Special Considerations: Use of Lithium in Children, Adolescents, and Elderly Populations

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Certain populations of patients require special considerations when lithium is prescribed. Children and adolescents have higher volumes of body water and more active renal glomerular filtration rates than adults. Their central nervous system is developing and therefore is vulnerable to the impact of substances, including medications such as lithium, that can cause side effects or adverse events. Elderly patients have less body water, slower metabolism, and often comorbid illnesses, so they also require close evaluation and monitoring when prescribed lithium. This paper examines the indications for, pharmacokinetics of, clinical uses of, and side effects of lithium in children, adolescents, and the elderly. Use of alternate mood stabilizers is also addressed briefly.

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At the beginning and end of the life cycle, patients demonstrate certain physiologic states that may render difficult the use of lithium for treating various behavioral disorders. Younger populations, including children and adolescents, have a higher volume of body water and more active renal glomerular filtration rates than adults. In addition, children's immature central nervous systems predispose them to various cognitive and neurologic adverse reactions when exposed to certain medications. At the other pole of the life cycle, elderly patients have less body water and a slower renal glomerular filtration rate. Also, their central nervous system is often more vulnerable to anatomic and physiologic alteration, partially due to normal aging changes and disease processes. The result is increased concentration, delayed metabolism, and increased side effects when an older patient is exposed to some medications. Lithium has a narrow therapeutic range so that side effects and toxicity are common in adults when the serum lithium level exceeds 1.5 mEq/L and can occur at therapeutic levels. Due to physiologic variables as well as less reserve and more vulnerability of their central nervous system, children, adolescents, and the elderly are more likely to suffer adverse effects of lithium therapy and require special treatment considerations.

In the sections below, we will review the indications for, pharmacokinetics of, clinical uses of, and side effects of lithium in these special populations of children, adolescents, and the elderly. We will also briefly review the role of alternate mood stabilizers valproate and carbamazepine to treat some behavioral symptoms and disorders in these populations.

USE OF LITHIUM IN CHILDREN AND ADOLESCENTS

Interest in the diagnosis and treatment of affective conditions in children and adolescents has increased in recent years. However, much of this research has been complicated by the high degree of diagnostic heterogeneity and comorbidity that is common in children and adolescents who present with affective symptoms. In addition, pharmacologic interventions, such as tricyclic antidepressants (TCAs), effective in adults for the treatment of depression, are not clearly as useful in children.[1] Also, neurodevelopment may affect the differential response of children to lithium.[2] The indications for lithium therapy, considered a mainstay in the treatment of adult bipolar disorder, are less clear in the treatment of children and adolescents. Although lithium has been used for many years in this population,[3] there are very few double-blind, placebo-controlled studies.[4,5] Probable indications for lithium use, however, are in the treatment of explosive, affectively charged aggression and bipolar affective disorder.[6,7] Less clear indications include augmentation therapy for the

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treatment of childhood or adolescent depression[7,8] and the treatment of aggression and affective symptoms associated with mental retardation,[9–11] autism,[11,12] and Tourette's disorder.[13] Lithium does not appear to be effective as monotherapy for the treatment of attention-deficit/hyperactivity disorder (ADHD).[11,14]

Potential Indications for Lithium Use in Children and Adolescents

Bipolar affective disorder. Bipolar affective disorder in children and adolescents has received increased interest in recent years, especially in regard to exact diagnosis and comorbidity. In a recent investigation, an incidence of 0.94% for bipolar disorder has been demonstrated in a high school population on the basis of structured interviews.[15] Eleven percent (2/18) met the full criteria for bipolar I disorder while the remainder were diagnosed as bipolar II or with cyclothymia. The mean age at onset of the first affective episode was 11.75 years. In another study, 20% of 206 children with ADHD received a comorbid diagnosis of mania while 98% of children with bipolar illness met criteria for ADHD.[16] Comorbidity of conduct disorder, ADHD, substance abuse, psychosis, and anxiety disorders has also been documented.[15,16] A placebo-controlled study of lithium used in adolescents with bipolar affective disorder and substance dependence showed improvement for both disorders.[17]

In a large open trial of lithium, 73.7% of bipolar children and adolescents responded with increased mood stabilization.[11] In another large open study of lithium therapy in acutely manic adolescents, 65.7% responded after 4 weeks compared with 33.3% of those with a prepubertal onset of illness. Patients with an early onset (< 12 years) of an Axis I diagnosis (primarily ADHD or conduct disorder) had a greater than threefold increase in first-degree relatives with bipolar I disorder, possibly suggesting a more virulent form of the illness with a poorer treatment response.[18] A naturalistic lithium maintenance study showed that only 37.5% of bipolar I adolescents relapsed while on lithium therapy compared with a 92.3% relapse rate for adolescents who discontinued lithium during the 18-month follow-up period.[19] In a subsequent study of 54 adolescents with bipolar I disorder,[20] 44% of the 52 who recovered from their index episode had one or more relapses during a 5-year follow-up while on lithium maintenance therapy. This study suggested a slower return to euthymia but a longer time in remission in adolescent compared with adult bipolar patients. Thus, the available studies suggest that lithium is an effective pharmacologic agent for the treatment of both the manic phase and maintenance state of bipolar disorder in children and adolescents. Clearly, controlled studies are necessary to address the efficacy and side effect profile of lithium compared with other mood stabilizers.

Aggression. Aggression is seen in many childhood and adolescent disorders and causes severe suffering and disability for the child, with adverse impact on society at large. However, aggression does not constitute a separate diagnostic category. Subtyping aggression into impulsive-affective and controlled-predatory subtypes may lead to better assessment of treatment outcomes.[21] Behavioral therapy may be more effective for controlled-predatory aggression, while pharmacologic and psychosocial interventions seem to work best for impulsive-affective aggression.[21,22] Although not specifically subtyped into predatory or affective aggression, two well-controlled, methodologically similar studies showed lithium to reduce generalized aggression and explosiveness in children 5 to 12 years old. In the first study,[6] 61 children were randomly assigned to one of three treatment groups: haloperidol, lithium, or placebo. Treatment duration was 4 weeks with a mean lithium dosage of 1166 mg/day and a mean blood level of 0.993 mEq/L. Lithium and haloperidol were statistically superior to placebo in reducing aggression. In a more recent study of 50 children with characteristics similar to the first group,[23] lithium was compared with placebo during a 6-week trial. The mean lithium dosage was 1248 mg/day and the mean blood level was 1.12 mEq/L. Interestingly, the results were favorable but less robust compared with the 4-week study, although essentially the same rating instruments were used. In a large open study of the use of lithium in the treatment of a variety of childhood diagnoses, lithium was found to be effective in reducing explosive behavior and aggression in a subgroup of children with behavior disorders.[11] However, in a shorter, 2-week trial,[24] lithium showed no advantage when compared with placebo in a double-blind fashion in 33 adolescent inpatients with conduct disorder. At the completion of the study, 1 of 12 patients taking placebo and 3 of 14 taking lithium met remission criteria. Therefore, the available studies suggest that lithium is probably an effective pharmacologic agent to treat explosive aggression in the majority of behaviorally disturbed children with Axis I disorders.

Major depression. Juvenile major depression (mean age = 11.2 years) has a high rate of conversion to bipolar disorder (32%) over time, 12.7% as bipolar I and 19% as bipolar II disorders,[25] but the efficacy of lithium monotherapy has not been formally studied in major depression in children or adolescents. However, two studies have looked at lithium augmentation or antidepressant therapy in treatment-refractory, depressed adolescents. In a retrospective chart review,[8] it was found that 6 of 14 patients achieved a good response to TCA-lithium combination after a minimum 4-week trial of a TCA alone. The response tended to occur gradually over the first month of lithium treatment. Responders could not be distinguished from nonresponders based on severity of initial episode, gender, or serum level. The combination therapy was well tolerated in all patients. In an open study of 34 depressed adolescents with

a poor response after 6 weeks of imipramine therapy,[7] 24 received a 3-week trial of additional lithium therapy and 10 served as controls. Of the lithium-treated patients, 42% showed evidence of clinical response in contrast to 10% of the controls. The addition of lithium was generally well tolerated, with tremor and polyuria as occasional side effects.

Some evidence suggests that certain populations of children and adolescents may be less responsive to lithium, including very young children, neurologically impaired youths, and adolescents with mixed mania or predatory aggression.[18,26] Patients with comorbid personality disorders may also show a less robust response to lithium.[27]

Combination pharmacotherapy. Published reports on the use of lithium in combination with other medications in children and adolescents have been rare. Some reports in the adult literature suggest increased neurotoxicity when lithium is combined with neuroleptics.[28] However, other studies show no adverse effects.[29] Although some practitioners use lithium and neuroleptic combination therapy in severely behaviorally disordered youths after conventional therapies have been unsuccessful, two studies showed that lithium alone is often effective in treating psychotic symptoms in children and adolescents.[30,31] In addition, one study demonstrated that lithium was as effective as haloperidol and better tolerated.[6]

Positive results have been reported using lithium and carbamazepine in combination in bipolar adolescents who are resistant to monotherapy.[32] However, in a case series of four encephalopathic adolescents, behavioral decline, lethargy, and seizures were increased with this combination.[33] In a study of adolescent patients with mania, five patients received concurrent valproate, lithium, and neuroleptic medications. Four out of the five improved and sedation was the only adverse effect reported.[34]

Comorbidity of ADHD with bipolar disorder is currently being investigated. It has been reported that 12% to 20% of children with ADHD also met criteria for bipolar affective disorder.[35] Because combination pharmacotherapy may be necessary in these children, more studies evaluating combination stimulant and mood-stabilizer therapy are needed. In a small crossover study of methylphenidate, lithium, and the combination of these two medications,[36] increased gastrointestinal side effects, insomnia, and irritability occurred more frequently with the combination compared with either drug alone. Behavioral improvement was observed but was not statistically significant.

In summary, the few available data on combining lithium and mood-stabilizing anticonvulsants (carbamazepine, divalproex) suggest that the combination might be effective in selected patients, but side effects may be greater with combination therapy than with monotherapy. Here again, we await controlled studies.

Pharmacokinetics and Clinical Use of Lithium in Children and Adolescents

Children have a higher volume of distribution and glomerular filtration rate than adults, resulting in the need for an increased lithium dose per body mass. Elimination half-life is shorter for children compared with adults, so young children may reach steady state faster.[37] In addition, switching from lithium carbonate to liquid lithium citrate may require a dosage reduction due to differences in absorption.[38]

Before starting a child on lithium, a complete blood count with differential, a urinalysis, and an electrocardiogram may be needed. Measurements may also include liver function, T_4, TSH, BUN, creatinine, and electrolytes. Consideration may also be given to obtaining a 24-hour creatinine clearance (or two 12-hour urine collections). Dosing can be approximated in three ways. First, gradually titrate the dose depending on steady-state drug levels. Start with a low daily dose (300–600 mg), check levels after 4 or 5 days, and make adjustments accordingly. The second method uses the Cooper nomogram to approximate the dosage after checking a serum lithium level 24 hours after a test dose of 600 mg (300 mg in preschoolers). This method has been shown to be safe, although adjustments in dosage may still be necessary.[39,40] The third method uses a dosage guide of 900 mg/m^2 or approximately 30 mg/kg day to achieve a mean steady-state level of 0.6 to 1.2 mEq/L. However, children may have lithium levels above 1.4 mEq/L when this method is used.[41] The duration of an adequate trial of lithium is at least 6 weeks. Drug levels should be measured weekly until they become therapeutic (0.6–1.2 mEq/L).

Side Effects of Lithium in Children and Adolescents

Overall, lithium is generally well tolerated in children and adolescents. Side effects occur most frequently in young children, especially those with neurologic deficits.[42] For example, reports of adverse effects were particularly prevalent in a study of autistic children.[12] The most prevalent side effects include nausea, tremor, polyuria, and enuresis. In a study of 91 conduct disordered children (aged 5–12 years) in a placebo-controlled trial of lithium therapy,[43] side effects occurring only in lithium-treated patients included enuresis (17.4%), ataxia (6.5%), diplopia (2.2%), dysarthria (2.2%), and polydipsia (2.2%). Vomiting (41.3%), nausea (28.3%), and tremor (26.1%) occurred in significantly more patients receiving lithium. Weight changes were not significantly different from those receiving placebo. Special concern for side effects should be exercised in children with a febrile or dehydrating illness, children involved in strenuous sports, children with an eating disorder, and those likely to use nonsteroidal antiinflammatory drugs (i.e., menstruating females).

Renal. Most studies report no adverse renal effects due to lithium other than polyuria, polydipsia, and enuresis.[22,43]

Table 1. Special Considerations in the Use of Lithium in Children and Adolescents

Indications
Probably effective in bipolar disorder
Probably effective in aggression
Possibly useful as augmentation therapy for major depression
Effectiveness appears limited in aggression with comorbid illness including mental retardation, autism, and Tourette's disorder
Probably not effective in attention-deficit/hyperactivity disorder
Pharmacokinetics and clinical use
Higher volume of distribution than in adults
Higher glomerular filtration rate than in adults
Shorter elimination half-life than in adults
Careful approximation of dosing needed
Side effects
Generally well tolerated
Occasional side effects include enuresis, vomiting, nausea, and tremor
Teratogenic effects are not common and occur less often than previously reported

One case series of four adolescents reported no renal impairment after they received lithium therapy for 3 to 5 years.[44]

Neurologic/cognitive. No impairments in attention, cognitive functioning, and learning were commonly found in children taking lithium.[45,46] However, a study of 20 preschool children taking lithium reported side effects in 60% of the cases, including tremor, drowsiness, ataxia, and confusion. These side effects were seen most often during the first week of therapy in those children with a diagnosis of bipolar affective disorder.[47]

Thyroid. Most studies indicate no changes in thyroid indexes in children and adolescents. However, one report did mention the development of lithium-induced goiter and hypothyroidism in children and adolescents.[4]

Teratogenicity. Lithium therapy has been associated with a variety of teratogenic effects, especially Epstein's anomaly, although the overall risk to the fetus is now thought to be less than previously reported.[48,49] Please refer to Table 1 for a listing of the special considerations of lithium use in children and adolescents.

Potential Use of Alternative Mood Stabilizers

Valproate. Divalproex has recently been approved for the treatment of mania in adult bipolar disorder. Controlled studies for adult maintenance therapy and acute treatment of adolescent bipolar disorder are ongoing. All patients improved in an open trial using divalproex for the treatment of mania in six adolescents.[50] In another open study of 11 adolescents with mania, who had failed to respond to lithium and antipsychotics,[34] valproate was added to their medication regimen. Nine of the 11 patients showed considerable improvement after 6 to 26 days of valproate therapy. A third open trial of 10 adolescents with explosive episodes showed definite improvement on divalproex after 5 weeks.[51] A review of liver failure deaths due to valproate found the greatest risk was in children 0–2 years of age who were receiving other anticonvulsive medications. The risk declined with age, to the extent that no hepatic fatalities occurred in patients above 10 years of age receiving valproate monotherapy.[52]

Carbamazepine. Carbamazepine has been reported to benefit behavioral and affective disorders in a number of children with and without concurrent seizure disorder, but methodological problems existed in many of these studies.[53] No trials have been done to assess the effectiveness of carbamazepine as a single agent in the treatment of child and adolescent bipolar disorder. In a double-blind, placebo-controlled study of 22 aggressive children, no benefit of carbamazepine over placebo was demonstrated.[54] In other carbamazepine studies of children, side effects were frequent; 33% to 92% of children had some type of adverse reaction including nausea, drowsiness, diplopia, and dizziness.[53,54] In one study, 46% of the children receiving carbamazepine developed moderate-to-marked leukopenia.[54] Also, behavioral activation and manic symptoms have been reported in children treated with carbamazepine.[53,55,56] Dosage reduction has been partially successful in decreasing behavioral toxicity as well as other adverse effects.[55]

USE OF LITHIUM IN THE ELDERLY

The principal use of lithium in the elderly is for the treatment of bipolar disorder.[57,58] Lithium appears to be equally effective in the treatment of mania and for the prophylaxis of bipolar disorder in the elderly as in the younger adult population.[59,60] However, the appearance of primary mania for the first time after the age of 60 years is relatively rare.[59,61,62] Most elderly patients with mania have a history of previous affective episodes in their early years. These patients who have bipolar disorder have typically experienced episodes of mania as well as major depression during the earlier decades of their lives and may experience similar exacerbations in their later years. Episodes of major depression and mania in patients with bipolar disorder may increase, decrease, or remain the same with age, but the disease rarely enters full remission.[59,63–65] Interestingly, approximately 10% of all bipolar patients suffer their first episode of major depression or mania after the age of 50 years.[59,61] However, in older patients, the course of bipolar disorder can be modified by neurologic disease. Furthermore, episodes of mania and depression not due to bipolar illness can be caused by central nervous system disease and medical illness. Approximately one third of the cases of late-onset mania have been associated with neurologic illness.[64,65] Although lithium can be a first-line treatment of bipolar illness and secondary mania in the elderly, its use is often associated with side effects. The most common predisposing causes for these adverse events are normal aging changes, neurologic disease, and medical conditions.[58,59]

Potential Indications for Lithium Use in the Elderly

Lithium is used principally to treat mania and for the prophylaxis of bipolar disorder in both adult and elderly populations.[57–60] However, although the diagnosis of mania in the elderly is based on the same criteria used to diagnose younger patients, certain signs and symptoms are more typically seen in older patients. Some of these characteristic presentations include confusion, irritability, paranoia, and impaired concentration. Neurologic disease, particularly dementia and vascular abnormalities, as well as medical disorders and medications, complicate the presentation and diagnoses of mania in the elderly. Mania can be precipitated by right-sided lesions of the frontal cortex such as a right-sided middle cerebral artery infarction. Other disorders that can present as late-onset secondary mania include hyperthyroidism, epilepsy, brain trauma, dementia, neoplastic disease, and virtually any disease of the right hemisphere.[59,61,63,66,67] Medications that can cause secondary mania include corticosteroids, levodopa, antidepressants, and broncodialators.[59,67,68] If there is no history of early-onset manic episodes and no family history of bipolar illness, secondary mania should be considered in any elderly patient who presents with mania symptoms.[58] Treating the underlying disorders may alleviate the manic symptoms, but pharmacotherapy with lithium or another mood stabilizer may be necessary.[59,68] Lithium can be a first agent of choice for the treatment of acute mania and prophylaxis therapy for bipolar disorder in the elderly and, after the primary cause has been addressed, for the adjunctive treatment of secondary mania in the older population. However, lithium may not be as effective in elderly patients with these diagnoses, particularly if there is comorbid neurologic disease or a medical condition affecting the central nervous system.[63,69,70]

Pharmacokinetics and Clinical Use of Lithium in the Elderly

The use of lithium in older patients requires certain precautions because of age-related changes and comorbid illness, both common in the elderly population. Physiologic age-related changes include decreased total body water, decreased renal blood flow, and reduced glomerular filtration rate.[58,59,69] Reduced body water decreases the volume of distribution of lithium throughout the body and tends to elevate blood lithium levels in older patients. Renal function can be reduced up to 60%, which results in decreased creatinine clearance. Although younger adults have an average lithium elimination half-life of 20 hours, elderly patients can exceed that by 50% to 100%. This is especially the case in elderly patients with chronic medical illnesses, such as congestive heart failure or hypertension.[58,71]

Prior to starting lithium therapy in the elderly, certain laboratory values usually should be obtained, including a complete blood count with differential, glucose, electrolytes, BUN, creatinine, urinalysis, thyroid profile, and ECG. Consideration may be given to obtaining a 24-hour creatinine clearance to better evaluate kidney function.[58,71] Detailed mental status and neurologic examinations are recommended because many side effects due to lithium toxicity affect the central nervous system. A detailed medication history is an important part of the evaluation because many medications affect blood lithium levels.[68,71] Some of the more common medications taken by the elderly that can increase blood lithium levels include thiazide diuretics, nonsteroidal antiinflammatory drugs, metronidazole, tetracyclines, angiotensin-converting enzyme inhibitors, and β-blockers.[57,68,72] In the elderly, it is important to initiate lithium therapy by utilizing a low dose that is given two or three times a day. Increases should be spaced out by several days. Starting doses of 150 to 300 mg per day are recommended for most healthy elderly patients.

Dosage increments of 150 to 300 mg every 3 to 5 days is usual. To effectively treat mania in healthy elderly patients, total daily doses of 900 to 1800 mg may be necessary to achieve blood lithium levels of 0.8 to 1.0 mEq/L. If serious side effects occur prior to achieving this blood level, it is recommended that the dose be lowered or the rate of increase be slowed.[58,73,74] For prophylaxis of bipolar disorder in healthy elderly patients, the dosage necessary to reach a blood lithium level of 0.4 to 0.8 mEq/L is generally 600 to 1200 mg/day.[71] Twice daily dosing is common, but studies have shown that once daily dosing is often adequate, providing no side effects occur during periods of peak blood levels.[75,76] Blood lithium levels in the elderly should be measured frequently, usually once or twice per week, while the dosage is being increased.[59,77]

When rapid behavioral control is needed for acute mania, adjunctive therapy with an antipsychotic medication such as haloperidol, 2 to 4 mg per day, is often effective. Alternate adjunctive treatment may include a benzodiazepine, such as 1 to 4 mg/day of lorazepam at 0.5 to 2 mg/day of clonazepam.[60] Newer antipsychotics such as olanzapine may prove useful, but are generally unstudied to date.

For the very old, frail, medically ill, or cognitively impaired elderly patients, the dosage regimen should be reduced. The starting dose to treat acute mania in these sick patients is in the range of 75 to 150 mg/day with similar incremental increases every 3 to 5 days. These impaired patients often require lower maximum dosage of lithium, and blood lithium levels should be generally held below 0.9 mEq/L. Doses of 300 to 900 mg/day often achieve therapeutic blood levels of 0.4 to 0.8 mEq/L in very old, frail, medically ill, or cognitively impaired elderly. This blood lithium level usually is adequate for behavior control and often only results in minimal side effects.[58,71] If adjunctive pharmacotherapy is necessary in these vulnerable patients, haloperidol or lorazepam can be used, but usually at daily doses not to exceed 2 mg.

As in a younger adult population, premature discontinuation of lithium can result in relapse of bipolar illness.[78]

There is also some evidence that reinstitution of lithium prophylaxis in previously responsive bipolar patients who relapse due to interruption of medication may result in nonresponse.[79,80] Therefore, caution should be exercised when consideration is given to stopping lithium therapy in the elderly bipolar patient.

Because the half-life of lithium in many healthy elderly patients approaches 36 to 48 hours (and is perhaps longer in sick or compromised patients) stable blood lithium levels are often not achieved for up to 8 to 10 days or longer. Therefore, measuring a follow-up blood lithium level is recommended for elderly patients 2 to 4 weeks after the last incremental increase in lithium dosage is made, even if an initial blood level at that dose is in the therapeutic range.

Table 2. Special Considerations in the Use of Lithium in the Elderly

Indications
Effective if tolerated in primary mania
If tolerated, assists in the management of secondary mania
Neurologic disease and medical illness complicate the diagnosis and treatment of bipolar disorder and mania
Pharmacokinetics and clinical use
Lower volume of distribution than in younger adults
Lower glomerular filtration rate than in younger adults
Longer elimination half-life than in younger adults
Low doses and blood levels recommended in the very old, frail, medically ill, and cognitively impaired
Side effects
Most healthy elderly tolerate lithium well
Side effects more likely in the very old, frail, medically ill, and cognitively impaired elderly
Slow-release lithium preparations may reduce certain side effects while enhancing compliance

Side Effects of Lithium in the Elderly

Lithium can cause side effects in the elderly at different doses and different blood levels, depending on idiosyncratic variables as well as physiologic and disease states of patients. Physically healthy elderly patients generally tolerate lithium well and may have only a few, mild side effects. In other elderly patients, however, particularly the very old, physically ill, frail, or cognitively impaired, side effects and toxicity are more common.[58–60,65,71,81] The most prominent side effects are polyuria, gastrointestinal abnormalities, trauma, ataxia, and cognitive impairment. It is important to note that these side effects can occur at both therapeutic blood levels as well as at higher levels.[59,71–73] Cognitive impairments due to lithium can include decreased memory, concentration, consciousness, and orientation. Neuromuscular effects may include course tremor, ataxia, myoclonus, and extrapyramidal symptoms including parkinsonism.[58,59,71,77,82] Occasionally, these cognitive side effects can lead to compliance difficulties resulting in ingestion of extra doses of lithium. Toxic blood lithium levels may result in seizures and coma. Polyuria, usually only an annoyance in younger patients, can be a serious problem in the elderly because of the frequency of comorbid prostatic hypertrophy. This combination can lead to progressive urinary retention and urinary tract infections.

Some side effects due to lithium occur mainly during periods of peak blood levels. While once- or twice-a-day dosing may enhance compliance, adverse effects might occur at times of peak blood levels.[58,71,77] Sustained-release or slow-release lithium tablets can partially remedy this physiologic effect.[83–87] Slow-release lithium tablets have been shown to decrease variability in blood level by as much as 50% and reduce maximum blood level concentration when compared with a standard-release lithium preparation.[83] Total lithium availability over 24 hours, fortunately, is not altered.[83–85,87] While some studies have clearly demonstrated benefits of slow-release lithium tablets,[83–87] other studies have failed to confirm the findings.[88,89] However, side effects that are frequently associated with maximum blood lithium levels such as tremor and nausea may be reduced and compliance maintained if slow-release lithium preparations are used.[83,87] Some studies have suggested that diarrhea is more common with some slow-release preparations.[86,89]

Please refer to Table 2 for a listing of special considerations of lithium use in the elderly.

Use of Alternate Mood Stabilizers

Although lithium is used as a first-line medication for treating mania and bipolar disorder in the elderly, anticonvulsant medications have also been used as first-line agents in recent years and may have a treatment role in a subset of patients. Valproic acid and carbamazepine are the two agents most used as alternatives to lithium.[59,90] They seem particularly useful in patients with mixed, rapid cycling, and lithium-resistant bipolar disorders and bipolar patients with abnormal electroencephalography.[68] The two principal concerns with the use of anticonvulsants for the treatment of mania and bipolar disorder in the elderly are their side effect profiles and the absence of multicenter, placebo-controlled, double-blind studies.[65] Side effects of carbamazepine include ataxia, sedation, cognitive impairment, confusion, and seizures. In addition, transient leukopenia is common, and agranulocytosis and hepatitis have been reported. The side effect profile for valproic acid includes ataxia, sedation, vomiting, and, rarely, hepatitis.[59] Clinical assessments of the effectiveness of these agents in elderly bipolar patients is anecdotal, consisting of case reports and case series.[59,65]

SUMMARY

Lithium treatment in children, adolescents, and the elderly is generally similar to its use in adult populations except for pharmacokinetic, dosage, and side effect considerations. In children and adolescents, indications for the use of lithium are not well defined. Probable indications

are for the treatment of explosive aggression and bipolar disorder. Possible indications include augmentation therapy for depression and the treatment of aggression associated with mental retardation, autism, and Tourette's disorder. If proper care is exercised in administering lithium to children and adolescents, the development of toxicity is not common and side effects are generally well tolerated.

Lithium continues to be used as a first-line medication for the prophylaxis of bipolar disorder and the treatment of primary manic episodes in the elderly and has been used in secondary mania as well. Proper diagnosis of these disorders in the elderly, however, is problematic. Comorbidity complicates both the diagnosis and treatment of these elderly patients. Diagnosis is especially affected by neurologic and medical disease. Advanced age, physical illness, frailty, and cognitive impairment predispose patients to serious side effects. Thus, it is recommended that vulnerable elderly patients on lithium treatment be maintained on lower dosages and blood lithium levels. Although many elderly patients can tolerate lithium well and experience only minor side effects, serious neurologic and cognitive adverse reactions can occur, especially in compromised patients. Slow-release lithium tablets may alleviate side effects such as tremor and nausea seen at maximum blood levels. Alternate mood stabilizers for the treatment of psychiatric illness in children, adolescents, and the elderly have been used increasingly in recent years, and the tolerability of these agents appears promising but has not been established by controlled studies.

Drug names: carbamazepine (Tegretol and others), clonazepam (Klonopin), divalproex sodium (Depakote), haloperidol (Haldol and others), imipramine (Tofranil and others), lorazepam (Ativan and others), olanzapine (Zyprexa), sustained-release lithium (Lithobid, Eskalith), valproic acid (Depakene and others).

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