. She agrees to take lamotrigine, which is initiated at 25 mg daily, increased to 50 mg at the end of week 2, and to 100 mg at the end of week 4. She begins to have some symptomatic improvement at week 3, with further improvement at week 5. However, she still has some depressive symptoms and you increase the dose of lamotrigine to 150 mg daily. At week 7, when you see Sara, she appears in good spirits and says she is feeling much better. You continue to be concerned with her lack of a support system, and provide her with information on local community support groups for people with bipolar disorders. You agree to continue to see her for maintenance treatment and at each visit you discuss treatment adherence and side effects of medications.

Section 5: Maintenance therapy for bipolar disorder

Need for long-term strategies

Estimated recurrence rates of 60–80% after discontinuation of lithium or antipsychotic therapy and 20–50% during ongoing therapy have been reported (225, 226, 228, 229, 232, 273–275) for bipolar disorder. In addition, a substantial proportion of patients with bipolar disorder, even those who undergo intense monitoring and treatment of acute episodes will experience considerable residual illness-related morbidity. As a result, the long-term treatment goals include not only preventing suicidal behaviour and recurrence of syndromal depression and mania, but also improving subsyndromal symptoms, treatment adherence, quality of life, cognition and functional outcomes.

Comorbid substance abuse, mood-incongruent psychotic features and a family history of schizoaffective disorder with manic features are risk factors for recurrence (276). Data indicate that more previous episodes are associated with future episodes (277), decreased quality of life and functioning (278), poorer response to treatment (279) and longer hospitalization (280). It has also been suggested that cumulative structural changes in the brain (281) may be a consequence of multiple episodes and are associated with cognitive impairment (282–284). These consequences of multiple episodes argue in favour of initiating preventive therapy early, even after the first episode.

Terminology

Several terms are used when discussing the long-term treatment of bipolar disorder. For example, 'relapse' and 'recurrence' refer to the return of symptoms, respectively, in the same or a new episode (285). However, there is little consensus on what that duration should be, and these episodes do not appear to differ in terms of how they respond to maintenance therapy. Therefore, these guidelines will use only the term recurrence to describe re-emerging episodes of mania or depression. Similarly, the terms 'continuation' and 'maintenance' have been used to define therapy during the early stable phase and the long-term prophylactic phase respectively (276, 285). Although there may be a higher probability of recurrence during the early period after an acute episode (285), these guidelines will refer to all prophylactic therapy after stabilization of acute manic or depressive episodes as maintenance therapy.

Adherence

According to prospective data, one in three patients with bipolar disorder fails to take at least 30% of prescribed medication (286). In bipolar disorders, non-adherence to treatment has been identified as an important cause of recurrence (287) and is

Table 5.1. Factors negatively influencing treatment adherence (118)

Patient factors
Younger age
Single status
Male gender
Low education level
Lack of psychosocial support
Illness factors
Hypomanic denial
Psychosis
Comorbid personality disorders
Comorbid substance abuse
Poor insight
Treatment factors
Side effects of medications
Unfavourable personal attitudes towards treatment

Table 5.2. Characteristics of effective therapies that maximize adherence (118)

Education
Self-monitoring
Recurrence prevention
Managing side effects
Identifying and managing stressors
Addressing belief system and attitudes to illness

associated with higher rates of both hospitalization (288) and suicide (289). Recognizing the factors that have a negative impact on adherence to therapy might help target interventions towards patients at risk of discontinuation (Table 5.1) (118).

Among the methods to enhance treatment adherence, interventions that include both patient and family members, those that incorporate a good understanding of the disorder, the medications and their side effects, and those that are integrated into a long-term management plan can have beneficial effects [reviewed by Sajatovic et al. (118)] (Table 5.2). Interventions that include family only, without participation of the patient, do not appear to impact adherence (290). Psychotherapeutic interventions found to be effective in enhancing adherence include interpersonal group therapy, CBT, and patient and family psychoeducation (see below) (118).

General principles

Currently, limited data exist to predict which patients will respond to which medications. Even for the most investigated treatments, such data are from retrospective evaluations. As many first-line treatments of manic or depressive episodes have also been shown to have prophylactic efficacy, it is generally wise to continue the index medication used for the acute episode. For those bipolar patients who are currently not on treatment, the essential starting point would be a careful history including details of clinical course, response (or lack thereof) to previously used medications and family history. Other variables should also be considered: the predominant polarity of the illness so far and whether the most recent episode was manic or depressive are particularly relevant. Because the depressive pole predominates in most bipolar patients (233, 291) and suicidal behaviour is over represented in this population (44–54), careful consideration should first be given to prescribing lithium, both on the strength of evidence for its role in bipolar prophylaxis and also because of its antisuicidal effects (60–63). Furthermore, as suicidal behaviour is more common when patients are experiencing syndromal/subsyndromal depressive episodes (48, 53), it is recommended that depressive symptoms be treated aggressively with appropriate first-, and where necessary, second-line treatments.

Although pharmacotherapy is the cornerstone of management of bipolar disorder, adjunctive psychotherapy or psychoeducation should be provided early in the course of illness to improve medication adherence, identify prodromes of recurrence, impart coping strategies to decrease residual symptoms and suicidal behaviour, and help move patients towards a more comprehensive functional recovery (84–96, 100–102, 292, 293).

The importance of follow up cannot be over emphasized, as it is crucial in enhancing patient adherence, detecting early symptoms of recurrence and monitoring side effects.

Psychosocial interventions

Psychoeducation (level 2). Psychoeducation should emphasize the importance of lifestyle regularity and healthy habits, early detection of prodromal signs and treatment adherence (88). In two RCTs, group psychoeducation added to pharmacotherapy delayed the time to recurrence, irrespective of the nature of the prior episode and reduced hospitalizations over a 2-year follow up (88, 91). In a third trial, psychoeducation aimed at teaching patients to recognize prodromal symptoms of recurrence was associated with prolongation of time to first manic recurrence, as well as improved social functioning and employment, but had no effect on depressive recurrence (92).

A significant reduction in suicidal behaviour in high-risk patients with bipolar I disorder has been demonstrated when patients were treated with adjunctive bipolar focused psychotherapy in a very supportive clinical environment (90), or in a specialized programme during lithium therapy (60, 63, 294). Group psychoeducation has also

been reported to improve quality of life and functioning in bipolar patients (293).

Cognitive-behavioural therapy (level 2). Controlled trials have demonstrated decreased recurrences, mood fluctuations, need for medications and hospitalizations, and increased functioning and treatment adherence with the use of concurrent CBT and mood-stabilizers compared to treatment as usual or wait-listed controls (93–95). In one study the benefits of CBT were clinically significant in those that had six or fewer episodes but not in those with more than six episodes (295).

Family therapy (level 2). Family-focused treatment in combination with pharmacotherapy has also been shown to reduce recurrences and hospitalizations and also improve depressive symptoms and medication adherence to a greater extent than individual therapy or a family crisis management intervention (100–102).

Interpersonal and social rhythm therapy (level 2). Interpersonal and social rhythm therapy, a modified form of interpersonal psychotherapy, focuses on four problem areas (grief, interpersonal role transition, role dispute and interpersonal deficits) with the objective of identifying interpersonal problems and providing therapy to stabilize social rhythms. Although a large controlled trial failed to demonstrate that IPSRT prolonged time to recurrence better than intensive clinical management (96), subsequent analysis showed that IPSRT did have a significant impact on subsyndromal symptoms, and patients spent more time euthymic and less time depressed (97).

Pharmacological treatments for maintenance therapy

The evidence base for effective maintenance therapies is most comprehensive for lithium, lamotrigine, olanzapine, and to a lesser degree for divalproex. Some data are also available for carbamazepine and for combination therapies. To date, there are no long-term RCT data for other atypical antipsychotics including risperidone and quetiapine, or other anticonvulsants including oxcarbazepine, topiramate and gabapentin. Maintenance treatments evaluated on strength of evidence for their use (Tables 1.1 and 1.2) are summarized in Tables 5.3 and 5.4.

First line. Lithium, lamotrigine, divalproex and olanzapine have the most data to support their use as first-line therapies for the maintenance treatment of bipolar disorder (Table 5.5).

Table 5.3. Strength of evidence for efficacy of maintenance monotherapy for bipolar mania

Agent	Level of evidence
Lithium	1
Anticonvulsants	
Divalproex	2
Lamotrigine	Depression: 1 Mania: 2
Carbamazepine	2
Gabapentin	4
Topiramate	4
Oxcarbazepine	4
Atypical antipsychotic	
Olanzapine	2
Aripiprazole	Mania: 2
Risperidone	3
Quetiapine	3
Clozapine	4
Other treatments	
ECT	4
Tricyclic antidepressants	2 (−ve)

ECT = electroconvulsive therapy.

Table 5.4. Strength of evidence for efficacy of maintenance combination therapy for bipolar mania

Agent	Level of evidence
Lithium + divalproex	2
Lithium + carbamazepine	2
Lithium or divalproex + olanzapine	2
Lithium or divalproex + risperidone	3
Lithium or divalproex + quetiapine	3
Lithium or divalproex + clozapine	3
Lithium + TCA	2 (−ve)
Lithium + SSRI	3
Lithium or divalproex + oxcarbazepine	3
Lithium or divalproex + omega-3-fatty acids	2
Adjunctive phenytoin	3
Adjunctive gabapentin	3
Adjunctive topiramate	3
Lithium or divalproex + ECT	3
Lithium + flupenthixol	2 (−ve)

ECT = electroconvulsive therapy; SSRI = selective-serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Table 5.5. Recommendations for maintenance pharmacotherapy of bipolar disorder

First line	Lithium, lamotrigine monotherapy (mainly for those with mild manias), divalproex, olanzapine
Second line	Carbamazepine, lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, aripiprazole, risperidone, quetiapine, ziprasidone, lithium + risperidone or quetiapine, lithium + lamotrigine or an SSRI or bupropion
Third line	Adjunctive phenytoin, clozapine, ECT, topiramate, gabapentin, omega-3-fatty acids, oxcarbazepine
Not recommended	Adjunctive flupenthixol, monotherapy with gabapentin, topiramate, antidepressants

ECT = electroconvulsive therapy; SSRI = selective-serotonin reuptake inhibitor.

Lithium. There is good evidence to support lithium monotherapy in the maintenance treatment of bipolar disorder from meta-analyses (221–223) and RCTs (224–229) (level 1). A meta-analysis of studies conducted prior to 1990 suggested that the magnitude of prophylactic benefit with lithium is greater for the prevention of manic episodes than for depressive episodes (45). This was confirmed in recent RCTs that showed clear benefit in preventing mania but not depression (225, 229). Lithium has also been shown to have antisuicidal properties (60–63).

Rapid discontinuation of lithium is followed by a high rate of recurrence in bipolar patients even after good response and a lengthy illness-free period (273). If lithium is discontinued, it should be done gradually, as abrupt discontinuation appears to be associated with a higher rate of recurrence (296, 297).

Lamotrigine. Three RCTs have demonstrated the efficacy of lamotrigine for the prevention of recurrence of bipolar disorder in patients with most recent episode manic, most recent episode depressed or rapid cycling patients (level 1) (225, 229, 275). Lamotrigine has demonstrated efficacy that was superior to placebo in prolonging time to intervention for any episode and for depressive episodes, but not for manic episodes. Hence, lamotrigine should not be used as a monotherapy for bipolar patients if prevention of recurrence of mania is a major objective. Lamotrigine appears to be beneficial in those with bipolar II disorder with rapid cycling (275), and in such cases, lamotrigine monotherapy is appropriate.

Divalproex. Although one RCT failed to demonstrate that divalproex was superior to placebo in preventing recurrence of bipolar episodes (298), in three other RCTs divalproex was as effective as lithium (219, 230) or olanzapine (231) in the prevention of recurrence. In the placebo-controlled trial, neither lithium nor divalproex showed superiority on the primary efficacy measure (298). However, a sub-analysis showed that divalproex was superior to placebo in severely ill bipolar patients, and was associated with a longer time to discontinuation for depression. The fact that two double-blind studies (219, 231), and an open controlled study (230), showed equivalency of divalproex and active comparators, together with the wealth of experience and good tolerability of this medication, led to the conclusion that divalproex should be considered as a first-line treatment option (level 2).

Olanzapine. Olanzapine treatment delayed recurrence in bipolar disorder, significantly reduced rates of both manic and depressive episodes compared with placebo (232) and was found to be as effective as both divalproex (231) or lithium (228) in prolonging remission (level 2).

Second line.

Carbamazepine. There are no large-scale, double-blind, placebo-controlled trials examining the efficacy of carbamazepine in the maintenance treatment of bipolar disorder. However, most, but not all, studies have shown that carbamazepine has similar efficacy to that of lithium (197, 224, 299, 300) and might provide better prophylactic efficacy than lithium in patients with non-classical presentations of bipolar mania (e.g. mood-incongruent features, comorbidities and bipolar II disorder) (level 2) (300).

Other atypical antipsychotics. Aripiprazole significantly prolonged the time to recurrence, and significantly decreased the number of mood episodes compared with placebo in a 6-month RCT (level 2) (301). However, a sub-analysis showed that aripiprazole was superior to placebo in preventing mania but not depression. Therefore, at present, it is recommended as a second-line treatment for bipolar patients with predominantly manic episodes.

There are no double-blind RCTs examining the long-term efficacy of risperidone, quetiapine or ziprasidone for bipolar disorder. Open-label data suggest that risperidone may be effective in sustaining improvement of bipolar disorder when used in combination with lithium/divalproex (level 3) (302–305) or topiramate (level 3) (306). Quetiapine alone or as add-on to mood-stabilizers (level 3) (307, 308) and ziprasidone monotherapy have also reported long-term improvements in open-label trials (level 3) (309).

Because aripiprazole and ziprasidone are not currently available in Canada, and the guidelines group has only limited clinical experience with these agents, recommendations for their use as maintenance treatments are based largely on the reported efficacy data and adverse event profile of these agents.

Combination therapy. Combination therapy is an important option for patients who have failed adequate trials of first-line monotherapy. However, there are no systematic comparisons of switching to alternate monotherapy versus using a combination of treatments, and there is little evidence to recommend one combination over another. Combinations that have demonstrated some efficacy include: lithium plus divalproex (level 2) (310, 311)

or carbamazepine (level 2) (197); as well as lithium or divalproex plus olanzapine (level 2) (312) or risperidone (level 3) (302–304). No data are available on lithium plus lamotrigine, but this combination is recommended based on the proven prophylactic efficacy of the two medications as monotherapies.

Third line.

Clozapine. Adjunctive treatment with clozapine was significantly better than treatment as usual in a small RCT of 12 months duration (level 3) (269). In addition, evidence from the schizophrenia literature demonstrating that clozapine has antisuicidal properties suggests a role for this agent in some patients with bipolar disorder (313).

ECT. Evidence from case series suggests that maintenance ECT (usually adjunctive to medication) is effective in reducing hospitalizations in bipolar disorder (level 3) (314). However, a review of data concluded that ECT had an acute but not a long-term beneficial effect on suicidality in patients with mood disorders (315).

Other agents. Open-label and preliminary data support the use of adjunctive oxcarbazepine (level 3) (316, 317) or phenytoin (level 3) (318). Open trials have also suggested the efficacy of topiramate as add-on to mood-stabilizers (level 3) (319, 320) or atypical antipsychotics (level 3) (306, 321). Ongoing, adjunctive gabapentin was effective for some patients who had responded to this agent acutely, but 30% of patients experienced a loss of efficacy over time (level 3) (322). In a 4-month, RCT, omega-3-fatty acids prolonged the time in remission compared with placebo (level 2) (323).

Not recommended.

Benzodiazepines. A systematic evaluation of benzodiazepines as prophylactic agents in bipolar disorder has not yet been conducted (276), but issues such as dependence, rebound anxiety, memory impairment and discontinuation syndrome argue against their long-term use (324). The absence of prophylactic efficacy and attendant risks associated with long-term use support the gradual titration of these agents to either discontinuation or to the lowest effective dose for essential symptomatic management (276).

Antidepressant monotherapy. Although antidepressants have efficacy in acute depressive episodes, a review of seven RCTs of antidepressants (predominantly TCAs) as monotherapy or adjunctive treatment concluded that they were ineffective in the prevention of future episodes (325). In a seminal maintenance study reported in 1973, manic episodes occurred in 12% of patients on lithium, 33% of patients on placebo, and 66% of patients on imipramine monotherapy (326). In another study of 1 year duration, 50% of patients randomized to desipramine as add-on to mood-stabilizers experienced a manic switch compared with only 11% of patients randomized to bupropion add-on treatment (247). These data clearly suggest that TCAs destabilize the course of bipolar disorder whether used in monotherapy or in combination with lithium or divalproex.

No double-blind, placebo-controlled trials have examined the efficacy of SSRI monotherapy for the maintenance treatment of bipolar disorder. However, in a 1-year clinical trial comparing lithium, divalproex and placebo, in which patients received SSRIs for breakthrough-depressive episodes, a significantly greater proportion of patients discontinued the study in the SSRI plus placebo group compared with the SSRI plus divalproex group (327). Therefore, SSRI monotherapy is also not recommended for maintenance treatment of bipolar disorder.

Other treatments. Flupenthixol does not appear to have prophylactic efficacy in patients with bipolar disorder (level 2, negative) (328, 329). Perphenazine in combination with a mood-stabilizer was not superior to mood-stabilizer alone, and in fact had led to increased incidence of depressive episodes in bipolar disorder (330). Agents such as gabapentin, topiramate and calcium channel blockers have been investigated for use in bipolar disorder, but insufficient data exist to recommend their use as monotherapy.

Clinical features that can help direct treatment choices

Psychoeducational interventions are an essential part of long-term management of bipolar disorder for all patients. Lithium has the best evidence of prophylactic efficacy in bipolar disorder, preventing both manic and depressive episodes and having important antisuicidal effects. Olanzapine, divalproex and lamotrigine have proven long-term benefits, with olanzapine and divalproex perhaps being more suitable for patients with manic recurrences, while the efficacy of lamotrigine appears to be mainly in the prevention of depressive recurrences. Lamotrigine should not be used as monotherapy in patients with a history of severe or frequent manic episodes.

Predictors of response to maintenance treatment have been investigated to a varying degree for different medications. While there are more and better data for predictors of response to lithium (331), the data for other maintenance treatments are limited. Lithium can be considered the treatment of choice in patients with typical bipolar disorder, an episodic clinical course, low rates of psychiatric comorbidity, and those who have a family history of lithium-responsive bipolar disorder.

For patients with rapid cycling, lithium, lamotrigine and divalproex have demonstrated efficacy, but it is likely that most patients will require a combination of treatments. The atypical antipsychotics have demonstrated equal efficacy in patients with and without rapid cycling in acute studies, and likely would be useful add-on therapies in long-term management.

Few patients manage a lifetime of bipolar disorder with monotherapy. Most require short- or long-term combination therapy with lithium, divalproex, atypical antipsychotics, antidepressants, lamotrigine and/or ECT. Serum levels of medication and other monitoring of bodily systems should be conducted as clinically indicated, but no less than once every 6 months (see Section 8).

Bipolar disorder with rapid cycling

Rapid cycling, which occurs in approximately 20% of patients with bipolar disorder (216, 217, 332), is associated with greater severity of illness on a number of clinical measures (333).

First line. As shown in Table 5.6, lithium, lamotrigine and divalproex are recommended first-line therapies for the long-term management of patients with bipolar disorder and rapid cycling.

Lithium. Although rapid cycling has been reported to be associated with a poorer response to lithium therapy (334), a meta-analysis of long-term treatment found that rapid cycling was associated with a poorer response to all treatments evaluated (level 2) (332).

Table 5.6. Pharmacological maintenance treatment of bipolar disorder with rapid cycling

First line	Lithium, lamotrigine, divalproex
Second line	Lithium + divalproex, lithium + carbamazepine
Third line	Lithium or divalproex + topiramate, olanzapine, quetiapine, risperidone, clozapine, oxcarbazepine, levothyroxine
Not recommended	Antidepressants

In a placebo-controlled RCT, patients on lithium experienced numerically, but not significantly lower rates of recurrence (level 2) (335). In the first of two trials against active comparators, lithium was as effective as carbamazepine but less effective than a combination of the two drugs (197). In the second trial, patients with rapid cycling who had a persistent response to the combination of lithium or divalproex were randomized to monotherapy with one of the agents (219). There were no significant differences in rates of recurrence of depression or mania/hypomania in patients treated with lithium or divalproex.

Based on overall prophylactic and antisuicidal effects in patients with bipolar I disorder, lithium is recommended as a first-line therapy, but it is likely that patients with rapid cycling will require a combination of treatments for maintenance therapy.

Lamotrigine. In a 6-month placebo-controlled RCT there were no significant differences in the primary end point of time to additional interventions between lamotrigine and placebo. However, there was a significantly lower rate of recurrence in the lamotrigine group (59%) compared with the placebo group (74%) (level 2) (275). The difference in recurrence rates was not significant for patients with bipolar I, but was significant for patients with bipolar II (54% versus 82% with lamotrigine versus placebo). Therefore, lamotrigine may be useful in monotherapy for patients with bipolar II and rapid cycling, but combination with lithium or divalproex may be required in patients with bipolar I.

Divalproex. As discussed above there were no significant differences in recurrence rates in patients with rapid cycling treated with lithium or divalproex (level 2) (219). Rates of recurrence into mood episodes with divalproex and lithium were: 50% versus 56% overall, 29% versus 34% into depression, and 22% versus 19% into hypomania/mania, respectively. However, median survival in the trial was longer on divalproex compared with lithium. Evidence from open case series provides additional support for the use of divalproex in rapid cycling bipolar disorder (334, 336).

Second line.

Lithium + divalproex. Although no long-term data are available, the combination of lithium and divalproex has been used effectively to stabilize patients with rapid cycling (level 4) (219).

Lithium + carbamazepine. In an RCT comparing the prophylactic efficacy of lithium, carbamaze-

pine and their combination, the sub-group of patients with a past history of rapid cycling did poorly on either monotherapy but significantly better on the combination (level 2) (197).

Third line.

Lithium or divalproex + topiramate. Open-label add-on topiramate demonstrated some efficacy in patients with rapid-cycling (level 3) (319).

Atypical antipsychotics. In acute treatment of mania, monotherapy with olanzapine (128, 191) or aripiprazole (337) appears to be equally effective in patients with and without rapid cycling. Risperidone was shown to effectively decrease the number of affective episodes in a series of 10 patients with rapid cycling followed for 6 months (level 3) (338). A case series of patients with rapid cycling receiving quetiapine as adjunctive therapy for up to 1 year reported that patients had early improvements in manic and depressive symptoms, but that 70% of patients dropped out, including 27% for lack of efficacy and 7% for depression or mixed episodes (level 3) (308). In a series of patients treated with clozapine as adjunct to mood-stabilizers, more than 80% showed at least some improvement over the 1-year study (level 3) (339). Clozapine was more effective in non-rapid cyclers than in those with rapid cycling. However, long-term safety concerns limit the use of clozapine (291).

Some data suggest a relationship between hypothyroidism and current but not lifetime rapid cycling, suggesting that thyroid dysfunction may contribute to mood destabilization (195, 216). This is supported by evidence from open trials that levothyroxine enhances maintenance therapy in some patients with rapid cycling (level 3) (340–345). Levothyroxine may be useful in combination with other agents in patients who are refractory to other treatments (346). In addition, some data suggest that bipolar II patients who became rapid cyclers as a result of lithium failure might benefit from thyroid augmentation in selected cases (195). However, studies have found no difference in thyroid hormone levels in those with versus those without rapid cycling (347, 348).

Bipolar disorder with mixed episodes

Although there have been relatively few studies to assess the role of various medications in the maintenance management of patients with mixed episodes, it is likely that these patients will require combination therapy to best address both depressive and manic symptoms. Two RCTs provide supportive evidence for olanzapine in this population.

Patients with a mixed index episode randomized to olanzapine maintenance therapy had significantly lower recurrence rates (59%) compared with those assigned to placebo (91%) over a 1-year follow up (level 2) (349). In a comparison of olanzapine and divalproex in which almost half of the patients had a history of mixed episodes, a lower rate of recurrence of mixed episodes was reported with olanzapine (1 of 14 episodes) than divalproex (3 of 13 episodes) (231).

In a sub-group of recently manic or hypomanic patients who were randomized to lithium, lamotrigine or placebo in an RCT, recurrence of mixed episodes was numerically greater with lamotrigine (4 of 28 episodes) or placebo (6 of 49 episodes) than with lithium (2 of 10 episodes) (level 3) (229).

There is also preliminary support from a post hoc analysis of an RCT that carbamazepine (212) and from an open trial that oxcarbazepine (317) may be effective in patients with mixed episodes (level 3).

Clinical questions and controversies

Should maintenance pharmacotherapy be discontinued, and if so, when? Maintenance pharmacotherapy is recommended for all patients with bipolar disorder who have had at least one moderately severe manic episode. For patients who refuse maintenance therapy, psychosocial strategies should include a clear discussion of risks and benefits associated with maintenance therapy. In those who refuse, the effective acute-phase dosages should be continued for at least 3–6 months. Attempts to simplify the medication regime should not be made until several weeks of stability have passed, and if a medication is discontinued, it should be tapered slowly, usually by no more than 25% per week (350). Medications should be reinstated promptly if symptoms recur.

Discontinuation of lithium appears to be followed by a high rate of recurrence in patients with bipolar disorder, even after a prolonged period of well-being (273, 296, 297). Rates of recurrence during the first 40 weeks after lithium discontinuation were much higher (58%) than in the year before treatment was discontinued (21%) (274).

Benzodiazepines, if used, must be weaned gradually. If an antidepressant has been used to treat an acute depressive episode, it should be continued at the same dose for 1–3 months following symptom resolution. Although this is a subject of much debate, generally this will mean discontinuing antidepressants after 3–6 months of use.

It may be appropriate to discontinue one or more maintenance pharmacotherapies before or during pregnancy or the postpartum period in some cases.

When is it appropriate to use lamotrigine in combination with lithium, divalproex or an atypical antipsychotic? Although lithium has demonstrated efficacy for the prevention of both manic and depressive episodes, it is better at preventing manic episodes. Similarly, divalproex and the atypical antipsychotic olanzapine have demonstrated prophylactic efficacy, and it is likely that the magnitude of benefit is greater against manic episodes. The prophylactic efficacy of lamotrigine, on the other hand, is greater for the prevention of depressive episodes. Although the use of lamotrigine in combination has not been studied, it may be useful for patients whose manias are well controlled on lithium, divalproex or an atypical antipsychotic, but are having depressive relapses.

In addition, there is little concern regarding the safety of combining lithium or atypical antipsychotics with lamotrigine. However, caution should be exercised when combining lamotrigine and divalproex, because divalproex doubles the serum levels of lamotrigine (351), and rapid up-titration of lamotrigine in those that are on divalproex can increase the risk of skin rash and Stevens–Johnson syndrome (352–354). Carbamazepine can reduce the levels of lamotrigine by up to half, and thus potentially decrease its efficacy (355).

Case study

Sara, 29 years old, has at least a 9-year history of bipolar disorder. She has recently returned to your clinic after living in another city for 4 years. During the past 2 years, the pressure of her job and the lack of family support have contributed to poor eating and sleeping habits; she has taken up smoking, and has been suffering from increasing mood instability: she has had at least four significant mood episodes in the past year. She stopped taking lamotrigine 3 years ago but continued to take lithium on an irregular basis. She lost her job because of some bizarre behaviour and frequent absenteeism when she felt 'so depressed that she couldn't get out of bed'. Since moving home with her parents, she says she would like to 'get well and rebuild her life'.

Sara has developed a rapid cycling course and is currently in a mixed state, describing bouts of anxiety, crying and irritability occurring in the same day with racing thoughts, increased energy and agitation. At the same time, she has no motivation, feels hopeless and has thoughts about suicide. She has multiple stressors in her life including no job, nicotine dependence and the need to regain her family's trust. She feels that her family 'blames' her for being in this state.

- What is your immediate course of action?
- What questions should you ask?
- What is your treatment plan?

Clinical management. Bipolar disorder is a chronic condition with frequent recurrences, in some cases despite maintenance treatment with one or more medications. It is important to first re-establish a therapeutic alliance with Sara and re-emphasize the chronic nature of her illness. Thinking about normal biorhythms, you first explain to her the importance of a regular routine and adherence to medication. Thyroid hormones are normal but lithium levels are low at 0.44 mEq/L. She recalls taking lamotrigine to help her depression a few years ago. She had a good response but discontinued when the prescription ran out. She also attended five or six weekly sessions of group therapy, which she felt helped but they took up too much time, so she stopped attending.

You assess her suicide risk; although she thinks it would not matter if she did not wake up tomorrow, she does not have any plans to harm herself and has made no past attempts. You discuss a management plan that includes optimizing pharmacotherapy and meeting family members to enhance psychosocial support. Over the next 3 weeks, despite optimizing lithium therapy (serum lithium level is now 0.84) and ongoing psychosocial support, she shows little improvement in her symptoms.

You discuss a number of treatment options with Sara including: (i) adding or switching to divalproex, (ii) adding lamotrigine or (iii) adding olanzapine. You review the risks and benefits of each strategy. Based on the discussion she decides to take divalproex in addition to lithium. Within 2 weeks she begins to have some symptomatic improvement, which continues over the next few weeks. After 4 weeks on the combined treatment, Sara appears in good spirits and says she is feeling much more stable. You ask her to make a list of the signs and symptoms of the onset of a depressive and a manic episode and ask her to bring her mother to the next appointment. Together, the three of you make a contract regarding what steps should be taken if Sara shows any of the identified signs of recurrence of an episode.

Section 6: Special populations

Issues in the management of bipolar disorder in women

Pregnancy, lactation and the use of oral contraceptives are just some of the issues that complicate the management of bipolar disorder in women. As 50%

Table 6.1. Planning for pregnancy

Counselling for all women of child-bearing age
Document birth control method (357)
Discuss risks of medication exposure during pregnancy
Enquire about pregnancy plans
Emphasize need for pre-pregnancy consultation
Birth control
Discuss effects of medications on OC efficacy
Carbamazepine and topiramate decrease levels of OCs (358)
OCs decrease lamotrigine levels by 49% and lamotrigine could potentially decrease contraceptive efficacy (359)
No known OC interactions with divalproex, lithium, gabapentin or atypical psychotics (360)
Pre-pregnancy counselling
Provide prenatal counselling at least 3 months before pregnancy
Discuss risks of medications during pregnancy, risk to child and mother of antenatal recurrences, and genetic transmission (361)
Develop management plans including treatment of recurrence during and after pregnancy (362)
Consider a pregnancy contract
Medication use
Prior to conception, consider that conventional antipsychotics and risperidone increase prolactin and may decrease fertility (363)
Stable patients may be able to discontinue one or more medications before attempting to conceive and during first trimester (364–366)
Assess response to gradual pregravid tapering of medication
If medication is required, use monotherapy at minimally effective doses, if possible (361, 363)
Assess patient's risk of recurrence and avoid medication during pregnancy especially during first trimester, if possible (361)

OC = oral contraceptive.

of pregnancies are unplanned (356), it is important that women with bipolar disorder receive education early in the course of illness about the effects of mood stabilizing and other medications on contraceptive effectiveness, as well as the need to plan medication management during pregnancy and the postpartum period (Table 6.1). It is recommended that the physician and patient enter into a pregnancy contract, which includes an explanation of the risks (teratogenic effects) and benefits (prevention of recurrence) of medication to the patient and the fetus before and during pregnancy. In case of recurrence, the contract will offer provisions for agreed-on treatments for specified symptoms depending on the trimester of pregnancy.

Management of acute depressive and manic episodes during pregnancy. Little data are available on the use of medications for the acute management of depression or mania in pregnant women with bipolar disorder. Treatment of breakthrough episodes should follow the guidelines for all patients (see Sections 3 and 4), with additional considerations about teratogenicity of medications (Table 6.2), as well as the risks of untreated episodes to both the mother and the child. When possible, mild-to-moderate episodes should be managed using psychosocial approaches during the first trimester to minimize the risk of teratogenicity.

Table 6.2. Medications and teratogenicity

Drugs	FDA classification	Overall risk of major congenital malformations in humans: reported events
Base rate: no drugs		2–4%
Lithium (357, 361, 367–369)	D	4–12%: Ebstein's anomaly (tricuspid valve malformation) (0.1%, risk 20 times higher than general population), polyhydramnios, premature delivery, floppy baby syndrome, thyroid abnormalities, perinatal mortality, diabetes insipidus
Divalproex (361, 362, 370)	D	11%: spina bifida and neural tube defects, fetal anticonvulsant syndrome, cardiovascular defects, cerebral haemorrhage, developmental delay, intrauterine growth retardation, coagulopathies
Carbamazepine (361, 362, 370–375)	D	5.7%: spina bifida and neural tube defects, fetal anticonvulsant syndrome, coagulopathies, cerebral haemorrhage, craniofacial defects, fingernail hypoplasia, developmental delay. Increased risk when administered with divalproex
Lamotrigine (361, 376, 377)	C	2.9%: pregnancy registry (n = 414 monotherapy exposures) showed no increased risk of teratogenicity; 12.5% rate in combination with divalproex. Teratogenic effects reported in animals
Gabapentin (360, 361)	C	No data: fetotoxic effects in rodents
Topiramate (360, 361)	C	No data: craniofacial and skeletal anomalies, decreased fetal weight in animals; reports hypospadias in male infants
Olanzapine (362, 378)	C	No data: pregnancy registry (n = 96 exposures) showed no increased risk of teratogenicity
Risperidone (360, 361)	C	No data: one case report of agenesis of corpus callosum; fetotoxic in animals
Quetiapine (360)	C	No data
Ziprasidone (360)	C	No data: developmental toxicity, possible teratogenic effects in animals
Clozapine (362, 379)	B	Not available: no evidence of increased risk of teratogenicity

US Food and Drug Administration's use-in-pregnancy ratings: A = controlled studies show no risk; B = no evidence of risk in humans; C = risk cannot be ruled out (human data lacking; animal studies positive or not done); D = positive evidence of risk (benefit may outweigh risk), X = contraindicated in pregnancy (360).

Table 6.3. Maintenance pharmacotherapy during pregnancy

Drug	Recommendations for use in pregnancy
Lithium	52% recurrence rate after discontinuation, lower with gradual withdrawal (274) Avoid during first trimester if possible (362) Recommendations for lithium use (367): Mild stable: gradual (>2 weeks) withdrawal pre-pregnancy and plan for pregnancy without maintenance treatment if appropriate Severe, moderate risk recurrence: consider risks and benefits; if possible avoid at least during first trimester if clinically appropriate Severe, high risk of recurrence: maintain lithium if patient is agreeable, counsel on risk of teratogenicity Serum levels may be lowered by pregnancy, regularly monitor (357)
Divalproex	Avoid during pregnancy and/or first trimester, if possible (362) Decrease risk by using <1000 mg/day (serum levels <70 μg/mL) in three or more divided doses (370, 387) Monitor divalproex levels (361) Vitamin K-12 supplementation in last month of pregnancy and to neonate (361, 388) Folate supplementation while attempting conception and during first trimester (375)
Carbamazepine	Avoid during pregnancy and/or first trimester if possible (362) Use as monotherapy if necessary, in divided doses (361) Folate supplementation while attempting conception and during first trimester (375) Vitamin K-12 supplementation in last month of pregnancy (361, 375) Women started after conception are at higher risk of serious side effects (agranulocytosis, hepatic failure, Stevens–Johnson syndrome) (389)
Lamotrigine	Caution during pregnancy (32) Folate supplementation should be encouraged in all women of childbearing age (390) Careful dose management required during pregnancy and early postpartum as significant increase in clearance during pregnancy (391, 392)
Gabapentin	Caution during pregnancy (32)
Topiramate	Caution during pregnancy (32)
Olanzapine	Should be used during pregnancy only if benefit justifies the potential risk (360)
Risperidone	Caution during pregnancy (32)
Quetiapine	No data; caution during pregnancy
Ziprasidone	No data; caution during pregnancy
Clozapine	Should be used during pregnancy only if clearly needed (360) Potential agranulocytosis warrants white blood cell counts in neonates

Maintenance therapy during pregnancy. There are conflicting data on the effect of pregnancy on recurrence of bipolar mood episodes: some studies show a protective effect, while others do not (274, 364, 365, 380, 381). In general, medications should be avoided or used as monotherapy in minimally effective doses, especially during the first trimester; however, this is not feasible for all patients (Table 6.3) (361). Risks and benefits of continuing medication during pregnancy should be based on severity and past response to treatment (362). Patients may require higher doses of some agents because of various physiological increases including plasma volume in the second and early part of third trimester, hepatic activity and renal clearance rates. However, lower doses may be required during the last few weeks before delivery (382, 383). Each pregnancy should be closely monitored and appropriate screening tests (e.g. fetal ultrasound, α-fetoprotein levels) should be performed (362).

As is the case for the acute treatment of breakthrough episodes, the choice of maintenance medication should be influenced by teratogenic potential (Table 6.2). If possible, avoid lithium, divalproex and carbamazepine, as these agents incur some teratogenic risk, particularly when used in combination (32). In situations where patients warrant treatment with a mood-stabilizer, lithium is preferred over the anticonvulsants as the absolute risk of Ebstein anomaly is only 0.1%. Lamotrigine may be considered, particularly in patients who primarily suffer depressive relapses, as data from a large pregnancy registry suggest no increased teratogenicity (376). Atypical antipsychotics may also be reasonable choices, however, with the exception of data on olanzapine and clozapine suggesting no increased teratogenic risk, data on the atypical antipsychotics are limited (362, 378, 379). Reports of gestational diabetes with atypical antipsychotics should also be considered (379, 384, 385).

Electroconvulsive therapy may be considered as alternative during pregnancy in cases of psychotic decompensation or suicidal ideation (32). The procedure is relatively safe if special precautions are taken (386), and there are no indications of teratogenesis (357).

Management of bipolar disorder during the postpartum period. The high risk of postpartum recurrence (about 50%) after discontinuing lithium

Table 6.4. Factors associated with increased risk of postpartum recurrence of bipolar disorder or puerperal psychosis

Postpartum mood episode in first pregnancy (365)
Depression during pregnancy (365)
Sleep-deprivation (397)
Euphoria after delivery (398)

during pregnancy suggests the need for prophylactic therapy (274, 393). In addition, women with bipolar disorder have a significantly increased risk of postpartum psychosis (394). Certain factors have been associated with a higher risk of postpartum psychosis and recurrent episodes of bipolar disorder during the postpartum period (Table 6.4). Little data are available on postpartum prophylaxis. However, lithium has been found to reduce the rate of recurrence from nearly 50% to about 10% (393, 395, 396). While prophylaxis is recommended, particularly for women at risk, the implications of selected treatments on breastfeeding need to be considered (Table 6.5).

Women should be educated on the potential risks and benefits of taking medication while breastfeeding, including recognition of the signs of infant drug toxicity (362). Most medications used for the treatment of bipolar disorder are excreted in breast milk (Table 6.5). Because of the potential for higher concentration of medication in colostrum, a 1- to 2-day washout (without breastfeeding) is recommended if medication was taken during pregnancy (362). Medication should be taken after breastfeeding to help minimize the risk of exposure (375). The use of hind milk and supplementing breast milk with formula feedings can also be considered.

Although data are limited, the American Academy of Pediatrics (AAP) and other groups have made some recommendations on the use of medications for bipolar disorder while breastfeeding (32, 362, 363, 375, 379, 399). The infant's clinical status and blood levels should be monitored if there are potential risks. Lithium should be used with caution, which includes monitoring for complete blood count (CBC), hypotonia, lethargy and cyanosis in infants. Divalproex and carbamazepine are considered compatible with breastfeeding, with monitoring of liver enzymes, CBC, and platelets to rule out hepatotoxicity and haematological toxicity, as necessary. Benzodiazepines, SSRIs, conventional antipsychotics, clozapine and lamotrigine are classified by the AAP as drugs for which the effect on nursing infants is unknown but may be of concern (375).

There are little or no data on the use of topiramate or gabapentin, and, as these agents are not well proven for the treatment of bipolar disorder, they are not recommended during breastfeeding. There are little data on atypical antipsychotics and the manufacturers do not recommend their use while breastfeeding (379).

Case study

Sara, 33 years old, has at least a 13-year history of bipolar disorder. She has been stable for the last 2 years on a combination of lithium and divalproex. She is planning to be married this month, and has come to you to discuss whether she will be able to have children. She is concerned about the effects of medications during pregnancy and breastfeeding, as well as the effect of bipolar disorder on her ability to raise children.

- What is your immediate course of action?
- What questions should you ask?
- What is your treatment plan?

Table 6.5. Medications and breastfeeding

Drug	Ratio of milk/maternal serum (%)	Ratio of infant/ maternal serum (%)	Related adverse effects
Lithium (32, 362, 363)	24–72	5–200	T-wave changes on ECG, cyanosis, lethargy, heart murmur, hypotonia, hypothyroidism
Divalproex (32, 362, 363)	<1–10	0–40	Thrombocytopenia, anaemia Hepatotoxicity reported in young children
Carbamazepine (32, 362, 363)	7–95	6–65	Hepatic dysfunction, hyperexcitability, seizure-like activity, drowsiness, poor feeding
Lamotrigine (390, 400–402)	60	23–33	No associated events in infants Life-threatening rash reported in children
Olanzapine (379, 403, 404)	10–84	0.22–2.5	Jaundice, sedation, cardiomegaly, shaking, lethargy, protruding tongue, rash, diarrhoea, poor sleep
Risperidone (379, 405, 406)	10–42	42	N/A, four patients, no adverse effects reported
Quetiapine (362, 379, 407)	N/A	N/A	N/A, one patient, mean 13 μg/L quetiapine in milk, no adverse effects reported
Clozapine (361, 379, 385, 408)	279–432%	1.2%	Sedation, decreased suckling, restlessness, irritability, seizures, cardiovascular instability

N/A = not available.

Clinical management. Your first concern is whether Sara has been using birth control, and she says she has being using oral contraceptives for the past 6 months. You assure her that her concerns are real but that with careful planning and close follow up she should be able to have a family. There is a risk of her offspring having bipolar disorder and many medications are not recommended during pregnancy. You enquire about her pregnancy plans and she states that because of her and her fiancé's older ages, they plan to have children within the next year or two. Her current medications should not interfere with the efficacy of her birth control, so you recommend that at least 3 months before she plans to become pregnant they meet again.

Sara returns to your office 1 year later, and expresses her intention to start trying to become pregnant and her desire to discontinue medication. You discuss with her the risks and benefits of prophylaxis with mood-stabilizers while trying to conceive and during pregnancy versus no medication, the treatment of acute episodes during and after pregnancy, and the need for a pregnancy contract. Balancing the risk to the fetus (teratogenicity), and the risk to Sara herself (recurrence of mood episodes), together you decide to gradually discontinue one of her medications and see if she remains stable. Over the course of the next month, she lowers the dose of divalproex weekly, and discontinues without any incident. She insists on discontinuing lithium, and you agree that if she can remain stable that is the ideal situation during the first trimester of pregnancy. She gradually discontinues lithium over the next 6 weeks and together you write a pregnancy contract describing her symptoms of depression and mania and what treatments she authorizes during pregnancy and the postpartum period.

Sara returns monthly, and 4 months later, declares that she is 1 month pregnant and has had no manic symptoms, but has been feeling a little tired and depressed. She feels strongly that she would like to continue medication free for the first trimester and so you continue to monitor her closely. Over the next 6 weeks, you can see that she is becoming increasingly depressed. Her husband has now come in with her, and supports you in encouraging her to resume a medication regimen.

You discuss with Sara and her husband the risk of not treating her depression versus the risk of teratogenicity of medications. As lamotrigine is associated with a low risk of teratogenicity, and adverse effects during breastfeeding, it is decided that this may be the best option for her at the present time. During titration over the next 6 weeks, her depression improves and she agrees to continue through the postpartum period. You caution her about the risk factors for recurrence during the postpartum period and recommend that she have her mother stay with her to ensure she does not become sleep deprived.

Issues in the management of bipolar disorder in children and adolescents

The child psychiatric workgroup on bipolar disorder has recently published guidelines for treatment of children and adolescents with this condition (409) and the reader is referred to this document for more details on this topic. Therefore, in the following section, we will provide only a very brief overview of some of the issues in this population.

Presentation and diagnosis. Approximately 53–66% of bipolar patients experience their first episode during childhood and adolescence, with a peak age of onset between 15 and 19 years of age (36, 37). About 20–30% of children who are diagnosed with MDD go on to have manic episodes (410–412). Mood disorders, including bipolar disorders, are among the most important risk factors for youth suicidal behaviour (413, 414); the earlier the onset of bipolar disorder, the greater the likelihood of suicide attempts (37).

The diagnosis of childhood bipolar disorder remains challenging, in part because of high rates of comorbidity with other common childhood disorders, and the fact that manic symptoms are frequently preceded by depressive or dysphoric-irritable symptoms. In addition, although diagnosis is based on the same DSM-IV criteria used to diagnose adults (18), children with mania frequently present with atypical symptoms (Table 6.6) (45, 415–420). Half of the children who manifest mood lability and sleep disturbance early in life, meet all DSM-IV criteria except episode-duration requirements (418). These atypical and complicated presentations have led to under diagnosis of bipolar disorder in teenagers (421) and misdiagnosis as schizophrenia (422–424).

Table 6.6. Presentation of mania in paediatric patients with bipolar disorder (45, 415–419)

Erratic, not persistent, changes in mood, level of psychomotor agitation, and mental excitement
Irritability, belligerence, and mixed state features more common than euphoria
Reckless behaviours: school failure, fighting, dangerous play, inappropriate sexualized activity
Psychotic symptoms, mood-incongruent hallucinations, paranoia, marked thought disorder
Severe deterioration in behaviour

A diagnosis of bipolar disorder should be considered for any youth with a marked deterioration in functioning associated with either mood or psychotic symptoms (425).

Risk factors for bipolar disorder in children. Risk factors predictive of mania include a depressive episode characterized by rapid onset, psychomotor retardation and psychotic features, a family history of affective disorders, especially bipolar disorder, and a history of psychomotor agitation or antidepressant-induced mania or hypomania (410, 412, 419).

Children who have a parent diagnosed with bipolar disorder display increased risks of bipolar disorder and other affective, anxiety and behavioural disorders, or substance abuse (426–428). In these offspring, the prodromal symptoms of childhood bipolar disorder may be more subtle presentations of mood regulation difficulties (428). A prospective study of the offspring of bipolar parents who were responsive and non-responsive to lithium treatment suggested that response to lithium may be inherited (429).

Comorbidities and mimics. Comorbid disorders further complicate both the diagnosis and course of early-onset bipolar disorder. Childhood bipolar disorder displays significant symptomatic overlap or comorbidity with attention deficit hyperactivity disorder (ADHD), MDD, dysthymia, anxiety and conduct disorders (422, 430–436). An estimated 88% of bipolar children had another psychiatric disorder and 76% demonstrated a comorbid anxiety disorder (437). In one study, 91% of children with current or past mania also met criteria for ADHD (430), which has been associated with a poorer response to therapy (438). High rates of substance abuse and cigarette smoking have also been noted in some samples (422, 423, 432, 439).

A diagnosis of early-onset bipolar disorder requires specific differentiation from ADHD and conduct disorder, due to symptomatic overlap (Table 6.7) (435, 440–442). Diagnostic tools including the Mania Rating Scale (443) and subscales on the Child Behaviour Checklist have demonstrated some benefit in distinguishing between children with mania and those with ADHD (444, 445). Parental reports have been shown to be more useful in facilitating a differential diagnosis of bipolar disorder in children than either teacher or adolescent self-reports (446).

Table 6.7. Differential diagnosis of early-onset bipolar disorder and ADHD (447, 448)

True euphoria, decreased need for sleep and hypersexuality are uncommon in ADHD but common in bipolar disorder
Onset of symptoms including inattention typically >7 years of age in bipolar disorder but earlier in ADHD
Family history of bipolar disorder more common in those with bipolar disorder whereas disruptive disorders such as conduct disorder are more common in those with ADHD
Periods of normal functioning may be seen in those with bipolar disorder but rare in those with ADHD

ADHD = attention deficit hyperactivity disorder.

Acute and maintenance treatment of paediatric bipolar disorder. The early course of bipolar disorder in adolescents is often chronic and refractory to treatment, while the long-term prognosis appears similar to that of adults (422–424, 449). Although available data are limited, and have methodological issues, the results of both RCTs and open clinical trials suggest that adolescent-onset bipolar disorder will likely respond to the same agents as adult-onset bipolar disorder (450). Like adult bipolar disorder, childhood-onset bipolar disorder has a chronic course with a high rate of recurrence and evidence suggests that prophylactic therapy is needed (451, 452).

Informed consent (addressing the rationale for treatment, as well as the potential risks and benefits of the therapy) should be obtained from the child or adolescent's legal guardian, and the patient's consent or assent should be obtained.

Lithium. As expected, there is more evidence evaluating the effectiveness of lithium than other agents. A placebo-controlled RCT in adolescents with bipolar disorders and comorbid substance abuse showed that acute treatment with lithium was effective in both disorders (level 2) (453). Open trials have also suggested that lithium is effective for acute treatment of children and adolescents with manic or mixed episodes (level 3) (454, 455). Lithium was effective in combination with other agents in a retrospective study (level 4) (456).

When lithium was used for the prevention of recurrence in a small RCT, there was no significant difference in recurrence rates compared with placebo, due to an unexpectedly high rate of recurrence in the lithium group (52.6%) (level 2, negative) (457). Naturalistic data suggest a rate of recurrence of 28% among patients on adequate doses of lithium (level 4) (456).

Data suggest that response rates with lithium are lower in patients with comorbid ADHD (level 4) (438). However, mood stabilization appears to be a prerequisite for successful treatment of ADHD in children with bipolar disorder (458).

Divalproex. In prospective, open trials, divalproex was effective for the treatment of children and

adolescents with bipolar disorder (455, 459), with response rates numerically, but not statistically, superior to lithium and carbamazepine (455) (level 3). Long-term treatment with divalproex has been associated with improved outcomes in the treatment of children and adolescents with bipolar disorder (level 4) (460).

Atypical antipsychotics. In an RCT, the combination of quetiapine and divalproex was significantly more effective than divalproex alone in the treatment of acute mania in adolescents with bipolar disorder (level 2) (142).

Open-label prospective and retrospective data suggest that either risperidone or olanzapine alone, or in combination with mood-stabilizers, may be effective in treating children and adolescents with bipolar disorder (level 3 and 4) (461–464).

Antidepressants. In general, antidepressant monotherapy is not recommended for the treatment of bipolar disorder (see Section 4). In addition, recent meta-analyses and Food and Drug Administration (FDA) position papers (465–468) demonstrate an excess risk of suicidality with SSRIs in children and adolescents with depression. A Statement for the Canadian Psychiatric Association on antidepressant prescribing for depression estimated one to three excess cases of suicidality for every 100 patients treated with an SSRI other than fluoxetine, which carried a lower risk (469). Although most of the data gathered to prepare these recommendations come from studies of MDD, the general recommendations of this statement would be appropriate when antidepressants are used in patients with bipolar depression. Discussion with the patient and family of potential side effects that may affect suicidality such as anxiety, agitation, hypomania and activation syndrome is recommended, and early reassessment (weekly for the first month) after initiation of therapy should take place (469).

ECT. Data on the use of ECT in adolescents and children come mainly from case series (level 3) (470). While there are concerns regarding possible adverse effects on the maturing nervous system, several follow-up studies have not found evidence of long-term cognitive impairment in adolescents treated with ECT (471, 472). The American Academy of Child Adolescent Psychiatry (473) stated that ECT may be an effective treatment for adolescents with severe mood disorders and other Axis I psychiatric disorders. They recommended that ECT be considered when there is a lack of response to two or more trials of pharmacotherapy or when the severity of symptoms precludes waiting for a response to pharmacological treatment.

Psychoeducation. Preliminary data suggest benefits from adjunctive group psychoeducation for families of children with mood disorders and child- and family-focused CBT (474–476).

Issues in the management of bipolar disorder in older patients

Presentation and course. Population-based surveys indicate that bipolar disorder becomes less common with age, with a prevalence of 0.1–0.5% among individuals 65 and older (28, 74, 477, 478). Bipolar disorder is a life-long illness, and in older adults bipolar depression accounts for 8–10% of psychiatric admissions and is frequently associated with neurological factors (479–483). Older adults also appear to have a higher prevalence of mixed episodes (480, 484) and a lower treatment response (484). Bipolar disorder of late-onset has a lower association with family history (484–487) and occurs more frequently in women than in men (483). Long-term studies indicate that bipolar disorder neither 'burns out' in old age nor follows a progressively deteriorating course (483, 488, 489).

The high risk of suicide in older people and in patients with bipolar disorder appears to be additive. However, results from a long-term survey indicate that the highest risk for completed suicide occurs during the first 7–12 years post-onset and in those under age 35 (490), suggesting that older patients with early-onset bipolar disorder may belong to a survivor cohort (483).

Comorbidity. The lifetime rate of substance abuse in those over 60 was 20–30%, significantly lower than that in mixed age populations (61%) (31, 483). Although anxiety disorders are frequent comorbidities, no data were found examining the rate of these psychiatric disorders in older patients with bipolar disorder.

The prevalence of neurological illness in older adults with bipolar disorder was 23% in a review of eight studies (483). The prevalence of neurological illness is reportedly higher in patients with bipolar disorder than in those with unipolar depression (36% versus 8%) (491). Bipolar disorder may be frequently complicated by or secondary to dementia in older patients (483, 492–494). Silent cerebral infarctions are more common in patients with late-onset manic symptoms versus patients with early-onset affective disorder (495).

Other medical comorbidities in older adults with bipolar disorder are extremely common (483). In a survey of psychiatric admissions, 20% of elderly bipolar patients had seven or more comorbid medical diagnoses (496). Rates of diabetes were significantly elevated in older bipolar patients compared to either a mixed-age bipolar population (497) or the general population (498).

Treatment of bipolar disorder in older adults. Surprisingly, there do not appear to have been any RCTs initiated exclusively in elderly bipolar patients to evaluate treatment outcomes (483). However, data suggest that acute treatment can improve cognitive performance in geriatric bipolar patients (479).

Acute treatment of mania. In open trials, 66% of older patients treated with lithium improved overall (494, 499–501). Renal clearance of lithium decreases with age, and the elimination half-life in older patients is twice that in younger patients (502). Renal disease, cardiac insufficiency, decreased body fat and use of concurrent medications can increase lithium concentrations and decrease clearance (502–504). Based on retrospective data, 59% of patients improved with divalproex therapy (500, 505–508). Increases in plasma concentrations of divalproex have been reported with ageing (509, 510) and with the concurrent use of aspirin (511). Few data are available on the efficacy of atypical antipsychotics in elderly bipolar patients. Two small open trials reported a positive response to clozapine in older mania patients (512, 513). Age-associated increases in serum concentrations have been reported with risperidone (514) and clozapine (515).

Acute treatment of bipolar depression. Lamotrigine was effective as an add-on to lithium or divalproex, in a small open study, with three of five geriatric patients with bipolar depression responding (516). In an RCT involving adult patients (age 21–71 years) with acute bipolar depression, the combination of paroxetine and lithium was more effective than lithium alone in those with low serum levels, with age having no impact on response (242). If antidepressants are used in older patients, SSRIs and bupropion are preferred over tricyclics, as they have a lower reported risk of switching to mania, which can also occur in older patients (517, 518).

Maintenance treatment. No RCT data are available on maintenance treatment of bipolar disorder in elderly patients. Naturalistic studies in mixed-age samples suggest a poorer response to lithium in older versus younger patients (499, 519–521). Factors that alter acute treatment outcomes may also influence long-term outcomes in these patients, but data are limited (522). Given the paucity of data on maintenance treatment of bipolar disorder in older patients, treatment choices should be informed by the safety and tolerability profiles of these medications in older patients.

Neurological side effects, ranging from mild tremor to disabling delirium, are reported in about 30% of patients treated with lithium (494, 501, 519, 523, 524). Almost 60% of older patients receiving lithium maintenance therapy experienced electrocardiographic abnormalities (525). Over 30% received thyroxine replacement or had elevated thyroid-stimulating hormone levels (526). Side effects such as polyuria and polydipsia, weight gain and oedema are reported in about 30–45% of older patients taking lithium (520, 527).

Neurological side effects, including sedation, tremor and gait disturbance, have been observed in up to 13% of elderly patients with bipolar disorder taking divalproex (505–508). Lamotrigine was well tolerated in elderly patients with seizures after stroke (528–530). Carbamazepine has been associated with bradycardia and atrioventricular conduction delays (531).

Some atypical agents such as clozapine, olanzapine and quetiapine can cause somnolence, but effects on cognition have not been studied in elderly patients. Atypical antipsychotic agents have demonstrated a lower tendency for acute motor side effects compared with conventional antipsychotics and some may also be associated with lower rate of tardive dyskinesia (532–535). Antipsychotic treatment can prolong the QT interval (QTc), particularly in patients with pre-existing conduction abnormalities (536). The clinical significance of QTc prolongation by ziprasidone is not known (537). Antipsychotic agents, especially low-potency conventional antipsychotics and olanzapine, have anticholinergic effects that can contribute to tachycardia, constipation and urinary hesitancy/obstruction, as well as cognitive impairment.

Antidepressants can cause sedation in older patients (522). SSRI treatment has been associated with neuromotor side effects, bradycardia and hyponatremia in older patients.

Factors that influence treatment response. Lith ium remains one of the treatments of choice for mania. Comorbid medical conditions and substance abuse have been shown to predict a poorer response to treatment overall and to lithium specifically (494, 538). A retrospective report sug-

gested that lithium had a better therapeutic effect than divalproex in elderly patients with classic but not mixed manic states (500). Divalproex is a rational alternative to lithium in manic elderly patients, particularly in patients who develop deterioration of cognitive performance during lithium treatment. More data are needed to determine the role of atypical antipsychotics in older patients with mania. Lamotrigine may be useful for bipolar depression in older patients.

Issues in the management of bipolar disorder in patients with comorbid conditions

Epidemiology. Patients with bipolar disorders frequently present with comorbid substance abuse, anxiety and other psychiatric disorders, and physical illnesses. There is an estimated sevenfold higher risk of drug and alcohol abuse compared to the general population, with higher rates in women versus men, and in bipolar I versus bipolar II (539–541). Patients with comorbid bipolar and substance abuse disorders are four times as likely to have other comorbid Axis I disorders than the general population (542).

Current and lifetime Axis I comorbidities are common in patients with bipolar I and II disorders (539). The risk of anxiety disorder is estimated to be 35-fold higher than that in the general population (539), including a higher risk of generalized anxiety disorder (GAD), simple phobia, social phobia, panic disorder and post-traumatic stress disorder (PTSD) (35, 539). During their lifetime, 65–90% of patients with bipolar I disorder will have a comorbid anxiety disorder (35, 539). The lifetime prevalence of personality disorders is estimated to be between 30 and 50% among patients with bipolar disorder (78, 543–546) compared with 9% in community samples (547).

Patients with bipolar disorder experience more physical illness than the general population, including higher rates of type 2 diabetes and cardiovascular disease (498, 548, 549). Mortality from cardiovascular disease is almost twofold higher than that seen in the general population (550–553). Higher rates of migraine and other pain syndromes have also been reported in patients with bipolar disorder compared with the general population (554, 555).

Comorbidity can have a significant negative impact on diagnosis, severity, suicidality, treatment adherence and response, as well as functional outcomes in bipolar disorder (40, 70, 171).

Treatment of bipolar disorder and comorbid conditions. There are no large, double-blind, placebo-controlled trials examining the efficacy of any pharmacotherapy in bipolar patients with comorbidity. Given the lack of efficacy data in this patient sub-population, we will briefly review open-label studies and studies that have examined the efficacy of various agents in conditions that commonly co-occur with bipolar disorder.

Substance abuse disorders. In patients with bipolar disorder, comorbid substance abuse was associated with lower rates of remission (556) and more psychiatric hospitalizations (79, 542).

The anticonvulsants lamotrigine, divalproex, carbamazepine and gabapentin, as well as the atypical antipsychotic quetiapine, have been evaluated in the management of patients with bipolar disorder and comorbid substance abuse.

In patients with bipolar disorder and comorbid cocaine dependence, open-label lamotrigine treatment resulted in statistically significant improvements in mood and drug cravings but did not significantly decrease drug use (level 3) (557). In a retrospective chart review, remission rates were higher in bipolar patients with a history of substance abuse who had received divalproex or carbamazepine versus lithium monotherapy (level 4) (556). The presence of alcohol abuse was associated with a positive response to open-label adjunctive gabapentin treatment in patients with bipolar disorder (level 3) (172). Open-label adjunctive quetiapine treatment demonstrated significant improvements in mania and depression scores, and drug cravings in patients with bipolar disorder and cocaine dependence (level 3) (558).

Divalproex, carbamazepine and topiramate have shown efficacy in patients with substance abuse disorders, but have not been evaluated in patients with both bipolar disorder and comorbid substance abuse disorders. In an RCT, divalproex reduced the symptoms of alcohol withdrawal faster than a benzodiazepine (level 2) (559). Carbamazepine demonstrated efficacy equal to lorazepam in decreasing the symptoms of alcohol withdrawal (560). Patients treated with topiramate demonstrated significantly less alcohol consumption and cravings compared with placebo in the treatment of alcohol dependence (561).

Anxiety disorders. Comorbid anxiety disorders are associated with more complicated bipolar illness, including higher rates of suicidality (80, 562–564), higher rates of cycle acceleration, increased severity of episodes (35, 564, 565), more frequent depressive episodes (80, 565) and poorer overall functional outcome (565–567).

The anticonvulsants topiramate and gabapentin have shown some benefits in the management of patients with bipolar disorder and anxiety disorders. In a small retrospective review of bipolar patients with comorbid psychiatric conditions, 73% of patients treated with topiramate experienced a significant improvement in their comorbid conditions (level 4) (568). Open-label adjunctive gabapentin has been shown to improve residual depressive symptoms, irritability, social withdrawal and anxiety in patients with refractory bipolar disorder (level 3) (172, 569).

Other therapies used for bipolar disorder including atypical antipsychotics, antidepressants and benzodiazepines have been shown to reduce anxiety symptoms, although specific data are not available in patients with both bipolar disorder and comorbid anxiety disorders. When used as add-on to antidepressant therapy in refractory patients atypical antipsychotics, including olanzapine, quetiapine and risperidone, have demonstrated efficacy in obsessive compulsive disorder (OCD) (570–573), PTSD (574–578) and GAD (171, 579, 580). Antidepressants including SSRIs and TCAs have demonstrated efficacy in social anxiety disorder (581, 582), PTSD (583–585), OCD (586) and panic disorder (587). Some benzodiazepines (588), antidepressants (589–591) and gabapentin (592) have demonstrated efficacy in GAD.

Personality disorders. Bipolar patients with comorbid personality disorders are reported to have poorer treatment outcomes (545, 593–596), a higher number of currently prescribed psychiatric medications (546) and poorer medication adherence (287).

The anticonvulsants divalproex and lamotrigine, as well as adjunctive psychoeducation, have shown some benefits in the management of patients with bipolar disorder and comorbid personality disorders. In contrast, data suggest that lithium prophylaxis is less effective in bipolar patients with comorbid personality disorders compared to those with bipolar disorder alone (level 4) (597, 598). In a small, placebo-controlled RCT, divalproex demonstrated efficacy in the treatment of women with bipolar II disorder and borderline personality disorder, significantly diminishing interpersonal sensitivity and anger/hostility, as well as overall aggression (level 2) (599). A retrospective analysis of two studies, in which 40% of bipolar patients met criteria for borderline personality disorder, found that borderline personality disorder responded to lamotrigine (level 4) (600). Similarly, subanalysis of an RCT suggested that psychoeducation might be a useful intervention for bipolar patients with comorbid personality disorders (level 3) (601).

Although olanzapine was significantly more effective than placebo in patients with personality disorders (602, 603), its benefit remains to be established in patients with both bipolar disorder and comorbid personality disorders.

Section 7: Bipolar II disorder: acute and maintenance management

Epidemiology

Bipolar II disorder is characterized by recurrent episodes of major depression and hypomania. The prevalence rates vary from 0.5 to 6.4% of the general population, depending on the criteria employed (20, 22, 28, 29, 604). However, evidence-based recommendations presented in these guidelines are based on DSM-IV criteria for bipolar II disorder.

Conceptually, bipolar II disorder can be viewed along a continuum from unipolar depression to bipolar I disorder, with intermediate differences in course of illness, gender ratio, family history and possibly treatment response (605–608).

Hypomania, the defining feature of bipolar II disorder, is often missed leading to the under diagnosis of this condition (609). As a result, it can take up to 12 years before patients are appropriately diagnosed with bipolar II or bipolar spectrum disorder, compared with 7 years for bipolar I disorder and 3.3 years for unipolar depression (72, 610).

However, bipolar II disorder can be reliably diagnosed when experienced psychiatrists use a careful, structured interview, in conjunction with collateral history from friends or family (610, 611). The MDQ is a simple self-report questionnaire which has moderate sensitivity and specificity in screening for past hypomania of undetermined duration (77, 612, 613).

By definition, hypomania, unlike mania, is not severe enough to cause marked functional impairment; thus, many patients will not intuitively recognize such states as part of an illness. Thus, it cannot be over-emphasized that detection of bipolar II disorder can be greatly improved by involving families and friends where possible in the evaluation of patients with mood disorders (68, 72, 610). It is also important to emphasize that the diagnosis requires an unequivocal change in mood and behaviour that is observable by others – a requirement that should limit over diagnosis.

Differential diagnosis of bipolar II disorder

The majority of patients with an eventual diagnosis of bipolar II disorder have a prior diagnosis of unipolar depression (MDD) (610). In some cases, this is because the illness has not yet declared itself, but often a careful screening for hypomania has not occurred (610). Bipolar II disorder and highly recurrent depression are closely related (610). Bipolar II disorder appears to be associated with a significant risk of suicide (614–617). Patients with a diagnosis of bipolar II disorder are more likely to have demonstrated an earlier age of onset, have a family history of bipolar II, and will experience higher rates of recurrence, anxiety disorders and substance abuse compared to patients with MDD (76, 609, 610, 618, 619). In addition, atypical depressive symptoms such as mood reactivity, increased appetite, carbohydrate cravings, over-eating, weight gain, oversleeping, extreme fatigue and interpersonal sensitivity occur more frequently in bipolar II depression (609, 620–622).

Bipolar II disorder and borderline personality disorder also share components of mood dysregulation and impulsivity as well as a history of instability in relationships (623). However, they differ in the quality, degree and duration of mood episodes, the degree of mood lability, the episodic pattern of troublesome behaviours (624), onset (625) and family history (45).

In contrast, specific cyclothymic or hyperthymic temperaments and cyclothymic disorder may cluster in families with bipolar disorder and in some cases are antecedents of a frank bipolar I or II disorder (615). These chronic conditions more often mimic the symptoms of hypomania and often, atypical episode of MDD, similar to those in bipolar II but of milder degree and without obvious dysfunction. In some cases, they can be productive or functionally enhancing (626).

It is important to emphasize that bipolar II is not simply a milder form of bipolar I disorder; it is associated with significant rates of rapid cycling and suicide and a comparable degree of psychosocial impairment as seen with bipolar I disorder (29, 217, 617, 627).

Management of bipolar II disorder

Other recent guidelines for the management of bipolar disorder have chosen not to include recommendations for the treatment of bipolar II disorder (9, 14, 17). However, we believe that the growing recognition of this disorder makes the need for a review of current, albeit limited data, important for physicians who are faced with an increasing number of such patients in their practice.

Acute management of hypomania

Untreated hypomania may be associated with major financial, legal and psychosocial problems, without ever commanding medical attention (30), yet virtually no studies have been carried out to assess effective treatments. The only study specific to the management of acute hypomania is an open-label study of risperidone that demonstrated acute benefit within 1 week (level 3) (304). Treatment approaches for acute hypomania otherwise have typically mimicked those for manic episodes.

Acute management of bipolar II depression

Acute management of depression is a major focus in the management of bipolar II disorder. To date, most studies have evaluated the effectiveness of antidepressants and anticonvulsants (Table 7.1), which are evaluated on the strength of the evidence (Tables 1.1 and 1.2). However, because of the paucity of evidence that is derived specifically for bipolar II disorder trials, it is necessary to combine evidence and expert opinion to formulate treatment recommendations (Table 7.2).

There is inadequate evidence to support any treatments as first-line therapy for the management of acute bipolar II depression; therefore, it is necessary to consider second-line options (Table 7.2).

Table 7.1. Strength of evidence for monotherapy treatments of acute bipolar II depression

Agent	Level of evidence
Lithium	3
Anticonvulsants	
Divalproex	3
Lamotrigine	3
Gabapentin	3 (−ve)
Atypical antipsychotics	
Olanzapine	No data
Risperidone	No data
Quetiapine	2 (−ve)
Ziprasidone	No data
Aripiprazole	No data
Clozapine	No data
Antidepressants	
Fluoxetine	3
Venlafaxine	3
Tranylcypromine	2
Combination therapy	
Lithium or divalproex + pramipexole	2
Lithium or divalproex + SSRI	3
Lithium or divalproex + topiramate	3
Atypical antipsychotic + antidepressant	4

SSRI = selective-serotonin reuptake inhibitor.

Table 7.2. Recommendations for pharmacological treatment of acute bipolar II depression

First line	Insufficient evidence
Second line	Lithium, lamotrigine, lithium or divalproex + antidepressants, lithium + divalproex, atypical antipsychotics + antidepressants
Third line	Switch to alternate antidepressant
Not recommended	See text on antidepressants for recommendations regarding antidepressant monotherapy

Lithium. Data on the acute antidepressant effects of lithium in bipolar II disorder are embedded in studies of both bipolar I disorder and recurrent unipolar depression. These studies show moderate acute antidepressant effects for lithium, but without separate analysis of bipolar II depression (level 3) (605, 628, 629).

Anticonvulsants. In an open trial, divalproex was effective in bipolar II depressed patients, with a trend towards a higher rate of response in naive patients compared to those who had received previous medications (level 3) (255). In a small RCT, involving women with comorbid bipolar II disorder and borderline personality disorder, divalproex significantly decreased irritability, anger and impulsive aggressiveness, but not depressive symptoms on the Symptom Check List-90 (599).

In an RCT comparing lamotrigine, placebo and gabapentin, including 14 patients with bipolar II and 11 with bipolar I, overall lamotrigine was more effective than placebo (level 3) (170). In an RCT that included eight patients with bipolar II depression, lamotrigine as add-on to the antidepressant fluoxetine, demonstrated some efficacy compared with placebo on measures of global improvement, but not on measures of depression (630).

Atypical antipsychotics. Again limited data are available on the use of atypical antipsychotics in patients with bipolar II depression. Quetiapine monotherapy was significantly more effective than placebo for the treatment of acute depression in a large RCT involving patients with bipolar I and II disorders (251). The effect size in the bipolar I sample was very large (0.88 and 0.73 on 600 and 300 mg, respectively), but was small in the bipolar II sample (0.22 and 0.16, respectively) (level 2, negative) (251). The recent trial of olanzapine and olanzapine-fluoxetine in bipolar depression excluded patients with bipolar II disorder (244).

Thus, available data suggest little antidepressant benefits of atypical antipsychotics alone. Current evidence would suggest that these agents should be used only in combination with an antidepressant for patients with acute bipolar II depression.

Antidepressants. The use of antidepressant monotherapy in bipolar II depression is a highly controversial area. Two RCTs support the use of the MAOI, tranylcypromine, in 'anergic bipolar depression.' In the first RCT, tranylcypromine monotherapy was superior to placebo in 59 patients with anergic depression, of which 19 had DSM-III-defined bipolar II depression (260). No separate analysis was reported for this sub-group. A second RCT found that tranylcypromine monotherapy was more effective than imipramine in bipolar II depression, and that patients with bipolar II had less risk of treatment-emergent mood swings than those with bipolar I (262). Safety concerns regarding food and drug interactions result in downgrading the recommendation for MAOIs to second-line use. Surprisingly there are very few reports involving the SSRIs in bipolar II depression. A small RCT, showing that the addition of an SSRI (paroxetine) to lithium or divalproex was as effective as combining lithium and divalproex in improving depressive symptoms, included 16 bipolar II patients in a sample of 27, but no separate analysis of these patients was conducted (level 3) (246).

Open-label data and post-hoc analysis of an RCT suggest that fluoxetine monotherapy is safe and effective for the short-term treatment of bipolar II depression with a relatively low manic switch rate (level 3) (631, 632). Preliminary open-label data also suggest that short-term venlafaxine monotherapy may be a relatively safe and effective antidepressant treatment in patients with bipolar II depression (level 3) (633, 634). However, in an RCT including both patients with bipolar I and bipolar II disorder, the switch rate was numerically greater with venlafaxine compared to paroxetine (253).

Although there is some evidence that the risk of hypomanic switch or cycle acceleration with antidepressants may be less in bipolar II patients (631, 635, 636), this has not been consistently reported (637–639). Antidepressants may also induce mixed symptoms, in particular agitation, irritability, rapid thoughts and distractibility, though these are not always recognized (621, 640, 641). Several of the acute trials of antidepressant monotherapy suggested 'agitation' may occur, but had no specific assessment of either hypomanic or mixed symptoms (262, 631–634).

If bipolar II disorder is conceptualized on a continuum of unipolar and bipolar I disorder, then it is possible that some patients will do well on monotherapy with SSRIs or other newer antide-

pressants, whilst others will not. If antidepressant monotherapy is being considered, then a careful longitudinal history should be taken, noting prior consequences of hypomanic episodes, history of any prior antidepressant-induced worsening, stability of bipolar II diagnosis and family history of bipolar I illness. Similarly, the patient must be made aware of the risks, educated to detect hypomania, mania, rapid-cycling and mixed mood, and must be monitored accordingly.

Although evidence is lacking, clinical consensus supports the use of mood-stabilizers in combination with antidepressants in bipolar II depression, and the cautious consideration of antidepressant monotherapy in a subset of what is likely a heterogeneous group.

Other agents. There is limited support for the role of dopamine agonists. Pramipexole as add-on to lithium or divalproex had significant antidepressant effects in patients with bipolar II depression, in a small RCT (level 2) (259). A chart review also suggested that pramipexole and ropinirole were useful adjunctive treatments for drug-resistant bipolar II depression (level 4) (642).

Open data suggested that adjunctive gabapentin was effective in 30–55% of patients, including some with bipolar II disorder (level 3) (643, 644). Similarly, in an open trial, adjunctive topiramate was useful in treating bipolar II disorder, with good response rates over 12 weeks in patients presenting with either hypomania or depression (645).

Maintenance therapy for bipolar II disorder

It has been reported that patients with bipolar II disorder in treatment spend 37 times more days experiencing depressive symptoms than hypomanic symptoms (235). Therefore, the focus of long-term therapy for patients with bipolar II disorder is on aggressive prevention of depressive episodes. The data for lithium, anticonvulsants and antidepressants have been rated on the strength of the evidence (Table 7.3) according to the preset criteria (Tables 1.1 and 1.2). However, because of the scarcity of trials, specifically in patients with bipolar II disorder, it is necessary to combine evidence and expert opinion to formulate treatment recommendations (Table 7.4).

First line. In most situations, patients will continue the acute treatment regimen, and some will require additional pharmacotherapy. There is evidence for the efficacy of lithium and lamotrigine for the maintenance of bipolar II disorder.

Table 7.3. Strength of evidence for maintenance treatments of bipolar II disorder

Agent	Level of evidence
Lithium	2
Anticonvulsants	
Divalproex	3
Lamotrigine	2
Carbamazepine	3
Gabapentin	4
Atypical antipsychotics	
Adjunctive risperidone	3
Antidepressants	
Fluoxetine	3
Imipramine	2 (−ve)
Combination therapy	
Lithium + imipramine	2 (−ve)
Lithium + SSRI, venlafaxine or bupropion	4
ECT	4

ECT = electroconvulsive therapy; SSRI = selective-serotonin reuptake inhibitor.

Table 7.4. Recommendations for maintenance treatment of acute bipolar II disorder

First line	Lithium, lamotrigine
Second line	Divalproex, lithium or divalproex or atypical antipsychotic + antidepressant, combination of two of: lithium, lamotrigine, divalproex or atypical antipsychotic
Third line	Carbamazepine, atypical antipsychotic, ECT
Not recommended	Gabapentin

ECT = electroconvulsive therapy.

Lithium. The prophylactic benefit of lithium in patients with bipolar II disorder has been replicated in three small RCTs (level 2) (646–648), however, in one trial the prophylactic benefit of lithium was less clear in bipolar II patients than in bipolar I patients (647), while in another, only the reduction in depressive episodes was statistically significant (646). Long-term observational data suggest that lithium maintenance has superior benefits in bipolar II patients, who experience significantly fewer episodes per year, and significantly less time ill, compared to the time prior to initiation of lithium therapy (608, 627).

Lamotrigine. In a large, 6-month RCT, there were no significant differences between lamotrigine and placebo in terms of time to additional therapy for bipolar I and II rapid cycling patients (level 2, negative) (275). However, significantly more patients treated with lamotrigine compared to placebo were stable without recurrence at 6 months among patients with bipolar II disorder (46% versus 18%) (level 2). Open-label data also support the adjunctive use of lamotrigine in bipolar II patients for prevention of depressive symptoms (649, 650).

Second line.

Divalproex. Divalproex has been evaluated as a maintenance therapy in rapid cycling bipolar II patients and in women with bipolar II and comorbid borderline personality disorder (336, 599). Divalproex did not significantly decrease depressive symptoms compared with placebo in a small RCT involving women with bipolar II disorder and comorbid borderline personality disorder. However, attrition was high with only 11 patients remaining in the study at 6 months (599). In a small open trial over 3 years, divalproex was effective in reducing mood episodes in patients with bipolar II disorder and rapid cycling (level 3) (336).

Lithium or divalproex or atypical antipsychotic + antidepressant. Lithium and divalproex, as well as the atypical antipsychotic, olanzapine, have proven benefit in preventing bipolar I depression (see Section 5), and as antidepressants have, by definition, antidepressant effects, the combination might be appropriate. However, an RCT comparing lithium, imipramine, lithium plus imipramine, or placebo, found that lithium was effective in preventing depressive relapse among patients with bipolar II, but imipramine, either alone or in combination with lithium, provided no additional benefit (level 2, negative) (648).

Third line.

Carbamazepine. In a large well-conducted RCT, carbamazepine had similar prophylactic efficacy to lithium over 2.5 years in a subset of patients with bipolar II disorder or bipolar disorder NOS, with a trend favouring carbamazepine. This was in contrast to the bipolar I group where lithium was superior to carbamazepine (level 3) (300).

Atypical antipsychotics. Risperidone, either alone or in combination with mood-stabilizers, was protective against hypomanic recurrences in patients with bipolar II disorder during a 6-month, open trial (level 3) (304).

Antidepressants. In an early prospective trial examining the incidence of hypomania in 230 patients with recurrent depression treated with imipramine, the sub-sample of 33 bipolar II patients had a similar rate of switch (2.5%) in both the acute and continuation phase as the unipolar group, perhaps reflecting the close relationship between recurrent unipolar depression and bipolar II disorder (651). In a post-hoc analysis of the bipolar II sample in a placebo-controlled trial, fluoxetine monotherapy was as effective for bipolar II depression as it was for unipolar depression (level 3) (632). Similarly, fluoxetine monotherapy was effective in 10 of 13 patients with bipolar II disorder over 10 or more months (652). In contrast, imipramine was ineffective in preventing depressive relapse in an RCT comparing lithium, imipramine, the combination and placebo (648).

The addition of bupropion to lithium and/or levothyroxine in a very small case series of six bipolar II patients with treatment-refractory rapid cycling was associated with significant improvements that were sustained over an average of 2 years of continued treatment (level 4) (653).

ECT. Based on retrospective chart review, ECT was as effective in patients with bipolar I ($n = 25$) and bipolar II ($n = 41$) as it was in unipolar depression, with more rapid clinical improvement and fewer treatments required in the bipolar sample (level 4) (654).

Clinical questions and controversies

How can I differentiate bipolar II disorder from borderline personality disorder? There are substantial phenomenological overlaps between these two disorders. As the duration requirement for hypomania in bipolar II has been shortened, it is even more difficult to distinguish between bipolar II and borderline personality disorder. Beyond affective instability, patients with bipolar II disorder have, at times, impulsivity, risk-taking, substance abuse, suicide attempts, unstable relationships and unstable work histories if untreated (623). However, a careful phenomenological, developmental and longitudinal history, in conjunction with family history, will help differentiate the two (Table 7.5) (655). While the first step is to attempt to establish one of these diagnoses, it is also recognized that the two conditions may be comorbid, particularly if an early cyclothymic temperament preceded the onset of bipolar II (78, 656).

Case study

George is a 21-year-old university student who appeared at a walk-in clinic complaining of depression and extreme tiredness. He says he has no desire to socialize with friends as he is always exhausted. He spends much of each day in bed sleeping. He says he has been snacking a lot on junk food and has gained about 3 kg (7 lbs) in the past 3 weeks. He recalls being very depressed, even suicidal, about a year ago, and says that the antidepressant he was given made him feel 'always too good'. Since then he has experienced frequent 'peaks and valleys' but his

Table 7.5. Relative differences between bipolar II and borderline personality disorder (18, 623–625, 655, 657)

Bipolar II disorder	Borderline personality disorder
Onset in teens or early 20s	No defined onset
Observable, unequivocal change in prevailing mood	Most often not observable
Spontaneous mood changes	Mood changes precipitated by internal or external events
Mood changes last days to months	Mood changes may last for hours, or at most a day
Euthymic, dysphoric, anxious and elated mood shifts	Euthymic, dysphoric, anxious and angry mood shifts but elated mood is rare
Irritable mood shifts may occur with use of antidepressants	
Ego-dystonic	Ego-syntonic
Episodic impulsivity and risk-taking	Chronic impulsivity and risk-taking
Binge-eating as part of atypical depressive episodes only	Binge-eating not uncommon
Episodic suicide attempts related to depressive episodes	Recurrent suicidal gestures associated with both depression and internal/external precipitants
Self-mutilation rare	Self-mutilation common
Endorse 'depressed mood' as descriptor	Endorse 'emptiness' as descriptor
Decreased need for sleep	'Too on edge' to sleep
Racing thoughts random and associated with elation or antidepressant-induced mixed mood	Racing thoughts anxious in content and associated with anxiety
Family history of bipolar I or II or recurrent depression	Family history negative for bipolar I, II and recurrent depression
Adverse developmental history less likely	Adverse developmental history more likely
Good response to mood-stabilizers	Good response to dialectical behaviour therapy

depression has not been as bad as it is now. He is not sure which medication it was, but would appreciate a prescription for something similar. On questioning, he admits to suicidal ideation, but no plan at the present time. The family practitioner has concerns about some of the atypical features of his depression, his suicidal ideation, and his description of 'feeling great' on antidepressants, and refers him to you.

- What is your first course of action?
- What questions should you ask?
- What is your treatment plan?

Clinical management. Before prescribing treatment for George, it is important to determine whether he is suffering from unipolar or bipolar depression. You specifically probe for the presence of manic or hypomanic symptoms. He admits there are times when he requires little sleep and is very outgoing; he is also very productive during these periods and says 'there is no down side to them'. On review of family history, he reports his mother had episodes of depression when he was younger but there is no history of bipolar disorder. You explain to him that he may be having hypomanic episodes as well as depression and you ask him to come back with a family member or a friend for a second visit. George presents to your office a few days later with his girlfriend of 2 years. He continues to be depressed. During discussions with him and his girlfriend, it becomes clear that George has experienced three to four episodes of hypomania in the last year, associated with intrusive and embarrassing behaviour as well as an uncharacteristically high sex drive. He is, however, much more frequently depressed. Furthermore, his girlfriend, in conversation with his mother, discovers that she also experienced hypomanic episodes, which did not settle until her doctor prescribed her lithium. You provide George with information on bipolar disorder, and discuss with him a course of action that includes long-term treatment with either lithium or lamotrigine, and the risks and benefits of each strategy. George is reluctant to give up what he says are his most productive, sociable periods. However, you explain to him the hazards associated with untreated mood episodes including the high risk of suicide and the likelihood of spending more time depressed than hypomanic. George agrees to start lithium. He begins to have some symptomatic improvement over the next few weeks. After 2 months of lithium therapy, George says he feels much more stable and would like to continue the lithium therapy for the time being.

Section 8: Safety and monitoring

Medical evaluation of new patients

Ideally, complete medical and baseline laboratory investigations should be performed before initiation of pharmacological treatment for bipolar disorder. However, if an acute clinical situation precludes immediate evaluation, assessments should be performed as soon as possible. Patients with bipolar disorder should be regularly monitored for weight changes and adverse effects of medication including extrapyramidal symptoms (EPS), and women should be assessed for polycystic ovary syndrome (PCOS).

Table 8.1. Baseline laboratory investigations in patients with bipolar disorder

CBC
Fasting glucose
Fasting lipid profile (TC, vLDL, LDL, HDL, TG)
Platelets
Electrolytes
Liver enzymes
Serum bilirubin
Prothrombin time and partial thromboplastin time
Urinanalysis
Urine toxicology for substance use
Serum creatinine
24-h creatinine clearance (if history of renal disease)
Thyroid stimulating hormone
Electrocardiogram (>40 years or if indicated)
Pregnancy test (if relevant)
Prolactin

CBC = complete blood count; HDL = high density lipoprotein; LDL = low density lipoprotein; TC = total cholesterol; TG = triglyceride; vLDL = very low density lipoprotein.

Laboratory investigations. The laboratory investigations shown in Table 8.1 should be performed at baseline. Data suggest that there is no need to do blood counts and liver function tests frequently (658, 659). These investigations should be repeated about 4 weeks after commencement of treatment, and every 3–6 months thereafter. Closer monitoring, however, is required in children younger than 10, seniors, medically ill patients and patients on more than one medication. Clinical symptoms and signs of haematological, hepatic, cardiovascular and neurological dysfunction are particularly valuable in predicting or timing investigations and remedial treatment (658, 659). During lithium maintenance therapy, thyroid and renal function tests should be assessed annually.

Monitoring medication serum levels

Regular monitoring of serum medication levels is required for patients on lithium or divalproex, particularly in patients who are non-adherent. The target serum lithium levels are 0.8–1.1 mmol/L and divalproex levels are 400–700 mmol/L. Serum levels should be repeated at the trough point (approximately 12 h after the last dose). For lithium, serum levels should be obtained about 5 days after the most recent dose titration, for divalproex about 3–5 days after the most recent dose titration. Common practice is to establish two consecutive serum levels in the therapeutic range during the acute phase. Thereafter, serum levels should be repeated every 3–6 months unless the clinical situation warrants otherwise. If patients are receiving concomitant carbamazepine or other inducers of hepatic enzymes, it may be necessary to monitor serum levels of risperidone and other psychotropic agents to ensure that the efficacy is not compromised because of lower serum levels.

Safety and tolerability of pharmacotherapy for bipolar disorder

Weight gain. Weight gain and obesity are common in patients with bipolar disorder and appear to be associated with both patient and treatment factors (660). Weight gain is perceived by patients to be the most distressing of all side effects (661, 662), and thus, frequently contributes to non-adherence with treatment. Many agents currently used in the treatment of bipolar disorder are associated with some degree of weight gain.

Lithium is associated with a mean gain of 0.7–2.4 kg over 12 weeks of therapy (121, 228), and the amount of weight gained increases with increasing duration of therapy (663). In a comparison study, there was a significantly higher incidence of weight gain with divalproex (21%) compared with placebo (7%) (298). There was also a higher incidence of weight gain with lithium (13%), but this was not significantly different from placebo.

Weight gain appears to occur, to some degree, with all atypical antipsychotics, but to a greater extent with clozapine and olanzapine (533, 664, 665). Over 47 weeks of follow up, mean weight gain was significantly greater with olanzapine (2.8 kg) compared with divalproex (1.2 kg) (231). Weight gain does not appear to be a significant issue with lamotrigine or carbamazepine.

Gastrointestinal symptoms. Nausea, vomiting and diarrhoea are commonly reported with lithium and divalproex, occurring in about 35–45% of patients (122, 298). However, divalproex is significantly better tolerated than valproic acid, and preferentially prescribed (666). Gastrointestinal side effects may be common with lithium when it is first initiated or if doses are increased rapidly (667). Gradual dose titration, taking lithium with food, and the use of slow-release preparations may reduce nausea (17, 668).

Renal toxicity. Lithium has been associated with several symptomatic renal conditions, including diabetes insipidus, nephrotic syndrome and renal failure (220). It is estimated that polyuria occurs in up to 20% of patients. About 30% of lithium-treated patients will experience an episode of lithium intoxication, which may lead to decreased glomerular filtration rate. Deteriorating renal function has been associated with higher plasma

lithium levels, concurrent medication, somatic illness, and age rather than time on lithium (669). Overall, there is minimal evidence that most patients are at risk for progressive renal failure but plasma creatinine concentrations should be measured at least annually in those on lithium therapy (220).

Haematological side effects. Dose-related hepatic and haematological effects have been reported with anticonvulsants (670, 671). Leucopenia has been reported during the first 3 months of treatment in about 12% of children and 7% of adults who received carbamazepine (670). In one study, the rate of leucopenia was five times higher with carbamazepine than with divalproex (672). However, a large survey found that the overall rate of blood dyscrasias was not different for carbamazepine, phenobarbital, phenytoin or divalproex (671). Leucopenia is generally reversible with dose reduction or discontinuation of carbamazepine (670, 672). Rapidly developing bone marrow suppression resulting from hypersensitivity can also occur with carbamazepine. The risk of blood dyscrasias increases with age, being two to four times higher in older patients (671, 673).

In a large survey of 122 562 patients, most of the changes in white blood cell counts, which were rated as probably or definitely drug-induced, were attributed to clozapine (0.18% of patients), carbamazepine (0.14%) and perazine (0.09%) (674). In patients on newer atypical antipsychotics, neutropenia rated as probably or definitely drug-related in only five patients during treatment with olanzapine and in one case with risperidone. Incidences of haematological changes for antidepressants were much lower (about 0.01%).

Analysis of post-marketing surveillance data showed that clozapine and remoxipride had the highest risks of haemopoietic reactions followed by the phenothiazine derivatives, thioridazine and chlorpromazine. All patients started on clozapine should have a baseline haematological profile and be enrolled in the clozapine monitoring programme that requires weekly or biweekly monitoring of haematological parameters. There was no evidence of an increased risk with haloperidol, pimozide, sulpiride or risperidone (675).

Cardiovascular side effects. In a comparison of clozapine, olanzapine, quetiapine, risperidone, haloperidol and thioridazine, QTc interval was prolonged to some degree by all agents, but only thioridazine prolonged QTc interval $\geq$75 ms, and only ziprasidone and thioridazine prolonged QTc interval $\geq$60 ms (676, 677). An increased risk of abnormal QTc $>$456 ms has been associated with age over 65 years, TCAs, thioridazine, droperidol and high antipsychotic dose (678). Abnormal QT dispersion or T-wave abnormalities were not significantly associated with antipsychotic treatment, but were associated with lithium therapy (678). Almost 60% of older patients receiving lithium maintenance therapy experienced electrocardiographic abnormalities (525).

Endocrine side effects. Lithium maintenance therapy increases the risk of hypothyroidism, which has been associated with an increased risk of affective episodes, rapid cycling and more severe depressive episodes in some studies (216, 679). Over 30% of older patients receiving lithium maintenance therapy required thyroxine replacement or had elevated thyroid-stimulating hormone levels (526). Routine screening of thyroid function is recommended during lithium treatment.

Evidence has suggested a risk of PCOS with the use of divalproex; however, this information is mainly derived from patients with epilepsy, which in itself has been associated with a high incidence of PCOS. In a small open-label study in women with bipolar disorder, divalproex was associated with higher rates of menstrual abnormalities and biochemical evidence of hyperandrogenism compared with lithium (680). In another small study, 100% of lithium-treated, and 60% of divalproex-treated patients reported some type of menstrual dysfunction, which had preceded the diagnosis of bipolar disorder in some cases; however, PCOS-like changes were not seen in women receiving divalproex or lithium (681).

Cognitive impairment. While patients commonly attribute lithium non-adherence to difficulties with memory (45), evidence of a negative effect is weak (284). When cognitive function was assessed in medication-free, carbamazepine-treated, and lithium-treated patients with bipolar disorder, no significant differences in attention, concentration, visuomotor function or memory were observed across the three groups when compared with non-bipolar control subjects (682). Other data have suggested a slowing of motor speed, and perhaps mild memory deficits with lithium therapy (683, 684). These effects of lithium may, however, be related to clinical or subclinical hypothyroidism (685, 686). Dosage reduction or substitution with divalproex may help reduce cognitive deficits (17, 687).

Lamotrigine and gabapentin appear to have benign cognitive profiles, while topiramate may cause cognitive impairment, especially when dosage is rapidly titrated (688).

Atypical antipsychotics have well demonstrated cognitive benefits in patients with schizophrenia (284). Preliminary data suggest improvements in measures of cognitive performance with risperidone and olanzapine in patients with bipolar disorder (284, 689, 690).

Sedation. Divalproex and gabapentin have been associated with sedative effects, whereas lamotrigine appears less likely to cause sedation (691). Patients taking divalproex are more likely to feel sedated than are those taking lithium (692). The atypical antipsychotics are associated with sedation in 30–50% of patients compared to 8–13% with placebo (127, 128, 132, 134, 140), and 21–29% with divalproex (124, 125). Amongst atypical antipsychotics, quetiapine, clozapine and olanzapine cause more sedation than ziprasidone, risperidone or aripiprazole.

Neurological side effects including extrapyramidal symptoms. Approximately 10–18% of patients taking lithium (121, 145, 693, 694) and 10–15% of patients taking divalproex experience tremor (145, 695). Tremor may be reduced by decreasing medication dose and by using sustained release formulations (279, 696, 697). Conventional antipsychotics, particularly the high potency drugs, are often associated with EPS (698), but atypical antipsychotics have a much lower rate of EPS comparable in most studies to that seen with placebo (533, 699). The incidence of EPS is dose related with risperidone with higher doses (i.e. 4 mg or higher) causing more EPS.

Dermatological reactions. Early clinical experience with lamotrigine was associated with a risk of non-serious rash of approximately 10%, and of serious rash, such as toxic epidermal necrolysis and Stevens-Johnson syndrome of 0.3–1% (352, 360). Concomitant divalproex administration and rapid dose escalation increase the risk of rash (352, 354, 700, 701). With decreases in the recommended starting dose to 25 mg, and following a gradual titration, with 25 mg increments weekly, the risk of serious rash may be as low as 1 in 5000 (353). Patients treated with lamotrigine should be informed about these concerns and told to contact their physician immediately should a rash occur; lamotrigine should be discontinued if a serious rash is suspected.

Divalproex and carbamazepine have been associated with increased risk of rash and Stevens-Johnson syndrome, primarily within the first 8 weeks of therapy (389). In a case-controlled study, the relative risk of Stevens-Johnson syndrome and toxic epidermal necrolysis among carbamazepine users was 25 and among valproic acid users was 24 (valproic acid data based on four cases, all of whom were using other associated drugs) compared with non-users of these medications (389). Lithium may be associated with the development of severe treatment-resistant pustular acne that only resolves with lithium discontinuation (702).

Hyperglycaemia and type 2 diabetes. Reports of increased prevalence of diabetes with the use of atypical antipsychotics have prompted the FDA to ask manufacturers to add a warning statement describing the increased risk of hyperglycaemia and diabetes in patients taking these medications. Patients with bipolar disorder appear to be at higher risk of developing hyperglycaemia and type 2 diabetes compared with the general population (498). The risk is further increased with atypical antipsychotics compared to conventional antipsychotics (703–707). The risk may be higher with clozapine and olanzapine but definitive prospective data are unavailable. While much of the risk may be related to weight gain, some individuals develop type 2 diabetes during treatment with atypical antipsychotics without measurable weight gain (708).

Product labelling for atypical antipsychotics now recommends that patients with existing diabetes be monitored regularly for worsening of glucose control, and those with risk factors for diabetes (e.g. obesity, family history of diabetes) undergo fasting blood glucose testing at the beginning of treatment and periodically thereafter. All patients on atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness; if identified, patients should undergo fasting blood glucose testing, discontinuation of the atypical antipsychotic if possible, and initiation of anti-diabetic treatment if necessary.

Dyslipidaemia. Much of the data on the effects of atypical antipsychotics on lipid parameters come from retrospective, cohort studies in patients with schizophrenia. Studies suggest significantly greater increases in lipid levels with olanzapine than risperidone (709, 710). Olanzapine was associated with nearly a fivefold increase in the risk of developing hyperlipidaemia compared with no antipsychotic exposure, and more than a threefold increase compared with those receiving conventional antipsychotics (710). Increases in triglyceride levels of about 40% have been reported with olanzapine over 3–4 months of therapy (711, 712). In a 47-week, RCT, there was a significantly

greater increase in cholesterol level with olanzapine compared with divalproex, but no significant difference in the incidence of treatment-emergent hypercholesterolaemia (231). In RCTs in patients with schizophrenia, treatment with olanzapine increased total cholesterol and LDL-C levels, while ziprasidone significantly decreased these measures (713). The rate of hypertriglyceridaemia was also significantly increased with olanzapine compared with ziprasidone (714). Small increases in cholesterol and triglycerides have been reported with quetiapine (715). Lipid profiles should be monitored and appropriate lipid-lowering medications prescribed as needed.

Mortality in Elderly with behavioural problems

There are no reports of increased risk of mortality with atypical antipsychotics in the treatment of patients with bipolar disorder. However, the FDA recently issued a public advisory black box warning on the increased risk of mortality with atypical antipsychotics in the treatment of elderly patients with dementia. The FDA opinion was based on a meta-analysis involving 5106 elderly patients with dementia treated with aripiprazole, olanzpaine, quetiapine and risperidone. The public advisory, however, also covered other atypicals including ziprasidone and clozapine. The FDA also said that the preponderance of deaths (30 days hazard ratio of 1.7) were related to cardiovascular and infectious (pneumonia) adverse events. Although the data are limited, FDA indicated that, in its opinion, typical antipsychotics carried a similar risk and that the FDA is conducting an analysis of this currently. The pathophysiological mechanism was not identified for this increased risk of mortality (FDA, April 11, 2005).

Appendix 1

Key resources for bipolar disorder

Psychoeducation manuals

Bauer M, McBride L. *Structured Group Psychotherapy for Bipolar Disorder*, 2nd edn. New York: Springer, 2003. This is the best manual, very detailed, and is available in French and English. Phase I describes a six-session psychoeducational intervention that has been used extensively in studies and in clinical practice.

Sperry, L. *Psychopharmacology and Psychotherapy: Strategies for Maximizing Outcomes*. New York: Brunner/Mazel, 1995. Useful for basic principles.

Miklowitz DJ, Goldstein MJ. *Bipolar Disorder: A Family Focussed Treatment Approach*. New York: The Guildford Press, 1997. Includes family psychoeducation, but goes far beyond into family therapy.

Cognitive therapy for bipolar disorder manuals

Basco MR, Rush, AJ. *Cognitive-Behavioral Therapy for Bipolar Disorder*. New York: Guildford Press, 1996. This was the first manual of this type; useful but perhaps too specific and now dated on medication aspects. Good session guidance.

Lam DH, Jones Sh, Hayward P, Bright JA. *Cognitive Therapy for Bipolar Disorder*. Chichester: Wiley, 1999. Widely regarded as the most used in clinical studies and very specific.

Newman CF, Leahy RL, Beck AT, Reilly-Harrington NA, Gyulai L. *Bipolar Disorder: A Cognitive Therapy Approach*. Washington, DC: American Psychological Association, 2001. More philosphical, less directive, less practical, but still good.

Key books for patients

Greenberger D, Padesky CA. *Mind Over Mood: A Cognitive Therapy treatment Manual for Clients*. New York: Guilford, 1995.

Mondimore FM. *Bipolar Disorder – A Guide for Patients and Families*. Baltimore, MD: John Hopkins University Press, 1999.

Duke P, Hochman G. *A Brilliant Madness*. New York: Bantam Books, 1993.

Jamison KR. *An Unquiet Mind: A Memoir of Mood and Madness*. New York: Random House, 1995.

Copeland ME. *Living Without Depression and Manic Depression: A Workbook for Maintaining Mood Stability*. Oakland, CA: New Harbinger, 1994.

Torrey EF, Knable MB. *Surviving Manic Depression: A Manual on Bipolar Disorder for Patients, Families and Providers*. New York: Basic, 2002.

Miklowitz DJ. *The Bipolar Disorder Survival Guide*. New York: Guildford, 2002.

Key web resources

Canadian Mental Health Association http://www.cmha.ca

Centre for Addiction and Mental Health http://www.camh.net/

Canadian Network for Mood and Anxiety Treatments http://www.canmat.org

Depression and Bipolar Support Alliance (USA) http://www.dbsalliance.org/

Mood Disorders Society of Canada http://www.mooddisorderscanada.ca/

National Institute of Mental Health (USA) http://www.nimh.nih.gov/

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