

# Continuation and Prophylactic Treatment of Bipolar Disorder

Verinder Sharma, MD, FRCPC<sup>1</sup>, Lakshmi N Yatham, MBBS, FRCPC, MRCPsych<sup>2</sup>, David RS Haslam, MSc, MD<sup>3</sup>, Peter H Silverstone, MD, FRCPC, MRCPsych<sup>4</sup>, Sagar V Parikh, MD, FRCPC<sup>5</sup>, Raymond Matte, MD, FRCPC<sup>6</sup>, Stanley P Kutcher, MD, FRCPC<sup>7</sup>, Vivek Kusumakar, MBBS, FRCPC, MRCPsych<sup>8</sup>

**Objectives:** To summarize the evidence for efficacy from published literature of biological treatments in the continuation and maintenance phases of bipolar disorder, as well as the recommendations about different treatment options made by the working group within the Bipolar Sub-Committee of the Canadian Network for Mood and Anxiety Treatments (CANMAT).

**Methods:** A review of relevant published literature and proceedings of international conferences was conducted. The quality of evidence was assessed and classified according to the Periodic Health Examination criteria. Treatment recommendations of the working group were based on quality of evidence, a consensus of expert views, and the opinions of psychiatrists and family physicians from across Canada.

**Results:** There is overwhelming evidence for the efficacy of lithium in the prophylaxis of bipolar disorder. The evidence for carbamazepine is less robust. There are no published double-blind studies with adequate numbers of subjects treated with divalproex sodium.

**Conclusions:** During and at the end of the continuation phase it is recommended that mood stabilizers should remain the mainstay of therapy and that other treatments should be gradually discontinued or maintained only if there is valid reason to do so. Efficacious maintenance treatment can reduce morbidity and mortality significantly and improve patients' quality of life.

(Can J Psychiatry 1997;42 Suppl 2:92S–100S)

**Key Words:** continuation, maintenance, prophylaxis, exacerbation, bipolar disorder, lithium, divalproex sodium, carbamazepine, neuroleptic, electroconvulsive therapy

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Manuscript received April 1997, revised and accepted July 1997.

<sup>1</sup>Assistant Professor and Director, Mood Disorders Unit, Department of Psychiatry, University of Western Ontario, London, Ontario.

<sup>2</sup>Assistant Professor and Director, Mood Disorders Clinical Research Unit, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia.

<sup>3</sup>Resident, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

<sup>4</sup>Associate Professor, Department of Psychiatry, University of Alberta, Edmonton, Alberta.

<sup>5</sup>Assistant Professor, Department of Psychiatry, University of Toronto; Head, Bipolar Clinic, Clarke Institute of Psychiatry, Toronto, Ontario.

<sup>6</sup>Associate Professor (Clinical) and Head, Outpatient Services and Mood Disorders Clinic, Department of Psychiatry, University of Sherbrooke, Sherbrooke, Quebec.

<sup>7</sup>Professor and Head, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

<sup>8</sup>Associate Professor and Head, the Division of Child and Adolescent Psychiatry; Director, Mood Disorders Group, Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia.

*Address for correspondence:* Dr V Sharma, Mood Disorders Unit, University of Western Ontario, London Psychiatric Hospital, 850 Highbury Avenue, PO Box 2532, London, ON N6A 4H1

The continuation phase of the illness (also called the early stable phase) is defined as commencing once euthymia and resolution of psychosis have been achieved. The duration of this phase is usually between 6 and 12 weeks and is followed by a maintenance or prophylactic phase. Bipolar disorder is a chronic illness characterized by relapses, recurrences, and remissions.

Recurrence has been reported to be associated with substance dependence (1–5), the presence of psychotic features (1–3), and family history of schizoaffective disorder with manic features or mania (2,6,7). Duration of illness does not seem to correlate with the rate of recurrence (1,6). There is suspicion, however, based on schizophrenia research, that duration of illness before treatment is instituted may have a direct relationship with increased deficits and reduced treatment response. Available evidence suggests that electroconvulsive therapy (ECT) does not affect the rate of recurrence (8). Five-year and 4-year follow-up studies have failed to find the number of prior mood episodes to be a predictor of the number of subsequent episodes (1,6). Subsyndromal symptoms have been observed in 50% of patients in a 3-year

treatment study, and these were associated with an approximately fourfold increase in risk of relapse (9). Naturalistic study has also observed the rate of relapse to correlate positively with the number of interepisode symptoms (10,11).

Predictive models have been used to study the cost (exposure to lithium) versus benefit (prevention of relapse) (12). The mortality of patients with untreated bipolar illness is 2 to 3 times higher than that of the general population; bipolar patients receiving treatment have a higher suicide risk when compared with the normal population (13). About one-quarter of bipolar patients attempt suicide (14).

To avoid psychopharmacotherapy that would induce unwanted side effects and be ineffective for target symptoms, clinicians must be able to determine which agent is most likely to be effective. Studies conducted to determine the predictors of response to treatment, however, have been mainly uncontrolled. In addition, in lithium studies the term "relapse" has been poorly defined (15), and the intraindividual treatment response is variable from one episode to the next (16). The predictive validity of applying predictors of lithium antimanic potential to prophylactic therapy is uncertain (17,18). Patients whose pattern of illness is mania followed by depression respond to lithium prophylaxis in approximately 80% of cases compared with a response rate of 25% to 30% in patients with a depression followed by mania and then a well interval pattern (15,19–21). Available data regarding prediction of prophylactic response to both divalproex and carbamazepine are weak and clinically not useful. Estimation of the risk of recurrence of mood episodes is less than precise.

### Quality of Evidence and Recommendations

The quality of evidence is per the Periodic Health Examination format. The classification of recommendations from the working group is the product of expert opinions and a consensus process and reflects a global impression based on the quality of evidence for efficacy, adverse effects, tolerability, and acceptability of a given treatment for the patient.

### Treatment during Continuation or Early Stable Phase

Treatment recommendations for the continuation or early stable phase of acute mania are discussed below and illustrated in an algorithm (Figure 1). Psychoeducation continues, with or without the addition of concomitant psychotherapy, during this phase of illness recovery. The range of available psychosocial interventions is discussed by Parikh and others in a previous article in this publication (22). Psychoeducation and psychotherapy are particularly important in fostering a collaborative approach in treatment with the patient. During this period, optimum serum levels of mood stabilizers are maintained, normal laboratory investigations are confirmed, and side effects are eliminated or minimized. The recommended approach to the use of mood-stabilizing agents

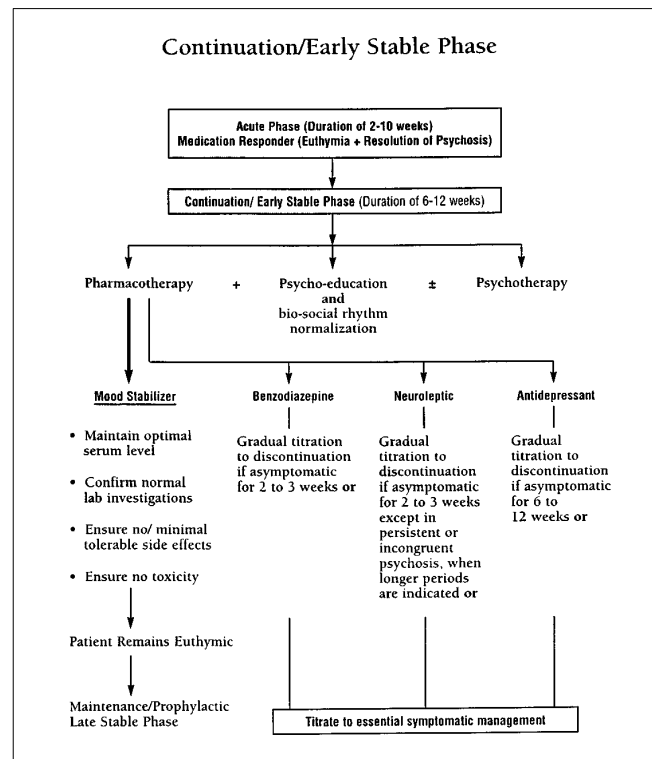


Figure 1. Continuation phase treatment algorithm reproduced courtesy of CANMAT.

during this phase will be discussed in the maintenance phase section of these guidelines.

The suggested adjustments to adjunctive medications during this phase of the illness are as follows:

#### *Benzodiazepines*

A systemic evaluation of benzodiazepines as prophylactic agents in bipolar disorder has not been conducted. Chronic use of these agents is associated with tolerance, dependence, and withdrawal (23–26). Administration in the elderly increases the risk of potentially fatal accidents secondary to impaired coordination (27,28). The absence of prophylactic efficacy and attendant risks associated with long-term use support the gradual titration of these agents to either discontinuation or the minimal effective dose necessary for essential symptomatic management.

#### *Typical Neuroleptics*

In the absence of evidence to support continued use in maintenance therapy and in the presence of the possibility of sustaining serious side effects (29–34), gradual reduction and eventual discontinuation of these agents during this phase of treatment is recommended unless there is a clear clinical indication to continue with the medication, for example, persistent psychotic symptoms. The lowest dose possible should be used for essential symptomatic management. After

a risk–benefit analysis, and if appropriate, attempts should be undertaken to discontinue these agents gradually.

#### *Atypical Neuroleptics*

Although risperidone and olanzapine may have better long-term side effect profiles, there are no currently available data for long-term efficacy of these agents in prophylaxis of bipolar mood disorder with the exception of a small case series for risperidone (35). An attempt should be made, therefore, to reduce and discontinue these agents within a few weeks of remission of acute symptoms. Clozapine is usually reserved for severe refractory bipolar disorder patients, and hence it may need to be continued during the maintenance phase of treatment (36–38).

#### *Antidepressants*

The duration of antidepressant administration during this phase cannot be derived from empirical evidence and is based on clinical judgement. Continuation of antidepressant therapy should exceed what would have been the duration of an episode in the absence of treatment. Where applicable, an estimation of this treatment interval can be based on the duration of previous depressive episodes. In the absence of such a history, a 6- to 12-week course is recommended when the patient is already on a mood stabilizer (39). Under the cover of a mood stabilizer, gradual downtitration over a 2- to 4-week period would be advisable in patients with antidepressant-induced mania, increased cycle acceleration, or precipitation of a mixed state (39). Although mood may have improved, gradual reduction of the antidepressant dose may be appropriate if the patient is experiencing intolerable side effects, especially if compliance is threatened.

#### *ECT*

The relapse rate after ECT administered during the acute phase and followed by lithium or antidepressant therapy is approximately 20% (40). Continuation ECT is indicated for patients who respond poorly to continuation medications or prefer ECT. During the continuation phase of the illness, ECT is usually indicated once weekly and the interval gradually decreased to once a month. Incomplete responders and those with a recurrent course may warrant more frequent ECT than at a monthly interval (40).

### **Summary of Continuation Phase Treatment**

Acute-phase treatment can usually last from 2 to 10 weeks, and the end of the acute phase is defined as the point when the patient reverts to euthymia and the psychotic symptoms are resolved. The acute phase of treatment presents opportunities for psychoeducation of family and friends and for building a collaborative therapeutic relationship with the patient. The patient is often only able to tolerate and digest focal bits of psychoeducational information during the acute phase.

Significant psychoeducational and psychotherapeutic interventions commonly and appropriately occur in the continuation phase, which lasts for a further 6 to 12 weeks. Normalization of biological and social rhythms is also an essential part of management. Mood-stabilizing medication is the mainstay of pharmacotherapy. Neuroleptics and benzodiazepines, used for acute behavioural suppression or for rapid control of manic behavioural dyscontrol, need to be gradually discontinued over 2 to 3 weeks after symptom control has been achieved. Neuroleptics need to be continued well beyond the acute phase only if there are persistent or incongruent psychotic symptoms. Similarly, antidepressants can be gradually discontinued over 6 to 12 weeks after the remission from bipolar depression provided that the patient continues to be on a mood stabilizer. If there is a previous history of the patient's symptoms being exacerbated every time neuroleptics, antidepressants, or other psychotropic medications are discontinued, however, there is justification in continuing these medications in addition to mood stabilizers during this phase and beyond. The clinician and patient should constantly weigh the benefits versus risks of continuing or discontinuing treatments. This is also the phase for active discussion with the patient and family about long-term treatment and the benefits and risks of prophylactic treatment.

Serum medication levels and monitoring of bodily systems should be done as clinically indicated in the continuation phase.

### **Treatment during Maintenance or Prophylactic Phase (Late Stabilization Phase)**

Estimation of the risk of recurrence of mood episodes is less than precise. Early studies with lithium (17) and more recent unpublished studies with divalproex and lithium (Bowden and others 1996, papers at the American and Canadian Psychiatric Association meetings) suggest that these mood stabilizers may yield prophylactic benefit in moderate to severe illness, but there is a subgroup of patients, some with mild illness, who may not benefit from prophylactic treatment. There is no consensus, however, about how to identify this subgroup accurately or make reliable predictions.

Definitive indications for the commencement of long-term maintenance treatment with mood stabilizers and the duration of this therapy are not available. The decision to proceed with indefinite maintenance pharmacotherapy after a single manic episode has been supported by decision analysis, which analyzed the costs (that is, lithium exposure) and the benefits (that is, preventing relapse). Long-term lithium treatment has also been associated with a significant reduction in the mortality rate in patients with bipolar disorder (41).

The authors of these guidelines suggest that the continuation phase psychoeducation, biosocial rhythm normalization, and pharmacotherapies be continued for not less than 6 months (preferably for 12 months) in those with a low risk

**Table 1. Prophylaxis**

Treatment	Quality of evidence <sup>a</sup>	Working group classification of recommendation <sup>b</sup>
Lithium	1	A
Divalproex	2.3	B
Carbamazepine	1	C
Lamotrigine and gabapentin	na	na
Lithium + divalproex	3	B
Lithium + carbamazepine	3	C
Divalproex + carbamazepine	3	C
Typical neuroleptic	1	D
Atypical neuroleptic	2.3	C
ECT maintenance therapy	2.3	C

<sup>a</sup>Quality of evidence rating system:

- 1 At least one randomized controlled trial.
- 2.1 Well-designed controlled trial without randomization.
- 2.2 Well-designed cohort or case-controlled studies, preferably multicentre or from more than one research group.
- 2.3 Very significant results from uncontrolled trials from more than one centre comparing results with and without intervention.
- 3 Opinions of respected clinical authorities based on clinical experience, descriptive studies, or reports of expert committees.

<sup>b</sup>Classification of recommendations:

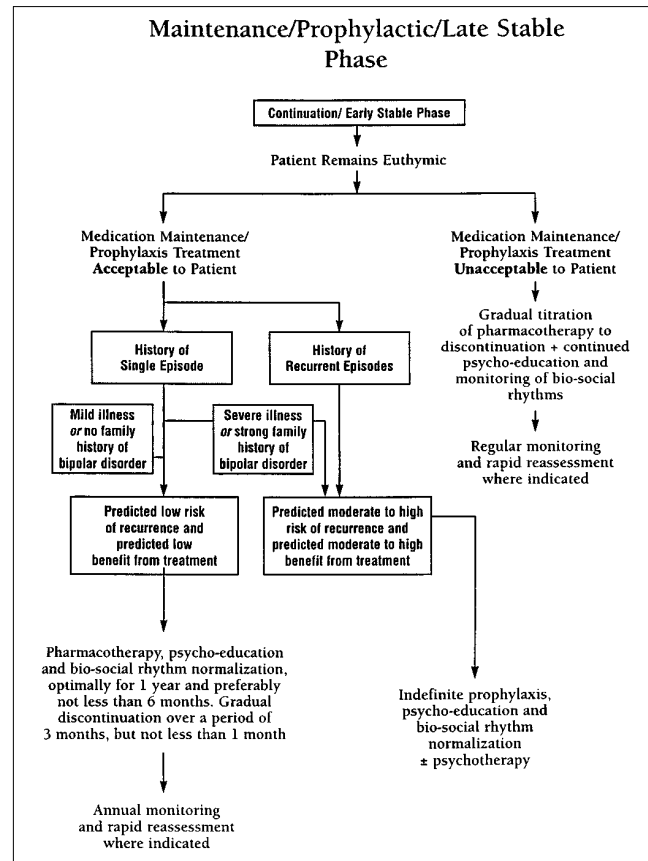
- A Good support for the intervention to be considered in clinical practice.
- B Fair support for the intervention to be considered in clinical practice.
- C Poor support for the intervention to be considered in clinical practice.
- D Fair support for the intervention to be excluded from clinical practice.
- E Good support for the intervention to be excluded from clinical practice.

and indefinitely in those with moderate to high risk of recurrence. Though empirical evidence has been inconsistent, variables proposed as presenting greater than a low risk of relapse in manic patients include poor occupational advancement prior to index episode (3), poorer psychosocial support (42,43), symptoms of depression (44), longer duration of illness (45), presentation of a mixed (46) or rapid-cycling state (47), comorbidity including history of alcoholism (1,3,48), psychotic features (1,6,49,50), and early (7) or late (45) age of onset. Moderate to high risk of recurrence is often dictated by the severity of illness and a strong family history of bipolar disorder. The assessment of moderate to high risk in a patient willing to accept maintenance treatment is an indication for psychoeducation, stabilization of biosocial rhythm, and prophylaxis pharmacotherapy of an indefinite duration. Treatment with benzodiazepines, neuroleptics, and antidepressants during the continuation or early stabilization phase has been discussed previously.

Long-term maintenance treatment with mood stabilizers is outlined below, and Table 1 presents the quality of evidence as per the Periodic Health Examination classification, as well as the recommendations for treatment made by the working group. The algorithm for treatment during this phase is shown in Figure 2.

*Lithium*

The prophylactic efficacy of lithium monotherapy has been demonstrated in controlled studies. Lithium maintenance



**Figure 2.** Maintenance phase treatment algorithm for bipolar disorder reproduced courtesy of CANMAT.

therapy reduces both the frequency and severity of mood elevation and depression episodes in bipolar patients (51–59). Compared with placebo, the maintenance effect of lithium may reduce the recurrence of a major affective episode to 20% to 40% within 2 to 3 years of follow-up (51,52,54,60,61). The mean risk of recurrent major affective episodes of either polarity has been reported to be, on average, sixfold lower with lithium than with placebo (62). Noncompliance in uncontrolled clinical samples is probably associated with the higher rates of mood dysregulation or major episode relapse (63). The target range of lithium is to maintain a serum level of 0.8 to 1.1 mmol/L. The effects of a lithium serum level between 0.6 and 0.8 mmol/L are currently being studied, but there are no published data. At serum levels of between 0.4 and 0.6 mmol/L, the risk of relapse is increased by about 250% (62). The target serum lithium level would need to balance the risk of higher rates of relapse with the risk of side effects and thus noncompliance. Serum lithium levels in the lower range (0.4 to 0.6 mmol/L) carry a higher risk of relapse, but there is likely increased risk of noncompliance at the higher range (0.8 to 1.0 mmol/L) (58,64). Lithium dosing in the elderly requires that particular consideration be given to issues of tolerability due to changes in renal clearance.

Many patients will respond poorly to maintenance therapy with lithium (65). Inadequate efficacy includes partial remission, resolution of one but not the other phase of illness, and relapse following a euthymic period. A favourable lithium response is associated with a family history of bipolar illness and a previous mania–depression–euthymia sequence of illness (65,66). Factors that are somewhat predictive of a poorer response to lithium include rapid-cycling course and substance abuse (4) and a negative familial affective style (67,68). The quality of evidence for lithium maintenance therapy is “1,” and the working group classified their recommendation as “A” (see Table 1).

#### *Divalproex Sodium*

The prophylactic efficacy of divalproex monotherapy in the prevention of bipolar episode relapse has been demonstrated in moderate to severe illness in a recent prospective, randomized placebo-controlled trial comprised of parallel placebo, lithium, and divalproex interventions over a one-year period (Bowden 1996, unpublished observations). The facts that the follow-up in this trial was for a period of only one year and that the detailed results are unavailable, however, have prompted the committee to conclude that the efficacy of divalproex as a prophylactic agent in bipolar illness has not been proved at this stage, although many centres are using this agent for prophylaxis. At this time, the only published evidence comes from open studies (69–71). The quality of evidence, therefore, is “2.3,” and the classification of recommendation, “B.”

#### *Carbamazepine*

The prophylactic efficacy of carbamazepine has been demonstrated in both uncontrolled and double-blind crossover comparisons with lithium and in double-blind, randomized placebo-controlled studies (72–74). Duration of follow-up, sample size, heterogeneity of the diagnosis, and confounding effects of concurrent medication all jeopardize the validity of its reported efficacy as a prophylactic agent in the treatment of bipolar disorder. Limited evidence of long-term prophylactic efficacy, including possible development of tolerance, poor patient acceptability, and rare, although serious, hematological side effects detract from the routine prophylactic use of this agent as an alternative to lithium (59,75–77). Maintenance use of carbamazepine as monotherapy or adjunctive therapy may be appropriate if initially proved to be effective in patients who responded poorly to lithium. The quality of evidence for carbamazepine treatment in this phase is “1.” The classification of recommendation made by the working group was “C” in view of limited evidence of long-term prophylactic efficacy, including possible development of tolerance, poor patient acceptability, and rare but serious hematological side effects.

#### *ECT*

Evidence of the prophylactic efficacy of long-term ECT has been contaminated by the concurrent administration of psychopharmacologic agents. Maintenance ECT may decrease the frequency and duration of major mood episode relapses. Possible indications for maintenance ECT include rapid relapse after ECT, relapse despite adequate maintenance medication, precipitous relapse of severe illness, inability to tolerate prophylactic medication, prior history of more favourable response to ECT as compared with maintenance medication, and patient preference in the setting of noncompliance with medication. Effective use of maintenance ECT in case studies has been reported, but no controlled trials have been published (40,78). (Quality of evidence: “2.3”; classification of recommendation: “C.”)

#### *Typical Neuroleptics*

Minimal and methodologically limited evidence exists for the prophylactic efficacy of neuroleptics as mood stabilizers in bipolar disorder (29–32). Interpretation of these results is complicated by a small placebo-controlled crossover trial, with limited power to detect a difference, which reported depot neuroleptic administration to have no treatment value as a prophylactic agent in bipolar patients (33). Patients with mood disorders may be at a relatively high risk of developing tardive dyskinesia following treatment with these agents (34). The quality of evidence for typical neuroleptics is high (“1”), but the classification of recommendation was “D” because of concerns about long-term side effects such as tardive dyskinesia.

#### *Atypical Neuroleptics*

Uncontrolled trials and case studies report an effective role for clozapine in the continuation and maintenance phases of patients who had been refractory to therapy with conventional adjunctive agents (36–38). The prophylactic potential of risperidone in the treatment of bipolar disorder has also not been rigorously studied and remains uncertain. There is, however, a report of a small case series indicating the usefulness of risperidone in the maintenance treatment of bipolar disorder (35): quality of evidence, “2.3”; classification of recommendation, “C.”

#### *Miscellaneous Treatments*

A recent study with a small number of patients showed that those treated with a combination of lithium and divalproex (see Table 1) were significantly less likely to suffer a relapse or recurrence than patients treated with lithium and placebo (78). Although there are not adequate published data to guide clinicians about the value and efficacy of combining other mood stabilizers, experienced clinicians note that this can be a useful strategy, particularly in the refractory patient.

The prophylactic efficacy and associated risks of calcium channel blockers, thyroxine augmentation, and novel anti-convulsant agents (lamotrigine and gabapentin) remain

unproved by rigorous investigation (75,80–82). Insufficient evidence exists to support specific recommendations regarding the long-term use of these agents. If stability and euthymia are achieved with one of these agents in a refractory patient, however, it would be inadvisable to discontinue these medications for at least 1 to 2 years. In the absence of systematic and valid data, the working group could not make any recommendation for the use of these agents in the prophylaxis of bipolar disorder.

### Special Populations

There is little in the way of published work at the extremes of the age range, but open studies with adolescents and the elderly suggest that mood stabilizers are an effective treatment (83,84) in acute mania. Although lithium can be effective in young people, there is some evidence that divalproex may be more effective in adolescent populations not only because mixed states and rapid cycling are more common in this age group but also because the side effects of lithium may be less acceptable to them (83). In the elderly, bipolar disorder is more commonly associated with medical and neurological difficulties. Although the anticonvulsants may be more acceptable to some of these patients, lithium may be as efficacious in this group (62). The specific issues of differential response by age or medical and neurological status have not been adequately studied. There is also no published work of well-designed studies of mood stabilizers in the prophylactic treatment of young people and the elderly.

The decision whether or not to use medications, particularly mood stabilizers, during pregnancy begins with a risk–benefit exercise in which the patient and her family should be fully involved (84). The risks of teratogenicity, which are present with all the mood stabilizers, although lithium likely poses a slightly lower risk, should be weighed against the risks of an illness recurrence, suicide, or the inability to look after self and the unborn child. If the patient's previous course of illness has been good with low severity and frequency of episodes, a planned pregnancy without mood stabilizers may be considered, with a gradual discontinuation of medication and a 4-week medication-free period before conception. Elective use of ECT, neuroleptics, and selective serotonin reuptake inhibitors in the first trimester can pose a lower relative risk to the fetus compared with mood stabilizers (85,86).

If a mood stabilizer must be used in the first trimester of pregnancy, clinicians should consider folic acid supplements with anticonvulsants and also monitor for teratogenicity using appropriate investigations. Mood stabilizer dose may need to be raised as the blood and fluid volume increases during pregnancy to maintain a therapeutic serum level. If mood stabilizer is being continued during delivery, the doses need to be reduced drastically in order to avoid the toxicity caused

by decreasing blood and fluid volumes immediately following childbirth.

The immediate postpartum period carries with it a greater than 50% risk of recurrence or exacerbation (87). Hence it is advisable to recommend reinstating mood stabilizer treatment if this had been discontinued earlier, or ensuring that serum therapeutic levels are achieved and maintained. All mood stabilizers are secreted through breastmilk. There are pooled data to suggest that the medication or metabolites secreted through breastmilk do not pose a significant immediate risk to the newborn (86). Nevertheless, there are no long-term data available to rule out conclusively any behavioural effects on the developing child exposed to mood stabilizers during the newborn period. It is a common practice, therefore, to recommend discontinuing breastfeeding of the newborn if this is clinically appropriate.

### Discontinuation of Pharmacotherapy

The risk of recurrent bipolar episodes for those who discontinue lithium treatment has been reported in a metaanalysis to be as much as 28 times greater per month than for those who continue with lithium therapy (88). If lithium is to be discontinued for whatever reason, it should be withdrawn gradually over several weeks because studies suggest that the 5-year overall risk of recurrence in the rapid-discontinuation (< 2 weeks) group was 1.77 times higher (94.1%) than in the gradual-discontinuation group (53.3%). The 5-year rates of recurrence were 96% and 73% in bipolar type I and 91% and 33% in bipolar type II after rapid and gradual discontinuation, respectively (21).

The effects of abrupt discontinuation of anticonvulsants, antidepressants, benzodiazepines, and neuroleptics have not been systematically studied, although there is growing evidence in clinical practice that abrupt discontinuation provokes relapse. Whenever possible, gradual pharmacotherapy discontinuation over one month or more would be prudent.

### Summary of Maintenance or Prophylactic Phase Treatment

If the patient has remained stable through the continuation phase of treatment, the clinician, patient, and family need to consider the value of prophylactic mood stabilizer treatment, which can reduce morbidity and mortality risks and improve the quality of life. The decision (see Figure 2) is relatively easier in patients who have had recurrent episodes, whose illness is very severe, or who have a strong family history of bipolar disorder. It is difficult, if not impossible, to predict accurately the minority of patients diagnosed with bipolar disorder who will never have a further mood disorder episode. Thus the recommendation for prophylactic treatment should be the rule. There should be very good reason not to recommend robust prophylactic treatment in a patient with a clear diagnosis of bipolar disorder. Apart from in the rare patient

who cannot tolerate any treatment, the decision to recommend indefinite prophylaxis may be deferred in patients with a single episode of hypomania with no history of depression and no family history of bipolar disorder. Even with these patients, however, every effort should be made to ensure mood stabilizer treatment for about a year. When medication is being discontinued, it should be done on a gradual basis over about 3 months, but not less than one month. Patients who discontinue treatment should have access to regular monitoring, rapid reassessment, and treatment if required.

Lithium is *the* medication with proved prophylactic efficacy in bipolar disorder. It has been used in large numbers of patients, been tested in double-blind conditions, and been used over many years. It has demonstrated efficacy in classical, nonrapid-cycling, and nonmixed states, as well as in primary bipolar disorder, at serum levels of 0.8 to 1.1 mmol/L. There is growing evidence from several open studies that divalproex has significant prophylactic efficacy similar to lithium. At 2 recent conferences, the results of a double-blind multicentre study comparing lithium, divalproex, and placebo in the prophylaxis of bipolar disorder showed that divalproex and lithium had equal efficacy and were superior to placebo in patients with moderate to severe illness. This study is as yet unpublished. Divalproex may also be useful in early-onset bipolar disorder and in secondary bipolar disorder. There is some good evidence that carbamazepine has prophylactic efficacy, but more recently, its efficacy has come into question in long-term use and in rapid-cycling conditions. It too, like divalproex, is useful in secondary bipolar disorder.

Few patients manage a lifetime of bipolar disorder with monotherapy. Most require short- or long-term polytherapy with mood stabilizers and/or ECT. A very small subgroup of patients may be totally refractory to mood stabilizers and may require maintenance ECT or an atypical neuroleptic like clozapine.

Serum levels of medication and other monitoring of bodily systems should be conducted as clinically indicated, but no less than once every 6 months.

### Early Symptom Exacerbation

Subsyndromal mood dysregulation that does not satisfy major mood episode criteria is common in bipolar disorder. The differentiation between intermittent subsyndromal symptoms, which are the precursor of an impending acute episode, and a period of symptoms unrelated to a major mood episode can be difficult. Subsyndromal symptoms with depressive features have been described as often resolving without intervention (9,89). Those subsyndromal symptoms which are hypomanic in nature may have a greater risk of evolving into full affective episodes (9,89). Optimally, the patient and his or her significant others should be prepared in advance to recognize the precipitating factors and early

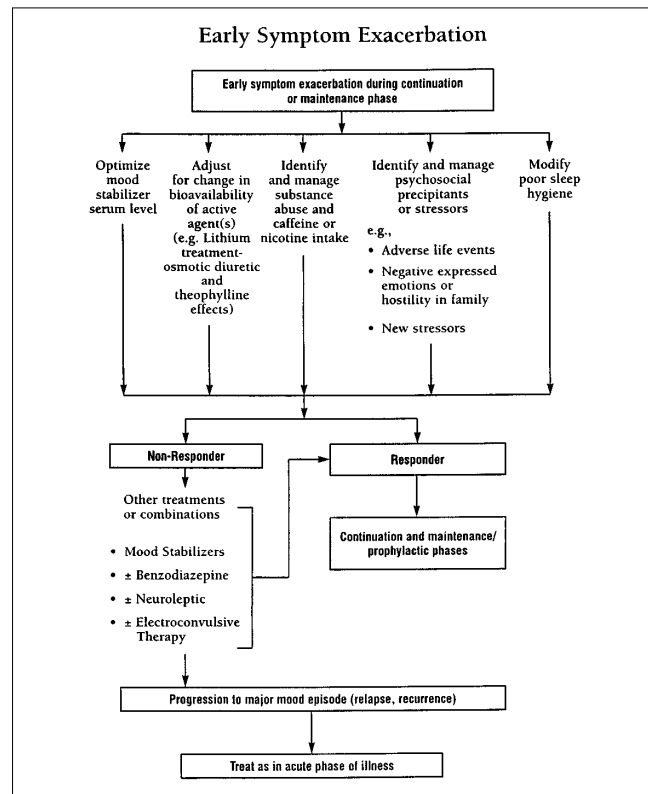


Figure 3. Treatment algorithm for early symptom exacerbation reproduced courtesy of CANMAT.

manifestations of such episodes so as to facilitate prompt reassessment and appropriate intervention.

A recommended approach to the management of early symptom exacerbation is outlined in an algorithm (Figure 3). Should the patient tolerate an elevation of the existing mood stabilizer to the upper 20% of the therapeutic range, this may obviate additional pharmacologic augmentation. Insomnia may represent either a precipitant and/or an early symptom of mania. Nonresponders to the initial management strategies outlined in Figure 3 may require short-term pharmacologic augmentation or ECT (9,89). Such augmentation may include periodic use of a benzodiazepine to promote sleep with the intention of avoiding the precipitation of a major mood episode (90–92).

These guidelines have applied a classification previously used to standardize the definition of unipolar depression treatment phases (93). If symptoms meet the criteria for an acute episode following a period equal to or greater than 8 weeks of remission, it is considered to be a recurrence, whereas an acute episode within an 8-week period of the onset of remission would be considered a relapse. Progression to a major mood episode requires the initiation of treatment for the acute phase of illness.

## Summary of Treatment of Symptom Exacerbation

It is not uncommon for patients who have been in remission to have exacerbations of symptoms. This may remain at a subthreshold level or, commonly, herald a full-blown episode of a mood disorder. Patients, families, and support networks need education and training to recognize symptom exacerbations. Patients may not recognize symptom exacerbations and may depend on supportive family, friends, or clinicians to do so. Patients should have rapid access to reassessment. Identifying and managing psychosocial precipitants or stressors, ensuring adequate sleep, dealing with alcohol and substance abuse, ensuring optimum serum levels of medication, and ruling out adverse drug interactions are important. Nonresponders to these measures may require the addition of other relevant biological and psychosocial interventions to produce a remission and to prevent the entry into another acute illness phase.

### Clinical Implications

- Prophylactic treatment of bipolar disorder with mood stabilizers can reduce morbidity and mortality.
- Prophylactic treatment can also improve quality of life.

### Limitations

- The evidence to support the use of carbamazepine and divalproex sodium for prophylaxis of bipolar disorder is limited.
- A significant number of patients with bipolar disorder may not

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## Résumé

**Objectifs :** Résumer les résultats relatifs à l'efficacité d'après la littérature publiée sur les traitements biologiques pendant les phases de stabilisation et d'entretien du trouble bipolaire, de même que les recommandations sur les différentes possibilités de traitement qui émanent du groupe de travail au sein du sous-comité du trouble bipolaire du réseau canadien pour les traitements de l'humeur et de l'anxiété (Canadian Network for Mood and Anxiety Treatments - CANMAT).

**Méthodes :** Nous avons examiné la littérature pertinente publiée au sujet de divers traitements biologiques et avons établi un rapport sur le consensus du groupe de travail, qui est fondé sur l'opinion d'experts, de même que sur une vaste consultation des psychiatres et des médecins de famille dans l'ensemble du Canada.

**Résultats :** Tout indique que le lithium est efficace à des fins de prophylaxie du trouble bipolaire. Les preuves de l'efficacité de la carbamazépine sont moins solides. Il n'existe aucune étude à double insu comportant un nombre de sujets suffisant pour tirer des conclusions à l'égard du traitement au divalproex sodique.

**Conclusions :** Pendant la phase de stabilisation et à la fin de celle-ci, on recommande de conserver les psychorégulateurs comme traitement principal et d'abandonner graduellement les autres traitements ou de les conserver seulement pour un motif valable. Un traitement d'entretien efficace pourra réduire la morbidité et la mortalité de façon significative et améliorer la qualité de vie des patients.