MANIC-DEPRESSIVE ILLNESS

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Medical Treatment of Manic Episodes

No one predicts how long it will be before the drugs take hold & [Robert Lowell] begins to be himself again. Meanwhile he writes and revises translations furiously and with a kind [of] crooked brilliance, and talks about himself in connection with Achilles, Alexander, Hart Crane, Hitler and Christ, and breaks your heart.

—William Meredith[1]

A patient in the throes of a manic episode can be intensely agitated, uncooperative, psychotic, aggressive, or dangerous. By the time the clinician is brought in, both patient and family are understandably confused and distraught. The bizarre, frightening behavior obviously must be controlled humanely, but the clinician has little time to ponder available choices. Which drugs are best for this patient in this situation? Should the patient be hospitalized? Should electroconvulsive therapy be used? Each decision calls for balancing the ravages of the illness against the consequences of intervention—a medication's potency against its side effects, for example, or the patient's safety against the stigma of hospitalization.

This chapter focuses on such issues in the medical management of acute manic episodes. Like others in this section, the chapter begins with a discussion of practical issues of clinical management, an approach to treatment drawn from the research evidence and our own clinical experience. The research literature is reviewed in the second part of the chapter, which some readers may choose to read first.

We are convinced that medical management is necessary for all patients who are truly manic or are hypomanic and likely to become manic. Based on that assumption, we devote the following discussion largely to criteria for appropriate pharmacological treatment for acute mania. One important caveat is in order, however. Not all activated patients are necessarily manic, or even hypomanic, and not all mildly hypomanic patients inevitably progress to mania. The line between normal exuberance and clinical hypomania is sometimes difficult to discern, and clinicians must approach the task of differential diagnosis with care (see Chapters 4 and 5). Once the diagnosis has been made, skillful psychological management must accompany the drug treatment of emerging or acute mania, especially if the patient or family resists the idea of medications (see Chapter 25).

Lithium, the first of the modern antimanic agents, remains the most important. Its therapeutic value was discovered by the Australian physician John Cade (1949), whose post-World War II experiments with guinea pigs signaled a revolution in the treatment of manic-depressive illness. Several years were to pass before the importance of Cade's pioneering work was recognized. European psychiatrists began to take notice in 1954, when his observations were confirmed and extended by Mogens Schou in Denmark. Although a handful of American psychiatrists were among the pioneers, lithium was not widely used in the United States until the late 1960s. This slow ac-

ceptance was partly traceable to earlier adverse experiences with lithium as a salt substitute.

Chlorpromazine, the prototypical antipsychotic medication for controlling the symptoms of schizophrenia, was first used clinically for a psychiatric disorder in a manic patient (Schneider, 1951, cited in Swazey, 1974). More extensive clinical observations in acutely manic patients followed (Lehmann and Hanrahan, 1954). Since lithium was still essentially unknown at that time, particularly to American psychiatrists, chlorpromazine quickly became the treatment of choice for acute mania. Haloperidol, a butyrophenone that also controls psychotic symptoms, was introduced in the late 1960s and was found to control psychotic behavior as effectively as chlorpromazine while producing less sedation and hypotension. As a result, many clinicians now prefer haloperidol and other high-potency neuroleptics, such as thiothixene.

The use of anticonvulsant drugs to treat manic episodes dates back to the 1970s (Okuma et al., 1973). Some anticonvulsant drugs that have shown considerable therapeutic promise, particularly carbamazepine, clonazepam, and valproate, are already widely used with manic patients. Although not yet approved by the U.S. Food and Drug Administration for marketing as antimanic agents, they can, of course, be used by physicians at their own discretion.[2]

CLINICAL MANAGEMENT

Clinical Factors Influencing Drug Choices

Clinical decisions in managing mania are influenced by the treatment setting, the nature and overall severity of the symptoms, and the presence of medical complications. The following recommendations are based on findings of the studies reviewed later in this chapter, modified and amplified by our own clinical experience and that of colleagues we surveyed.

Symptoms

The most important consideration in choosing a treatment for manic symptoms is their nature and severity. Mild manic symptoms (hypomania or stage-I mania) usually respond well to lithium alone. Restoring a normal sleep pattern (Hudson et al., 1989) can often avert escalation to more severe stages of mania. This might be accomplished by using an adjunctive sedative hypnotic, such as the benzodiazepines clonazepam or lorazepam, during the evening.

A neuroleptic may be needed to control severe symptoms, particularly gross hyperactivity and psychotic features. Whether to chose a neuroleptic of high potency (e.g., haloperidol, thiothixene) or low potency (e.g., chlorpromazine, thioridazine) is still an unsettled issue. High-potency drugs have a relatively low level of hypotensive and sedative side effects, a feature that allows more rapid initial dose escalation and, therefore, presumably more rapid control of the psychosis. Low-potency neuroleptics, on the other hand, are more sedating—actually an advantage in achieving early control of the acute mania. In addition, low-potency drugs carry less of a risk of extrapyramidal effects,[3] including tardive dyskinesia, and neurotoxic reactions, and also the rare neuroleptic malignant syndrome[4] (Casey, 1984; Pope et al., 1986).

Both the research literature and our own clinical experience suggest that the anticonvulsants and neuroleptics are superior to lithium in the early phase of treating severe mania, that is, during the first week or two. After the first 2 weeks, lithium and, perhaps, carbamazepine are more effective than neuroleptics. Because of their greater specificity, lithium and carbamazepine calm the patient with a minimum of sedation and nonspecific tranquilization. These drugs are also superior because they are less likely to be associated with postmania depressions and, even more important, carry no appreciable risk of tardive dyskinesia.

The proper role of the anticonvulsants in treating acute mania has not yet been fully established. As reviewed later, carbamazepine is clearly effective, even when used alone (although in most trials it was given in combination with lithium or neuroleptics). Existing data suggest that carbamazepine may be as effective in acute mania as lithium or neuroleptics, but its overall efficacy requires more study. Compared with lithium, carbamazepine is similar in its relative specificity against the affective core of mania and often faster in achieving its antimanic effects. Less clear is whether it can match the effectiveness of neuroleptics in the short-term control of

the extreme hyperactivity seen in psychotic mania, although some evidence is encouraging.

As a treatment for manic-depressive illness, carbamazepine is best established as an alternative for patients who do not respond to lithium or cannot tolerate it.[5] Thus, carbamazepine is the treatment of choice for managing acute mania in patients with a history of lithium-resistant rapid cycles, lithium failure or intolerance, or kidney dysfunction. Because of its antidepressant properties, carbamazepine, alone or combined with lithium, may be particularly useful in the acute treatment of mixed states, which may not respond well to lithium alone (Secunda et al., 1985). Because it lessens aggression, carbamazepine may also be a good choice for suicidal patients. Until further information is available, the other anticonvulsants should generally be reserved for patients who do not respond satisfactorily to carbamazepine. A possible exception to this rule may be clonazepam, which, because of its sedative profile and safety, can be an important adjunct in the initial treatment of mania.[6]

Setting

The treatment setting also influences the choice of drugs or electroconvulsive therapy (ECT). Mania subsides more gradually with lithium than with neuroleptics, the anticonvulsants, or ECT. This lithium lag, 7 to 12 days when the mania is moderate to severe, might be tolerable in a well-staffed inpatient research unit, but very rapid control of symptoms has priority in most settings and is clearly a necessity in some, such as an emergency room without a closed psychiatric unit for backup.[7] In these settings, neuroleptics and/or anticonvulsants (or, selectively, ECT) are preferable for highly agitated patients. A decision tree outlining the choice of treatments for mania is illustrated in Figure 21-1.

Contraindications

Medical conditions or medication needs sometimes limit the choice of drugs.[8] Although we are concerned here with the short-term use of drugs in treating acute mania, the medical factors discussed subsequently are also relevant to discussions of long-term prophylactic treatment (see Chapter 23). Medical contraindications for antimanic drugs, although rare, must always be balanced against the risks of untreated mania. Table 21-1 lists, in approximate rank order, contraindications to antimanic drugs. (The subjective and behavioral side effects of lithium and its effect on organ systems are fully reviewed in Chapter 23.)

Impaired kidney function is a relative contraindication for lithium treatment because lithium is eliminated principally through the kidney and can influence renal tubular activity. Lithium can be used for patients with moderate or stable impairment, but the blood level should be carefully monitored, since a therapeutic level usually can be reached with lower doses than those needed for patients with normally functioning kidneys. Carbamazepine can be substituted for lithium when severe renal impairment precludes its use.

Cardiac disease is another important consideration in treating mania. By virtue of its ionic properties and especially its ability to substitute for potassium, lithium produces changes in the electrocardiogram (particularly T-wave flattening) that are generally benign and reversible. There are, however, rare and scattered case reports of patients with certain kinds of cardiac pathology who experience lithium-induced complications (Jefferson et al., 1987).

Myocardial infarction requires a balancing of risks. Lithium can conceivably produce complications in an already compromised myocardium (primarily because it can increase irritability). This risk must be weighed against possibly even greater risks, such as the effect of the untreated manic patient's uncontrolled activity, psychophysiological stress, and uncertain compliance with cardiac medication, as well as the hypotension that may result from taking neuroleptics. Lithium should, therefore, be considered for managing a manic or hypomanic episode, even during or shortly after myocardial infarction. Carbamazepine or perhaps clonazepam may provide useful alternatives to lithium or neuroleptics in this situation. (For comprehensive reviews of the cardiac effects of lithium, see Albrecht and Müller-Oerlinghausen, 1980; Jefferson et al., 1987.)

Neurological conditions that influence treatment decisions in mania include epilepsy, parkinsonism, dementia, cerebellar disease, and myasthenia gravis. The risk of neuroleptic-induced tardive dyskinesia increases with age, particularly in women. In addition, the risk appears to be

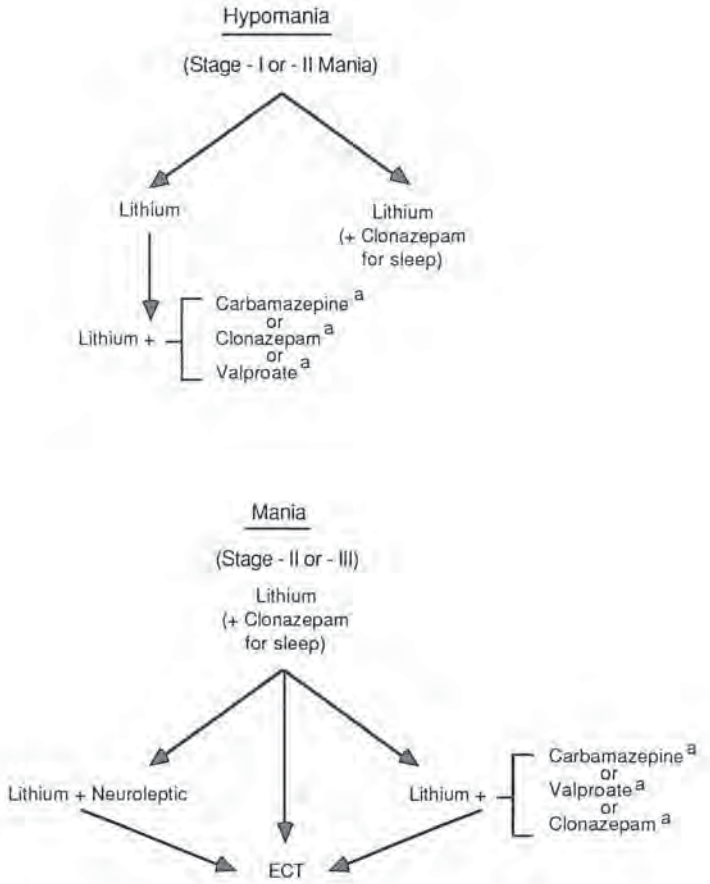

Figure 21-1. A treatment decision tree for mania. [a]The anticonvulsants are more likely to be indicated when there is a history of rapid cycles, lithium resistance, or temporal lobe–like symptoms.

substantially greater for patients with affective illness than for those with schizophrenia (Casey, 1984). Intermittent use of a neuroleptic, more typical in manic-depressive illness than in schizophrenia, may also be associated with a greater risk of tardive dyskinesia, but this association is controversial.

Neither lithium nor the neuroleptics are contraindicated for acute mania in patients with classic epilepsy, although both drugs can produce activation of the electroencephalogram (EEG). The obvious choice for treating manic-depressive illness in patients with seizure disorders is carbamazepine, which has anticonvulsant activity.

Lithium can aggravate preexisting Parkinson's disease, an effect that is not surprising, since lithium decreases dopamine synthesis in the brain (see Chapter 13) (Makeeva et al., 1974).[9] Carbamazepine, which does not markedly affect the dopamine system, is preferable to neuroleptics in managing the mania that can emerge when parkinsonian patients are treated with L-dopa. It is also best for manic patients with preexisting tardive dyskinesia.

Neuroleptics or anticonvulsants may be better than lithium for manic patients with dementia, cerebellar disease, or other pathology of the CNS because lithium is more likely to intensify the underlying dysfunctions. However, some patients with dementia are particularly sensitive to the organic confusional effects of neuroleptics or anticonvulsants. In the neuroleptics, this effect is probably due to their potent hypotensive action.

The tendency of lithium to produce muscle weakness makes it unsuitable for treating manic patients with myasthenia gravis. It has been used successfully to treat the pathological mood lability associated with multiple sclerosis without

Table 21-1. Relative Contraindications for Antimanic Drugs

Lithium
Usually contraindicated:
Renal function impairment
Acute myocardial infarction
Myasthenia gravis
Pregnancy - 1st trimester
Breast feeding
Compromised fluid or salt balance
Use with close medical supervision, including limited dosage:
Other cardiac pathology
Parkinson's disease
Pregnancy - 2nd or 3rd trimester
Delivery
Epilepsy
Thyroid disorders
Use with caution, including limited dosage:
Cerebellar disorders
Dementia
Other CNS disorders
Diabetes mellitus
Ulcerative colitis
Psoriasis
Senile cataracts
Osteoporosis
Certain drugs (see text)
Neuroleptics
Myocardial infarction
Parkinson's disease
Compromised liver function
Porphyria
Hypotension
Tardive dyskinesia
Carbamazepine
Compromised liver function
Porphyria
Hematopoietic system abnormality
A-V block
Clonazepam
Neurological disorders affecting balance
CNS depression

A previous history of allergic reaction to any antimanic drug would be a contraindication for that particular drug.

aggravating the neurological disorder (see, e.g., Kemp et al., 1977), although such patients may have a lower threshold for some of lithium's side effects in the CNS.

Other medical conditions also may be affected by drug treatments for mania. Neuroleptics and perhaps carbamazepine should be ruled out for patients with compromised liver function and porphyria, for example. Carbamazepine and the new atypical neuroleptic, clozapine, both have been associated with bone marrow suppression and should be avoided in patients with disturbed hematopoietic function. Although lithium is not contraindicated for patients with diabetes, the disease process should be monitored closely once the drug is started since it has been reported to exacerbate diabetes, especially in patients taking it for several years (see, e.g., Mellerup et al., 1983).

Thyroid disease can be aggravated by the chronic use of lithium, but in the relatively brief acute treatment phase, the administration of thyroid hormone can offset any effects of lithium. Hypothyroidism may also contribute to inadequate lithium response. One severely manic patient, for example, was unresponsive to a lithium–neuroleptic combination until after her hypothyroidism was corrected (Balldin et al., 1987). Similarly, postpartum mania may be associated with poor lithium response (Targum et al., 1979), which may be caused by a correctable low estrogen state (Wehr and Goodwin, 1981). Conditions in which electrolyte imbalance exists, such as severe diarrhea, complicate the use of lithium and perhaps also of carbamazepine, and neuroleptics might be favored. Any abnormality in the hematopoietic system may complicate the use of carbamazepine. To our knowledge, there are no medical contraindications to the use of clonazepam or other benzodiazepines.

Pregnancy

Birth defects, principally involving the cardiac system, occur at rates that are significantly higher than normal rates in babies whose mothers received lithium in the first 3 months of pregnancy. Thus, lithium should be avoided during the first trimester whenever possible. Mild manic episodes during pregnancy should probably be managed without drugs, but it is prudent to treat more severe episodes, since the possible consequences of an untreated episode (such as injury, psychophysiological stress, dehydration and malnutrition, profound sleep deprivation, and suicide) could pose a greater risk to the fetus than the side effects of lithium. The risk–benefit considerations for the use of lithium during pregnancy are thoroughly reviewed in Chapter 23. Clonazepam

is not known to be associated with fetal abnormalities and, therefore, might be used in these circumstances. Another option is ECT, which can be used without special risk to the fetus. The clinical management of mania during pregnancy has been reviewed by Nurnberg (1980) and by Sitland-Marken and colleagues (1989).

Concurrent Medications

Although several drugs interact with lithium, neuroleptics, and the anticonvulsants, only a few combinations are contraindicated (see Table 23-5 and discussion in this chapter). Knowledge of these interactions will influence the choice of one drug over another, but potential drug interactions generally should not take precedence over the clinical indications outlined previously.

The concurrent use of lithium and diuretics deserves special attention. Loop diuretics, such as furosemide, do not substantially alter lithium excretion and can be administered together safely (Saffer and Coppen, 1983; Jefferson et al., 1987). The thiazide drugs are more problematic, since they decrease tubular reabsorption of sodium and indirectly increase lithium reabsorption and decrease its excretion. When these drugs are used, lithium should be started at a low dose and increased very gradually, with frequent monitoring of the blood level.

Other medical drugs with potential lithium interactions include anti-inflammatory agents, such as indomethacin and phenylbutazone, which increase lithium levels (Reimann et al., 1983); cardiovascular medications, especially the antihypertensive methyldopa, which decreases renal clearance; and digoxin, which has been shown to reduce the acute manic efficacy of lithium (Chambers et al., 1982). Finally, some antibiotics prescribed for lithium-associated acne have nephrotoxic potential.

Because they compete for hepatic metabolism, certain drugs may significantly increase carbamazepine blood levels and produce toxicity. Consequently, the combination of valproic acid and carbamazepine is contraindicated (Meyer et al., 1984; Lambert and Venaud, 1987; Meijer et al., 1984). Among the other drugs that should be used cautiously with carbamazepine for this same reason are verapamil, isoniazid, diltiazem, and erythromycin and related antibiotics (Berrettini, 1986; Sovner, 1988). By contrast, other drugs—phenobarbital, primidone, and phenytoin—can decrease carbamazepine blood levels, presumably by inducing hepatic metabolism (Post et al., 1985).

Concurrent administration of carbamazepine and neuroleptics has been reported in more than 100 patients. The two drugs produce some additive effects in the CNS, and there is some evidence that they enhance each other's effects. Carbamazepine does not appear to alter lithium levels. Additive CNS effects, especially sedation and cognitive and memory functions, should be kept in mind when deciding how fast to increase dosages and the ultimate dose level. Patients with preexisting CNS disease may be especially vulnerable to neurotoxicity with this combination (Shukla et al., 1984).

Determining Medication Dosage

Neuroleptics

Clinicians traditionally have used larger doses of neuroleptics for acute mania than for schizophrenia, but recent experience suggests that more modest doses can be effective. The lower dose is feasible if the patient is carefully monitored for early signs of improvement and takes lithium along with the neuroleptic. Chlorpromazine doses averaged more than 1 g per day in controlled studies, and comparably high doses have been reported for the high-potency neuroleptics, such as haloperidol and thiothixene. Blood level determinations for neuroleptics are not yet routinely available as they are for lithium. Clinical state, age, sex, and weight must be considered in setting dose levels; higher doses are required for more disturbed and highly active patients and for patients who are male, young, or heavy. Haloperidol is usually started at 5 to 15 mg intramuscularly (or 10 to 25 mg orally) every 4 to 6 hours. For chlorpromazine, the preferred dosage is 50 to 100 mg, which can be administered intramuscularly every 6 hours and then gradually replaced by oral doses.[10] The need for such high doses of neuroleptics should be reevaluated continually throughout treatment of the acute manic episode. To minimize the possibility of neurotoxicity, extrapyramidal side effects, or postmania depression, dosage should be reduced as soon as manic symptoms begin to subside.

Lithium

The gap between therapeutic and toxic levels of lithium is the narrowest of any drug routinely used in psychiatry. Fortunately, the level of lithium in plasma is readily determined, and dosage requirements have been studied extensively. In managing acute mania with lithium alone, it is best to use a dosage schedule that produces the highest plasma level consistent with acceptable side effects. These blood levels usually are higher than those considered necessary or safe for maintenance therapy. The dose/blood level relationship is influenced by the individual's sex, age, weight (especially muscle mass), salt intake, amount of sweat, intrinsic renal clearance capacity for lithium, and, as noted, other medications. A relatively higher dose/blood level ratio is associated with being younger, male, and heavier and having a higher salt intake.

In the lithium treatment of acute mania, the patient's clinical state is one of the most important factors affecting the dose/blood level relationship. Some patients, when manic, retain lithium in body pools outside the plasma, probably largely in bone (Greenspan et al., 1968; Almy and Taylor, 1973). In practice, more lithium is needed to achieve a given blood level during mania than during euthymia or depression (Goodwin et al., 1969; Serry, 1969; Kukopulos et al., 1985). When mania begins to subside, a dosage reduction usually is necessary to avoid lithium toxicity. Obviously, blood levels should be monitored more frequently when the clinical state is changing, especially from mania to euthymia or depression.

To predict dosage requirements, some investigators recommend a test dose of lithium followed 24 hours later by a plasma level determination (Cooper and Simpson, 1976; Perry et al., 1984). Fava and colleagues (1984) showed that, by using this technique, therapeutic levels were obtained faster, and fewer blood level determinations were required. Although this technique probably can be applied reliably when the mood state is stable, its practical value in treating acute mania is limited by the state-dependent kinetics of lithium. Errors in the predicted dose may, for example, be due to changes in patients' sleep and activity, which presumably cause changes in renal clearance (Perry et al., 1984). In addition, use of this method necessitates a 24-hour delay in treatment. Norman and colleagues (1982) proposed a faster technique that can also account for changes in renal clearance. This technique may be impractical, however, since it requires a 4-hour urine collection along with a blood sample.

The plasma level of lithium needed to produce a clinical response differs substantially from one manic patient to another. The same is true of toxicity. These differences are partly caused by variability in tissue sensitivity, a variability encountered with any drug. More important, however, are individual differences in the ratio of plasma lithium to intracellular lithium, as reflected in red blood cell (RBC) determinations. Toxic reactions reflect intracellular lithium, whereas serum levels reflect only the extracellular compartment.

These issues are important to treatment because increasing plasma levels of lithium (up to 1.4 mEq/liter) are associated with proportionately higher rates of therapeutic response (Stokes et al., 1976). Although there is reason to push the dose in patients who fail to respond, blood levels above 1.5 mEq/liter are not generally recommended, and even levels between 1.2 and 1.5 mEq/liter require considerable care to avoid toxicity. Indeed, an increase in the RBC/plasma lithium ratio often precedes the development of neurotoxicity (see, e.g., Dunner et al., 1978; Carroll and Feinberg, 1977). In most cases, blood levels in the therapeutic range can be achieved at doses between 900 and 1,800 mg daily of lithium carbonate.

In deciding the maximum lithium level to use with a manic patient, the clinician should keep in mind that the most important potential toxic effects are those involving the CNS. This task is made more difficult by the fact that the delirium-like symptoms that can occur in severe mania may be nearly indistinguishable from neurotoxic effects. (Specific neurotoxic effects of lithium are discussed in Chapter 23.)

Some authors have suggested using a loading dose strategy for treating mania with lithium,[11] both to achieve the maximum blood level quickly and to speed therapeutic onset. The value of this strategy is questionable, however, especially in light of animal and human data indicating that lithium is slow to enter the brain from the blood,

even when plasma levels are high. In one study, CSF lithium levels increased 50 percent, on average, from the first to the third week on a constant lithium dose (Rey et al., 1979).

Lithium Plus Neuroleptics

The additive and possibly synergistic effects of lithium and neuroleptics must be considered when combining the two drugs. A severe encephalopathy syndrome was first reported in four manic patients treated with high doses of both lithium and haloperidol by Cohen and Cohen in 1974. Since then, some 50 additional cases of neurotoxic syndromes resulting from the combination of lithium and a neuroleptic have been reported. Most of these conditions are reversible. On the other hand, eight prospective and retrospective studies with a total of more than 600 patients have generally failed to find any special neurotoxicity with this combination.[12] This literature suggests that the risk of neurotoxicity is associated with pre-existing encephalopathy and high dose levels, especially of the neuroleptics.[13] Thus neuroleptics should be used in substantially lower dosages when combined with lithium than when used alone. We also recommend that the lithium level be kept below 1.0 mEq/liter, in part because neuroleptics increase the RBC/plasma lithium ratio (Von Knorring et al., 1982). Although lithium and neuroleptics generally can be combined safely and effectively when done in this way, it is important to monitor CNS function and, in hospital settings, to alert the staff to watch for symptoms of neurotoxicity. Patients in seclusion rooms, who can rapidly become dehydrated, require special caution, including temperature monitoring (see later discussion of seclusion and restraints). One report of a high frequency of neurotoxicity with lithium–neuroleptic combinations in people over 65 suggests caution in this age group as well (Miller et al., 1986).

Carbamazepine and Valproate

When carbamazepine is used alone, the starting dose is usually 200 to 400 mg, which is increased to the 800 to 1,000 mg range during the first week. Further increases (up to about 1,600 mg) are appropriate if no response is evident after the first 2 weeks and if not limited by unacceptable side effects. The blood level generally should be between 6 and 12 ng/ml. When carbamazepine is combined with lithium or neuroleptics, the dose and target blood level are typically somewhat lower. Over time, carbamazepine can induce its own hepatic metabolism, and blood levels can fall. This problem is more troublesome in prophylactic treatment (see Chapter 23).

Side effects are more likely to occur when dosages are increased rapidly in treating acute mania than when the dosage is built up slowly in the first phase of prophylactic treatment. These early side effects—drowsiness, dizziness, ataxia, confusion, double vision, and nausea—usually do not persist beyond the first week or two and often respond to temporary dosage reduction.

Carbamazepine produces side effects about as frequently as lithium and less often than neuroleptics. Skin rashes of varying degrees of severity are a frequent problem (10 to 15 percent of patients). Those that are unaccompanied by evidence of a systemic allergic response can be treated with 20 to 30 mg of prednisone administered daily for a few weeks, then gradually discontinued. Liver enzyme levels, complete blood count, and platelet count should be obtained before treatment and weekly for the first 3 to 4 weeks of treatment and then every 4 to 8 weeks.

Although transient suppression of white blood cells and platelets is common, it does not require discontinuation of the carbamazepine. Serious hematopoietic complications (agranulocytosis and aplastic anemia) are rare, occurring once in about 15,000 to 20,000 patients. Nevertheless, the drug should be discontinued if the white count drops below 3,000 or if the patient shows clinical signs of these complications, such as sores, infections, fever, easy bruising, or petechiae. In one report, the benign suppression of white blood count by carbamazepine was offset by the addition of lithium (Brewerton, 1986). Comprehensive reviews of the clinical pharmacology of carbamazepine (dosage, blood levels, and side effects) are now available.[14] Differences in the side effect profile of carbamazepine and lithium influence treatment choices for long-term maintenance; these profiles are compared in Chapter 23.

In treating acute mania with sodium valproate or valproic acid (generally used in combination with lithium), it is usual to start at 500 to 1,500 mg/day in divided doses, with peak doses ranging from 750 to 3,000 mg/day, corresponding to

blood levels between 50 and 100 μg/ml (with a median of about 75 μg/ml). No serious adverse effects have been found in the 268 psychiatric patients reported in the literature, and side effects are minimal or absent. However, hepatic function should be monitored in light of rare reports of potentially fatal hepatitis in epileptic patients. Also, when valproate is combined with carbamazepine, blood levels should be monitored closely and dosages may need to be adjusted, since there are complex metabolic interactions between the two drugs.

Clonazepam

Clonazepam has become popular among some clinicians for the rapidly, albeit perhaps nonspecific, control of manic symptoms because it is relatively safe and easy to use (e.g., it requires no blood monitoring) (Santos and Morton, 1987). In high doses (10 to 15 mg), it may be well suited to emergency room or inpatient settings where the profound sedation presents a more manageable risk. For outpatient use, the dose-dependent sedative and related dissociative reactions may present problems, such as in driving a car or operating machinery. In these situations, it is wise to use the smallest possible dose needed to restore sleep and, it is hoped, abort an emerging manic episode (the 2 to 5 mg range). Experience to date indicates that clonazepam can be administered safely in combination with any of the other drugs discussed previously, and its effects are additive. Other sedative benzodiazepines, such as lorazepam, are also used for mania.

Strategies for Drug Treatment of Severe Mania

In the first few days of treating moderately severe to severe mania (stages II or III), the three choices are neuroleptics, carbamazepine, or clonazepam. Of the neuroleptics, haloperidol is generally preferred. After 3 to 4 days, or as soon as the acute hyperactive and psychotic symptoms begin to subside, the dose of neuroleptic can be reduced and lithium added—cautiously, since side effects are additive. By not giving the drugs concurrently, the clinician can assign the side effects to the appropriate drug. Careful monitoring of both clinical effects and side effects permits gradual decrease of the dose of neuroleptic and increase of the lithium dose. By the third week, most patients can be maintained on lithium alone, although some will require modest doses of neuroleptics for a longer period. For patients with substantial schizoaffective features, adjunctive neuroleptics may have to be maintained indefinitely.

Carbamazepine, initially reserved for lithium nonresponders, is now being seriously considered as a first-choice alternative to neuroleptics as an adjunct to lithium. If additional studies continue to show that carbamazepine is at least as effective as neuroleptics without the same potential for tardive dyskinesia, postmania depression, or cycle induction, carbamazepine may be preferable.

Finally, for the reasons noted above, clonazepam and related benzodiazepines are being used increasingly for acute mania.

Electroconvulsive Therapy

ECT is a valuable alternative to medications in treating acute mania, a point that was underlined by two favorable comparisons with lithium, a randomized controlled trial (Small et al., 1988) and a large retrospective study (Black et al., 1987, 1989). ECT may be especially useful for severely manic patients, for those who have proven unresponsive to drugs, and for those in mixed states with a high risk of suicide. If ECT is to be used, lithium should not be administered simultaneously (even in reduced doses) because neurotoxic complications have been reported to occur with this combination (see, e.g., Small, 1980; Rudorfer and Linnoila, 1986). Some clinical investigators believe that bilateral electrode placement may be necessary to obtain the full antimanic effect of ECT (Small et al., 1985), whereas others find no difference between unilateral and bilateral placement (Black et al., 1987).

Hospitalization

Patients exhibiting fully developed psychotic (stage-III) mania almost always need to be hospitalized, often involuntarily. When their manic symptoms are still in the mild to moderate range, judging the need for and timing of hospitalization can be more difficult. The family's support and collaboration are essential when hospitalizing a patient. They are also needed to help control a patient who can stay out of the hospital by, for example, assuring compliance with medication.

In deciding whether to hospitalize a patient, the clinician must keep in mind that mild mania can progress to severe mania rapidly and unexpectedly. The possible social, occupational, or legal consequences of such extreme behavior must be weighed against the professional and personal consequences of hospitalization.

Since manic patients rarely recognize their need to be hospitalized, informed consent presents a dilemma, and involuntary commitment is often necessary. In some states, such legal procedures can be difficult and cumbersome, and commitment can result in stigmatization and loss of some legal rights for the patient. On the other hand, to acquiesce to the patient's refusal is to court disaster. A possible humane alternative to this no-win dilemma may be to obtain consent in advance, an application of the so-called Odysseus principle discussed in Chapter 24.

The hospital treatment of mania often requires decisions concerning the use of seclusion rooms and physical restraints. Seclusion substantially reduces the level of stimulation to a severely manic patient, thus ameliorating a factor that often seems to drive and perpetuate the episode. The potential for self-injury, including physical exhaustion, and the need for medical monitoring often necessitate the use of physical restraints. Indeed, failure to use restraints has been the basis for successful malpractice litigation.

Treatment of Mania in Children and Adolescents

Issues related to the treatment of mania in children and adolescents have become increasingly important with the growing recognition that mania and manic-like states occur frequently in adolescents and even in prepubertal children (see Chapter 8). Resolving these issues is more urgent if the early episodes alter the brain in such a way as to facilitate subsequent episodes—a prediction based on biological models of kindling and sensitization (see Chapters 16 and 20). Added to the already well-recognized psychological and social scarring that results from manic episodes, this possibility of an ever-worsening, accelerated course implies that the earlier the illness is treated the better the long-term outcome.

In general, the treatment of mania in children and adolescents follows the same principles that apply to adults.[15] Compared with manic episodes in adults, those in the young are more likely to involve delusions and psychotic disorganization, perhaps reflecting the impact of the manic process on a still developing nervous system (Ryan et al., 1987). Despite the severity of their symptoms, manic children and adolescents generally respond to lithium as well as do adults (see, e.g., DeLong and Nieman, 1983). Indeed, some evidence suggests that the young may actually respond better to lithium than adults with similar mood and psychotic symptoms (Van der Velde, 1970; Varanka et al., 1988), and supplemental neuroleptics may be less necessary. Within the adolescent group, however, those with a very early onset of disturbance may not respond as well to lithium as do those with symptom onset in adolescence (see, e.g., Strober et al., 1988, reviewed later in this chapter). It has also been suggested that very early onset bipolar disorder is more likely to involve mixed states and rapid cycling (Ryan and Puig-Antich, 1987), conditions that may require supplemental anticonvulsants.

Although controlled studies are lacking, open trials suggest that therapeutic blood levels for children and adults are about the same. When adjusted for differences in body weight, the lithium dosage required to reach these blood levels is somewhat higher in children than in adults, presumably due to the greater capacity of the young kidney to clear lithium (Weller et al., 1986). For the acute treatment of mania in children, side effect considerations appear similar to those in adults, although some investigators have noted fewer side effects in children. In dealing with medication compliance among the young, it is well to be aware of the special concerns experienced by this age group (body image, peer pressure, motor coordination, acne, to name a few). These issues are discussed in Chapter 25.

Treatment of Mania in the Elderly

As detailed in Chapter 5, mania in the elderly may be obscured by concurrent signs of organic brain syndrome or by prominent schizophrenia-like symptoms. Thus, before diagnosing mania in an elderly patient who has no history of manic episodes, the clinician should consider the possibility that the manic symptoms are caused by another medical condition or by medications (see Chapters 5 and 18 for a full discussion of secondary mania). If the identified primary factor cannot

be corrected, pharmacological treatment of the manic symptoms is appropriate.

When using antimanic agents in an elderly patient, other medical problems and possible interactions with other drugs must be considered (Sargenti et al., 1988). Although systematic reviews generally do not support a direct correlation between age and overall side effects, there is an age-associated increase in moderate to severe side effects (Smith and Helms, 1982), perhaps related to important pharmacodynamic differences, such as reduced renal lithium clearance. Moreover, some case reports suggest an age-related increase in sensitivity to the neurotoxic effects of antimanic drugs (see, e.g., Strayhorn and Nash, 1977). This possibility must be kept in mind to avoid mistaking neurotoxic symptoms for the normal deficits of aging. Of special concern is the increased vulnerability among the elderly to tardive dyskinesia secondary to neuroleptics.

REVIEW OF THE LITERATURE

Lithium

Uncontrolled and Single-Blind Studies

In the earliest clinical trials of lithium, researchers did not define their diagnostic criteria for mania, notably failing to differentiate manic and schizoaffective states. Nor did they use a double-blind design or rating scales to evaluate clinical response. Despite these shortcomings, the early studies provide many rich clinical descriptions and give a good sense of patients' responses to the drug. In many reports from this period, for example, clinicians observed that typical manic patients were most likely to respond to lithium and that the patients with schizoaffective states did not appear to respond as well. Although conducted by many groups over several years, the uncontrolled studies consistently demonstrated a high rate of response, which usually began within about a week of starting lithium. When the results of these 10 early studies are combined, 334 of 413 patients (81 percent) showed lessened mania during acute lithium treatment (Goodwin and Ebert, 1973). This improvement did not necessarily mean complete remission, nor is it clear how much time it took for a full response to occur.[16]

More recent open studies of lithium appear to demonstrate its efficacy for mania in children. For example, Varanka and colleagues (1988), in a careful open study of 10 manic prepubertal children between the ages of 6 and 12, found that all patients responded well to lithium alone, with most of the improvement occurring in an average of 11 days. All of the patients exhibited mood-congruent psychotic symptoms that responded to lithium in about the same amount of time as did the mood symptoms.

Controlled Studies

The first controlled trial of lithium in mania (Table 21-2) was done in Denmark by Mogens Schou and colleagues in 1954. Almost a decade later, in 1963, Maggs, working in England, did a double-blind evaluation of lithium's effects on acute mania, the first such study to use formal rating instruments of manic behavior and to analyze the data statistically. The earliest American controlled study of lithium, done in 1968 by Bunney and co-workers at the National Institute of Mental Health (NIMH), offered longitudinal double-blind data on two patients, demonstrating the sensitivity of manic symptoms to temporary withdrawal of lithium medication. The NIMH group extended its study to 30 manic-depressive patients, of whom 12 were manic (Goodwin et al., 1969). A fourth study, by Stokes and his associates at the New York University and Cornell University Medical Colleges (1971), used a double-blind design with alternating 7 to 10 day periods on lithium or placebo in 38 manic-depressive inpatients.

Despite methodological differences, results of the four controlled studies are remarkably consistent. The overall response rate in the 116 patients is 78 percent, a figure very close to that derived from the open studies. Clearly, these four studies demonstrated that lithium is superior to placebo in the acute treatment of mania. They also revealed some characteristics of lithium discussed in the first part of this chapter. First, despite its demonstrated effectiveness, lithium is relatively slow to produce clinical changes, usually requiring a 2 week trial to reach maximum therapeutic effect. Second, although the diagnostic criteria used in these studies are not necessarily comparable to DSM-III, the lithium responders tended to be classic bipolar patients (manic phase), often in

Table 21-2. Lithium in Mania: Placebo-Controlled Studies

Study	Method	N	Response Rate %	Comments	Assessment
Schou et al., 1954	Random crossover[a]	30 typical	90	40% definite 50% probable	Global impression
		8 atypical	62	25% definite 37% probable	
Maggs, 1963	Random crossover	28		Lithium superior to placebo	Wittenborn scale
Goodwin et al., 1969	Nonrandom crossover	12	75	67% complete 8% partial	Modified Bunney-Hamburg scale
Stokes et al., 1971	Nonrandom crossover	38	75[b]	40% improved on placebo	Quantification of nurses' observations
Overall Response			78%		

[a] Not all cases included
[b] Refers to numbers of episodes

This table was originally produced by Goodwin & Zis, 1979, and reproduced by Tyrer, 1985.

stage I or II of mania, and nonresponders tended to be schizoaffective or in stage-III mania.

Once it had been unequivocally demonstrated that lithium did have antimanic activity, other questions could be asked: How does lithium alone compare with neuroleptics (major tranquilizers, antipsychotics)? Do the relative merits of these drugs differ with various manic symptom patterns? What sort of manic patients would benefit from lithium alone? When and how should lithium be used in combination with other drugs? The studies described subsequently partially answer these questions.

Case reports and controlled studies suggest that a relatively broad spectrum of clinical states in adolescents and children appears to respond to lithium. This diversity probably reflects, first, some lack of specificity in the action of lithium and, second, the variety of clinical presentations of mania in these age groups, as noted in Chapter 8. The reports of patients whose symptoms fit or approximate DSM-III criteria for mania[17] suggest that the efficacy of lithium is comparable to that reported for the treatment of mania in adults,[18] with the possible exception of children with very early onset of disturbance. Results are confounded, however, because in many of these reports, unlike the adult literature, lithium was given in combination with other drugs.

In one of the largest and most rigorous studies done on the subject to date, Strober and colleagues (1988) found that, when symptoms began after puberty, the rate of response to lithium was twice as great as when they began before puberty. Only 40 percent of bipolar adolescents with very early onset of symptoms responded to lithium, whereas 80 percent of those whose symptoms began in adolescence responded ($p < 0.02$).[19] Strober's group studied 50 adolescents with bipolar-I disorder who were treated with lithium and, as needed, neuroleptics and carbamazepine.[20]

> . . . the poor lithium response in these probands is in accordance with data relating lithium failure to longer histories of illness preceding treatment . . . and greater overall personality disturbance. . . . Increased refractoriness to treatment in this group is also in line with theoretical speculation . . . that responsiveness to lithium carbonate may decrease over time in patients who experience a chronic, uninterrupted progression of their illness. (Strober et al., 1988, p. 265)

High-Potency vs Low-Potency Neuroleptics

In one of the few studies that directly compared the butyrophenone haloperidol with chlorpromazine under controlled conditions, Entwistle and colleagues (1962) noted that tranquilization was achieved more rapidly with haloperidol, requiring an average of 4 days for full effect, and that

hyperactivity could be controlled even more rapidly, within 2 or 3 days. The more recent literature is reflected by the study of Janicak and colleagues (1988a), who found that chlorpromazine and thiothixene were similarly effective in manic patients who were also receiving lithium. As expected, the profile of side effects was different for the two drugs (extrapyramidal symptoms were significantly greater in the thiothixene group). Clozapine, a high-potency neuroleptic with a low incidence of extrapyramidal side effects, has not yet been fully evaluated in manic patients, but shows promise, perhaps especially for schizomanic patients.[21]

Lithium vs Neuroleptics

In most studies comparing lithium with neuroleptics, both manic and schizoaffective patients were treated (Table 21-3). With the exception of a Japanese study in which relatively low doses of lithium were used (Takahashi et al., 1975), lithium treatment was associated with marked improvement or remission in about two thirds of the patients in these comparison trials. These findings are in good agreement with the results of controlled studies of lithium alone and of open or single-blind studies. Furthermore, with the exception of the study conducted by the Veterans' Administration (VA) and NIMH (discussed later), lithium, over time, proved superior to chlorpromazine in treating acute mania, as judged by the proportion of patients showing marked improvement or remission. The evidence also strongly suggests that lithium ameliorates the very affective and ideational symptoms most specific to the manic syndrome. Chlorpromazine can match or exceed lithium in the initial control of psychomotor hyperactivity, but this effect may be due to nonspecific sedation. Comparisons of lithium and neuroleptics have been limited largely to chlorpromazine. The one study that did compare lithium with both chlorpromazine and haloperidol found that the latter neuroleptic has the most rapid action (Shopsin et al., 1975a).

The VA-NIMH study (Prien et al., 1972) warrants more extensive discussion because of its size—255 newly admitted manic and schizoaffective patients in 18 VA hospitals—and its unusual findings. Patients were differentiated not only by diagnosis but by activity level: "highly active" or "mildly active." Among the highly active patients who completed the 3-week treatment trials, both the lithium-treated and the chlorpromazine-treated groups improved significantly on a wide range of symptoms. However, 38 percent of the lithium-treated patients dropped out, compared with only 8 percent of those treated with chlorpromazine, in part reflecting more side effects attributable to lithium in this group, since the dose was pushed in an effort to control the hyperactivity. Both drugs produced significant improvement in the mildly active patients who completed the study, but in this group severe side effects were more frequent among the chlorpromazine-treated patients.

The investigators concluded that chlorpromazine was superior to lithium in the initial treatment of the highly active patients. The neuroleptic not only reduced motor activity, excitement, grandiosity, hostility, and psychotic disorganization, but it also sharply decreased the patients' need for ward supervision in the first week. By the end of 3 weeks, however, the two drugs were equivalent. Among the mildly active patients, there were fewer dropouts related to lithium than to chlorpromazine, primarily because lithium did not make them feel as "sluggish and fatigued."

Neither discharge rates nor overall improvement rates were reported in this study. In other studies, however, discharge rates and clinical impressions favor lithium over neuroleptics, thus underscoring the ultimate advantage of lithium. The dropout rate in the VA-NIMH study may reflect limitations in clinical management more than inherent limitations of the drugs in question.

Diagnosis is also a critical issue. Prien and associates did not specify how the differential diagnosis was made between the manic phase of manic-depressive illness and that of schizoaffective psychosis. Other investigators might have diagnosed their highly active patients as schizoaffective or "atypical." Although some studies have suggested that such patients do not respond as well to lithium as the more typical manic-depressive patients do (reviewed by Goodwin and Ebert, 1973), other investigators failed to find any difference in lithium response between the groups (reviewed by Goodnick and Meltzer, 1984). This discrepancy is probably more apparent than real. Goodnick and Meltzer (1984) have shown that compared with manic patients, schizoaffective manic patients require more than

Table 21-3. Lithium vs Neuroleptics in Mania

Study	Drug	N	Marked Improvement or Remission %	Qualitative Differences: Hyperactivity	Qualitative Differences: Normalization of Mood and Ideation	Comments
Johnson et al., 1968	LI	18	78	CZ > LI	LI > CZ	
	CZ	11	36			
Johnson et al., 1971	LI	13	Not reported		LI > CZ	BPRS, CGI, NOSIE, TRAM, SCI
	CZ	8				
Spring et al., 1970	LI	9	88	LI > CZ	LI > CZ	Target symptom assessment; N includes the crossover trials
	CZ	6	50			
Platman, 1970	LI	13	Most	?	LI > CZ	Quantified behavioral ratings
	CZ	10	None			
Prien et al., 1972	LI	59[a]		CZ > LI	CZ > LI	Multihospital study; BPRS, IMPS, PIP
	CZ	66[a]	Not reported			
	LI	69[b]		CZ > LI	LI > CZ	
	CZ	61[b]				
Takahashi et al., 1975	LI	37	32	CZ > LI	LI > CZ	Multihospital study; special rating scale; 5 weeks; low doses; higher incidence of depression with CZ
	CZ	34	12			
Shopsin et al., 1975a	LI	10	70	HAL > LI > CZ	LI > HAL > CZ	BPRS, CGI, SCI, NOSIE
	CZ	10	10			
	HAL	10	20			

Except as indicated, all studies were double-blind, random assignment, 3-week duration

CZ = chlorpromazine, LI = lithium, HAL = haloperidol
BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression, NOSIE = Nurse's Observation Scale for Inpatient Evaluation
TRAM = Treatment Response Assesment Method, SCI = Structured Clinical Interview, IMPS = Inpatient Multidimensional Psychiatric Scale
PIP = Psychotic Inpatient Profile

[a]Highly active group; higher dropout rate with LI

[b]Mildly active group; higher frequency of severe side effects with CZ

This table was originally produced by Goodwin and Zis, 1979, and reproduced by Tyrer, 1985.

twice as long to achieve a full antimanic response to lithium alone (9 weeks against the 4 weeks for manic patients). Many of the reports of relatively poor lithium response rates among schizoaffective manic patients involve trials of 4 weeks or less. Again, from a practical point of view, this means that schizoaffective manic patients are likely to require other medications in addition to lithium for the acute treatment of mania.

Before lithium became available in the United States, the neuroleptics were the drugs of choice for treating mania. The willingness of many physicians to try lithium, a new and potentially toxic drug requiring careful monitoring, suggests that they found neuroleptics inadequate for many, if not most, patients. The fact that today virtually all clinicians include lithium in their treatment approach to mania is consistent with findings that this drug has an overall advantage over the major tranquilizers.

Neuroleptics still have a place in the treatment of acute mania, however. As we have seen, chlorpromazine is probably superior to lithium in the initial control of increased motor activity, and, as noted earlier, there are indications that haloperidol may act even more rapidly than chlorpromazine. Along with clozapine, another neuroleptic deserving further study as a rapid-onset treatment for acute mania is pimozide, a more or less specific dopamine blocker. In a 1980 study, Post and colleagues noted rapid control of manic symptomatology and behavior with this drug. Therapeutic effect with pimozide began within 24 hours, compared with a 5-day lag with lithium. Comparing pimozide and chlorpromazine in acute mania, Cookson and associates (1980) found that both were equally effective in controlling the syndrome but that pimozide produced less sedation.

Lithium–Neuroleptic Combinations

Surprisingly, no major systematic studies have been done comparing the combination of neuroleptics and lithium with either drug alone in treating acute mania, although such a comparison has been done for schizoaffective mania (as defined by the RDC). Biederman and associates (1979) found that both predominantly affective and predominantly schizophrenic schizoaffective patients did better on a combination of haloperidol and lithium than on haloperidol alone, but the addition of lithium was more beneficial for the affective schizoaffective patients. In addition to producing a more satisfactory remission, lithium more often prevented the postmania depressions frequently experienced by patients whose mania is treated with neuroleptics alone.

Neuroleptics have been associated with the phenomenon of postmania depression (Kukopulos et al., 1980; Morgan, 1972), although at least one study did not observe this link (Lucas et al., 1989). In their longitudinal study of 434 bipolar patients over periods averaging 17 years, Kukopulos and colleagues (1980) also observed that treatment of manic episodes with neuroleptics contributed to a shortening of the intervals between episodes, thus worsening the long-term course of the illness. This finding, if validated in controlled studies, would underline the importance of limiting the use of neuroleptics in mania. Such a limitation contrasts with data showing improved long-term course in schizophrenic patients treated early and consistently with neuroleptics (Wyatt et al., 1988).

Anticonvulsant Drugs

The relationship between seizure disorders and manic-depressive illness is discussed in Chapter 5, and in Chapter 16, we suggest that kindling, a neural mechanism involved in seizures, provides a promising model for cyclic mood disorders.

Carbamazepine

Carbamazepine, which can prevent or reverse kindling, is an established treatment for temporal lobe epilepsy (Penry and Daly, 1975), a condition that not only is phasic but also is frequently associated with affective and other psychological changes. Reviewing 40 studies of the drug's effects in epileptic patients, Dalby (1975) estimated that carbamazepine showed a significant psychotropic effect in half of the patients, who reported feeling more alert and sociable and less anxious, irritable, and depressed than they had been before taking carbamazepine.

The first trial of carbamazepine in mania (Okuma et al., 1973) was a nonblind study of 64 acutely manic patients, half of whom were "markedly" or "somewhat" improved when the drug was added to the existing treatment regimen, which often included lithium or neuroleptics.

Later, Okuma and colleagues (1979) conducted a double-blind comparison of carbamazepine and chlorpromazine in 63 patients with acute mania. Marked to moderate improvement was seen in 70 percent of the carbamazepine group and 60 percent of the chlorpromazine group. In both groups most patients improved within the first week. Both drugs produced considerable sedation, although carbamazepine had fewer overall side effects.

At about the same time, Ballenger and Post (1978, 1980) reported positive antimanic results using a longitudinal double-blind crossover design with alternating periods of carbamazepine alone and placebo. The sample size was increased in succeeding years. To date, 12 of 19 acutely manic patients have responded to carbamazepine (Post et al., 1987). The time from administration of the drug to antimanic response was similar to that seen with neuroleptics and slightly shorter than with lithium. It is of interest that most of the patients who responded well to carbamazepine in this trial had previously not responded to lithium, although these authors did not conduct a direct comparison with random assignment. Strömgren and Boller (1985), in their review of 15 reports of carbamazepine treatment of 176 manic patients, note that a "marked or moderate" antimanic effect was reported in 55 percent (69 percent among the four double-blind studies). Among the 12 studies involving carbamazepine alone, 85 patients (61 percent) were reported to have "marked or moderate" improvement.

Only two studies have directly compared the efficacy of carbamazepine and lithium in mania. Placidi and co-workers (1986) found that both drugs were of equivalent efficacy in a mixed group of 83 manic and schizomanic patients, with about two thirds of the patients in each drug group showing a marked or moderate response. Among the schizoaffective patients with mood-incongruent psychotic features, those on lithium had a significantly higher dropout rate than those on carbamazepine, suggesting that the anticonvulsant might be superior to lithium for this group of patients. The authors also indicated that lithium may have been somewhat superior to carbamazepine among the "classical, pure" manic patients. Lerer and colleagues (1987) studied 28 manic patients, employing a randomized double-blind design, and noted a trend for lithium to be superior. The lithium effects were more uniform: 11 of the 14 lithium-treated patients showed a global improvement of two or more points on the Clinical Global Impressions scale, whereas only 4 of 14 carbamazepine patients showed that level of response ($p < 0.05$). Two of the three best responders to carbamazepine had rapid cycles, and all three had a prior history of lithium failure.

In the studies by Okuma's group and Post's group, as well as in several case reports, some of the patients received carbamazepine in addition to either lithium or chlorpromazine, and the anticonvulsant appeared to potentiate the antimanic effects of the other drugs without increasing toxicity. Likewise, many patients who fail to improve when taking carbamazepine alone do respond when lithium is added to the treatment regimen (Kramlinger and Post, 1989). Three direct studies of carbamazepine–neuroleptic combinations (Klein et al., 1984; Muller and Stoll, 1984; Möller et al., 1989) showed such potentiation, which was reflected in a reduced need for the neuroleptic after carbamazepine was added. The studies of carbamazepine in the treatment of mania are outlined in Table 21-4. Clinical predictors of the relative antimanic response to carbamazepine and lithium are discussed later.

Valproate

Another anticonvulsant drug, valproate, has attracted attention as a potential antimanic agent because, like carbamazepine, it reduces kindling and enhances the activity of γ-aminobutyric acid (GABA), a major CNS transmitter especially important in inhibiting central dopamine systems (see Chapters 16 and 17). Following the initial reports of antimanic effects by French investigators (Lambert et al., 1966, 1971), several studies have appeared, predominantly from Europe (reviewed by McElroy et al., 1987, 1989; Fawcett, 1989). More than half of the 181 manic or schizomanic patients in these studies had a therapeutic response to valproate, usually within 2 weeks, a response rate that was also noted in a large community based open trial (Brown, 1989). Most patients had previously failed to respond satisfactorily to lithium or lithium combined with neuroleptics, and in most cases the valproate was added to existing treatments. In the only two double-blind studies performed to date, however, 10 of 13 manic patients had a marked response to

valproate alone after withdrawal of previous medications (Emrich et al., 1980; Brennan et al., 1984). The specificity of valproate for manic-depressive illness is suggested by the relatively poor results among 63 schizophrenic patients. In a study from the McLean Hospital group in Boston (McElroy et al., 1987), marked or moderate responses among the manic patients (11 of 17, or 64 percent) were initially associated with the presence of nonparoxysmal EEG abnormalities, but this relationship lost statistical significance as the sample size was increased. Among the four patients with rapid cycles, three showed a marked response to valproate.

The therapeutic profile of valproate appears similar to that of carbamazepine. Whether valproate will be useful in carbamazepine nonresponders or vice versa remains to be seen. So far, Post and colleagues have reported one patient with an antimanic response to carbamazepine but not to valproate (1984) and one with the opposite profile (1987). The prophylactic effects of valproate are discussed in Chapter 23. The widely used anticonvulsant, diphenylhydantoin, which has been tried as a treatment for mania with only very scattered responses (Himmelhoch, personal communication), has not been studied systematically.

Clonazepam

The benzodiazepine anticonvulsant clonazepam shows promise as an effective antimanic agent, at least for the initial phase of treatment. Chouinard and co-workers (1983; Chouinard, 1987) conducted double-blind crossover trials, one with lithium. Clonazepam, in daily doses ranging from 4 to 16 mg, was significantly more effective, with patients on clonazepam requiring less haloperidol to control agitation.[22] The specificity of the antimanic response to clonazepam remains unresolved, although the drug's sedative effects undoubtedly contribute to its efficacy.

Lorazepam

In a related finding, Modell and colleagues (1985; Modell, 1986) found that parenteral lorazepam 2 to 4 mg intramuscularly every 2 hours could be substituted for neuroleptics as an adjunct to lithium in the early phase of treating acute mania. In four cases, doses of 10 to 30 mg/day were used over the first 3 to 5 days to control manic agitation while lithium was being given. The response occurred after 1 week, a period similar to that of lithium–neuroleptic combinations, but side effects (e.g., extrapyramidal effects, delirium, akathisia) were fewer. This preliminary observation, coupled with the clonazepam and carbamazepine data, suggests that even patients in severe stage-III mania might be managed effectively without neuroleptic drugs.

Experimental Treatments

As noted in Chapters 15 and 17, pathophysiological theories of mania have focused primarily on disturbances in neurotransmitter function, especially the monoamines dopamine, norepinephrine, and serotonin. More recently, other transmitters have been considered, including those of the cholinergic, GABAergic, and endorphin systems. In this section, we briefly review experimental treatments developed to test various pathophysiological hypotheses.[23]

Serotonin-Related Drugs

Methysergide and *cinanserin,* drugs that block postsynaptic serotonin receptors, were tried therapeutically to test the old hypothesis that mania represented serotonin overactivity (Lapin and Oxenkrug, 1969). Two trials of methysergide (Dewhurst, 1968; Häskovec and Soucek, 1968) produced clear antimanic effects, particularly when given intramuscularly. These results could not be replicated in three controlled clinical trials using an oral preparation (Coppen et al., 1969; McCabe et al., 1970; Fieve et al., 1969), and no further trials have been conducted. Like methysergide, cinanserin was also noted to have antimanic properties (Itil et al., 1971; Kane, 1970), but these preliminary observations did not stimulate further clinical trials.

Para-chlorophenylalanine (PCPA), a potent inhibitor of central and peripheral serotonin synthesis both in animals (Koe and Weissman, 1966) and in humans (Goodwin and Post, 1972), was also used to test the hyperserotonin hypothesis of mania. In the human study, PCPA evidenced no specific antimanic effects at doses up to 4 g daily. No further trials of this drug have been conducted with manic patients, in part because of concern over such side effects as retroperitoneal fibrosis.

Table 21-4. Studies of Carbamazepine in Acute Mania

Study	N	Diagnosis	Design	Dose of CBZ (mg / day) (blood level)	Other Drugs	Duration	Results
Controlled Studies							
Okuma et al., 1979	30 CBZ 25 CZ	MD psychosis	Double blind	300-900 (2.7-11.7 µg/ml)	Bedtime hypnotics	3-5 wk	21/30 improved on CBZ 15/25 improved on CZ
Grossi et al., 1984	11 CBZ 15 CZ	MD	Double blind with CZ (150-800 mg/day)	300-1,600	Bedtime hypnotics	21 day	10/15 improved on CBZ; 13/15 improved on CZ
E. Klein et al., 1984	23	Excited psychoses[a]	Blind with PBO	600-1,600 (6-18 µg/ml)	HAL	5 wk	18/23 improved on CBZ + HAL
Müller & Stoll, 1984	6	MD	Blind with PBO	600-1,200	HAL+ hypnotics	3 wk	CBZ better than PBO (p <.01)
	10	MD	Blind with PBO (15-50 mg/day)	600-1,200 OXCBZ	HAL+ hypnotics	2 wk	OXCBZ = HAL
Emrich et al., 1985	7	Manic psychosis	Double blind with PBO	1,800-2,100 OXCBZ		variable	6/7 (>25% improvement on IMPS)
Brown et al., 1986	8	Manic	Double blind with HAL (20-80 mg/day)	400-1,600	CZ to 3 pts (only 1 after 2nd day)	42 day	5/8 marked improvement
Lenzi et al., 1986	11 CBZ 11 LI	MD or other	Blind with LI (900 mg/day) double PBO with CZ	1,200 (7-12 µg/ml)	CZ	3 wk	Equal efficacy in CBZ and LI groups; less CZ required in CBZ group
Desai et al., 1987	5	Manic	Blind with PBO in addition to LI	400 fixed dose		4 wk	CBZ + LI p <.05 better on BRMS than LI alone by 2nd week

Lerer et al., 1987	14 CBZ 14 LI	MD	Blind with LI (900 mg/day)	600 (8-12 µg/ml)		4 wk	11/14 improved on LI; 4/14 improved on CBZ
Post et al., 1987b	19	MD psychosis	Double blind	600-2,000 (7-15.5 µg/ml)		11-56 day	12/19 improved - time course similar to neuroleptics; frequent relapses on PBO substitution
Möller et al., 1989	10 CBZ + HAL 10 HAL	Manic or schizomanic	Double blind	600	levome-promazine	35 day	Compared to HAL alone, CBZ + HAL required significantly less supplemental neuroleptic
Summary	176[c]						71% improved[c]

Summary of open studies	Dose Range	Duration	
N = 331	200-1600[b] CBZ was coadministered with LI or neuroleptics in most studies (one study compared CBZ and CZ and reported that CZ was better)	1-26 mos	53% improved

Overall rate of moderate to marked improvement among 507 patients (controlled and open): 60%[c]

CBZ = carbamazepine, CZ = chlorpromazine, LI = lithium, PBO = placebo, HAL = haloperidol, OXCBZ = oxcarbazepine, IMPS = Inpatient Multidimensional Ratings Scale, BRMS = Bech - Rafaelsen Mania Scale, MD = manic-depressive

[a]11 excited manics, 7 excited schizoaffectives, 5 excited schizophrenics

[b]One study administered 2.1-3.06 mg of OXCBZ / day

[c]Does not include studies which did not give number of improved (Müller & Stoll, Lenzi, and Desai)

Adapted from Post & Uhde, 1988; Post et al., 1987b; and Strömgren & Boller, 1985

In contrast to the excess serotonin hypothesis, the idea that mania (and perhaps bipolar illness itself) may involve diminished functional activity of brain serotonin systems (Coppen et al., 1972; Prange et al., 1974; Kety, 1971) has had more staying power. Pharmacological evaluations of this deficiency hypothesis have involved a serotonin-receptor agonist, fenfluramine, and the amino-acid precursor of serotonin, L-tryptophan. The limited evidence on fenfluramine is equivocal, but the L-tryptophan results are encouraging. When oral doses of 1 to 4 g are accompanied by pyridoxine and niacin, L-tryptophan produces an increase in serotonin synthesis in the CNS (Dunner and Goodwin, 1972). However, further use of L-tryptophan will have to await resolution of a major problem that surfaced in 1989: More than 1,000 cases of eosinophilia myalgia syndrome (EMS) were linked to the ingestion of gram quantitites of L-tryptophan, and, as of this writing, it has been withdrawn from the market. This syndrome may depend on concomitant suppression of the HPA axis, as occurs, for example, with certain benzodiazepines (E. Sternberg, personal communication).

L-Tryptophan in the treatment of mania has been studied in four double-blind clinical trials: Three have had positive results (Prange et al., 1974; Murphy et al., 1974; Chouinard et al., 1985), and one had negative results (Chambers and Naylor, 1978). Prange and colleagues compared the amino acid to chlorpromazine and found it "slightly superior to CPZ in all regards," whereas the other studies compared L-tryptophan to placebo. Murphy and colleagues found that L-tryptophan was more effective against moderate than against severe manic symptoms.

One double-blind study assessed L-tryptophan as an adjunct to lithium in the treatment of mania (Brewerton and Reus, 1983). The amino acid was added to lithium or placebo in 16 bipolar or schizoaffective patients, who received concomitant neuroleptics as needed. Although the L-tryptophan and lithium combination produced significantly greater improvement, the results were confounded by the greater, although nonsignificant, doses of neuroleptics in the L-tryptophan group.

Taken together, the studies of L-tryptophan in mania are encouraging, especially those in which the drug was combined with another antimanic agent. Further studies are warranted if the EMS puzzle can be solved and as long as caution is paid to the finding that large doses can produce ultrastructural changes in the liver of rats (Trulson and Sampson, 1986). Also, in 1989, several hundred cases of eosinophilia were associated with L-tryptophan.

Catecholamine-Related Drugs

Pharmacological and biochemical data have suggested that the manic syndrome reflects increased function of catecholamines, such as norepinephrine and dopamine. *α-Methylparatyrosine* (AMPT) is a potent and specific inhibitor of dopamine and norepinephrine synthesis, centrally as well as peripherally. When Brodie and colleagues (1971) gave AMPT to seven patients hospitalized for mania, five showed a significant drop in mania ratings. Two of the five responders relapsed after the drug was discontinued; they subsequently improved when AMPT was started again. AMPT responders showed changes in manic thinking and behavior that seemed more specific than the sedative effects observed with large doses of barbiturates or phenothiazines. Nevertheless, sedative effects were more pronounced with AMPT than with lithium, and overall, its antimanic effects appeared to be somewhat less specific than with lithium.

AMPT does not differentiate between norepinephrine and dopamine, since the synthesis of both depends on tyrosine hydroxylase, the enzyme inhibited by AMPT. The enzyme that converts dopamine to norepinephrine and exists only in norepinephrine neurons is dopamine β-hydroxylase (DBH). Goodwin and Sack (1974), in a trial of a DBH inhibitor, fusaric acid, evaluated how manic patients are affected clinically when norepinephrine but not dopamine is decreased. They found that although these amine changes were in fact produced, as validated by the changes observed in CSF amine metabolites, fusaric acid had only a slight antimanic effect in hypomanic patients. In those with more severe mania, including psychotic features, DBH inhibition worsened their condition, shifting manic symptoms from more purely affective to schizoaffective.

Reserpine, a drug that depletes neuronal stores of amines (see Chapter 17), was used as an antipsychotic before the development of chlor-

promazine. Bacher and Lewis (1979) and Telner and colleagues (1986) reported their clinical observations of manic or schizoaffective-manic patients who did not respond to lithium combined with unspecified neuroleptics. Most patients responded quite favorably to a combination of lithium and reserpine (average dose of 5 mg/day intramuscularly). This combination, rarely tried for lithium-resistant mania, merits further consideration.

Another way to test the hypothesis that elevated noradrenergic activity produces mania is to administer *propranolol* or related drugs that block the postsynaptic β-receptor for norepinephrine. Several studies in manic patients (Von Zerssen, 1976; Volk et al., 1972; Möller et al., 1979) demonstrated some improvement. Since one form of the drug, the D-isomer, which does not block the β-receptor, still had some clinical effect (Möller et al., 1979), it is possible that it acts partly by other mechanisms. From a clinical perspective, although the effects of propranolol seem to go beyond sedation or tranquilization, they require very high doses (in the range of 800 to 2,000 mg a day), which produce substantial side effects, such as hypotension and bradycardia; therefore this approach remains primarily of theoretical interest.

Clonidine is a drug that reduces the presynaptic release of norepinephrine by a direct agonist action on the inhibitory presynaptic α_2-adrenergic receptor. It has been found to have antimanic effects in several open trials and case reports in doses ranging from 0.2 to 1.2 mg/day.[24] Three double-blind studies (Giannini et al., 1983, 1986; Janicak et al., 1988b) have not been as encouraging, however, and even suggested that the drug might increase depression. Nonetheless, clonidine deserves further exploration, since its clinical effects occur at doses that do not produce debilitating hypotensive or sedative effects.

Catecholamine Agonists. Drugs that are presumably stimulatory (agonistic) to norepinephrine or dopamine systems have been reported to have paradoxical antimanic effects. Beckmann and Heinemann (1976) observed substantial suppression of the euphoric symptoms of mania (but not the aggressive symptoms) following intravenous *amphetamine,* whereas Brown and Mueller (1979) and Garvey and colleagues (1987) reported similar beneficial effects of oral amphetamine (45 to 60 mg/day). Decreased manic symptoms were also reported after *methylphenidate,* administered both intravenously (Janowsky et al., 1973a) and orally (Brown and Mueller, 1979). These investigators also noted antimanic effects of oral L-dopa, a catecholamine precursor, and of *apomorphine,* a dopamine-receptor stimulant.

In a controlled study, Post and co-workers (1978) noted antimanic effects of low doses of another dopamine-receptor stimulant, *piribedil.* In a preliminary double-blind controlled study, however, Smith and colleagues (1980) found no antimanic effects with *bromocriptine,* a dopamine agonist with pharmacological effects similar to those of piribedil.

In 1962, Akimoto, a Japanese investigator, and his colleagues, reported the antimanic effects of large doses of the tricyclic antidepressants *imipramine* and *amitriptyline.* This finding, potentially the most interesting from a clinical viewpoint since it involves widely available drugs, was not verified by Klein (1967), however. The notion that drugs of the same class can both precipitate and alleviate mania seems counterintuitive. The nature of the effect, however, may depend on when in the natural cycle of the illness the drug is administered. A drug that accelerates or drives the underlying cycle might be expected to hasten the arrival of the next phase so that, when given during mania, it might bring on depression. These issues are discussed more thoroughly in Chapters 19 and 20.

Cholinergic Drugs

Neurobiological theories of affective disorder have evolved in recent years from models focusing on single transmitters to ones that consider how two or more transmitter systems are interrelated. Trials of the serotonin precursor L-tryptophan in both mania and depression, for example, were based on the permissive hypothesis that a serotonin deficiency underlies the vulnerability to both conditions. Studies of the therapeutic potential of cholinergic agents in mania evolved from the theory that mood regulation involves, in part, a balance between the adrenergic and cholinergic systems, the former subserving excitation and arousal, the latter, inhibition. According to this hypothesis, depression involves relative cholinergic predominance, whereas mania involves adrenergic predominance.

Physostigmine, a reversible, centrally active acetylcholinesterase inhibitor, enhances cholinergic function by interfering with its degradation. The first controlled study of physostigmine in mania was conducted by Janowsky and colleagues (1973b) in eight manic patients, two of whom also had schizophrenic symptoms. Pretreatment with methscopolamine, a peripherally active anticholinergic agent, partially blocked physostigmine's peripheral cholinergic effects. Physostigmine was administered intravenously (in doses up to 3 mg). Neostigmine, a potent cholinesterase inhibitor that essentially does not penetrate the brain, was used as an active placebo in six patients. Both drugs were administered through a continuous intravenous tube, and both were alternated with placebo.

In all eight patients, manic symptoms, assessed by the NIMH Beigel-Murphy mania scale (1971), diminished after physostigmine but not after the active or inactive placebos. A parallel increase in depression was seen in some patients. The antimanic effect began to appear within 15 minutes and, with repeated infusions, was substantial within an hour. Scaled reduction in individual manic symptoms ranged from 48 to 78 percent. The drug also produced a generally retarded, inhibited, and somewhat organic state in the patients, an observation that has led to questions about the specificity of its antimanic action. Two subsequent studies (Shopsin et al., 1975b; Davis et al., 1978) confirmed the original observations. Although a research tool of some interest, physostigmine is not likely to become a clinically useful alternative in the management of acute mania.

Cohen and co-workers (1980, 1982) also attempted to enhance cholinergic function in mania in a double-blind study. They gave six manic patients, who were already being treated with either lithium or neuroleptic, large amounts of *lecithin*, the dietary precursor of choline, which is in turn the precursor of acetylcholine. Five of the six improved rapidly, and three of them relapsed when the preparation was withdrawn. This observation could be of some clinical relevance, since no toxic effects were observed, but it still awaits confirmation.

Other Experimental Drugs

The following agents also have been employed in the evaluation of various hypotheses of mania.

Findings of alterations in serum and CSF calcium in mania (see Chapter 17) led Carman and Wyatt (1979) to administer synthetic *calcitonin*, a peptide hormone that lowers serum calcium, to 12 hospitalized patients with "psychotic agitation or mania." They reported an overall depressant or tranquilizing effect, which did not, however, appear to be a specific antimanic response.

Several studies using a theoretically related treatment strategy have suggested that the calcium-channel blockers, such as *verapamil* (160 to 240 mg/day), have antimanic effects (Dubovsky et al., 1982, 1985; Dubovsky and Franks, 1983). In a controlled study of manic inpatients, Höschl and Kozeny (1989) showed that verapamil was as effective as neuroleptics alone or a neuroleptic–lithium combination, without producing the sedative, hypnotic, or cataleptic effects associated with neuroleptics. Although an open study of verapamil was negative (Barton and Gitlin, 1987) and a controlled trial in 10 acutely manic patients (Emrich et al., 1983) yielded only modest results, other calcium-channel blockers deserve additional study as adjunctive agents in the treatment of mania. The need for additional data is highlighted by the fact that these clinically available drugs are now being rather widely used for mania by clinicians in practice.

In an open preliminary trial, Caillard (1985) administered the calcium antagonist *diltiazem* to five manic patients with bipolar illness and two patients with organic manic syndrome (some had additional neuroleptics). The five bipolar patients showed significant clinical improvement within 14 days (although three briefly required additional neuroleptics for extreme agitation), although the two patients with organic manic syndrome did not. Side effects were minimal. Calcium-channel blockers highly selective for the CNS are being developed. These drugs (e.g., nimodipine) will be of great interest as potential antimanic agents.

The opiate antagonist *naloxone* has been evaluated for antimanic effects. Reasoning from a very rough analogy between the euphoria seen in some stages of mania and the euphoriant effect of opiates, Janowsky and colleagues (1978) tested a daily dose of 20 mg of intravenous naloxone and found that it had an antimanic action, with the

most dramatic effect seen in the most manic patients. However, Emrich and his colleagues (1979) saw no antimanic effect in two patients, one of whom had an exacerbation. Similarly, Davis and colleagues (1980) were unable to observe any antimanic effects following 20 mg of naloxone administered subcutaneously (Davis et al., 1980). These negative results were later replicated in a well-controlled double-blind, placebo crossover study of 25 manic patients (Pickar et al., 1982). Unlike Janowsky's patients, those in the two NIMH studies (Davis; Pickar) were able to remain in the normal ward environment during the trials, since the drug was given subcutaneously rather than intravenously.

The ability of the tetracycline-like antibiotic *demeclocycline* to inhibit adenylcyclase has led to the proposal that such drugs, by inhibiting this postsynaptic second messenger involved in a variety of neurotransmitter-mediated functions, might have antimanic properties. However, the one trial so far with this antibiotic has been negative.

Because of indirect indications that abnormalities in the Na^+-ATPase may underlie mania, Naylor and colleagues (1975) administered *digoxin,* an inhibitor of this enzyme, to mania patients but without effect. Conversely, treatments designed to correct a hypothesized deficiency of ATPase activity by reducing levels of an endogenous ATPase inhibitor, *vanadium,* have been reported as successful in mania. Since all of these reports (involving ascorbic acid, methylene blue, and low vanadium diets) originate from a single group (Naylor, 1983; Naylor et al., 1988), independent replication will be important.

Electroconvulsive Therapy

After ECT was introduced as a therapeutic modality in the early 1940s, there were several clinical reports of its efficacy in treating acute mania. As reviewed by Fink (1979, 1987), these early uncontrolled studies generally cited response rates of 65 to 75 percent but provided little or no systematic data on the characteristics of the patients or their responses to ECT. Later, as the efficacy of drugs became established, the use of ECT in mania virtually ceased. It remains today a treatment alternative that is, perhaps unfortunately, used only occasionally. In his 1979 and 1987 reviews, Fink pointed to the virtual absence of valid information on the efficacy of ECT in mania compared with drugs. In their 1987 naturalistic study of 438 manic patients, however, Black and colleagues attempted to answer this question directly. They found that a significantly greater proportion of the patients showed a "marked" response to ECT than to adequate lithium treatment—78 percent compared with 62 percent ($p < 0.05$).[25] This finding recently has been supported by a randomized double-blind trial in which ECT was found to be superior to lithium during the first 8 weeks, especially for severely manic patients and those with mixed states (Small et al., 1988). McCabe and Norris (1977) directly compared ECT, chlorpromazine, and no treatment in hospitalized manic patients and found that both active treatments were superior to no treatment. The advantage of ECT when mania is complicated by pregnancy has already been noted.

Clinical Predictors of Antimanic Response

We now turn to the clinical prediction of response to various antimanic agents, a problem implicit in the foregoing review of the literature on treatment efficacy but here brought into focus. Many of these issues were introduced in Chapter 17 in the discussion of biological and pharmacological correlates of treatment response.

One problem confounding attempts to evaluate predictors of antimanic response is the variability of treatment response in the same patient from one episode to the next (Stokes et al., 1971). This tendency may reflect the influence of state variables, such as the severity of the episode or the point in the natural course of the episode when treatment is initiated. A second problem, noted in our earlier discussion of the response to lithium among patients with pure mania as opposed to those with schizoaffective mania, is that an apparent differential response may actually reflect a difference in the time needed to achieve it (see Goodnick and Meltzer, 1984). A third problem concerns research design. For example, schizoaffective manic patients undergoing a controlled trial of lithium who happen to require a brief period of neuroleptics to control hyperactivity or psychoses are sometimes dropped from the study (see, e.g., Prien et al., 1972), making the response rate for lithium appear worse than it might otherwise be (Carroll, 1979).

Despite these difficulties, it is possible to delineate clinical features that correlate with response. In some cases, they simply reflect the features of the most responsive diagnostic group, bipolar illness. In others, they describe the characteristics of a subgroup within the bipolar diagnostic category that might be preferentially responsive (or unresponsive) to a particular treatment—for example, patients with rapid cycles responding to anticonvulsants. A third possibility is that they reflect personality or other variables that are independent of bipolar illness but that nevertheless bear on treatment response—for example, personality attributes that contribute to poor compliance or the presence of drug abuse or alcoholism. The relationship between personality variables and lithium response is discussed in Chapter 12 (see especially Table 12-9).

Factors that stand out as predictors of a poor acute antimanic response to lithium are the presence of a mixed state, substance abuse, and a history of rapid cycles (see Table 21-5 for a summary of the literature).[26] As we have seen, mixed states are quite common, characterizing approximately 40 percent of manic episodes. As discussed in Chapter 9, the alcohol and drug abuse frequently associated with mixed states may represent the patient's attempt to achieve symptomatic relief from the intensely dysphoric wired feeling state.

Clinical variables associated with the acute antimanic response to carbamazepine are summarized in Table 21-6 (Post et al., 1986). Many of the features that predict poor response to lithium appear to predict good response to the anticonvulsant. Although preliminary, these data are consistent with suggestions that carbama-

Table 21-5. Clinical Predictors of Antimanic Response to Lithium

Patient Characteristics	Prediction
Demographic	
Age	None
Sex	None, but lower compliance rates in males (Chapter 25)
Marital status	Not known
Clinical	
Diagnosis	Some note poorer response for schizomania, others do not (Goodnick & Meltzer, 1984); slower response in this group accounts for the difference
Family history	Not reported for antimanic response
Age of onset	None
Duration of illness	None
Severity of mania	More severe symptoms predict poorer response (Prien et al., 1972; Swann et al., 1986) but time to response may be important variable
"Reactive" mania	Less likely to respond (Aronoff & Epstein, 1970; Jones & Wilson, 1972)
Mixed manic and depressive symptoms	Poorer response (Swann et al., 1986; Himmelhoch et al., 1976a)
Predominance of paranoid over elated / grandiose symptoms	Poorer response in one study (Murphy & Biegel, 1974) but not another (Swann et al., 1986)
Rapid cycles	Poor response (Dunner & Fieve, 1974; Post et al., 1986d)
Initial response	Poor response in the first week predicts poor outcome at 3-1/2 weeks (Swann et al., 1986); early dropouts (due to personality factors?) may or may not have been responsive (Taylor & Abrams, 1981b)
Drug abuse	Poor response (Himmelhoch et al., 1976a)

Table 21-6. Clinical Predictors of Antimanic Response to Carbamazepine

Patient Characteristics	Prediction
Severity of mania	Responders significantly more ill
Mixed manic or depressive symptoms	Responders tended to be more dysphoric
Rapid cycles	Responders had significantly more episodes in year prior to trial
Family history of bipolar illness	Responders had significantly less family history

From Post et al., 1986d

zepine, and perhaps also valproate, may be especially useful in patients who have responded poorly to lithium.

SUMMARY

The choice of medical treatment for acute manic episodes should be based primarily on the nature and severity of the symptoms. Lithium, the most specific antimanic drug, remains the treatment of choice. Because sleep deprivation can contribute to the progression of the manic syndrome, it may be wise to use clonazepam, which has sedative properties, in addition to lithium early in treatment. When symptoms are more severe, the urgency of achieving behavioral control often requires that lithium be supplemented with neuroleptics (briefly) or with the anticonvulsants carbamazepine, valproate, or clonazepam. The anticonvulsants may be the treatment of choice for patients with rapid cycles or a prior history of lithium failure or intolerance to it. Whether the anticonvulsants are preferable for patients with mixed states remains to be seen.

Fully developed psychotic mania usually requires hospitalization. The possible stigma that may result should be weighed against the sometimes rapid progression of mania into a condition that is even more dangerous for the patient.

Children and adolescents also suffer from mania, and their treatment is similar to that for adults. Early recognition and treatment are imperative to minimize lifelong psychological, social, and possibly biological consequences.

NOTES

1. Cited in Hamilton, 1982, p. 285.
2. The appropriateness or the legality of prescribing drugs for uses other than those listed in their official labeling is sometimes a cause of concern and confusion. The Federal Food, Drug, and Cosmetic Act does not, however, limit a physician's use of an approved drug. The *FDA Drug Bulletin* clarifies the issue as follows:

   > Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature. . . . accepted medical practice often includes drug use that is not reflected in approved drug labeling. (*FDA Drug Bulletin*, 12(1):4–5, 1982).
3. One high-potency neuroleptic, clozapine, has a low incidence of extrapyramidal effects and may be effective among neuroleptic-resistant patients. It is discussed later in the literature review section.
4. The concurrent use of neuroleptics and lithium has been reported to result in lethargy, tremulousness, severe neuromuscular symptoms, hyperthermia, impaired consciousness, and even irreversible brain damage (Cohen and Cohen, 1974; Goldney and Spence, 1986).

   Neuroleptic malignant syndrome is an uncommon reaction to neuroleptic medications, especially those with high potency (e.g., haloperidol). First identified in 1960 by French psychiatrists (Delay and Deniker, 1968), it is characterized by muscular rigidity, extremely high fever, autonomic dysfunction, and altered consciousness (Levenson, 1985). Although its pathogenesis is not understood, disturbances in the hypothalamic–adrenal axis have been hypothesized (Horn et al., 1988).
5. These issues are discussed further in relation to prophylactic treatment, in Chapter 23.
6. A potential complication of using clonazepam for mania is the emergence of depression early in treatment. The effect may depend on dose (Cohen and Rosenbaum, 1987).
7. In addition to the needs of the clinical setting, ethical considerations argue for early vigorous treatment of mania.
8. Psychiatrists treating manic-depressive patients

should be sufficiently knowledgeable about relevant medical issues to work closely with internists and other specialists. Patients are not well served when they are simply turned over to the nonpsychiatric specialist. For many issues—the subtle CNS effects of mild hypothyroidism, for example—the psychiatrist should provide the expertise for the collaborative management of the patient.

9. The interaction of lithium with dopamine systems has also been put to therapeutic use in managing the on–off phenomenon that complicates the use of L-dopa in Parkinson's disease.
10. In treating schizophrenia, a 20:1 chlorpromazine /haloperidol dose ratio has generally been used. However, recent data suggest that in mania a ratio of approximately 13:1 is more appropriate (Janicak et al., 1988a). A similar ratio applies when comparing other neuroleptics with low potency to those with high potencies.
11. Administering a loading dose means to start with a super maximal dose rather than building up to the usual therapeutic dose.
12. Baastrup et al., 1976; Juhl et al., 1977; Krishna et al., 1978; Garfinkel et al., 1980; Carman et al., 1981; Perényi et al., 1983; Goldney and Spence, 1986; Miller and Menninger, 1987.
13. For example, Miller and Menninger (1987) found neurotoxicity in 6 of 22 manic patients (27 percent) on a lithium–neuroleptic combination. The average neuroleptic dose was 563 mg (chlorpromazine equivalents) in the nontoxic group vs 1,780 mg in the toxic group, whereas lithium doses were not different.
14. See, for example, Trimble, 1981; Pisciotta, 1982; Hart and Easton, 1982; Tompson, 1984; Post et al., 1987.
15. Even ECT has been used successfully in the treatment of mania in children (see, e.g., Carr et al., 1983).
16. In psychopharmacology, nonblind studies such as these are often dismissed as essentially meaningless. In the case of mania, however, they can be informative, since clinical experience suggests that patients with this major psychotic illness are not responsive to the subtle environmental and interpersonal factors that contribute to high placebo response rates.

    A greater difficulty in interpreting these open trials derives from the fact that mania is cyclic and, even without treatment, will generally remit spontaneously. It is unusual, however, for spontaneous remission to occur during any given period of 2 weeks. Thus, the disappearance of manic symptoms observed during lithium therapy in most patients was probably a real effect of treatment, not the result of spontaneous remission or a placebo effect.
17. In a double-blind study, for example, DeLong and Nieman (1983) studied 11 children who met DSM-III criteria for manic episodes. Given lithium alone and placebo alternately for 3 weeks each, they improved when on the lithium, as rated from parental reports.
18. Reviewed in Youngerman and Canino, 1978; Jefferson, 1982; Campbell et al., 1984.
19. The adolescents with prepubertal onset of behavioral pathology (before age 12) had significantly more first-degree relatives with bipolar-I illness. Strober and colleagues speculate that, despite reservations about the validity of some parental recollections of their children's early behavior, it is possible to hypothesize that the early-onset pathology represents very early, subacute expressions of a bipolar genotype, which may be more severe than adolescent-onset disorder. The investigators note, however, that lithium maintenance treatment is usually found to be more effective in patients with positive family history of bipolar illness. Their findings suggest, by contrast, that lithium response in the acute treatment of manic episodes in adolescents may be negatively correlated with family history of bipolar illness.
20. The children were diagnosed by RDC using the Schedule for Affective Disorders and Schizophrenia at admission and discharge, as well as ongoing review of the course of symptoms during hospitalization and previous medical records. Semistructured interviews were also done with parents to obtain qualitative information on the adolescents' childhood—the Schedule for Affective Disorders and Schizophrenia for School-Age Children and the Psychosocial Schedule for School-Age Children.

    The children were first administered lithium carbonate (titrated to achieve plasma levels of 0.9 to 1.5 mEq/liter), as well as neuroleptic drugs as needed to control agitation and psychotic symptoms. Those who failed to respond satisfactorily in the first 4 to 6 weeks were also administered carbamazepine.
21. The demonstrated effectiveness of clozapine in schizophrenic patients who have responded poorly to neuroleptic drugs (Kane et al., 1988) is one of the most significant recent developments in the pharmacotherapy of serious mental illness. The drug is a prototype of antipsychotic neuroleptics called *atypical* because they produce little or no extrapyramidal side effects, selectively block some dopamine receptors (e.g., mesolimbic > nigrostriatal), or broadly affect other CNS neurotransmitter systems (e.g., antiserotonergic, antiadrenergic properties) (see Meltzer, in press). Although the use of clozapine in patients with bipolar illness has yet to be systematically examined, pilot data from intramural NIMH researchers suggest that it may be superior to typical neuroleptics in reducing persistent psychotic symptomatology in schizoaffective patients (D. Pickar, personal communication). Further, it is emerging as the neuroleptic of choice for patients who have tardive dyskinesia. The significant risk of agranulocytosis

(approximately 1 percent), however, limits its use to treatment-resistant psychotic patients, those who poorly tolerate extrapyramidal side effects of conventional neuroleptics, or those with tardive dyskinesia.

22. Subsequent case reports (Victor et al., 1984; Freinhar and Alvarez, 1985) documented clonazepam's antimanic efficacy when given alone in both bipolar and schizoaffective patients. Others showed an accompanying disinhibition of behavior (Binder, 1987).
23. In this context *experimental* simply means that the treatment is not currently considered to be part of the ordinary clinical armamentarium. The anticonvulsants are considered along with the standard drugs because they are widely used in practice.
24. Jouvent et al., 1980; Jimerson et al., 1980; Zubenko et al., 1984; Hardy et al., 1986; Maguire, 1987; Kontaxakis et al., 1989.
25. Whether the ECT treatment of mania requires bilateral electrode placement is controversial. In the study of Black and colleagues (1987), unilateral ECT was found to be as effective as bilateral. This is an important issue, since unilateral treatment is associated with a lower residue of memory impairment.
26. The study of Taylor and Abrams (1981) is cited frequently, albeit incorrectly, as having failed to find a variety of clinical variables associated with lithium response. Actually, this was a retrospective study of outcome in manic inpatients treated by physicians' choice. Of the 111 patients, only 14 received lithium alone. The others were treated either with lithium plus neuroleptics, neuroleptics alone, or ECT. Obviously, no conclusions should be drawn concerning treatment response prediction, since the individual clinicians may already have given different treatments to patients with different clinical profiles.

23

Maintenance Medical Treatment

He [Robert Lowell] showed me the bottle of lithium capsules. Another medical gift from Copenhagen. Had I heard what his trouble was? "Salt deficiency." This had been the first year in eighteen he hadn't had an [manic] attack. There'd been fourteen or fifteen of them over the past eighteen years. Frightful humiliation and waste. He'd been all set to taxi up to Riverdale five times a week at $50 a session. . . . His face seemed smoother, the weight of distress-attacks and anticipation both gone.

—Richard Stern[1]

Preventing new episodes of manic-depressive illness has been an ambition of clinical investigators since they first recognized the inherently recurrent nature of the illness. In the middle of this century, the pursuit led many clinicians to undertake intensive psychotherapy, without much success. Others tried maintenance electroconvulsive therapy and considered it modestly effective. It was finally pharmacology, however, that provided the realization of that long-standing ambition. The development of lithium as an effective prophylactic treatment for manic-depressive illness, one of the most important advances in modern psychiatry, fundamentally altered both the prognosis for patients and the concepts of the disorder. The widespread clinical acceptance of lithium in treating and preventing manic-depressive illness is indicated by estimates that several years ago in Scandinavia, Great Britain, and the United States 1 of every 750 to 1,000 persons was being treated with this drug (Schou, 1981, 1989).

In the first part of this chapter, we provide practical guidelines for the long-term prophylactic treatment of manic-depressive illness. These guidelines cover the complex issues of patient selection for maintenance treatment, the problem of breakthrough episodes, the question of long-term side effects, and the increasingly important topic of alternative prophylactic strategies, including the use of carbamazepine and other anticonvulsants. Although bipolar illness is our main focus, we also review the prophylaxis of recurrent unipolar depression to emphasize the relationship between these two forms of affective illness. As noted throughout this book, classically the concept of manic-depressive illness included both bipolar and recurrent unipolar forms; in contemporary usage, however, *manic-depressive illness* is too often assumed to represent only the bipolar form.

The second part of the chapter examines the relevant research literature, emphasizing studies of treatment efficacy, predictors of response, and the important issue of the effects of long-term treatments on organ systems. We also discuss more recent efforts to assess the effect of lithium prophylaxis on long-term outcome in bipolar disorder. Some of the studies examining this issue tracked the course of illness in patients maintained on prophylactic lithium for 10 to 15 years, whereas others approached the question indirectly by scrutinizing changes in hospital admissions for mania since lithium was introduced.

Lithium prophylaxis was first described in 1951 by Noack and Trautner, who observed that the drug appeared to prevent additional manic episodes in patients whose acute mania had been

alleviated by it. In 1954, Schou and colleagues provided the first case report demonstrating the benefits of lithium for both manic and depressive episodes. The 10 to 12 episodes a year that Schou's patient had experienced before treatment were markedly attenuated in duration and severity after 2 years of taking lithium continuously.[2]

Schou and associates were not encouraged by their early and brief attempts to treat depression with lithium. They continued to explore the drug's potential as an antimanic agent but did not systematically investigate its prophylactic effects. In 1959, Hartigan (the first to refer to lithium treatment as prophylaxis, published in 1963) and, later, Baastrup (1964) independently observed that bipolar patients treated with lithium for mania reported substantially fewer depressive episodes, as well as manic ones, during follow-up. Reviewing these early reports in 1973, Schou noted that neither Hartigan nor Baastrup had expected lithium to ameliorate depression and were initially reluctant to believe their own observations. Schou concluded that their skepticism made the findings all the more credible.

CLINICAL GUIDELINES

Most bipolar patients are maintained on lithium alone or in combination with other drugs. The following general guidelines, although emphasizing lithium, apply to alternative prophylactic drugs as well.

Selection of Patients for Maintenance Treatment

Before beginning treatment of an acute episode of illness with a drug such as lithium, the clinician should have already weighed the potential for medical complications and tested the patient's ability to tolerate the drug. Often the decision to embark on the maintenance treatment phase comes after the patient has already received the drug for the treatment of an episode. These acute and continuation phases of treatment allow for ongoing evaluation of side effects, functioning between episodes, and psychological reactions.

Even though most bipolar patients eventually experience recurrences frequently enough to justify prophylactic treatment, not all patients should be placed on maintenance treatment at the first sign of the illness. The clinician and the patient together must weigh the overwhelming likelihood of a relapse, keeping in mind that the natural recurrences of bipolar illness tend to become more frequent as the illness progresses, at least up to the point where the relapse frequency becomes constant or the disease chronic. Restructuring a patient's history into a life chart can be useful in determining the need for prophylactic treatment. One example of such a chart is illustrated in Figure 23-1.

Criteria for patient selection usually involve the type, frequency, total number, and severity of prior episodes. Bipolar or unipolar patients who experience episodes requiring hospitalization every year or two clearly need prophylactic treatment. Studies reviewed later demonstrate that such patients have a very high relapse rate, averaging 73 percent within the first year, when treated only with placebo (Schou, 1979). As discussed in Chapter 6, relapses also may follow catastrophic life events in some patients (Aronson and Shukla, 1987).

The need for prophylaxis is less obvious in patients with lower relapse rates. Naturalistic observation of 95 bipolar patients over many years led Angst (1981) and Grof and colleagues (1979a) to the conclusion that a total of two previous episodes is the best minimum criterion for lithium prophylaxis. If more stringent criteria were set, a substantial number of patients would be deprived of prophylaxis and would relapse. Considering the relative safety of long-term lithium treatment and the devastation caused by bipolar illness, treating some patients during a period when they would not relapse seems preferable to excluding from treatment many patients who would otherwise relapse quickly. If the criteria were more rigid—two episodes in 2 years, for example—two thirds of the patients excluded from lithium maintenance would relapse within 2 years. Zarin and Pass (1987) have proposed a quantitative model for deciding whether to initiate lithium after the first manic episode. Applying their model to the available literature, they estimate that approximately 5 years of maintenance lithium is needed to avoid an additional episode. Waiting to start maintenance lithium until the patient has already had a second episode requires 2 years of lithium to avoid a third episode.[3]

The wisdom of basing selection for prophylaxis on number rather than frequency of epi-

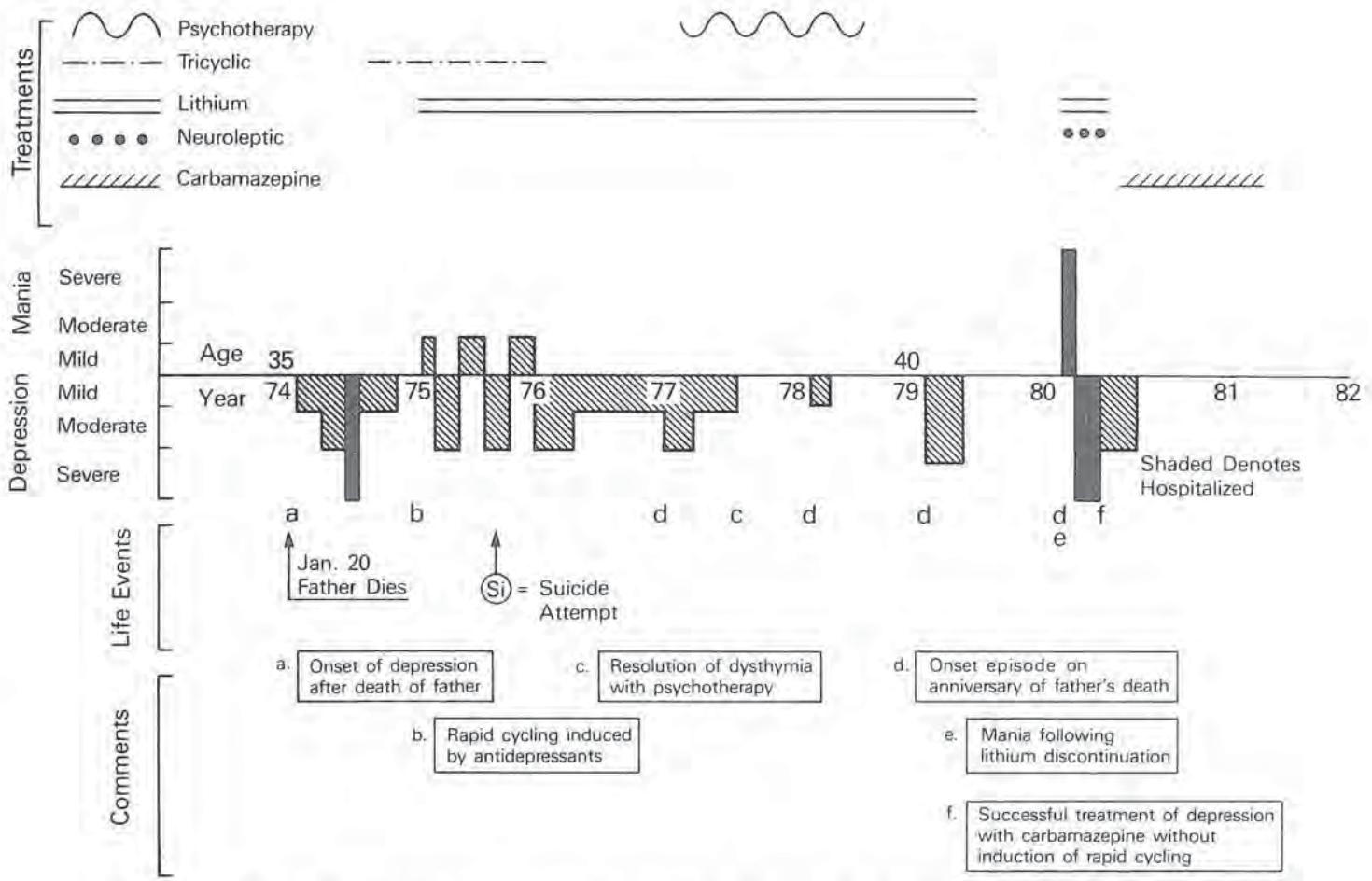

Figure 23-1. Graphing the course of affective illness. Prototype of a life chart (from Post, 1989).

sodes is underscored by the irregularity in the course of the illness, since episodes sometimes occur in bursts. Experienced clinicians do use other selection criteria, however. Many are so wary of the potential danger of future episodes that they initiate maintenance lithium after the first manic episode, even if it is the first episode of illness (NIMH/NIH Consensus Statement, 1985). In one study, for example, 57 percent of first-admission manic patients in Edinburgh were taking lithium at discharge (Mander, 1986).

It is now well established that episodes of bipolar affective illness tend to occur closer together as the illness progresses, particularly through the first several episodes. Some evidence suggests that the latency between the first and second episodes is longer in patients with an early age of onset (see Chapter 6). Women may thus be able to avoid taking lithium during their middle to late 20s, the prime childbearing years—an important advantage, given the drug's potential harm to a fetus in the first trimester.

On the other hand, the kindling models reviewed in Chapters 15 and 20 suggest that early treatment may reduce the long-term morbidity of the illness. Perhaps related to this is recent evidence from bipolar adolescents indicating a very high relapse rate among those who stop lithium prophylaxis after acute treatment for a manic episode (Strober et al., in press).[4]

Lithium prophylaxis is crucial when the patient is more vulnerable to mania than to depression. Since evidence suggests that a manic first episode may predict a course dominated by mania (Perris, 1968), early prophylaxis may be justified when the first episode is mania. Similarly, evidence of a higher ratio of manic to depressive episodes in men than women (see Chapter 6) implies that prophylaxis should start earlier in men (Mander, 1986).[5]

The rapidity of onset of previous episodes should also be considered when deciding whether to initiate maintenance treatment. Sudden onset of the prior manic episode provides a strong indication for prophylaxis, since there may be no warning period of hypomania during which treatment could be started.

A final illness characteristic to be considered is, of course, the severity of episodes. Obviously, when there is a history of psychotic mania, no real question exists. But what about severe cyclothymia? The literature on this question is thin. The effect of lithium on the hypomanic pole seems more clear, although it is more often the depressive phases that bring such patients into treatment (Peselow et al., 1980).

Individual patient characteristics also affect decisions about prophylaxis. Questions the clinician should consider include: How reliable is the patient in noting early signs and seeking early treatment? What is the risk of suicide? Is the patient likely to deny difficulty until it is too late? Does the patient have family help or other support systems available? Since a patient may not consider hypomania a problem requiring treatment, concerned family members may have to detect it early and persuade the patient to seek professional care (Jacobsen, 1965; Molnar et al., 1988).

Some clinicians advise taking into account extenuating circumstances that might have contributed to the first manic episode, such as high levels of psychosocial stress, physical illness, or drugs of abuse. This recommendation is based on the assumption that so-called precipitated manias represent less inherent vulnerability and, therefore, less need for prophylaxis. Although this supposition seems reasonable to us, it is not well documented by research.

In summary, although no set of guidelines can be applied uniformly to all patients, some general principles can be followed. For almost all bipolar patients, lithium maintenance is indicated after the second major episode. Prophylaxis should be considered earlier if the first episode is manic, the patient is male, onset is sudden or later than age 30, the episode(s) has been severe and disruptive and/or involved a high suicide risk, the episode was not precipitated by external factors, the patient has a poor family and social support system, and the patient is an adolescent, especially one with substantial genetic loading.

Pretreatment Evaluation

Pretreatment evaluation should emphasize contraindications that could mitigate against the use of lithium (see discussion in Chapter 21 and Table 21-1). Most, if not all, contraindications are relative rather than absolute and involve the three systems most likely to be adversely affected by lithium: the kidney, the cardiovascular system, and the CNS. The routine pretreatment laboratory evaluation is outlined in Table 23-1. Some con-

Table 23-1. Pretreatment Evaluation for Lithium Maintenance (Healthy Individuals Under Age 50)

Laboratory[a]
Minimum Recommendations:
BUN
Creatinine
T_4, Free T_4
TSH
Urinalysis including protein and microscopic examination
Additional Tests Recommended by Some Authorities:
24-hour urine volume
Creatinine clearance
Urine osmolality
T_3 resin uptake
Complete blood count
Electrolytes
EKG (over age 50)
Blood pressure (over age 50)
Clinical
Medical History Focusing on Renal, Thyroid, Cardiac, and Central Nervous Systems
Catalog of Present and Past Drug Use:
Prescription drugs
Over-the-counter preparations
Illicit drugs
Caffeine, nicotine, alcohol
Baseline Weight and History of Recent Weight Change
Dietary Habits, Including Estimate of Salt Intake
Exercise and Recreational Habits

[a]From Goodwin & Roy-Byrne, 1987

traindications may justify the use of alternative medications.

Monitoring of Maintenance Lithium

The Appropriate Lithium Level

The optimal blood level for maintenance lithium treatment generally is between 0.5 and 1.0 mEq/liter, the lower range being most appropriate in older patients. In earlier studies of prophylaxis, blood levels were maintained near the high end,[6] but a lower range more recently has become the accepted norm. Several studies indicate that, for patients stabilized on lithium for some time, a drop in prophylactic efficacy is unlikely to occur until blood levels fall below 0.6 mEq/liter (Jerram and McDonald, 1978; Hullin, 1980; Sashidharan et al., 1982; Maj et al., 1986; Goodnick et al., 1987). There are two random-assignment, double-blind prospective study that consider this issue: (1) Coppen and colleagues (1983) observed a significant decrease in affective morbidity among a group of bipolar and recurrent unipolar patients who had their maintenance lithium dose reduced, compared with those who did not.[7] (2) Gelenberg and colleagues (1989) randomly assigned 94 bipolar-I patients to either standard-dose lithium (dose adjusted to give 0.8–1.0 blood level, with group median of 0.83) or to low-dose lithium (dose adjusted to give 0.4–0.6 level, with group median of 0.54). The low-dose group showed a 2.6 times greater risk of relapse. These are group data, however, and individuals vary in their responses. Therefore, the best approach is to start with a blood level near the point at which side effects become troublesome and very gradually reduce it until side effects almost disappear completely or until 0.6 or 0.7 is reached. For older patients, however, a lower limit of 0.5 is not uncommon.

Fine-tuning the lithium dose is very important,

Table 23-2. Achieving 75-mg Increments of Lithium Using the 300-mg and 450-mg Dosage Forms

Dosage Level (mg)	Number of 300-mg Tablets[a]		Number of 450-mg Tablets[a]
150	–[a]		
225			1/2
300	1		
375	–[a]	&	1/2
450			1
525	1	&	1/2
600	2		
675			1+1/2
750	1	&	1
825	2	&	1/2
900	3	*or*	2
975	1	&	1+1/2
1,050	2	&	1
1,125			2+1/2
1,200[b]	4		
1,275	2	&	1+1/2
1,350			3
1,425	4	&	1/2
1,500[c]	5		

[a] 150 mg is available as a capsule or as 1/2 of a scored 300 mg pill

[b] Could also be one 300 mg and two 450 mg

[c] Could also be two 300 mg and two 450 mg

but it can require ingenuity, at least in the United States, where the drug (in tablet or capsule form) is available in only three strengths, 150, 300, and 450 mg of the carbonate salt (the last a sustained-release preparation). Table 23-2 illustrates how these strengths can be combined to provide increments of 75 mg. Lithium citrate in liquid form can be used for even finer tuning (1 ml = 60 mg of the carbonate salt), but many patients find the liquid inconvenient.

When maintenance treatment first begins, the frequency of blood level monitoring varies with the clinical situation. For the first several weeks, levels should be evaluated every week to determine the dose/blood level ratio for that patient. As noted in the discussion of acute treatment, the patient's clinical state, as well as a variety of other factors (sex, age, muscle mass, and diet), contribute to that ratio. Frequent monitoring during the initiation phase of maintenance treatment also helps establish compliance by emphasizing to the patient the importance of the blood level. Once the dose and blood level have been stabilized, most patients can be adequately managed by monitoring every 4 to 8 weeks during the first year or so and less frequently after that. Continuous monitoring remains important because unexpected medical conditions can alter the lithium level. Monitoring is also important for its psychological effects, since it reminds the patient of the illness and the importance of the medication, and it offers the patient an opportunity to participate in pharmacological management of the illness. Poor compliance is the most important factor limiting the prophylactic efficacy of lithium. For example, Baastrup (1969) estimated that 75 percent of his relapsing patients did so because of poor compliance. As discussed in Chapter 25, regular monitoring of blood levels is one important aspect of the psychological enhancement of compliance. Monitoring every 4 to 8 weeks indefinitely is, of course, not necessary for everyone. Some highly reliable patients who self-monitor side effects and who are aware of the factors that can alter lithium blood levels can be managed with less frequent monitoring.

Ever since lithium was introduced for treating manic-depressive illness, investigators have attempted to circumvent the need to draw blood by using alternative methods for monitoring lithium levels. The most promising is salivary monitoring, a method that is far easier to use with children, with adults with needle phobias, and in settings where needles are difficult to obtain. Although salivary monitoring has been widely studied, it has not generally been used in clinical settings (for a review of the subject, see Cooper, 1987). Concentrations of lithium in saliva, roughly twice as great as those in plasma, vary substantially from one individual to the next. Consequently the ratio of salivary levels to plasma levels must be established for each patient. Whether salivary levels more accurately reflect tissue levels is still unclear.

Several studies have suggested strategies by which the plasma level response to a single test dose of lithium might be used to predict the dose levels needed to produce the desired maintenance plasma level.[8] However, these approaches have not yet been applied generally in clinical practice.

Frequency of Other Laboratory Tests

Patients on lithium who do not show clinical indications of developing problems can be monitored according to the routine program summarized in Table 23-3. Authorities differ on the extent of minimum monitoring.

Special Circumstances

Both clinician and patient must be aware of circumstances that can affect lithium levels. Medical illness is probably the most common. The plasma lithium level can be elevated, for example, by even brief episodes of influenza severe enough to substantially reduce food (and therefore, salt) intake and produce changes in fluid balance. Distinguishing the early signs of lithium toxicity from symptoms of the medical illness itself can sometimes be difficult. One helpful clue is the prominence of CNS symptoms associated with lithium toxicity. If the illness persists for more than a few days, plasma lithium should be checked, and if it is accompanied by vomiting or diarrhea, plasma electrolytes should be measured.

Surgical Procedures. Surgical procedures that involve general anesthesia require attention, but there are no absolute contraindications to general anesthesia in patients on lithium. Two or three days before surgery, it is generally advisable to reduce the dose by half, withholding it altogether

Table 23-3. Medical Monitoring of Healthy Patients on Maintenance Lithium

Test	Frequency
Minimum recommendations	
Plasma lithium	4-8 weeks[a]
T_4, Free T_4, TSH	6 months
Creatinine[b]	6 months
Urinalysis	1 year
Additional recommendations by some authorities	
24-hour urine volume	6-12 months
Creatinine clearance	6-12 months
Urine osmolality	6-12 months
CBC	6-12 months
EKG (over age 50)	6-12 months
Special circumstances that can alter dose/blood level relationships	
• Medical illness, especially with diarrhea, vomiting, or anorexia	
• Surgery	
• Crash dieting	
• Strenuous exercise	
• Very hot climate	
• Advanced age	
• Pregnancy and delivery	

[a] This frequency can be reduced over time, especially with reliable patients

[b] Recently Schou (1989) has expressed his doubt that routine creatinine monitoring is still necessary, in light of the failure to find any decrease in glomerular filtration among his cohort of patients followed over a long period of time.

for 24 hours before the procedure. Lithium levels can be brought up to the therapeutic range as soon as the fluid and electrolyte balance is normalized, that is, after the patient is again taking nourishment by mouth. Lithium has been found to potentiate some anesthetics which has also been noted in a few case reports (reviewed in Jefferson et al., 1987), and patients on lithium have been noted to need less pain medication during postoperative recovery.

Diet. Alterations in diet can sometimes be the source of puzzling changes in the lithium level. Crash diets (i.e., severe weight-reducing efforts), undertaken without the physician's knowledge, are most frequently the cause. The bulk of daily salt intake comes from food, and severe dieting can cause sodium depletion, producing increased plasma lithium levels. Patients on diets should pay special attention to salt intake; more frequent plasma monitoring is also advisable.

Physical Activity. Major changes in physical activity can be important. For example, when a program of strenuous exercise, such as long-distance running, is started, care is required to maintain adequate hydration, replace lost electrolytes (especially sodium and potassium), and monitor lithium more closely. Clinical experience suggests that strenuous physical activity in hot climates may increase the risk of lithium intoxication, although not all experienced clinicians observe this effect. Two groups (Jefferson et al., 1982; Norman et al., 1987) report cases in which the selective excretion of lithium (over sodium) in the sweat during exercise actually produced a lower plasma lithium level. Whatever the real physiological effect of increased sweating on plasma lithium, it is probably advisable to monitor the lithium dose more closely.

Clinical State and Age. In some patients on a constant lithium dose, changes in the blood level can occur in association with major shifts in mood state (see Chapter 21 for a review of the literature). A shift into depression can be accompanied by an increase in plasma lithium, and a shift into hypomania can be associated with a decreased level.

Renal lithium clearance gradually decreases with age (Vestergaard and Schou, 1984), indicating that periodic dosage reduction will probably be necessary in the course of long-term lithium administration. One of the few groups that has studied lithium prophylaxis in the elderly (Hardy et al., 1987; Shulman et al., 1987) recommends a 12-hour serum lithium concentration of 0.5 mEq/liter or less, achieved at an average dose of 400 mg/day given in a single dose at bedtime.

Experience with lithium prophylaxis in adolescents and children dates back to its early use in adults, but the research is scattered and unsystematic. As noted in Chapter 21, the faster renal clearance in the young would predict a greater tolerance of the drug. Clinical reports substantiate this prediction. In general, dosages and serum levels should follow adult guidelines. As noted earlier, saliva monitoring may, in some conditions, serve as an alternative to plasma monitoring for children averse to having their blood drawn (see, e.g., Weller et al., 1987). Carbamazepine has also been used in manic-depressive children and adolescents, although

systematic studies are lacking (for a review, see Evans et al., 1987).

Pregnancy and Birth. The many issues involved in deciding whether a woman should be off lithium or on an alternative drug during pregnancy are discussed later in this chapter (see Table 23-7). Here we simply note that if lithium is to be used, peaks should be avoided by using divided doses, and plasma levels should be followed closely because the hormonal and physiological changes accompanying pregnancy can alter the dose/plasma level ratio. These changes are particularly profound during delivery and require a temporary dosage reduction of at least 50 percent, which is best accomplished by gradually stepping the dose down during the week before the due date. The full maintenance blood level should be reestablished as soon as possible after the delivery, as normal dietary intake resumes and fluid balance and electrolytes normalize. The prompt reestablishment of prophylactic lithium levels should substantially reduce the likelihood of postpartum mania. Although preventing postpartum depression may require a longer period of restabilization, this is largely offset by the longer lag after parturition before depression develops.

Management of Side Effects

Managing the side effects of lithium is as much a psychotherapeutic as a medical task. Even before lithium is prescribed, the physician should mention the type of side effects that can occur and reassure the patient about their meaning. Patients should regularly be encouraged to voice their concerns about the subject, especially since side effects often lead to poor compliance. (These issues are covered in depth in Chapters 24 and 25.) Here we are concerned with the medical aspects of managing side effects.

Although any side effect that intensifies with the dose should respond to a reduction in dose, such a course of action is not always wise, particularly if prior experience suggests that the risk of relapse is unacceptably high. Some patients may tolerate side effects after simple reassurance, but others may require supplemental treatment. Fine tremor, a common side effect of lithium, is one of the easiest to treat; if left untreated, it can contribute to poor compliance. Although reducing the blood level may help, the tremor often persists even at the minimum level needed for prophylaxis. β-Adrenergic receptor blockers, such as propranolol (10 to 80 mg/day), metoprolol (20 to 80 mg/day) or atenolol (50 mg/day) control lithium-induced tremor very effectively and, at modest dosage, are essentially without other effects. These drugs usually begin to reduce tremor within 30 minutes and continue to do so for 4 to 6 hours.[9] When other drugs with a potential for causing tremors (e.g., tricyclics, caffeine) are used with lithium, propranolol may be less effective.

Excessive polyuria, that is, lithium-induced nephrogenic diabetes insipidus (NDI), can occasionally become so severe that either the patient or the clinician stops the drug. In a patient who clearly needs lithium and whose problem is not alleviated by a reduction in dosage, two alternate strategies are available: The first involves addition of a diuretic, preferably a loop diuretic, such as furosemide, which is considerably safer than a thiazide in combination with lithium.[10] Amiloride, a potassium-conserving diuretic, has also been used to treat lithium-induced polyuria (for review, see Boton et al., 1987). The second strategy for managing polyuria is to substitute (completely or partially) carbamazepine for lithium, since the former does not antagonize the antidiuretic hormone. Carbamazepine will not reverse NDI in the presence of a continued high lithium level, but it may substantially decrease the need for lithium.

The antithyroid effects of lithium can and should be treated with supplemental thyroid when both laboratory and clinical evidence confirms hypothyroidism. Clinical manifestations may be limited to such nonspecific symptoms as lassitude, tiredness, weight gain, and decreased cognitive functioning. The use of adjunctive thyroid hormone as an experimental treatment for breakthrough depressions or for lithium-resistant cycling in the absence of chemical evidence of hypothyroidism is discussed later.

One of the most troublesome of the common side effects of lithium and one frequently associated with poor compliance is weight gain. We are not referring to the small amounts (less than 5 to 7 pounds) gained by most patients when they begin lithium therapy, much of which is probably due to fluid retention and can be expected to recede gradually. Instead, we are considering the

approximately 25 percent of patients who gain more than 10 pounds over and above what can be explained by fluid retention. Women, especially those who have had prior difficulty controlling their weight, are particularly likely to experience this weight gain. It must be managed early and vigorously, at first by restricting carbohydrates and encouraging regular exercise. Lithium treatment frequently produces a mild hypoglycemia-like pattern in which the patient will experience carbohydrate craving associated with low plasma glucose 2 to 3 hours after ingesting carbohydrates, especially sugar. Sometimes simply eliminating sugar-containing foods (such as orange juice at breakfast) can alleviate the midmorning or late-morning hunger that might otherwise contribute to the weight problem. Lithium-induced hypothyroidism, also associated with weight gain, can be corrected easily. Patients should also be warned not to increase their caloric intake inadvertently by using high-calorie drinks to quench lithium-induced thirst.

For patients who experience discrete periods of carbohydrate craving, either of two amino acids (L-glutamine or L-tryptophan) may prove to be helpful. L-Glutamine in doses of 500 to 1500 mg can suppress carbohydrate craving in some patients. If the time of the craving can be anticipated, the amino acid can be taken to prevent its onset. L-Tryptophan in similar doses may also suppress carbohydrate craving. Because of its sedative properties, it may be more useful for carbohydrate cravings that occur in the evening or at night. These two amino acids are available over the counter, although some preparations may be too impure to be useful. Two precautionary notes are necessary here. Instances of a switch into mania have been reported following large doses of L-glutamine, and large doses of L-tryptophan have recently been associated with a serious eosinophilia myalgia syndrome, causing its withdrawal from the market. Finally, we should note that although the above strategies can be helpful to some, weight gain remains a difficult problem for patients on lithium.

The management of lithium's effects on memory and cognition first involves reducing the dose to the lowest level consistent with effective prophylaxis. Since there is some evidence that increased CNS symptoms may be related to lower plasma levels of folate (Coppen and Abou-Saleh, 1982),[11] it is advisable to maintain all lithium-treated patients on a high-potency, multivitamin B preparation supplemented with 400 μg of folic acid. In our experience this strategy can attenuate the cognitive and memory side effects of lithium in some patients.

Treatment of Lithium Toxicity

Prevention is the most important principle in managing lithium toxicity or intoxication. By detecting early signs and adjusting dosages, the problem can be averted. The most sensitive indicator of incipient lithium toxicity is the CNS, perhaps particularly the cerebellum. Patients must be alerted in advance to CNS symptoms, and each encounter with the patient should include some assessment of CNS functioning. The agitation and restlessness of early intoxication are similar to symptoms of mixed affective states, and distinguishing between the two phenomena can be difficult. The signs of lithium intoxication are listed in Table 23-4.

If the intoxication is so severe that lithium withdrawal is not sufficient, the patient should be admitted to a hospital and cared for by a specialist in the treatment of poisoning. The first of several methods used to treat lithium poisoning (Table 23-4) is the vigorous application of general supportive measures appropriate in any CNS poisoning. Obviously, kidney function should be preserved by maintaining blood pressure and by replacing fluids and salt, but if it falters, hemodialysis is necessary. Although most patients recover after deliberately or accidentally overdosing on lithium, some are left with a persistent neurological or renal defect, and a few die. Because of these severe complications, the possibility of lithium intoxication should never be taken lightly. Patients with pre-existing vulnerabilities, particularly in kidney or CNS function, plainly require more careful monitoring.

Interaction of Lithium with Other Drugs

Surprisingly few problems are associated with the use of lithium in combination with other drugs. The major interactions are outlined in Table 23-5.

Psychoactive Drugs

Sedative hypnotics, as well as the benzodiazepines and other related minor tranquilizers, have no clinically significant interactions with lithium,

Table 23-4. Lithium Intoxication

Mild

Recurrence and/or intensification of a previously transient or mild side effect
- Difficulty concentrating, cognitive impairment
- Muscle weakness, heaviness of the limbs
- Irritability
- Nausea

Moderate
- Drowsiness, lassitude
- Dullness, disorientation, confusion
- Slurred or indistinct speech
- Blurred vision
- Unsteady gait
- Coarse hand tremor
- Restlessness
- Muscle twitches
- Lower jaw tremor
- Giddiness
- Vomiting

Severe

Intensification of any of the above
- Marked apathy, impaired consciousness, may progress to coma
- Ataxia
- Irregular hand tremor
- Prominent generalized muscle twitches
- Choreiform/parkinsonian movements

Neurotoxicity Treatment Guidelines[a]

- Withdraw lithium
- Obtain serum lithium, electrolyte, creatinine levels
- Carry out complete physical examination
- Increase lithium clearance by saline infusion in mild to moderate toxic reactions (plasma lithium < 3 mmol/liter)
- Closely monitor and maintain fluid and electrolyte balance
- Measure plasma lithium level at least every 12 hours
- Start renal hemodialysis (or peritoneal dialysis) **if**:
  - patient is comatose, in shock, severely dehydrated, **and/or if**
  - plasma lithium level ≥ 3 mmol/liter; **or if** patient fails to respond to 24 hours of conservative treatment, **or if** patient's condition deteriorates

[a]Adapted from G. Johnson, 1984

although the CNS depressant effects can be additive. The most widely studied interaction is that with neuroleptic drugs, particularly haloperidol. Studies discussed in Chapter 21 suggest that lithium and neuroleptics can be administered together safely as long as the clinician is aware of potential additive effects and uses the lowest effective doses of both drugs (Schou, 1989).

Lithium is quite compatible with tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and carbamazepine and other anticonvulsants, although some side effects may be additive. For example, patients on lithium plus carbamazepine may experience problems with cognition, memory, and alertness if full doses of both are used.[12] Lithium plus a tricyclic could theoretically have additive effects on cardiac conduction in susceptible individuals, and it is probably unwise to use this combination in patients with pre-existing severe or unstable cardiac conduction defects. This combination may exert additive and even synergistic effects on the production of tremors.

Nonpsychoactive Drugs

Some diuretics (especially the thiazides) can elevate serum lithium levels and produce toxicity, but, as discussed subsequently, this lithium–diuretic synergy can be used therapeutically in some patients. The effects of certain drugs (such as quinidine) on cardiac conduction could, at least theoretically, be potentiated by lithium. Some animal data suggest that lithium potentiates digitalis toxicity by lowering intracellular potassium, but whether this occurs in humans is not clear. What is clear is that the combination of lithium with cardiac drugs, although not contraindicated, requires particularly careful monitoring, including periodic electrocardiograms initially.

Any drug that alters renal function should be used cautiously in patients on lithium, especially if there is a history of kidney disease. Some nonsteroidal anti-inflammatory agents can increase lithium levels and, since these are readily available over the counter, patients should be cautioned accordingly.

Lithium is known to prolong the action of neuromuscular agents. Primarily for this reason, some authorities have suggested that lithium be temporarily discontinued during a course of electroconvulsive therapy (ECT). Small and colleagues (1980) have shown that ECT can be neurotoxic when administered to a patient taking lithium.

Although lithium does not generally interfere with alcohol-induced highs, some patients report that they need more alcohol to produce the de-

Table 23-5. Clinically Important Drug Interactions with Lithium

Drug	Interaction
Diuretics	
Thiazides	Reduce lithium clearance by effect on distal tubular function
Loop diuretics (furosemide)	No effect on lithium clearance
Potassium-sparing diuretic (amiloride)	Can be used to treat lithium-induced polyuria
Nonsteroidal Anti-inflammatory drugs	
Indomethacin, Phenylbutazone, Naproxen, Ibuprofen and others	May increase lithium level by interfering with clearance
Sulindac	No effect on serum lithium levels and lithium clearance
Antibiotics[a]	
Metronidazole, Erythromycin	Probable renal effect; may increase lithium level; may also induce diarrhea
Antihypertensives	
Methyldopa	May increase lithium level, may cause neurotoxic symtoms; mechanism uncertain
Clonidine	Lithium may decrease antihypertensive effect
Cardiac Medications	
Digitalis	In combination with elevated lithium levels may cause serious prolonged dysrhythmias
Calcium channel blockers (verapamil, etc.)	May increase rate of lithium excretion
Bronchodilators Aminophylline, Theophylline	Significantly increased lithium excretion, possibly increased risk of mortality in those with certain cardiovascular abnormalities
Insulin and Oral Hypoglycemics	Careful monitoring of glucose levels is necessary, since lithium can increase glucose tolerance; mechanism unclear
Digoxin, Quinidine	Cardiac conduction effects may be potentiated by lithium; digoxin may reduce effect of lithium
Neuroleptics	Increased risk of neurotoxicity (?); tardive dyskinesia
Anticonvulsants	
Carbamazepine	Additive CNS effects can produce neurotoxicity unless doses are modified
Valproate	May decrease lithium level

[a] In 1978, a case report suggested that tetracycline might cause an increase in lithium levels (McGennis, 1978). This report caused some concern, since tetracycline is commonly used to treat skin eruptions secondary to lithium. However, no other such cases have been reported (Jefferson et al., 1987), and in normal volunteers tetracycline has actually been shown to decrease lithium levels (Fankhauser et al., 1988).

sired alteration in mood, and some inadvertently drink more alcoholic beverages in response to the lithium-induced increase in thirst. Alcohol-related complications, such as cirrhosis, could result. Some patients, on the other hand, drink less alcohol on lithium, particularly if their drinking had been strongly linked to extremes of mood. Lithium has been reported to interfere with cocaine- and amphetamine-induced highs.

Lithium may also decrease the need for certain

medications. Some forms of headache respond to lithium (Abou-Saleh and Coppen, 1983), as does labile hypertension, at least partially. The interaction of lithium with other drugs has been extensively reviewed by Himmelhoch and colleagues (1980) and by Jefferson and Greist (1987).

Impact of Lithium on Other Functions

Lithium produces noticeable effects in addition to attenuating bipolar episodes, and these become especially apparent in the periods between episodes. Patients on lithium sometimes report an apparent intensification of smaller cycles. A woman might become aware of the mood changes accompanying her menstrual cycle, or another patient might identify subtle cycles of activity and energy. These observations are of interest in light of the occasional reports of lithium-induced rapid cycling (see Chapter 22). Such experiences could, however, simply reflect the elimination or attenuation of the major cycles of the illness, which allows the more subtle phenomena to manifest themselves.

Lithium alters sleep, as monitored by the electroencephalogram. Overall depth and length are increased, as are the duration of REM sleep and its latency (reviewed by F.N. Johnson, 1984). It is not clear how much these changes represent alterations in the illness or generalized effects of lithium per se, but lithium's clinical effects on sleep are not striking. In most patients, a large dose at bedtime has a mild sedative effect. Occasionally, patients will report feeling activated after their nighttime dose of lithium, a state that may reflect a high blood level.

One interesting but almost unstudied aspect of long-term lithium maintenance is its potential to improve some aspects of general health. Many lithium-treated patients note fewer common colds and flu-like episodes—a phenomenon that, if real, may be traceable to stimulatory effects of the ion on the immune system. Anecdotal reports have suggested that myocardial infarctions occur less frequently than expected in men maintained on lithium. If true, this might be partially due to a general decrease in mood-related stress or perhaps a direct membrane effect of the drug.

Management of Breakthrough Manias and Depressions

Managing breakthrough episodes (Table 23-6) involves strategies similar to those used for acute treatment and described in Chapters 21 and 22. When breakthrough symptoms appear, the most important initial consideration should focus on psychological issues (see Chapter 24), alcohol or drug abuse (Chapter 26), and, especially, compliance (see Chapter 25). Enhanced psychotherapeutic support is especially important at this time and may obviate the need for new medications.

Table 23-6. Management of Breakthrough Episodes

Hypomania/Mania (including mixed states)
Increase clinical contact; consider interfering factors (e.g., alcohol, drugs, stress)
Increase lithium to maximum tolerable level
Benzodiazepine for sleep (e.g., clonazepam)
Add clonazepam, neuroleptic, or carbamazepine for rapidly escalating manic symptoms
Moderate Depression
Increase clinical contact; consider interfering factors
Increase lithium to approximately 1.2 mEq/liter level (for bipolar patients)
Maximize thyroid function
Add tricyclic (or heterocyclic) antidepressant or MAO inhibitor
Consider alternative/adjunctive experimental approach:
Partial sleep deprivation/phase advance
High-intensity light (if seasonal)
Carbamazepine
Valproate
Severe Depression
Increase clinical contact; consider interfering factors
Add antidepressant and optimize lithium and thyroid function
Consider alternative or adjunctive approaches, including ECT

Breakthrough Hypomania and Mania

Detecting hypomania early is critical and often can be done by watching for a decreased need for sleep. If correction of interfering factors or compliance problems does not suffice, the symptoms of hypomania should be treated with increased doses of lithium while closely monitoring the blood level. If hypomanic symptoms persist after reaching a maximum tolerable lithium level, clonazepam, a neuroleptic, or carbamazepine may be added, initially in small doses and preferably at bedtime. Clonazepam is perhaps the easiest to use and, if it aborts the episode by en-

hancing sleep, may be all that is necessary. Because carbamazepine often is prophylactically effective in patients with rapid cycles, it may be the best alternative for breakthrough episodes in such patients, who can then be maintained on it. Schizoaffective symptoms may require neuroleptics. An alternative for breakthrough hypomania is to add 1.5 to 3 g of L-tryptophan, although use of this strategy cannot be resumed until the origins of the serious eosinophilia myalgia syndrome in patients on L-tryptophan can be clarified.

If full manic symptoms appear rapidly, that is, without a warning period of hypomania, the adjunctive agent must be added immediately without waiting to adjust the lithium level. In this circumstance, neuroleptics may be needed. If these agents are used, they should be tapered off and discontinued soon after the symptoms are under control. A few bipolar patients, generally those with schizoaffective symptoms, will have further breakthrough symptoms when the neuroleptics are discontinued, and for such patients, low maintenance doses generally will be sufficient.

Mania (or hypomania) is associated with a profoundly decreased need for sleep, a symptom that in turn reinforces the mania. Once set in motion by other factors, mania and sleep reduction could keep triggering one another in a vicious cycle that might escalate out of control. Clinicians should counsel patients at risk for mania to avoid situations likely to disrupt sleep routine, help them manage emotional crises that might disturb sleep, avoid using drugs known to interfere with sleep, and carefully monitor drug withdrawal that could precipitate insomnia, such as the rapid withdrawal from antidepressants. When sleep disruption cannot be avoided, such as that associated with flying across several time zones (jet lag), short-acting hypnotics should be employed.

Breakthrough Depression

Breakthrough symptoms of depression, which range from mild to severe, are among the most frequent challenges in managing bipolar patients on lithium. The first response to the appearance of depressive symptoms should include a reevaluation of interfering substances, of compliance, and of the lithium level and thyroid function, as well as a reassessment of the patient's life situation, with particular attention to real or perceived losses. The lithium level should be raised to at least 1.2 mEq/liter or higher, since some breakthrough depressions will respond to increased lithium, usually within 7 to 10 days.[13]

A diagnosis of hypothyroidism that is supported by chemical indices should be corrected by supplemental thyroid medication. Even indices in the low-normal range can justify the use of thyroid supplements in the presence of breakthrough depressive symptoms. Since thyroid indices have a wide normal range, it is not always clear whether a normal value is really optimal for a given patient. Many patients with affective illness have low-normal thyroid function before starting on lithium (see Chapter 17). Thus, lithium-induced hypothyroidism may not be obvious from the chemical indices.

Among the lithium clinics surveyed,[14] 44 percent indicated that they would place a patient on supplemental thyroid medication if chemical indices were in the low-normal range and the patient was complaining of fatigue, apathy, and possible depression. Thirty-three percent said they use supplemental thyroid medication even when the indices are in the normal range if the patient is suffering from a refractory depression characterized by psychomotor retardation.

In our own practices, we find that rigid adherence to the range of thyroid indices usually considered normal would deprive many patients of the considerable benefits provided by small doses of supplemental thyroid medication. Dosages should start at 10 μg of T_3 or 25 μg of T_4 once a day (but not in the evening or night) and progress in increments of 10 (or 25) μg, with monitoring of blood thyroid indices.[15]

If the response to thyroid optimization and increased lithium is not satisfactory, the clinician and patient must decide whether to add an antidepressant drug. If the depression is only moderately severe, more psychological support is preferable to antidepressants, which could precipitate mania and worsen the course of the illness, particularly among patients who are especially vulnerable to this (see Chapter 22). This conservative approach is especially appropriate for the patient who has been on lithium for only 1 or 2 years, since clinical experience suggests that prophylactic efficacy may improve with time.

Antidepressants are indicated for patients whose depression is severe enough to cause considerable suffering, especially if it significantly impairs normal functioning. Tricyclics and the

newer heterocyclics are the most frequently used antidepressants in this situation. Those with less sedative effects, such as bupropion, fluoxetine, desmethylimipramine, or nortriptyline, are preferred, since breakthrough depressions in bipolar patients on lithium are frequently characterized by anergy and lassitude rather than anxiety, sleep disturbance, and intense psychic distress.

The second-generation heterocyclic antidepressants (e.g., fluoxetine or bupropion) may be preferred if side effects associated with the traditional tricyclic drugs are a source of concern. The efficacy of these new drugs is generally less well established than that of traditional tricyclics, especially when the breakthrough depression is quite severe. However, these new drugs are already widely used, and it would not be surprising if they replaced the classic tricyclics for bipolar patients.

Antidepressant dosages generally should be somewhat lower than those used in the absence of lithium, since some side effects, such as tremor and sedation, can be additive. Because of the risk of precipitating mania or hypomania (even in the presence of lithium), these drugs should be withdrawn gradually shortly after the antidepressant response is achieved.

The use of MAOIs has undergone a minor renaissance, and they are increasingly used as an alternative to tricyclic (or heterocyclic) antidepressants to treat breakthrough depressions in patients on lithium. Some authorities now even recommend MAOIs as the treatment of choice in such cases, and a recent study directly comparing imipramine and tranylcypromine in the treatment of bipolar depression (Thase et al., 1988) found significantly better results with the MAOI. (Studies of the combination of MAOIs and lithium are reviewed in Chapter 22.)

The use of ECT to treat breakthrough depressions in patients on lithium has been advocated by some clinicians, such as Kukopulos and colleagues (1980), because ECT is less likely than antidepressant medication to precipitate a postdepression mania. However, ECT has been reported to cause increased memory loss and neurological abnormalities when administered to patients on lithium (Small et al., 1985; El-Mallakh, 1988).[16] Breakthrough depressions occurring in patients on maintenance lithium often do not fall in the very severe range usually associated with ECT treatments. Nevertheless, it remains an important alternative for this indication.

The alternate antidepressant treatments discussed in Chapter 22 (carbamazepine, partial sleep deprivation or phase advance, high-intensity light) also should be considered in dealing with breakthrough symptoms during prophylactic management. As noted earlier, when carbamazepine and lithium are administered together, dosages may need to be reduced because of possible additive effects on the CNS.

Other Issues in Lithium Maintenance

Timing of the Dose

The pharmacokinetics of lithium have been the subject of a great deal of attention in the medical literature, as have the advantages and disadvantages of various lithium preparations and schedules of administration. Clinical investigators have argued extensively about these issues and whether the greater cost of sustained-release preparations is justified.[17]

It has been suggested that renal side effects (secondary to decreased concentrating ability) are somewhat less frequent when a single daily dose is used, the lower rates presumably due to the rest given the kidneys during the trough in plasma lithium levels 18 to 24 hours after the dose (see, e.g., Hetmar et al., 1986). Several clinical investigators in our survey reported that side effects were exacerbated or illness recurred in some patients shifted from standard preparations to a sustained-release preparation, or vice versa.

Patients prefer as few doses a day as possible. Once a day dosing is more convenient, easier to remember (especially when there are few, if any, symptoms to serve as reminders), and less socially embarrassing; as a result, compliance is better. If the entire dose is taken at bedtime, the peak blood level and the worst side effects occur at night, when the patient is unaware of them. There is extensive evidence that the prophylactic results of once a day administration are as satisfactory as those of divided doses. Some patients require relatively high maintenance levels of lithium but are exquisitely sensitive to its cognitive side effects. They may do better on divided doses or sustained-release preparations, which make it possible to avoid the morning carryover of nighttime peak levels from regular lithium.

Plasma Monitoring

Plasma monitoring should be done as closely as possible to 12 hours after the last dose of lithium, that is, the morning after a bedtime dose. Patients who take their entire dose at night have 12-hour blood levels about 15 to 20 percent higher than those on a divided dose of the standard preparation. Patients who cross several time zones while on lithium must be careful to avoid confusion about the timing of the doses. Anecdotal evidence that jet lag can be associated with mood destabilization in some patients (probably secondary to sleep disruption) indicates that an adequate lithium level is important. For our own patients who travel, we suggest splitting the difference between the old and the new time in planning the dosage schedule.[18] Adequate hydration must be scrupulously maintained during travel, since flying across meridians can induce shifts in fluid and electrolyte balance. Because of the risk of precipitating a switch into mania, sleep disruption should be minimized during travel by using hypnotics when necessary.

Lithium Holidays, Including Pregnancy

Lithium holidays, analogous to neuroleptic holidays, have been advocated by Ayd (1981). They are intended to minimize long-term side effects by giving the body's systems an opportunity to recover from sustained exposure to the drug. Ayd reported mixed results; some patients were able to sustain progressively longer holidays (to the point of withdrawal) without relapse, but others relapsed relatively quickly. In fact, the phenomenon of rapid relapse after lithium withdrawal has now been extensively documented by others (see review in the second part of this chapter). Thus, although lithium holidays may deserve further exploration, they certainly cannot be recommended for clinical practice. A brief holiday is equivalent to lowering the lithium level. Using the lowest maintenance levels that preserve effective prophylaxis, a good practice to follow, can be accomplished best by gradually reducing the daily doses, a procedure that does not produce repeated sudden changes in plasma level. When lithium must be discontinued for appropriate medical reasons, it should be reduced gradually to avoid withdrawal symptoms, particularly sleep disruption.

Lithium holidays may subtly encourage poor compliance. Patients who find themselves free of symptoms and side effects while off lithium with the doctor's blessing may mistakenly assume that they no longer need the drug. Every experienced clinician knows that when patients are taken off lithium for medical or surgical reasons, it can be difficult to convince them to go back on it. If the clinician believes that a patient may be receiving more lithium than needed, the preferred approach is to lower the daily dose gradually. If it is necessary to take a patient off lithium, the safest approach is to decrease the dose gradually until the drug is fully withdrawn rather than gradually lengthening the drug-free periods. Some patients can identify a time of the year associated with less vulnerability, the best time to be off lithium. Conversely, it may be advisable to increase the lithium dose during certain times of the year in patients with a history of seasonal exacerbations.

The most common reason for withdrawing lithium is when the patient wishes to become pregnant. Table 23-7 outlines the risks and the clinical considerations involved in this decision. Many, but by no means all, manic-depressive patients can tolerate being off lithium during pregnancy. Because of the high risk of postpartum mania or depression, those who do go off should resume taking lithium at least a few weeks before the birth is expected.[19] As discussed earlier in this chapter, lithium levels should be lowered immediately before parturition and followed carefully during the immediate postpartum period until the fluid and electrolyte balance is normalized again. Carbamazepine had been suggested as an alternative to lithium because fetal anomalies associated with the anticonvulsant were thought to be rare (Elia et al., 1987), but a recent report (Jones et al., 1989) challenges this opinion.

Lithium Withdrawal or Discontinuation

Extending the lithium holiday into total lithium withdrawal raises the question of whether the patient is thereby rendered even more vulnerable to relapse in the near term. Some investigators have found no difference in relapse rates between the period before lithium was started and after it was withdrawn. Others, however, focusing on bipolar patients, have found relapse rates during with-

Table 23-7. Risks of Lithium During Pregnancy

Teratogenic effects – (Primarily a risk during the first trimester)

Animal studies
- Evidence of abnormal fetal development (Szabo, 1970; Smithberg & Dixit, 1982)
- Limitations in extrapolating animal findings to humans
  - Species differences in susceptibility
  - Harmful in humans; may not be in animals (e.g., thalidomide)

Lithium birth-registry data (Schou & Weinstein, 1980)
- Increased rate of congenital malformations (11.5% vs 1-3% in general population) especially cardiac anomalies (8%), e.g., Ebstein's anomaly
- Limitations to interpretation
  - No control groups
  - Potential for bias — overreporting of pathology
  - Low overall incidence of birth defects
- 5-year follow-up of 50 normal lithium infants (Schou, 1976)
  - No significant differences in incidence of developmental anomalies compared with 51 siblings (20% vs 12% in sibs)
  - But findings based on subjective report rather than objective examination

Swedish cohort study (Källén & Tandberg, 1983)
- 350 infants born to manic-depressive mothers compared with all infants born during same period
- Higher than expected rates of perinatal death and congenital malformations
- 4/59 infants (7%) born to lithium-treated mothers had heart defects
  - 3/4 of these infants died (none had Ebstein's anomaly)
  - No cardiac defects in 38 infants whose mothers were treated with psychotropic drugs other than lithium
  - 2/80 infants of mothers treated without drugs had heart defects (1 had Down's syndrome)

International register of lithium babies (Elia et al., 1987)
- Approximately one case of Ebstein's anomaly per 100 exposures (0.1%)
- Substantially lower risk than earlier estimates, but still 20 times the general population rate
- Fetal ultrasound at 18 weeks can help detect major cardiovascular anomalies (Elia et al., 1987)

Absence of evidence for any teratogenic effect of paternal lithium treatment

Risks during later pregnancy — fetal toxicity potential and blood level changes

Increased glomerular filtration rate during pregnancy speeds lithium clearance
Increased lithium dose may be necessary to maintain symptom control
Lithium freely crosses placenta
Toxicity in neonate manifested by hypotonia, cyanosis, lethargy

Risks during and following delivery

Decreased maternal glomerular filtration rate leads to reduced lithium clearance, higher serum level
Lithium concentration in breast milk about one-half maternal serum lithium level

drawal to be higher than expected from the natural course of the illness. On the other hand, Molnar and associates (1987) found a 12-month relapse rate lower than expected from the literature after they had gradually terminated lithium in 15 bipolar patients, although these results require confirmation in more rigorous studies.[20] At any rate, it is known that sudden discontinuation of lithium can produce a cluster of disturbing withdrawal symptoms, such as anxiety, irritability, and emotional lability (King and Hullin, 1983), and it may precipitate a new episode.

We wish to emphasize the common clinical belief that the great majority of bipolar patients withdrawn from lithium will eventually relapse. The wisdom of this assumption is reinforced by long-term follow-up studies (Bouman et al., 1986; Abou-Saleh and Coppen, 1986; Page et al.,

Table 23-7a. Lithium During Pregnancy: Considerations

Manic-Depressive illness itself is associated with some risk to fetus:
- Cohort study found higher than expected rates of perinatal death and congenital defects regardless of maternal treatment, if any
- Potential for suicide during an affective episode
- Potential for harm or injury to fetus during an affective episode
- Extremely high risk of postpartum depression/mania, especially with previous history of such an episode, results in potential risk to mother and infant due to interference with bonding. While lithium (re)administered after delivery may prevent postpartum mania, it often takes longer term administration to achieve prophylaxis against depression

On the other hand
- Some patients report a positive effect of pregnancy on mood
- A regular pattern of episodes may permit planning a pregnancy during a "safe" period

Lithium treatment during pregnancy is associated with some risks
- Early lithium registry data and cohort study each showed similar high rate of cardiac anomalies (7-8%), but recent more extensive registry data indicate a substantially lower risk
- Maternal and/or fetal toxicity is possible since increased GFR (and therefore faster lithium clearance) may necessitate higher dose for control of affective symptoms

On the other hand
- Recent technological advances permit:
  - A. neonatal echocardiography to screen for cardiac defects
  - B. early surgical correction of most cases of Ebstein's anomaly
- Careful monitoring of maternal lithium levels:
  - A. reduces risk of developing toxicity
  - B. facilitates maintaining minimal effective dose
- Alternative drugs are available, i.e., carbamazepine

1987). The Page study involved 101 bipolar and recurrent unipolar patients maintained on lithium for a median time of 13 years. Of the 31 who stopped lithium, all but 2 suffered relapses, and those 2 were unipolar patients; that is, all bipolar patients who discontinued lithium relapsed. We return to these issues later in the review of the literature.

Approaches to Lithium Resistance

Management of Contributing Factors

A poor prophylactic response to lithium is associated with three principal conditions, which frequently overlap: rapid cycling, mixed manic-depressive states, and concomitant alcohol or drug abuse. As discussed in Chapter 22, most rapid cycling occurs when patients are taking antidepressant or neuroleptic drugs. In light of the evidence that some rapid cycling will stop when these drugs are withdrawn (Kukopulos et al., 1980; Wehr et al., 1988), we recommend doing so whenever it is possible. Once off these potentially cycle-inducing drugs, bipolar patients may again become responsive to lithium (Reginaldi et al., 1981).

Mixed states are often confounded with rapid cycling. Because of the mixture of manic and depressive symptoms, patients in these states are usually already taking antidepressants, neuroleptics, or both and are also more likely to be abusing drugs or alcohol. Thus, it is difficult to know whether pure mixed states are in fact resistant to lithium. We recommend that substance abuse be treated aggressively before alternative or adjunctive treatments to lithium prophylaxis are begun.

The Anticonvulsants

Carbamazepine. Like lithium, carbamazepine has been shown to have prophylactic effects in manic-depressive illness in addition to its acute antimanic and antidepressant effects. Although the proper role for this drug in maintenance treatment is not yet completely established, the most important indication for it is unsuccessful prior lithium treatment, because of either unacceptable side effects or prophylactic failure (Table 23-8).[21] When used in these circumstances, carbamazepine is usually given in conjunction with lithium. To minimize CNS side effects for such patients, the maintenance lithium blood

Table 23-8. Alternative or Adjunctive Treatments for Poor Responders to Lithium (Often Rapid Cyclers)

- Evaluate possible cycle-inducing effect of adjunctive antidepressant or antimanic medication
- Evaluate contribution of drug or alcohol abuse
- Anticonvulsants (carbamazepine or valproate)
- MAO-A inhibitor (clorgyline)
- Thyroxine (hypermetabolic doses)
- L-tryptophan
- Calcium channel blockers (verapamil and others)
- Maintenance ECT
- Periodic sleep deprivation
- Magnesium aspartate

level may need to be somewhat lower than that previously described for lithium alone.

Some authorities now recommend that patients with rapid cycles be treated initially with lithium–carbamazepine combinations without first establishing failure on lithium alone. In most instances, however, it is probably still wise to first evaluate the prophylactic efficacy of lithium alone. Nevertheless, most rapid-cycling patients will probably end up on the lithium–carbamazepine combination. Patients may have a continuously circular course (i.e., no true symptom-free interval of more than 3 or 4 weeks) yet not meet the criteria for rapid cycling because they have long, low-amplitude episodes. In our experience, some of these patients respond to lithium and others respond like typical rapidly cycling patients to carbamazepine.

Another important candidate for carbamazepine plus lithium maintenance is the patient who cannot tolerate prophylactic levels of lithium, often because of the onset of nephrogenic diabetes insipidus (NDI). Although carbamazepine (a vasopressin agonist) will not reverse lithium-induced NDI, it may sufficiently potentiate the effects of lithium to allow a substantial lowering of maintenance levels and, therefore, of dose-related side effects.

For patients who cannot tolerate any lithium, carbamazepine alone—generally given twice a day—may provide an alternative. In fact, some studies suggest that carbamazepine is as effective prophylactically as lithium in manic-depressive patients without rapid cycles. More studies will be needed before this can be recommended as standard treatment. As an agonist of vasopressin, which is involved in recall mechanisms, carbamazepine may become especially useful as an alternative in patients who experience memory difficulties on lithium. One emerging potential limitation of carbamazepine is that some patients apparently will relapse after several years of successful prophylaxis, a topic we revisit later in the review of the literature.

The side effects of carbamazepine are outlined in Table 23-9, which also contrasts them with side effects associated with lithium. It is best to start with a low dose (100 mg), building it up gradually (100 mg every 4 or 5 days) until the blood level is just within the range reported as therapeutic for its use in convulsive disorders (6 to 10 μg/ml). A too rapid buildup of the dose or a blood level that is too high can produce troublesome CNS side effects, especially if the patient is also on lithium. Although systematic studies are lacking, at least one group (Nolen et al., 1988) recommends using plasma level determinations performed just before the next dose of the drug is administered. These trough levels should be kept between 6 and 8 μg/ml, and peak levels (2 to 4 hours after drug administration) should generally not exceed 10 μg/ml.

The pretreatment laboratory evaluations for carbamazepine are outlined in Table 23-10 and routine monitoring in Table 23-11. During carbamazepine maintenance, a complete blood count, particularly the white count and numbers of platelets, should be monitored regularly (every 2 to 3 weeks initially, then every 1 to 3 months). Although a benign and transient decrease in the white blood count (to the 3,000 to 4,000 range) is not uncommon, true aplastic anemia is rare.[22] Carbamazepine levels should also be monitored, since, over time, the drug can induce the liver to accelerate its metabolism, and blood levels may decrease on a fixed dose. The clinically important interactions between carbamazepine and other drugs are listed in Table 23-11a. Those that increase carbamazepine toxicity, particularly interactions between carbamazepine and verapamil, are especially important and may require a sub-

Table 23-9. Carbamazepine Side Effects Contrasted with Lithium

Side Effect	Carbamazepine %	Lithium %	Comments
Dizziness/Ataxia	19	<1	Transient, associated with rapid increase in carbamazepine dose
Skin problems:			
Acne		1	Essentially absent for carbamazepine
Rash	13	<1	
Psoriasis		1	Not uncommon in lithium-treated patients who have previously had psoriasis or have a family history of it
Gastrointestinal problems:			
Nausea	10	4	G.I. symptoms are generally transient
Diarrhea	<1	9	
Drowsiness, sedation	10	12	Transient and dose-related
Visual problems:			
Blurred vision		0-14	
Diplopia	8		Transient and dose-related for lithium
Slurred speech	4		Transient and dose-related for lithium
Tremor	3	27	
Paresthesia	3		Transient and dose-related
Confusion	2		Memory problems reported by 28% of lithium-treated patients
Excessive thirst		36	
Excessive weight gain		19	
Polyuria	<1	30	

Carbamazepine data from Post, personal communication; lithium effects from Johnson et al., 1984, and Vestergaard et al., 1980

stantial reduction in the carbamazepine dose (Macphee et al., 1986).

Valproic Acid. Valproic acid was initially evaluated primarily as an antimanic agent, but it does appear to have prophylactic efficacy for some patients. Like carbamazepine, it may be most useful in lithium-resistant patients, and it may also benefit patients who have failed to respond to both lithium and carbamazepine. Side effects of valproic acid are generally mild. Coadministration with lithium may not produce the lethargy sometimes associated with lithium–carbamazepine combinations. For prophylaxis, a low dose (300 to 400 mg) is used at first and gradually built up, depending on clinical response, to a blood level in the 50 to 100 μg/ml range. This level is usually achieved at a dose around 1,500 mg, but it may require up to 5,000 mg in some patients. Unlike carbamazepine, valproate does not induce its own metabolism and, therefore, ongoing dose increments are not generally needed. When carbamazepine is administered along with valproate, blood levels should be monitored closely and dosages may need to be adjusted, since there are complex metabolic interactions between the two drugs (Bowdle et al., 1979).

Table 23-10. Pretreatment Evaluation for Carbamazepine

- Complete blood count, including platelets, WBC, reticulocyte, and serum iron
- Liver function tests
- Electrolytes
- Thyroid function: T_3, T_4, and TSH
- Complete urinalysis and BUN
- Rule out history of cardiac, hepatic, or renal damage
- Rule out history of adverse hematological response to other drugs

Adapted from Post et al., 1984a, and PDR, 1989

Table 23-11. Clinical Monitoring for Patients on Carbamazepine

Parameter	Finding	Action	Comment
Dose	400-1,800 mg/day	Individualize	Start slowly, decrease if side effects
Blood level	4-12 μg/ml	Individualize	Enzyme induction after 2-3 weeks may necessitate dose increase
WBC	Consistent mild decreases	Monitor, inform; discontinue drug if WBC below 3,000[a]	Very rare, idiosyncratic aplastic anemia
Rash	10-15%	Discontinue	Restart and treat with steroids if carbamazepine requirement continues
Thyroid	↓T_4, T_3, little ↑ in TSH		Larger decreases in responders
Liver	Occasional ↑enzymes		Discontinue if persistent; very rare hepatitis
Sodium	Mild hyponatremia		Very rare water intoxication
Calcium	Mild hypocalcemia		No osteoporosis
Cardiac	Slows AV conduction		Avoid use in heart block

[a] Below 4,000 the clinician should become more vigilant, inform the patient and monitor frequently. Carbamazepine might be discontinued earlier, (i.e., between 3,000 and 4,000) if the platelets are also down, in the presence of red cell abnormalities or systemic symptoms. Also, since lithium produces a nonspecific increase in WBC, a drop below 4,000 in a patient on the combination should trigger discontinuation of carbamazepine.

Adapted from Post and Uhde, 1985, 1987

Other Anticonvulsants. Clonazepam, a benzodiazepine derivative, has been used prophylactically without much success so far. In addition to dubious efficacy, the problems of sedation and the development of tolerance would argue against its maintenance use, although periodic use to abort breakthrough hypomania or manic symptoms is quite sensible. There are anecdotal reports of patients occasionally showing a prophylactic response to diphenylhydantoin, but no systematic data are yet available.

Other Adjunctive Approaches. Aside from the anticonvulsants, the principal alternative to lithium in prophylactic treatment is to maintain optimal or even supraoptimal thyroid function using T_4 supplementation. The experimental use of thyroid preparations alone for prophylaxis is described later. Here we simply emphasize that a bipolar patient should not be considered a lithium prophylactic failure until plasma T_4 levels at least in the high normal range (10 to 12 μg/ml) have been achieved. Other adjunctive approaches are discussed later in this chapter.

REVIEW OF THE LITERATURE

Open Trials of Lithium Prophylaxis

The first major systematic study of lithium's prophylactic efficacy in manic-depressive illness occurred through the collaboration of Baastrup and Schou in 1967. They analyzed the results of a retrospective study initiated at the Psychiatric Hospital in Glostrup, Denmark, involving all patients with recurrent affective disorders admitted from 1960 through 1966. Patients selected for analysis had an episode frequency ranging from two or more episodes in a year to one episode a year for at least 2 years before lithium administra-

Table 23-11a. Clinically Important Interactions Between Carbamazepine and Other Drugs

Increased Carbamazepine Levels and Toxicity Produced by	
	Erythromycin (and analogs)
	Triacetyloleandomycin
	Viloxazine
	Isoniazid
	Verapamil
	Diltiazem
Decreased Carbamazepine Levels Produced by	
	Phenobarbital
	Phenytoin
	Primidone
Carbamazepine Decreases Effects of	
	Haloperidol (decreases blood level)
	Clonazepam
	Phenytoin
	Valproate
	Ethosuximide
	Theophylline
	Dexamethasone
	Dicumarol
	Warfarin
	Pregnancy Tests

From Post and Uhde, 1987

tion. All had taken lithium for at least 1 year.

The study's results were striking. Compared with the period before lithium was introduced, episodes during the lithium period had become less frequent among 83 of the 88 patients (94 percent) meeting criteria for the study. The magnitude of the effect is suggested by the fact that before lithium, on average, patients were ill 13 weeks a year compared with less than 2 weeks a year while on lithium, a nearly sevenfold reduction. The frequencies of manic and depressive episodes were affected equally. However, lithium's ability to prevent depression, not always evident initially, seemed to improve with time. In this sample, lithium was equally effective in bipolar and recurrent unipolar patients but was less so in schizoaffective patients. The data from this study are illustrated in Figure 24-3.[23]

In 1970, Angst and colleagues undertook a cooperative follow-up study involving 244 patients in Denmark, Czechoslovakia, and Switzerland. The data from all three countries were similar: Most patients on lithium experienced fewer manic and depressive episodes. Regression analysis indicated that the intervals between the episodes were prolonged and the episodes themselves shortened. As in the original Danish study, bipolar and recurrent unipolar depressives showed similar results, with schizoaffectives showing less pronounced lithium-related changes in the course of their illness.

Baastrup and Schou's 1967 report, a medical landmark, stimulated many trials of this sort in the prophylactic management of manic-depressive illness. By 1972, more than 60 clinical studies comparing the prelithium course of the illness with that found while taking the drug had been published. Like the 1970 international collaborative study, these were based on nonblind administration of lithium to patients with a certain minimum frequency of episodes before lithium (generally about one episode per year). Most studies dealt with groups of 30 to 100 patients and 2 to 3 year observation periods. Although a wide range of criteria was used for scoring an episode, these studies consistently showed good to excellent results. Virtually all showed decreases in the frequency, duration, and severity of episodes. Many of the studies did not distinguish between manic and depressive episodes, but of those that did, most reported that lithium reduced both types of episodes. Some, however, reported more impact on mania, others more on depression. These issues are discussed further below.

By this time, most clinicians who had studied lithium's effects on recurrent affective illness were very favorably impressed. However, skeptics, such as Blackwell and Shepherd in England (1968; also see *Lancet* editorial, 1969), noted that, among patients selected for a trial because of a history of relatively frequent episodes, the natural course of the illness might be expected to show a decreased frequency of episodes during the study period; this decrease reflects a regression toward the mean rather than a drug effect. However, the underlying assumption—that the natural course of manic-depressive illness is random—was contradicted by data indicating a strong tendency for the average frequency of manic-depressive episodes to be nonrandom and to increase with time (see Chapter 6). Three independent studies (Laurell and Ottosson, 1968; Isaksson et al., 1969; Angst et al., 1970) examined the natural course of manic-depressive illness in patients with 2-year histories of frequent episodes—that is, the kind of patients selected

for the trials just discussed. In all three of these natural course studies, patients remained at high risk for subsequent episodes in the next 2 years if they remained off lithium. Blackwell and Shepherd had also noted that in the absence of double-blind procedures, observer bias or patient expectation might have accounted for the favorable results. Clinicians very familiar with the illness knew, however, that major episodes of mania (and probably also depression) are unlikely to respond fully to subtle psychological suggestion alone.

Placebo-Controlled Studies

The definitive response to the criticism came when the Danish team undertook a study in which female patients given lithium in a clinic setting and stabilized on it for at least a year were then given either lithium or placebo under double-blind conditions (Baastrup et al., 1970). If anything, the results were even better than those of the earlier open studies. Of the 39 bipolar and unipolar patients switched to placebo, 21 relapsed within 5 months, whereas of the 45 given lithium, not one relapsed. This dramatic difference was, of course, highly significant statistically ($p < 0.001$).

A subsequent study by Coppen and colleagues in England (1971) was especially influential in lessening skepticism in Europe, in part because of its more traditional design, in which comparable groups of patients were randomly started on either lithium or placebo. The design permitted psychiatrists who knew the patients' conditions to administer any additional drugs deemed necessary for episodes of mania or depression in both groups. Criteria for selecting bipolar and unipolar patients resembled those of the earlier studies. Only 1 of the 37 placebo-treated patients could be rated as having had "no conspicuous affective disturbance during the trial period" (averaging 1½ years), in contrast to 20 of the 28 lithium-treated patients. Almost all of the placebo-treated patients (35 of 37) received some additional treatment (tricyclics or ECT for depressions and neuroleptics for manias), whereas only half of the lithium-treated patients did (antidepressant drugs and a few instances of neuroleptics for breakthrough hypomania). No lithium-treated patient required ECT for depression, although 16 of the 37 placebo-treated patients did.

The major study influencing the acceptance of lithium prophylaxis in the United States was that of Prien and colleagues (1974), a collaborative effort of the VA and the National Institute of Mental Health (NIMH). This study, which formed the principal basis of the U.S. Food and Drug Administration's 1974 decision to approve the marketing of lithium, was initiated at a time when the drug was poorly accepted in the United States, largely because of unfortunate experiences with toxicity that had occurred before the importance of maintaining sodium was understood.

The data from these studies further document two aspects of lithium maintenance mentioned frequently in the open studies: the common occurrence of mild or moderate depressive breakthroughs, and the unlikelihood of severe episodes (i.e., those that would have required hospitalization and would have been treated with ECT in this setting).

For most observers, the controlled studies of Baastrup and Schou and of Coppen and colleagues essentially laid to rest reservations based on nonblind administration or selection bias. However, the question remained whether patients selected for and maintained on lithium became dependent on it and, therefore, were more likely to relapse when taken off. Two studies examined this question directly. Schou and colleagues (1970a) and Grof and colleagues (1970) both compared patients' relapse rates during lithium withdrawal and before lithium treatment, and both found no difference in either frequency or severity.

There are ten major double-blind studies comparing lithium prophylaxis to placebo in bipolar patients (Table 23-12). Thirty-four percent of those on lithium relapsed during the trial period compared with 81 percent of the patients on placebo. Nine of the ten studies independently established a statistically significant difference between lithium and placebo; the one that did not had only seven patients on lithium (Melia, 1970). Although the placebo and lithium relapse rates differ across studies, probably reflecting differences in patient selection and in criteria for relapse, the percent difference between placebo and lithium is reasonably comparable, as is the power of the statistical significance.

That lithium has profound prophylactic effects

in bipolar illness is now incontrovertible. However, many important clinical questions remain. For example, how does lithium's ability to prevent depression compare with its ability to prevent mania? What is the likelihood of breakthrough episodes not severe enough to require additional treatment or hospitalization? How does lithium affect subclinical mood lability between episodes? How do additional treatments affect patients receiving long-term lithium? Systematic data are available to answer these questions partially, but the information is thin compared with the data proving that lithium is an effective prophylactic agent in manic-depressive illness.

Relative Prophylactic Efficacy in Mania and Depression

Some reviewers, primarily Americans, appear to assume that lithium prevents mania better than it prevents depression, a position that is perhaps influenced by the prevailing biological theories that postulate that mania and depression are opposite states. Conversely, many European investigators apparently expected that both phases would respond equally, since both were viewed as intrinsic aspects of the same illness. Of the important early European studies, most did not distinguish manic from depressive episodes in reporting relapse frequencies.

In their landmark 1967 study, Baastrup and Schou did not specifically analyze the differential effects of lithium on mania and depression. However, inspection of their individual case histories indicates equivalent prevention of depressive and manic episodes (defined as a period in which symptoms were sufficiently pronounced to require hospitalization or supervision in the home). They also noted that "very many of the patients suffered during these nonpsychotic intervals from phases with slight to moderate depressive or, less often, hypomanic symptoms" (p. 168). This comment suggests that there may have been more mild depressions than hypomania, but they do not discuss whether or how this effect might be related to differences in the relative number of manic and depressive episodes before lithium administration.

Among the open studies, some found both phases affected equally, some found mania more affected than depression, and others reported the opposite. Petterson (1977) compared the number and duration of manic and depressive episodes before and during at least 6 months of lithium treatment in a group of 79 bipolar patients. She found that for men, manic episodes on lithium decreased more than depressive episodes did, but for women, both types of episodes were equally reduced. For both men and women, lithium's effect on the duration of episodes was equivalent for mania and depression.

Three studies using balanced mirror-image pretreatment and lithium-treatment periods, careful selection of patients, and quantitative rating instruments directly tried to answer the question of lithium's relative efficacy in preventing depression and mania (Table 23-13). Holinger and Wolpert (1979) reported on 56 bipolar patients followed over at least 5 years on lithium. All had experienced at least one manic or depressive episode yearly for at least 5 years before lithium treatment. On lithium, manic and depressive episodes each showed a similar decrease. This study is of interest because it includes mild episodes defined by well-delineated criteria. Two later studies indicated better prophylaxis against depression than mania. Rybakowski and colleagues (1980) studied a group of 61 bipolar patients on lithium for 1 to 8 years. An episode was defined as at least 2 weeks of symptoms severe enough to require additional drugs or psychiatric hospitalization. The rate of manic episodes on lithium was 28 percent of the prelithium rate, but depressive episodes were reduced to 16 percent of baseline ($p < 0.01$). Poole and co-workers (1978) conducted a retrospective study of 100 randomly selected patients with clearly diagnosed clinical depression or hypomania-mania, who had been ill an average of 10 years before receiving lithium. A comparison of episodes during the 5 years before lithium treatment with those during the first 5 years on the drug indicated a significantly better prophylactic effect against depression than against hypomania-mania ($p < 0.01$). In this study, however, only major episodes were counted, not milder mood swings.

Of the eight double-blind, placebo-controlled studies that tried to answer this question, two found a greater effect in preventing mania or hypomania than depression (Cundall et al., 1972; Dunner et al., 1976a), two were indeterminate (Stallone et al., 1973; Fieve et al., 1976), and

Table 23-12. Lithium Prophylactic Effectiveness in Bipolar

Study	Trial Period (months)	Design	Treatment	N	% Patients Relapsing[a]
Baastrup et al., 1970	5	DD	LI	28	0[d]
			PL	22	55[d]
Melia, 1970	24	DD	LI	7	57
			PL	8	78
Coppen et al., 1971b, 1973	4 to 26	PR	LI	17	18
			PL	21	95
Cundall et al., 1972	12	CD	LI	12	33[b]
			PL	12	83[b]
Stallone et al., 1973	22[e]	PR	LI	25	44[d]
	8[e]		PL	27	93[d]
Prien et al., 1973a	24	PR	LI	101	43[d]
			PL	104	80[d]
Prien et al., 1973b	24	PR	LI	18	28[b]
			PL	13	77[b]
Fieve et al., 1976	40[e]	PR	LI	17	—[a]
	18[e]		PL	18	—[a]
	30[e]		LI	7 BPII	57
	21[e]		PL	11 BPII	73
Dunner et al., 1976e	17[e]	PR	LI	16 BPII	—[a]
	15[e]		PL	24 BPII	—[a]
Quitkin et al., 1978	10[e]	PR	LI	3 BPII	0
	5[e]		PL	3 BPII	67
		Totals	LI	251	34%
			PL	263	81%

CD = Crossover design; patients already stabilized in lithium maintenance assigned randomly to placebo or lithium; switched to other condition after 6 mo.
PR = Prospective design; patients assigned randomly to treatment condition
DD = Double-blind discontinuation design; patients already on lithium maintenance switched to placebo or lithium
LI = Lithium, PL = Placebo

[a] In studies analyzing manic (hypomanic) and depressive episodes separately, the number of patients relapsing may not have been reported; some patients may have had both manic and depressive relapses.
Reported significance of difference in placebo vs. lithium relapse rates:
[b] $p < 0.05$
[c] $p < 0.01$
[d] $p < 0.001$
[e] Mean trial period

four found lithium equally effective against both phases of the illness.[24] As is clear from a detailed analysis of the controlled studies,[25] there is little support for the notion that lithium is prophylactically more effective against mania than against major episodes of depression. However, mild depressive symptoms do seem to be noted more frequently than mild hypomanic symptoms among patients on maintenance lithium. In interpreting this finding, we should remember that

Patients: Double-Blind, Placebo-Controlled Studies

Relapses %		
Manic/Hypomanic	Depressive	Comments
0[c]	0[c]	Relapse defined as episode requiring hospitalization or supplemental therapy. 1 relapse was a mixed state
27[c]	23[c]	
		Relapse defined as episode requiring hospitalization. 2 patients in each group had history of schizophrenic features in addition to bipolar manic-depressive illness
		Relapses in lithium group were significantly shorter than in placebo group
8[b]	25	3 patients had more than one relapse on placebo. 1 patient remained well throughout trial. High rate of manic or hypomanic relapses on placebo: effect of lithium withdrawal?
75[b]	42	
20[b]	28	More rapid dropout rate in placebo group; lithium group in remission significantly longer
56[b]	48	
32[d]	16	Relapse defined as episode requiring hospitalization (severe) or supplementary drugs (moderate) Part of a larger design comparing lithium, imipramine, and placebo
68[d]	26	
11	22	
38	62	
59	29	3/17 lithium-treated required hospitalization compared with 9/18 placebo-treated
94	44	
0	57	
9	64	
6	56	BPII and BP "other" patients only. Relapse defined as requiring supplemental medication. Lithium reduced severity of depressive relapses
25	50	
	0	BPII patients previously stabilized on imipramine. Part of a study comparing lithium with and without imipramine to placebo with and without imipramine in BPII and UP patients
	67	
LI 23%	21%	
PL 56%	37%	

Manic relapses appear to be more common than depressive relapses overall (regardless of drug condition). Lithium appears more effective in attenuating the rate of manic relapses, relative to the rates of each in patients on placebo (problem of base-rate of nonresponders)

Potential sources of underestimation of relapses:

- Dropouts were more likely to occur in response to a manic relapse. A patient first suffering a manic relapse might not remain in the study long enough to have a subsequent depressive relapse counted
- Some investigators reported that lithium reduced the *severity* of depressive relapses; in studies with *hospitalization* as the criterion for relapse, the number of depressive relapses may be underestimated
- Hypomanic episodes may not be experienced by the patient as abnormal

patients are probably less likely to report hypomanic symptoms than depressive ones. In a survey of patient and physician attitudes toward lithium, Jamison and colleagues (1979) found physicians more likely than patients to report lithium as less effective against depression than mania. Perhaps some physicians, on theoretical grounds, have more difficulty accepting lithium's antidepressant effects than their patients do. Cultural differences are also likely to influence the reporting of depressive or manic symptoms. Thus, compared with their American counterparts, Scandinavian and British authors generally seem more impressed with lithium's prophylactic effects against depression. This could reflect a relative underreporting of depressive symptoms by Scandinavian and British patients, who are probably more likely than American patients to

Table 23-13. Relative Prophylactic Efficacy of Lithium: Mania vs Depression: Longitudinal Studies with Mirror-Image Design

Study	BP Patients N	Episode Frequency (% of Prelithium Baseline)		
		Mania		Depression
Holinger & Wolpert, 1979	56	16		18
Rybakowski et al., 1980	61	28	($p < .01$)	16
Poole et al., 1978	100	Depression prevented more effectively than manias ($p < .01$)		

suffer depressive symptoms quietly and "tough them out." Likewise, tolerance for hypomanic symptoms undoubtedly also differs in various cultural settings, thus affecting the relative impressions of lithium's prophylactic efficacy.

Quality of the Prophylactic Response

Although research demonstrates that 80 to 90 percent of bipolar patients show some prophylactic response to lithium, no systematic studies have been done to clarify how complete and satisfactory that response is. Some tentative conclusions can be reached, however, by drawing on both the available literature and our survey of experienced colleagues.

One would expect large individual differences in the extent of response, for a variety of reasons. First, patients differ considerably in overall severity of illness and in the frequency, type, and pattern of their cycles. In addition, there are wide differences in clinical management of patients, differences that encompass both pharmacological and psychological factors. Finally, patients differ in the adequacy of their psychosocial support systems.

Although acknowledging this considerable variability, we can still draw some general conclusions about the quality of lithium's prophylactic effects. The most consistent finding in the literature is a decrease in intensity of subsequent episodes. This is probably the fundamental effect of lithium on the illness, and it is fair to say that most patients with typical bipolar illness experience some attenuation of episodes on lithium. Baastrup (1980) estimated that no more than 10 percent of manic-depressive patients show absolutely no prophylactic response. It is, of course, the degree of attenuation that determines whether the response is clinically adequate. Lithium's effect in decreasing the duration of subsequent episodes could be viewed, at least in part, as reflecting the fundamental modulation of intensity, so that only the most severe tip of the episode now appears in the pathological range—that is, the episode appears shortened. This is illustrated in Figure 23-2.

By lessening the intensity of episodes, lithium also decreases their frequency, since most, if not all, expressions of the cycle are brought below a threshold necessary to be considered an episode. Thus, in the controlled studies of lithium's prophylactic efficacy, episodes were scored according to strict criteria reflecting major pathology. Any substantial attenuation of episodes was probably recorded as a reduction in frequency.

Lithium also changes the nature of symptoms that characterize breakthrough episodes. Despite the lack of systematic studies in this area, the descriptive literature, along with our own clinical impressions and those of the colleagues we surveyed, suggest that during breakthrough depressions while a patient is taking lithium, anxiety, depressive mood, psychic pain, suicidal ideation, and psychotic features all are attenuated considerably. By contrast, depressive psychomotor slowing and inhibition, which may be less affected by lithium, can become relatively more prominent.[26] However, lithium-altered hypomania or mania has primarily been viewed as an across the board modulation without a noticeable qualitative shift in the nature of the symptoms.

An interesting but as yet unanswered question

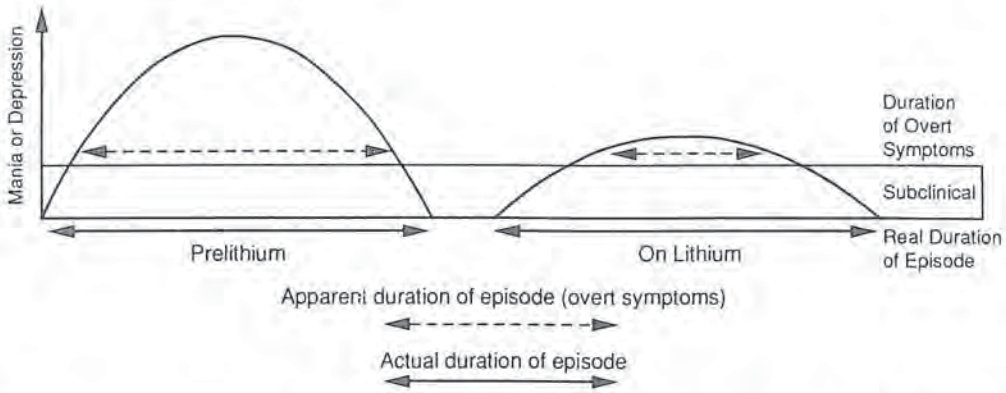

Figure 23-2. Lithium can shorten the apparent duration of episodes by attenuating their severity. By dampening the intensity of an episode, lithium can shorten the duration of overt symptoms. The actual duration of the full episode, including a subclinical phase, need not be shortened. Some episodes will be dampened to a level below the threshold criteria for a clinical episode, contributing to a decrease in frequency as well.

is whether lithium reduces mood lability between episodes. In their classic paper, Baastrup and Schou (1967) noted that patients value this aspect of lithium almost as much as they do the actual prevention of major episodes. Referring to patients' subclinical mood shifts between episodes, these authors noted that:

> It was with these patients that some of the most gratifying lithium results were obtained. Hypomanic over-optimism and hyperactivity disappeared, depressive periods with tiredness and lack of initiative were prevented, and capricious phase shifts no longer occurred. (p. 168)

Subsequently, Pons and colleagues (1985) noted an interepisode stabilizing effect of lithium, based on changes in a word-association test. On the other hand, Goodnick and associates (1987) found no difference in interepisode functioning between patients above and below the median lithium level (0.82 and 0.52, respectively). DePaulo and colleagues (1982) noted that when bipolar patients on lithium rated their mood using visual analog scales, they reported less mood variation than normal subjects did. This finding may mean that lithium exerts a general mood-stabilizing effect (i.e., attenuating normal mood fluctuations) or that bipolar patients are accustomed to greater mood variability, which causes them to judge the truly normal range as less variable than normal. The impact of this on medication compliance is discussed in Chapter 25.

In summary, almost all patients have some response to lithium, but reminders of the illness remain while on the medication. Many experienced clinicians have concluded that, in general, the overall quality of the prophylactic response to lithium does appear to improve with time. It is not clear whether this observation primarily reflects progressively improved interepisode mood stability or gradually increased attenuation of the episodes themselves. It is unlikely to be entirely explained as the consequence of poor responders' dropping out of treatment early. Nevertheless, the question of whether one should persist with lithium prophylaxis with patients who fail early in treatment is still unsettled in the literature (Prien et al., 1983).

Prophylaxis in Children, Adolescents, and the Elderly

Although lithium has been used in all age groups since the initial prophylactic trials, studies of treatment efficacy in the very young and the elderly are for the most part uncontrolled. Thus, conclusions about the parameters of lithium administration for these age groups must be more tentative.

DeLong and Aldershof (1987) analyzed the outcome of 59 manic-depressive children and adolescents (mean age, 10.9; range 3.1 to 20) who had been treated with lithium for up to 9 years. For 66 percent of the subjects, lithium prophylaxis was retrospectively judged to be successful. Efficacy in many cases was inferred from the relapses that followed temporary discontinuation of the drug. Those younger than 14 years did

as well as those 14 or older. Children who had other conditions without a clear mood component (e.g., attention deficit disorder) did not respond to lithium, although among a group of seven children with unspecified symptoms but with a lithium-responsive parent, five did respond to lithium.

Retrospective parental ratings of the behavior of 21 manic-depressive children were significantly better after successful lithium treatment than before in a study by Younes and colleagues (1986). Posttreatment ratings were still significantly more deviant for the manic-depressive children than those for the control children, however.

In one of the most careful studies done to date on young manic-depressive patients, Strober and colleagues (in press) prospectively followed 37 bipolar-I adolescents stabilized on lithium over 18 months (with serum levels ranging from 0.7 to 1.4 mEq/liter). The relapse rate among the 13 patients who discontinued lithium shortly after being discharged from the hospital was 92.3 percent, nearly three times greater than patients who continued taking the drug. Among those who continued, early relapse was associated with an increased risk of recurrence.

The prophylactic efficacy of lithium among the elderly has rarely been studied, although the sensitivity of these patients to certain side effects and the lower dosages they require have been emphasized.[27] In their prospective study of 166 bipolar and recurrent unipolar outpatients, Murray and colleagues (1983) found no age-related decrease in lithium efficacy. They did note that, with age, manic symptoms grew increasingly prevalent and severe, a trend they interpreted as reflecting the natural course of the illness. The lithium treatment of the elderly has been reviewed by Foster and Rosenthal (1980).

Lithium Prophylaxis of Bipolar-II and Cyclothymic Disorders

As noted in Chapter 4, the subgroups of bipolar-II and cyclothymia probably exist on a continuum with bipolar-I manic-depressive illness. Although most of the prophylactic studies reviewed previously are limited to bipolar-I patients, it is not always clear whether some patients from these subgroups are included. Although bipolar II and cyclothymia are often referred to as "milder forms" of bipolar illness, this notion can be misleading, especially for the bipolar-II patient with serious depressive episodes. Less obvious is the potential severity of cyclothymia, where the relentless recurrences can produce cumulative damage to the individual's life.

Unfortunately, there are very few studies of lithium prophylaxis in these subgroups. Dunner and colleagues (1976a) compared bipolar patients on lithium ($n = 12$) with those on placebo ($n = 20$) over a long period of study with an average of about 16 months and found a significant prophylactic effect against hypomania and a trend toward less severe depressive episodes (i.e., fewer hospitalizations for depression in the lithium group). Quitkin and colleagues (1978, 1981b), as part of a larger study, found that three of four bipolar-II patients given lithium remained free of depressive symptoms over the 1-year trial. Peselow and associates (1982), using a longitudinal life table analysis of 102 bipolar-II patients on lithium for 2 years, found that the probability of a depressive relapse averaged about 50 percent. It is difficult to know what this means, since there was no placebo comparison group or an estimate of the relapse rate before lithium was started, nor did the authors comment on preventing relapses of hypomania.

There are even fewer data available on lithium prophylaxis among cyclothymic patients, perhaps partly because the issue of diagnostic boundaries is more difficult. Dunner and colleagues (1976a), during a 14-month study period, noted that one of four cyclothymic patients on lithium had a depressive relapse compared with two of the four on placebo. In a life table analysis by Peselow's group (1982), the cyclothymic patients on lithium ($n = 69$) had a 70 percent probability of a depressive relapse over 2 years. However, as with the bipolar-II patients, no placebo or pretreatment comparisons are available, and the impact of a hypomania is not discussed. Akiskal and colleagues (1979) conducted an open study of lithium over 1 year in 15 cyclothymic patients compared with 10 with "nonaffective personality disorder." Focusing on nonadaptive behavior associated with hypomania, they found clinically significant improvement (greater than a 50 percent decrease in the behavior) in 60 percent of the cyclothymic patients vs only 20 percent of those with personality disorders. Prophylaxis against

depression, although not specifically commented on, is suggested by the fact that the majority of the cyclothymic patients on lithium opted to remain on it.

Alternative or adjunctive prophylactic approaches (e.g., antidepressants) are capable of inducing mania or shortening the cycle length in bipolar patients (discussed in Chapter 22). Given these potential risks, it is all the more important that there be a credible research base on which to make prophylactic treatment decisions for bipolar-II or cyclothymic patients. Until more data are available, we continue to believe that if prophylactic medication is to be used for these milder cyclic mood disorders, the regimen should include lithium (or another mood stabilizer).

Comparison of Bipolar and Recurrent Unipolar Illness

How does lithium's prophylactic efficacy compare in bipolar and recurrent unipolar illness? As noted earlier, most of the early open studies of lithium prophylaxis included both unipolar and bipolar patients, although generally bipolar patients predominated. Of the studies that make the distinction, four reported equivalent efficacy in both groups,[28] and two noted slightly better prophylactic effects in the recurrent unipolar patients (Misra and Burns, 1977; Hullin et al., 1975). Davis (1976) conducted a critical review of the literature and concluded that unipolar patients had a slightly better response than bipolar patients when differences in numbers of subjects were weighted (Davis, 1976). Interestingly, none of these studies reported a better prophylactic effect in bipolar than in unipolar patients, although the inclusion of a few rapid-cycling patients in some of the bipolar samples could have biased the results somewhat. Overall, the results of the open studies suggest that lithium is as effective in preventing recurrent unipolar illness as it is in preventing bipolar illness. As observed by Baastrup and Schou (1967), "Patients with predominantly depressive phases in the history almost always became ardent devotees of the treatment and attended to the daily intake with great punctuality" (p. 168).

Four controlled studies compared lithium and placebo in unipolar and bipolar groups separately. Three of these (Prien et al., 1973b; Coppen et al., 1971; Baastrup et al., 1970) showed no difference between the two groups. In a crossover study, Cundall and colleagues (1972) reported a strong effect in bipolar patients, but they could draw no conclusions about unipolar patients because of a high dropout rate.

In his review of the literature, Schou (1978), using weighted means of the percentages of patients relapsing within 1 year, calculated that the proportions of unipolar and bipolar patients relapsing on lithium were virtually identical (22 percent vs 20 percent) (Table 23-14).

In a collaborative study, Prien (1984) found maintenance imipramine superior to lithium overall in preventing unipolar depression, a difference primarily due to the superior efficacy of the tricyclic against more severe depressive episodes. On the other hand, several groups have found lithium equivalent or superior to tricyclics in the prophylaxis of unipolar illness.[29]

In his review of prophylaxis in recurrent unipolar illness, Schou (1979b) calculated that the 1-year relapse rate was 35 percent for TCAs among 187 patients vs only 22 percent for lithium among 76 patients (Table 23-14). The difference between these data and the results of Prien and others might be explained by two factors: First, patients with more severe depressions may do better on tricyclics. Second, the unipolar data reviewed by Schou are drawn from patient groups having recurrence rates similar to the bipolar patients, that is, an episode every 12 to 24 months. Many of the patients in the Prien study had less recurrent forms of unipolar illness. Indeed, the median number of prior episodes in Prien's bipolar group was nearly twice that in the unipolar sample.

As pointed out by Baldessarini and Tohen (1988), the literature on pharmacological prevention of recurrences among unipolar patients is dominated by heterogeneous unipolar samples and by relatively short-term trials, with only a few studies going on for 2 years and fewer still for 3 years, probably the minimum time needed to evaluate the true prophylactic effect of a drug. In other words, what is probably the dominant phenomenon assessed in these studies is the ability of a drug to stabilize the recovery from an acute episode, that is, diminish the likelihood of an episode reemerging (continuation treatment as opposed to prophylaxis). In an interesting reanalysis of the 1984 collaborative study of Prien

Table 23-14. Prevention of Manic-Depressive Illness with Lithium and with Tricyclic Antidepressants: Summary of the Controlled Trials

Diagnostic Group	Medication	Patients[a] N	Relapsing Within a Year[b] %
	Lithium vs Placebo		
Bipolar	Lithium	186	20
	Placebo	187	73
Unipolar	Lithium	76	22
	Placebo	77	65
	Antidepressants vs Placebo		
Bipolar	Antidepressants[c]	26	65
	Placebo	10	68
Unipolar	Antidepressants[d]	187	35
	Placebo	187	67

[a]Excludes patients who withdrew from trial for reason other than relapse
[b]Includes patients who withdrew from trial because of relapse
[c]10 patients received imipramine; 1 received maprotiline
[d]72 patients received imipramine; 107 received amitriptyline; 8 received maprotiline

Update of Schou, 1979b

and colleagues, Shapiro and colleagues (1989) established the importance of the type of index episode for the prevention of relapse or recurrence in a 2-year follow-up period. For patients whose index episode was manic, lithium provided the greatest stability and imipramine the least, whereas results with the combination were intermediate. For those whose index episode was a depression, the combination was superior to either drug alone (lithium and imipramine results were similar). The importance of the index episode may reflect the fact that much of what is being measured in relatively short-term studies is the impact of postepisode stabilization during the traditional continuation phase of treatment.

After their review of the so-called long-term maintenance studies of recurrent unipolar depression, Baldessarini and Tohen (1988) conclude:

> These studies provide strong evidence for a partial protective effect of lithium or of a few imipramine like agents for several months after apparent recovery from an acute episode of major depression. . . . The evidence for a longer-lasting average protective effect against major recurrences . . . and for reduced morbidity . . . over 1–2 years is good for lithium alone or in combination with a TCA [tricyclic], but not as strong for a TCA alone. (pp. 137–138)

We strongly support Baldessarini and Tohen's call for longer-term studies of unipolar patients, starting when they have fully recovered and stabilized, perhaps 6 to 9 months after remission of the acute symptoms. However, as we and others (Prien et al., 1984) have noted elsewhere, it is difficult to recruit such successful patients into long-term, placebo-controlled studies, since they are being asked to run the risk of suffering a relapse by being assigned to the placebo group. Hence, contemporary long-term studies tend to attract patients who have not responded to treatment or are otherwise dissatisfied with it.

Lithium Prophylaxis of Schizoaffective Disorders

The problematic diagnostic category of schizoaffective disorder has undergone various evolutions and transformations (see Chapter 5). After reviewing studies employing RDC or DSM-III criteria, we concluded that the bulk of what has been called schizoaffective disorders (especially schizomania) cannot be distinguished from bipolar illness on the basis of family history, outcome, or response to treatment. Smaller segments of the schizoaffective spectrum appear to represent a

variant of schizophrenia or a true coexistence of schizophrenia and affective illness.

Diagnostic heterogeneity confounds the literature on lithium prophylaxis of schizoaffective disorder, especially in early studies that did not use quantifiable criteria of proven reliability. In their comprehensive review of ten studies comparing lithium's prophylactic efficacy among schizoaffective patients (n = 220) with that among bipolar patients (n = 574), Goodnick and Meltzer (1984) noted that the earlier studies generally reported somewhat better results with bipolar patients, whereas the more recent studies find equivalent efficacy. Perhaps the most important difference between the earlier and the more recent studies is that contemporary diagnostic criteria for schizoaffective disorder require a return to normal functioning between episodes. The study of Bouman and colleagues (1986) is representative of the more recent literature. Using the individual retrospective control method over a 10-year period,[30] they found that lithium was associated with a 92 percent reduction in the number of episodes among schizoaffective patients compared with a 71 percent reduction among the bipolar patients. One of the criteria defining an episode in this study was a preceding symptom-free period of at least 1 month.

Patients with a predominance of schizomanic episodes have a better prophylactic response than those with more schizodepressive episodes (Brockington et al., 1980a, b; Kemali et al., 1985; Maj, 1988). This observation is consistent with the data reviewed in Chapter 5 that links schizomania with bipolar disorder and schizodepressive syndromes with schizophrenic disorders.

Impact of Lithium on Naturalistic Outcome

What is the relevance of the impressive results of the earlier controlled studies of lithium prophylaxis to the ordinary bipolar patient? Although approximately 70 percent of the bipolar patients studied remained free of relapses when maintained on lithium, their experience may not be typical. They were carefully selected, treated in optimal settings, and followed for relatively short periods.

Several attempts have been made to examine the impact of prophylactic lithium from a larger public health perspective. These efforts range from studies of outcome among bipolar patients receiving treatment in the community to analyses of year by year changes in hospital admission rates for mania as a function of when lithium became established as a standard treatment.

In one major outcome study, for example, Harrow and colleagues (in press) followed 73 bipolar patients for 1.7 years after hospitalization for mania and found that overall outcome was not encouraging: 26 percent good, 40 percent intermediate, and 30 percent poor. Poor outcome was similar among those on lithium (36 percent) and not on lithium (32 percent) during the month before follow-up. Similar findings have been reported from the Chestnut Lodge follow-up study (McGlashan et al., 1984). On the other hand, a recent report from a major lithium clinic in the United Kingdom (Coppen and About Saleh, 1988) continues to report very high effectiveness in both bipolar and recurrent unipolar illness, using the same indicators employed in the original double-blind studies.

Length of follow-up cannot be invoked to explain the differences between these recent studies and the earlier controlled trials for two reasons. (1) Like the controlled trials, the follow-up studies also involved relatively brief periods. (2) Long-term studies (10 to 15 years) of lithium prophylaxis have produced results that are at least as good as the short-term controlled studies (see, e.g., Page et al., 1987), as one would expect from other data suggesting that short-term prophylactic outcome is predictive of subsequent long-term outcome (Carroll, 1979; Cazzulo et al., 1980; Page et al., 1987).

Disparities in patient characteristics probably explain some of the discrepancy in findings. Given the widespread use of lithium, it is likely that patients who are referred to university-based research settings may already have failed to respond to lithium when administered as part of the standard treatment available in the community. They also may be diagnostically atypical. For instance, lithium was a much better prophylactic agent for the bipolar patients in the 1973 VA-NIMH collaborative study (Prien et al., 1974) than it was in the 1984 NIMH collaborative study (Prien et al., 1984), conducted after lithium was an established treatment in the community.

Differences in treatment setting also explain some of the discrepancy between recent follow-

up studies and the earlier prophylactic trials. The optimal maintenance treatment of bipolar disorder is generally not simple, especially finding the appropriate treatment for breakthrough episodes and dealing with compliance issues. Since lithium's prophylactic efficacy is widely accepted, clinicians may not pay sufficient attention to psychosocial factors that influence the patient.

Dickson and Kendell's report (1986) of a threefold increase of admissions for mania to the Royal Edinburgh Hospital between 1970 and 1981 has generated considerable interest. During that 12-year period, lithium use increased tenfold in that hospital, and the authors assert that the increase in admissions for mania "cast some doubt on the efficacy of lithium prophylaxis in ordinary clinical practice" (p. 521). However, it is questionable whether there has been a real increase in the diagnoses of mania in Edinburgh.[31] Certainly, major diagnostic shifts from schizophrenia to bipolar illness have been demonstrated in the United Kingdom (Horgan, 1981) and elsewhere (Baldessarini, 1970; Parker et al., 1985). Dickson and Kendell dismiss this possibility, citing stability in the proportion of manic, hypomanic, and schizoaffective diagnoses in their hospital over the 12 years. However, since the diagnostic shift in question is from schizophrenia to affective illness, it is difficult to see how the point helps their argument.

It is also quite possible that the actual incidence of bipolar illness could have increased, as it has in the United States (see Chapters 7 and 16).[32] Although the rate of mania in Scotland was apparently stable over those 12 years, the possibility of an increase in Edinburgh, possibly caused by immigration, was not considered. Drug and alcohol abuse increased sharply in Edinburgh during that period, which could increase the baseline rate for mania and also render more bipolar patients resistant to lithium. Also not discussed was the likelihood of increased use of antidepressant drugs during this period, with the attendant greater risk of mania and lithium-resistant mania, as suggested by Kukopulos and Tondo (1980) (see Chapter 22).

Despite its problems,[33] the Dickson and Kendell study is useful because it emphasizes two important points: First, more than two thirds of patients with major affective illness do not seek treatment (Shapiro et al., 1984), and, of those who do, many comply poorly with medication regimens (see Chapter 25). Second, the treatment available to many manic-depressive patients in the community is unfortunately still not the optimal treatment used in many studies and outlined here.

Clinical Predictors of Prophylactic Response to Lithium

Interpretation of data on response predictors for lithium prophylaxis is clouded by variability in the patient groups studied, in methods of lithium administration, in compliance, and in criteria for response. Some conclusions are nonetheless possible if the interdependence of some presumptive predictors is kept in mind. For example, if typicality of the manic-depressive features predicts lithium response, one might expect that a family history of affective illness would also predict it, since diagnostic features and family history are related. The same predictive power might also be expected from any of the biological measures associated with bipolar illness. Unfortunately, these variables are usually studied individually. The clinical predictors of response are summarized in Table 23-15.

General Demographic Characteristics

There is no association between patients age and response to lithium prophylaxis. The relationship between gender and lithium response is less clear. Only a few studies analyze results for men and women separately. Hofmann and colleagues (1974) reported better prophylactic effects for women. Rybakowski and co-workers (1980) noted that men had a greater preponderance of antidepressant over antimanic prophylactic effect, and Petterson (1977) found that although lithium's prophylactic effect on depressive episodes is the same for both sexes, it is more effective against mania in men than in women. Race, nationality, marital status, and other demographic factors have not been studied sufficiently to permit any conclusions, although Prien and colleagues (1974) found marital status to be unrelated to prophylactic outcome.

Diagnosis

The nature of the illness is probably the single most important predictor of prophylactic lithium response. Baastrup and Schou (1967) reported

Table 23-15. Clinical Predictions of Prophylactic Response to Lithium

Patient Characteristics	Prediction
Demographic	
Age	None
Sex	May differ for prevention of mania and depression
Marital status	None
Clinical	
Diagnosis	"Pure" bipolar may respond better than schizoaffective
Family history	For bipolar, shown predictive in some but not all studies. Some confounding with diagnosis
Age of onset	None
Duration of illness	Later stages may be less responsive; confounded with rapid cycling and with tricyclic use
Presence of mixed states	Somewhat poorer response
Frequency of episodes	Rapid cycling (>3 episodes / year) predicts poor reponse (? role of antidepressant treatment)
BPI vs BPII	Unclear
Episode sequence	MDI course significantly more responsive than DMI (see text)
Quality of symptom-free intervals	Fewer symptoms during intervals predict better episode prevention
Pharmacological	
Acute antimanic and/or antidepressant response	Probably predictive but no systematic data
Initial prophylactic response	4 of 5 studies report significant predictive value
Substance abuse	Interference with prophylactic efficacy

lessened response among patients with the most "atypical" features of manic-depressive illness. Although they do not define atypical precisely, their sample apparently included a number of patients in whom schizophrenia-like symptoms occurred both during manic or depressive episodes and during the interval between episodes. Such patients would probably qualify as schizophrenic by contemporary diagnostic criteria. We have just reviewed the data indicating that lithium's prophylactic efficacy among patients with recurrent schizoaffective disorder is equivalent to that among pure bipolar patients. There we noted that an episodic course with well intervals was more predictive of lithium response than was the symptomatic picture within an episode.

Clinical Features

Rosenthal and colleagues (1979) found that among bipolar patients who functioned well between episodes, those with psychotic symptoms during mania responded better to lithium prophylaxis than those without such symptoms. Several groups of investigators have associated the presence of mixed states with a relatively poor prophylactic response to lithium, at least in the short term (Keller et al., 1986; Himmelhoch et al., 1976; Prien et al., 1988). Some of the atypical patients included among the poor responders in other studies were, no doubt, patients with such mixed states.[34]

Neither the age of onset of the illness nor its overall duration predicts prophylactic response to lithium (Prien et al., 1974; Dunner et al., 1976a), although as described before, both of these variables may be useful in selecting patients most likely to need long-term prophylaxis. Prien (1984) found that bipolar patients whose first episode was manic experienced better prophylactic effects with lithium than did those whose first episode was a depression.

Frequency of Episodes

Virtually all studies of lithium's prophylactic efficacy have focused on patients with relatively frequent episodes, a practical necessity for outcome-based research. However, clinical experience supports the assumption that patients with less frequent episodes also respond to lithium prophylaxis, and at least two controlled

studies provide some support for this conclusion. When Prien and colleagues (1974) and Dunner and associates (1976a) separately compared patients with moderate frequencies (one to two episodes every 2 years) and those with lower frequencies (no episodes in two years preceding the study), no significant difference in lithium prophylaxis was found. Patients with rapid cycles (three to four or more episodes per year) have a significantly reduced prophylactic response to lithium.[35] There is some evidence that depressive episodes of patients with rapid cycles are more resistant to lithium than manic ones. The relationship among antidepressant drugs, rapid cycling, and lithium resistance in patients with rapid cycles, as well as alternate approaches to the management of these patients, are discussed in Chapter 22 and previously in this chapter.

Type and Sequence of Episodes

The differential prophylactic effect of lithium in bipolar-I and bipolar-II patients is difficult to tease out of the original lithium prophylactic studies, which were conducted when the boundaries between bipolar I and bipolar II had not been delineated. Undoubtedly, some of the patients included in earlier bipolar groups would be classified as bipolar II under RDC.

Dunner and colleagues (1976a) initially noted that depressive episodes were more effectively prevented in bipolar-I than in bipolar-II patients, although in an update of their data (Dunner et al., 1979), they did not replicate this finding. Kukopulos and colleagues (1980) and Quitkin and coworkers (1978) found that bipolar-II patients experienced a significant prophylactic effect of lithium against depression. When interpreting any pharmacological differences between bipolar-I and bipolar-II patients, one must consider the possibility that the higher incidence of personality and other axis-II disorders among bipolar-II patients (substance abuse, e.g.) could affect drug response (Abou-Saleh and Coppen, 1986).

How lithium prophylaxis is related to episode sequence has not been considered in the major controlled studies. However, in their systematic observations on 434 bipolar patients in a clinical setting, Kukopulos and colleagues (1980) noted significant differences in lithium prophylaxis as a function of episode sequence. They divided their patients into three groups on the basis of the sequence of their episodes: the classic mania-depression-normal interval (MDI) course, which involves a switch into mania from a normal interval, followed by depression, then back to a normal interval, the depression-mania-interval (DMI) course, in which the most profound change occurs—the switch from depression into mania—and the continuous circular (CC) course, in which there is essentially no normal interval (i.e., any symptom-free period is less than 2 weeks). The differential lithium response rates in the three groups are summarized in Table 23-16. The classic MDI course was associated with the most favorable prophylactic response. The DMI course had significantly more patients with only partial responses. Patients with the CC course and short cycles (analogous to rapid cycles) show essentially no response to lithium, and continuous cycles with long cycle lengths respond reasonably well. The best lithium responders in this study were bipolar-II patients with the classic MDI course; all of them showed at least a partial response. Kukopulos's finding has been replicated by three groups (Haag et al., 1987; Grof et al., 1987; Maj et al., 1989), all of whom noted a significantly more favorable prophylactic response among the MDI patients than among the DMI patients. The study of Maj and colleagues is especially noteworthy, since it is limited to patients not previously treated with lithium and prior course was evaluated independently of lithium efficacy. The relatively poor results in patients with the DMI course may reflect the impact of tricyclics given to treat depression; that is, the mania following a depression may often be drug-induced, and such manias may be relatively resistant to lithium treatment.

The pattern of the onset of manic episodes (abrupt vs gradual) was evaluated by Dunner and colleagues (1976a) and found to be unrelated to prophylactic response to lithium. This important issue merits further study. Finally, Post and associates (1988) have suggested that lithium prophylactic efficacy is reduced in the later stages of the illness, an observation that is confounded by rapid cycling and antidepressant treatment.

Acute Response in Mania or Depression

To our knowledge and surprise, there are no systematic studies on the relationship between acute

Table 23-16. Differential Lithium Response Rates

Type of Course	Patients N	Response to Lithium Prophylaxis % Good	Partial	Poor
MDI	119	61	19	20
DMI	78[a]	33		67
CC-long cycle	56	57	20	23
CC-short cycle (rapid cyclers)	50	16	12	72

MDI = Mania, followed by depression, followed by a well interval
DMI = Depression, followed by mania, followed by a well interval
CC = Continuously circular (no well interval exceeding 2 weeks)

[a]32 of these patients (41%) developed a continuously circular course while on lithium

Adapted from Kukopulos et al.,1980; similar results have been obtained by Haag et al., 1986, and by Maj et al., 1989.

antimanic or antidepressant response to lithium and prophylactic response, although clinical experience suggests that acute response probably does predict prophylactic response. There are reports of a significant association between the initial response (during the continuation phase, i.e., the first 6 to 12 months) and the subsequent response.[36] Likewise, in their follow-up study, Prien and colleagues (1974) found that patients who relapsed during the first 6 months on lithium showed a strong tendency to additional relapses in the ensuing 18 months. We must remember, however, that nonpharmacological factors could influence these results. In the multihospital VA setting with a large number of clinicians using lithium for the first time, early relapses may have resulted in considerable discouragement for both physicians and patients, causing less vigorous continued management and reduced compliance. Further study is needed in this area, since clinical experience suggests that an initial failure does not represent adequate justification for discontinuing lithium. We must recall also the frequently cited observation (based primarily on gradual improvement in subclinical episodes) that lithium's prophylactic efficacy improves with time (Schou et al., 1970a). Whether this also applies to major relapses in patients carefully maintained on optimal levels of lithium with good psychosocial support and compliance has not been systematically studied.

Coexisting Problems

Some conditions that exist along with manic-depressive illness, such as the previously noted schizophrenic-like symptoms, also affect lithium's prophylactic efficacy. Presence of alcohol abuse has been associated with decreased lithium response (see, e.g., Himmelhoch et al., 1976; Prien et al., 1974), although the contribution of poor compliance to these results has not been evaluated. Alcohol abuse may be more likely to occur in association with mixed states, which, as we have seen, are associated with relatively poor prophylactic response to lithium. Himmelhoch and associates (1980) noted a relationship between coexisting neurological difficulties and relatively poor response to lithium. The primary problem was the patients' decreased ability to tolerate adequate prophylactic levels of lithium because unacceptable neurotoxicity developed even at low levels. At least one study (Himmelhoch et al., 1976) has shown that the coexistence of other medical illnesses, although complicating administration of lithium, does not interfere with its prophylactic efficacy.

The coexistence of drug abuse has been associated with poor prophylactic response (Himmelhoch et al., 1980). This area requires further study to evaluate the contributions of diagnostic specificity and of lithium compliance. Regarding this latter point, it is possible that individuals prone to alter their moods by taking drugs might also alter them by stopping a drug such as lithium.

Personality characteristics have been examined as predictors of lithium response (reviewed by F.N. Johnson, 1984 and by Abou-Saleh and Coppen, 1986), most in relation to short-term response. It is difficult to interpret these findings because variations in compliance have not been

controlled. Lane (1985) noted that patients who did not respond to lithium evidenced continued psychopathology between episodes as measured by the Minnesota Multiphasic Personality Inventory (MMPI). Similarly, O'Connell and colleagues (1985) found that the quality of the patient's social support system predicted good outcome among 60 bipolar patients, but here too differences in compliance were not controlled. Personality predictors of lithium response are discussed in Chapter 12 (see, especially, Table 12-9).

Family History

Many studies that have examined family history show a significant association between a positive family history of bipolar illness and a good prophylactic response to lithium,[37] but not all agree (Dunner et al., 1976a; Misra and Burns, 1977). In an interesting twin study, Mendlewicz (1979) found that identical twins concordant for affective illness have a significantly higher rate of lithium prophylaxis compared with those whose identical twin did not have the illness.

Patient Compliance

All efforts at prophylaxis with lithium are affected by patient compliance. Some estimates of lithium noncompliance exceed 50 percent (see Chapter 25), making it probably the most important variable contributing to differences in prophylactic efficacy (Baastrup, 1969). It may be an especially important intervening variable in the association between certain personality types or behavioral disorders (e.g., substance abuse) and poor lithium response.

Predictors Among Unipolar Patients

Some of the studies cited previously, principally the European ones, included recurrent unipolar patients in the sample but generally did not analyze them separately. Abou-Saleh and Coppen (1986) found that among their recurrent unipolar patients, good prophylactic response to lithium was predicted by more endogenous features, the presence of pure familial depressive disease (see Chapter 5), less personality disturbance, and a good response to lithium during the first 6 months. It has also been suggested that effective lithium prophylaxis among unipolar patients is predicted by the presence of bipolar features, such as high episode frequency, early age of onset, and family history of mania (Ramsey and Mendels, 1978). Thus, Schou (1979) concludes that the prophylactic efficacy of lithium among unipolar patients with a cycle length between 12 and 24 months (i.e., an episode every year or two, a typical cycle frequency for bipolar patients) is equivalent to that among bipolar patients. Akiskal cites early age of onset and family history of mania ("pseudounipolar" characteristics) as associated with a good prophylactic response to lithium (Akiskal, 1983; Akiskal and Mallya, 1987). Although this formulation corresponds with our clinical experience, controlled data are lacking.

Conclusion

As in general prophylactic studies, investigations of predictors of response to lithium prophylaxis tend to select patients with relatively serious forms of manic-depressive illness and use relatively narrow episode frequency criteria. These limitations must be kept in mind in applying response predictors to clinical practice. In addition, as noted earlier, since the studies we have reviewed focus on a single variable at a time, the contribution of any individual variable relative to the others is not known.

Grof and associates (1979a) tried to remedy this situation in a very careful longitudinal study of 90 patients followed on lithium for an average of 9 years. Evaluating a wide range of clinical features, they conducted a discriminate function analysis on an initial sample, then replicated it with a separate group of patients. The majority of variance in lithium prophylactic response (i.e., reduction in episode frequency) could be accounted for by the following three factors: (1) the diagnosis, (2) the quality of the symptom-free interval, and (3) the recent frequency of episodes. They noted that a good prophylactic response to lithium became increasingly more likely the closer the patient met the criteria for a true recurrent endogenous disorder (involving not only disturbances in mood but also functional incapacity and other carefully defined diagnostic features of manic-depressive illness). They also observed that the more normal the free interval between episodes, the more likely was a good response to lithium. Patients with a history of very frequent recurrences did not show good prophylactic re-

sponses. Using this multivariant discriminant analysis, the investigators predicted prophylactic response (or nonresponse) correctly in 87 percent of the patients.

Side Effects of Lithium

In this section, we review the extensive literature on the side effects of lithium, examining first the subjective complaints of patients, then evidence of the drug's effects on organ systems.[38] Studies reporting rates of individual subjective complaints, which are critical to compliance, are summarized in Chapter 25 (Table 25-8), and the pooled data[39] from these individual studies are displayed in Table 23-17.

Subjective Complaints

Most patients receiving lithium experience some side effects. Some effects are relatively pronounced at the beginning of treatment but generally diminish or disappear rapidly (e.g., gastrointestinal symptoms) or more gradually (e.g., tremor in some patients). Surveys of large numbers of patients in lithium clinics (see Chapter 25) indicate that frequency of subjective complaints of individual side effects ranges from approximately 65 percent to 90 percent, roughly twice the rate recorded in manic-depressive patients not on medication (Cassidy et al., 1957).

Not listed in Table 23-17 are the less frequent side effects, including skin problems, loss of libido, and altered taste sensation. In some of the studies reviewed, certain complaints were elicited by specific questions (e.g., tremor, thirst, weight gain, diarrhea, and edema in the Vestergaard study), whereas others were volunteered by the patients, thereby introducing some bias based on what was expected. Indeed, in an earlier study from the same clinic as Vestergaard's (Schou et al., 1970b), the "big five" were reported far less frequently when only spontaneous reports were counted. The very important issue of memory complaints is discussed subsequently.

Table 23-17. The Most Frequently Reported Subjective Side Effects of Lithium[a]

Side Effect	Pooled %
Excessive thirst	35.9
Polyuria	30.4
Memory problems	28.2
Tremor	26.6
Weight gain	18.9
Drowsiness/Tiredness	12.4
Diarrhea	8.7
No complaints	26.2

[a] Pooled percentages from 12 individual studies. Refer to Table 25-9 for data on the individual studies

Sex differences in the rates of reported side effects have received little study. Although Vestergaard and colleagues (1980) and Johnston and co-workers (1979) did report that men complain of tremor more frequently than do women, Duncavage and associates (1983) and a more recent and extensive study from Schou's group (Vestergaard et al., 1988) found no such sex difference.

Side effects become increasingly problematic as people age. The very young tend to tolerate lithium as well or better than middle-aged adults, even over long periods (DeLong and Aldershof, 1987). The elderly must be carefully monitored for signs of toxicity, primarily because of decreased renal clearance.[40]

Some studies, such as those of Judd and colleagues (1977; Judd, 1979), have used normal subjects to evaluate subjective side effects of lithium in order to isolate them from symptoms of the illness being treated. Interpretation of these studies is somewhat limited, however, because lithium was administered for too short a duration for side effects to begin to attenuate, as they are observed to do in clinical practice.

In Chapter 25, we deal with the relationship between subjective side effects and noncompliance and review the complaints most frequently cited as reasons for discontinuing lithium. Side effects may be the most important reason for discontinuing lithium. In a 10-year follow-up of 74 patients, 9 percent had to permanently discontinue lithium because of side effects (Holinger and Wolpert, 1979). McCreadie and Morrison (1985), in a study of lithium discontinuance patterns in southwest Scotland, found that 40 percent of the lithium patients had discontinued the drug; 28 percent of the total patient population attributed their having stopped to side effects. In a long-term follow-up study of 59 lithium patients treated in Britain, Page and associates (1987) found that 19 percent stopped lithium because of side effects. Interestingly, the

three side effects that contribute most to noncompliance involve the CNS, a system that has received perhaps too little emphasis in the studies summarized in Table 23-17.

The well-established, clear relationship between lithium blood level and side effects in individual patients does not appear in cross-sectional studies (Vestergaard et al., 1980; Johnston et al., 1979), probably because clinicians lower the dose (and blood level) in response to side effects. The relationship between blood levels and side effects may also be obscured by individual differences in tissue sensitivity to lithium. Nevertheless, longitudinal studies do show that the lower doses of lithium currently in use (average blood level of 0.67) are associated with a lower incidence of a broad range of side effects when compared with the earlier practice associated with blood levels that were, on average, 30 percent higher (Coppen and Swade, 1986; Vestergaard and Schou, 1988).

Elizur and colleagues (1977) and Zakowska-Dabrowska and Rybakowski (1973) have suggested that the ratio of red cell lithium to plasma lithium may correlate more closely with certain side effects than the plasma level alone, but not all studies support this hypothesis. The type of lithium preparation appears unimportant. Neither Vestergaard and co-workers (1980) nor Johnston and colleagues (1979) could find any difference in overall subjective side effects when they compared sustained-release lithium with standard preparations. Bone and associates (1980) found that patients complained significantly less frequently of lithium side effects when euthymic than when either depressed or manic, but Lyskowski and colleagues (1982) found the opposite.

Effect of Long-Term Lithium on Organs and Systems

Lithium affects all parts of the body, but three targets are the most important: thyroid, kidney, and the CNS, especially when treatment extends over a long period. These effects are outlined in Table 23-18.

Thyroid. Since the first description of goiter in lithium-treated patients (Schou et al., 1968), the ion's antithyroid effects have been studied extensively and shown to involve several different mechanisms (Berens and Wolff, 1975; Cho et al., 1979). Although relatively few patients experience actual clinical hypothyroidism when treated with lithium, milder manifestations of lowered thyroid function are frequent. From the literature, Männistö (1980) calculated that definite clinical hypothyroidism occurs among 3.28 percent of lithium-treated patients, with women predominating nine to one. However, goiter was encountered in about 5 percent of patients, primarily in those without clinical hypothyroidism, and slightly more frequently in males (Myers et al., 1985). Using broader criteria for hypothyroidism, Wolff (1974) calculated an overall rate of 14 percent. Even higher figures, with estimates ranging up to 34 percent (Männistö, 1980), were obtained when patients were counted who had at least one abnormal thyroid laboratory test during lithium administration. However, Schou's group found that when T_4 and TSH were studied longitudinally, the initial decrease in T_4 was reversed with time, returning to the prelithium level within 12 months (Maarbjerg et al., 1987). These investigators found a low incidence of patients requiring thyroxine treatment for hypothyroidism and recommended that single low values be reevaluated over time.[41] A substantially higher incidence of hypothyroidism has been noted in three other longitudinal studies—7.8 percent at a mean of 3.4 years on the drug (Yassa et al., 1988), 19 percent at a mean of 6.8 years (Joffe et al., 1988), and 42 percent at a mean of 15 years (Stancer and Forbath, 1989).

One problem in evaluating the effect of lithium on thyroid function is the relatively wide range of normal values; substantial changes can occur in individual patients without their falling outside the normal range. In one study that measured the effect of lithium on thyroid, Transbøl and coworkers (1978) evaluated 86 patients on long-term lithium treatment and compared them with a control population. Elevated TSH levels were found in 23 percent (39 percent of the women) of the lithium-treated patients. Significant reductions in free T_3 and T_4, averaging 25 percent, were associated with the TSH elevations. This reduction within the normal range may have clinical significance. Thus, in a group of patients who had been on lithium for at least 6 months, Hatterer and colleagues (1989) found a significant association between low-normal T_4 and complaints of lethargy and cognitive impairment. Moreover,

Table 23-18. Systemic Effects of Lithium

Thyroid
- Hypothyroidism in 5-35% of patients — *apparently dose-related*
- Nontoxic goiter in 4-12% of patients

Kidney[a]
- Tubular function impairment — *related to dose and duration of treatment*
  - Decreased renal concentrating ability in 15-30% of patients
  - Polyuria in 50% of patients transiently — *persists in 20-40% of patients on long-term maintenance therapy*
- Glomerular function preserved
- Histological change not lithium specific

Nervous System[a]
- *Usually transient and dose-related; significant as reasons for noncompliance; intensification may be evidence of neurotoxicity*
- Fine tremor in 33-65% of patients — *more frequent in males; persists in 4-50% of patients in maintenance therapy*
- Decreased motor coordination — *mild ataxia may signal toxicity*
- Muscular weakness
- Extrapyramidal
- "Cogwheel" rigidity (slight in most) in 48-59% of patients — *associated with longer treatment*
- Nonspecific EEG changes
- Cognitive and memory function (see Chapter 18)

Metabolic
- Weight gain in 11-33% of patients — *some may be secondary to hypothyroidism or to thirst-related increases in caloric intake*
- Altered glucose metabolism
- Hyperparathyroidism — *rare*
- Mild decalcification, but without clinical osteoporosis

Dermatological[a]
- Maculopapular and acne-like lesions — *occur early; reversible; may not recur on resumption of lithium*
- Psoriasis — *not uncommon in patients with a past or family history of psoriasis*
- Moderate hair loss infrequently reported — *almost all cases female*

Cardiovascular[a]
- EKG: T-wave flattening or inversion — *benign; reversible*
- Sinus node dysfunction — *rare; reversible*
- Cardiac arrythmias — *rare, generally dose-related*

Gastrointestinal
- *Transient, related to rapid dose increase and timing of dose*

Respiratory (see text)

Teratogenic (see discussion of lithium and pregnancy in Table 23-7 & 23-7a)

Many of the systemic effects are reflected in subjective complaints (see Table 25-10).

FN Johnson (1984) has reviewed the literature on the potential effects of lithium on sensory systems.

[a]Effects to these systems constitute the majority of the inquiries received at the Lithium Information Center (Carroll et al., 1986).

mean T_3 within the normal range was significantly lower in patients who relapsed, and it inversely correlated with affective state.

One of the factors contributing to the relatively high rate of lithium-related thyroid effects is a higher than normal rate of prior thyroid disease in this population (Whybrow et al., 1969), especially among rapid-cycling patients (Cowdry et al., 1983; Bauer and Whybrow, 1988a). There is also a greater frequency of a family history of thyroid disease, reported as 14 percent in one study (Lazarus et al., 1981). Of the many potentially abnormal thyroid indices in patients on lithium, a relatively high prevalence of thyroid autoantibodies (15 to 30 percent in different studies) is of interest because it suggests a mechanism for

antithyroid effects (Lazarus et al., 1981, 1986; Deniker et al., 1978). In fact, two studies (Calabrese et al., 1985; Myers et al., 1985) suggest that the presence of autoantibodies before treatment may be disproportionately associated with the development of hypothyroidism on lithium, since the ion produces a further rise in antibody levels. The effects of lithium on thyroid and other endocrine systems has been extensively reviewed by Lazarus (1986).

Kidney. Since the kidney provides virtually the only excretion route for lithium, good renal function is critical for lithium-treated patients. It has long been known that lithium reduces the kidney's ability to concentrate urine, an effect that is largely reversible.[42] Similarly, although serious renal complications were long known to accompany lithium intoxication, the renal effects seen in normal dose ranges were considered innocuous and reversible. Reports of histological changes in the kidneys of patients on long-term lithium prompted a major reevaluation of the question of renal effects, however.

The initial studies of kidney morphology[43] were conducted in patients already showing signs of lithium toxicity or renal problems, such as severe polyuria. Among the 54 patients examined in these studies, 53 had at least one abnormal biopsy. These alarming initial histological reports stimulated a more careful renal biopsy study in which the patients on lithium were not selected for clinical evidence of renal pathology or intoxication (Rafaelsen et al., 1979). Of the 37 patients who volunteered for biopsy, 6 (15 percent) showed histological abnormalities. As in the earlier report, the histological changes involved interstitial fibrosis, tubular atrophy, and sclerotic glomeruli.

Although there is still some controversy concerning the incidence and specificity of the histological changes, the reports set in motion a useful, comprehensive evaluation of lithium's effect on kidney function. The conclusions are summarized in Table 23-18. There is little evidence of any deleterious lithium effect on filtration, the most important renal function. In the studies reviewed, more than 90 percent of the patients showed glomerular filtration rates (GFR) in the normal range, with very few below 50 ml/minute and none below 20 ml/minute.[44] In an interesting study comparing 101 patients on long-term lithium with a control group of patients with affective disorders but not on lithium, no effect of the ion on glomerular filtration (creatinine clearance) was found, and, in fact, men who had never been exposed to lithium (but who had received other psychotropic drugs) actually had a significantly lower clearance than did men treated with lithium (Coppen et al., 1980). In a similar study comparing 268 patients treated with lithium for an average of 38 months with 59 affectively ill controls not on lithium, Gelenberg and colleagues (1987) found no renal damage associated with lithium and only a slight but not significant decrease in GFR. They did, however, note a modest, statistically significant decrease in GFR in association with concomitant antipsychotic therapy. A study using a sensitive measure of GFR (DePaulo et al., 1986) reported a small negative correlation with duration of lithium therapy in a group of 86 patients, but the correlation could be attributed to just a few subjects apparently predisposed to progressive lithium-induced polyuria. Caution in the long-term use of neuroleptics and lithium together is, however, suggested by the small study of Bucht and colleagues (1980), who found more pronounced histopathological changes and lower concentrating capacity in ten patients on combination therapy than in ten who were taking lithium alone.

Thus, the combined clinical experience of a large number of lithium clinics suggests little or no clinically important effect of lithium on glomerular function. This experience is reinforced by individual studies and reviews[45] indicating that while lithium decreases GFR slightly, by and large the measure remains within the normal range. Furthermore, no association has been found between lithium administration and renal failure or terminal azotemia requiring dialysis, even in patients continually on the drug for 20 years or more. It is important to note, however, that lithium administration under research clinic conditions (careful monitoring, tendency to use lowest effective dose) is not always replicated in practice settings (Masterton et al., 1988). Thus, the possibility of glomerular filtration problems cannot be ignored.

The effects of lithium on renal tubular function are well established. Estimates of lithium-related impairment in renal concentrating ability range

from 15 to 30 percent, an effect that appears to be related to dose. Among 788 patients in nine separate studies, persistent lithium-related polyuria (24-hour urine volume greater than 3 liters) was found in 23 percent. More severe cases of polyuria have been described as lithium-induced NDI, sometimes requiring discontinuation of lithium (Schou, 1968). The study by Coppen and colleagues (1980) is again of interest, since these investigators reported only a very modest difference in concentrating ability between lithium-treated patients and manic-depressive patients not treated with lithium. The low incidence of this effect in the British study may be due, in part, to the practice at that time of using lithium doses lower than in the Scandinavian studies, where more polyuria was encountered.

In summary, the continuous use of lithium over many years does not seem to lead to clinically significant alterations in glomerular filtration. However, tubular concentrating ability is impaired in some patients, and the extent of impairment appears to be related to dosage and, to a lesser extent, to the duration of lithium treatment. Initially, Schou suggested that this effect may be greater in patients who have high peak blood levels associated with once a day administration of regular lithium preparations. Plenge and colleagues (1982) and Grof and co-workers (1982) reported lower urine volume with single-dose lithium, and Rafaelsen and colleagues (1979) suggested there may be an advantage to a single-dose regimen. To answer this question, a study directly compared the Schou and the Rafaelsen clinics (Schou et al., 1982). Single daily doses of regular lithium were found to be associated with less effect on distal tubular function, as reflected by urinary volume.[46]

Certainly, renal problems are more extensive in patients who have had episodes of lithium overdose and intoxication. The possibility that these changes could become irreversible provides a strong reason for scrupulously avoiding periods of lithium intoxication. It is now clear, however, that when lithium intoxication occurs it is due to deliberate overdose or an inappropriately high blood level, usually the result of a failure to adjust the dose during periods of physical illness with fever and dehydration (Schou et al., 1989).[47]

Knowledge concerning lithium's effects on the kidney is quite extensive, more so than most long-term drug effects in medicine. The main effect, decreased concentrating ability in some patients, does not portend a functional deficit in the kidney. Rather, it constitutes an inconvenience that only infrequently becomes a reason for discontinuing lithium. Knowledge of this complication of course underlines the need to monitor kidney function carefully and to maintain adequate hydration.

Nervous System. Side effects related to the nervous system are prominent at the initiation of lithium treatment, but as some accommodation develops, they recede to a more subtle place in the hierarchy of symptoms. Neurological and neuromuscular effects are generally sensitive to blood level, the presence of other CNS-active drugs, and individual patient characteristics, such as age and preexisting neurological status. The importance of these effects stems from two considerations. First, the exaggeration of these subtle changes (particularly those affecting the CNS) often provides the first and most reliable clue to impending toxicity. Second, CNS effects seem to be disproportionately important as reasons for noncompliance. Indeed, because of the importance of the cognitive effects of lithium to compliance, we have chosen to review that entire topic separately.

Tremor, one of the most commonly reported side effects, affects from 30 to 70 percent of lithium-treated patients. It is generally a fine tremor of the hands that tends to become exacerbated with intentional fine coordinated movements. Tremor can vary in intensity, perhaps in relation to mood, psychological stress, and drugs, such as caffeine and antidepressants. In some patients, it decreases with time, although not invariably. It can be treated with β-adrenergic receptor blockers, such as propranolol and atenolol.

Decreased motor coordination occurs more frequently than is generally assumed, perhaps because patients do not volunteer complaints. It is most noticeable early in treatment, but gradually becomes attenuated, a process that probably includes elements of true tolerance as well as adaptive learning. This phenomenon is most clear in athletes,[48] who frequently alter the way they play a game (such as tennis or golf) to compensate for their decreased coordination.

Muscular weakness is noted primarily at the

beginning of treatment. Although most patients do not complain of it beyond this point, some experience decreased tolerance for prolonged exercise, such as long-distance running. It is not clear to what extent these subtle effects are neuromuscular in origin or related to other metabolic changes.

Although extrapyramidal side effects are not commonly seen, concern about them increased after Shopsin and Gershon (1975) reported cogwheel rigidity in 16 of 27 patients receiving lithium, with the incidence related to duration of treatment. Of the 20 patients on lithium for a year or more, 15 showed evidence of cogwheeling. However, in a careful study of 100 patients on lithium alone, Asnis and colleagues (1979) found a moderate level of cogwheel rigidity in 7 percent and very slight evidence of it in an additional 26 percent. Among those on lithium plus neuroleptics, the rate jumped to 55 percent, although symptoms were moderate in most of these patients. Since lithium has some modest antidopamine effects, one might expect mild extrapyramidal symptoms and synergism with neuroleptics. In addition to their association with neuroleptics, the cogwheel symptoms were correlated with older age, higher lithium levels, longer duration of treatment, and the presence of a more marked lithium tremor. These side effects do not respond to anticholinergic medications.

Some (Perényi et al., 1984; Mukherjee et al., 1986) but not all (Waddington and Youssef, 1988) studies of tardive dyskinesia in manic-depressive patients[49] show an association between the syndrome and the duration of neuroleptic treatment. The suggestion that lithium might induce tardive dyskinesia, an inference drawn primarily from case reports, has not been supported by most systematic studies (Perényi et al., 1984; Mukherjee et al., 1986; Waddington and Youssef, 1988). One study, however, links a higher incidence of tardive dyskinesia with longer periods of lithium administration (Dinan and Cohen, 1989), and the question remains unresolved.

Changes in the electroencephalograph (EEG), such as increased amplitude and generalized slowing, are clinically benign at usual lithium doses and may not be detectable. As blood levels of lithium increase, so do EEG changes, which then correlate with the emergence of neurotoxic symptoms (Small and Small, 1973). A few seizures have been cited in case reports, but the relationship to lithium is often not clear. At any rate, at routine blood levels and in the absence of neurotoxicity, a seizure would be an extremely rare occurrence. Among bipolar patients with concomitant seizure disorders, Shukla and colleagues (1988) did not find any worsening of seizure frequency on lithium, and it did not induce seizures in those whose seizure disorder was in remission. Benign intracranial hypertension (pseudo-tumor cerebre), that is, increased intracranial pressure of unknown etiology, has been linked to lithium administration by scattered case reports (see, e.g., Saul et al., 1985 and Cermeño, 1989). Since the syndrome typically occurs and remits spontaneously, a link to lithium is not yet established.

Cognitive Effects. The well-known neurotoxic effects of lithium are documented extensively in the literature.[50] Since the drug's primary action is mediated through the central nervous system, it is not surprising that lithium can cause cognitive impairments of varying types and degrees of severity. Indeed, memory problems are among the side effects of lithium treatment that patients report most frequently (see Chapter 25). Although affective illness itself contributes both to cognitive deficits (see Chapter 11) and complaints about such deficits (Coppen et al., 1978; Abou-Saleh and Coppen, 1983; Englesmann et al., 1988), it is important to bear in mind that impairment of intellectual functioning caused by lithium is not uncommon and, in many patients, leads to noncompliance. Creativity can also be affected (see Chapter 14).

The many complex methodological problems involved in studying cognitive changes associated with lithium have led to conflicting results.[51] In their review of the literature, Ananth and colleagues (1987) found that evidence was equivocal for lithium-induced cognitive impairment, partly because of sample heterogeneity and concurrent affective illness. Animal studies reviewed by Ananth and colleagues were inconclusive, since it is difficult to distinguish toxic effects from pharmacological effects of the drug in nonhuman animals. The authors concluded: "There is no convincing proof that lithium causes memory disorders." Jefferson and associates (1987), on the other hand, while acknowledging the major

methodological problems in this literature, found "evidence of impaired cognitive and motor functioning" caused by lithium. Judd and colleagues (1987) came to similar conclusions and wrote, in their summary of lithium's effects on normal subjects, that

> . . . lithium often induces subjective feelings of cognitive slowing together with decreased ability to learn, concentrate and memorize. In addition, controlled studies have consistently described small but consistent performance decrements on various cognitive tests, including memory tests. The available data suggest that the slowing of performance is likely to be secondary to a slowing in rate of central information processing. (p. 1468)

Evidence for lithium's detrimental effects on long-term memory, associative processing, semantic reasoning, memory retrieval, and speed of cognitive and psychomotor performance comes, in fact, from many studies.[52] Results from investigations of lithium and intellectual functioning in patients are less consistent, although certainly suggestive.[53]

Evidence to date, although somewhat inconclusive, leads us to believe that cognitive problems from lithium are far from rare. Our clinical experience, along with that of many of our colleagues, suggests the same conclusion. Furthermore, the fact that lithium exerts its ameliorative effects through the CNS and, at high doses, is neurotoxic suggests that cognitive processes also might be affected. Cognitive problems are too often dismissed as being simply secondary to the affective illness rather than to lithium or to some combination of lithium and underlying illness. Because these effects usually vary with the serum level, here is yet another reason for keeping patients at the lowest effective lithium level.

Neurotoxicity. Clinical signs and symptoms of neurotoxicity (see Table 23-4), which are quite similar to those encountered with other CNS poisonings, provide an early indication of generalized lithium toxicity. Early signs, occurring at levels of 1.3 to 2.0 mEq/liter and entirely reversible, include confusion, cognitive impairment, lassitude, disorientation, slurred speech, restlessness, and irritability. The last two symptoms can be difficult to distinguish from the mixed affective states that are part of the illness in many patients. West and Meltzer (1979) reported on five patients who developed neurotoxicity, some at relatively modest blood levels (0.7 to 1.7 mEq/liter). These patients had marked anxiety and psychosis during mania, symptoms that the investigators suggested might be associated with increased vulnerability to neurotoxic effects. This finding is of interest in light of the naturalistic observation that psychotic mania is frequently associated with organic symptoms, such as delirium (Kraepelin, 1921; Carlson and Goodwin, 1973). Lithium-induced delirium resolves 1 to 2 weeks after levels return to normal (DePaulo et al., 1982). As the neurological syndrome progresses, frank cerebellar symptoms, ataxia, choreiform or parkinsonian movements, and seizures can occur. This stage is not always reversible, and coma and even death may follow.

In his literature review on long-lasting neurological consequences of lithium intoxication, Schou (1984) noted that coexisting physical illness and use of neuroleptics were very frequent in such patients. Fortunately, the early symptoms usually begin over a number of days. Thus, if the clinician, patient, and family are alert to this possibility, early intervention can be effective.

One group noted the benefits of the early use of hemodialysis (Apte and Langston, 1983). After reviewing the charts of 55 patients with lithium intoxication, Gadallah and colleagues (1988) concluded that hemodialysis should be used when symptoms are severe or when serum lithium levels are high in chronically intoxicated patients (who almost always do show severe symptoms). They found that serum lithium concentrations alone were a poor indicator of severity of the intoxication. Toxicity that developed gradually during maintenance therapy, even at serum concentrations in the therapeutic range, was associated with more serious symptoms than the acute intoxication resulting from a suicidal overdose. However, none of the patients in the Gadallah sample died or suffered permanent impairment as a result of the lithium intoxication.

Reports of more frequent lithium-related neurotoxicity in older patients are somewhat misleading. Age per se probably does not substantially increase the risk of neurotoxicity, but since renal clearance in older patients is decreased, they achieve higher lithium levels on standard doses and are more likely to have elevated blood levels unless the clinician is very careful. Older

people are also more vulnerable to lithium-induced neurotoxicity because neurological problems that are independent of their psychiatric illness or its treatment become more common with increasing age, as does the likelihood of being on other drugs.

Some investigators have reported a relationship between neurotoxicity and a higher ratio of red cell to plasma lithium (see, e.g., Elizur et al., 1977), although others have disagreed (West and Meltzer, 1979). Evidence from animal and human studies suggests that brain concentration of lithium may be a more significant measure of neurotoxicity than is serum level. Brain concentrations of lithium rise more slowly after initial administration and stay higher than serum levels after a steady state is attained. Lithium uptake in the brain is not uniform. Some parts of the brain may have toxic concentrations even though the serum level is within the therapeutic range (reviewed by Sansone and Ziegler, 1985).

Since the report by Cohen and Cohen (1974) of irreversible brain damage associated with the combined use of lithium and haloperidol (see Chapter 21), there has been considerable interest in this question. However, recent extensive reviews indicate that if any special synergistic neurotoxicity exists at all, it is uncommon. Nonetheless, these two classes of drugs certainly have additive effects, and when high doses of both are used together, some neurological symptoms can be expected.

In summary, we should refer to the experience of Schou and his colleagues (1989), who studied all cases of lithium intoxication that were recorded for their region of Denmark over a 9-year period. During a total exposure time of 4,900 patient years, there were 24 cases of intoxication. Because each case had a probable cause, principally a suicide attempt or obvious mismanagement, the authors concluded that this complication is quite predictable and, therefore, preventable in most cases.

Cardiovascular System. Lithium has a variety of effects on the heart, which are generally benign. Most common is flattening and inversion of the T-wave on the EKG, seen most often when sensitive measures are used. Lithium's ability to affect conduction mechanisms (Tilkian et al., 1976) or to cause sinus node dysfunction (Roose et al., 1979) or sinoatrial block (Mitchell and MacKensie, 1982) may be particularly relevant for elderly patients, who are generally more prone to develop these dysfunctions than are younger patients.

There are occasional reports of arrhythmias in patients on lithium. After comprehensively reviewing the literature, Albrecht and Müller-Oerlinghausen (1980),[54] concluded that with careful lithium management, arrhythmias are extremely rare. Six of the ten reported cases involved preexisting heart disease or additional psychotropic medication. Shopsin and colleagues (1979) reported that 4 of their 105 patients taking lithium had died suddenly, a rate that is well above the expected mortality rate. The patients, who were 47, 61, 66, and 69 years old, had family histories of severe cardiac pathology. The authors suggested that lithium may unmask an underlying cardiac defect in highly susceptible individuals.

In a follow-up study of 791 Scottish patients treated with lithium for more than 2 months between 1967 and 1976, Norton and Whalley (1984) found that the mortality rate was similar to the (excess) mortality observed among manic-depressive patients in the prelithium era (see Chapter 6).[55] Similarly, Glen and colleagues (1979) found no relationship between death while on lithium and the length of time on the drug.

Metabolic Effects. Studies of the metabolic effects of lithium have focused on alterations in glucose metabolism, partly because of the very common side effect of weight gain (Peselow et al., 1980; Mellerup et al., 1983; Garland et al., 1988). These studies are confusing and conflicting, probably because of lithium's multiple effects on enzymes and receptors involved in these processes. Lithium's inhibition of cyclic AMP formation is well established and would be expected to produce insulin-like effects, particularly increased cellular glucose uptake, decreased lactate formation, and increased glycogen formation and storage. Although lithium has intensified diabetes in some patients (Mellerup et al., 1983), its long-term use is not associated with any increase in blood sugar (Vestergaard and Schou, 1987), and to our knowledge, it has not been associated with the induction of diabetes de novo.

Lithium produces mild to moderate primary hyperparathyroidism, reflected both in increased

parathyroid hormone concentrations (Christiansen et al., 1978) and in modest increases of serum calcium and magnesium. Although earlier studies suggested that these changes were rarely of clinical significance, a more recent report by Stancer and Forbath (1989) challenges this conclusion.[56] Also, the association between increased calcium and depression (Carman and Wyatt 1979) suggests that this phenomenon may contribute to breakthrough depressions. The clinical importance of other endocrine effects of lithium (Männistö, 1980) has not been established. The metabolic effects of lithium have been comprehensively reviewed by Lazarus (1986).

Skin Reactions. Skin reactions to lithium are reported infrequently. Fifty cases in the literature have been reviewed by Bakker and Pepplinkhuizen (1980). The most serious dermatological reaction, although not the most common, is the exacerbation of pre-existing psoriasis, or, rarely, its induction de novo (Skoven and Thormann, 1979). A family history of psoriasis has been suggested as a predisposing factor in some cases, and psoriasis frequently responds to the discontinuation of lithium.

The most frequently encountered skin reaction is a nonspecific maculopapular eruption that generally appears early in treatment, disappears with cessation, and frequently does not reappear when lithium is reintroduced. Acneiform eruptions have been reported occasionally, and rarely folliculitis and exfoliative dermatitis. One study (Sarantidis and Waters, 1983) suggested that skin reactions occur far more frequently in women than in men. Most skin reactions, with the exception of some psoriatic cases, can be managed without discontinuing lithium. The mechanism of lithium-induced skin reactions is not clear, although it probably involves an allergic component. Lithium is excreted in the sweat, and some patients may be sensitized to a foreign substance on or in the skin. Reports that lithium may increase immunoglobulin formation (Weetman et al., 1982) and alter antibody function (Presley et al., 1976), as well as a report of a lithium-induced lupus-like syndrome (Shukla and Borison, 1982), may provide some insight into these dermatological effects.

Hair loss attributed to lithium has been the subject of a number of case reports, which have been reviewed by Mortimer and Dawber (1984). The great majority of the patients have been female. In some cases, the hair loss can be attributed to hypothyroidism and responds to hormonal replacement. Generally the loss begins to be noticed about 6 months after the initiation of lithium treatment. From the relatively infrequent case reports, we might assume that this side effect is uncommon. However, in a survey of 99 lithium-treated patients questioned about hair changes (McCreadie and Morrison, 1985), 42 percent answered in the affirmative, about equally divided between complaints of hair thinning and texture change. These effects may correlate with the concentration of lithium in the hair (McCreadie and Farmer, 1985). Total alopecia areata may occur, but it is very rare (Silvestri et al., 1988).

Bone. Since lithium is known to accumulate in bone, there has been some interest in the possibility of its causing bone decalcification. Earlier reports of this phenomenon were apparently in error, however, and subsequent research indicates that lithium has no clinically significant effect on the mineral content of bone (Birch et al., 1982). There are no reports of increased pathological fractures associated with lithium use.

Respiratory System. The effects of lithium on the respiratory system were noted much later than in other body systems. Although one investigator has reported coincidental improvement of asthma in two patients taking lithium, two reports note that lithium can induce a clinically significant opiate-like depression in patients with chronic obstructive pulmonary disease (Weiner et al., 1983; Wolpert et al., 1985).

Teratogenic Effects. The discovery of lithium-induced teratogenic effects in animals led to the establishment in 1968 of registers for babies born to mothers who had been on lithium during the first 3 months of pregnancy. Fetal abnormalities occur more frequently in these "lithium babies" than in the general population. These very important findings and their clinical implications are discussed in the clinical guidance section of this chapter (see especially Table 23-7).

Adjunctive Treatments for Breakthrough Episodes During Lithium Prophylaxis

Lithium alone is not always adequate as a long-term treatment of manic-depressive illness. When asked how many bipolar patients require supplemental drug treatment, respondents to our survey of clinical investigators gave estimates ranging from 10 to 90 percent, with a median of 50 percent. Some of this variance seemed to arise from differences in patient populations. Respondents with hospital experience, especially in large public hospitals, were less optimistic about the efficacy of lithium alone than were those from private outpatient settings. As demonstrated by Dunner and colleagues (1976a), some breakthrough depressive episodes can be treated successfully by increasing the lithium level. Additionally or alternatively, enhancing thyroid function can ameliorate a depressive episode (Hatterer et al., 1988).

The use of supplemental antidepressants and neuroleptics and other drugs for breakthrough depressions and manias is common clinical practice. In a comprehensive survey of 20 major lithium clinics, Gitlin and Jamison (1984) found that 25 percent of bipolar patients on lithium had been given supplemental tricyclics and 16 percent supplemental MAOIs. Although potentiation of antidepressant effects with combined treatments has been reported (see Chapter 22), remarkably few controlled studies have been done on the treatment of breakthrough depression in bipolar patients receiving lithium.

In Chapter 22, we introduced evidence suggesting that in some bipolar patients antidepressants can precipitate manic or hypomanic episodes and can accelerate the underlying cycle. We reintroduce this important topic here to emphasize that it remains an issue even in patients maintained on prophylactic lithium. Few systematic studies have examined the two important parts of this issue. First, how effective are supplemental antidepressants in preventing or reversing breakthrough depressions when administered continuously or intermittently? And, second, what effect do these treatments have on the long-term course of lithium-treated bipolar patients?

At this writing, we are aware of only two prospective, double-blind studies of bipolar patients that have compared the prophylactic efficacy of lithium alone with lithium supplemented by a tricyclic antidepressant (Quitkin et al., 1981a; Shapiro et al., 1989). Although reviewed previously, both of these studies warrant mention here also. In the Quitkin study, combined treatment was associated with 50 percent more total relapses and two and a half times more manic relapses than lithium alone over the 3-year follow-up period. Women were significantly more vulnerable to manic relapses than were men ($p < 0.05$). What is more, the added cost of the additional tricyclic (i.e., the increase in manic relapses) was not offset by any additional protection against depressive relapses—they occurred at virtually the same (low) rate in both treatment groups. Patients who were most vulnerable to tricyclic-related manic relapses were mania prone—that is, their most recent episode had been a manic episode. In the reanalysis of the original 2-year NIMH collaborative study on maintenance drug therapy in recurrent affective illness (Prien et al., 1984) done by Shapiro and colleagues (1989), lithium provided greater stability than lithium combined with imipramine for patients whose index episode was manic, but this difference did not achieve statistical significance. Unlike the Quitkin study, however, the NIMH collaborative study found that for those whose index episode was depressive, the combination of lithium plus imipramine was superior to lithium alone. It is possible that differences in the results of these two studies reflect differences in the length of follow-up or in dropout rates.

In Chapter 22, we focused on the longitudinal observations of Kukopulos and colleagues (Kukopulos et al., 1980; Kukopulos and Tondo, 1980), who followed 434 bipolar patients over an average of 17 years (Figure 23-3). Kukopulos and Tondo, commenting on the resistance to lithium among patients who developed a postdepressive excitement, offered this hypothesis:

> We suspected that the antidepressant drugs given during the depressive phase were responsible. . . . Therefore, whenever possible, we let the depression finish without antidepressant drugs. The subsequent course of the cases was very different: the end of the depression was gradual; in most cases no hypomania followed. . . .
>
> We tried all of the antidepressant drugs: tricyclics, tetracyclics, MAOIs . . . and all had the effect of mak-

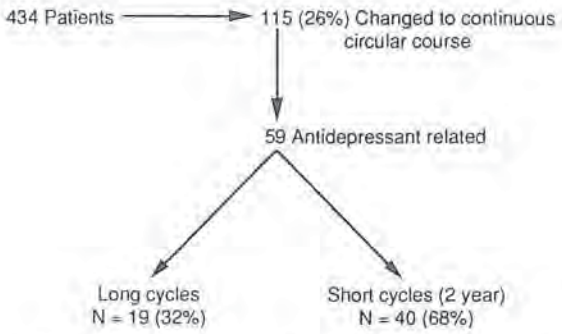

Figure 23-3. An open longitudinal study of 434 bipolar patients (from Kukopulos et al., 1980).

ing the post-depressive mania or hypomania refractory to lithium. Ten non-responders became responders as a result of *not* receiving antidepressants. [emphasis in the original]. . . .

When antidepressants are not given during the depressive phase, the following mania or hypomania disappears [if lithium is maintained]. . . . Only one [continuously cycling patient] kept switching rapidly from depression to mania during lithium treatment, even though he was not given antidepressants. (1980, pp. 146–147)

Kukopulos's experience probably approximates routine treatment approaches with bipolar patients; that is, supplemental antidepressants are used frequently. We recognize, however, that firm conclusions cannot be based on this report alone, since it is not a controlled study, nor does it say how many of the patients who did not develop cycling were treated with tricyclics. Also, it does not indicate how many were continuously on antidepressants. Most problematic is the absence of information on the pretreatment cycle frequency in this group of patients.[57]

In Chapter 22, we discussed the possibility that the impact of antidepressants on the course of the illness in some bipolar patients could be contributing to the higher recurrence rates when the recent (drug) era is compared with the earlier era before drugs were introduced (see Chapter 6). The relative importance of this factor compared to others (e.g., better detection of hypomania, intrinsic change in the illness, greater use of illicit drugs) can only be clarified by further long-term prospective studies, which are sorely needed.

The impact of MAOIs on the long-term course of bipolar illness is even less clear than is the case with the tricyclics, and we know of no systematic studies on this issue. In his review of the literature, Bunney (1978) noted that MAOIs were apparently as likely to precipitate mania or hypomania as were tricyclics. These data were not derived from patients maintained on prophylactic lithium, however. As noted in Chapter 22, both Himmelhoch's group and Quitkin's group reported that the majority of their lithium-treated bipolar patients whose breakthrough depressions had not responded to TCAs did respond when an MAOI was added to the lithium. The previously discussed study of Kukopulos and colleagues (1980) included an unspecified number of patients whose breakthrough depressions had been treated with an MAOI. These authors imply that the course and outcome were similar to the course and outcome of patients treated with tricyclics. Clearly, further systematic studies are needed.

Two new heterocyclic antidepressants, fluoxetine and bupropion, because of their favorable side effect profiles, are now being used extensively to treat breakthrough depressions in patients on maintenance lithium. Although each of these drugs appears to be less likely to precipitate mania than are the classic tricyclics, this advantage is not yet established. Nor is it yet known what effects these two new drugs will have on the long-term course of the illness.

Even less information is available on how the use of neuroleptics in bipolar patients affects the course of the illness. As will be noted in the section on maintenance neuroleptics, this approach has received little systematic attention. Although the initial study of flupenthixol in bipolar patients

suggested that manic episodes might be controlled with the neuroleptic (Ahlfors et al., 1981), a later, better controlled study (Esparon et al., 1986) showed that depot flupenthixol was no better than placebo in preventing breakthrough manias in bipolar patients for whom lithium was inadequate. Nevertheless, experienced clinicians reported in our survey that they continue maintenance neuroleptics in 5 to 30 percent (median 15 percent) of their patients on lithium. The patients most likely to be managed in this way are those who have schizoaffective features while manic, those with rapid cycles, and those with repeated histories of breakthrough manias or mixed states on lithium.

Although the frequency of brief occasional use of neuroleptics to supplement maintenance lithium is not known, this practice is probably more common than the continuous use of these drugs. Several authors have noted the potential for increased incidence and severity of postmania depressions and for tardive dyskinesia when the manic episode has been treated too vigorously and too long with neuroleptics (see Chapter 21).

The effect of acutely administered ECT on the subsequent course of illness has been studied by Small and associates (1986), who reported that patients treated for mania with ECT, then given lithium prophylactically, have lower relapse rates than patients treated with lithium acutely and then maintained on it. This finding may have special relevance for kindling models (see Chapter 15), since ECT has been shown in animals to counteract kindling effects.

MacNeil and co-workers (1975) and Himmelhoch and colleagues (1977) have suggested that some patients with lithium-refractory affective episodes will respond to lithium and thiazide diuretics administered together. This combination should be used with considerable caution, however, since thiazide diuretics produce electrolyte changes and interfere with lithium clearance by the kidney. In Himmelhoch's patients, however, clinical improvement apparently was associated with an increase in plasma lithium to levels that previously could not be achieved without unacceptably severe NDI. These investigators have suggested that, in addition to producing higher lithium levels, thiazide may exert some synergistic action contributing to the improvement, a possibility that requires further study.

Lithium Withdrawal

Several studies document recurrence of illness within a few days to a few weeks in substantial portions of patients withdrawn from lithium (reviewed by Balon et al., 1988).[58] Some authors also report typical withdrawal symptoms, including insomnia. Since sleep loss can precipitate mania, this might explain the unusually high proportion of patients who appear to relapse with sudden lithium withdrawal.

For both theoretical and practical reasons, it would be interesting to know whether long-term lithium treatment produces a rebound effect—that is, a greater likelihood of relapse during withdrawal than would have been the case before lithium was administered. This question has received little attention, and studies that have considered it are difficult to interpret.

The original double-blind study of prophylactic lithium involved its discontinuation (with placebo substitution) for a period of 5 months (Baastrup et al., 1970). The relapse rate during this phase was similar to the prelithium rate and was seen as reflecting simply a recrudescence of the illness. Similar findings were noted by Grof and colleagues (1970). Sashidharan and McGuire (1983) were unable to find any evidence of rebound in their careful retrospective study of 22 patients, and in an open 12-month prospective study of gradual lithium discontinuation, Molnar and colleagues (1987) found no evidence of rebound among 15 bipolar patients.

In contrast, two studies have shown a higher relapse frequency during withdrawal of lithium in bipolar patients. Lapierre and colleagues (1980) compared the frequency of relapse during withdrawal with the pretreatment state, and Mander (1987) compared it with a nonrandomly selected control group of bipolar patients who had not received lithium and who were matched for factors proposed as predictive of outcome. Mander found that 8 of the 29 patients relapsed in the first 3 months, and 7 of the 8 relapses were manic.

The issue is clouded by the heterogeneity of the patient groups. Three of the studies that found no rebound effects involved both unipolar and bipolar patients, and those that did find it involved

bipolar patients only. The rate at which lithium is withdrawn may be important, as suggested by Molnar and associates (1987). At this point, the probability of a rebound during lithium withdrawal is still difficult to assess.

Alternate or Adjunctive Approaches to Prophylactic Treatment

Alternatives to lithium in the prophylactic management of bipolar illness have been the subject of a few studies, many of which focus on patients who have failed to respond adequately to lithium. Some alternate treatments are given to supplement rather than to supplant lithium. Some are considered experimental because their efficacy in manic-depressive illness has not been fully demonstrated, whereas others are not truly experimental because major aspects of their clinical use, such as dosage and safety, have already been established. This area has been reviewed by Prien and Gelenberg (1989).

The Anticonvulsants: Carbamazepine and Valproate

Carbamazepine is used to treat a wide range of seizure disorders, especially psychomotor epilepsy or complex partial seizures, and various paroxysmal pain syndromes, such as trigeminal neuralgia. It was tried in manic-depressive patients because it had stabilized the moods of some patients with convulsive disorders, and it counteracted kindling in laboratory animals (see Chapter 17). It was used initially in acute manic states (see Chapter 21), then in prophylactic trials, and the results have continued to be encouraging. So widespread is its use that the practical aspects of prophylactic carbamazepine administration were covered earlier in the clinical guidelines section. Table 23-19 displays the results of the controlled trials, as well as a summary of the open trials.

In a preliminary open study, Okuma and colleagues (1973) reported a prophylactic effect in 14 of their 27 bipolar patients. Ballenger and Post (1978), in the first double-blind trials, noted a prophylactic effect in 13 bipolar patients maintained on carbamazepine for up to 4 months (Figure 23-4). Many of their patients had rapid cycles or had failed to respond to lithium. Okuma and colleagues (1981) conducted a 1-year, placebo-controlled prophylactic trial in 22 bipolar patients drawn from eight centers. Six of the ten carbamazepine-treated patients, compared with two of the nine placebo-treated patients, had no affective recurrences during the trial, a result that tends to indicate a prophylactic effect ($p < 0.1$). These authors did not indicate how many of their patients had previously responded to lithium. Kishimoto and colleagues (1983) have suggested that responders to carbamazepine prophylaxis are likely to be those with an onset of illness before age 20 and those with frequent illness episodes.

Carbamazepine may be a useful alternative for the prophylactic management of bipolar patients who respond poorly to lithium (see, e.g., Placidi et al., 1986; Watkins et al., 1987), including those with rapid cycles and, perhaps, some with schizoaffective features. Further research is needed to determine whether a carbamazepine–lithium combination is more effective than the anticonvulsant alone. Whether carbamazepine will be as effective as lithium among patients without rapid cycles also requires more investigation, although one study suggests that it is at least as effective prophylactically as lithium in severely ill patients (Lusznat et al., 1988). Kobayashi and colleagues (1988) described a recurrent unipolar patient who was treated successfully with carbamazepine. Among some patients, it appears that the initial prophylactic effect of carbamazepine is not sustained after 3 to 4 years (Frankenburg et al., 1988; Post, 1988a). Post has suggested that this "conditioned tolerance" might be prevented if a symptomatic period off the drug is allowed to ensue.

Although the studies of carbamazepine are encouraging, the number of patients evaluated in double-blind controlled studies is still quite small (less than 50 at this writing), and even these studies suffer from major methodological problems, such as the uncontrolled use of adjunctive medications for breakthrough symptoms. Given the availability of this marketed anticonvulsant, it may never be possible to do the kinds of large studies necessary for its approval by the FDA as a prophylactic agent in manic-depressive illness.

Another anticonvulsant derived from theoretical considerations is *valproate* (or valproic acid), an agent that enhances the action of GABA, an inhibitory neurotransmitter in the CNS hypoth-

Table 23-19. Carbamazepine Prophylaxis in Manic-Depressive Illness

Study	Patients N	Diagnosis	Design	mg / day CBZ (blood level)	Other Drugs	Duration	Results
Controlled Studies							
Ballenger & Post, 1978b	10 CBZ	6 BP 2 UP 2 SA	CBZ vs PBO double-blind controlled on - off	200-1600	Acute treatments added when necessary in 3 patients	Varied	7/10 improved
Okuma et al., 1981	12 CBZ 10 PBO	MDI	CBZ vs PBO double-blind	400-600 (5.6 ± 2.0μg/ml)	Acute treatments added during episode breakthroughs	12 mos	6/10 improved on CBZ
Placidi et al., 1986	29 CBZ 27 LI	20 CAD 9 ADSF 19 CAD 8 ADSF	CBZ vs LI random assignment	400 CBZ 300 LI (7-12 mg/L CBZ) (0.6-1.0 mEq/L LI)	Acute treatments added during episode breakthroughs	2-36 mos	At least 2/3 from each group were very much to moderately improved within 3 mo. Diagnostic groups not separated
Watkins et al., 1987	19 CBZ 18 LI	20 BP 17 UP	CBZ vs LI double-blind random assignment	5-12 mg/L CBZ 0.4-0.9 mEq/L LI	Acute treatments added for episode breakthroughs (63% of CBZ patients, 61% of LI patients)	16 mos (CBZ) 20 mos (LI)	Approximately 75% significantly improved on each; but LI associated with a significantly longer remission (16 mo vs 9.4 mo; $p < 0.001$)
Lusznat et al., 1988	20 CBZ 20 LI	Mania or hypomania	12 month follow-up after double blind random assignment	200 CBZ 400 LI (0.6-1.2 mg/ml CBZ) (0.6-1.4 mmol/ml LI)	Acute treatements (antidepressants or neuroleptics) added for episode breakthroughs		9/20 CBZ patients vs 5/20 LI patients were "satisfactory responders"

Summary of open and controlled studies

- Most were LI resistant prior to CBZ administration
- CBZ appears effective in both rapid cyclers and nonrapid cyclers
- Some patients have a better reponse to the combination of CBZ and LI than either drug alone

Overall improvement rate: 271/417 (65%)

CBZ = carbamazepine, PBO = placebo, LI = lithium, CAD = "classic" affective disorder, ADSF = affective disorder with schizophrenic features, SA = schizoaffective

Post and Uhde, 1988, Strömgren and Boller, 1985, and Prien and Gelenberg, 1989, revised and updated

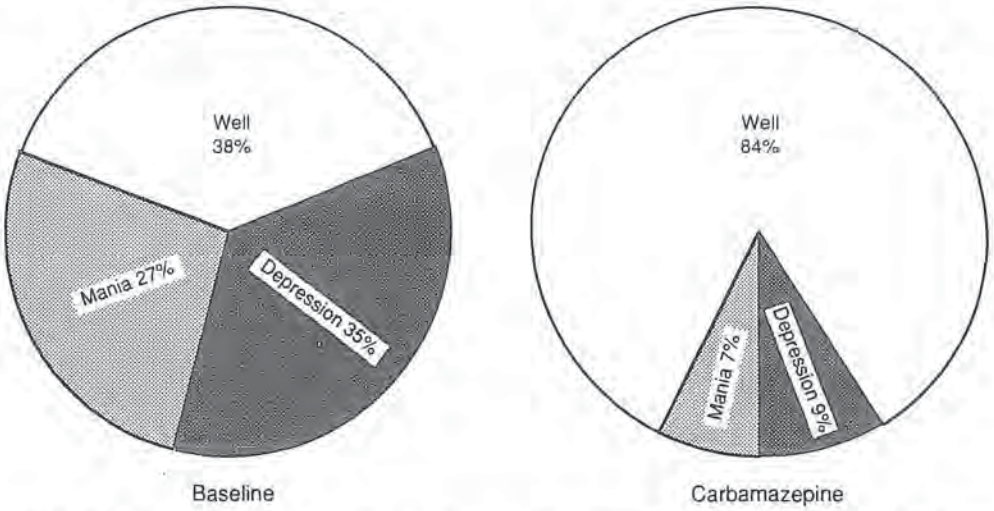

Figure 23-4. Reduction of time spent manic or depressed after treatment with carbamazepine. Thirteen patients with a prior history of rapid cycles or lithium resistance were crossed over to carbamazepine under double-blind conditions. The pie charts illustrate the dramatic reduction in the total time spent ill for the group as a whole (from Post and Uhde, 1987).

esized to be reduced in manic-depressive illness. After a preliminary success in treating acute mania with this drug (see Chapter 21), Emrich and colleagues (1981) conducted a prophylactic trial in seven patients, all of whom remained well during the 18 to 36 month period of observation. This finding suggests an active drug effect, since these patients had histories of relatively frequent relapses. Other studies have confirmed these results.[59] Its prophylactic efficacy may be enhanced when given in combination with lithium (see, e.g., Calabrese and Delucchi, 1989). To date, the prophylactic effect of valproate has been evaluated in nearly 300 bipolar patients, approximately half of whom have been judged as responders. Earlier uncontrolled studies of dipropylacetamide (DPA), which is rapidly metabolized to valproate in the body, showed prophylactic efficacy in bipolar patients when used alone (Lambert et al., 1966) or in combination with lithium (Lambert et al., 1975).

Two other anticonvulsants, diphenylhydantoin and clonazepam (reviewed by Chouinard, 1987), also have been used prophylactically in some bipolar patients,[60] but to our knowledge, controlled studies have not yet been published.

Thyroid Hormone

Thyroid abnormalities have been associated with periodic psychotic states for many years. Gjessing (1976) conducted an extensive series of now classic studies on periodic catatonia, in which he demonstrated major shifts in thyroid function. On the basis of this work, they undertook therapeutic trials with large doses of exogenous thyroid hormone in an attempt to suppress these endogenous fluctuations. Later, Stancer and associates (1970) established the effectiveness of this approach in a controlled trial. Although some therapeutic successes have been achieved, side effects and medical management complications prevented this approach from being pursued in manic-depressive illness. Our survey of clinical investigators revealed anecdotal reports that several lithium-resistant, usually rapid-cycling manic-depressive patients improved when replacement doses of thyroid hormone were used. No further systematic studies have been done, however, and the potential for complications suggests caution in using these hypermetabolic doses of thyroid except under experimental conditions.

A related and more clinically feasible approach has been studied by Bauer and Whybrow (1988b). They found that supplemental T_4, in doses sufficient to produce "supranormal" T_4 levels, successfully converted 10 of 11 lithium-resistant patients with rapid cycles into lithium responders. Of the 4 patients taken off T_4 under double-blind conditions, 3 quickly relapsed. This interesting preliminary finding is consistent with

the previously reviewed data (see Chapter 17) indicating an association between low-normal thyroid indices and relapse in bipolar patients on lithium (see, e.g., Extein et al., 1982 and Hatterer et al., 1988).

A Selective Monoamine Oxidase-A Inhibitor

MAOIs appear to be effective antidepressants in some bipolar patients, including some who do not respond to TCAs. The case report literature indicates that MAOIs, like the tricyclics, can precipitate mania and worsen the course of the illness. The clinically available MAOIs are nonspecific. They inhibit both the A and B form of the enzyme (see Chapter 17). Indirect evidence suggests that inhibition of the B form may be associated with some of the deleterious behavioral effects of MAOIs, particularly those associated with the induction of mania and cycles. In a trial of *clorgyline*, an MAOI specific for the A form, the NIMH group noted sustained prophylactic effects in a group of bipolar patients with rapid cycles previously unresponsive to lithium and a variety of other treatments (Table 23-20) (Potter et al., 1982). Despite the small number of patients involved, these dramatic changes are difficult to ignore. Several of the patients have been continued successfully on clorgyline, usually in combination with lithium, for up to 8 years. Preliminary data on two standard (mixed A and B) MAOIs also suggest that there may be a modest lengthening of the cycle among patients with rapid cycles (Table 23-20) (Cowdry, unpublished data). *Moclobemide* is a selective MAO-A inhibitor on the market in several European countries. To our knowledge, it has not yet been evaluated as a treatment for rapid-cycling patients.

Table 23-20. Effect of MAO Inhibitors on Average Cycle Length in Days

Patient	Placebo	Lithium	Lithium +TCA	MAOI[a]
		Clorgyline[b]		
1	>220		39	>510
2	32	38		93
3	145	43		90
4	23	10		72
5		35		50
		Tranylcypromine or Phenelzine[c]		
6[d]	>220		39	>58
7[e]	32	38		53
8	25	28	16	>350
9	111			>300
10	75	>72	61	49
11	>106	96	63	42
Adjusted Means	99	45	44	152

TCA = Tricyclic antidepressant
MAOI = Monoamine oxidase inhibitor

[a] Given with conventional treatment in most cases
[b] Adapted from Potter et al., 1982
[c] Adapted from Cowdry, unpublished data
[d] Same as patient 1
[e] Same as patient 2

Serotonergic Agents

The so-called permissive hypothesis of serotonin was formulated after serotonin metabolites were observed to be low in both mania and depression. Low serotonin function, according to this hypothesis, is associated with decreased modulation of other mood-related neurotransmitter systems, such as norepinephrine, and thus is viewed as part of the predisposition to manic-depressive cycles (see Chapter 17). The hypothesis led to trials of serotonin precursors in the acute treatment of mania and depression (see Chapters 21 and 22). They have been tried also, but less extensively, for prophylactic management.

Van Praag and DeHaan (1980) conducted interesting preliminary work that integrates the evaluation of drug efficacy with biochemical measures in patients (the biochemical data are discussed in Chapter 17). These investigators reported on a prophylactic trial of the serotonin precursor, 5-hydroxytryptophan (5-HTP) in 20 patients with recurrent major affective disorder, including 6 bipolar patients. Using a drug–placebo crossover paradigm (with patients receiving either a year of 5-HTP followed by a year of placebo, or vice versa), they showed a significant effect of 5-HTP compared with placebo. The prophylactic effect was significantly superior in those patients whose serotonin metabolite levels were relatively low after recovery from the depressive episode.

Use of another precursor of serotonin, L-tryptophan, has, as noted, been suspended pending clarification of its role in the eosinophilia myalgia syndrome. Chouinard and colleagues (1979) reported a case of a rapid-cycling bipolar woman who did not respond to lithium until L-tryptophan

was added, a combination that resulted in substantial prophylaxis against both manic and depressive phases. Chouinard later reviewed his clinical experience with this use of tryptophan (1987). Beitman and Dunner (1982) reported a case of a bipolar woman with two episodes a year for 16 years. Although unresponsive to lithium and imipramine, she responded to L-tryptophan (2 gm 4 times daily) alone.

Another approach to evaluating the low serotonin (permissive) hypotheses was taken by Coppen and colleagues (1984), who used a drug presumed to enhance serotonergic neurotransmission by selectively inhibiting the reuptake of the neurotransmitter. They found that this treatment (zimelidine) could not be substituted for lithium in the prophylactic management of bipolar patients, and the drug was later withdrawn from the market because of toxicity.

Fluoxetine is another antidepressant thought to be selective for the inhibition of serotonin uptake. Its antidepressant effects are reviewed in Chapter 22. To our knowledge, no studies have been done of its potential usefulness as an adjunctive agent in the prophylaxis of bipolar disorder, although it has been reported to effectively prevent relapses in recurrent unipolar illness (Montgomery et al., 1988), and, as noted, it is being widely used to treat breakthrough depressions. Its evaluation as an adjunct for the prophylaxis of bipolar illness should be a high priority.

Maintenance Neuroleptic

The prophylactic efficacy of a maintenance neuroleptic (*flupenthixol decanoate*) was evaluated by Ahlfors and colleagues (1981) in 85 bipolar patients, all of whom had been treated with lithium but either responded poorly or had problems with compliance or side effects. When the 2 years before the study were compared with the 18 months on flupenthixol, both the frequency of manic episodes and the percent of time spent ill with mania were significantly reduced. Unfortunately, the frequency of depressive episodes and the percentage of time spent depressed increased significantly. In a later, smaller, but methodologically superior, double-blind study of similar patients, Esparon and colleagues (1986) found no prophylactic effect of supplemental flupenthixol, and, in fact, they found that the patients did worse than on the placebo. At this juncture it is not clear that this strategy deserves further evaluation, particularly given the risk of tardive dyskinesia (Gardos and Casey, 1984).

Miscellaneous Agents

The new antidepressant drug *bupropion* (see Chapter 22) may also have prophylactic efficacy against both phases of the illness (Shopsin, 1983; Wright et al., 1985). This question clearly deserves further evaluation, particularly in light of the low side effect profile of this agent.

A few case reports and at least one double-blind study (Giannini et al., 1987) suggest that the calcium-channel blocker *verapamil* may have prophylactic effects in rapid-cycling bipolar illness, although not all reports are positive (Barton and Gitlin, 1987). The fact that this drug, unlike other calcium-channel blockers, also blocks dopamine receptors suggests that dopaminergic effects might be mediating its clinical effects. Giannini and colleagues (1987) compared lithium and verapamil in a 1-year, double-blind, crossover study of 20 manic-depressive men already stabilized and maintained on lithium. They found that the patients treated first with verapamil showed clinical improvement after 60 days, whereas the lithium-treated patients improved after 180 days; 60 days after crossover, the group first treated with verapamil and then switched to lithium no longer showed improvement, and the other group was still doing well. The complex interaction of lithium and verapamil suggested by this study warrants further investigation.

Rubidium, an element related to lithium but with physical properties and biological effects opposite to it, has been investigated as an acute antidepressant agent with mixed results in very small numbers of patients. To our knowledge, there is only one report of rubidium as a possible prophylactic agent in manic-depressive illness (Paschalis et al., 1978). Among five bipolar patients with fairly frequent recurrences of episodes, two showed a prolongation of manic episodes and one showed prolongation of both the depressive and manic phases. These changes reversed when the rubidium was withdrawn. Because of the long biological half-life of rubidium and its resulting tendency to accumulate in the body, further trials of this agent probably are not justified.

Magnesium aspartate has been reported to have mood-stabilizing properties in rapid-cycling bipolar patients (Chouinard et al., 1988). To our knowledge, however, no controlled data have been published.

Hypotheses of membrane instability in manic-depressive patients (see Chapter 17) and evidence of abnormal aldosterone fluctuations prompted Hendler (1978) to reason that an *aldosterone antagonist* might stabilize the illness. Of the six patients given spironolactone after demonstrating lithium intolerance, four became stable for 12 to 18 months. Although the follow-up period was short, the fact that the patients had suffered frequent relapses before treatment suggests that there was a medication effect.

Another group of experimental treatments is based on a hypothesized deficiency of membrane ATPase (the sodium pump) in manic-depressive illness and the notion that this deficiency is caused by an endogenous ATPase inhibitor, vanadium. *Methylene blue,* which dampens the effects of vanadium on Na,K-ATPase, was initially reported to be effective in both phases of the illness based on open clinical experience (Narsapur and Naylor, 1983). In a subsequent double-blind, 2-year prophylactic trial in bipolar patients already on lithium, methylene blue was associated with significant additional prophylaxis against depression but not against mania (Naylor et al., 1986). In other studies, this group has noted therapeutic effects of *ascorbic acid* and ethylene diaminetetraacetic acid (*EDTA*), both of which also decrease endogenous vanadium (Kay et al., 1984). Low-vanadium diets (Naylor and Smith, 1981) have been tried with some success as well. Although theoretically interesting, the acceptance of these approaches awaits independent replication.

Sleep Deprivation

As indicated in Chapter 22, sleep deprivation may provide a nonpharmacological alternative or adjunct to psychotropic drugs in some patients. Its prophylactic potential has been explored briefly by one group (Christodoulou et al., 1978; Papadimitriou et al., 1981). Frequency of episodes in the 2 years before initiating weekly sleep deprivation therapy and in the 2 years of follow-up treatment was compared in a mirror-image design. Among the five bipolar patients, two met criteria as responders, one had an equivocal response, and two failed to respond. Further work on this very interesting question is eagerly awaited.

Maintenance ECT

As an approach to prophylaxis, the intermittent use of one or two ECT treatments on an ongoing basis actually predated the use of lithium (Kramer, 1986; Abrams, 1988). Clinical accounts suggest that it is successful in some patients, although to our knowledge, no controlled studies have been done. Clarke and his associates (1988) reported considerable success with the use of maintenance ECT in sustaining ECT-induced remissions among patients with drug-resistant (or drug-intolerant) major depression (whether unipolar or bipolar was not specified). Seventeen of the 24 patients (71 percent) sustained remissions over a minimum follow-up period of 6 months. Almost all of those who relapsed (six of seven) had already dropped out of the maintenance ECT program (described only as "weekly treatments for a few weeks, then biweekly, then monthly for at least four months"). Loo and colleagues (1988) presented case reports of four treatment-resistant patients with affective disorders who also benefited from maintenance ECT. Decina and colleagues (1987) used ECT for continuation treatment of three seriously ill patients over a period of 3 to 6 months and found that it prevented relapses in the two who complied with the treatment schedule.

The use of psychosurgery in patients with severe, treatment-resistant bipolar illness is reviewed in Chapter 18.

SUMMARY

Many years of research were required to convince a skeptical medical community that maintenance lithium can lessen the frequency and severity of episodes in bipolar manic-depressive illness (and in the more recurrent forms of unipolar depression). Substantial clinical research evidence supports the prophylactic power of lithium with striking consistency. Contrary to common belief, among bipolar patients lithium maintenance has been shown to be equally effective against major episodes of mania and of depression, although it

may prevent less serious manic episodes more effectively than less serious depressive ones. By lessening the intensity and altering the character of recurrent episodes, lithium reduces their apparent frequency, bringing some below perceptible thresholds. It also alters mood lability between episodes.

For the recurrent unipolar patient who requires maintenance treatment, the clinician must choose between lithium and an antidepressant. Since both have shown prophylactic efficacy in controlled trials, the decision must be based on individual patient characteristics. A maintenance tricyclic (or MAOI)[61] is most appropriate with the more severely depressed patient who required the antidepressant to recover from the acute episode and who has neither a family history of bipolar illness nor bipolar characteristics, that is, a history of cyclothymia, early age of onset, or frequent episodes. For patients with these bipolar characteristics, lithium is the better choice for prophylaxis, even if the severity of the depression required antidepressants for the acute and continuation phases of treatment.

For the bipolar patient, the principal selection criterion for lithium maintenance is a history of at least two major episodes, regardless of frequency. It should be considered earlier when the first episode is manic, the patient is male, onset is sudden or later than age 30, and the patient's family and social network offer little support. For the more recurrent forms of unipolar illness, a minimum of three episodes, usually within 5 years, is generally considered a threshold for prophylaxis, although, compared with bipolar illness, there is less known about the natural course of untreated unipolar illness.

Bipolar patients least likely to respond to lithium prophylaxis include those with atypical, particularly schizophrenic, features, mixed manias, or rapid cycling (perhaps especially when it is related to antidepressants). Patient compliance may well be the most powerful factor of all affecting prophylactic responses.

During lithium maintenance, moderate breakthrough depressive episodes may respond to optimization of lithium and of thyroid supplements, along with additional psychotherapeutic support. More serious episodes generally call for adjunctive antidepressant drugs. Adjunctive tricyclics have received more study than other antidepressants, but recent data suggest that, among bipolar patients, MAOIs, or the newer heterocyclics, fluoxetine and bupropion, may be preferable for this indication. Other alternatives for breakthrough depression include ECT, sleep deprivation, high-intensity light (for winter episodes), and other experimental agents. For breakthrough mania, clonazepam, carbamazepine, or neuroleptics can be added, depending on the type of patient and the severity of the episode.

Promising alternatives to lithium prophylaxis are the anticonvulsants, primarily carbamazepine. In addition to the drug's importance for the patient who cannot tolerate lithium, preliminary data suggest that it is effective for lithium-resistant patients, especially those with rapid cycles. Whether it has a legitimate role in patients who would otherwise be responsive to lithium is not yet clear.

The side effects of lithium have been studied extensively and found to vary considerably in importance and severity. Some, if mismanaged, can be life threatening. Patients most frequently mention such effects as tremor, thirst, weight gain, and gastrointestinal symptoms, most of which subside spontaneously over time. Extensive studies of lithium's bodily effects have revealed three main targets of particular concern—kidney, thyroid, and CNS. Lithium does not impair renal filtration appreciably, but tubular concentrating ability is reduced in some patients, an effect apparently related to dose and duration of administration and one that necessitates monitoring kidney function and ensuring adequate hydration.

Lithium lowers thyroid function (which may already be low or low-normal in some patients). Although most patients compensate for this on their own, many require thyroid supplementation. The effects of lithium on the CNS (initially prominent but then usually subsiding) include decreased motor coordination and cognitive impairment. These effects must be tracked carefully, not only because they can portend impending neurotoxicity but also because they are one of the major reasons for noncompliance.

An additional effect of concern is an elevated rate of a cardiac anomaly (Ebstein's) in infants born to lithium-treated mothers—approximately 1 in 1,000 exposures or 20 times the rate in the general population. Thus, in those cases where it is feasible, lithium should be withheld in antic-

ipation of pregnancy and during at least the first trimester.

The optimal blood level for lithium maintenance treatment of the bipolar patient is generally between 0.6 and 0.9 mEq/liter, somewhat lower than the level recommended for acute treatment of mania. Prophylactic levels for recurrent unipolar illness can be slightly lower. The prophylactic effects of once a day dosing (generally at bedtime to minimize side effects) are as satisfactory as divided doses.

During the first several weeks, blood levels should be monitored weekly to determine the dose/blood level ratio for the individual patient. After stabilization, the frequency of monitoring can be flexible. The patient's clinical state, sex, age, muscle mass, and diet all contribute to the ratio. Special circumstances that require close monitoring and possible adjustment of dosage include the initiation of surgery, weight reduction diets, or unusual physical activity such as long-distance running.

Many of lithium's early side effects can be readily alleviated by altering dosage or giving the appropriate supplemental treatment, such as propranolol (10 to 40 mg/day) for tremor. Loop diuretics can be added to help control lithium-induced NDI. Supplemental thyroid medication can aid in treating hypothyroidism or its clinical manifestations, which can include breakthrough depressions or continued cycling. Weight gain, often associated with noncompliance, requires early and vigorous carbohydrate restriction and attention to the possibility of reactive hypoglycemia and be combined, if necessary, with the use of L-glutamine, which may reduce carbohydrate craving.

Lithium toxicity can be averted by early detection and dose reduction. Patient education and cooperation are essential to aid in monitoring CNS symptoms. Rarely, hospitalization and specialized care may be required for severe intoxication. Lithium has relatively few adverse interactions with psychoactive and nonpsychoactive drugs. The effects of some combinations may be additive, however, requiring dose adjustments of both drugs.

We do not recommend the routine use of lithium holidays, especially when dealing with bipolar patients. Not only is relapse a serious risk, but such holidays may encourage noncompliance when the medication is resumed.

The fact that lithium maintenance treatment for manic-depressive illness is one of modern medicine's major success stories should not engender complacency. There are still too many patients who do not respond completely. Further pharmacological developments for the treatment of bipolar disorder are urgently needed. We encourage the pharmaceutical industry and the research community to redouble their efforts.

NOTES

1. *Tri-Quarterly* 5, (Winter, 1981) pp. 270–271. Cited in Hamilton, 1982, p. 370.
2. In light of subsequent studies indicating that patients with rapid cycles often do not respond to prophylactic lithium, it is interesting that the initial report of prophylactic efficacy was in a rapidly cycling patient.
3. This complex actuarial study examined increasingly aggressive maintenance strategies. In addition to the most aggressive—starting patients on maintenance lithium after the first episode (an average of 5 years on lithium required to prevent another episode)—the second most aggressive was waiting for the second episode to start maintenance lithium, and the third was to not start maintenance lithium unless the patient experienced a second episode within 2 years. "Patients who do not believe it would be worth 5 years on lithium to avoid one episode but believe it would be worth 2 years should choose one of these two 'wait-and-see' strategies," according to the authors.
4. The majority of patients in this study (21 of 37) were placed on maintenance lithium after their first manic episode. Of those who discontinued the drug during the 18-month follow-up period, 92 percent relapsed, compared with a 37 percent relapse rate among those who stayed on lithium ($p < 0.001$). As noted in Chapter 8, bipolar illness with a very early onset (adolescence) appears to have an unusually high degree of genetic loading, a factor that may predict both greater morbidity and responsiveness to lithium prophylaxis.
5. In assessing the proportion of patients who were maintained on lithium after discharge, Mander (1986) did not differentiate between continuation treatment (up to 1 year) and true prophylaxis (beyond 1 year).
6. The "desirable" lithium level cited in the *Physician's Desk Reference* and package inserts (0.6 to 1.2) is based on earlier literature.
7. In the Coppen et al. (1983) study, the independent variable was the lithium blood level during the trial rather than assignment to one or the other of

the two dose-reduction groups. This leaves open the possibility of an uncontrolled variable. For example, patients who are feeling well over some time may reduce their dose on their own, contributing to the association between lower plasma level and favorable course.

8. Cooper et al., 1973; Perry et al., 1982; Zetin et al., 1986; Lobeck et al., 1987; Rosenberg et al., 1987; Karki et al., 1987.
9. Since some patients may develop tolerance to beta-blockers after prolonged use, Schou and Vestergaard (1987) suggest that their use be on an as needed basis, such as before a social occasion or public appearance. Atenolol, which has a long half-life, can be administered once a day, although its usefulness may thereby be limited for patients who are instructed to take it as needed.
10. Thiazides can be used with caution, however. Himmelhoch and colleagues (1977) offered rough guidelines for the combined use of lithium and thiazide diuretics: 500 mg of chlorothiazide produces approximately a 50 percent increase in lithium levels, and 1 g produces a 70 percent increase. To initiate this combined regimen, the lithium dose should be cut in half, then a low dose (250 mg) of chlorothiazide given. Gradually, both drugs should be increased, with frequent monitoring of the lithium level, electrolytes, and urine output.
11. The association between low folate levels and affective morbidity was not replicated in a later study involving a small number of patients (Stern et al., 1988), and the issue remains unresolved.
12. Compared to carbamazepine, another anticonvulsant, valproic acid, may produce fewer CNS effects when combined with lithium (Calabrese and Delucchi, 1989).
13. A breakthrough depression may result from a drop in the lithium level 10 to 14 days earlier. In other words, the lag in onset of efficacy seems also to be mirrored by a lag in offset of the beneficial clinical effect.
14. Data on the lithium clinics were drawn from the survey conducted by Gitlin and Jamison (1984).
15. Data reviewed in Chapter 22 (Joffe et al., 1988) indicate that T_3 is more effective than T_4 in potentiating antidepressant response to a tricyclic. Whether this also applies to the use of thyroid in patients on lithium is not known. T_3 has the disadvantage of confounding the plasma monitoring of thyroid hormone level.
16. Carbamazepine can complicate ECT treatment by raising the seizure threshold.
17. See reviews by Amdisen and Schou, 1980; Grof et al., 1979b; Coppen et al., 1983; Cooper, 1987.
18. For example, a patient who was flying from the east coast of the United States to Europe would take medications 3 hours earlier on the day before and the day of departure (i.e., the dose schedule would be moved up 3 hours to split the difference between the time in the eastern United States and western Europe). Once in Europe, the dose timing would be according to local time.
19. For a discussion of conflicting opinions on this subject, see Targum et al., 1979; Brockington et al., 1982; Oates, 1986; Stewart, 1988.
20. This was an open prospective study with a sample that was not randomly selected.
21. Among the alternatives to lithium for patients with rapid cycles is magnesium aspartate, a treatment studied as early as 1932 (Mestrallet and Larrivé, 1932).
22. The *Physician's Desk Reference* and package insert warnings about the risk of carbamazepine-induced bone marrow suppression were apparently based on earlier literature, in which carbamazepine was administered in combination with other anticonvulsant drugs.
23. Figure 24-3, from the 1967 Baastrup and Schou study, provides both an excellent illustration of the variability of the natural course of the illness and a dramatic demonstration of lithium's efficacy. It is reproduced in Chapter 24 because we find it useful as part of one important component of psychotherapy in teaching patients about the illness and its treatment.
24. Baastrup et al., 1970; Coppen et al., 1973; Prien et al., 1973a; Prien et al., 1973b.
25. In the first double-blind lithium–placebo discontinuation study, Baastrup and colleagues (1970) reported that 12 of 22 bipolar patients relapsed (6 manic, 5 depressive, 1 mixed state) within 5 months when switched from lithium to placebo. None of the 28 bipolar patients maintained on lithium relapsed within that time. In the double-blind prospective trial by Coppen and co-workers (1973), the mean "affective morbidity" was virtually the same for mania and depression. Cundall and associates (1972) studied lithium prophylaxis in a crossover design with 12 patients already stabilized on lithium. The predominance of manic episodes during placebo treatment, especially in contrast to the low incidence on lithium, suggests a greater antimanic than antidepressive effect for lithium.

    Prien and co-workers (1973a) reported a study of 205 patients hospitalized for mania, then randomly assigned to either lithium treatment or a placebo for 2 years after discharge. The overall incidence of severe relapses was reduced by half in the lithium group, compared with no reduction in the placebo group ($p < 0.001$), a difference primarily due to the impact of lithium on manic episodes. The proportion of patients with depressive relapses was reduced from 16 percent before treatment to 8 percent after lithium treatment. For patients on placebo, comparable figures were 13 and 11 percent, but the lithium–placebo difference was not significant given the low numbers involved. The relatively low number of depressive

relapses is probably an artifact, resulting from a large number of dropouts in both groups after their first manic relapse. Thus, lithium's relative efficacy in preventing depression and mania cannot be determined. Nonetheless, the study is frequently cited as evidence that lithium more effectively prevents mania than depression, although the investigators themselves made no such claim and, in fact, have pointed out that the large difference in the distribution of manic and depressive relapses makes any such comparisons meaningless. This same group (Prien et al., 1973b) also reported on a somewhat smaller number of patients with bipolar illness hospitalized for depression and randomly assigned at discharge to placebo, lithium, or imipramine. During the 2-year follow-up, the placebo vs lithium difference in manic episodes was 21 (from 33 percent to 12 percent) compared to 43 for depressive episodes (from 55 percent to 12 percent). This indicates that lithium prevented the recurrence of depressive episodes at least as well as it prevented manic ones.

Fieve and colleagues (1976) studied 35 bipolar-I patients randomly assigned to either lithium or placebo and followed for periods ranging from 2 ½ to 4 ½ years. The placebo–lithium difference appeared to be greater for manic episodes (from 94 percent to 59 percent) than for depressive episodes (from 44 percent to 29 percent). As with the study by Prien and colleagues, the most interesting aspect of these data is the relatively low number of depressive relapses in both groups, probably reflecting dropouts resulting from manic episodes in both group. The mean number of depressive episodes per year among lithium-treated patients was one fourth that of the placebo-treated patients ($p < 0.01$), but unfortunately the authors do not present comparable data for manic episodes. Thus, this study does not clarify whether lithium is more effective prophylactically against mania or depression. In a related study from the same group, Dunner and colleagues (1976a) reported on 40 bipolar-II patients followed in an outpatient clinic, 16 of whom received maintenance lithium and 24 placebo. Although lithium did not appear to reduce the total number of depressive episodes, there was a threefold reduction in hospitalization for depression. The depression-related dropout rate was three times higher in the placebo group than in the lithium group, again an indication of considerable lithium protection against the more serious forms of depression.

In a 2-year prospective double-blind study of 38 lithium-treated bipolar patients, Quitkin and coworkers (1981a) found that of the 21 percent who relapsed on lithium, half were depressive and half manic. Prien and associates (1984) also noted a similar rate of depressive and manic relapses in 42 lithium-treated bipolar patients over a 1 to 2 year follow-up period.

26. Some patients experience activation on lithium. The reasons for these individual differences have not been clarified.
27. Hewick et al., 1977; Fann and Wheless, 1977; Roose et al., 1979; Murray et al., 1983.
28. Hartigan, 1963; Baastrup and Schou, 1967; Poole et al., 1978; Angst et al., 1970.
29. Coppen et al., 1976; Kane et al., 1982; Glen et al., 1981, 1984.
30. The literature on the efficacy of lithium prophylaxis in schizoaffective disorder suffers from a dearth of placebo-controlled studies. This is understandable when one considers that the focus on this diagnostic group is relatively recent, coming after the efficacy of lithium is well established. Thus, ethical considerations mitigate against placebo-controlled trials even for a diagnostic group for which baseline rates of relapse (i.e., on placebo) are not established.
31. These points are well-expressed in letters written in response to the *Lancet* editorial of February 21, 1987; note especially Schou's response.
32. The U.S. increase occurred especially among the young. Dickson and Kendell noted that their 1981 patients were younger than those in 1970.
33. Only a minority of Dickson and Kendell's patients were taking lithium before admission (22 percent in 1970 and 1971 vs 35 percent in 1980 and 1981). The median length of stay for the patients previously on lithium was only half as long as that for the patients not treated with it. The authors cite this as "no difference" even though the small numbers preclude meaningful statistical evaluation.
34. As noted earlier, bipolar patients with mixed states are more likely to be on antidepressants and to be abusing illicit drugs or alcohol, all factors that would compromise their response to prophylactic lithium.
35. Stancer et al., 1970; Dunner and Fieve, 1974; Prien et al., 1974; Kukopulos et al., 1980; Misra and Burns, 1977.
36. Prien et al., 1974; Dunner and Fieve, 1974; Abou-Saleh and Coppen, 1986; Page et al., 1987.
37. Stallone et al., 1973; Mendlewicz et al., 1972b, 1973; Grof et al., 1979b; Mendlewicz, 1982; Maj et al., 1984; Smeraldi et al., 1984; Abou-Saleh and Coppen, 1986.
38. Several excellent comprehensive reviews of lithium side effects are available, including those of Reisberg and Gershon, 1979; Johnson, 1980; Vestergaard et al., 1980; Jefferson and Greist, 1977, 1987.
39. These averages include only data from patients on lithium alone. Thus, Bone and co-workers (1980) and Lyskowski and colleagues (1982) report significantly higher rates of various side effects in patients on combinations of lithium and other psychotropic agents than on lithium alone, although this was not confirmed by Duncavage and associates (1983).

40. Roose et al., 1979; Vestergaard and Schou, 1984; Hardy et al., 1987; Shulman et al., 1987.
41. In the Maarbjerg et al. study, the incidence of lithium-induced hypothyroidism was calculated at two per hundred years of lithium exposure, a figure similar to that of Smigan et al., 1984.
42. The reversibility of the effect of lithium on the urine concentrating ability may be explained by the fact that this effect is partly caused by the ion's interference with antidiuretic hormone.
43. Hansen et al., 1977, 1979; Hestbech et al., 1977; Aurell et al., 1981; Thysell et al., 1981.
44. Because the direct measurement of GFR requires a 24-hour urine collection, attempts have been made to estimate changes in GFR by changes in blood levels of creatinine or more recently B_2-microglobulin. Although the former does not correlate with GFR, the latter does (Viberti et al., 1981; Samiy and Rosnick, 1987).
45. Bendz, 1983, 1985; Smigan, et al., 1984; Jørgensen et al., 1984; Johnson et al., 1984; Tyrer et al., 1983; Boton et al., 1987; Mellerup et al., 1987; Gelenberg et al., 1987; Schou et al., 1989; Santella et al., 1988; Conte et al., 1989.
46. As Masterson and colleagues (1988) pointed out, these clinics keep patients maintained at modest blood lithium levels. Once a day dosing may not be as benign when higher blood levels are maintained.
47. The cohort study of Schou and colleagues covered 4,900-patient years. Of the 24 instances of lithium intoxication recorded, 15 were due to deliberate overdose (suicide attempts). The authors note that "in no instance did lithium intoxication develop as a consequence of gradually deteriorating kidney function."
48. In adolescents and young adults, particularly males engaged in competitive sports, the deleterious effects of lithium on muscle coordination can contribute to compliance problems. To prevent this, the lithium dose should be reduced to the minimum necessary to control the illness.
49. The general issue of tardive dyskinesia in manic-depressive illness, its relationship to other signs of CNS dysfunction, and its relevance to course are discussed in Chapter 18.
50. See, for example, Donaldson and Cunningham, 1983; Johnson, 1984; Schou, 1984; Sansone and Ziegler, 1985.
51. These issues have been reviewed by Shaw et al. 1986, 1987; Ananth et al., 1987; Jefferson et al., 1987; and Judd et al., 1987.
52. See, for example, Schou et al., 1968b; Judd et al., 1977b; Karniol et al., 1978; Judd, 1979; Kropf and Müller-Oerlinghausen, 1979; Weingartner et al., 1983a,b, 1985; Glue et al., 1987.
53. Those reporting detrimental effects of lithium on cognitive abilities and speed of performance include, among others, Demers and Heninger, 1971; Reus et al., 1979b; Lund et al., 1982; Pons et al., 1985; Shaw et al., 1986, 1987. Additionally, Aminoff et al., (1974) found that lithium caused a reversible deterioration in cognitive functioning in patients with Huntington's disease. The degree of cognitive impairment was not correlated with the degree of dementia in these patients.

    Studies reporting no significant effect of lithium on memory or other cognitive abilities include, for example, Telford and Worrall, 1978; Kjellman et al., 1980; Ghadirian et al., 1983; Engelsmann et al., 1988. A comparison of manic-depressive patients (who were medication free, lithium treated, or carbamazepine treated) with normal controls found no differences among groups on tests of attention, concentration, visuomotor function, or memory (Joffe et al., 1988b).
54. In addition to the review by Albrecht and Müller-Oerlinghausen (1980), other excellent reviews of cardiac effects include those by Jefferson and Greist (1977), Tilkian and colleagues (1976), and Mitchell and MacKenzie (1982).
55. In the Norton and Whalley study (1984) there was a relationship between prelithium signs of physical illness and later death on lithium. Thus, of the 14 patients who died of cardiovascular disease, 9 had clinical abnormalities attributable to cardiovascular disease before they began taking lithium, and 6 had multiple signs or symptoms.
56. Stancer and Forbath (1989) studied 19 patients who had been on lithium for more than 10 years. They found 8 (42 percent) with elevated parathyroid hormone levels, 3 of whom had clinical signs of hyperparathyroidism, including degenerative spine disease, osteoporosis, and hypertension/cardiomegaly.
57. Notwithstanding imperfections in its study, this group's work merits attention, particularly in light of its interesting subclassification of patients by different illness courses. Since the DMI sequence is relatively infrequent, the tendency for tricyclics to worsen the course of illness in such patients may simply have gone unnoticed by others with smaller patient samples. An additional factor is probably relevant to American clinicians in particular. Shorter follow-up periods and higher dropout rates (in part, a product of the mobility of the population) decrease the likelihood of any individual clinician or group detecting the longer-term effects of treatment interventions. As reported by Kukopulos, some of the patients in the depression-mania-interval group went on to become continuously cycling.
58. Bunney et al., 1968; Goodwin et al., 1969; Baastrup et al., 1970; Small et al., 1971; Lapierre et al., 1980; Klein et al., 1981; Margo and McMahon, 1982; Christodoulou and Lykouras, 1982.
59. Puzynski and Klosiewicz, 1984; Vencovsky et al., 1984; Prasad, 1984; Brennan et al., 1984; McElroy et al., 1988; Hayes, 1989; Calabrese and Delucchi, 1989.

60. An open study of clonazepam prophylaxis in five lithium-refractory bipolar patients (Aronson et al., 1989) was quite discouraging. All of the patients relapsed quickly when switched to clonazepam. However, the report of Sacks (1989) is more encouraging.

61. Among the antidepressants, only imipramine and amitriptyline have been evaluated in controlled studies of prophylaxis. However, open studies and clinical experience suggest that the MAOIs also have prophylactic efficacy in recurrent unipolar depression.