CHAPTER 14. MOOD DISORDERS

14.8 MOOD DISORDERS: TREATMENT OF BIPOLAR DISORDERS

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Treatment of the mood disorders has reached a new level of sophistication based on a variety of advances. The descriptive and diagnostic aspects of bipolar disorders are now explicitly spelled out, recognizing that it is almost always recurrent with potential for severe morbidity and even mortality. There is increasing recognition that bipolar affective disorders have a prominent genetic component interacting with environmental events, and neurobiological alterations have been documented with biochemical assays and functional brain imaging. Thus, different treatment approaches are recognized as a function of type, severity, and course and as in other branches of medicine require the utmost clinical management skills.

Convergent with this increased knowledge about the classification, course, and mechanisms underlying acute episodes and their recurrences is an expanding array of effective psycho- and pharmacotherapeutic modalities and related somatic treatments. Whereas single drugs in one or two classes were available for the treatment of bipolar disorders several decades ago, multiple therapeutic modalities now exist, often including many agents within each class. Thus, the physician must be aware of the nuances in approach to the patient with acute and recurrent mood disorder, so that treatment can be optimized from the outset and the impact of the illness on patients and families minimized.

A growing consensus surrounds a series of new treatment principles. Early recognition and intervention in an acute episode may not only save the patient months of pain and suffering, but also may be life saving. More-careful assessment of the efficacy of an agent at early and regular intervals and early revision of the treatment modality if no improvement is shown are recognized guidelines. This is the case for somatic treatments and also for targeted psychotherapeutic approaches using cognitive,

behavioral, and interpersonal therapies.

A substantial body of evidence indicates the efficacy of long-term prophylactic treatments in the management of the recurrent affective disorders. Moreover, earlier institution of long-term prophylaxis is critical to the patient with recurrent mood disorders; it will affect the morbidity of the illness and likely also its subsequent course and treatment responsiveness. Consensus is growing that a patient with a positive family history and a first episode of bipolar disorder is a candidate for continuation therapy after resolution of that episode and for long-term prophylaxis. These factors have dramatically changed the physician's approach to the patient with an acute episode of a mood disorder. The illness should be approached with the same respect accorded the early diagnosis and treatment of a malignancy. Delayed or inadequate treatment may be associated with considerable acute and long-term morbidity from both the illness and its secondary consequences. Thus, it appears appropriate to reconceptualize the recurrent mood disorders not as illusory mental phenomena that can be modified by the patient's will, but as a serious and potentially life-threatening medical illness that has clearly defined mood, cognitive, motor, somatic, and neurobiological concomitants.

Bipolar I disorder occurs in approximately 1 percent of the population, which translates into 2.5 million people in the United States alone. It is estimated that the average woman with onset of bipolar illness at age 25 will lose 14 years of effective lifetime functioning through her illness. Bipolar II disorder and bipolar disorder not otherwise specified may each account for another 1 percent or more. Fifteen to 20 percent of patients with bipolar illness commit suicide. It is against this backdrop of a recurrent, potentially disabling, medical illness that diagnostic and long-term treatment approaches should be conceptualized.

HISTORY

Over the course of this century a revolution has occurred in the treatment of bipolar disorders. In the first half of the century no adequate treatment was available; in the second half, lithium (Eskalith) emerged as a wonder drug for short-term and prophylactic management of the disorder. However, oscillations in the assessment of lithium's safety, efficacy, and utility have persisted. The drug was initially abandoned as unsafe until its concentration could be adequately monitored in blood, which virtually eliminated its most serious and potentially lethal cardiovascular and central nervous system (CNS) toxicities. However, concerns about long-term renal complications have not entirely dissipated after the kidney scare of the 1980s.

There is also greater recognition of lithium's efficacy limitations. As with penicillin, these limitations do not imply that lithium no longer works, but that the spectrum of therapeutic efficacy is narrower. More than 50 percent of patients do not show adequate response to lithium even with adjunctive antidepressant and neuroleptic treatment and using conservative criteria for clinical response (e.g., one episode of illness in a 2-year follow-up).

In the middle of the century electroconvulsive therapy (ECT) emerged as the most effective approach to treating acute episodes. Antipsychotics rapidly became a mainstay of treatment for both mania and psychosis. In the 1960s the first-generation monamine oxidase inhibitors (MAOIs) and tricyclic drugs were introduced and widely used in conjunction with lithium. Now, selective serotonin reuptake inhibitors (SSRIs), bupropion (Wellbutrin), venlafaxine (Effexor), mirtazapine (Remeron), and monoamine oxidase (MAO) type A selective modalities are available. Similarly, the phenothiazine, butyrophenone, and thiothixine antipsychotic classes have given way to the serotonin-dopamine antagonists (atypical antipsychotics), such as clozapine (Clozaril) and risperidone (Risperdal); olanzapine (Zyprexa); quetiapine (Seroquel); and sertindole (Serlect). These new agents include drugs

with novel structures and mechanisms of action and more benign adverse effect profiles than the original agents.

This new range of psychopharmacological agents raises a series of important issues for the clinician, particularly when these agents must be chosen on the basis of an inadequate literature on relative efficacy or clinical and biological markers of responsiveness. There is a consensus that with the exception of ECT, no antidepressant modality is more effective or more rapid in onset than another. Thus, the choice of agents is typically based on their adverse effect profile and clinical lore regarding syndromal selectivity of response.

Fortunately, as the limitations of lithium as a mood stabilizer have been increasingly recognized, a variety of other treatment modalities have become available, particularly the anticonvulsants carbamazepine (Tegretol); valproate (Depakene); divalproex (Depakote); as well as the calcium channel inhibitors. Other promising anticonvulsants are being explored as possible third-generation mood stabilizers, including lamotrigine (Lamictal), and possibly gabapentin (Neurontin), and topiramate (Topamax). However, as with targeting therapeutic modalities to specific patients in the depressive disorders, the data are not yet adequate to choose among the accepted mood stabilizers or establish how to use them in combination, which has been increasingly necessary in recurrent bipolar disorders.

Thus, the clinician often has to resort to educated guesses and systematic and sequential clinical trials in individual patients to delineate optimal responsivity (Table 14.8-1). Even with the availability of many new treatments, episodes of illness can often emerge through otherwise partially successful pharmacoprophylaxis and necessitate adjunctive measures. The role of complex combination therapies is well recognized in many branches of medicine and is indispensable in the approach to tuberculosis, acquired immune deficiency syndrome (AIDS), congestive heart failure, or cancer chemotherapy. Systematic research of combination therapies has lagged markedly behind clinical practice, and clinicians are often left to their own devices, without the aid of controlled studies in the literature to guide the optimal algorithm for approaching the patient who is refractory to standard treatment interventions.

Table 14.8-1 Steps in the Treatment Algorithm of the Bipolar Patient

IMPEDIMENTS TO SHORT- AND LONG-TERM TREATMENT

Although the bipolar disorders are eminently treatable, illness-related variables complicate diagnosis, accessibility to treatment, and the ability of the patient to follow through with treatment. It is estimated that as many as 40 percent of bipolar I disorder patients in community surveys are not in treatment.

Depressed patients often do not recognize that their symptoms are related to a medical illness, and the symptoms themselves (e.g., motor retardation, a sense of inertia, and hopelessness) may preclude the patient's seeking treatment. Thus, the patient's family, acquaintances, and physician may have to actively encourage the patient to initiate treatment.

Treatment must be conducted against the backdrop of the patient's distorted depressive cognitions (e.g., hopelessness, and view of the untreatability of the illness), which must be explained as symptoms of the illness that are not consistent with optimism of treatment response on the basis of the literature and the physician's knowledge base. The therapist's empirical basis for hope of recovery needs to be conveyed to the patient without the promise of immediate results, so that the expected lags in response are not further misinterpreted as a confirmation of the patient's worst fears. Moreover, each phase of the treatment needs continual review in relation to the potential for suicide.

There are major impediments to effective treatment of manic patients. In the early stages of hypomania, the sense of well-being and increased productivity may lead the patient to ignore more severe aspects of the illness, including irritability, argumentativeness, insomnia, poor judgment, and engaging in sexual and other high-risk behaviors without appropriate appreciation of the consequences. These deleterious activities may severely affect the patient's social structure, marriage, and employment. Early recognition that these symptoms and the denial of illness (anosognosia) are components of the illness itself may be crucial to instituting appropriate treatment and preventing escalation to destructive and full-blown manic episodes.

Again, family participation is crucial in both the diagnostic evaluation and the ongoing treatment. The family can assist in overcoming illness denial and thought disorder associated with hypomania and mania, which can be as problematic to receiving adequate treatment as the hopelessness and suicidality of the depression.

Therefore, therapeutic activism, engagement of the family, and early and aggressive treatment of both manic and depressive syndromes are of paramount importance. Individual patients and their families should receive initial and ongoing informational support regarding the medical aspects of the illness, its potential course, and response to treatment, with the long-term goals of increasing compliance, “medicalizing”, and destigmatizing the illness. Destigmatization may become a crucial issue later in therapy when recommendations for long-term prophylaxis may elicit society's negative attitudes toward taking maintenance medications for psychiatric indications (in contrast to most other types of medicine). Conceptualizing the recurrent mood disorders as medical illnesses deserving the same attention, care, and long-term respect as disorders of other organ systems and may help the patient and family accept appropriate long-term treatment options.

A variety of societal, attitudinal, and illness-related variables may interfere with appropriate help-seeking and maintenance behavior in the various treatment phases, including initiation of acute care, continuation treatment, and long-term prophylaxis. During each of these phases patients and their families should be helped to evaluate the medical data and the potential impact of the illness on the patient. Do not introduce all of these variables at the beginning; approach them sequentially in each phase as appropriate. For example, it may be better to discuss the importance of continuation and long-term prophylactic therapy after patients have begun to show an antimanic or antidepressant response, rather than raise this issue with acutely ill patients and possibly frighten them from pursuing further treatment.

Early discussion of long-term prophylaxis—with graphic, statistical, and both written and verbal presentation of the data to the patient and family—may be critical for achieving an optimal outcome. Even in an illness such as juvenile diabetes, where it is unequivocally demonstrated that the patient cannot survive without adequate insulin treatment, many adolescents nevertheless directly or indirectly test the need for insulin and suffer periods of marked hyperglycemia, often requiring hospitalization. In a parallel fashion, patients with bipolar disorder are likely to be tempted to discontinue treatment, especially when the data regarding the morbid or lethal consequences are less well delineated. Nevertheless, the treating clinician must provide the patients and their families with the now

overwhelming data showing the high likelihood of a recurrence in a relatively short period of time in patients with one or more prior episodes and the ability of a variety of agents to prevent recurrences of both manic and depressive episodes.

In bipolar disorders the high likelihood of relapse (50 percent in the first 5 months following lithium discontinuation and 80 to 90 percent within the first year and a half) is now also widely recognized and should be explained to the patient. In addition, it has always been assumed that patients who experience a relapse will be readily treatable once their former therapeutic modality has been reinstituted. Most investigators have observed lithium-discontinuation-induced refractoriness in which a small percentage of patients who discontinue successful prophylactic treatment and experience a relapse fail to respond when the treatment is reinstituted. In other instances, patients may not respond as rapidly as they did initially or require increased adjunctive neuroleptic medication.

Many studies report that lithium is less effective in patients who have had more than three or four prior episodes than in those whose prophylaxis is initiated earlier in the illness course. Thus, not only should the potential morbidity and mortality of an episode itself be factored into the decision-making process for long-term prophylaxis, but also the possibility that new episodes could affect the subsequent course of the illness and its pharmacological responsivity.

PSYCHIATRIC HISTORY

A thorough medical history and examination are important, given the many syndromes that mimic both manic and depressive syndromes. The older patient with late-onset illness, in particular, should be approached with the possibility of an associated medical cause, and attention should be paid to obvious or subtle hallmarks of associated pathology. The physician should be alert to symptoms indicating CNS neuropathology, underlying endocrinopathy, or other associated medical illness. Although physicians should aggressively explore these themes with patient and family, they should remember—and even directly tell the patient—that all of the somatic and vegetative symptoms reported are consistent with, and most likely indicate, typical primary affective illness.

The earliest parts of the history can be used to uncover diagnostic clues and to educate the patient about the types of symptoms that are typical of the disorder, are associated with its natural course of spontaneous exacerbation and remission of episodes, and are likely to respond to somatic and pharmacological intervention. The medical history and examination should also seek evidence of cardiac, renal, or thyroid abnormalities that may help guide subsequent treatment choices.

The physician should cover each psychological and somatic symptom category associated with depression while simultaneously educating the patient, providing target symptoms for future assessment of the efficacy of psychological and pharmacological intervention, and constructing the framework for longitudinal monitoring of the patient. The symptoms that are typical for a given patient are likely to be involved in a future episode, and thus they provide an early warning system for illness detection and institution of additional treatment.

A detailed family history of medical and psychiatric illness is also crucial to the initial diagnostic assessment of the patient. Graphic construction of a formal family tree is recommended, with each first-degree relative specifically inquired about for their potential diagnosis, course of illness, and response to therapy (Fig. 14.8-1), since these may help guide the choice of therapies for the patient. A positive family history of bipolar illness may further support the recommendation of long-term prophylaxis after the emergence of the first manic episode.

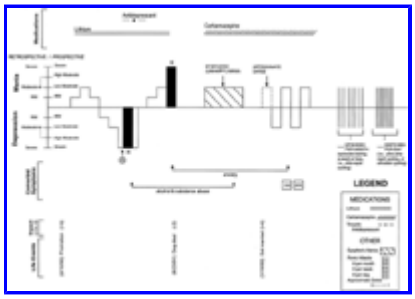


FIGURE 14.8-1 Schema for graphing the course of mood disorders: Retrospective and prospective.

A bipolar disorder family history, especially one with bilineal loading for mood disorder, should markedly raise suspicion of a juvenile- or adolescent-onset bipolar disorder, even if its presentation is less than typical. The clinician should recognize that even in an adult-onset bipolar disorder, the passing of a decade between affective symptom onset meeting diagnostic thresholds and the initiation of treatment is not uncommon. Moreover, in the prepubertal child, a bipolar disorder may present differently from the classic adult picture (Fig. 14.8-2). Instead of showing discrete episodes that easily meet the durational criteria of the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), there may be a pattern of tantrums, mood lability, irritability, and marked and rapid fluctuations in mood and behavior. Hypersexuality and grandiosity (if not frank delusions), high-risk behaviors, sleep disturbance, extremes of anger or aggression, or expressions of suicidal ideas may be particular clues that one is dealing with more than attention-deficit/hyperactivity disorder in the hyperactive and inattentive child. Moreover, prepubertal onset of a psychotic depression may herald the beginning of bipolar illness, since a 30 percent switch rate into mania upon treatment with antidepressants has been reported. Similarly, bipolar disorders may present atypically in adolescence, either with extremes of mood lability or with more psychotic and schizophreniform features. In prepubertal children and adolescents, antidepressants may exacerbate the illness, and mood stabilizers, often in combination, are frequently required.

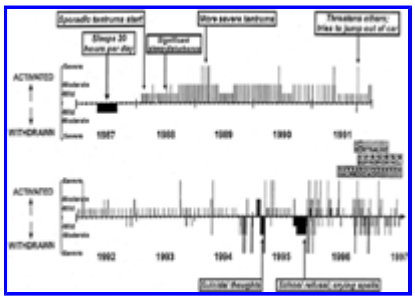
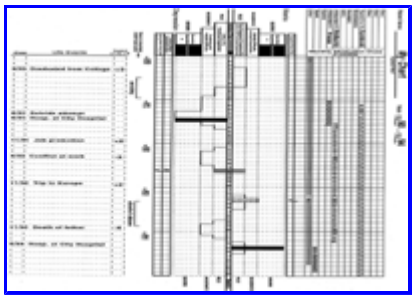


FIGURE 14.8-2 Kiddie Life Chart (K-LCM) of a 10-year-old child with affective dysfunction from the first year of life.

Graphing the Course of Illness The author suggests developing a graphic representation of the patient's prior depressive and manic episodes (Fig. 14.8-3). This graph will form a basis for evaluating the efficacy of previous treatments and assessing current and future prescription. A formal graphic representation of the patient's longitudinal course of illness is useful for several reasons: (1) it provides a clear picture of the earlier illness course, which appears to be the best predictor of the future episode pattern; (2) it clarifies prior and future medication responsiveness; (3) it helps medicalize the patient's history and management, as well as facilitate the recognition of low-level manic symptoms, and (4) it encourages the patient's collaboration and thus may enhance the doctor-patient relationship, making the patient an active partner rather than a passive participant.

FIGURE 14.8-3 National Institute of Mental Health (NIMH)-life chart


method (LCM) self ratings—retrospective.

If a number of past episode recurrences are uncovered in the history, such a graph may also help in the subsequent long-term approach to the illness and in the patient's compliance with prescribed regimens. Moreover, the author has found that this process often uncovers important psychosocial events and possible precipitants of the illness, as well as unique characteristics of the illness, such as cycle characteristics, illness rhythmicity or lack thereof, seasonal variation, relation to anniversaries, and other longitudinal treatment response patterns (such as tolerance or cycle acceleration) not easily uncovered without systematic, graphic representation of the illness. Carefully examining the periods of increased vulnerability to illness provides a template for future treatment intensification or augmentation of therapeutic modalities as appropriate.

With a little practice, the course of an illness can easily be graphically depicted. The author suggests that this be done as part of the initial intake session and be the primary mode of recording a patient's history, even preferable to an extensive written account intended for later conversion to a graph. In this way, both the patient and the physician are immediately and systematically focused on the longitudinal course of the illness and its variation over time, rather than having this focus develop later or possibly be completely sidetracked by attention to acute symptoms. The graphic approach and its associated temporal landmarks can also facilitate recall of important events, dates, and episodes that would otherwise be obscured or forgotten. Typically in this process, supposed first-episode patients will often uncover multiple prior minor or major episodes.

Levels of Severity Physicians can devise their own ways of plotting the course of illness or adopt a system like the one the author and his colleagues have used successfully over the past decade, that is, graphing three levels (mild, moderate, and severe) of mania or depression on the basis of the degree of associated symptom-driven functional incapacity, which can be most readily assessed retrospectively, on the National Institute of Mental Health NIMH–life chart method (NIMH-LCM) (Fig. 14.8-3).

At the mild level, the patient or family notes a distinct change in the patient's mood, with no notable impairment in the patient's social, educational, or employment roles. This state is readily recognized by depressed patients and may represent the dysthymic baseline from which more severe episodes erupt (i.e., double depression). However, hypomanic patients may deny this mild state, so additional information and input from family members and relatives is important. This observation also reemphasizes the utility of a nonpsychoanalytic approach to the patient's diagnosis and treatment, including the participation and support of family members from the outset. This may be of value both in gaining historical information, and in managing potential suicidality of depression and denial of the adverse consequences of hypomania and mania.

Hypomanic signs and symptoms representing distinct periods of increased energy, productivity, and creativity and decreased need for sleep should be sought directly, and not raised in a negative fashion. These milder periods may be easier to explore after the more severe phases of a patient's illness have been detected and the characteristics of their early presentation agreed upon.

Moderate levels of depression and mania that represent phases with distinct functional impairment are graphed at the next level. Patients can continue their social or employment responsibilities, but only with obvious difficulties, such as absences from work or not being able to perform some routine social tasks. In prospective forms of the NIMH-LCM, moderate dysfunction has been divided into low and high categories, representing some and much dysfunction in usual roles, respectively (Fig. 14.8-4). The manic patient may reveal these levels of dysfunction more easily if asked whether coworkers, friends, or family members are commenting or complaining about the patient's behavior or directing them to seek help.

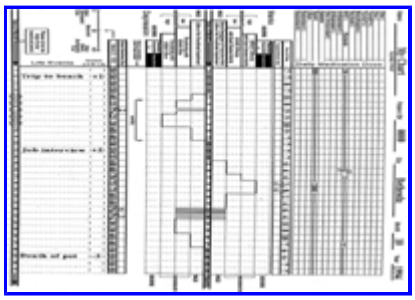


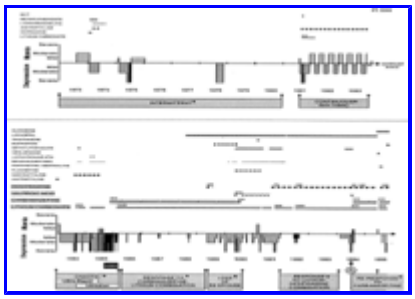
FIGURE 14.8-4 NIMH-LCM self ratings—prospective.

In severe impairment patients are functionally incapacitated and unable to perform their usual roles. Hospitalizations can be coded by shading in the severe manic or depressive episode on the graph. A past episode whose precise timing is unknown or unavailable can be graphed and coded with broken or dotted lines.

For prepubertal onsets a Kiddie-LCM is available that allows graphic depiction of symptom-driven dysfunction whether or not these often highly disturbed and dysfunctional children meet the artificial durational criteria intended for classical adult presentations. Such documentation may be crucial to a child's receiving adequate pharmacological intervention, which is often withheld because of diagnostic controversy and the attendant fears of using medications in children. Professional and societal attitudes and stigma would appear to be highly relevant here, as there is less concern about medications in children with epilepsy, rheumatoid arthritis, infections, malignancies, asthma, and many other medical illnesses with typical or atypical early onsets. Not only is childhood- and adolescent-onset bipolar illness prognostically more disabling than the adult variety in some long-term outcome studies, but the illness also puts the child at increased risk for alcohol and other substance abuse and for other potentially deleterious high-risk behaviors. Moreover, adolescent suicide is one of the fastest growing categories of early mortality.

Psychopharmacological Interventions The history of prior psychopharmacological interventions should be plotted directly above the episodes on this retrospective template of mood fluctuation as illustrated in Figure 14.8-1 of the life-chart schema and in the case example in Figure 14.8-5. When graphed in this fashion, the efficacy of earlier treatments is often more precisely categorized and reclassified. On careful reexamination, a treatment previously deemed ineffective may have partially decreased the frequency or severity of prior episodes. If so, one may now want to consider supplementing this partially effective treatment rather than abandoning it. Previous psychotherapeutic interventions should also be noted, so that their impact on the illness and patient satisfaction can be assessed. As illustrated in Figure 14.8-1 and Figure 14.8-3, important psychosocial events (e.g., significant anniversaries, suicide attempts) and notes about adverse effects (e.g., dosage, reasons for discontinuation of medications) can be entered below the mood graph.

FIGURE 14.8-5 Phases of illness evolution and treatment response in a


woman with bipolar II disorder.

Descriptive Symptoms The anamnestic account of specific symptoms and their associated dysfunction also provides the basis for following clinical improvement during an acute episode and during future possible episodes. In particular, one should try to determine the best descriptors and early predictors of an individual patient's episode. For some patients it may be impaired sleep with early morning awakening; for others it may be an inability to concentrate. Still others may experience decreased energy or increased agitation, isolation, anxiety, appetite, or weight gain. The sequential ebbing of symptomatology during a treated episode may also help delineate the need for continued augmentation treatment or reciprocally yield clues to the earliest symptoms of a recurrence. Should these or other residual symptoms break through during prophylaxis or emerge while tapering medication, they can be used to indicate roughening and the need for renewed, more aggressive management of a potential episode.

Similarly, clinicians should contract with their patients in advance about specific symptoms that may herald depressive or manic episodes and require additional monitoring and intervention. Early signs of the emergence of the patients' typical symptoms—such as increased energy or religiosity or decreased sleep—that may be welcomed, may actually presage more consequential manic symptoms. Attention to these early warning signs while insight is still preserved and denial manageable may save patients and their families from a more prolonged or catastrophic episode. A specific contract such as “call if you should have two nights with less than 5 hours of sleep” is often more helpful than a more general suggestion to call if needed.

Prospective Charting For the bipolar patient with several episodes, the author suggests that some elements of this life chart process be continued prospectively, preferably on a daily basis. This can be accomplished quite easily in a number of ways, including having the patient keep a nightly calendar and write a number on a visual analog scale from 0 (worst ever felt) to 50 (normal or balanced) to 100 (most energized or manic ever). Following discussion with the clinician, this score can be converted to life-charted episodes based on functional incapacity.

In this fashion or with a more complete daily prospective mood chart such as the NIMH-LCM-p patients can track their mood fluctuations in a systematic manner that is unobtrusive and takes only seconds to complete. Pocket life charts and computer graphics packages are now available. Mood rating, like self-assessment of urine glucose concentration by the diabetic patient, may provide an important measure of how well the patient's illness is responding to a given treatment modality, and its dosage adverse-to-effect efficacy ratios and titration. The morbidity and mortality of the mood disorders can be as severe as those of many medical illnesses for which a great deal more attention is paid to the longitudinal and systematic monitoring of fluctuations in symptomatology, biochemistry, and underlying pathology. Patients should be encouraged to help in this life-chart process if they are amenable to it. The completed retrospective and ongoing prospective charts may also help in any future transfers of medical care, orientation of hospital staff, or consultation request should the patient move or suffer future episodes requiring review and revision of treatment.

Subjective and Objective Differences Finally, asking patients to make a calendar, rate their moods (with a specific number on the 100-mm line), and assess illness-driven functional incapacity, may have other secondary benefits. Patients can become better attuned to possible subjective versus objective differences in illness assessment. Some depressed patients can detect mood changes and adverse effects before therapist observation, but many bipolar depressed patients can show remarkable improvement in major aspects of their symptomatology, including sleep, appetite, energy, spontaneity, and sociability, without any subjective sense of mood improvement. If patients do not recognize that their depression is improving despite objective signs, it may lead to further therapeutic pessimism and also may increase the possibility of suicide, as they now may have more energy to carry out such a plan. Moreover, return to previous optimal social and occupational function may lag even further behind objective and subjective appreciation of symptomatic improvement, so that the patient requires additional support, encouragement, and possible retraining during this time frame.

TIME FRAME OF EDUCATION

Although a hopeful perspective about the treatability of a patient's episode should be maintained, a series of drug trials may be needed before the best treatment regimen is found. Evaluation of an acute antidepressant treatment response often requires 3 to 6 weeks, and a given agent's lack of efficacy should be treated as additional information about the patient's illness rather than an indication that the illness is not responsive. Several recent studies in unipolar depression suggest that a lack of some improvement after 4 weeks is a very poor prognostic sign for eventual response with further continuation into 5 and 6 weeks.

Thus, augmentation approaches, in particular, should be triggered at these early times rather than after several months, particularly if high doses or adequate blood concentrations of a given compound have been achieved. In the treatment of acute mania, in which response is typically more rapid (days to weeks), one should consider additional and alternative approaches if improvement is not observed over much shorter periods (days to a week). At the outset of treatment the availability of different effective treatments, with many drugs in each class, should be brought to the patient's attention. This puts possible treatment sequences in their proper perspective and emphasizes that a lack of response to, or an intolerance of, one drug does not portend an ultimate negative therapeutic outcome.

These points should be reemphasized throughout the entire therapeutic process, particularly in light of the different time frames available to the therapist and the patient. The therapist is aware of the many treatment alternatives and the extended treatment course sometimes required to achieve optimal efficacy. The patient (and perhaps even the family) may be overwhelmed by a sense of immediacy and desperation about the current mood-disordered state. Particularly for the depressed patient, this feeling of pain and hopelessness can too easily overtake the realities of the situation and increase the risk of suicide before a positive treatment outcome is achieved.

Reassurance without overpromising immediate therapeutic effects thus appears to be an important part of the treatment. A similar but inverse process may be required for the manic patient, who also may see only the immediate time frame and not the longer-term perspective. The therapist should encourage and help supply the ego for the longer-term view in both of these cases. Thus, supportive, interpersonal, cognitive, and behavioral approaches to the psychopharmacotherapy of the mood disorder may be essential. Patients should also be counseled not to make important long-term decisions on the basis of a distorted view of themselves and their future during an acute depressive or manic episode.

Stressing the time needed to evaluate a given treatment may help maintain the patients' and families' morale and help obtain an adequate informed consent while avoiding malpractice litigation. In this

regard, the patient must be told the possible adverse effects of each drug treatment, so that these effects are expected and not seen as dangerously unpredictable, or conversely, they can be recognized as something that merits closer attention, a call to the physician, or an extra visit when indicated.

HOSPITALIZATION

The decision to hospitalize severely depressed or manic patients depends on a variety of clinical and (disappointingly) economic issues. Hospitalization is often indicated for the acutely suicidal patient and may also be considered for the patient with associated medical problems or one who needs close management and monitoring of complicated or novel psychopharmacological regimens. For the knowledgeable patient and supportive family, one or more of a series of psychopharmacological approaches can often be accomplished on an outpatient basis, particularly if there is close coordination between the patient and physician regarding dosage, titration, adverse effects, and indicators of improvement. Despite many of the largely societal criticisms of the modern use of ECT, this modality should be given a higher priority when treating patients with extreme suicidality, associated medical illnesses, difficult adverse reactions to routine psychopharmacological agents, or other medical emergency situations (such as malignant catatonia or hyperthermia) that demand the most rapid treatment response available. For the recurrent manic patient who has refused voluntary hospitalization at the height of an episode or might be likely to do so, obtaining informed consent in advance (during a well interval) for future involuntary hospitalization and pharmacological treatment may avoid many cumbersome practical and medicolegal difficulties should another manic episode requiring hospitalization occur.

PSYCHOTHERAPY AND PHARMACOTHERAPY

Depression is a serious, potentially life-threatening medical illness, and patients and their families deserve much support. Combining psychosocial and pharmacological approaches is important for most because of their potential mutual interaction and support in the context of ongoing pharmacotherapy.

Cognitive-behavioral therapy may enhance medication compliance and provide support for the patient in the interval before psychopharmacological interventions are successful, especially if several agents are required before an effective regimen is found. Moreover, stress and other psychosocial issues may be involved in the onset and recurrence of some depressions and manias and may be indicators for more aggressive pharmacological management.

Frequent meetings with the patient may also help in assessing response to pharmacotherapy and suicide risk. In a depressed patient with severe pain and suffering, frequent meetings may facilitate the fastest maximal application of pharmacological leverage; regimens can be revised as quickly as possible (days to a week in mania, and several weeks in depression) if improvement is not forthcoming. Combined treatment may also be helpful in instances of partial response to monotherapy, a protracted episode, poor interepisode recovery of function, an associated personality disorder, or the presence of acute psychosocial stressors.

NEUROTRANSMITTER THEORIES

Because most of the effective treatments for mood disorders were discovered by serendipity, pharmacological agents have propelled theoretical formulations rather than vice versa. Neurotransmitter theories of the basis of depression have included serotonergic, noradrenergic, cholinergic, dopaminergic, γ-aminobutyric acid GABAergic, and, most recently, glutamatergic, each based on presumed mechanisms of effective pharmacotherapeutic interventions. For example, finding that several drugs that

acutely potentiated catecholamines and indolamines were antidepressants and that reserpine (which depleted these neurotransmitters) could exacerbate depression and treat mania led to the amine hypotheses of deficiencies in depression and excesses in mania.

Relatively selective manipulations of each of several different neurotransmitter systems (serotonin, noradrenergic, and dopaminergic) now seem to be associated with antidepressant effects (Table 14.8-2 and Table 14.8-3), which raises a critical psychopharmacological question, whether an individual may respond to one type of treatment with a postulated mechanism of action targeting one neurotransmitter system, but not to another (Fig. 14.8-5). In the absence of definitive studies of this question, one is tempted to recommend the sequential use of drugs that act differently within or among classes of agents (e.g., changing from a relatively more serotonergic to a relatively more noradrenergic tricyclic reuptake inhibitor or from a tricyclic drug to an MAOI to lithium). Few validated clinical or biological markers of response to given treatment agents exist, so one must move through the various treatments or adjuncts for the refractory patient until an effective one is found, largely through trial and error. An MAOI trial should be considered for a patient who has failed to respond to multiple previous antidepressants, as response rates remain 50 to 60 percent with this agent. A similar strategy of using agents with different mechanisms of action sequentially or concurrently in mania may also be warranted (Table 14.8-4 and Table 14.8-5).

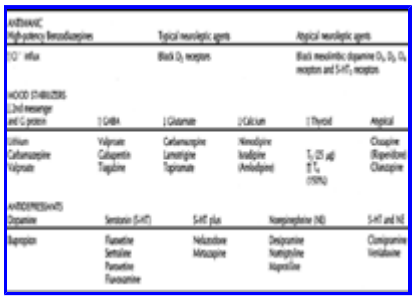


Table 14.8-2 Targets of Action of Antidepressants and Mood Stabilizers

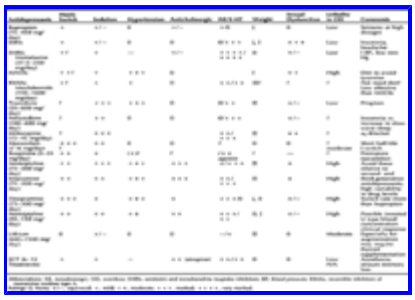


Table 14.8-3 Adverse Effects of Biological Treatments Used to Treat Depression in Bipolar Disorder Patients

Table 14.8-4 Putative Psychotropic and Mechanistic Effects of the Anticonvulsants

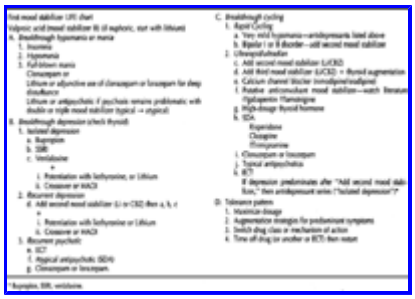


Table 14.8-5 Algorithm for Augmentation and Switching Strategies, Treatment of Bipolar Disorder, Manic Phase, Dysphoric Type

Since 1 month must elapse between treatment with serotonin-active compounds and an MAOI, a transition may be achieved with bupropion, a noradrenergic-selective agent, lithium, or an anticonvulsant. With increasing levels of refractoriness, one should reevaluate the diagnosis (especially with a careful assessment of possible physical, psychological, or drug abuse comorbidity) and consider consultation, psychotherapy revision, as well as more complex combination treatment approaches.

Lithium, valproate, and carbamazepine each alter dopamine and noradrenergic function and upregulate γ-aminobutyric acid (GABA) type B ($GABA_B$) receptors in the hippocampus (Fig. 14.8-6). They also target G protein systems, decrease protein kinase C activity, and inhibit calcium influx through the glutamate *N*-methyl-D-aspartate (NMDA) receptor. Lithium and valproate increase myristoylated alanine-rich C kinase substrate (MARCKS) and activator protein–1 (AP-1) binding, as well as messenger ribonucleic acid (mRNA) levels for BCL-2, and brain-derived neurotrophic factor, the latter two of which may be involved in the prevention of apoptosis. GABAergic effects are enhanced by valproate and gabapentin, whereas topiramate, carbamazepine, and lamotrigine decrease excitatory amino acid release or function in part via blockade of sodium ion channels.

FIGURE 14.8-6 Common and different mechanism of mood stabilizers. PI, phosphoinositol; AC, adenylate cyclase; IMPase, inositol monophosphatase; PLC, phospholipase C; cAMP, cyclic adenosine monophosphate; NPY, neuropeptide y; ACh, acetylcholine; DA, dopaminergic; Ne, noradrenergic; PKC, protein kinase C; $A1_R$, adenosine A1 receptors; T_4, thyroxine; CRE, cyclic response element; CBZ, carbamazepine; TRH, thyrotropin-releasing hormone; CREB, cyclic response element binding protein; VPA, valproate; SRIF, somatostatin; t.o., turnover.

TREATMENT OF ACUTE MANIA

Lithium Lithium has been the paradigmatic treatment for acute and prophylactic treatment of mania. In comparative studies with antipsychotic agents, it yields better overall improvement in most aspects of manic symptomatology, including psychomotor activity, grandiosity, manic thought disorder, insomnia, and irritability. However, the onset of antimanic action with lithium can be rather slow (Fig. 14.8-7), even with aggressive dosing; thus acutely deteriorating aggressive or psychotic manic patients may require supplementation of lithium in the early phases of treatment. Until recently, this was traditionally accomplished with the typical neuroleptic drugs, including the phenothiazines, thiothixines, or butyrophenones such as haloperidol (Haldol). Because of the rapidly growing evidence for the parallel acute antimanic efficacy of the mood-stabilizing anticonvulsants carbamazepine (Fig. 14.8-7) and valproic acid, it is suggested that these alternative agents or the more recently available atypical

serotonin dopamine antagonists be used as initial supplements rather than in place of the conventional antipsychotics for a variety of reasons related to their adverse effect profiles and the risk of tardive dyskinesia.

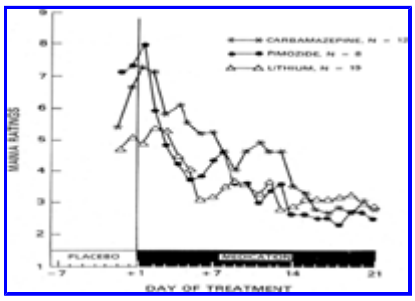


FIGURE 14.8-7 The time course of onset of antimanic response to blind administration of carbamazepine in 12 patients is compared with other similarly diagnosed and rated patients treated with pimozide (*N* = 8) or lithium (*N* = 19).

Double-blind controlled evaluations in many different laboratories have indicated that the onset of antimanic efficacy with carbamazepine is as rapid, or almost as rapid, as it is with traditional antipsychotic drugs, including chlorpromazine (Thorazine), thioridazine (Mellaril), haloperidol, and pimozide (Orap) (Fig. 14.8-7). As of 1998 19 double-blind studies of carbamazepine in acute mania indicated clinical efficacy. Fewer controlled studies have been performed with valproate, but they represent the largest placebo-controlled studies of both lithium and valproate, and they also indicate acute antimanic efficacy. Because initial acute antimanic response may be a guide to subsequent prophylaxis (the major focus of therapeutics of bipolar illness), the author also encourages the investigation of an individual's acute response to these anticonvulsant agents as adjuncts. Antipsychotic agents can always be used later in the sequence if dictated by a lack of clinical response to the mood stabilizers and the adjunctive high-potency benzodiazepines.

Lithium Response The typical clinical profile of the manic patient most responsive to lithium carbonate is one with a classic presentation and euphoric mania, rather than severe or dysphoric mania with paranoid or destructive trends; a pattern of mania followed by a depression and then a well interval rather than a pattern of depression, mania, well interval or continuous cycling; a history of fewer prior episodes and no rapid cycling (i.e., four episodes a year); a positive family history of primary mood disorder in first-degree relatives; and a lack of substance abuse and other comorbidities such as panic disorder. These characteristics can make the difference between a 70 and a 30 percent response rate (Fig. 14.8-8).

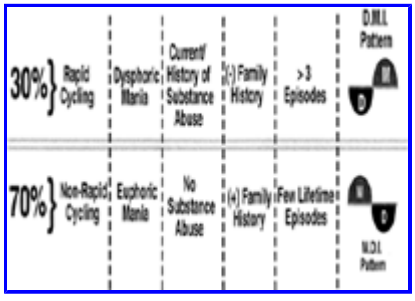


FIGURE 14.8-8 Variable lithium-response rate based on bipolar disorder subtype. D.M.I., depression, mania, well interval; M.D.I., mania, depression, well interval.

Lithium doses should be administered to achieve concentrations in serum between 0.6 and 1.2 mEq per liter. Although a high-dose strategy is advocated by some investigators (concentrations of 1.5 or above), the author has not seen many patients who fail to respond at more typical lithium blood concentrations and respond well when pushed to higher levels that are associated with greater side effects. Dose-limiting adverse effects may include gastrointestinal disturbances (particularly diarrhea) as well as

neuropsychiatric syndromes including tremor, subjective sense of cognitive slowing, confusion, and myoclonic twitches. Concentrations of lithium in blood achieved at a given dosage may increase further if the patient switches from mania to depression, leading to greater adverse effects. For the inadequate responder to lithium at levels associated with few side effects, the author recommends potentiation with other agents, rather than discontinuing lithium and requiring a new agent to treat any additional withdrawal emergent symptoms.

The most recent and largest placebo-controlled study of lithium indicated that only 50 percent of patients achieved a 50 percent or greater improvement by 3 weeks. Those with a prior anecdotal history of lithium nonresponse by self-report were particularly at risk for nonresponse in this controlled study. However, even in the responsive group, many symptoms remained at the end of 3 weeks. Thus, even without the increased pressures from managed care for rapid discharge from the hospital, most full-blown manic patients require adjunctive treatment to achieve a timely and adequate antimanic response. A broad range of such options are now available (Table 14.8-6).

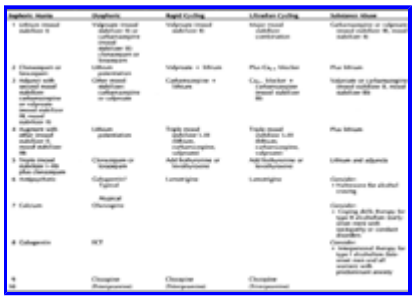


Table 14.8-6 Speculative Differential Approaches to Bipolar Disorder Subtypes

Valproic Acid Typical dosages of valproic acid are 750 to 2000 mg a day, achieving blood concentrations between 50 and 120 μg/mL. Rapid oral loading with divalproex using 15 to 20 mg/kg from day 1 of treatment, has been well tolerated and associated with a rapid onset of response. Blood concentrations above 45 μg/mL have also been associated with earlier response. In several case series, patients with more-typical manic syndromes and fewer schizoaffective symptoms appeared to show a high frequency of response. In contrast to lithium, those with a history of lithium nonresponse, dysphoric mania, or rapid cycling are not less likely to respond to valproate (Table 14.8-6).

Carbamazepine Several preliminary studies have suggested that some of the variables associated with a poor response to or intolerance of lithium may be associated with a good antimanic response to carbamazepine. Thus, the drug may be considered for lithium-nonresponsive manic patients (Fig. 14.8-5).

Typical dosages of carbamazepine to treat mania have ranged between 600 and 1800 mg per day associated with blood concentrations between 4 and 12 μg/mL. However, within this dosage and blood-concentration range, there does not appear to be a clear relation to the degree of clinical response across patients. For an individual patient, however, clinical response and adverse effects are likely dose related. Dosage administration with this anticonvulsant must be individualized, as there is wide variability in the dosage and blood concentration at which adverse effects occur. Increasing the dosage to achieve a clinical effect and titrating the increases against the emergence of adverse effects is the appropriate strategy for such wide individual variability. After several weeks carbamazepine induces hepatic enzymes that lower its levels and may require additional upward dose titration.

Carbamazepine and valproic acid have been used in combination to treat epilepsy, but only preliminary evidence for the efficacy of this combination in acute and prophylactic management of the refractory

bipolar patient is available. Valproate may increase concentrations of carbamazepine and its active 10,11-epoxide metabolite, indicating a need for lower carbamazepine dosage when both drugs are used in combination. Typical adverse effects of carbamazepine and other antimanic drugs are listed in Table 14.8-7.

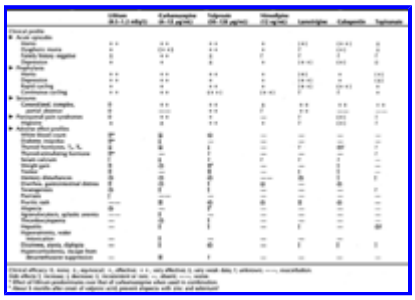


Table 14.8-7 Comparative Clinical and Adverse-Effect Profiles of Lithium, Nimodipine, and the Putative Mood-Stabilizing Anticonvulsants (Preliminary Clinical Impressions)

Clonazepam and Lorazepam The high-potency benzodiazepine anticonvulsants studied in acute mania include clonazepam (Klonopin) and lorazepam (Ativan). Both appear effective and are widely used for adjunctive treatment of acute manic insomnia, agitation, aggression, and dysphoria as well as panic. As noted above, the benign adverse-effect profiles of these agents render them ideal adjuncts to lithium, carbamazepine, or valproate and preferable to the dopamine receptor antagonists (typical antipsychotics) for first-line augmentation. The sedating effects of clonazepam may be problematic in some outpatients, but this property of the drug may be used for bedtime medication for severely insomniac manic patients.

Both of these two high-potency benzodiazepines work rather selectively at the central-type benzodiazepine receptor; in contrast, carbamazepine is not active at this receptor and appears to act at the so-called peripheral-type benzodiazepine receptor (Table 14.8-4). Classic central-type benzodiazepine receptors modulate GABA receptors that facilitate chloride influx and neuronal inhibition (Fig. 14.8-9). In contrast, the peripheral-type benzodiazepine receptor appears to be more closely associated with mitochondrial neurosteroid biosynthesis and calcium channels. These findings are noteworthy in regard to possible differential psychotropic responsiveness between these two classes of anticonvulsants.

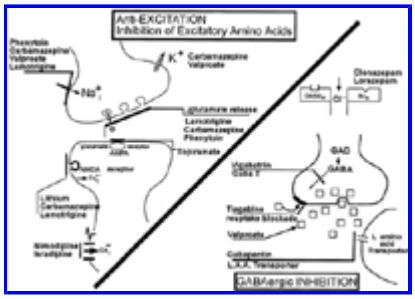


FIGURE 14.8-9 Dual targets of mood stabilizers. Bz_R, benzodiazepine type R receptors, AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; GAD, glutamic acid decarboxylase; L.A.A., L amino acids.

Dopamine Receptor Antagonists Studies indicate that short-term use of conventional antipsychotics (Table 14.8-8) in the treatment of mania results in unintended and often unneeded persistence of antipsychotic use 6 months or more after the acute episode. Such intermittent to chronic maintenance treatment with traditional neuroleptic drugs should be avoided, if possible, since bipolar disorder patients are reported to be at high risk for tardive dyskinesia (20 to 40 percent of those exposed), equal to or greater than that of patients with schizophrenia.

Table 14.8-8 Antipsychotic Drug Use in Mania

Thus, the author recommends exploring potential mood-stabilizing alternatives to lithium (e.g., valproate and carbamazepine), short-term adjuncts (e.g., clonazepine or lorazepam), or serotonin-dopamine antagonists before using dopamine receptor antagonists in bipolar disorder. Intermittent neuroleptic drug use, rather than being a protective factor may actually increase the risk of tardive dyskinesia, according to both clinical and preclinical studies.

The strategy of rapid tranquilization with suprathreshold doses of antipsychotic agents should be avoided. Many double-blind evaluations of this strategy in acutely psychotic schizophrenia patients and one trial in manic patients have shown that the high-dosage strategy (40 to 60 mg a day of haloperidol) is no more efficacious than traditional dosage regimens (10 mg a day) and is associated with greater adverse effects. Particularly for extremely manic patients, the use of heroic antipsychotic dosages to decrease psychomotor activation may not be justifiable considering the added risk of ordinary toxicities, the risk for neuroleptic malignant syndrome, and the sporadic reports of reversible and irreversible organic impairments when used in conjunction with lithium.

Serotonin-Dopamine Antagonists The availability of new atypical antipsychotics with their presumed equal efficacy but superior adverse effect profiles (Table 14.8-9 and Table 14.8-10) may change the algorithm for the treatment of acute mania. A minority of patients appear to require antipsychotics for short- and long-term mood stabilization. Not only can the typical neuroleptic drugs predispose to a variety of acute extrapyramidal effects and long-term tardive dyskinesia, they can also exacerbate the depressive phases of bipolar illness, increasing the frequency or duration of depression or both. These potential liabilities should lead one to use the newer atypical neuroleptic agents if additional antipsychotic treatment is required.

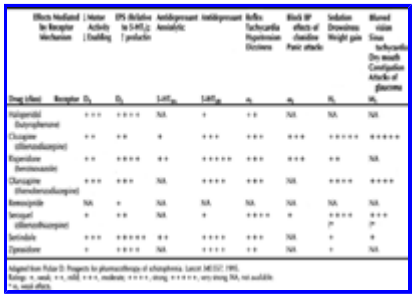
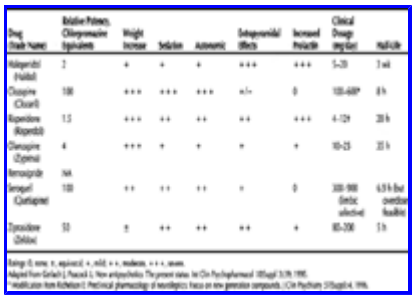


Table 14.8-9 Receptor Activities of Atypical Antipsychotics Relative to Haloperidol

Table 14.8-10 Clinical Profiles of the Atypical Antipsychotics Relative to Haloperidol



Clozapine appears to be particularly efficacious in refractory bipolar I disorder characterized by either dysphoric mania or rapid cycling. Its efficacy in bipolar disorders equals or betters that in schizoaffective disorder and schizophrenia as well. However, it has considerable liabilities: inconvenience, cost, and risk of agranulocytosis, which requires weekly blood monitoring. Olanzapine has a biochemical profile similar to that of clozapine, and preliminary evidence suggests that this newly approved agent will assume a similar role in the treatment of refractory bipolar disorder patients. Initial trials of olanzapine in acute mania yielded positive results, and the drug appears to be generally well tolerated, except for substantial weight gain in some patients.

The use of low dosages of risperidone appears promising, although there are several case reports of depressed patients switching into mania when treated with high dosages of this agent. Low dosages are associated with increased prolactin, and dosages over 8 mg a day are associated with both extrapyramidal effects and weight gain.

Other atypical agents should be watched for their spectrum of efficacy in acute mania and prophylaxis, as they may have beneficial profiles in the treatment of mania such as relative lack of sedation (olanzapine and sertindole); lack of prolactin increases (clozapine, quetiapine, and sertindole); fewer anticholinergic adverse effects (seroquel and sertindole); and less weight gain (ziprasidone). The possible antidepressant aspects of these putative mood stabilizers, perhaps related to their positive effects in the negative symptoms of schizophrenia, also deserve close scrutiny. Table 14.8-9 and Table 14.8-10 summarize preliminary data on the mechanisms of action, adverse effects, and potential efficacies of the serotonin-dopamine antagonist.

A potentially unique approach to the dopamine system might be attained with the tricyclic drug trimipramine (Surmontil). This long-approved antidepressant had an unknown mechanism of action, since it was not a potent reuptake blocker of any of the amine systems. It was recently shown to be a moderately potent antagonist of type 2 dopamine (D_2) and D_4 receptors, somewhat similar to clozapine. It has also been reported in open studies to be effective in monotherapy for acute schizophrenic episodes and psychotic depression. Therefore, in light of its D_2 and D_4 blocking properties as well as its efficacy as an antidepressant, some have recommended using trimipramine in bipolar patients with refractory rapid cycling depressions.

L-Type Calcium Channel Inhibitors A series of preliminary reports suggest that the calcium channel inhibitor verapamil (Calan, Isoptin) has acute antimanic efficacy. Whereas a number of controlled studies suggest the antimanic utility of verapamil, several recent studies suggest the superiority of lithium. Moreover, one randomized study in acute depression indicated that verapamil is no more effective than placebo and less effective than routine antidepressant treatment. These data led to a search for a more effective calcium channel blocker that might have better spectrum of antidepressant and prophylactic effects than verapamil.

Several groups chose to study the dihydropyridine L-type calcium channel inhibitor nimodipine

(Nimotop) because of its (1) ability to penetrate the CNS, (2) relative lack of tolerance development in the treatment of migraine (in contrast to many other calcium channel inhibitors, (3) better profile in many types of animal seizure models than verapamil, and (4) greater ability to block cocaine-induced hyperactivity and associated dopamine overflow. One study reported that 10 of the first 30 evaluable treatment-refractory patients had a clinically relevant response to nimodipine, including patients with rapid and ultradian cycling frequencies (Fig. 14.8-10 and Fig. 14.8-11). Responsivity was confirmed and reconfirmed in some of these patients in a double-blind, off-on-off-on design. Almost all of these patients needed their regimens further supplemented with another agent such as lithium or carbamazepine for a more complete response, however. Carbamazepine augmentation of nimodipine was effective (moderate or marked response on the Clinical Global Impression Scale) in only 5 of 14 patients treated with the combination.

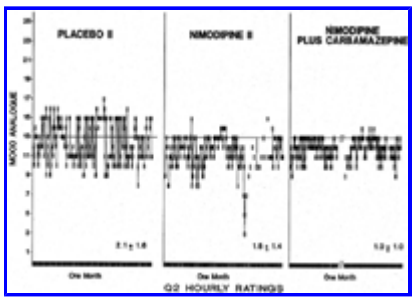


FIGURE 14.8-10 Efficacy of Nimodipine plus carbamazepine combination in a bipolar II female with ultradian cycling.

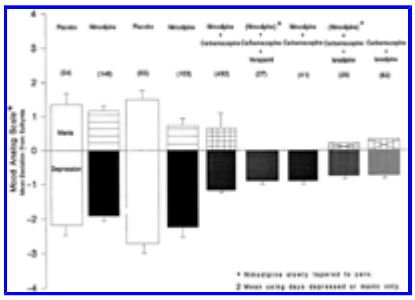


FIGURE 14.8-11 Nurse ratings of the efficacy of dihyropyridine L-type calcium channel inhibitors in a woman with bipolar II disorder.

Of considerable interest were several patients who clearly responded to either monotherapy or combination therapy with nimodipine and transitioned from nimodipine on a double-blind basis to maximally tolerated doses of verapamil, without maintaining response (Fig. 14.8-11). They later either reresponded to nimodipine or to another dihydropyridine L-type calcium channel inhibitor such as isradapine (Dynacirc) further confirming the initial responsivity to this drug class but also suggesting that responsivity might be better conferred by the dihydropyridine subtype of L-type calcium channel inhibitor (with the binding site deep inside the calcium channel) than the phenylalkylamine verapamil (which blocks at the outside of the channel) (Fig. 14.8-10).

Although there is some evidence that patients with extremely rapid cycling fluctuations within a 24-hour period (ultra-ultra rapid cycling) are among those who respond best to the dihydropyridines, the question of whether this subgroup is selectively targeted remains open. Depressed patients with the more classical pattern of global and frontal hypometabolism on positron emission tomography (PET) were among those who responded best to nimodipine. In contrast, those with a hyperactive metabolic pattern were more likely to respond to carbamazepine. Much work remains to define the precise role of the calcium channel blockers in the treatment of bipolar refractory depression (Table 14.8-5 and Table 14.8-6).

Lamotrigine A series of preliminary reports and two controlled trials suggest that lamotrigine, the

newly approved anticonvulsant for add-on therapy, has antidepressant and possibly mood-stabilizing properties. In an open study 67 patients were studied usually with the drug as an adjunct to previously ineffective treatment regimens; 27 of 39 (69 percent) who presented in the depressed phase and 19 of 25 (76 percent) in the manic phase showed moderate-to-marked improvement.

A randomized, double-blind study at the NIMH found a significantly greater incidence of good response to blind lamotrigine monotherapy (17 of the first 3 patients [52 percent] than to (9 of 33 gabapentin [27 percent]) or placebo (7 of 32 [22 percent] placebo ($P < .05$). Many patients with refractory depression profiles were among those who showed a good response. Patients with bipolar I disorder depression showed a non-significantly better response than those with bipolar disorder II or a depressive disorder. Another large multicenter study indicated that both 50 and 200 mg a day of lamotrigine were superior to placebo in a 7-week trial in depressed bipolar I disorder patients.

Lamotrigine treatment should be initiated slowly in monotherapy with one 25-mg pill for the first 2 weeks and then 50 mg for 2 weeks, with slow increases thereafter to avoid a moderately high incidence of rash. The rate of increase should be halved if patients are on a regimen including valproate, which can markedly increase lamotrigine blood concentrations and the propensity for rash and more serious dermatologic complications. Conversely, carbamazepine decreases lamotrigine concentrations by approximately 50 percent, and one can start with higher dosages.

The precise anticonvulsant or psychotropic mechanisms of action of lamotrigine remain to be delineated. However, lamotrigine, like valproate, is a broad-spectrum anticonvulsant, effective not only in complex partial and generalized seizures, but also in absence and atonic seizures, in contrast to carbamazepine, which can exacerbate absence seizures. This is important because recent studies have suggested that carbamazepine, lamotrigine, and phenytoin have highly similar properties in the blockade of type 2 sodium channels and consequent inhibition of release of excitatory amino acids such as aspartate and glutamate (Fig. 14.8-9 and Fig. 14.8-12). However, the differential clinical profiles of these drugs in epilepsy and the preliminary evidence that lamotrigine may be effective in some patients who respond inadequately to carbamazepine suggest that lamotrigine has additional mechanisms not shared by carbamazepine. Recent evidence suggests that lamotrigine affects different types of calcium channels (N-type and P-type) and blocks serotonin reuptake and is active at serotonin (5-hydroxytryptamine [5-HT]) type 3 (5-HT_3) receptors, but the high concentrations at which these serotonergic effects are observed suggest that they are not clinically relevant. Preliminary data suggest that depressed patients with the more classical topographic pattern of frontal hypoperfusion on PET studies are likely to respond to lamotrigine.

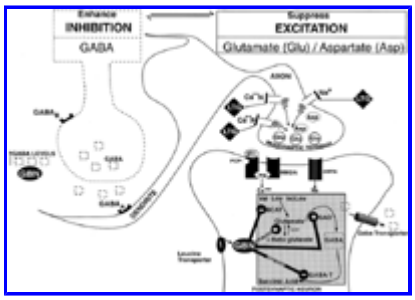


FIGURE 14.8-12 Targets of action of lamotrigine (LTG) and gabapentin (GBN). AMPA, α-amino-3-hydroxy-5-methyl-4-isoxalone propionate; GAD, glutamic acid decarboxylase; GDH, glutamate dehydrogenase; PCP, phencyclidine.

Gabapentin Open adjunctive studies indicate that gabapentin, a newly approved anticonvulsant for adjunctive therapy may also have some mood-stabilizing effects in bipolar patients. The drug appears to have positive effects on sleep and anxiety. However, two double-blind studies of monotherapy, one in acute mania and the other in refractory affectively ill patients showed no benefit over placebo. Whether

gabapentin's prominent effects on the L–amino acid transport mechanism (Fig. 14.8-9) and resulting increases in brain GABA concentrations (Fig. 14.8-11) are related to its anticonvulsant or putative psychotropic properties remains to be determined.

Topiramate A recently approved add-on agent for treatment of refractory epilepsy, topiramate, is just beginning to be studied in bipolar disorders (Table 14.8-7). Preliminary uncontrolled data suggest it may have mood-stabilizing properties in rapid-cycling patients, with better antimanic than antidepressant effects. A major asset of topiramate is its positive effect of weight loss in contrast to lithium, valproate, gabapentin, many antidepressants, and most antipsychotic drugs. As a carbonic acid inhibitor it has a 1 percent risk of renal calculi (virtually all occurred in males); the calculi are made of calcium and respond well to emergency lithotripsy. Cognitive slowing and difficulty with word finding, may appear with rapid dosage escalation or in combination therapy. Topiramate is a selective inhibitor of glutamate α-amino-3-hydroxy-5-methyl-4-isoxalone-propionate (AMPA) receptors (Fig. 14.8-9) that also has GABAergic actions and blocks sodium ion channels.

Other Anticonvulsants The clinical utility of other GABA-active anticonvulsants, such as the GABA reuptake inhibitor tiagabine (the transamine inhibitor γ-vinyl GABA (vigabatrin [Sabril]) and the agonist progabide (all remain to be further explored, as does the older anticonvulsant phenytoin (Dilantin). Acetazolamide (Diamox) has been reported to be effective for atypical psychoses associated with dreamy, confusional states as well as those occurring premenstrually or in the puerperium. Whether this profile is shared by other carbonic acid inhibitors such as topiramate remains to be determined.

Electroconvulsive Therapy Older clinical observations and recent controlled clinical trials continue to document the efficacy of ECT in acute mania. Bilateral treatments appear to be required; unilateral, nondominant treatments have been reported to be ineffective or to exacerbate manic symptoms in some studies. In light of the many effective pharmacological treatments noted above, and the utility of using the assessment of their acute antimanic efficacy as a surrogate marker for putative efficacy in long-term prophylaxis, ECT may be reserved for the very rare refractory manic patient or one with medical complications, as well as extreme exhaustion (lethal catatonia) or malignant hyperthermia (Table 14.8-6). Antimanic effects of a brief course of repeated transcranial magnetic stimulation (rTMS) of the brain at 20 Hz over the right but not left frontal cortex or 1 Hz rTMS bifrontally have been observed; whether this well-tolerated nonconvulsive strategy will eventually have a role in clinical therapeutics remains open.

OTHER THEORETICAL AND MECHANISTIC CONSIDERATIONS

Antiadrenergic Drugs A series of other nonanticonvulsant compounds with some neurotransmitter selectivity has been reported to be efficacious in treating mania. Clonidine (Catapres) an α_2-adrenergic agonist, is used to treat hypertension. It acutely inhibits the firing of the noradrenergic locus coeruleus and has been reported to show short-term antimanic efficacy in some (but not all) controlled trials. Response in the first few days of treatment may not be associated with an ultimate long-term response, however. Another agent that inhibits noradrenergic function is the β-adrenergic receptor antagonist propranolol (Inderal). Because very high dosages of either the dextrorotatory or levorotatory of this agent isomer form have been effective, it is questionable whether the β-antagonist properties or the membrane-stabilizing effects of this drug account for its short-term antimanic efficacy.

Cholinomimetics One open study reported that high dosages of choline (3 to 8 grams per day) possess antimanic and anticycling effects in refractory bipolar patients. Intravenous administration of the indirect cholinergic agonist physostigmine (Antilirium) has been demonstrated to have an almost immediate antimanic effect. Physostigmine inhibits acetylcholine esterase function, making more

acetylcholine available at the synapse. Although this strategy can rapidly decrease manic symptomatology, it also has a rapid half-life and can be associated with rather marked increases in dysphoria and other adverse effects, such that its long-term utility is doubtful. The success of attempts to increase cholinergic function in the long term through other methods (e.g., lecithin, deanol, or direct acetylcholine agonists) has not been adequately delineated.

Overview of Antimanic Agents The ability to achieve rapid antimanic effects with intravenous physostigmine (an acetylcholinesterase inhibitor) suggests that given appropriate pharmacological intervention and pharmacokinetics, there is no theoretical reason why an acute antimanic response cannot be achieved extremely rapidly, even though most antimanic treatments have a moderate delay in onset. Manipulations of a variety of neurotransmitter systems (inhibition of nonadrenergic and dopaminergic and potentiation of the cholinergic, benzodiazepine, GABA, and perhaps serotonergic systems) all can induce antimanic effects. The antipsychotic agents block dopamine receptors; clonidine and propranolol appear to decrease α- and β-noradrenergic function, respectively. Reserpine (Diupres) which depletes catecholamines and indoleamines, has also been reported to have antipsychotic and antimanic effects.

As noted in Table 14.8-2 and Table 14.8-3, awareness of the multiple neurotransmitter approaches to the treatment of mania may be clinically useful in both changing and combining treatments that target different systems in nonresponsive patients. Alterations in endogenous neuropeptide function also have been postulated in mania. Although manipulations of opioids or cholecystokinin have not yielded consistent results in psychotic schizophrenia patients, isolated reports that thyrotropin-releasing hormone (TRH) or calcitonin were successful in treating excited psychotic states, including mania, deserve replication. The potential efficacy of peptide interventions in mania is mentioned because peptides could represent the next generation of antimanic treatments, particularly in light of the evidence of peptide neurotransmitters coexisting in neurons with more classical neurotransmitter substances that have been indirectly linked to the manic syndromes and the early reports of the antidepressant effects of a substance P antagonist.

Preliminary evidence indicates that the L-type calcium channel inhibitors that inhibit calcium influx through voltage-dependent channels may be effective in treating acute mania. New data indicate that lithium, carbamazepine, lamotrigine, and valproate all block calcium cation (Ca_{2+}) influx through the glutamate NMDA receptor (Fig. 14.8-9), which raises the theoretical rationale of using different mechanisms of blockade of Ca_{2+} influx for more effective or complete effects in refractory patients. Multiple studies of platelets and lymphocytes of bipolar disorder patients indicate increased baseline levels of, or serotonin- or thrombin-stimulated rise in, intracellular calcium.

A new approach examining common effects of chronic lithium and valproate has revealed inhibition of protein kinase C as a putative target for antimanic effects. This idea of H. Manji received preliminary support from the observations of rapid-onset acute antimanic effects in six of nine patients treated with the protein kinase C inhibitor tamoxifen (Nolvadex).

Many of the principles of treating unipolar depression are applicable to the treatment of depression in bipolar disorders, but the critical role of concomitant treatment with mood stabilizers and targeting the symptoms most characteristic of bipolar disorder depression—such as its atypicality, and reverse vegetative symptoms of hypersomnia, increased appetite, weight, lethargy, and psychomotor retardation—require emphasis. Antidepressant drugs that are particularly useful in bipolar disorder patients are listed in Table 14.8-2.

MAINTENANCE TREATMENT OF BIPOLAR DISORDERS

Lithium Prophylaxis Lithium originally appeared to be effective in some 70 to 80 percent of bipolar disorder patients, but current estimates suggest that even with adjunctive use of antidepressants and antipsychotics, a response rate of 40 percent or less in many lithium clinics is more accurate (Fig. 14.8-13).

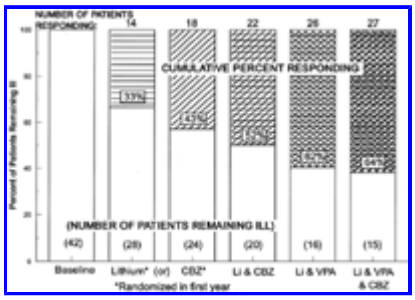


FIGURE 14.8-13 Cumulative response and failure rates on mood-stabilizing regimens. CBZ, carbamazepine; VPA, valproate.

Although initial studies indicated the need for blood concentrations between 0.8 and 1.2 mEq per liter, some series have suggested that concentrations of 0.5 to 0.8 mEq per liter might be effective in maintenance treatment. However, a recent controlled study indicated that the lower levels of adverse effects are achieved at a cost; the relapse rate with a low lithium concentration range (0.4 to 0.6 mg/L) is three times that at higher concentrations (0.8 to 1.0 mg/L). Monitoring of trough levels (performed in the early morning with the AM dose withheld) at 1- to 2-month intervals (or more frequently if the patient's course is unstable) is recommended. A 1-year controlled study reported that the greater the lithium-induced decreases in plasma free thyroxine (T_4) concentration, (but not lithium blood levels) the greater the severity of depression and cycling.

Because of the substantial data on long-term efficacy and prevention of suicide with lithium treatment, preventive treatment should be considered after one or two manic episodes and after a single severe episode of mania, particularly if there is a positive family history of bipolar disorder. The development of a life chart, so that the frequency, severity, and interval between episodes can be accurately assessed, may also assist in arriving at the decision for prophylaxis. If previous episodes were severe—socially incapacitating and requiring hospitalization—or associated with extremely adverse events for the patient and family, one would be more likely to consider prophylaxis earlier rather than later, despite moderately long well intervals between episodes. These factors should be discussed with the patient during a euthymic interval so that the appropriate risk-benefit ratios can be weighed carefully with adequate informed consent. Data from numerous studies indicate that greater numbers of prior episodes (more than three or four) are associated with a poor response to lithium prophylaxis, so delayed prophylaxis may have negative consequences not only for the increased morbidity during these recurrences, but also for ultimate treatment response. Whether greater numbers of prior episodes also predispose to the development of tolerance (Fig. 14.8-14) or lithium discontinuation-induced refractoriness (Fig. 14.8-15) remains to be studied.

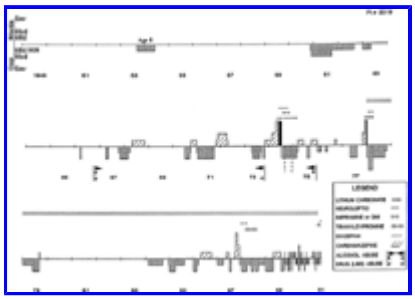


FIGURE 14.8-14 Development of refractoriness to lithium in the course of malignant progression of mood disorder. DMI, desipramine; LSD, lysergic acid diethylamide; DOB, date of birth.

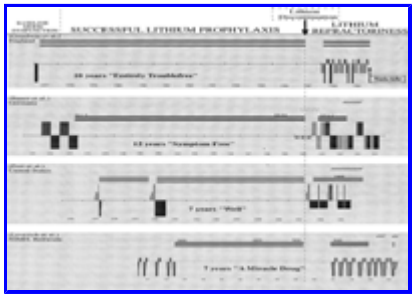


FIGURE 14.8-15 Lithium discontinuation–induced refractory illness.

Carbamazepine and Other Mood Stabilizers One alternative to traditional unimodal antidepressants for depressive breakthroughs is the addition of first-generation anticonvulsant mood stabilizers such as carbamazepine or valproate, or putative second-generation anticonvulsants such as lamotrigine (Table 14.8-11). Although the controlled evidence concerning the efficacy of carbamazepine used as monotherapy for primary depression is inadequate those findings taken with the more substantial emerging literature on the efficacy of carbamazepine prophylaxis for both manic and depressive episodes, raise the priority of using this agent to supplement lithium in depressive breakthroughs, particularly those of the rapid-cycling variety. Although only one-third of refractory depressed patients responded in one study, the responders tended to be the patients with greater initial severity of depression and clearer prior histories of discrete episodes rather than chronic depression.

Table 14.8-11 Drugs in the Prevention of Manic Depressive Episodes and Cycling

When antidepressant response to carbamazepine was observed, it tended to occur with the typical lag observed with other agents, so that only minor improvement was noted in the first and second weeks of treatment, but considerable improvement was observed after the third and fourth weeks. Surprisingly, the degree of antidepressant response was correlated with the degree of decrease in T_4 and free T_4. An abnormal EEG or increased psychosensory symptoms did not predict an acute response to carbamazepine in one series, but did in another when carbamazepine was used for augmentation, and a 53 percent response was observed compared with an even higher rate for lithium augmentation.

More than a dozen controlled studies support the comparative efficacy of carbamazepine and lithium in the prophylaxis of both manic and depressive episodes. One study reported lower antimanic effects of carbamazepine than with lithium as did another study in patients with classic euphoric mania. However, the latter study indicated a better response to carbamazepine in those with atypical presentations (i.e., dysphoric mania, schizoaffective disorder, rapid cycling and comorbidities).

In a small series of patients who responded inadequately to carbamazepine alone, one half showed a rapid onset of antidepressant effect with lithium augmentation. Thus, the combination of carbamazepine and lithium appears to help a substantial subgroup of otherwise refractory patients (Fig. 14.8-5). In one randomized study in bipolar outpatients with a high incidence of rapid cycling, response rates were

under 25 percent with either lithium or carbamazepine monotherapy for 1 year, even when adjunctive antidepressants and antipsychotic drugs were allowed, but over 50 percent with both drugs in combination (Fig. 14.8-16). Thus, one might consider combination mood stabilizer treatment from the outset in this rapid-cycling subgroup.

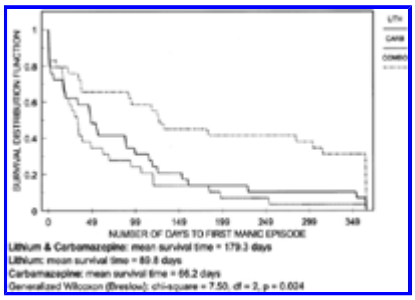


FIGURE 14.8-16 Mean survival time to first manic episode is longer on the combination of lithium and carbamazepine than with either lithium and carbamazepine alone (*N* = 29).

Carbamazepine has been reported effective in some patients failing multiple traditional antidepressant trials, especially in those with a history of head trauma or EEG abnormalities, in one series. As noted for refractory bipolar disorder patients discussed below, the anticonvulsants carbamazepine and valproate may be used in combination with unimodal antidepressants, and the role of these and other combination treatments for the refractory depressed patient deserves much further systematic research to provide adequate statistical and sequence-ordering guidance for the clinician.

Valproic Acid In many open series, valproic acid alone or in addition to lithium has been reported to be successful in the long-term treatment of a substantial subgroup of previously lithium- or carbamazepine-refractory patients. The acute antidepressant efficacy of valproic acid is much less well delineated than its antimanic efficacy, and the utility of this treatment for an acute depressive episode remains to be further elucidated. Nonetheless, the combination of lithium and valproate offers another excellent option in the long-term management of bipolar patients who do not respond to lithium alone. A response to one anticonvulsant may not predict a response to another, and positive long-term effects of valproic acid plus lithium have been noted in patients who did not respond to lithium or carbamazepine prophylaxis (Fig. 14.8-17 and Fig. 14.8-18).

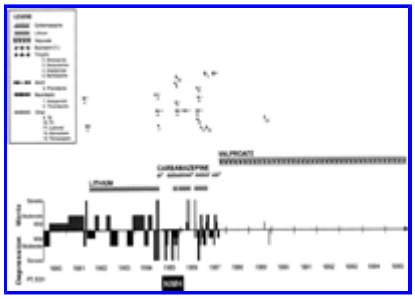
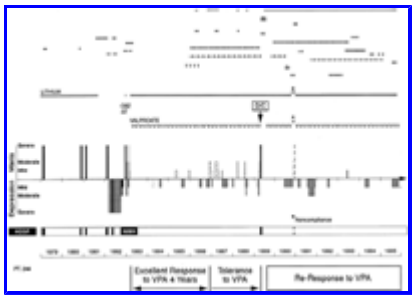


FIGURE 14.8-17 Prophylactic response to valproate in a nonresponder to lithium and carbamazepine.

FIGURE 14.8-18 Tolerance and reresponse to the prophylactic effects of valproate (VPA). CBZ, carbamazepine; D/C, discontinuation.



Lamotrigine A series of open studies suggests the possibility of mood stabilizer effects of lamotrigine, in many instances in those not responsive to conventional treatments. One double-blind, controlled study of short-term prophylaxis in ultrarapid-cycling patients revealed significant antidepressant and antimanic effects over those of either gabapentin or placebo. These data, taken with the large controlled trial of lamotrigine in bipolar I disorder depression suggest that the addition of lamotrigine to lithium or another mood stabilizer is an alternative option to the addition of a unimodal antidepressant. Response rates of 60 to 70 percent were observed in open studies when lamotrigine was used adjunctively.

Calcium Channel Inhibitors The few uncontrolled studies of calcium channel inhibitors suggest their promise as prophylactic treatments, but they may be less effective for depressive breakthroughs than for manias. One study reported better prophylactic efficacy of 1 year of the combination of lithium and nimodipine compared with 1 year of either drug alone. Further controlled studies of prophylaxis are sorely needed. Although data are limited to just one double-blind series at the NIMH, in the several patients crossed over blindly from one L-type calcium channel inhibitors to another, agents in the dihydropyridine class (nimodipine and isradapine) had better antidepressant and mood-stabilizing effects than the phenylalkylamine verapamil (Fig. 14.8-10 and Fig. 14.8-11).

Gabapentin Gabapentin may show positive effects on mood, anxiety, and sleep in 30 to 40 percent of refractory bipolar disorder patients, but much higher rates of response are reported in open studies when gabapentin is used as add-on treatment. The mood-stabilizing anticonvulsants (carbamazepine, valproate, lamotrigine, and gabapentin) certainly also deserve more consideration for a patient's profound sleep disturbance, with or without associated posttraumatic stress disorder, especially if the patient has comorbid alcoholism or bipolar disorder depression and benzodiazepines are to be avoided.

Thyroid Although thyroid potentiation similar to that observed in unipolar depression can be attempted, treatment with dosages above suppressive doses should be approached with caution. Several investigators found associated medical toxicities with high-dosage thyroid treatment and inadequate maintenance of long-term prophylaxis unless other routine agents were used concurrently. Thus liothyronine (Cytomel), the levoratatory isomer of triiodothyronine (T_3), is recommended for short-term augmentation strategies because of its short half-life, and levothyroxine (Levoxyl, Synthroid) the levorotatory isomer of T_4 is recommended by some as more appropriate for long-term maintenance during prophylaxis. As noted above, addition of liothyronine to levothyroxine has been reported to benefit nonresponders.

Hypermetabolic Dosages of Levothyroxine Recent data indicate that high-dosage levothyroxine treatment—μg a day targeted toward achieving a free thyroxin index 150 percent of normal—may be helpful as an adjunctive treatment in rapid-cycling patients. Another report further suggests that this high-dosage augmentation strategy may benefit patients with persistent refractory depression. The data indicating improvement in both manic and depressive phases with hypermetabolic levothyroxine augmenting strategies speaks to the potential importance of this modality for bipolar disorders. However, systematic long-term trials must be conducted, and the issue of whether some patients lose

responsivity to such thyroid augmentation strategies with the development of tolerance requires further exploration.

Serotonin-Dopamine Antagonists Given their short-term antimanic and longer-term antipsychotic effects against the positive and negative symptoms of schizophrenia, the serotonin-dopamine antagonists are becoming increasingly important in prophylaxis of mood and schizoaffective disorders. Their better profile of acceptability (Table 14.8-8) and safety than the conventional antipsychotics impels their use instead of these conventional antipsychotics even before adequate data on long-term efficacy become available.

POTENTIAL CORRELATES OF RESPONSE TO THE MOOD STABILIZERS

From a clinical and theoretical perspective it would be valuable to know whether the efficacy of carbamazepine, valproate, or the other putative mood-stabilizing anticonvulsants is related to their ability to stabilize neural excitability in temporal lobe and limbic structures (independent of whether or not a seizure disorder underlies the mood disorder) (Fig. 14.8-8 and Fig. 14.8-19). Only a minimum of evidence is available indicating that carbamazepine, for example, acts via its effects on temporal lobe or limbic substrates. However, the approximate rank ordering of carbamazepine, valproate, and phenytoin according to their degree of limbic selectivity is roughly related to their psychotropic efficacy and provides at least indirect support for the limbic hypothesis.

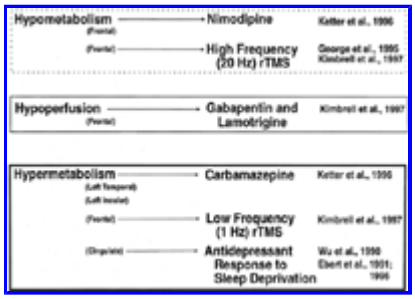


FIGURE 14.8-19 Preliminary predictors of clinical response—functional brain imaging. rTMS, repeated transcraneal magnetic stimulation.

An indirect marker of limbic dysfunction—degree of psychosensory symptoms—is not related to carbamazepine response in primary affective disorder, although others disagree. Recent PET data, however, suggest that patients with initial baseline hypermetabolism, particularly in the left insula, are among those who respond best to carbamazepine, whereas those with a pattern of baseline frontal hypometabolism respond best to nimodipine. These preliminary data are among the first to provide suggestive evidence that increased metabolism in mesiotemporal structures could be associated with the therapeutic response to carbamazepine. Patients with relative hypoperfusion at baseline show normalization upon successful treatment with lamotrigine or gabapentin, whereas nonresponders tend to be closer to normal at baseline and decrease significantly with treatment with these agents. Some preliminary data also link baseline hypometabolism with response to high-frequency rTMS, which normalizes this pattern. Those with relative hypermetabolism at baseline respond to low-frequency (1 Hz) rTMS in association with normalization of this pattern. Although not clinically useful at present, one can only hope that replication and extension of these studies will assist in better matching individual treatments to individual patients.

A number of studies suggest an equally good response to valproate in dysphoric compared to euphoric mania, in contrast to the relatively poor response to lithium in the dysphoric subtype. One small study suggested that carbamazepine responders tended to be more dysphoric at baseline than nonresponders.

More than 15 studies have reported a relatively poor response to lithium in rapid-cycling patients; only 2 studies have reported a good response, and 4 have reported no differential response. The relation of carbamazepine response to rapid cycling is less clear. In one acute mania study and several prophylaxis studies, a high response percentage was observed in rapid-cycling patients. However, when rapid-cycling patients were compared with non-rapid-cycling patients in two studies, both found a higher prophylactic response rate to carbamazepine in non-rapid-cycling patients. Data from Japan are revealing in that the 53 percent response rate to carbamazepine in patients with a history of rapid cycling (compared with 76 percent in those without) is still substantially higher than the 30 percent response rate observed for lithium in patients with a history of rapid cycling (compared with 64 percent in those without such a history).

Taken together, these data suggest that rapid cycling is a poor prognostic indicator for both carbamazepine and lithium treatment, although some patients with rapid cycling respond positively to carbamazepine. NIMH data suggest the potential utility of treatment of rapid-cycling patients on the combination of lithium and carbamazepine from the outset (with its 53 percent response rate) in light of the poor response to either monotherapy in these patients (28 percent response to lithium and 19 percent response to carbamazepine).

Rapid cycling and prediction of response to valproate is less well studied, but initial indications from a large double-blind collaborative study are that the short-term antimanic response is robust in these individuals, which agrees with other data from open studies indicating an excellent acute and prophylactic response in several large cohorts of rapid-cycling patients treated with either monotherapy or combination treatment. However, one study reported that an accelerating course of illness was a poor prognosis factor for predicting valproate response. Initiating treatment with valproate (Fig. 14.8-17) or lithium and valproate in rapid-cycling or dysphoric manic patients from the outset may thus be a particularly useful alternative to lithium and carbamazepine for this subgroup.

Some evidence suggests that a negative family history of mood disorders may be associated with a good response to carbamazepine; seven of eight studies reported that a positive family history of affective illness in first-degree relatives is associated with a positive response to lithium. These data, in conjunction with clinical case reports illustrating that patients with evidence of delirium, dementia, and other cognitive disorders show a relatively poor response to lithium, a high potential for toxicity, and a potentially good response to the anticonvulsants carbamazepine or valproate, suggest that the familial genetic subtype of mood disorders may be more responsive to lithium than the subtype mediated through other nonhereditary pathophysiological mechanisms, which may be better targeted with the mood-stabilizing anticonvulsants. These possible mechanisms include neuronal and environmental insult related to birth trauma, infection, secondary mood disorder, and substance abuse. Further study of this issue is clearly required.

The mood-stabilizing anticonvulsants (carbamazepine, valproate, and possibly lamotrigine and gabapentin) certainly also deserve higher consideration for a patient's profound sleep disturbance (with or without associated posttraumatic stress disorder), especially if the patient has a comorbid alcohol use disorder or a bipolar disorder, and benzodiazepines are to be avoided.

RELATIVE ADVERSE-EFFECT PROFILES OF LITHIUM AND THE MOOD-STABILIZER ANTICONVULSANTS

Since only a modicum of data suggests clinical or biological predictors of response to the mood stabilizers (Fig. 14.8-8 and Fig. 14.8-19), adverse effect profiles and tolerability in long-term prophylaxis (Table 14.8-7) as well as mechanisms of action (Table 14.8-4, Fig. 14.8-6 and Fig. 14.8-9)

become potential selection factors.

The general profile of lithium-induced side effects has proven to be relatively benign in the long-term maintenance treatment of bipolar patients. However, several of lithium's more prominent adverse effects deserve comment, as do the relative comparisons with and among the mood-stabilizing anticonvulsants.

Thyroid Function Lithium clearly can impair thyroid function by several different mechanisms; it has even been used to treat hyperthyroidism. Lithium uniformly lowers T_3 and T_4 concentrations in the plasma and, in some patients, increases thyroid-stimulating hormone (TSH). TSH concentrations above normal can be taken to indicate that the hypothalamic-pituitary-axis is working overtime to maintain normal levels of thyroid hormones. Lower free T_4 concentrations during lithium prophylaxis in one study were associated with more-severe depression and more-rapid mood fluctuation. Thus, one might consider thyroid replacement with levothyroxine when levels of TSH are elevated, even when thyroid hormone indexes are still within their normal lower limits. Occasional checks of thyroid function at 6-month to 1-year intervals are wise, as is an earlier check if there is a breakthrough of depressive symptomatology during otherwise adequate lithium maintenance treatment. In these instances, treatment of underlying hypothyroidism can help alleviate a depression that is linked to this hormonal deficit. Whereas levothyroxine is generally used for suppression of TSH and replacement, anecdotal evidence suggests that addition of liothyronine to the levothyroxine replacement may help some patients with refractory depression or cycling.

Carbamazepine tends to decrease T_4, free T_4, and T_3 concentrations (as does lithium), and in combination, the decreases are additive. During carbamazepine treatment there is a negligible incidence of clinical hypothyroidism or above-normal increases in TSH. Consequently, thyroid supplementation of carbamazepine is rarely needed. When the two drugs are used in combination, however, the lithium effect on TSH may override that of carbamazepine, and the patient may then require thyroid supplementation.

Renal Function By the late 1980s the fear regarding the possible high incidence of long-term adverse consequences of lithium on the kidneys had largely dissipated. Original reports of severe nephrotoxicity and pathology with elevated creatinine and low clearance originally attributed to lithium were, in part, related to the absence of an age-matched control group of psychiatric patients not treated with lithium. Thus, although lithium rather consistently impairs vasopressin function at the level of adenylate cyclase and often produces a syndrome of diabetes insipidus, it is less consistently associated with other evidence of renal toxicity, although isolated case reports persist. Preliminary data suggest that less renal toxicity may occur in patients using single nighttime dosing (producing higher peaks, but lower nadirs) than occurs with conventional dosing regimens. Single nighttime dosing may also facilitate compliance.

Current practice suggests that frequent monitoring of renal function during lithium treatment is not generally indicated; however, baseline measures of renal function including creatinine clearance should be obtained before beginning lithium treatment in patients with a history of some renal alterations. Patients must have adequate fluid intake to maintain an appropriate fluid and electrolyte balance because of the induction of diabetes insipidus syndrome related to the blockade of antidiuretic hormone actions. Several patients have been reported in whom high levels of lithium during intoxication were associated with irreversible cerebellar toxicity. Thus lithium levels, fluid and electrolyte status, or both, should be monitored closely during periods of febrile illness, decreased fluid intake, or greater-than-ordinary fluid loss (e.g., during extreme athletic stress or during gastrointestinal illnesses with vomiting or diarrhea).

Amiloride (Midamor) (5 to 10 mg) has been useful in the treatment of lithium-induced diabetes insipidus. If diuretics (furosemide [Lasix] or thiazides) are used, lower dosages of lithium are indicated

because these agents will increase lithium concentrations.

Because carbamazepine appears to act as a vasopressin agonist either directly or by potentiating vasopressin effects at the receptor, it will not suffice to reverse lithium-induced diabetes insipidus, which occurs by an action of lithium below the receptor level at the adenylate cyclase second-messenger system. Demeclocycline (Declomycin) and doxycycline (Vibramycin) may counter the hyponatremic effects of carbamazepine, as may lithium. The hyponatremic effects of the ketoderivative oxcarbazepine may be more prominent than those of carbamazepine. To the extent that the minor cognitive impairments of lithium are in part related to its ability to impair vasopressin function in the brain, these data suggest that not only would carbamazepine be less likely to cause this adverse effect, but also during combination treatment, the adverse effects of lithium might override those of carbamazepine.

Carbamazepine tends to induce a benign hypocalcemia that is generally not associated with bone demineralization. In contrast, lithium often produces a transient increase in serum calcium concentration.

Tremor Tremor can be problematic for a small but substantial percentage of patients treated with lithium. The tremor is frequently exacerbated by social stress. When the tremor persists at doses near the lower end of the therapeutic range or at the minimum doses necessary for therapeutic efficacy, attempts can be made to treat it symptomatically. Some investigators find that 10 to 40 mg of the β-blocker propranolol in divided daily doses may reduce lithium tremor. Relief may occur within 30 minutes and may last from 4 to 6 hours. Valproate also has dose-related tremorogenic effects. Gabapentin, in contrast, has been used to treat essential tremor. The dihydropyridine L-type calcium channel inhibitors may provide a nontremorogenic adjunct or alternative to lithium.

Gastrointestinal Effects Gastrointestinal adverse effects (diarrhea and indigestion) can also be problematic for many patients on lithium and valproate but may be attenuated by reducing the dose or giving it at mealtimes (for indigestion). Antidiarrheal agents should be restricted to short-term treatment. The calcium channel blockers (which may be constipating) may substitute for lithium or partially counter its adverse effects when used in combination. Histamine type 2 receptor (H_2) inhibitors may help counter valproate's gastrointestinal adverse effects.

Cognitive Effects Patients may express concern about the effects of lithium on their memory, spontaneity, or creativity. Although some impairment can be objectively delineated in some, but not all, types of detailed neuropsychological testing, most patients either do not experience this effect or do not find it unduly impairing. In fact, productivity and creativity may, overall, be enhanced during lithium treatment, because it prevents unproductive manic and depressive phases. Although no adequate approach to the subjective cognitive effects of lithium has been demonstrated (other than reducing the dose), associated causes for cognitive impairment must be ruled out, including possible hypothyroidism or an inadequately treated coexistent depression. Donepezil (Aricept) has been reported helpful in isolated case reports and deserves further exploration and study.

Many so-called drug-related adverse effects are also evident during placebo treatment phases and thus appear to be more closely associated with illness-related variables than with a particular psychopharmacological treatment. This perspective on lithium maintenance treatment clearly needs to be explored with the patient to avoid premature discontinuation of treatment or noncompliance. Carbamazepine and valproate are noted for their benign cognitive side effects in the epilepsies and may be better tolerated than lithium in some instances, although they, too, can be associated with subjective complaints and word-finding difficulties. Lamotrigine does not appear to have lithium's occasional liability of stabilizing mood slightly below baseline, and some patients may be stabilized at a mood or

energy level slightly over baseline (i.e., above 50 millimeters on the mood analogue scale). Topiramate clearly causes cognitive motor slowing, speech, or word-finding difficulties in a small percentage of patients, particularly with high initial doses, rapid upward titration or in combination therapy. Valproate has been associated with a reversible organic brain syndrome with EEG slowing and a dementia-like presentation in isolated patients with epilepsy.

Weight Gain Lithium-induced weight gain can be a vexing problem for a moderate percentage of patients, and in one study was a correlate of better mood-stabilizing response. Thyroid indexes should be rechecked, and the patient reminded not to use calorie-containing beverages when maintaining the necessary increased fluid intake associated with diabetes insipidus.

Weight gain can also be problematic with valproate. Whether this is a correlate or causal link in the reported occurrence of polycystic ovary syndrome in epileptic patients taking valproate remains for further study.

Like most dopamine receptor antagonists (with the possible exception of molindone [Moban]), the serotonin-dopamine antagonists are also associated with weight gain; clozapine, olanzapine, and risperidone are particularly problematic for some patients. One should watch for replication of one anecdotal report of the antidiabetic drug troglitazone (Rezulin) which helped to cause substantial weight loss in a patient who gained considerable weight on olanzapine. Topiramate has a strong tendency to help with weight loss, apparently by both decreasing carbohydrate craving and possibly increasing metabolism as well. Early clinical vignettes suggest it may help overcome lithium or valproate weight increases when used in combination with them. Carbamazepine and gabapentin are less problematic, and, L-type calcium channel inhibitors are relatively weight neutral. Patients lost about 2 pounds in 6 weeks on lamotrigine in one controlled study, compared with a gain of about 2 pounds on gabapentin.

Headache Many mood stabilizers, such as lithium, valproate, and the L-type calcium channel inhibitors are reported to be effective in migraine prophylaxis. Carbamazepine increases substance P concentrations and sensitivity and may treat cluster headaches but can exacerbate migraine. Lamotrigine, with its weak serotonin reuptake effects, may either ameliorate or exacerbate headaches. Lamotrigine and gabapentin have apparent antipain long-term effects in some syndromes.

Rash Lithium may precipitate or exacerbate psoriasis and acne. Lamotrigine treatment must be started extremely slowly to help avoid the otherwise high incidence of rash (10 percent); some estimates suggest that 1 in 500 patients progresses to severe, potentially lethal extremes of Stevens-Johnson or Lyell's syndromes. Risk factors, in addition to rate of titration, include use with valproate (requiring a halving of the lamotrigine dose) and a history of multiple or severe rash on other medications.

Carbamazepine may also produce a common pruritic rash (10 to 15 percent), but severe deterioration to Stevens-Johnson syndrome may be less common than during lamotrigine treatment. Nonetheless, in most instances, carbamazepine treatment should be discontinued with the onset of a rash. However, when patients respond to carbamazepine and other effective treatments are not available, prednisone has reportedly suppressed uncomplicated carbamazepine-induced rashes (i.e., those without evidence of systemic involvement with fever or lymphadenopathy) in a very high percentage of patients. Whether a similar strategy would be effective for lamotrigine remains unstudied.

Hepatitis Valproate has been associated with reports of severe hepatitis in the neurological literature; most of the fatalities have been in children under the age of 2 years, particularly those on polytherapy. Few serious hepatic adverse effects have been reported in adult psychiatric patients on valproic acid, but liver function might be monitored periodically when using this agent, and patients should be warned to

report symptoms that might be referable to hepatitis such as fever, right upper quadrant pain, malaise, nausea, anorexia, Coca-Cola–colored urine, and jaundice. Benign elevation of liver function test (LFT) results to two or three times normal are not uncommon in patients taking valproate, carbamazepine, and other anticonvulsants, and LFTs can be followed without drug discontinuation. Zinc and selenium supplements are recommended with valproate, since they are reported anecdotally to decrease the incidence of hepatitis, pancreatitis, and alopecia. Rare cases of carbamazepine-induced hepatitis have been reported, but routine monitoring for this adverse effect does not appear to be indicated. Since lithium and gabapentin are excreted by the kidney, they have no liability in those with evidence of liver pathology or toxicity.

Hematological Effects The side-effect profile of carbamazepine tends to be quite different from that of lithium or valproate (Table 14.8-7). Whenever lithium and carbamazepine act on a common target system, the effects of lithium tend to override those of carbamazepine. In other instances this is a clinical disadvantage, except for the ability of lithium to increase the white count (via increases in colony stimulating factor) which will override the white count-suppressing effects of carbamazepine (via decreasing colony-stimulating factor), and may thus be clinically useful. However, lithium is effective in this regard only against carbamazepine's benign suppression of the white count, and its effects are doubtful if there is evidence of more problematic interference by carbamazepine in hematological function manifest in other cell lines, such as platelets or red cells (RBCs), indicating a possible pancytopenic or aplastic process. The risk of agranulocytosis or aplastic anemia in patients taking carbamazepine has been estimated to be from 1 in 10,000 to 1 in 100,000. If there are normal levels of other blood elements (platelets and RBCs), potentiation with lithium will likely reverse the benign white-count suppression of carbamazepine. Valproate has been associated with thrombocytopenia; the potential impact of lithium on this syndrome has not been reported.

Teratogenic Effects Cardiac (Ebstein's) anomalies of great vessels have been reported to occur with a higher frequency than expected in patients treated with lithium during pregnancy, although recent studies suggest the risk may not be much greater than that in the general population. Thus, the previous prohibition against use of lithium during pregnancy is being reevaluated. In some instances in which the discontinuation of lithium treatment would put the mother at high risk for a severe depression or mania, continuing lithium treatment may be appropriate, especially with increased ability for fetal monitoring.

An increased risk (several percent) of spina bifida has been reported for valproate (which may be dose-related) as well as a slightly smaller risk for carbamazepine, and use of these agents should be avoided in pregnancy if possible. Folate supplements should be used. Persisting biochemical alterations have been found in some animal studies of fetal exposure to typical antipsychotics but have not been assessed systematically in human follow-up studies. Few data are available for lamotrigine and gabapentin, but no specific teratogenic effects have been described. Topiramate causes some bone deformity in animals, but the risk for humans has not been systematically evaluated. ECT may have the lowest risk to the fetus among the somatic treatments, but the effect of maternal seizures has also not been systematically evaluated. The calcium channel blockers have a benign record for fetal abnormalities, and these agents remain among the better candidates for continuation of a putative mood stabilizer during pregnancy. As needed, short-term augmentation with minimal dosages of antipsychotics or high-potency benzodiazepines may be tolerated.

Approaches to Adverse Effects: Dosage Reduction, Adjunctive, Alternative Treatment Dosage reduction may be a first maneuver in treating a variety of lithium-induced problems (tremor, weight gain, thirst, urinary frequency, diarrhea, or psychomotor slowing). If these lower dosages are not adequate for prophylaxis, combination or alternative treatment, especially with carbamazepine or a dihydropyridine calcium channel adverse blocker (which have different side-effect profiles), or other putative mood stabilizers such as valproate may be indicated (Fig. 14.8-5). The renal clearance of

lithium appears to decrease with age, so that a lower dose may be necessary and adequate in the older patient on lithium maintenance.

TREATMENT OF BREAKTHROUGH DEPRESSIVE EPISODES DURING LITHIUM AND OTHER MOOD-STABILIZER PROPHYLAXIS

Antidepressant Augmentation Approaches to a depression in an untreated bipolar patient or during an episode emerging during lithium prophylaxis differs from that in a unipolar depressive disorder patient, and few antidepressants have been systematically evaluated in bipolar disorders. The author emphasizes possible choices of agents based on adverse-effect profiles (Table 14.8-3), the differential presenting symptom clusters and comorbid syndromes (Fig. 14.8-20), and mechanisms of action (Table 14.8-2). However, a strong empirical database for these recommendations is lacking. Moreover, given the necessity for protracted clinical trials (of many weeks) to evaluate the clinical efficacy of each individual drug, attempting to potentiate a specific drug treatment once adequate dosages or blood concentration have been reached is recommended before switching treatment modalities. Thus, thyroid or lithium potentiation deserves emphasis in the treatment sequence before multiple trials with single alternative agents. Figure 14.8-21 illustrates a possible treatment algorithm for a depressed patient with a bipolar disorder.

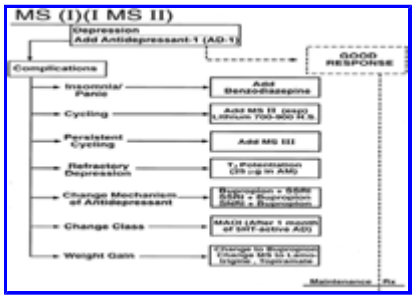


FIGURE 14.8-20 Algorithm for treating bipolar depression and treatment complications. MS I, first mood stabilizer; MS II second mood stabilizer

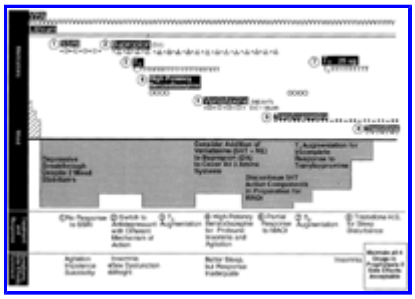


FIGURE 14.8-21 Possible sequential algorithm for the bipolar disorder patient with refractory depression. DA, dopaminergic; NE, noradrenergic.

Potentiation of the Antidepressant Given the long time frame that may be required to evaluate the adequacy of an antidepressant response, antidepressant potentiation should be considered in either the first or second antidepressant trial before switching antidepressants, even to a new category of agents. Thus, when a patient appears to be at either maximally tolerated dosages (or adequate blood concentration of the drug) and has not responded adequately, one might consider adding thyroid hormones or lithium (Table 14.8-5, Fig. 14.8-20).

A sizable but mixed literature exists regarding the efficacy of thyroid potentiation in converting (20 to 50 percent) antidepressant nonresponders to responders. This effect appears to be independent of initial clinical thyroid status or any evidence of hypothyroidism. A response to the addition of liothyronine (25 to 37.5 μg per day in the morning) may occur within days and usually occurs within the first week or

two of treatment. Therefore, if there is no response in this time frame, the clinical trial of liothyronine potentiation can be exchanged for other options. Adverse effects are very unusual but could include tachycardia, hypertension, anxiety, or flushing.

A second option is potentiation with lithium. An extensive literature, particularly in unipolar depressions, reveals that addition of lithium carbonate to a variety of antidepressant modalities, including tricyclic drugs, heterocyclic drugs, MAOI, or even carbamazepine, often yields clinical improvement (40 to 60 percent). Response may begin within 24 to 48 hours but may be slower in onset and stretch over 1 to 3 weeks. Dosages of lithium slightly below those conventionally used for monotherapy are generally effective (i.e., 750 to 900 mg in a single dose at bedtime may suffice to reach a target of 0.75 mg/L, which is the concentration reported to be needed for potentiation in unipolar depression). When used in this fashion, the adverse-effect profile of lithium appears quite benign. Lithium potentiation may be effective for all subtypes of depression.

New data suggest that concurrent treatment of acute depression with lithium and antidepressants from the outset also results in more rapid response than with an antidepressant alone. Thus, for the untreated bipolar disorder patient presenting with a depressive episode, the combination of an antidepressant and a mood stabilizer such as lithium is highly recommended. The initial reports of estrogen potentiation of antidepressant response do not appear as promising as those of either thyroid or lithium potentiation but may be considered for postmenopausal women.

Shifting Antidepressant Classes: MAOIs One might consider shifting treatment from one type of antidepressant to another if unacceptable adverse effects appear before adequate blood concentrations or a clinical response has been achieved. If adequate dosages and blood concentrations have been achieved without antidepressant effect, one may switch to a drug with a different biochemical profile within the same class or to a different class, such as an MAOI, but only after a 2- to 4-week period off agents with high potency in blocking serotonin reuptake (Table 14.8-5, Fig. 14.8-20). Problems with orthostatic hypotension may become more prominent in the second and third weeks of MAOI treatment. Salt loading, pressure stockings, and fludrocortisone (Florinef) or the peripherally acting α_1 agonist midodrine may prove effective in the treatment of MAOI-induced hypotension. MAOIs can be given in single morning doses or in divided doses. If marked insomnia occurs, nighttime doses of trazadone (Desyrel) have been recommended by some authorities. Bouts of daytime drowsiness and sedation may also become a problem. One might attempt to titrate the dosage against adverse effects, as variations in dosage or timing may be helpful.

The necessity of restricting substances that release tyramine or catecholamines and can produce hypertensive crises during MAOI treatment should be emphasized to the patient. These crises may be clinically manifested as explosive headaches, flushing, palpitations, perspiration, and nausea. Immediate treatment with a slow infusion of phentolamine (Regitine) (5 mg intravenously) in an emergency room is recommended. Most authorities suggest that the patient carry a 10-mg nifedipine (Adalat, Procardia) capsule with them that they could use sublingually or bite and swallow in the event of a presumptive hypertensive crisis.

Although tricyclic and heterocyclic drugs, SSRIs, serotonin-noradrenaline reuptake inhibitors (SNRIs), and MAOIs are central treatments for the unipolar depressed patient, there is reason for caution in their use for the bipolar patient. Some but not all studies have reported an increased incidence of switches into hypomania or mania during tricyclic or MAOI therapy, higher than expected for the patient's natural course of illness, particularly in previous rapid cyclers (Fig. 14.8-22). Whether this increased incidence of switching or cycle acceleration is sufficient to avoid the initial use of antidepressants in favor of mood stabilizers remains controversial. Thus, a shorter depression may occur at the cost of the more

rapid onset of the following manic episode, whereas withdrawal of tricyclic drugs and MAOIs has also been shown to slow this cycle acceleration in a small number of patients.

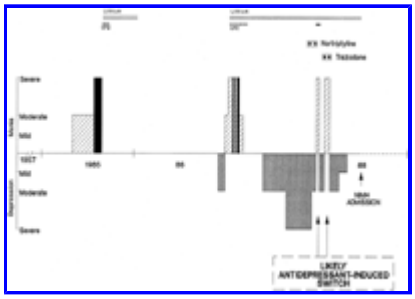


FIGURE 14.8-22 Antidepressant-induced mania in a male patient with bipolar I disorder. CPZ, chlorpromazine.

Uncontrolled observations suggest that tricyclic antidepressants and related compounds may be implicated in the development of continuous cycling phases (i.e., successive episodes without a well interval) (Fig. 14.8-23). This phase of the illness becomes difficult to treat and tends to be relatively lithium refractory. Anecdotal evidence and one double-blind, randomized study indicate that bupropion may not be associated with the same switching tendency as the tricyclic antidepressant desipramine (Norpramine). SSRIs may be less involved in the switch phenomenon and in cycle induction than the tricyclic drugs, but this too requires further investigation, since the commencement of rapid or continuous cycling coincident with the use of SSRIs has been observed anecdotally.

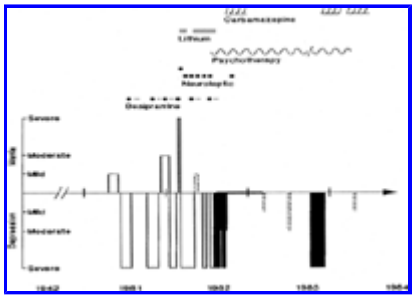
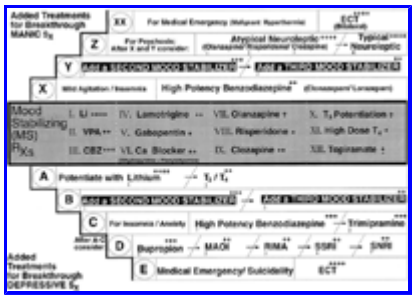


FIGURE 14.8-23 Life chart of a patient rated likely to have had antidepressant-induced cycle acceleration. *Solid black shading* indicates patient was hospitalized.

Once a switch has been observed with an MAOI, reexposure to even a different MAOI may also lead to an earlier onset of a switch, as observed in one controlled study, perhaps reflecting a sensitization phenomenon. Naturalistic data, however, raise questions about whether antidepressant-induced switches occur on each exposure to these drugs. Moreover, it is unclear whether a drug-induced switch appears only in those predestined to have spontaneous switches or whether this occurrence actually predisposes the patient to develop further spontaneous manic episodes. Women and those with rapid cycling may be at higher risk for tricyclic-induced switching or cycle acceleration.

Adding a Second Mood Stabilizer The unimodal antidepressants should be used cautiously and in conjunction with mood stabilizers for bipolar disorder depressive episodes, and particularly if there is a prior history of drug-induced switches, other options should be considered. There is much to recommend adding a second or even a third mood stabilizer (lithium, lamotrigine, carbamazepine, valproate, or a dihydropyridine L-type calcium channel inhibitor) in the rapidly (or ultrarapidly or ultradian) cycling depressed bipolar disorder patient prior to the use of a unimodal antidepressant (Table 14.8-5, Fig. 14.8-24).

FIGURE 14.8-24 Treatment algorithm for bipolar disorder patients



with rapid and ultrarapid cycling. VPA, valproate; CBZ, carbamazepine.

If unimodal antidepressants are used for a bipolar disorder depression, clinical lore suggested that they should be tapered and discontinued as soon as possible, to avoid the potential for drug-induced switches and cycle acceleration, especially since lithium may not be able to prevent these phenomena. However, maintenance therapy with bupropion and lithium has been reported to be effective in rapid-cycling patients, and use of unimodal antidepressants in conjunction with the new putative mood stabilizers deserves study. Several case reports suggest that alprazolam (Xanax) may, like the tricyclic drugs, also induce switches into hypomania and mania (even in unpredisposed patients) and this high-potency benzodiazepine should be avoided in favor of the long half-life compounds clonazepam and lorazepam, which do not appear to share the proclivity of the triazolobenzodiazepine compounds for the induction of mania. These high-potency benzodiazepines may be useful adjuncts to the mood stabilizers; however, the rare patient may experience these classical benzodiazepines as mood destabilizing or even depressogenic.

Some evidence suggests that the MAOIs, in general, may be less prone than tricyclic drugs to induce switches. The MAOIs should be given relatively greater consideration, especially for the reversal of vegetative (anergic, hypersonic, or hyperphagic) states in the bipolar patient. A substantially higher rate of antidepressant response was reported in one controlled series for tranylcypromine (Parnate) (81 percent) compared with imipramine (Tofranil) (48 percent) in bipolar disorder patients. Clorgyline, a selective *MAO type A* inhibitor not yet clinically available has been reported to slow cycling frequency. The reversible inhibitor of monoamine exiduse type A (RIMA) moclobemide (Aurorix) (Table 14.8-3) is widely available in Europe and Canada but not in the United States; this drug is not believed to be as effective an antidepressant as the nonselective MAOIs, such as tranylcypromine and phenelzine (Nardil); however, these MAOIs are unique in potentiating all three amine systems (serotonin, noradrenaline, and dopamine). One could attempt such an equivalent effect by using venlafaxine (for its serotonergic and noradrenergic effects) in combination with bupropion (for its dopaminergic effects).

It is possible that the anticholinergic rather than the noradrenergic effects of the tricyclic drugs makes them prone to cause switches or cycle acceleration. A comparison of SSRIs with the noradrenaline selective agents (desipramine, nortriptyline [Aventyl], and maprotiline [Ludiomil]), or to the SNRI venlafaxine would clarify the putative role of norepinephrine reuptake blockade in inducing these phenomena.

Dopamine-Active Compounds and Other Treatments

Bupropion Bupropion in conjunction with a mood stabilizer has shown promise in short-term and prophylactic management of bipolar disorder patients, including rapid cyclers. Although it may be added to lithium or valproate prophylaxis without pharmacokinetic interactions, when used with carbamazepine its blood concentrations are markedly decreased and those of an active metabolite increased (Fig. 14.8-25).

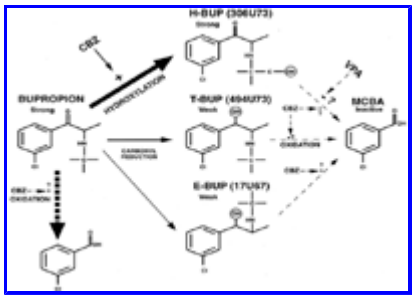


FIGURE 14.8-25 Bupropion metabolism. CBZ, carbamazepine; VPA, valproate; MCBA, metachlorobenzoic acid.

Psychostimulants The role of psychostimulants as short-term augmentation has not been systematically explored, although it is apparently widely used by some experts in the field. However, one investigator has indicated that this is not a useful long-term strategy, since many patients appear to develop tolerance to this modality. This strategy should perhaps be reserved for temporary augmentation while awaiting more-effective antidepressant response to other modalities.

The same investigator also observed that tolerance does not appear to develop when the psychomotor stimulants are combined with MAOIs. This strategy should be reserved for only the most refractory patients, since the *Physician's Desk Reference* (PDR) lists an absolute contraindication to combining stimulants and MAOIs. Nonetheless, this appears to be effective and tolerated by most patients in many small case series.

Dopamine Agonists Small clinical series have also suggested some antidepressant efficacy of the direct dopamine agonist bromocriptine, which is used to treat parkinsonian patients. One double-blind study indicated that it was as effective as imipramine. A related dopamine agonist, piribedil (Trivastal), has been effective for the occasional refractory depressive patient. Pergolide (Permax) was reported to be an effective augmenting agent in one series on refractory depression but not in another.

Pramipexole, a potent D_3 as well as D_2 agonist recently approved for use in parkinsonism, is reported (at 1 mg a day or higher) to have antidepressant effects equivalent to those of fluoxetine (Prozac). Treatment should be started at low dosages and titrated toward 1 mg a day very slowly to avoid adverse effects such as nausea and orthostatic hypotension.

Dopamine-active drugs has been reported to be more effective in patients with low concentrations of the dopamine metabolite homovanillic acid in their cerebrospinal fluid (CSF). A similar relation to low concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and a better response to the serotonin active compounds clomipramine (Anafranil) and sertraline (Zoloft) have been reported. The results are inconclusive as to whether urinary concentrations of the noradrenergic metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) can predict the response to noradrenergically active antidepressants. Consistent biochemical markers of antidepressant response have not yet been identified.

Light in Morning and Melatonin at Night Systematic trials of augmentation with bright light (more than 7500 lux) may also be worth considering in patients with marked disruption of circadian rhythmicity and the typical bipolar disorder hypersomnia. In these instances, high-intensity light might be more useful in the morning, although this issue needs to be reexamined with more-systematic prospective randomized studies.

An additional approach to altering sleep activity cycles (which are common in bipolar disorder patients) might be to use melatonin adjunctively at night, although this, too, requires caution and prospective studies. In addition, isolated reports exist of exacerbation of sleep or mood in some patients when using melatonin supplementation.

Sleep Deprivation as a Short-Term Antidepressant Paradoxically, sleep deprivation may be an adjunctive procedure to hasten antidepressant response (Fig. 14.8-26). A rapid, transient, antidepressant response to 1 night of sleep deprivation has been reported consistently in studies from many different laboratories. Preliminary evidence suggests that sleep deprivation in the last half of the night (from 3 to 7 AM) may be just as effective as total sleep deprivation and may thus be more convenient for clinical use and outpatient treatment.

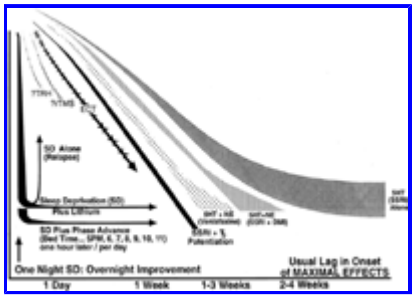


FIGURE 14.8-26 Nine potential clinical approaches to rapid-onset antidepressant effects. rTMS, repeated transcranial magnetic stimulation; NE, noradrenergic; DMI, desipramine.

Although most responsive patients relapse after 1 night's recovery sleep, some modalities (especially lithium) may help sustain the sleep deprivation response. One recent report also indicates that progressive changes in the hours of sleep (from 5 PM on the sleep deprivation day to 6 PM the next, and so forth toward an 11 PM bedtime) also help hold a sleep deprivation response.

The rapid onset (overnight) effects achieved differs from the slower but sustained effects following selective deprivation of rapid eye movement (REM) sleep, that is, a modality that is not readily amenable to clinical use. Response to sleep deprivation may be related to phase or duration of a bipolar disorder depressive episode, with less responsivity early in the episode and a greater responsivity late in the episode. Several, but not all, studies indicate that the degree of antidepressant response to sleep deprivation is correlated with the degree of increase in morning plasma TSH concentration, presumably driven by endogenous increases in TRH. Parenteral TRH administration (500 mg intravenously) has also been reported to have rapid-onset effects, and two case reports suggest more-sustained effects with low dosage (50 μg a day at bedtime).

Inositol Inositol (12 to 16 grams a day) has recently been reported to have antidepressant, antianxiety, and antiobsessive-compulsive effects. This remains to be more systematically explored in bipolar disorder patients (in light of no reports of patients switching in one series reporting a 50 percent response rate in patients who were concomitantly treated with lithium, carbamazepine, or valproate. Theoretically, inositol should not only relieve some lithium-induced adverse effects, but could potentially reverse its therapeutic efficacy to the extent that inositol depletion from reduced phosphoinositide (PI) turnover is related to lithium's mechanism of action. This has not been reported, however. Myoinositol measured by magnetic resonance spectroscopy (MRS) has been reported to be low in brains of bipolar disorder patients (in proportion to the severity of their depression); and lithium lowers it further. One would then predict that inositol augmentation might make carbamazepine even more effective, because carbamazepine has effects opposite to that of lithium, and increases the inositol-1 phosphatase enzyme, which should increase inositol. Lithium, carbamazepine, and valproate are all reported to downregulate the transporter for inositol that has recently been isolated and cloned.

Choline One open study reported that potentiation with choline (3 to 8 grams a day) may be helpful in stabilizing mood in refractory cyclers, and this approach, too, requires further systematic study.

Folate and Ascorbate In two single, randomized, placebocontrolled studies, the vitamins folate (300 to

400 mg a day) and ascorbate (3 grams a day) have each been reported to have some beneficial effects on amelioration of mood in long-term prophylaxis of bipolar disorder patients and, in light of their benign side-effect profiles, might be worthy of consideration in the treatment regimen of the refractory bipolar disorder patient.

Omega-3 Fatty Acids One randomized double-blind study comparing the addition of omega-3 fatty acids (9 grams a day) or an olive oil placebo in bipolar disorder patients poorly controlled on mood stabilizers was terminated early because of the marked superiority of the omega-3 fatty acid to the control. Virtually all of the breakthrough depressive episodes occurred in the placebo control group.

APPROACHES TO SUICIDALITY

Regular psychiatric visits during the prophylactic well phase are recommended on an interval ranging from weekly to biweekly in unstable patients to 1 to 4 months in better stabilized patients, depending on a variety of ancillary circumstances including completeness of response, lack of psychosocial crises, history of compliance, insight into the illness and its treatment, absence of adverse effects, financial constraints, and the wishes of the patient. In addition to periodic assessment of all of these issues, regular treatment visits are recommended to assess the potential risks of suicide independently of the occurrence of discrete episodes. This is particularly important when there is a positive family history of suicide or other risk factors, including male sex, older age, comorbid alcohol abuse, high levels of anxiety, and prior suicide attempts (particularly if they have been severe).

Suicidal impulses and acts may not always vary directly with either severity of depression or reemergence of a full-blown episode requiring hospitalization and should be part of the careful ongoing clinical assessment of patients in all phases of their illness and treatment. Severe overwhelming psychic anxiety and agitation are predictors of completed suicide, and with the high comorbidity of panic disorder with either phase of bipolar disorder, one should be particularly alert to this and other high-risk factors. Specific contracting for communication with the clinician upon remergence or escalation of suicidal thoughts should be considered in high risk patients (Table 14.8-12).


Dual treatment: Focus acute short-term and prophylaxis
Mania: Treat first, do chemistries later
Load valproate and lithium; slowly start lamotrigine treatment
Use second mood stabilizers over antipsychotics
Benzodiazepines instead of antipsychotics
Combination treatment decreases adverse effects
Chart illness
Augment rather than substitute
Simplify (for adverse effects)
Taper of lithium slowly, if at all
Educate the patient's family
Assess compliance and suicidality
Develop an early warning system
Develop specific contracts
Regular visits; monitor course and adverse effects
Phone contact (PRN) when needed
Develop a "fire drill"
Prevent comorbid alcohol and other substance abuse
Psychotherapy and medicalization of illness
Give statistics: 50% relapse in first 5 months off lithium treatment
Patient as a co-principal investigator
Conservative treatment, if successful
Radical treatment, if inadequate response

Table 14.8-12 Principles in the Treatment of Bipolar Disorders

Electroconvulsive Therapy ECT may benefit bipolar depressed patients who do not respond to lithium or other mood stabilizers and their adjuncts. This is particularly true when intense suicidality presents as a medical emergency. Whether ECT would continue to help abbreviate each bout of recurrent depressive episodes in rapid-cycling patients or whether it would be useful in long-term prophylaxis must be further investigated. The author has observed several instances in which tolerance appeared to develop to the therapeutic effects of repeated series of ECT. Moreover, concern about cognitive adverse effects remains, and the author has recently seen a number of otherwise healthy individuals with rather profound and sustained retrograde memory loss.

TREATMENT OF MANIC BREAKTHROUGHS

A wide range of drugs is available for breakthrough manic episodes occurring during lithium or other prophylactic treatment, including the entire spectrum of drugs indicated for the treatment of acute mania (Table 14.8-5 and Table 14.8-6; Fig. 14.8-24). Ranking high in these treatments are carbamazepine and valproic acid, because of their longer-term prophylactic efficacy. Lamotrigine, nimodipine, and topiramate all require further study. Clonazepam or lorazepam may also be useful acute alternatives to antipsychotic supplementation, even though the benzodiazepines (and antipsychotic agents) appear to have a less primary role in the long-term management of bipolar disorders than the mood stabilizers carbamazepine or valproic acid.

The use of clozapine for bipolar disorder and schizoaffective disorder patients refractory to lithium, carbamazepine, and valproate is now well documented in many case series, especially for those with rapid cycling and dysphoric mania. Its lack of ability to induce tardive dyskinesia makes it particularly attractive, and one looks forward to a possible similar role for other atypical antipsychotics (Table 14.8-8 and Table 14.8-10) without clozapine's liability for agranulocytosis and the attendant need for weekly white blood count monitoring. Given the high liability of tardive dyskinesia even with intermittent use of typical antipsychotics, these drugs should be relatively avoided in favor of the atypical agents and other mood stabilizers whenever possible.

COMPLEX COMBINATION THERAPY

Data from the NIMH also support the notion that many depressed patients with refractory bipolar illness can be treated with a variety of approaches not typically involving the traditional unimodal antidepressant or typical antipsychotic modalities. Analysis of successive 5-year epochs in the tertiary-referral 3-West Clinical Research Unit of the Biological Psychiatry Branch showed that approximately the same high percentage (75 to 80 percent) of patients achieved marked or moderate improvement on the CGI at discharge in the past 25 years. However, patients in the years 1970 to 1974 required only monotherapy on discharge more than 75 percent of the time; this decreased to less than 25 percent in the most recent 5-year period, and the average number of medications on discharge increased from one to three per patient over the same time period (Fig. 14.8-27). Yet, unimodal antidepressants or antipsychotic drugs were used in less than 15 percent of the patients. Although these data based on sequential double-blind trials and augmentation strategies in this discharge phase of the hospitalization, did not involve a systematic randomized approach to therapeutics they nonetheless reveal that the vast majority of patients with refractory depressive and cycling presentations can be managed largely in the absence of the unimodal antidepressants or neuroleptic drugs. Multiple mood stabilizers in combination, often with thyroid augmentation, were used most of the time.

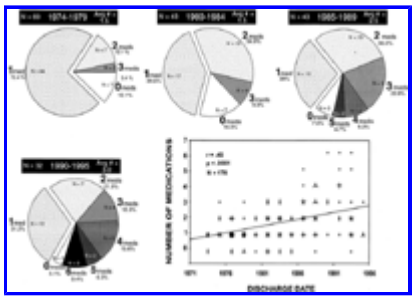


FIGURE 14.8-27 Increasing number of medications at discharge.

As in the late phases of other medical syndromes, complex combination treatment is often required for the treatment-refractory bipolar disorder patient. Although it may at first seem inappropriate to consider a regimen with four or five drugs for the treatment of refractory bipolar illness, this strategy is standard practice in many other areas of medicine such as the treatment of malignancies, tuberculosis, AIDS, or

congestive heart failure. In these instances, multiple therapeutic modalities with different symptom targets and different mechanisms of action are often combined for optimal therapeutics.

With the availability of a variety of agents for bipolar disorders, it now befits the field to engage in more systematic clinical trial approaches to delineate the optimal strategies for achieving the most rapid response rates in the highest numbers of patients, so that even the most refractory bipolar disorder patients have an excellent chance at achieving and maintaining clinical remission.

Attempting to supplement the clinical effects of lithium and the mood-stabilizing anticonvulsants such as carbamazepine and valproic acid is often more effective than using lithium or the anticonvulsant alone. By augmenting rather than substituting a mood stabilizer, withdrawal-induced exacerbations will not confound the evaluation of the next agent, and time may be saved in the assessment of the combination in one clinical trial rather than two sequential trials (the anticonvulsant alone and then the combination). For patients who are unable to tolerate lithium carbonate, evidence does suggest that carbamazepine or valproate may be useful long-term maintenance treatments in preventing both manic and depressive episodes. A rather substantial literature on double-blind randomized studies provide evidence of carbamazepine's prophylactic efficacy. Most of the prophylactic data on valproate are based on clinical case series, however, with the exception of one randomized open trial showing efficacy equal to that of lithium and one blind trial showing that valproate has greater efficacy than placebo or lithium for recurrent depression. The choice of carbamazepine or valproate may depend on the future development of clinical predictors or on the current assessment of their relative side-effects profiles (Table 14.8-13). The data are even more preliminary for the L-type calcium channel inhibitor and the new putative mood-stabilizing agents such as lamotrigine and possibly topiramate and gabapentin.

Table 14.8-13 Positive and Negative Selection Factors for Choice of Mood Stabilizer

All of these agents have differential presumptive biochemical mechanisms of action. One can begin to use augmenting strategies (Table 14.8-6), not only empirically (Fig. 14.8-5), but also based on combining agents with different actions (Table 14.8-2, Fig. 14.8-6 and Fig. 14.8-9), symptom targets (Table 14.8-4), side-effect profiles (Table 14.8-7), or benign pharmacokinetic and pharmacodynamic interactions. It is unclear whether using drugs with slightly different actions targeted to a single transmitter system such as GABA (i.e., enhancing GABA by reuptake blockade [tiagabine], transaminase inhibition [γ-vinyl GABA], transport effects [gabapentin], or multiple enzymatic actions [valproate]) will be more or less effective than simultaneously targeting two or more entirely different systems (e.g., enhancing GABA and inhibiting glutamate (Fig. 14.8-9).

Using several drugs in combination (Table 14.8-6) may actually help reduce the incidence of adverse effects by keeping each drug below its adverse-effects threshold (Table 14.8-7) rather than pushing one drug to maximum dosages for full therapeutic effect. Preclinical evidence indicates that such a combination strategy may also be less susceptible to the loss of effectiveness via tolerance. Optimally, one would like to use drugs with additive or synergistic therapeutic effects in the relative absence of adverse effects (Table 14.8-13); for this, knowledge of both pharmacokinetic and pharmacodynamic

interactions is of considerable importance.

Pharmacokinetic Interactions There do not appear to be major pharmacokinetic interactions among lithium and the other mood stabilizers. There have been occasional reports of neurotoxicity when lithium and carbamazepine are used together. Because both agents can cause these adverse effects at or below clinically accepted dosage ranges, neurotoxicity may occasionally result from the combination treatment as well. In most instances the combination appears to be well tolerated. Many of the adverse effects reported in the literature appear to be caused by starting treatment with relatively large dosages of carbamazepine (rather than using slow increases) in combination with other agents, and assuming that the attendant adverse effects are related to the combination treatment rather than to carbamazepine alone. Carbamazepine enhances its own metabolism and that of other agents metabolized by the hepatic microsomal P450 system (CYP) isoenzyme CYP, 3A4 such as haloperidol or estrogen, and concentrations of these substances (as well as birth control pills) are markedly reduced by carbamazepine (Fig. 14.8-28). Despite this reduction in haloperidol blood concentrations, most studies report improvement with carbamazepine supplementation, suggesting that carbamazepine might potentiate antipsychotic effects because of actions other than dopamine receptor blockade.

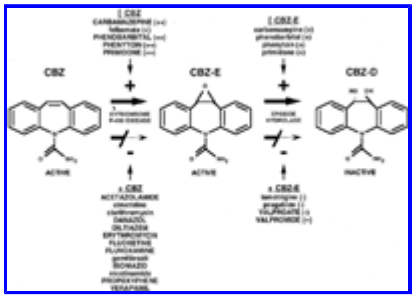


FIGURE 14.8-28 Carbamazepine (CBZ) metabolism.

Agents commonly used in medical practice can markedly increase carbamazepine concentrations and thus produce attendant toxicity (Table 14.8-14, Fig. 14.8-28). The most frequent dose-related toxic manifestations are dizziness, drowsiness, ataxia, diplopia, and confusion. These may occur in someone otherwise tolerating the drug well until other drugs are added. Erythromycin, triacetyloleandomycin (TAO), isoniazid (Nidrazid) (but apparently not other MAOIs), fluoxetine and fluvoxamine (Luvox), and the calcium channel inhibitors verapamil and diltiazem (Cardizem) (but not nifedipine, nimodipine, amlodipine [Norvasc], or isradipine) will increase carbamazepine concentrations. Less marked increases occur during cotreatment with propoxyphene (Darvon) and, transiently, with cimetidine (Tagamet). Carbamazepine will lower the blood concentrations of various agents (especially birth control pills) and interfere with some tests that depend on protein binding, including some pregnancy tests.

Table 14.8-14 Carbamazepine-Drug Interactions

In contrast to the multiple pharmacokinetic interaction of carbamazepine with other drugs, based largely on its properties as an inducer of hepatic P450 enzymes, valproate has few problematic effects in this

area. However, if carbamazepine and valproate are used together, one should consider reducing the carbamazepine dosage (because valproate increases concentrations of the 10,11-epoxide metabolite) as well as increasing the free fraction of carbamazepine (Fig. 14.8-28). Lithium and valproate are generally well tolerated in combination, but effects on tremor, weight gain, and gastrointestinal distress may be additive.

Carbamazepine markedly reduces the concentration of bupropion but increases that of its active hydroxy metabolite (Fig. 14.8-25), an action not shared by valproate. Valproate approximately doubles blood concentrations of lamotrigine and thus increases the likelihood of a severe lamotrigine rash; starting dosages of lamotrigine should be halved accordingly. If no rash occurs, lamotrigine and valproate have excellent tolerability and efficacy in epilepsy (and perhaps in affective illness) when used in combination. In contrast, carbamazepine decreases lamotrigine concentrations by about one-half, and these two drugs may be less useful in combination because of their similar adverse effects and pharmacodynamics.

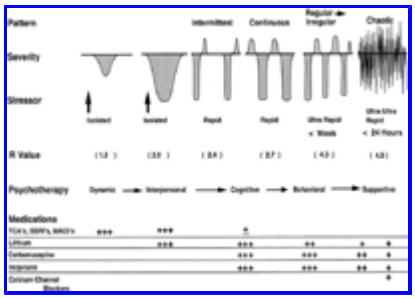
Fluoxetine and paroxetine (Paxil) are inhibitors of CYP 2D6, and may increase concentrations of many agents such as desipramine and the secondary tricyclic antidepressants and phenothiazines (Table 14.8-15). Fluvoxamine is a potent inhibitor of CYP 1A2 (potentially producing theophylline toxicity) and CYP 2C19 (increasing warfarin [Coumadin] levels) as well as CYP 3A4. Nefazodone (Serzone) is also potent at CYP 3A4, producing cardiac arrhythmias with astemizole (Hismanal), cisapride (Propulsid), and terfenadine (Seldane), and likely increasing carbamazepine concentrations.

Table 14.8-15 Substrates, Inhibitors, and Inducers of Some Important Cytochrome P450 Isoforms

SENSITIZATION EFFECTS ON THE MOOD DISORDERS AND IMPLICATIONS FOR PROPHYLAXIS

Early clinical observations and more-recent systematic controlled studies suggest that recurrent bipolar affective disorders may undergo a transition from initial episodes that are typically precipitated by psychosocial stressors to later episodes that tend to occur more spontaneously. This transition often occurs in the context of an overall pattern of cycle acceleration with a trend toward shorter well interval between successive episodes (Fig. 14.8-29). Both the effects of psychosocial stressors and recurrent mood episodes themselves may not only cause acute biological perturbations, but may also leave behind residual biological vulnerabilities, or memory traces, based on their ability to alter gene expression (Fig. 14.8-30). Preliminary data from the Stanley Foundation Bipolar Treatment Outcome Network suggest that experiences of early verbal, physical, or sexual abuse are associated with a greater incidence of early-onset bipolar disorder and ultra-ultra-rapid (ultradian) cycling; physical abuse in childhood was associated with increased mania and sexual abuse with increased suicidality.

FIGURE 14.8-29 Phases in evolution of mood cycling: potential relation to treatment response.



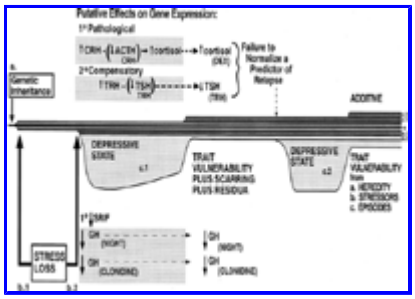


FIGURE 14.8-30 Accumulating experiential genetic vulnerability in recurrent mood disorders. CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; DEX, dexamethasone; SRIF, somatostatin release-inhibiting factor.

Following stress and episode-induced changes in neurotransmission, a cascade of neurobiological effects is thought to take place that includes not only short-term adaptations but also longer-lasting alterations initiated by a variety of transcription factors, including the immediate early genes, such as the transcription factors c-*fos* and c-*jun* as well as a variety of neurotrophic factors. These transcription factors can then induce changes in the long-term regulation of late effector genes (i.e., transmitters, receptors, and neuropeptides). This type of episode-related upregulation in transcript could account for the increase in corticotropine releasing hormone (CRH) in brain and CSF of depressed patients and its associated hypercortisolemia as well as the microstructural and synaptic organization of the brain revealed in many models of maternal deprivation and learning and memory.

If this conceptualization proves correct, it suggests the potential dual importance of preventing episodes of affective illness. Not only would episode-associated morbidity and potential mortality be prevented, but the longer-lasting neurobiological vulnerabilities associated with the experience of repeated affective episodes themselves (sensitization) might be attenuated as well. Although the mechanisms and direct causality have not been clarified, greater numbers of prior mood episodes are associated with greater degrees of cognitive dysfunction on a variety of neuropsychological tests in euthymic bipolar disorder outpatients.

Thus, given the increasing evidence that greater numbers of affective episodes are a poor prognostic sign and may be associated with resistance to effective treatment with lithium, both the clinical and theoretical data speak to the importance of early institution and long-term maintenance of prophylaxis, particularly in patients already identified as being at high risk for recurrence.

Treatment efficacy may thus also vary as a function of the stage of illness evolution (Fig. 14.8-29). For example, pharmacotherapies such as lithium and unimodal antidepressants may be more effective in initial and midphases of the illness, but with the emergence of rapid and ultra-rapid cycling, adjunctive treatments with the anticonvulsants may be required, with the antidepressants used more sparingly. In the latest stages of illness, sometimes associated with ultradian cycling, dihydropyridine *L*-type calcium channel inhibitors augmented by mood-stabilizing anticonvulsants may be required.

Similar transitions may occur in psychotherapeutic approaches wherein psychotherapy may be effective

in the early, milder forms of stress-related depressive illness, but with major recurrent episodes (and particularly, melancholic and psychotic syndromes), aggressive acute and maintenance pharmacotherapy may be mandatory. Adjunctive interpersonal, cognitive, and behavioral techniques may become increasingly important in (1) the later, more automatic shifts in mood, (2) helping to maintain active treatment compliance with pharmacotherapies, (3) implementing an early intervention system based on the development of a structured early warning system; and (4) maintaining morale in the face of therapeutic adversity and incomplete response, all of which, in turn, may prevent suicide.

The past several decades have seen important advances in the understanding of the neurobiology of the depressive and bipolar disorders. Clearly these illnesses involve multiple areas of brain dysfunction and affect a variety of organ systems, altering not only mood, but also motor, cognitive, sleep, appetite, hedonic reward, and other somatic systems. Neurobiological alterations are evident at the level of endocrine dysfunction, reflected not only in altered regulation of glucocorticoids and CRH, TRH, and somatostatin release-inhibiting factor (SRIF) but even the size of the pituitary and the adrenals.

Some of these changes may involve episodic and cyclic alterations in gene transcription related to the primary pathology of the illness (such as increases in CRF), but others may be secondary and adaptive (e.g., increases in TRH) (Fig. 14.8-30). The author has postulated that the ratio of a host of pathological factors (“the bad guys”) to the compensatory adaptations (“the good guys”) determines the proportions of periods of illness versus well intervals (Fig. 14.8-31). To the extent that exogenous medications can change this ratio by either inhibiting the bad guys or enhancing the good guys, sustained remissions can be achieved, if adequate prophylactic treatment is maintained. This conceptual model based on preclinical data also predicts that clinical loss of prophylactic efficacy via development of tolerance would be delayed or prevented by (1) earlier rather than later treatment; (2) sustained full dosages rather than marginally effective ones; (3) use of the most effective agents with a wide therapeutic margin; and (4) combinations of several marginally effective agents (Table 14.8-16, Fig. 14.8-32). These propositions remain to be directly tested, however.

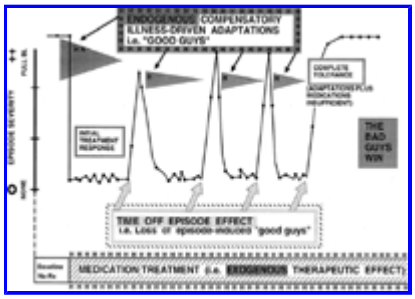
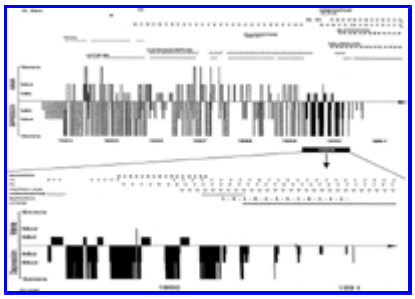


FIGURE 14.8-31 Ratio of “good guys” and “bad guys” drives episode cycling.

Table 14.8-16 Other Clinical Predictions From the Preclinical Model of Tolerance Development

FIGURE 14.8-32 Response to combination therapy in a patient with


refractory bipolar I disorder. TCAs, tricyclic antidepressants.

Functional brain imaging has revealed alterations in blood flow and glucose utilization, often reflecting hypofrontality in depression, at times in direct proportion to the severity of the depressive syndrome. Evidence of hyperactivity in the ventral anterior cingulate gyrus and the medial temporal lobes is also present in some patients, and these differential patterns may be linked to differences in therapeutic outcome. Both patient and clinician should be aware that a wealth of clinically relevant neurobiological evidence indicates that the mood disorders are potentially life-threatening medical illnesses not different from those that afflict the other major organ systems of the body and, as such, should be treated with equal care and vigor.

FUTURE DIRECTIONS

During this most exciting era for the development of psychobiological theories and therapies for the mood disorders, one hopes for clearer definitions of the different psychotherapies and pharmacotherapies critical for adequate therapeutic intervention in individual patients whose severities, types, patterns, and stages of illness differ. Since the last half of the century, successive generations of pharmacotherapies have led to critical neurobiological hypotheses of the mechanisms underlying the mood disorders, and one hopes that a continued mutually interactive process of more specific treatments, theories, and therapies will be derived from synergistic clinical and basic research in this area.

Not only is there a wealth of information to be learned through controlled research, but each patient has much to teach the practitioner and the theoretician. Precise life charting of the course of recurrent mood disorders and its response to treatment may be invaluable to the patient and clinician in arriving at optimal therapeutics, particularly when evidence from controlled studies currently provides so little direction for most crucial decisions. Although a host of well-tested, promising treatment alternatives are now available and one can anticipate many novel interventions in the near future, a much wider systematic clinical research base is urgently needed to guide the physician to the best therapeutic regimen for each individual bipolar patient. The author hopes that some of the preliminary data, guidelines, and principles outlined in this chapter will assist in this process and that more rapid progress occurs in the study and treatment of this relatively neglected major psychiatric illness.

SUGGESTED CROSS-REFERENCES

Biological therapies are discussed in Chapter 31. Section 14.7 provides a thorough discussion of the treatment of depressive (unipolar) disorders. Obsessive-compulsive disorder is covered in Chapter 15. The rest of Chapter 14 can be consulted for other aspects of mood disorders.

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