Bipolar Disorder

A Summary of Clinical Issues and Treatment Options

Online Diagnosis

Bipolar Disorder Sub-Committee
Canadian Network for Mood and Anxiety Treatments (CANMAT)
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Introduction

The Canadian Network for Mood and Anxiety Treatments (CANMAT) is a group of clinicians, teachers and researchers from across Canada with a special interest in promoting education, evidence based practice and research in depression, bipolar disorder and anxiety disorders.

The Bipolar Sub-Committee of CANMAT is promoting or co-ordinating training modules and preceptorship training programs for psychiatrists, family physicians and other mental health professionals in addition to encouraging multicentre research in Bipolar Disorder. This group has also conducted an extensive and intensive study of evidence based practice in Bipolar Disorder. This evidence and an expert group's recommendations will be the basis of a special series of articles on the Treatment of Bipolar Disorder: Guidelines and Options. This will be published after independent peer review later in 1997.

This monograph is a summary of clinical issues and treatment options in Bipolar Disorder and is directed towards psychiatrists, other mental health professionals and family practitioners in a variety of settings. The treatment algorithms were a result of deliberations by an expert group reviewing published work and clinical practice as well as extensive consultations with over 150 psychiatrists and family practitioners from across Canada.

This CANMAT publication is intended to give clinicians a handy summary of many of the major clinical issues and treatment options, particularly psychopharmacological treatment, in Bipolar Disorder in order to expand the knowledge and scope of their practice. It is not intended to be a reference book, a “cook-book” for treatment or a substitute for good clinical judgement and practice. These are not protocols or guidelines. The reader is provided with some relevant, not exhaustive, list of references placed close to blocks of text.

Patients with bipolar disorder often present with complex clinical issues, ranging from comorbid conditions like alcohol and substance abuse, personality and relationship dysfunction to breakdown in scholastic or work functioning. The authors recommend

that a vast array of treatment and rehabilitative interventions are often needed. While recognizing that healthy therapeutic relationships and systematic psychosocial interventions are the cornerstone of good management, the authors acknowledge that the details of these issues are beyond the scope of this monograph. And, needless to say, with exciting new advances in treatment of Bipolar Disorder on the horizon, such a publication will have to be updated periodically to make it relevant to contemporary practice.

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Epidemiology of Bipolar Disorder

The Epidemiological Catchment Area Study (Regier et al, 1988) indicates that Bipolar I and II disorders combined are more common than previously thought. Akiskal (1996) presents a persuasive argument for considering the diagnosis of hypomania even if it is present for 1-2 days, and not at least 4 days as required in DSM-IV. If this approach is adopted, Bipolar II disorder will have a much greater prevalence than hitherto considered and will certainly broaden the concept of bipolar disorder.

Alcohol and substance abuse are common comorbid, masking and complicating conditions in the presence of bipolar disorder, and most of the research on treatment outcome in bipolar disorder has not included these groups of patients thus making it difficult to extrapolate the results of research treatment outcome studies to this clinical population. There is an established association between cocaine abuse and underlying bipolar disorder.

Akiskal HS. The Prevalent Clinical Spectrum of Bipolar Disorders: Beyond DSM-IV. J Clin Psychopharm. 1996.16:2 Suppl 1. 4S-14S

Regier DA, Boyd JH, Rae DS, Burke JD, Locke BZ, Myers JK, Kramer M, Robins LN, George LK, Karno M. One-month Prevalence of Mental Disorders in the United states: Based on Five Epidemiologic Catchment Area Sites. Arch Gen Psychiatry. 1988. 45: 977-986.

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Classification of Bipolar Disorder

Bipolar I - Mania and Major Depression
Bipolar II - Hypomania and Major Depression
Bipolar III - Cyclothymia
Bipolar IV - Antidepressant induced hypo/mania
Bipolar V - Major Depression with a family history of bipolar disorder
Bipolar VI - Unipolar Mania

This classification, based on the concepts of Young and Klerman (1992), has been commonly used in descriptive work and in identifying groups of subjects in the bipolar spectrum. Bipolar I is the condition that has the best inter-rater reliability and has been most researched in terms of phenomenology, course and outcome with and without treatment. Bipolar II is being increasingly recognised to be commoner than previously thought, particularly in young people, and should be screened for in every patient who presents with depression. There is growing evidence to suggest that Bipolar II responds to mood stabilizers like Bipolar I. Cyclothymia can be present over a lifetime without the development of a full-blown Bipolar Disorder. Some workers treat Cyclothymia as they would a rapid-cycling bipolar disorder. There is no consensus on whether Antidepressant Induced Hypo/Mania is purely an adverse effect of medication or the unmasking of a true underlying vulnerability for bipolar disorder. Recurrent major depression without hypomania or mania and with a significant family history of Bipolar Disorder is a well recognized condition. A significant proportion of patients with bipolar disorder may begin their lifetime of mood problems with depression. This is particularly

so in juvenile onset bipolar disorder. Unipolar Mania is a relatively uncommon yet recognised entity, and if it appears for the first time after the age of 40, should be screened for medical or neurological etiology.

Young RC, Klerman CL. Mania in late life: focus on age at onset. Am J Psychiatry 1992: 149: 867-876.

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Clinical States and Course Specifiers: Implications for Treatment

There is growing evidence that the course or symptoms of bipolar disorder, particularly the presence of rapid cycling or mixed states, may have major clinical significance. Bipolar disorder can manifest with a variety of clinical presentations along the course of a lifetime. Mixed states, rapid cycling and psychosis may occur as phases of the disorder. Rapid cycling and psychotic features may also be more consistently present and be part of a “sub-type” of the disorder. These factors may influence the use of different medications and combinations of medications at different periods during the treatment of bipolar disorder. There is significant evidence that monotherapy with a mood stabilizer over a lifetime benefits only a minority of patients. Hence, classifying the bipolar disorder into specific “subtypes”, like mixed states, rapid cycling and or psychosis, at different points in the course of the illness may allow more specific choice of biological treatment.

Classical Bipolar I with three or fewer cycles per year runs a less turbulent course than bipolar disorder with rapid cycling, and responds very well to Lithium, although it also responds to Divalproex Sodium (DVPX) and Carbamazepine (CBZ). Bipolar II Disorder has not been studied as carefully as Bipolar I disorder, but there is no evidence to suggest that one mood stabilizer is more efficacious than another in this condition. However, future work may show that certain compounds may have both mood stabilizing and superior antidepressant properties, hence making them more suitable for use in Bipolar II Disorder. Rapid Cycling is associated with relatively better response to Divalproex and failure to respond to Lithium and, possibly, Carbamazepine. Rapid Cycling may be a phase in the course of a bipolar disorder, whereas in some subjects it may also be a type of disorder. It can be induced by antidepressant treatment, particularly tricyclic antidepressants (TCAs), and can sometimes be precipitated by abrupt discontinuation of any psychotropic medication in bipolar disorder. Mixed State needs to be screened for in every mania and depression as it is more common than previously thought. It responds to DVPX or CBZ and has a relatively poorer response to Lithium. The newer anticonvulsants, like Lamotrigine and Gabapentin, hold promise, particularly in bipolar depression, but data from double blind controlled trials should be studied before recommendations about these compounds can be made.

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Diagnosing Biphasic Mood Dysfunction

The expressions “feeling high” and “depressed” have come into common use, and as descriptions of Bipolar Disorder are readily available in the public domain, it is essential to distinguish a disorder with mood swings from ordinary mood fluctuations. To be called a “disorder” a condition should, ideally, fulfill the “**4 Ds**”: sufficient *duration* of difficulties (not needed in acute or crisis situations, eg mania), significant *distress to self or others*, feeling *despondent* (as in depression) or being *driven* (as in mania), and evidence of significant *dysfunction*.

Hypomania, in particular, because it can present with a low-grade severity, is frequently missed without particular screening and specific criteria being explored. However, the overzealous clinician can easily overdiagnose hypomania by assuming that “feeling high” is the single most common symptom in the condition. In the ECA Study it was demonstrated that a decreased need for sleep, increased energy and racing thoughts are more commonly reported than feeling high or elated. Hypomania may be missed in the presence of certain adolescent behaviours and lifestyles, but one should take care not to overdiagnose hypomania in adolescence as some ordinary adolescent behaviours can sometimes be mistaken for hypomania.

Mania is more readily diagnosed than a hypomania using standard DSM IV criteria. However, mania can, occasionally, go unnoticed or be masked due to the extreme demands of a subject's work or life situation, during which changes in sleep, energy, drive and

activity, aggression etc. may well be required or be a consequence of the situation.

Irritable mood is much more common in Major Depression than previously realized, and can occur without a miserable or depressed mood, although almost always accompanied with depressed thinking and cognitions. This is particularly so in adolescence and in the elderly. Early onset depression with psychotic features should alert the clinician to the risk of future bipolar disorder. Not every episode of depression in a bipolar disorder may meet the full criteria for a major depression. However, the subject should have at least one episode of major depression and one episode of either hypomania or mania to make a diagnosis of bipolar disorder.

Mixed states are more common than previously thought, particularly in young people. Mania with dysphoric features has been reported in 5-70% of different samples (McElroy et al, 1992). Depressive mixed states, where depression is more predominant but with many features of a hypomania or mania being present, are now being increasingly recognised and may be more common than previously thought (Akiskal, 1996). Mixed states are associated with better response to Divalproex Sodium and Carbamazepine, and relatively poorer response to Lithium hence the accurate diagnosis of this condition has clinical relevance.

Akistal HS. 1996. The Prevalent Clinical Spectrum of Bipolar Disorders: Beyond DSM-IV. J Clin Psychopharmacology. 16:2 Suppl 1. 4S-14S.

McEIroy SL, Keck PE, Pope HG, Hudson Jl, Faedda GL, Swann AC 1992. Clinical and Research Implications of the Diagnosis of Dysphoric or Mixed Mania or Hypomania. Am J Psychiatry. 149:12. 1633-1644.

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Co-Morbidlty or Masking?

Bipolar disorder can be masked or be co-morbid with conduct disorder (Kovacs et al 1995) ADHD, alcohol abuse, cocaine abuse, other substance abuse (Regier et al, 1990), psychotic symptoms, obsessional or panic symptoms, borderline personality functioning and post-traumatic stress disorder. ADHD and Conduct Disorder commonly have an earlier age of onset often before age 8, than bipolar disorder. Episodicity with periods of asymptomatic good functioning especially in the presence of a family history of bipolar disorder, may suggest an underlying bipolar disorder. However, all the above conditions can be truly comorbid with bipolar disorder, making both diagnosis and management difficult. Whereas the clinician should attempt to rule out bipolar disorder in the presence of the above conditions, s/he should also guard against unwarranted speculative overdiagnosis of bipolar disorder. This can be done by employing systematic, structured and standardized algorithms for both diagnosis and treatment. The value of longitudinal monitoring using mood diaries and a meticulous study of family history of psychiatric illnesses are of immense value, especially where there is high suspicion but no clear picture initially to make a diagnosis of bipolar disorder.

Kovacs M, Pollock M. Bipolar Disorder and Comorbid Conduct Disorder in Childhood and Adolescence. J Am Acad Child Adolesc Psychiatry. 1995. 34: 6. 715-723.

Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of Mental Disorders with Alcohol and other Drug Abuse: results from the ECA Study. JAMA. 1990. 204: 2511-2518

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Age of Onset and Gender Issues in Bipolar Disorder

It is being increasingly recognised that bipolar disorder often has its onset in adolescence or early adulthood. First affective symptoms appear in early teenage, and even in preadolescence. There is a growing interest, with little consensus, in the affective and behavioural symptomatology in childhood and adolescence preceding the first onset of a clearly diagnosable bipolar disorder. There is a significant time-lag between the onset of the illness and first treatment. This may put patients at risk of increased morbidity, including effects on personality, school, work and social functioning. There is growing evidence in the schizophrenia literature that this time-lag may

predict a poorer response to treatment. Although there is no clear evidence of this in bipolar disorder, this issue should be borne in mind.

Early onset is often defined as occurring before the age of 25. The younger the age of onset of bipolar disorder, the more likely it is to find a significant family history of the condition. Early onset bipolar disorder most commonly begins with depression and there may be many episodes of depression before the first hypomania. Depression with psychotic features may be a predictor of future full-blown bipolar disorder in the early onset group. Akiskal (1995) has argued that syndromal dysthymia with its onset in childhood, particularly in the presence of a family history of bipolar disorder, may herald a bipolar disorder. Rapid cycling, mixed states, and psychotic features are more common in early onset conditions. The presence of early onset substance abuse should raise one's suspicions about bipolar disorder. Early onset bipolar disorder is more commonly associated with response to Divalproex and a relative failure of response to Lithium not only because rapid cycling, mixed states and substance use are common in this group but also because adolescents and young adults are less tolerant to the side effects of Lithium.

Female gender is more commonly associated with rapid cycling bipolar disorder (Calabrese et al, 1995), with or without thyroid dysfunction, perimenopausal exacerbation of the condition, the risk of exacerbation post-partum and being diagnosed as borderline personality disorder (especially in adolescents or young adults) when, in fact, some of these presentations could be explained by rapid cycling bipolar disorder. Biphasic mood dysregulation is being increasingly recognized as being more common in subjects with borderline personality functioning and there is merit in treating clearly established biphasic mood dysregulation even in the presence of personality dysfunction. Postpartum psychotic and serious mood disorders may well be part of a bipolar spectrum. There is also growing evidence that the pharmocokinetics of many psychotropic medications, including mood stabilizers, is altered in pregnancy, post-partum and even around menstruation. Bipolar disorder secondary to underlying medical or neurological conditions are associated with the condition in the elderly (Evans et al, 1995).

Akiskal HS. Developmental Pathways to Bipolarity: Are Juvenile-Onset Depressions PreBipolar? J Am Acad Child Adolesc Psychiatry. 1995. 34:6. 754-763

Calabrese JR, Woyshville MJ. A Medication Algorithm for Treatment of Bipolar Rapid Cycling? J Clin Psychiatry. 1995. 56 (Suppl 3) 11-18

Egeland JA, Hostetter AM. Amish Study 1: Affective Disorders among the Amish, 1976-1980. Am J Psychiatry. 1983. 140(1): 56-61.

Evans DL, Byerly MJ, Greer RA. Secondary Mania: Diagnosis and Treatment. J Clin Psychiatry. 1995. 56 (Suppl 3): 31-37.

Strober M, Carlson C. Bipolar Illness in Adolescents with Major Depression. Clinical, Genetic and Psychopharmacologic Predictors in a Three to Four Year Prospective Follow-Up Investigation. Arch Gen Psychiatry. 1982. 39: 549-555.

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Bipolar Disorder in Pregnancy and Post-Partum

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 (Packer, 1992). The risks of teratogenicity, posed by all the mood stabilizers, should be weighed against the risks of an illness recurrence, suicide and inability to look after self and the unborn child. If the patient's previous course of illness has been good with low severity of and frequency of episodes, a planned pregnancy without mood stabilizers may be considered, with a gradual discontinuation of medication and a four week medication-free period before conception. Elective use of ECT, neuroleptics and SSRls in the first trimester can pose a lower relative risk to the fetus compared with mood stabilizers. (Altshuler et al, 1996; Packer 1992; Stowe et al, 1995).

If any mood stabilizer is being used in the first trimester of pregnancy, consider folic acid supplements with anticonvulsants, and also monitor for teratogenicity using appropriate investigations. Mood stabilizer dose may need to be raised to maintain a therapeutic serum level as the blood and fluid volume increases during pregnancy. It is advisable to gradually discontinue medication, if this is

appropriate clinically, about four weeks before delivery. If the 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. (Altshuler et al, 1996; Cohen et al, 1995; Stowe et al, 1995). The newborn should also be monitored for and protected from toxicity from mood stabilizers.

The immediate post-partum period carries with it a greater than 50% risk of recurrence or exacerbation. (Cohen et al, 1995), hence it is advisable to recommend re-instituting 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 breast-milk. There is pooled data to suggest that the medication or metabolites secreted through breast-milk do not pose a significant immediate risk to the newborn (Stowe et al, 1995). However, there is no long-term data available to conclusively rule out any behavioural effects on the developing child exposed to mood stabilizers during the newborn period. Hence, it is common practice to recommend discontinuing breast-feeding of the newborn if this is clinically appropriate.

Altshuler LL, Cohen LS, Szuba MP, Burt VK, Gitlin M, Mintz J. 1996. Pharmacologic Management of Psychiatric Illness During Pregnancy: Dilemmas and Guidelines. Am J Psychiatry. 153: 3. 592-606.

Cohen LS, Sichel DA, Robertson LM, Heckscher E, Rosenbaum JF. 1995 Post-Partum Prophylaxis for Women with Bipolar Disorder. Am J Psychiatry. 152:11. 1641-1644.

Packer S. 1992. Family Planning for Women with Bipolar Disorder. Hospital and Community Psychiatry. 43.5. 479-482.

Stowe ZN, Nemeroff CB. 1995. "Psychopharmacology during Pregnancy and Lactation." In Textbook of Psychopharmacology. Ed. Schaatzberg AF, Nemeroff CB. American Psychiatric Press. Chapter 41: 823-835.

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Effects of Undertreated and Untreated Bipolar Disorder

Bipolar is commonly undiagnosed or diagnosed as another condition for an average of 8 years, patients do not seek help for up to ten years after the first appearance of symptoms, and over 60% of patients are untreated, undertreated or inappropriately treated at any given time.

The vast majority of patients with bipolar disorder have multiple recurrences (Keller et al, 1993), and it is very rare for patients to have a single episode of hypo/mania or depression in a bipolar disorder over a lifetime. The length of symptom-free intervals often decreases with age. The presence of first-rank symptoms may predict chronic psychosocial dysfunction, while the risk of relapse is high in the presence of mood-incongruent psychotic features (Tohen et al, 1992).

Untreated bipolar disorder is commonly associated with substance use, abuse and dependence (Tohen et al, 1995); school and work failure; interpersonal dysfunction and relationship breakdown; personality dysfunction could be the result of a turbulent clinical course at crucial stages of development; the lifetime risk of suicide is 10-15% (Tsuang et al, 1978); and there is an increased risk of violence and homicide, especially with poorly controlled psychotic bipolar disorder.

The average female with bipolar disorder with an onset at age 25 will lose, on average, 9 years in life expectancy, 14 years of lost productivity and 12 years of normal health compared with normal controls (US DHEW, 1979). This is in addition to the risk of suicide.

Keller MB, Lavori PW, Coryell W. 1993. Bipolar I: A Five Year Prospective Follow-Up. J Nerv Ment Dis. 181:238-245

Narrow WE, Regier DA, Rae DS. Use of Services: Findings from the NIMH Epidemiologic Catchment Area Program. Arch Gen Psychiatry. 1993. 50:95-107.

NDMDA. National Survey of NDMDA Members Finds Long Delay in Diagnosis of Manic Depressive Illness. Hosp Commun

Psychiatry. 1993. 44: 800-801

Tohen M, Tsuang MT, Goodwin DC. 1992. Prediction of Outcome in Mania by Mood Congruent or Mood Incongruent Psychotic Features. Am J Psychiatry. 149: 1580-1584.

Tohen M, Zarate C, Turvey C. 1995. The McLean First-Episode Mania Project Proceedings of the 148th Annual Meeting, American Psychiatric Association, Miami, Fl.

Tsuang MT, Woolson RF. 1978 Excess Mortality in Schizophrenia and Affective Disorders. Do Suicides and Accidental Deaths Solely Account for this Excess? Arch Gen Psychiatry. 35: 1181-1185.

US DHEW Medical Practice Project 1979. A State of the Service Report for the Office of the Assistant Secretary for the US Dept of Health, Education and Welfare. In: Policy Research.

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Changed Outcome with Mood Stabilizer Treatment

Mood stabilizer treatment can dramatically halt the turbulent course of bipolar disorder, reduce the risk of suicide, increase life expectancy, increase productivity and functioning and 40-75% of patients who respond to mood stabilizers achieve a reasonable occupational status and ability to live independently (Goldberg et al, 1995; Tsuang et al 1979).

Goldberg JF, Harrow M, Grossman LS. Course and Outcome in Bipolar Affective Disorder: A Longitudinal Follow-Up Study. 1995. Am J Psychiatry. 152: 379-384.

Tsuang MT, Woolson RF, Fleming M. 1979. Long-Term Outcome Of Major Psychosis - I. Schizophrenia and Affective Disorders Compared with Psychiatrically Symptom-Free Surgical Conditions.

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Psychoeducation, Psychotherapy and Life Style Changes

As bipolar disorder is not only a life-long condition that can have multiple recurrences, high morbidity and 10-15% mortality through suicide, but also responds well in many instances to robust long-term mood stabilizer treatment, the clinician and team should focus on developing of an effective therapeutic alliance with the patient and his/her family and friends. This alliance should form the basis for psychoeducation, psychotherapy, biological treatments and regular monitoring (Milkowitz, 1996).

Understanding and acknowledging the disorder by the subject, family and friends is associated with improved treatment adherence in depression (Kusumakar et al, 1996) and bipolar disorder (Miklowitz, 1996). Attention should be paid to regulating social and bio rhythms and avoiding or regulating alcohol or substance use. Lack of sleep can provoke a hypomanic or manic episode. Substance use, including nicotine and caffeine, may exacerbate a mood disorder, particularly rapid cycling. Patients with bipolar disorder appear to not only report more adverse life events but also are significantly reactive to stress, including high expressed negative emotions within the family. Hence, proactively dealing with interpersonal conflict, high expressed negative emotions, and loss while promoting healthy functioning and realistic self-esteem should be regular interventions along with biological treatments (Miklowitz, 1996). Specific strategies to monitor moods, reduce or contain suicidality, and improve medication adherence can all promote a better prognosis. There is little empirical evidence of efficacy for psychoanalytic psychotherapy in the treatment of biphasic mood dysregulation.

Good “medication”, information and education about medications, can be invaluable in promoting a collaborative therapeutic relationship and treatment adherence. Interventions conducted in the context of the patient's family or supportive social network have

a higher chance of producing desirable outcomes when compared with interventions that only focus on the patient. Negative attitudes towards medication in the patient, key family member or friend, or a member of the health care team can have adverse effects on compliance.

Kusumaker Y, Kennedy S. 1996. Promoting Therapeutic Alliance and Adherence to Medication Treatment in Depression. The Canadian J of Diagnosis. Suppl Oct. 1-9.

Milkowitz DJ. 1996. Psychotherapy in Combination with Drug Treatment for Bipolar Disorder. J Clin Psychopharmacology. 16: 2. Suppl 1. 56S-66S.

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Lithium

Lithium is a tried and tested medication, efficacious in acute mania, prophylaxis of classical bipolar disorder (Groff et al, 1993) and when the disorder has a mania/hypomania-depression euthymia course (Faedda et al, 1991). Although systematic studies have not been conducted or reported, analysis of data and clinical experience suggest that Lithium is likely less effective in rapid cycling, mixed states, with comorbid substance abuse and in secondary bipolar disorder (Calabrese et al, 1996). It has proven, significant antidepressant properties when compared with Divalproex and Carbamazepine.

Lithium has a narrow therapeutic range between 0.8 and 1.1 mmols/l. Above this there is markedly increased risk of adverse events and toxicity, while below this there is increased risk of relapse. At levels of 0.4-0.6 mmols/l the risk of relapse is increased by more than 2.5 times (Gelenberg et al, 1989). The onset of action is usually between 7-10 days. Acute adverse effects can create nonadherence in 30-50% of cases and there is the significant long-term risk of hypothyroidism, which is treatable. The teratogenic risk, of Ebstein's cardiac anomaly, is present but much lower than previously thought (Cohen, 1992). The teratogenic risk is likely lower than that posed by Divalproex and Carbamazepine.

Calabrese JR, Fatemi SH, Kujawa M, Woyshville MJ. 1996. Predictors of Response to Mood Stabilizers. J Clin Psychopharmacology. 16. 2 Suppl 1. 24S-30S.

Cohen LS. 1992. The Use of Psychotropic Drugs during Pregnancy and Puerperium. Currents in Affective lllness. Vol XI: 9. 5-13.

Faedda GL, Baldessarini RJ, Tohe M, Strakowski SM, Waternaux C. Episode Sequence In Bipolar Disorder and Response to Lithium Treatment. 1991. Am J Psychiatry. 148. 1237-1239.

Gelenberg AJ, Kane JN, Keller MB. 1989. Comparison of Standard and Low Serum Levels of Lithium for Maintenance Treatment of Bipolar Disorders. N Engl J Med 321:1489-1493.

Grof P, Alda M, Grof E, Fox D, Cameron P. 1993. The Challenge of Predicting Response to Stabilizing Lithium Treatment: the Importance of Patient Selection. Br J Psychiatry. 163:16-19.

Predictors of Lithium Response

Previous good response to lithium, positive family history of bipolar disorder and response to lithium, pure but not severe mania, classical bipolar disorder with an episode sequence of mania-depression-euthymia and adequate serum lithium levels are all associated with good response to lithium (Faedda et al, 1991; Gelenberg et al, 1989: Groff et al, 1993).

Faedda CL, Baldessarini RJ, Tohe M, Strakowski SM, Waternaux C. Episode Sequence In Bipolar Disorder and Response to Lithium Treatment. 1991. Am J Psychiatry. 148. 1237-1239.

Gelenberg AJ, Kane JN, Keller MB. 1989. Comparison of Standard and Low Serum Levels of Lithium for Maintenance Treatment of Bipolar Disorders N Engl J Med 321:1489-1493.

Grof P, Alda M, Grof E, Fox D, Cameron P. 1993. The Challenge of Predicting Response to Stabilizing Lithium Treatment: the Importance of Patient Selection. Br J Psychiatry. 163:16-19.

Predictors of Lithium Failure

Multiple previous episodes, rapid cycling and mixed states, significant comorbidity with alcohol or substances and personality disorder and serum levels below 0.6 mmols/l are all predictive of failure to respond to lithium (Calabrese et al, 1996).

Calabrese JR, Fatemi SH, Kujawa M, Woyshville MJ. 1996. Predictors of Response to Mood Stabilizers. J Clin Psychopharmacology. 16. 2. Suppl 1. 24S-30S.

Lithium: Adverse Effects and Interactions

The high frequency of non-adherence to lithium treatment (30-50%) is often associated with adverse effects, particularly in the early stages of treatment. Cognitive impairment, tremor, acne, polyuria and polydipsia, muscle weakness and weight gain can be associated with noncompliance, particularly in adolescents, young adults and the elderly. (Gitlin et al, 1984). Long term adverse effects on thyroid functioning and the kidneys, especially in patients with a previous or family history of renal problems, suggest the value of caution and the usefulness of regular monitoring. Lithium has teratogenic potential, albeit posing less risk than previously stated for Ebstein's cardiac anomaly, and lower risk when compared with the anticonvulsants. Lithium has a narrow therapeutic range and toxicity can be induced by changes in electrolyte and fluid balance. Lithium can be lethal in overdose.

Many medications interact adversely with Lithium. Commonly, this results from alterations in serum concentrations of either Lithium or the concomitant medications. Potential for neurotoxicity with Carbamazepine, decreased serum lithium levels with calcium channel blockers and xanthines, and increased serum levels with most psychotropics, thiazides and ACE inhibitors should be borne in mind. Patients should be informed about these potential interactions in advance, and screened closely for the use of other medications, including over the counter medications, when side effects appear.

Gitlin MJ, Jamison KR. 1984. Lithium Clinics: Theory and Practice. Hosp Comm Psychiatry. 35:363-368.

Effects of Abrupt Discontinuation of Lithium

Lithium should only be discontinued gradually when it has been used successfully for prophylaxis in bipolar disorder. This discontinuation should be achieved over 2-3 months, and not before 4 weeks if possible. Abrupt or rapid discontinuation (less than 2 weeks) is associated with significantly higher relapse rates not only in the first few months but also over 3-5 years (Baldessarini et al, 1996). It is reasonable, at this stage, to extrapolate these findings and caution against the abrupt discontinuation of any mood stabilizer treatment.

Baldessarini RJ, Tondo L, Faedda GL, Suppes TR, Floris C, Rudas N. 1996. Effects of the Rate of Discontinuing Lithium Maintenance Treatment in Bipolar Disorders. J Clin Psychuatry. 57:10. 441-448.

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Divalproex Sodium

Divalproex Sodium (DVPX) has emerged as an effective broad-spectrum alternative to Lithium. It is effective in acute mania (Bowden et al, 1994), rapid cycling and mixed states, with comorbid substance abuse and in secondary bipolar disorder (Calabrese et al, 1996). In an ongoing prophylactic study comparing Divalproex, Lithium and placebo in bipolar disorder, Bowden et al (APA, 1996) reported that, in moderate to severe bipolar disorder, Divalproex was as effective as Lithium and superior to placebo at the end of one year of treatment. However, although there is a body of open labelled data pointing towards the prophylactic efficacy of Divalproex, there is not a single published double-blind study to support this at this time. Divalproex has no proven efficacy in acute bipolar depression.

Bowden et al (1996) in an analysis of data from an acute mania study have reported that Divalproex is more effective when the serum valproic acid level is over 350 mmols/l. Over 700 mmols/l is associated with markedly increased adverse effects. It can have a rapid onset of action, often within 3 days when an oral loading dose of 20 mg/kg/day is used (Keck et al, 1993). Non-adherence rates are 10-25% and lower than with Lithium or Carbamazepine. Neural tube defects occur when it is used in the first trimester of pregnancy. There is relatively low drug-drug interaction when compared with other mood stabilizers and no proven long term risk.

Divalproex sodium has fewer gastrointestinal side effects when compared with valproate, and patients can thus tolerate divalproex even when the total daily dose is taken two rather than three divided doses.

Bowden CL, Brugger AM, Swann AC, Calabrese JR et al. 1994. Efficacy of Divalproex vs Lithium and Placebo in the Treatment of Mania. JAMA. 271:12. 918-924.

Bowden CL, Janicak PG, Orsulak P et al. 1996. Relation of Serum Valproate Concentration to Response in Mania. Am J Psychiatry. 153: 6. 765-770.

Calabrese JR, Fatemi SH, Kujawa M, Woyshville MJ. 1996. Predictors of Response to Mood Stabilizers. J Clin Psychopharmacology. 16. 2. Suppl 1. 245-305.

Keck PE, McElroy SL, Tugrul KC, Bennett JA. 1993. Valproate Oral Loading in the Treatment of Acute Mania. J Clin Psychiatry. 54. 305-308.

Predictors of Response and Non-Response to Divalproex

Divalproex is effective in acute mania, rapid cycling, mixed states, secondary bipolar disorder, and may be effective in the presence of personality dysfunction and substance abuse (Calabrese et al, 1996). Because of its efficacy in a variety of clinical presentations of bipolar disorder, growing evidence for prophylactic efficacy, and broad serum therapeutic range it is being increasingly used as a broad-spectrum mood stabilizer. Although there is a good body of literature of open studies showing the usefulness of Divalproex, there is no published data from any double-blind placebo controlled study of its efficacy in the prophylaxis of bipolar disorder. There is little evidence to support that Divalproex is efficacious in acute bipolar depression.

Calabrese JR, Fatemi SH, Kujawa M, Woyshville MJ. 1996. Predictors of Response to Mood Stabilizers. J Clin Psychopharmacology. 16. 2. Suppl 1. 24S-30S.

Divalproex: Adverse Effects and Interactions

Gastrointestinal, sedative and hematological (thromobocytopenia and leucopenia) side-effects with Divalproex (DVPX) appear to be associated with serum levels above 700 mmols/l (Bowden et al, 1993). Serious hepatic side effects have not been reported in subjects above the age of 10. Mild, transient and non-lethal changes in hepatic functioning are common. Hepatic functioning should be particularly monitored when polytherapy is being used. Neural tube defects with DVPX use in the first trimester of pregnancy is around 2% (Lindout et al, 1986). Hair loss or thinning occurs in a small percentage of patients and can be transient and self-limiting. It may be helped with supplementation with selenium and or zinc. Cognitive side-effects are lower than with Lithium, thus making DVPX an attractive alternative. Weight gain is not uncommon. There are relatively few drug interactions associated with DVPX. Care should be taken, however, to monitor for bleeding time and bruising when DVPX is used along with any agent that alters platelets or is an anticoagulant. Monitoring of hematological and hepatic functions, and serum levels are needed only if clinically indicated after close monitoring in the first few weeks of therapy with DVPX. (McElroy et al, 1995)

Bowden CL, May RB, Sunder TR. 1993 Hematological Manifestations of Long-Term Valproate Therapy. Epilepsia. 34. 1098-1101.

Lindout D, Schmidt D. 1986. In Utero Exposure to Valproate and Neural Tube Defects. Lancet. 1392-1393.

McElroy SL and Keck PK. 1995. Antiepileptic Drugs Ch 17, Pg 351-375. In Textbook of Psychopharmacology. Ed. Schatzberg and

Nemeroff. APA Press.

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Carbamazepine

Carbamazepine (CBZ) is efficacious in acute mania, mixed state and secondary bipolar disorder (Post, 1990). Although there is some data on its prophylactic efficacy the data is not as impressive as with Lithium. It is now suggested that it is not very effective in rapid cycling (Okuma, 1993). It has weak antidepressant properties. It is commonly used when there has been failure to respond to Lithium.

The therapeutic serum level for CBZ has not been established although it is common practice to stay within the range of 4-15 mi.gm/ml. Onset of action is between 7-14 days. Non-adherence to treatment occurs in 20-35% of cases and is often associated with the side effects of the medication. Side effects and drug interactions may persist even after discontinuation of CBZ as its metabolite remains active long after the parent compound becomes undetectable. (Denicoff et al, 1994). Neural tube defects have been reported with CBZ use in the first trimester, and it probably has a teratogenic risk higher than Lithium (Rosa, 1991).

Denicoff KD, Smith-Jackson E, Disney E et al 1994. Outcome in Bipolar Patients Randomized to Lithium or Carbamazepine Prophylaxis and crossed over in year two. Abst. First Int Conf on Bipolar Disorder. Pittsburg, PA.

Okuma T. 1993. Effects of Carbamazepine and Lithium on Affective Disorders. Neuropsychobiology. 27. 138-145.

Post RM 1990. Alternatives to Lithum for Bipolar Affective Illness. In: Review of Psychiatry. Tasmana Ed. American Psychiatric Press. 170-202.

Rosa FW. 1991. Spina Bifida in Infants of Women Treated with Carbamazepine during Pregnancy. N Engl. J Med 324. 674-677.

Predictors of Response to Carbamazepine

Acute mania, mixed states and secondary bipolar disorder are associated with good response to Carbamazepine.

Okuma T. 1993. Effects of Carbamazepine and Lithium on Affective Disorders. Neuropsychobiology. 27. 138-145.

Post RM. 1990. Alternatives to Lithium for Bipolar Affective Illness. In: Review of Psychiatry. Tasmana. Ed. American Psychiatric Press 170-202.

Predictors of Non-Response to Carbamazepine

Carbamazepine is likely relatively ineffective in rapid cycling contrary to previous opinion and has little efficacy in acute bipolar depression and in recurrent or relapsing bipolar disorder with predominantly depressive episodes (Okuma, 1993; Post, 1990).

Okuma T. 1993. Effects of Carbamazepine and Lithium on Affective Disorders. Neuropsychobiology. 27. 138-145.

Post RM. 1990. Alternatives to Lithum for Bipolar Affective Illness. In. Review of Psychiatry. Tasmana. Ed. American Psychiatric Press. 170-202.

Carbamazepine: Adverse Effects and Interactions

Sedation, cognitive impairment, neurotoxicity, minor hemotopoetic suppression, gasto-intestinal distress, dizziness, rash heralding significant dermatological complications, elevations in liver enzymes, failure of concomitant oral contraceptives, weight gain, and neural tube defects in the developing fetus are all associated with Carbamazepine. (McElroy et al 1995; Denicoff et al, 1994; Rosa, 1991)

Carbamazepine (CBZ) induces its own metabolism, has profound effects on the liver including induction of the cytochrome enzyme system thus potentiating many drug interactions. There is an increased hematological risk with medications like clozapine. Divalproex, cimetidine, erythromycin, isoniazid, SSRls and calcium channel blockers may increase CBZ serum levels. CBZ may lower serum levels of TCAs, theophylline and warfarin, and increase the metabolism of contraceptive hormones.

Denicoff KD, Smith-Jackson E, Disney E at al 1994. Outcome in Bipolar Patients Randomized to Lithium or Carbamazepine Prophylaxis and crossed over in year two. Abst. First Int Conf on Bipolar Disorder. Pittsburg PA.

McElroy SL and Keck PE 1995. Antiepileptic Drugs. Ch. 17, Pg 351-375. In Textbook of Psychopharmacology. Ed Schatzberg and Nemeroff APA Press.

Rosa FW. 1991. Spina Bifida in Infants of Women Treated with Carbamazepine during Pregnancy. N Engl J Med 324. 674-677.

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ECT

ECT is a truly bi-modal treatment, effective in the treatment of acute mania and depression in bipolar disorder. Although the methodology to study ECT has not had the same rigour as that with mood stabilizer medications, it is reported to be as effective as, if not more effective than, medications most of the time. It has broad-spectrum efficacy and is an underutilized treatment in refractory bipolar disorder. It is relatively safe to use in pregnancy and in the presence of medical conditions. Bilateral ECT is more effective than unilateral ECT in Bipolar Disorder, and patients commonly need more than 6 treatments, and it is not uncommon for patients to require 10-15 treatments. ECT should be continued through the phase of ECT-induced mania or depression to achieve full euthymia. Anticonvulsants should be discontinued when ECT is being used in order to ensure seizures. Lithium dose should be reduced to decrease risk of acute neurotoxicity after ECT. Despite the fact that the long-term cognitive side-effects are less severe and common than feared, ECT continues to be unacceptable to many patients. (Black et al, 1987; McCabe et al, 1977; Mukherjee et al, 1994; Small et al, 1988). There is work suggesting that maintenance ECT, once every 4-6 weeks, may be an option in some patients who are totally refractory to, unable to tolerate or use medication.

Black DW, Winokur G, Nasrallah H. 1987. Treatment of Mania: A Naturalistic Study of ECT vs Lithium in 438 patients. J Clin Psychiatry. 48. 132-139.

McCabe MS, Norris B. 1977. ECT vs Chlorpromazine in Mania. Biological Psychiatry. 12. 245-254.

Mukherjee S, Sackheim HA, Schnurr DB. 1994. ECT of Acute Manic Episodes: a Review. Am J Psychiatry. 151. 169-176.

Small JG, Klapper MH, Kellarns JJ. 1988. ECT compared with lithium in the Management of Manic States. Arch Gen Psychiatry. 45. 727-732.

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Typical Neuroleptics

Typical neuroleptics are effective in acute mania. The onset of action is quicker than with lithium in acute mania, although there has been no real comparison with an oral loading dose of divalproex. Clearly, in acute mania with severe behavioural disturbance, the ability to use typical neuroleptics parenterally can be an advantage. The risk and discomfort of acute extrapyramidal side effects should not be underestimated. The evidence for the prophylactic effects of typical neuroleptics is less robust and the clinician should bear in mind the potential increased risk of tardive dyskinesia particularly in patients with a mood disorder. Typical neuroleptics are also known to provoke or maintain depression in bipolar patients. (McElroy et al, 1996)

McElroy SL, Beck PE, Strakowski SM.1996. Mania, psychosis and antipsychotics. J Clin Psychiatry. 57 (Suppl 3). 14-26.

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Benzodiazepines

There is evidence for both Lorazepam and Clonazepam being effective as primary antimanic agents, although Lorazepam may be superior in this respect (Bradwejn et al, 1990). However, concerns about provoking disinhibition, the risk of dependence and the lack of efficacy of benzodiazepines in the prophylaxis of bipolar disorder have limited the use of these medications.

There is growing and robust evidence for the use of benzodiazepines as an adjunctive treatment with mood stabilizers in acute mania. Lorazepam (Bowden et al, 1994) and clonazepam have been used successfully as adjunctive treatments in acute mania instead of neuroleptics. Lorazepam has the advantage of being available for parenteral use. Benzodiazepines are useful in the first few hours and days of the treatment of acute mania to suppress behaviour disturbance and tackle insomnia. It is becoming common practice to taper down and discontinue benzodiazepines within 2-3 weeks of achieving adequate symptom control in mania.

Bowden CL, Brugger AM, Swann AC, Calabrese JR et al 1994. Efficacy of Divalproex vs Lithium and Placebo in the Treatment of Mania. JAMA. 271:12. 918-924.

Bradjewn J, Shriqui C, Kosycki D et al. 1990. Double-blind comparison of the effects of clonazepam and lorazepam in acute mania. J Clin Psychopharm. 10. 403-408.

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Antidepressants

In Bipolar Depression, a number of double blind control trials with tricyclic antidepressants report an average efficacy of 55%. The response rate of fluoxetine treated subjects is not vastly different. Paroxetine too has been studied in bipolar depression with success. Both TCAs and SSRls can produce a switch into hypo/mania, with TCAs being recognized as a more common offender. Tricyclics are linked with a higher propensity to switch patients into an expanded mood state and to induce rapid cycling. MAOls appear to have better efficacy in anergic depression when compared with TCAs. MAOls too can cause a switch into hypomania. However, it should be emphasized that the majority of patients with bipolar depression do not switch or go into rapid cycling on antidepressants. Despite this there is growing reluctance to use antidepressants as first-line or monotherapy agents, without concomitant use of mood stabilizers, as there is suspicion that antidepressants interfere with eventual mood stabilization. This issue warrants rigorous study. Bupropion, an agent that is available in the USA and through an emergency drug release program in Canada has a novel method of action through dopamine and noradrenergic systems. In reports of small series of cases of bipolar depression, Bupropion appears to be efficacious and may possess a lower propensity to produce a switch into hypo/mania or accelerate cycling. These issues have been well reviewed by Srisurapont et al (1995).

Srisurapanont M, Yatham LN, Zis AP. 1995. Treatment of Acute Bipolar Depression: a Review of Literature. Can J of Psychiatry. 40: 533 544.

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Novel Treatments

There are no published double-blind controlled studies of almost all novel treatments in bipolar disorder. Most inferences have been drawn from case reports and case series, or systematic open studies.

Thyroxine continues to be used despite a lack of strong evidence for its efficacy in bipolar disorder. Thyroxine has been used in

refractory rapid cycling disorder with or without a raised TSH. The doses of Thyroxine have varied from 50 to 150 micrograms, and there is little evidence to support the use of hypermetabolic doses.

Risperidone shows some promise in bipolar disorder with or without psychosis, but there have been recent reports of mania induced with doses above 6 mg per day. Increasingly, in many centres, Risperidone has become a front-line neuroleptic in the adjunctive treatment of mania. Many clinicians use Flupenthixol, which at low doses may have a profile similar to Risperidone, as an adjunctive treatment in bipolar disorder.

There is reasonably good and growing evidence that Clozapine is effective both in refractory depression and mania in bipolar disorder, with or without psychosis, but its use has been restricted by its potential hematological adverse effects and lack of ready availability for bipolar disorder in many parts of the world.

Calcium channel blockers, like verapamil, have been well studied, and although they held initial promise, there is little evidence to support their use as a front-line mood stabilizer. There are case reports of the usefulness of the lipophilic calcium channel blocker, Nimodipine. (Bowden, 1996).

Lamotrigine (Calabrese et al, 1996; Yatham et al, 1996; Yatham et al, 1997; Kusumakar et al, 1997) has shown promise in bipolar depression and rapid cycling bipolar disorder in open studies. Double-blind studies are currently being conducted. Doses ranging from 50 mg to 300 mg per day have been used. It is wise to start at a low dose of 12.5 mg to 25 mg per day, titrated up slowly. There is early evidence, albeit in open studies, that, when combined with Divaproex or Lithium, patients may often respond to doses between 75 mg to 150 mg per day. Monitoring of liver functions, PT & PTT, CBC and skin rash is essential. The appearance of skin rash could herald a Steven-Johnson's Syndrome or a severe dermatological crisis.

Gabapentin has been used successfully in bipolar depression and publication of a recent open trial is awaited. It has a very good side effect profile and is relatively safe to use with most psychotropic medications by virtue of the fact that it is virtually totally excreted by the kidneys. Dose ranges of Gabapentin used in bipolar disorder have ranged from 600 mg to 1200 mg per day, with a low starting dose titrated up over a few days. Systematic studies are underway with Gabapentin.

Adrenergic blockers, calcium channel blockers, acetazolamide, sex hormones, choline and tryptophan have been used in bipolar disorder, although the evidence for their efficacy is weak at this stage. (Bowden, 1996). Future directions include the study of the efficacy of dopamine agonists, peptidomimetics and antagonists, and drugs that target second-messenger systems and transcription factors.

Borden CL. 1996. Role of Newer Medications for Bipolar Disorder. J Clin Psychopharmacology. 16.2. Suppl 1. 48S-55S.

Calabrese JR, Fatemi SH, Woyshville MJ. et al. 1996. Lamotrigine in Rapid Cycling Bipolar Disorder. Amer J Psychiatry. 153.1236.

Kusumakar V and Yatham LN. 1997. An Open Study of Lamotrigine in Refractory Bipolar Depression. Brief Report submitted for publication.

Yatham LN and Kusumakar V. 1997. Lamotrigine in Bipolar Depression. Letter in press, American Journal of Psychiatry.

Yatham LN and Kusumakar V. 1996. "Treatment of Bipolar Depression" in conference on Mood Disorders: Recent Advances. Halifax, Canada. Oct 1996.

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Treatment Induced or Maintained Mood Dysfunction

Medications or substances that induce or maintain a mood disorder should be reduced or stopped in order to achieve effective control of the treatment of the disorder. TCAs, MAOls, SSRls, inadequate number of ECTs, sleep deprivation, Nicotine, Caffeine, and Risperidone have all been associated with this phenomenon. There is a continuing debate about whether antidepressant induced

hypomania and mania is simply a transient adverse effect purely related to the medication or an unmasking of and a pointer towards underlying bipolar disorder.

Typical neuroleptics can provoke or maintain depression. Abrupt cessation of psychotropic medications can induce rapid cycling, so these medications, if associated with causing or maintaining a mood disorder, should be tapered down gradually before being stopped if indicated.

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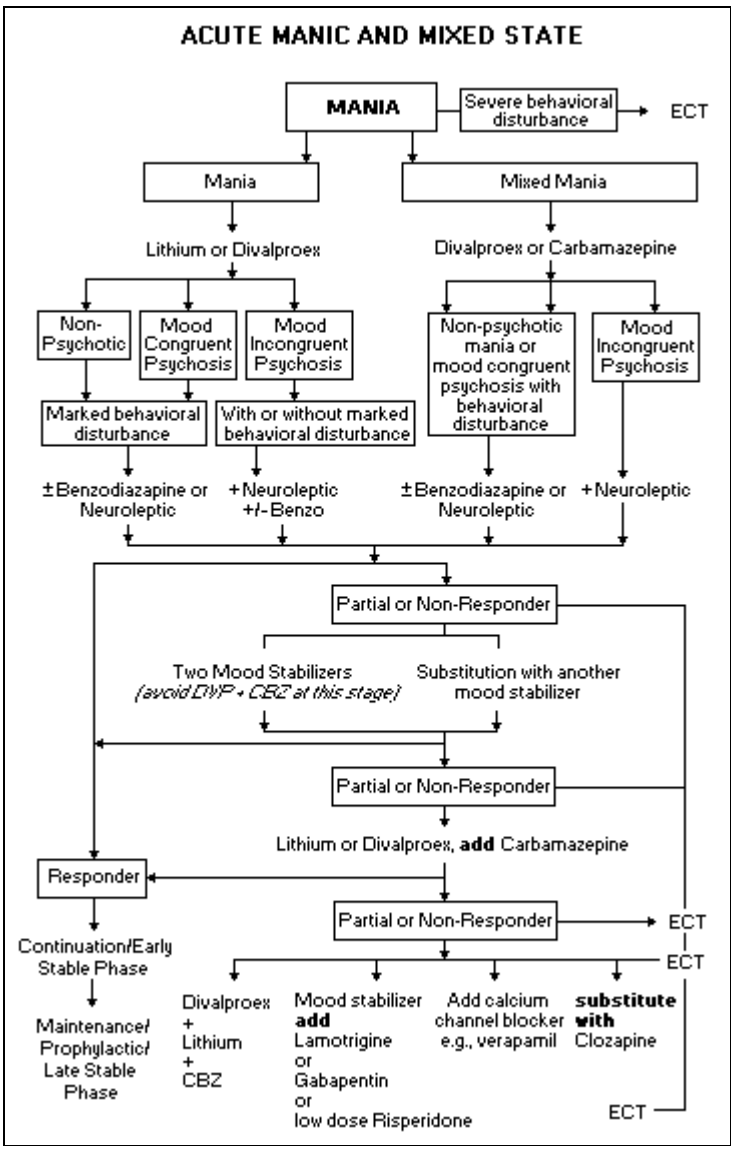
Acute Mania and Mixed States



In acute mania it is recommended to begin treatment with a mood stabilizer, either Lithium or Divalproex. In mixed mania, Divalproex (DVPX) and Carbamazepine are the drugs of choice. The principle is to use the medication that has both antimanic efficacy and is likely to be used for prophylaxis. In moderate to severe mania there is often a need to achieve rapid stabilization. This can be achieved by using a loading dose of 20 mg/kg/day of DVPX, the use of lorazepam or clonazepam in doses from 2 mg to 12 mg per day, and or, where there is severe behavioural disturbance and marked psychosis, the use of a neuroleptic or ECT. Both typical and atypical neuroleptics have specific anti-manic effects. Neuroleptics should be discontinued after the patient has been stabilized usually about two weeks into treatment unless there are persistent and/or mood incongruent psychotic symptoms. Behaviour suppressors, like Lorazepam and Clonazepam have been used successfully as adjuncts instead of neuroleptics (Sachs, 1996). Neuroleptic use is indicated in the long term if there is persistent or mood incongruent psychosis. It is important to taper down and

stop antidepressants or other manicogenic agents and stabilize sleep patterns. Substance and alcohol use should be discontinued.

If the mania or mixed state is refractory to treatment, there should be a reassessment of the possibility of an underlying treatable medical cause. Any medical condition or substance abuse should be treated. If this is not present, the addition of a second mood stabilizer is acceptable practice while concurrently evaluating the need for ECT depending on the clinical situation. In partial or non-responders, the combination of three mood stabilizers (Lithium, DVPX and CBZ), or the addition of an atypical neuroleptic, Risperidone, in doses below 4 mg per day or substitution with Clozapine at may tried. The addition of a calcium channel blocker or a novel agent, like Lomatrigine or Gabapentin may also be considered.

It is usually sufficient to do serum medication levels no more frequently than once a week in the acute phase. Serum medication levels should be repeated until two consecutive levels have been obtained in the therapeutic range. After baseline investigations, the monitoring/investigations of bodily systems should be conducted as clinically indicated.

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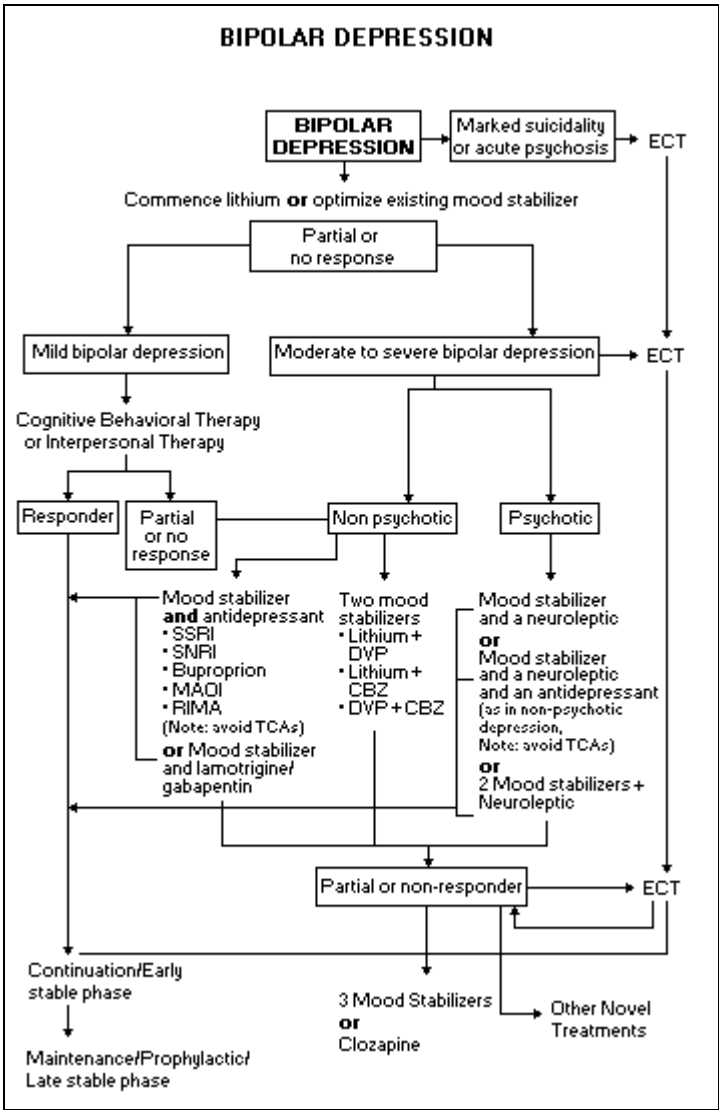
Bipolar Depression



The treatment of bipolar depression is one of the conundrums of psychiatric practice. Although antidepressants are efficacious, lithium is increasingly being recommended as the first choice in non-psychotic, non-suicidal acute bipolar depression. If a patient is already on Lithium, Divalproex or Carbamazepine, dose optimization is the first step. If suicidality is a major concern, ECT should be considered early on in the algorithm of treatment choices. Cognitive behavioural and/or interpersonal therapy can be useful as

adjuncts, particularly with patients who are able to actively participate in these therapies. In moderate to severe bipolar depression mood stabilizers may be combined with antidepressants *or* a second mood stabilizer *or* with lamotrigine *or* gabapentin. Antidepressants are effective in bipolar depression but there is little evidence that one is more efficacious than another. If psychotic features are present, the addition of a neuroleptic is advisable. Risperidone is increasingly commonly used. It is advisable to avoid a TCA, as these medications have the highest risk of switch into hypo/mania and induction of rapid cycling when compared with other antidepressants. Bupropion, which is available in Canada on an emergency drug release program, is reputed to present the least risk of switch into hypo/mania. However, this has not been systematically studied. Although antidepressants induce switch into hypo/mania and accelerate cycles only in a minority of patients, there is a concern that antidepressants interfere with achieving mood stability. If one uses an antidepressant, and the patients remains refractory to treatment, the usual augmentation strategies with antidepressants may be considered. ECT should also be considered at various points in the algorithm. Finally, the use of 3 mood stabilizers in combination or Clozapine may be considered in truly refractory situations. An essential and early component in management to deal with any alcohol and substance abuse which may be exacerbating the depression.

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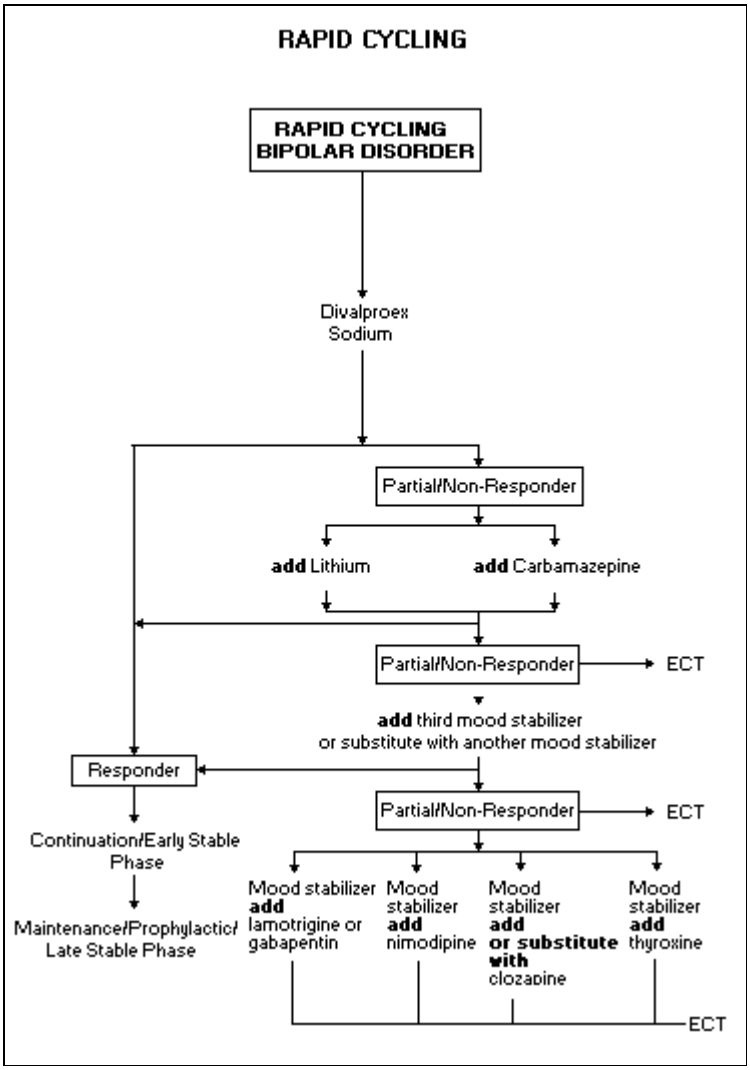
Rapid Cycling Bipolar Disorder



Rapid cycling bipolar disorder may be a phase of the disorder or, in some cases, a type of disorder. It is important to stabilize sleep, reduce or stop the use of caffeine, nicotine, alcohol and substances. Antidepressant medications, particularly tricyclics, may provoke rapid cycling. Care should be taken to gradually discontinue and not to abruptly discontinue any psychotropic agent.

Divalproex sodium is the first treatment of choice. In partial or non-responders, Lithium or Carbamazepine may be added to the

Divalproex. Further on, the combination of three mood stabilizers or ECT could be tried. Lamotrigine, gabapentin, nimodipine or thyroxine in addition to an established mood stabilizer may be used. Clozapine should be considered in the truly refractory patient.

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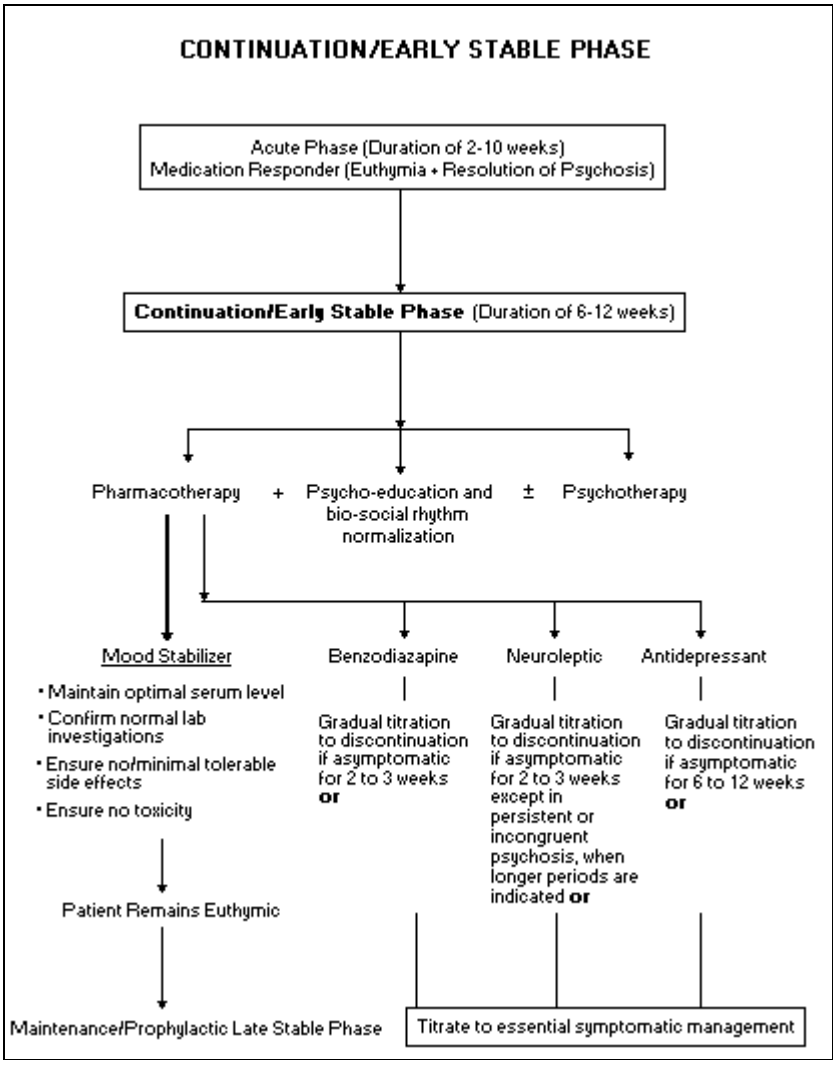
Continuation Phase Treatment



Acute phase treatment can last from 2-10 weeks, and the end of the acute phase is defined as a point when the patient reverts to euthymia and where the psychotic symptoms are resolved.

The acute phase of treatment presents opportunities for psychoeducation of family and friends, and 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 (also called the early stable phase) which lasts for a further 6-12 weeks. Normalization of biological and social rhythms is an essential part of management too. Mood stabilizers are 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 2-3 weeks after symptoms control has been achieved. Neuroleptics need to be continued well beyond the acute phase only if there is persistent or incongruent psychotic symptoms. Similarly, antidepressants can be gradually discontinued over 6-12 weeks after the remission from bipolar depression provided that the patient continues to be on a mood stabilizer. However, if there is a previous history of the patient's symptoms being exacerbated every time neuroleptics, antidepressants or other psychotropic medications are discontinued, 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/investigations of bodily systems should be done as clinically indicated in the continuation phase.

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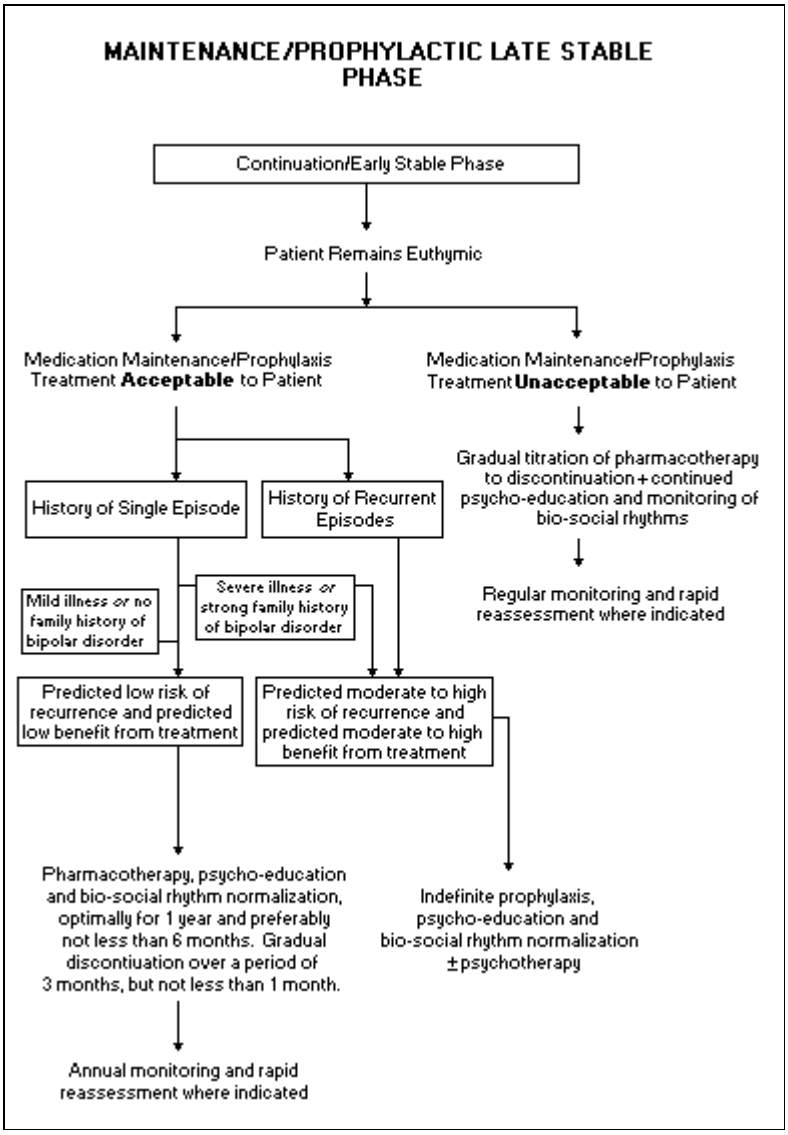
Maintenance Phase/Prophylactic Treatment



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 is relatively easier in patients who have had recurrent episodes, where the illness is very severe, or where there is a strong family history of bipolar disorder. It is difficult, if not impossible, to accurately predict the small minority of patients diagnosed with bipolar disorder who will never have a further episode of mood disorder during their lifetime. Hence, 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 well diagnosed bipolar disorder. Apart from the rare patient who cannot tolerate any treatment, the other situation where the decision to recommend indefinite prophylaxis may be deferred is in patients with a single episode of hypomania with no history of depression and no family history of bipolar disorder. However, even with these patients every effort should be made to ensure

mood stabilizer treatment for about a year. When medication is being discontinued this should be done on a gradual basis over about 3 months, but not less than I month. Patients who discontinue treatment should have access to regular monitoring, rapid reassessment and treatment if required.

Lithium is the medication with proven prophylactic efficacy in bipolar disorder. It has been used in large numbers of patients, tested in double-blind conditions, and used over many years. It has proven efficacy in classical, non-rapid cycling, non-mixed states, primary bipolar disorder at serum levels of 0.8-1.1 mmomls/l. There is an increased risk of relapse at serum levels below 0.8 mmols/l, particularly below 0.6 mmols/l. There is growing evidence from several open studies that Divalproex has significant prophylactic efficacy similar to Lithium. At two 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 patients require short or long term polytherapy with mood stabilizers and or ECT. A very small sub-group of patients may be totally refractory to mood stabilizers and may require an atypical neuroleptic, like Clozapine, or maintenance ECT.

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

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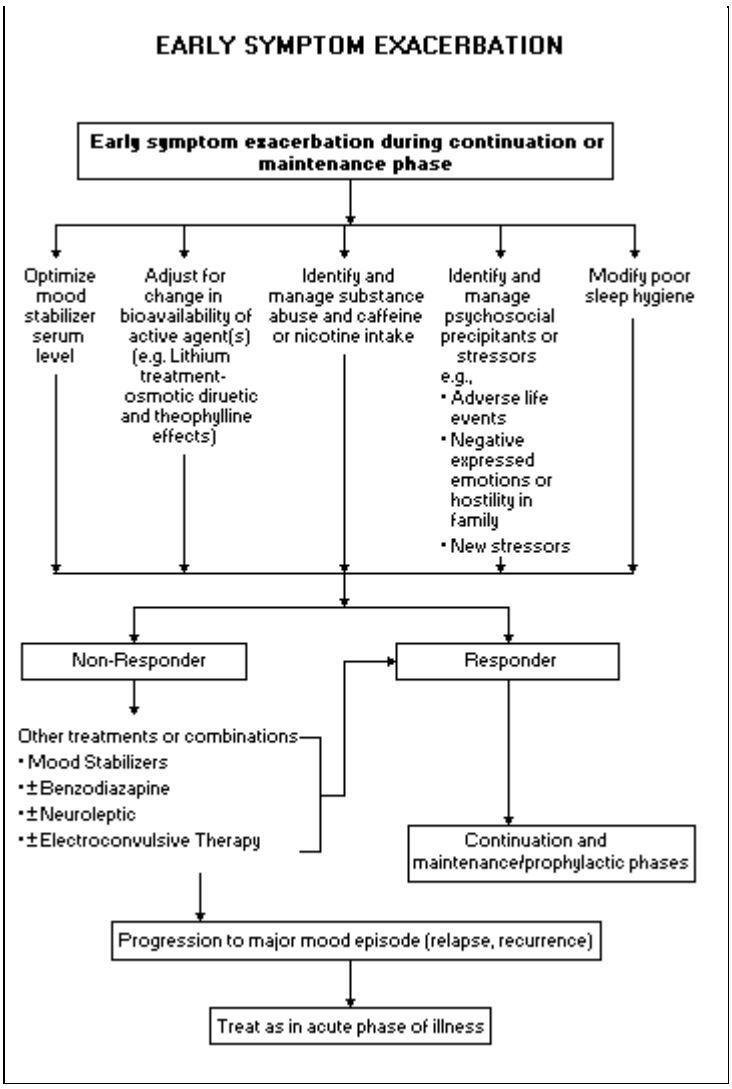
Treatment of Symptom Exacerbations



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 and families/support networks need education and training to recognize symptoms 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-drug interactions are important. Non-responders to these measures may require the addition of other relevant biological and psychosocial interventions to produce a remission and prevent the entry into another acute illness phase.

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