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CME Objectives

After completing this CME activity, the psychiatrist should be able to:

- Review the mechanism of action of lithium and other mood-stabilizing drugs
- Assess important aspects of pharmacotherapeutics in clinical practice
- Describe important characteristics of bipolar illness in children and adolescents
- Compare pharmacotherapeutic options for the treatment of bipolar illness

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Faculty List

Chairman: Richard C. Shelton, M.D., Vanderbilt University, Nashville, Tennessee. ***Presenters:*** Ross J. Baldessarini, M.D., McLean Hospital, Belmont, Massachusetts; Robert Kowatch, M.D., University of Texas Southwestern Medical Center, Dallas; Michael E. Thase, M.D., Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania.

Faculty Disclosure

In the spirit of full disclosure and in compliance with all Accreditation Council for Continuing Medical Education Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: ***Dr. Baldessarini*** has received grant support from Solvay Pharmaceuticals Inc. ***Dr. Kowatch*** has no significant relationships with any entity that may have influenced the presentation in any way. ***Dr. Shelton*** has received research grant support from Eli Lilly & Company, Glaxo Wellcome Inc., Janssen Pharmaceutica, Pfizer Inc., Rhone-Poulenc Rorer, Sanofi Winthrop Pharmaceuticals, SmithKline Beecham Pharmaceuticals, Pharmacia & Upjohn, Wyeth-Ayerst Laboratories, and Zeneca Pharmaceuticals; is a consultant for Pfizer Inc.; and is a member of the speakers bureau for Bristol-Myers Squibb Company, Eli Lilly & Company, Janssen Pharmaceutica, Pfizer Inc., SmithKline Beecham Pharmaceuticals, Pharmacia & Upjohn, Solvay Pharmaceuticals Inc., and Wyeth-Ayerst Laboratories. ***Dr. Thase*** has received research grant support from Bristol-Myers Squibb Company, Eli Lilly & Company, Glaxo Wellcome Inc., Lipha Pharmaceuticals Inc., Organon Inc., Pfizer Inc., and Wyeth-Ayerst Laboratories; is a consultant for Bristol-Myers Squibb Company, Eli Lilly & Company, Organon Inc., Pfizer Inc., and Wyeth-Ayerst Laboratories; and is a member of the speakers bureau for Bristol-Myers Squibb Company, Eli Lilly & Company, Glaxo Wellcome Inc., Pfizer Inc., SmithKline Beecham Pharmaceuticals, Solvay Pharmaceuticals Inc., and Wyeth-Ayerst Laboratories.

Discussion of Investigational Information

During the course of their talks and discussions in this *Journal*, faculty have presented the following investigational information about pharmaceutical agents that is outside Food and Drug Administration–approved labeling. This information is intended solely as continuing medical education and is not intended to promote off-label use of any of these medications. *Carbamazepine has not been approved by the FDA for treatment of bipolar disorder.*

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Update on the Management of Bipolar Illness

Chairman: Richard C. Shelton, M.D. Participants: Michael E. Thase, M.D., Robert Kowatch, M.D., and Ross J. Baldessarini, M.D.

In his opening remarks, Richard C. Shelton, M.D., chairman of the conference, remarked that he and his colleagues were recently lamenting the difficulty in recruiting subjects for clinical trials of unipolar and bipolar disorders. One of the factors influencing the current lack of patients for research studies is that there are fewer untreated or inadequately-treated individuals with these disorders because of the relative success of pharmacotherapeutic interventions. On the other hand, he offered, clinicians now see a larger proportion of treatment-refractory unipolar and bipolar patients; consequently, clinicians are shifting their thinking toward more complex treatment approaches. As an educator, Dr. Shelton noted, he is somewhat concerned that the older effective treatment modalities—such as lithium, tricyclic antidepressants, and monoamine oxidase inhibitors—are being overlooked in favor of newer pharmacologic agents. Many psychiatric residents complete their training without ever having used lithium, he said, and one of the focuses of this conference is the examination of the current position of lithium as a pharmacologic intervention in the treatment of bipolar illness.

Advances in the Mechanism of Action of Pharmacotherapeutic Treatment Modalities

Present-day knowledge of the mechanism of action of lithium may be related to possible sites for the pathophysiology of bipolar disorder, said Richard C. Shelton, M.D. Since a comprehensive discussion of the cellular effects of lithium and other mood stabilizers could fill an entire agenda, the focus of his presentation was away from cell-surface receptors and toward transductional mechanisms and the ultimate regulation of gene products—the current area of research for targeting drug actions.

Much early development of pharmacotherapeutic modalities for bipolar illness was serendipitous, Dr. Shelton acknowledged, and there was little hard evidence for the mechanism of action of the antidepressants, antipsychotics, and benzodiazepines until the 1980s. Various avenues of psychotropic drug development include the imitation of binding sites—the method by which "me too" drugs have evolved—animal behavioral models, and pathophysiologic modeling. The use of pharmacologic interventions as a tool for targeting or understanding the basic pathophysiology of the various disorders is emerging as a research strategy, and, in turn, investigators also use pathophysiologic modeling as a device for discovering new targets of action for pharmacologic interventions.

The traditional targets of psychotropic drug action important in the mechanisms of action of psychotropic agents include presynaptic storage sites, transmitter reuptake sites, metabolic enzymes (such as monoamine oxidase inhibitors), presynaptic and postsynaptic transmitter receptors, and ion channel binding sites. However, Dr. Shelton offered, as researchers move forward into a deeper understanding of the basic pathophysiology of psychiatric disorders and the mechanisms by which psychotropic drugs work, other important potential targets of drug action and potential sites of pathophysiology for affective illness are being investigated. These targets include the novel transmitter receptors (e.g., serotonin receptor subtypes), polypeptide receptors, and intracellular targets such as G proteins (guanylyl nucleotide regulatory proteins), adenylate cyclase (cAMP), protein kinases (A,C), and immediate early genes and gene products.

Lithium inhibits turnover activity mediated through the second messenger systems of both major transductional (cAMP-dependent or phosphotidylinositol-dependent) systems, a significant mechanism of action that has been known since the 1970s.[1,2] Since lithium appears to have fairly nondiscriminate effects on the 2 major transductional systems, Dr. Shelton said that it is difficult to explain the mood-stabilizing effects of the drug without some understanding

Table 1. Transmitters Acting Through G Proteins*

• Norepinephrine
• Serotonin
• Dopamine
• Acetylcholine
• GABA[a]
• Histamine
• Glutamate
• Purines
• Prostaglandins
• Thromboxane

*From reference 3.
[a]GABA = gamma-aminobutyric acid.

of the transductional mechanisms for transmitter action.

There are many transmitters that act through G proteins and their subtypes (Table 1).[3] Four major subtypes of G proteins are involved in the transduction of signals produced by neurotransmitter binding: G_s, G_i, G_q, and G_o. Norepinephrine binds to cell-surface β receptors that are coupled through G_s proteins to cAMP. G protein activation is dependent on the binding of GTP (guanosine triphosphate) to G_s proteins and the subsequent coupling of G_s to cAMP. This reaction catalyzes the formation of cAMP, activation of cAMP kinase—which is the focus of much of the research in depression—and ultimately, the phosphorylation of transcription factors like CREB (cAMP response elements binding protein) and the regulation of gene expression by the binding to CREs and other immediate early genes. Binding at the G_s and other G proteins is important and may provide a greater appreciation of lithium's mechanism of action.

G proteins have α, β, and γ subunits. After the neurotransmitter binds to the receptor, GTP binds to the α subunit causing the G protein to dissociate and release the active γ subunit, which (in this particular case) binds to cAMP. The phosphoinositide (PI) system activates the cascade as well, but the α subunit of the G protein is an important mechanism by which lithium may act. The two G protein subunits that were originally recognized (G_s and G_i proteins) are coupled through cAMP. There are other mechanisms whereby G_i proteins are stimulatory through actions on phospholipase. G_o proteins, coupled through ion channels, including sodium channels, are also important. There are categories and further subtypes within each subtype of G proteins, and it is likely that mood-stabilizing agents have nonspecific—but not totally indiscriminate—actions such as inhibition of G_s, G_i, and G_o proteins.

— The use of pharmacologic interventions as a tool for targeting or understanding the basic pathophysiology of the various disorders is emerging as a research strategy, and, in turn, investigators also use pathophysiologic modeling as a device for discovering new targets of action for pharmacologic interventions. —

To grasp the importance of G proteins in bipolar illness, Dr. Shelton explained that one must understand first that G proteins may possibly be a target of action of mood-stabilizing drugs and then apply that information to the core or basic pathophysiology of bipolar illness. Although other target cells have been investigated, Schreiber and associates[4] examined G proteins in monocytes of patients with bipolar illness. This representative study compared untreated manic patients, lithium-treated euthymic bipolar patients, and healthy volunteers by investigating the binding of a GTP ligand in monocyte membrane preparations incubated with carbamylcholine (a muscarinic-cholinergic agonist coupled through G_i proteins) or isoproterenol (a β agonist coupled through G_s proteins). Hyperactive function of G proteins was detected in the untreated manic patients and elevated G_i and G_s binding occurred in the manic and euthymic patients, as compared with controls. In a recent paper,[5] G protein measurements were evaluated in both manic and depressed states of bipolar illness. Bipolar patients in the manic state showed elevation of G protein binding of the GTP analogue, and bipolar patients in the depressed state showed reduction of G protein binding of the GTP analogue. These findings suggest an abnormal regulation of G proteins as a possible pathophysiology for bipolar illness, said Dr. Shelton, and similar findings have been reported in other studies.[6,7]

If bipolar patients experience instability in G protein function and if binding to G protein functioning corrects the instability, then evidence should exist for the interaction of mood-stabilizing drugs with G proteins. In a publication in *Nature*, Avissar et al.[8] showed the effects of isoproterenol and carbamylcholine on tritiated GTP binding in animals. In the absence of basal receptor activity, there was little binding of GTP to G proteins, but when isoproterenol or carbamylcholine were added to the cell preparation, there was a marked increase in GTP binding. In animals exposed to lithium administration for 12 to 21 days, the drug markedly inhibited GTP binding to the G proteins. In animals in which lithium treatment was withdrawn, there was a return of normal function of GTP binding to G proteins; thus, it appears that lithium produces temporary inhibition and/or stabilization of G protein functioning.

Dr. Shelton concluded his presentation by briefly discussing the effects of lithium on long-term potentiation, particularly G protein-mediated long-term potentiation. Long-term potentiation is a predominantly postsynaptic effect

that occurs as a result of glutamate binding to G protein-linked NMDA receptors, and lithium appears to inhibit the G protein-linked mechanism. Many transmitters act through G protein-dependent mechanisms; obviously, norepinephrine and serotonin are important in affective illness, he said, but long-term potentiation and effects of mood-stabilizing drugs on cycling in bipolar illness may be dependent upon interactions with glutamate. The audience was reminded of the work of Post and Weiss[9] on the importance of the hippocampus and NMDA (N-methyl-D-aspartate) receptor binding of glutamate in the kindling phenomenon. To study hippocampal long-term potentiation, Ballyk and Goh[10] made extracellular and intracellular recordings of isolated rat CA_1 hippocampal slices treated with bath and micropipette application of 20/100 mM lithium chloride. The results of this study showed that extracellular lithium application blocked the induction of stimulus-induced long-term potentiation. Intracellular lithium blocked the postsynaptic G protein-mediated response to baclofen, resulting in hyperpolarization and inhibitory postsynaptic potentiation. This is an important activating and inhibiting paradigm and is another possible target for the action of lithium and other drugs to produce mood stabilization.

In summary, said Dr. Shelton, there are a number of known effects of mood-stabilizing drugs on G protein functioning, including the inhibition of G protein binding of GTP. There is also evidence for inhibition of G protein-linked second messenger activity. Ultimately, some of the mechanisms of action of these drugs may depend on factors that are further downstream—beyond G protein activity—such as gene products. Finally, there is evidence of G protein-mediated inhibition of long-term potentiation theoretically coupled to G protein-linked NMDA receptors, thereby inhibiting the kindling phenomenon.

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Aspects of Pharmacotherapeutics in Clinical Practice

Lithium had been formally approved for use in the United States for less than a decade when Michael E. Thase, M.D., entered the field of psychiatry in the late 1970s. Consequently, he said, the academic staff spent considerable time—as consultants to both the state hospital and the university hospital—rediagnosing many patients with complex and difficult mood disorders who had formerly been diagnosed with schizophrenia. The concerted effort to reevaluate patients was made because lithium was a powerful and potent new treatment modality, not only in the acute phase of illness, but also (perhaps more importantly) in long-term prophylaxis of mood disorder. Psychiatric residents at the time were taught that lithium was such an incredibly effective treatment—with 80% to 90% efficacy rates—that if the patient failed to respond, the diagnosis was questioned. Dr. Thase then commented that it is human nature to overvalue a powerful new treatment initially just as it is to devalue the same treatment over time.

It is now clear that a substantial minority (if not a majority) of manic depressive patients suffer a chronic, relapsing illness, said Dr. Thase. Recent outcome studies of lithium maintenance treatment of bipolar disorder show that: (1) 54% of patients were unstable 4 years after the first episode, and treatment was unrelated to outcome,[1] (2) 40% had a recurrence of mania within 1.7 years after recovery from acute mania, and the outcome was the same in patients both on or off lithium therapy,[2] and (3) more than one third of patients with bipolar disorder relapsed, especially into depression, despite optimal treatment with lithium or carbamazepine.[3] Clearly, he said, bipolar illness has a favorable prognosis only when compared with chronic schizophrenia and a few other organic mental disorders.

Each year, approximately 1 of 10 individuals who become ill with manic depression are treated appropriately and have a complete recovery without subsequent recurrence; this means that 10% of the patients who become ill with manic depression have such good prognoses that they will not be considered in subsequent studies. A large pool of potentially lithium-responsive patients was available in the early 1970s, but, over time, the lithium-

responsive patients with favorable prognoses have moved out of the pool, and the remaining patients—especially those seeking treatment at university medical centers—are the primary subjects in various clinical trials.

In the years since lithium was approved for use in the United States, there has been a slow accumulation of resistant and/or refractory cases, said Dr. Thase. When lithium was first introduced in 1970, approximately 70% of the manic depressive patients treated were fully lithium-responsive and another 20% were partially responsive; in 1990, only about 45% of patients (in this country and abroad) were lithium-responsive. With each decade of research, there is approximately a 10% drop in the lithium response rate, but Dr. Thase suggested that this is the natural history of many medications used in multiple controlled studies. When a drug is first available as treatment, the numbers of people who have never received the compound are infinite; however, after 20 years, many individuals who are studied have a history of poor response. The same is true for prophylactic efficacy. The original report of lithium's prophylactic efficacy against subsequent episodes was 80%. By the second wave of studies, the rate was 66%, and by 1984, it was about 50%. Nevertheless, even though the percentages for response rate are increasing and prophylactic efficacy is falling, the individuals who do respond to lithium may require very little additional treatment beyond prophylactic pharmacotherapy. Most practitioners have a few patients who come in once a year just to have their lithium prescription refilled, he said, and those patients are excluded in modern statistical reports.

Changes in diagnostic practices also have resulted in the recognition of greater numbers of chronic, severe, and complicated cases of bipolar illness. American psychiatrists were traditionally strict constructionists in diagnosing manic depression, Dr. Thase commented. When the same patients were interviewed by 2 different groups of psychiatrists prior to the approval of lithium for use in this country, English psychiatrists were approximately twice as likely to make a diagnosis of manic depression, and American psychiatrists were about twice as likely to make a diagnosis of schizophrenia or schizoaffective disorder. Once lithium became available, the tendency to diagnose schizophrenia diminished, and American and English psychiatrists began to diagnose manic depressive disorder at the same rate. An appropriate diagnosis includes complicated features of the illness such as mood incongruent features, psychotic features, and mixed states that are relatively common and less responsive to lithium. Part of the benefit of an effective treatment is that it can be applied across a broad spectrum, but lithium is usually not as effective in patients with more complicated or complex disorders as it is in those with pure types of the disorder.

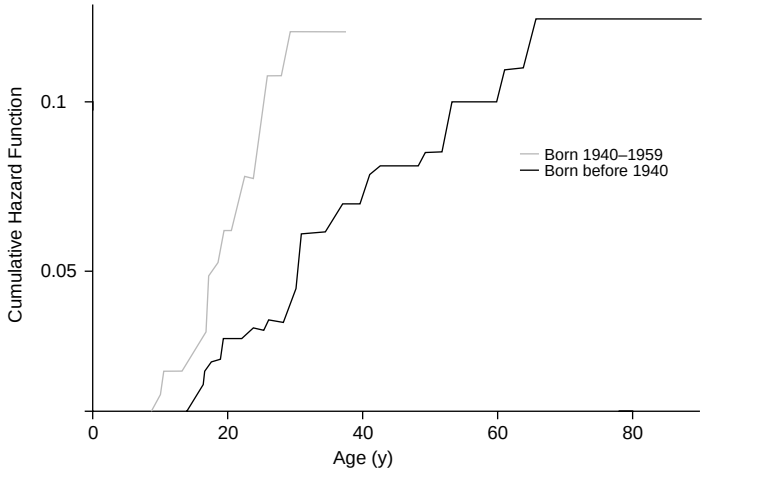
Over the past 3 or 4 generations, there has been a progressive reduction in the recorded age at onset of bipolar disorder, although some investigators think that the disorder has always had an early onset, and clinicians are simply recognizing it earlier. Trends have been observed in bipolar and schizoaffective illness in relatives pooled into pre- and post-1940 cohorts, said Dr. Thase, and a baby boomer's lifetime risk for bipolar and schizoaffective illness at age 25 years is comparable to his or her parents' lifetime risk at age 65 years (Figure 1).[4]

In terms of the natural history of bipolar illness, an early age at onset has always carried an unfavorable prognosis. One reason is that the earlier the age at onset, the higher the genetic loading or, at least, the penetrance of the genes involved. From another perspective, there are different implications of having a severe psychiatric illness that requires hospitalization at an early age, e.g., age 19 years versus age 29 years. The educational process is interrupted and personality development is incomplete at age 19 years, and it is possible that a protracted and severe period of illness will actually have personality-modifying effects. Unfortunately, said Dr. Thase, adolescent bipolar patients tend to gravitate toward substances such as drugs and alcohol that have immediately measurable (and sometimes perilous) effects on their already altered mental states.

Nevertheless, even though the percentages for response rate are increasing and prophylactic efficacy is falling, the individuals who do respond to lithium may require very little additional treatment beyond prophylactic pharmacotherapy.

It is also true, noted Dr. Thase, that when a treatment is effective, the possibility exists for iatrogenesis. For example, the average number of episodes has increased, and highly recurrent bipolar illness has become more common since 1960. Switch rates in manic depression were higher by almost 2-fold when the treatment of choice was the vigorous use of antidepressants, as opposed to supportive therapy or mood stabilization with neuroleptics. Double-blind, placebo-controlled case series collected at the National Institute of Mental Health[5] show that cycling is accelerated by the use of antidepressants. Thus, depression time is shortened at the expense of accelerating the frequency—and possibly the severity—of the next manic episode. It now appears that selective serotonin

Figure 1. Bipolar and Schizoaffective Illnesses in Relatives Pooled into Pre-1940 and Post-1940 Cohorts*



*From reference 4.

reuptake inhibitors are less likely to cause cycling than tricyclic antidepressants (TCAs),[6] he said, and it also appears that bupropion[7] may be less likely to cause cycling than either TCAs or monoamine oxidase inhibitors. Therefore, alternate possibilities exist to dampen cycling, but the administration of antidepressants has probably worsened the natural history of manic depressive disorder in some individuals.

Mood-stabilizing alternatives to lithium include carbamazepine and divalproex. Controlled studies [8–10] indicate that carbamazepine is no more effective and has no fewer side effects than lithium. A large multicenter study[11] showed that divalproex was the equal of lithium in efficacy, with fewer side effects, and both drugs had positive tangible therapeutic efficacy over placebo. Of the lithium-treated patients, half the patients improved, 20% showed no improvement, and a small number of patients worsened. Thus, Dr. Thase said, one subpopulation was clearly lithium-refractory and another subpopulation was clearly lithium-responsive. Slightly different patterns of response occurred in divalproex-treated patients. It was later determined that among those with a prior history of nonresponse to lithium, divalproex was much more effective, whereas lithium was highly effective for the remainder.

On the basis of these data, Dr. Thase said, lithium should be the first-choice treatment in bipolar patients with a history of lithium response, and divalproex should be the first-choice treatment in bipolar patients with a history of lithium nonresponse. If the patient has no prior history of drug treatment or response, lithium generally should be the first-choice treatment because of its 40-year history of efficacy and low cost. Moreover, compelling long-term data on reduction in attempted and completed suicides in lithium-treated patients are now available,[12] while that benefit is yet to be determined for patients taking other mood stabilizers.

If lithium is the first-choice treatment for bipolar disorder, appropriate lithium management should be reviewed, Dr. Thase cautioned. Most lithium side effects are dose-dependent; therefore, a reduced drug dose and/or a change to sustained-release formulation that produces lower peak blood lithium levels[13] can be advantageous. Most side effects occur near the peak blood level (not at the mean blood level) and are associated with the speed from trough to peak. Therefore, if the peak can be lowered while the mean blood lithium level is maintained, a therapeutic effect with fewer side effects may be achieved, he said. Sustained-release lithium preparations are also bioavailable, i.e., the area under the curve is the same as that of immediate-release preparations; thus, both preparations may produce the same mean blood lithium level. Sustained-release formulations also may result in a substantial improvement in tolerability compared with immediate-release preparations.

…the administration of antidepressants has probably worsened the natural history of manic depressive disorder in some individuals.

Lithium remains a beneficial and powerful treatment for a large and definable subgroup of patients who have classical elated mania, but not in those patients with mixed-states, rapid-cycling, or mood-incongruent psychotic features, said Dr. Thase. The best indicator of a potentially beneficial response to lithium is a prior history of response to the drug; however, each time the drug is discontinued, the chance of the patient responding to subsequent doses may be reduced, perhaps by as much as 10%. In fact, Gelenberg et al.[14] found evidence that response to lithium prophylaxis was significantly lower among patients with 3 or more lifetime episodes. From a psychoeducational standpoint, the

patient should be taught that off-again, on-again treatment may diminish the response to lithium. When lithium is discontinued, it should be tapered slowly—even over a 6-month period—and the patient should be cautioned to avoid alcohol and drug abuse.

In summary, Dr. Thase submitted, there is evidence that the prognosis of manic depressive illness is worsening, which may be a consequence of various understandable and explainable factors such as changes in diagnostic practices, epidemiology, earlier age at onset, and the consequences of powerful treatment. An awareness of these factors may help to identify areas in which clinicians can improve delivery of care to their patients and lead to a reversal of the downward trend in the course of manic depressive illness.

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Treatment of Bipolar Disorder in Children and Adolescents

Bipolar children (less than 11 years) and adolescents (11–19 years) have multiple problems that are difficult to manage and cause considerable chaos in their families, said Robert Kowatch, M.D., whose presentation focused on prevalence, signs and symptoms, treatment, and prognosis of illness in patients in these age groups. According to Dr. Kowatch, the seminal study on the prevalence of bipolar disorder in a community sample of older adolescents was reported in 1995 by Lewinsohn et al.[1] Of 1709 randomly selected adolescents with a mean ± SD age of 16.6 ± 1.2 years, the lifetime prevalence of bipolar disorders (primarily bipolar II disorder and cyclothymia) was approximately 1%. A total of 5.7% of the sample, called *core positive* patients, reported a distinct period of abnormally and persistently elevated, expansive, or irritable mood even though they failed to meet the full criteria for a DSM diagnosis of mania. Compared with adolescents with a history of major depression and another group without a history of mental illness, both the bipolar and core positive samples exhibited significant functional impairment and high rates of comorbidity (particularly anxiety and disruptive behavior disorders), suicide attempts, and mental health services utilization.

Major depressive disorder (MDD) is fairly common among adolescents (7%–8%), and approximately one third of children who have severe MDD will develop bipolar disorder. The age at onset of symptoms was determined in a large survey[2] of bipolar members of the National Depressive and Manic Depressive Association. Of the respondents, 59% had their first symptoms before the age of 20 years, Dr. Kowatch noted. Initial symptoms were either depressive or mixed (depressive and manic/hypomanic), and the early age at onset was associated with frequent recurrences and increased rates of psychosocial morbidity.

A study that has caused some controversy in the field, said Dr. Kowatch, suggests that mania may be relatively common in children referred to psychiatrists.[3] To examine the prevalence, characteristics, and correlates of mania among children (≤ 12 years), investigators conducted structured interviews of children in a pediatric psychopharmacology clinic and subsequently divided the children into 3 groups: 43 children who satisfied the criteria for mania, 164 ADHD children without mania, and 84 non-ADHD controls. Compared with ADHD children without mania, manic children had substantially higher rates of major depression, psychosis, impaired psychosocial functioning, along with anxiety, conduct, and oppositional defiant disorders. The clinical picture was compatible with a DSM-III-R diagnosis of mania in 16% of the referred children. Although the results may be controversial, Dr. Kowatch said, the incidence of mania is similar

in his pediatric subspecialty clinic in Texas.

Dr. Kowatch underscored the importance of 4 factors that account for difficulties in identifying and diagnosing manic disorders in children and adolescents.[4] First, the low prevalence (1%) of the disorder makes it unlikely for these children to be identified except in a subspecialty clinic. Second, the disorder has a variable clinical presentation within and across episodes. Third, there is frequent symptomatic overlap with more common childhood disorders; in fact, there are few clean-cut diagnostic categories in child psychiatry, and comorbidity is the rule. Finally, there are constraints placed on symptom expression by the developmental stage of a child, i.e., a grandiose flight of ideas presents differently in a 7-year-old and a 25-year-old.

The most frequent symptom of bipolar illness in youngsters is an irritable mood, which can potentially modify a family's entire lifestyle.

Rapid-cycling patterns in children and adolescents have also been studied, and data from one study by Geller et al.[5] provide support for complex and rapid-cycling patterns in childhood-onset bipolar disorder. A diagnosis of bipolar disorder was established in 26 subjects, ages 7 to 18 years. Complex cycling patterns were observed in the sample (mean ± SD age at onset 8.5 ± 4.4 years); the patterns included numerous brief episodes that suggested continuous rapid cycling in 80.8% of cases. In this small sample, suicidality, hyperactivity, and mixed mania (depression and irritability with some euphoria) were highly prevalent. As expected, said Dr. Kowatch, controversy exists (especially among psychiatrists who treat adult patients) when the duration of symptoms are less than the DSM-IV criteria of 1 week, but symptomatic cycling in children rarely lasts a week. More commonly, children have numerous short episodes daily that are now called complex or ultradian. Adolescent patients tend to be euphoric and giddy in the morning and cranky and irritable in the afternoon, and they may have 3 or 4 daily mood swings, each one lasting several hours. Child psychiatrists continually struggle with the DSM-IV criteria for mania and hypomania in children and adolescents.

The most frequent symptom of bipolar illness in youngsters is an irritable mood, which can potentially modify a family's entire lifestyle. Children are highly irritable, with frequent intense outbursts of anger, while adolescents are extremely oppositional, belligerent, and hostile. These anger outbursts are not merely temper tantrums; the response is entirely out of proportion to the stimulus, e.g., the child may punch holes in walls at the slightest provocation. Thus, the parents may be understandably reluctant to take a bipolar child out in public. Bipolar adolescents have a clear history of mood swings and are typically intrusive, difficult to work with, and in-your-face; they also tend to be somewhat threatening and challenging to others and many have been labeled as having a borderline personality disorder.

An elevated or expansive mood is seen more commonly in adolescents than in children. Bipolar children tend to be inappropriately silly or giggly; they may sing constantly and appear to be happier than their situation warrants, whereas adolescents may be overly silly or unrealistically optimistic or grandiose. Neither group seems to have any insight into the inappropriateness of their moods. Although adolescents rarely exhibit a full-blown psychosis, they may demonstrate delusional thinking as they become more manic, and there may be little connection to reality. Bipolar children also exhibit a decreased need for sleep during manic episodes. Some 4- or 5-year-old children may resist going to bed until midnight and then sleep for only 4 or 5 hours. Adolescents may stay up all night and nap for short periods during the day.

An increase in goal-directed activity is another symptom, said Dr. Kowatch. Although manic children are often labeled hyperactive, they may be able to complete multiple projects—in contrast to hyperactive children. Mothers typically report that these children exhaust their playmates. They have endless energy, are motor driven, and shift rapidly from activity to activity. Distractibility is seen in both manic and hyperactive children, but the symptom tends to be more episodic in manic children; ADHD children tend to be chronically distractible. Pressured speech, which is more frequent in hospitalized patients, may become continuous and sometimes unintelligible. These youngsters may exhibit a flight of ideas and racing thoughts, and may make rhymes and clang associations. An excessive involvement in pleasurable activities may manifest itself in prepubescent manic children as inappropriate touching of peers and adults in an attempt to engage them in "sex." Manic adolescents usually experiment with alcohol, drugs, and marijuana and may engage in reckless, thrill-seeking behavior such as promiscuity, binge-drinking, and shopping sprees.

Prepubescent and young adolescents may present with a complex cycling pattern (3 or 4 mood swings daily) that includes affective storms and mixed features; the initial episode tends to be that of a major depressive episode. Older adolescents usually present with mania, but a past history of depression should be explored. Euphoria, if present, occurs for shorter

Figure 2. Hypothesized Clinical Course by Age at Onset*

	Prepubertal and Young Adolescent	Older Adolescent and Adult
Initial Episode	Major depressive episode	Mania
Episode Type	Rapid-cycling, mixed	Discrete with sudden onsets and clear offsets
Duration	Chronic, continuous	Weeks
Interepisode Functioning	Poor	Improved

*From reference 6, with permission.

periods of time. A chronic continuous cycling pattern commonly occurs in prepubertal children and their interepisode functioning is poor. In older adolescents, the duration usually lasts for weeks, and they tend to function fairly well when out of the episode (Figure 2).[6]

Dr. Kowatch then emphasized the importance of separate interviews with each parent and a careful family history of both maternal and paternal sides of the family. Premorbid functioning should also be assessed. To determine a cycling pattern, parents should be asked to describe the child's behavior early in the morning, after school, and on weekends. Response to pharmacologic agents and a negative response to stimulants may also provide clues to the diagnosis; prepubescent bipolar children who take stimulants tend to have an increase in labile moods and become more irritable.

One of the tools used by Dr. Kowatch and colleagues to assess bipolar patients is the Child Behavior Checklist (CBCL),[7] which is a formalized rating scale that can be filled out in the waiting room by the parents and scored by computer. To determine the discriminative ability of the CBCL in identifying children with structured interview-derived diagnoses of bipolar disorder, Biederman et al.[8] evaluated the convergence of CBCL scales with the diagnosis of mania in 31 children with mania, 120 children with ADHD, and 77 prepubertal normal control children (≤ 12 years). Excellent correlation was found between the diagnosis of mania and the CBCL scores of delinquent behavior, aggressive behavior, somatic complaints, anxious/depressed, and thought problems, and the authors concluded that the CBCL could serve as a rapid and useful screening instrument to identify manic children in a clinical setting.

— The symptoms of ADHD or conduct disorder are not simple to tease away from the symptoms of mood disorder. —

In comparison to the 1% prevalence of bipolar disorder, attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent (4%) behavioral disorders in children.[6] The symptoms of ADHD or conduct disorder are not simple to tease away from the symptoms of mood disorder. In children, much of the difficulty in making an accurate diagnosis arises when a prepubertal child has both ADHD and bipolar illness. Generally, ADHD is primarily a disorder of attention not mood; it tends to be persistent, not episodic, and the age at onset is 7 years or younger. Conduct disorders tend to be more predatory, but there is usually a secondary gain; these children tend to steal or rob for a reason, in contrast to children with mood disorder. Children with conduct disorder have a chronic pattern of irritability or belligerence and exhibit no grandiosity, flight of ideas, reduced need for sleep, or loss of reality testing. If a child has both conduct disorder and bipolar disorder, treatment should be directed at the mood disorder; occasionally the conduct disorder will be rendered euthymic or eliminated altogether with this approach.

According to Dr. Kowatch, lithium trials account for most of the studies of mood stabilizers in children and adolescents 4 to 20 years. The anticonvulsant carbamazepine has been studied primarily in young patients in whom seizures were comorbid with mood disorders, and there are only a few reports of divalproex trials in children.

A recently published, double-blind placebo-controlled trial[9] of lithium examined random weekly urine specimens for drug assays and random weekly blood specimens for lithium levels in 25 adolescent subjects with bipolar disorder who secondarily developed substance abuse disorders. The mean age at onset of bipolar disorder was 9.6 years and the mean age at onset of substance abuse (primarily alcohol or alcohol and marijuana) was 15.3 years. There was a substantial difference of continuous and categorical measures of both psychopathology scores and random weekly urine drug assays between both the active and placebo groups, and the authors concluded that lithium treatment of bipolar disorder with secondary substance dependency disorders was efficacious in adolescents. They also urged the earliest possible diagnosis of bipolar illness in children because of the mean 6-year interval to substance abuse.

The dosage of lithium in children is 30 mg/kg/day, given in 2 to 3 daily doses to maintain a blood lithium level of 1.0 to 1.2 mEq/L. Prepubertal patients usually take approximately 900 mg/day and adolescents take 1500 to 2000 mg/day, and an extended-release formulation may be given. Full efficacy of lithium can be expected to occur in 6 to 8 weeks. Lithium is generally well tolerated, but both baseline and routine laboratory monitoring should be done since the drug is usually administered long term. Pregnancy is a continuing concern in adolescent females with bipolar illness, and pregnancy testing should be done in sexually active females.

West et al.[10] conducted an open-label trial of valproate in 11 adolescent inpatients with bipolar disorder who had failed to respond to lithium and typical antipsychotics. All patients were concurrently receiving antipsychotics, and 9 of 11 patients showed moderate-to-marked improvement with the addition of valproate. Dr. Kowatch tends to use valproate in adolescent rapid-cycling or mixed states. The dose is 20 mg/kg/day and the blood valproate level should be maintained at about 100 mg/mL (range of 75–125 mg/mL). Full efficacy of valproate can be expected by 6 to 8 weeks, but may occur sooner. Side effects include nausea, sedation, weight gain, and transient hair loss. The major caution in the use of valproate—especially in children—is hepatotoxicity, and baseline and routine monitoring of liver function every 6 months is mandatory. Reproductive disorders, such as menstrual disturbances, polycystic ovaries, and hyperandrogenism are more common in women who have epilepsy, and these disorders have been attributed both to the epilepsy itself and to the anticonvulsants used to treat the epilepsy.[11] Consequently, there is concern and controversy in the field of child psychiatry about the use of antiepileptic drugs in young females.

Adolescent psychotic patients with bipolar illness are often given anticonvulsants, including carbamazepine, which may have a sedative effect. Dr. Kowatch recommended starting with a low dose of carbamazepine and slowly increasing the dose to a therapeutic blood level of 9 or 10 mg/mL. Gabapentin can be associated with disinhibition and may be more efficacious when used as adjunctive therapy with lithium. Lamotrigine has been effective in some patients, but the drug has been associated with the development of serious rashes. Topiramate is another new anticonvulsant that may demonstrate mood-stabilizing effects.

Antipsychotics, especially atypical antipsychotics, are also used commonly in these patients. Risperidone can be given in low doses of 0.5 or 1 mg once or twice daily. Clozapine is often effective in psychotic bipolar adolescents who fail to respond to other drugs, but weekly blood monitoring must be performed. Olanzapine, another new antipsychotic, may also prove to be efficacious in bipolar patients.

When young patients with a history of mood disorder are first evaluated, they should usually be tapered off stimulant or antidepressant medications, said Dr. Kowatch. If symptoms of mood disorder persist after 2 weeks, the child can be reevaluated and started on either lithium (in euphoric states) or valproate (in mixed-states) treatment. Once the child is stable, there may still be symptoms of ADHD, such as difficulty with attention at school. At that point, a Conners Parent and Teacher Questionnaire may be sent to the child's teacher for additional information about the child's behavior. If ADHD is still present (as indicated by the questionnaire) the child may be started on low-dose stimulants such as Adderall, which can be given in combination with lithium or divalproex. One mood stabilizer may not be effective, explained Dr. Kowatch, and combination therapy may often be necessary for control of the patient's symptoms.

Bipolar children and adolescents must be taught that they have a biologic disorder that is exacerbated by environmental stresses, Dr. Kowatch added. The purposes, benefits, and risks of medications must be explained and reviewed regularly. Most school officials do not understand bipolar illness, and it may be helpful to speak directly with school counselors who may provide help in monitoring symptoms. The National Institute of Mental Health has organized a Kiddie Life Chart that plots the course of bipolar illness. Parents can monitor the daily moods and record whether the child is activated or withdrawn, and clinicians can then decide on future treatment strategies by reviewing the record.

Strober and associates[12] have done much of the work on recovery and relapse in adolescents. All of the 54 adolescents discharged from their inpatient unit were treated with mood stabilizers. LIFE (Longitudinal Interval Follow-up Evaluation) assessments were made every 6 months for a total of 5 years. Roughly half (44%) of the youngsters had a relapsing course, and about 20% made a medically significant suicide attempt. A rapid recovery was observed in subjects with pure mania or mixed states, and a protracted index episode was seen in subjects with pure depression. Multiple relapses were most often seen in subjects with mixed or cycling episodes at intake. The authors concluded that recurrence risks varied as a function of age at onset or stage of the disease process.

In summary, bipolar illness in children and adolescents often causes serious dysfunction. The disease is treatable, but more research into effective treatment strategies is needed.

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The Spectrum of Clinical Use of Pharmacotherapeutic Treatment Options

Bipolar disorders are increasingly being recognized in all age groups, said Ross J. Baldessarini, M.D. Bipolar disorder in the geriatric population may have a variable prognosis and relatively high risk of mortality because of concurrent medical or neurological illness, or suicide. Geriatric bipolar disorder can represent a continuation of illness or can arise de novo after the age of 65 when mania and depression are frequently severe and difficult to treat because of limited responsiveness or low tolerance of the patient to mood-altering agents. Moreover, secondary mania and depression may be associated with dementing degenerative disorders or as a sequel to stroke.

According to Dr. Baldessarini, the management of bipolar depression is a particularly challenging problem that has been systematically excluded from most of the experimental therapeutic research of depression. In part, he said, this avoidance reflects a strong clinical impression that most antidepressants have a substantial, possibly dose-dependent, risk of inducing agitation, mania, or psychosis in bipolar depressed patients. The cautious short-term use of bupropion and the shorter-acting serotonin reuptake inhibitors (SRIs) for the treatment of bipolar depressive episodes may be relatively safer than other antidepressants, provided that adequate mood-stabilizing therapy is already in place, he noted. SRIs may also be safer than tricyclic antidepressants or monoamine oxidase inhibitors in geriatric patients. Electroconvulsive treatment also remains a powerful option as a treatment modality for all phases of bipolar disorders, including mixed or psychotic states.

Lithium is relatively specific for the treatment of mania but the onset of useful action (5–10 days) is slow. Additionally, there is a limited margin of safety (low therapeutic index) in acutely disturbed, poorly cooperative, and/or metabolically compromised patients; therefore, lithium is generally not used in the treatment of acute mania. As a rapidly-acting alternative, an antipsychotic—which may be more dramatically effective in mania than schizophrenia—or a sedative, such as a high-potency benzodiazepine like lorazepam or clonazepam, plus a high loading dose (20 mg/kg) of valproate can be given. Lithium can then be added in gradually increasing doses with continuing use during aftercare. Lithium is particularly useful for follow-up treatment in the months after clinical recovery from an acute episode of mania and for long-term minimization of the risk of future or severe recurrences of mania or bipolar depression, said Dr. Baldessarini. During maintenance periods, lithium may be more effective against manic than depressive phases of bipolar disorder; it is also effective in type II bipolar disorder (recurring major depression with hypomania) and probably effective adjunctively in nonbipolar depression, including cases of apparent antidepressant unresponsiveness or intolerance.

A poor response to lithium can be anticipated in patients who present with mixed, agitated, psychotic bipolar states, and rapid-cycling (≥ 4 episodes/year). Those patients who present with depression before mania may derive less benefit from lithium treatment

Table 2. Reported Rates of Suicidal Acts With and Without Lithium Maintenance*

Measure	Value
Studies, N	
On lithium	22
Not on lithium	13
Subjects, N	16,208
Years-at-risk, mean ± SD	8.22 ± 4.53
Rate of suicidal acts, % of subjects/year	
Without lithium, mean ± SD	1.778 ± 1.444
With lithium, mean ± SD	0.255 ± 0.403
Apparent risk-reduction	6.97-fold

*From reference 1, with permission. Includes bipolar, schizoaffective, and some recurrent unipolar major depression cases, or unselected major affective disorders, and includes both life-threatening and fatal suicidal acts (per 100 patient-years). Mean rates differ highly significantly (t [34 df] = 3.43, p < .001).

than those presenting with mania first. Some of the beneficial effects of lithium in the treatment of apparent "nonbipolar" depression may reflect an underdiagnosis of bipolar disorders or related conditions such as cyclothymia, and some cases of apparent nonbipolar depression may be phenotypic variants, or pseudo-unipolar disorders. Additionally, there is growing suspicion that overuse of antidepressants may destabilize some individuals who have recurring depression, particularly those with subtle undiagnosed bipolar traits.

Lithium may also be useful as an adjunct in treatment-resistant unipolar depression and in the treatment of other conditions such as secondary bipolar disorder associated with neurologic disorders, schizoaffective disorders, episodes of aggressive outbursts, and in some individuals without clear evidence of a primary mood disorder. Other potential medical applications of lithium lack substantial support, such as in the treatment of hyperthyroidism and leukopenia. It is important to realize that there are no well-controlled experimental studies of lithium or other mood-stabilizing agents in the elderly and very few in children or adolescents, although lithium and valproate appear to be effective and are often tolerated by both age groups. Tolerability to lithium is particularly limited in the geriatric population, in whom the adult dosage may have to be adjusted downward.

Lithium also has virtually unique status in having demonstrated antisuicide effects in a wide range of severe, recurring mood disorders, and particularly in bipolar disorders (Table 2).[1] It is not clear whether this apparent antisuicide effect is a reflection of the mood-stabilizing actions of lithium or a more direct and specific effect against aggression and impulsivity, which are known risk factors for suicidal behavior. Since approximately 90% of suicidal acts in bipolar disorder are associated with depressive or recurrent mixed (dysphoric mania) episodes of mood disorder, protection against bipolar depression is a particularly important means of preventing suicide. A recent direct comparison found lithium to be more effective than carbamazepine against suicide[2]; evidence of reduced suicidal risk with other alternatives to lithium is not available.

— Since approximately 90% of suicidal acts in bipolar disorder are associated with depressive or recurrent mixed (dysphoric mania) episodes of mood disorder, protection against bipolar depression is a particularly important means of preventing suicide. —

There is a growing impression that anticonvulsants vary in their effects on bipolar depression. The newer anticonvulsant lamotrigine may minimize depression, while lamotrigine, gabapentin, and the novel antipsychotic agents risperidone and perhaps olanzapine may elevate mood and even induce agitated states in some bipolar patients.

Dose-response of lithium has not been investigated extensively, but available evidence indicates that daily minimum blood lithium levels of 0.6 to 1.2 mEq/L are within the standard therapeutic range; levels below 0.6 mEq/L are less effective while levels above 1.2 mEq/L may provide limited additional benefit but increase the risk of side effects and are best reserved for acute mania, rapid cycling, or treatment-resistant cases. Levels of 0.6 to 0.7 mEq/L are often effective and better tolerated than higher levels.

Side effects of lithium include frequent initial polyuria and thirst, and about a l0% risk of developing a persistent (but usually reversible) clinically significant diabetes insipidus that is associated with elevated circulating levels of antidiuretic hormone and is unresponsive to exogenous synthetic antidiuretic peptides, including DDAVP (1-desamino-8-D-arginine vasopression). Weight gain, skin disorders, and subtle neurologic and cognitive effects are the most common reasons for discontinuing lithium. High risk neurologic effects include mild resting tremor and impaired handwriting, which often respond to reducing lithium dosage or administering propanolol or nadolol. Additionally, varying degrees of mental confusion and delirium—particularly in elderly or neurologically impaired patients—can occur at trough blood concentrations within the nominal therapeutic range of lithium. Potentially irreversible motor and cognitive sequelae can occur after acute lithium overdosage or sustained excessive blood lithium levels, which may rise with the gradually diminishing ability to clear the drug. Clinical myxedema is relatively unusual during lithium therapy. Diffuse, nontoxic, non-precancerous goiter can occur, with an occasional lowering of blood thyroid hormone indices into the low-normal or subnormal range.

Although data are inconclusive,[3] the repeated suggestion of an association between lithium treatment and increased risk of major cardiovascular malformations (such as Ebstein's anomaly) during the first trimester of pregnancy strongly supports the avoidance of pregnancy while lithium is being administered. However, Dr. Baldessarini cautioned, the risk of malformations (which may be exaggerated) should be weighed against the risk of a major recurrence of bipolar disorder if lithium is discontinued. Lithium may induce muscular hypotonia in the newborn; in the mother, the elimination of and tolerance to lithium typically decrease after delivery, and

lithium is present in the breast milk of nursing mothers. Valproate and probably carbamazepine are associated with an increased risk of spina bifida,[4,5] and carbamazepine has been associated with an increased risk of facial malformations in infants of epileptic women.[6] It is not clear if similar risks occur in infants of bipolar women, but it would be prudent to assume so.

While mood-stabilizing anticonvulsants probably are unsafe during early pregnancy, the cautious use of neuroleptics or antidepressants in low-normal doses can be considered when necessary. Some experts now advise the use of lithium or other mood-stabilizing agents in the third trimester of pregnancy and the neonatal period to avoid potentially catastrophic postpartum psychotic affective illness with risks of suicide or infanticide.[7]

Sudden discontinuation of lithium—even in patients who have been euthymic for several years—carries a high risk of early relapse which can be minimized by slowly tapering the doses[8,9]; hypothetical cross-protection with alternative mood-stabilizing agents is untested.

Innovative alternatives to lithium include certain anticonvulsant agents that have been found especially useful in partial seizures with complex symptomatology (psychomotor, temporal lobe), said Dr. Baldessarini. Carbamazepine has been included in some long-term maintenance trials, although tolerability as monotherapy—at doses that provide blood concentrations of 6 to 12 mg/mL—is limited because of sedation, confusion, nausea, headache, and blood dyscrasias. The long-term efficacy of carbamazepine is uncertain although it may be effective as adjunctive therapy with lithium, and it may be particularly effective in psychotic bipolar or schizoaffective disorders. Carbamazepine interacts significantly with some antidepressants, neuroleptics, anticoagulants, and antifertility agents by inducing hepatic oxidative metabolism to lower the blood drug level. Although the long-term prophylactic efficacy of valproate remains unproved, the drug is increasingly accepted empirically for manic patients of all ages as either an alternative or adjunct to lithium.

Valproate may produce upper and lower gastrointestinal symptoms, headache, excessive sedation, and hair loss. Valproate has relatively little pharmacokinetic interaction with other agents; i.e., it tends to increase blood concentrations of many agents moderately, whereas most standard anticonvulsants increase clearance and lower drug levels. Except for the sedative effects, valproate tends to be better tolerated than carbamazepine. High- and low-potency neuroleptic agents and sedatives, especially potent benzodiazepines, are useful adjuncts in the short-term management of manic patients, but their long-term efficacy and that of other experimental agents, such as the newer anticonvulsants, calcium channel blockers, L-tryptophan, and magnesium salts, is not proved. While there is limited evidence that antipsychotic agents may have beneficial effects in bipolar and schizoaffective disorders—and the majority of bipolar patients are exposed to antipsychotics at some time during their illness—there is substantial epidemiologic evidence that episodic mood disorders (particularly unipolar depression) may carry an increased risk of neuroleptic-induced tardive dyskinesia.[10] Atypical antipsychotics carry a lower risk of tardive dyskinesia and may be useful adjunctively in otherwise unstable bipolar or schizoaffective patients. Although valproate is now used commonly on an empirical clinical basis as treatment for adolescent and geriatric mania, Dr. Baldessarini emphasized that anticonvulsants and other alternatives to lithium, as well as lithium itself, have limited investigational support in these populations.

In summary, mood-stabilizing agents, particularly lithium—administered either alone or combined with an anticonvulsant—are the cornerstone of rational long-term medical management of bipolar patients.

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Instructions

Psychiatrists may receive 1 hour of category 1 credit toward the American Medical Association Physician's Recognition Award by reading the article starting on page 484 and correctly answering at least 70% of the questions in the posttest that follows.

1. Read each question carefully and circle the correct corresponding answer on the Registration form.
2. Type or print your full name, address, phone number, and Social Security number in the spaces provided.
3. Mail the Registration form along with a check, money order, or credit card payment in the amount of $10 to: Physicians Postgraduate Press, Office of CME, P.O. Box 752870, Memphis, TN 38175-2870.
4. For credit to be received, answers must be postmarked by the deadline shown on the CME Registration form. After that date, correct answers to the posttest will be printed in the next issue of the *Journal*.

All replies and results are confidential. Answer sheets, once graded, will not be returned. Unanswered questions will be considered incorrect and so scored. Your exact score can be ascertained by comparing your answers with the correct answers to the posttest, which will be printed in the *Journal* issue after the submission deadline. The Physicians Postgraduate Press Office of Continuing Medical Education will keep only a record of participation, which indicates the completion of the activity and the designated number of category 1 credit hours that have been awarded.

1. Which of the following statements is correct?
- a. Potential targets of drug action include intracellular G proteins, adenylate cyclase, protein kinases, and immediate early genes and gene products.
- b. Lithium has very discriminating effects on the 2 major transductional systems.
- c. An abnormal regulation of G protein may be a possible pathophysiology of bipolar illness
- d. Answers a and c
- e. Answers a, b, and c

2. Lithium and other mood-stabilizing drugs may:
- a. Inhibit G protein binding of GTP (guanosine triphosphate)
- b. Inhibit G protein-linked second messenger systems
- c. Gain their mood-stabilizing effects in bipolar cycling from interactions with glutamate that inhibit the kindling phenomenon
- d. All of the above
- e. None of the above

3. Which of the following statements is *not* correct?
- a. In 1990, the efficacy rate of lithium was 45% to 50%.
- b. Each year, 10% of the patients who become ill with manic depression will recover, remain well subsequently, and be excluded from subsequent clinical trials and statistics.
- c. Lithium pharmacotherapy is effective in Type II patients as it is in Type I patients with bipolar disorder and in both mania and bipolar depression.
- d. Each time lithium is discontinued, the chance of the patient responding to subsequent doses is reduced by about 10%.
- e. None of the above

4. The age at onset of bipolar disorder:
- a. Is below 21 in at least half of the cases
- b. Has no relationship to prognosis
- c. Includes some patients over 65
- d. Is not correlated with comorbid alcohol and drug abuse
- e. Answers a and c

5. Symptoms of bipolar illness in children and adolescents may include:
- a. 3 to 4 daily mood swings
- b. Delusional thinking
- c. Marked periods of irritability
- d. Thrill-seeking behavior
- e. All of the above

6. Bipolar children and adolescents can be distinguished from children with other behavioral disorders by which of the following characteristics?
- a. Distractibility is more episodic in manic than in hyperactive children.
- b. Children with conduct disorder tend to steal and rob for no reason.
- c. Manic children may be able to complete multiple projects, in contrast to hyperactive children.
- d. When given psychostimulants, manic children may become less irritable.
- e. Answers a and c

7. Which of the following statements is *not* correct?
- a. Lithium is generally used in the treatment of acute mania.
- b. An antipsychotic or high-potency benzodiazepine may be used for treatment of acute mania.
- c. Carbamazepine may be useful in adolescent psychotic bipolar patients.
- d. Divalproex is more effective in mania than in schizophrenia.
- e. All of the above

8. Which of the following statements is *not* correct?
- a. Lithium may be associated with neonatal hypertonia.
- b. In pregnancy, the risk of discontinuing lithium should be weighed against the risk of cardiac malformations.
- c. Lithium is not excreted in breast milk.
- d. The use of divalproex and carbamazepine in pregnant women has been associated with spina bifida in offspring.
- e. Answers a and c

Answers to the March 1998 CME posttest

1. b 2. c 3. d 4. a 5. c 6. d

Circle the one correct answer for each question.

1.	a	b	c	d	e
2.	a	b	c	d	e
3.	a	b	c	d	e
4.	a	b	c	d	e
5.	a	b	c	d	e
6.	a	b	c	d	e
7.	a	b	c	d	e
8.	a	b	c	d	e

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