Antidepressant Augmentation with Lithium

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Depression is one of the most prevalent disorders seen in primary care. About 50% of depression is treated in general medical settings. Although depression is highly treatable, incomplete response to a single antidepressant is common. We describe two clinical cases in which antidepressant augmentation was a therapeutic option and lithium carbonate was an appropriate choice. A brief review of the practical aspects of the clinical pharmacology of lithium is included. Lithium is a well-tolerated, safe, and effective medication for antidepressant augmentation.

Key words. Lithium; antidepressants; drug therapy, combination; bipolar disorder; depression.
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Depression is one of the most common medical disorders seen in primary care.[1] Kamerow[2] estimated that 30% of all primary care patients have depressive symptoms. Even mild levels of depression carry grave consequences for economic productivity, interpersonal stability, and somatic discomfort.[3–5] The primary goal of treatment for the family physician is complete relief of depressive symptoms and prevention of recurrence over time. According to the Agency for Health Care Policy and Research (AHCPR) Clinical Practice Guideline for Depression,[6] 40% to 60% of patients with depressive symptoms remit with the first antidepressant medication. The American Psychiatric Association[7] has estimated that, for patients who continue their medication, the rate of response to antidepressant therapy is as high as 60% to 70%. The rate of complete remission, however, may be substantially lower.[7]

It is unclear why depression fails to remit on a single antidepressant medication. Possibilities include inadequate drug dosage, inadequate drug trial duration, medical noncompliance, substance abuse, medical conditions comorbid with depression, presence of a severe personality disorder, misdiagnosis, or primary (idiopathic) nonresponse.[6,8] The most common cause of treatment failure is undertreatment; therefore, it is advisable for physicians to follow established guidelines for adequacy of medication dose and duration of treatment.[8]

When an adequate trial of an initial antidepressant fails to produce full remission of depressive symptoms, the choice usually becomes one of either switching to another single antidepressant medication or augmenting the primary antidepressant with a second medication. Clinicians may have individual preferences for one modality or the other, but, according to Phillips and Nierenberg,[8] no available research data suggest that one modality is better than the other. The advantages of augmentation over switching primary medications are numerous: patients have reached therapeutic levels on the initial antidepressant, are accustomed to any side effects, and often show a partial response to the first antidepressant that might be eliminated if the first antidepressant were to be discontinued. Additionally, augmentation may provide symptom remission more quickly than switching to another primary medication.[9,10]

Lithium carbonate is considered a drug of first choice for antidepressant augmentation, unless contraindications exist for its use.[7,11,12] Randomized controlled trials have established its clinical usefulness in the treatment of unipolar and bipolar patients.[9,13,14] Many clinicians consider lithium the most effective adjunct in the treatment of major depression, and when used in an augmentation role, it has been reported to be effective in about 50% of nonresponders to a single antidepressant.[7,13]

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Case Reports

Case 1

The first case involved a 35-year-old mother of three children who often had difficulty with depression and anxiety. She remembered periods of severe symptoms as early as her high school years.

When she was depressed, which occurred approximately every 6 months, she tended to sleep and eat more, although duties at home made it inconvenient to sleep more. She had recurrent headaches, occasionally accompanied by nausea and vomiting, and her premenstrual period could be disabling. During the week when she was premenstrual, she experienced migraine headache occasionally severe enough to make her seek parenteral pain relief. These headaches were treated with meperidine hydrochloride and promethazine hydrochloride on four occasions over 2 years. She smoked but did not drink alcoholic beverages (her father was a recovering alcoholic). Nothing suggested that she overused any medicine except acetaminophen and ibuprofen, which she took daily.

She presented during the week before her menses complaining of a "headache that needed a shot." Her scores on the Zung depression scale[15] and the Zung anxiety scale[16] reflected moderate levels of both depression and anxiety. She was not suicidal because of stated religious convictions. She maintained that her "down" times generally lasted 2 or 3 months and then subsided. Further history revealed that she had experienced a particularly severe period of depression after the death of her mother. A physician prescribed amitriptyline hydrochloride to "regulate her sleep" and relieve some anxiety. Side effects prevented dose titration beyond 50 mg per day.

Because the patient had a tendency toward hypersomnia and overeating during depression, she was given samples of fluoxetine hydrochloride 20 mg daily and an appointment for a 2-week follow-up. On follow-up, she felt significantly more energetic and calm, noticing less frequent headaches. Mild nausea was the only side effect mentioned. She received a prescription for 1 month of fluoxetine and an appointment for a 4-week follow-up.

One week before her appointment, she called the office to complain of headaches, nerves, and frequent crying. Fluoxetine had worked well until the previous week, when her symptoms had reappeared and intensified. The dose of fluoxetine was increased to 40 mg per day, which resulted in 1 or 2 weeks of improvement followed by a resurgence of depressive symptoms. The addition of lithium carbonate 300 mg twice daily produced a return of the antidepressant response, beginning about 72 hours after lithium was initiated. Her headaches ceased, and she subsequently experienced no significant worsening of mood during premenstruation. Her lithium level at this dose was 0.5 mEq/L (0.5 mmol/L). She experienced no side effects beyond polyuria and a transient metallic taste.

Case 2

In the second case, a 28-year-old man presented with a 7-month history of depression characterized by daily fatigue, irritability, and lack of motivation. For 2 months, he had been taking nortriptyline hydrochloride 100 mg daily prescribed by a local psychiatrist for treatment of depression. The patient reported that he had improved somewhat while taking the medication but that he was still struggling and did not feel like himself. He was an unmarried secondary school teacher considering divinity school. The psychiatrist, who attributed the patient's lack of complete improvement to repressed homosexual feelings, recommended psychotherapy in addition to continuation of the medication.

The patient experienced dry mouth and mild constipation, which was managed with increased fluid intake and a stool softener. A nortriptyline level obtained at the consultation visit measured 110 ng/mL (418 nmol/L), well within the therapeutic window for nortriptyline of 50 to 150 ng/mL (190 to 570 nmol/L). His family history was positive for depression, but he had never been affected by the illness until the current episode. A thorough physical examination and laboratory testing were unremarkable. He did not smoke, occasionally drank alcoholic beverages, and used marijuana socially once or twice a year.

Lithium augmentation in this case avoided a delay in response that would have been caused by weaning the patient from the nortriptyline and reinstituting another medication. It also bypassed the increase in undesirable side effects expected with an increase in nortriptyline dosage. The patient began lithium carbonate at 600 mg daily in divided doses and increased his dose to 900 mg daily after 1 week. At a 2-week follow-up visit, he reported feeling significantly better. All symptoms of depression resolved after 6 weeks of combined nortriptyline and lithium. His lithium level was 0.7 mEq/L (0.7 mmol/L). He experienced some fine motor tremor that lessened on caffeine reduction and over time.

Pharmacology of Lithium

Lithium is a metal with chemical characteristics similar to those of sodium, calcium, and magnesium. Lithium is rapidly and completely absorbed from the gastrointestinal tract and is 95% eliminated by the kidneys. Peak serum levels are attained in 2 to 4 hours. The half-life of the drug

Table 1. Contraindications to Lithium Therapy in Patients with Preexisting Medical Conditions

Contraindicated
Renal tubular disease
Acute myocardial infarction
Myasthenia gravis
Pregnancy, first trimester
Breast-feeding
Requires close monitoring
Renal failure
Cardiac conduction defects
Parkinson's disease
Pregnancy, second and third trimesters
Caution
Tardive dyskinesia
Dementia
Cerebellar disorders
Diabetes mellitus
Ulcerative colitis
Psoriasis
Senile cataracts

Adapted from Oritz et al[17] with permission of the publisher.

is 24 to 36 hours in persons with normal renal function and longer in patients with renal insufficiency.

The 24- to 36-hour half-life of lithium permits once-daily dosing in many patients. For other patients, peak serum levels reached shortly after dosing cause annoying side effects. Some patients may prefer dosing twice or three times daily. Following tolerance assessment, patients should be started on split doses of lithium and moved to a single daily dose, if desired. Some clinicians believe that the immediate-release lithium preparations cause more nausea than the sustained-release forms and that sustained-release preparations cause more diarrhea. These findings vary widely. Lithium is inexpensive in both forms but is relatively less expensive in the generic, immediate-release tablets or capsules. No compelling reason exists to choose sustained-release lithium instead of immediate-release lithium, at least in the initial prescription.

The total daily dose of lithium required for augmentation varies. A dose of 300 to 600 mg per day may be sufficient, because augmentation is seen at lithium levels as low as 0.3 to 0.4 mEq/L (0.3 to 0.4 mmol/L). To achieve standard therapeutic levels of 0.6 to 1.2 mEq/L (0.6 to 1.2 mmol/L) may require 600 to 1500 mg of lithium per day. It is appropriate to determine blood levels following dosage changes to confirm compliance and adequacy of dose and whenever lithium toxicity is suspected. Patients on stable maintenance doses of lithium should have laboratory monitoring once or twice per year.

Table 1 summarizes the contraindications to lithium use in patients with preexisting medical conditions. A general history and physical examination should be completed before dispensing lithium in order to exclude these contraindicated conditions. Baseline thyroid and normal renal functions also should be established. Table 2 summarizes the recommended baseline investigations. The purpose of testing renal function is to exclude hidden renal compromise that may affect lithium levels or to detect a contraindication to lithium therapy. Blood glucose measurement may uncover diabetes mellitus. Testing for a baseline level of thyroid-stimulating hormone (TSH) is necessary. An abnormal TSH level would have profound implications in the treatment of a refractory depressed patient because both hypothyroidism and hyperthyroidism may lead to refractory status. Additionally, chronic lithium therapy may cause hypothyroidism in some patients.

Table 2. Recommended Pretreatment Laboratory Investigations Before the Initiation of Lithium Therapy

Electrolytes
Blood urea nitrogen, creatinine
Blood glucose
Liver function tests
Thyroid function, including thyroid-stimulating hormone
Complete blood count with differential
Urinalysis
Electrocardiogram (optional)

Most side effects of lithium are dose-related, mild, and transient (Table 3). In general, serum lithium levels at the lower end of the therapeutic range have been found to

Table 3. Side Effects of Lithium

Gastroinestinal
Nausea, vomiting
Diarrhea
Metallic or altered taste
Increased salivation
Neuromuscular
Muscle weakness
Tremor
Easy fatigability
Central nervous system
Confusion
Disorientation
Dysarthria
Seizures
Impaired mentation
Ataxia
Skin
Rash (relatively uncommon)
Renal
Polyuria
Polydipsia
Hematologic
Leukocytosis (mild, typically 11,000 to 15,000 white blood count/mm^3)

be as effective as those in the higher range and are better tolerated by most patients.

Lithium has some important drug-to-drug interactions, particularly with nonsteroidal anti-inflammatory drugs (NSAIDs) and diuretics.[18] Both classes of interactions can increase serum lithium levels and thus the potential for toxicity. Lithium should be used with caution in patients taking benzodiazepines to avoid excessive sedation. Lithium also should be used cautiously with digoxin because of its theoretical effect on sodium pump activity, although Cooper and colleagues[19] found no significant interaction between the two drugs. The concomitant use of lithium and angiotensin-converting enzyme inhibitors has been reported to increase serum lithium levels.[20]

Lithium toxicity occurs on a continuum, with mild symptoms preceding more severe toxicity. Patients should be educated about these symptoms and cautioned to notify the physician promptly if they occur. Toxicity is suggested when mild tremor and gastrointestinal symptoms progress to sluggishness, ataxia, cognitive impairment, vomiting, and weakness. Seizures may occur in cases of severe toxicity. Cessation of lithium, rehydration, correction of electrolyte disturbances, seizure precautions, and, in the most severe cases, dialysis are the treatments of choice. Fluid replacement with saline should restore normal water balance; however, overhydration should be avoided because severe lithium toxicity may impair renal function.

The long-term effects of lithium therapy are a concern for many physicians. Morphologic changes observed in the kidneys of patients treated with lithium in the 1970s led to fears of nephrotoxicity.[21] Large longitudinal and cross-sectional studies, however, showed that at therapeutic doses, lithium has no effect on glomerular filtration rates.[21,22] In these studies, renal morphologic changes were confined to the collecting ducts and distal tubule and were reversible.[23] Less than 5% of patients maintained on long-term lithium therapy develop hypothyroidism,[24] but because subclinical or clinical hypothyroidism can trigger an episode of affective illness, TSH monitoring once or twice per year is recommended. Replacement therapy with levothyroxine overcomes any deficit.

Lithium Use for Augmentation

The figure suggests a protocol for lithium augmentation. Patients should be fully informed of the common side effects of lithium, as well as their relationship to dosage. Knowing that lithium in lower doses is well tolerated and effective should be reassuring. Lithium may rarely exacerbate depressive symptoms when used in augmentation. If this complication occurs, patients should discontinue the medication and inform the physician.

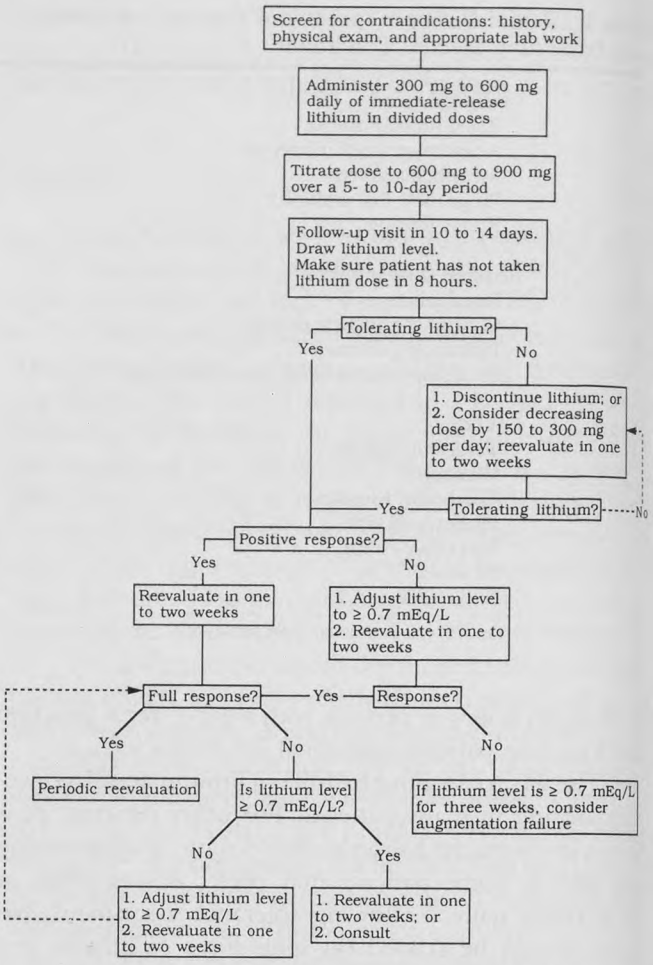

Figure. Protocol for lithium augmentation in the treatment of family practice patients with depression.

The patient in the first case exemplifies elements of presentation, history, and response common to the management of depression. Since the goal of antidepressant therapy is to eliminate depressive symptoms, patients are not considered optimally treated until they achieve sustained normal mood. This patient initially responded positively to therapy with fluoxetine, but the response ended rather abruptly. In her case, doubling the dose of fluoxetine to 40 mg duplicated the nonresponse pattern. The abruptness of her deterioration suggested that the problem was not related to an inadequate dose of the antidepressant. The 6-week period of treatment may seem too brief to be conclusive until it is taken into consideration that she had previously achieved full remission of symptoms after only 2 to 3 weeks of treatment.

Lithium augmentation was particularly appropriate in this case for several reasons. Investigation of the pa-

tient's family history revealed a paternal aunt with undiagnosed features of bipolar disorder and a father with an entrepreneurial, energetic, driven personality. The patient herself identified periods of extremely high energy and activity occurring 1 or 2 days per month and lasting a maximum of 24 hours. These "up" days occurred without adequate cause and were followed by a period of particularly severe depressive symptoms lasting 1 or 2 days. Her diagnosis was closer to bipolar II disorder, although she did not fully meet the criteria for this condition.[25] Her illness was in the "soft" bipolar spectrum.[26]

The patient completed an initial 9-month treatment with fluoxetine and lithium. She declined a medication-free period because of the recurrent nature of her depression. As this report was written, after 22 months of maintenance fluoxetine and lithium, she remained asymptomatic.

In the second case, the patient's depression was noncycling or unipolar. His response to the nortriptyline was less than full remission, despite 8 weeks of adequate treatment. Although lithium treatment may be more familiar for bipolar depressions, patients with nonbipolar illness also benefit from the drug. His response was not as rapid as that of the patient in the first case; however, he made steady progress and eventually gained complete recovery from depression without additional psychotherapy. Lithium augmentation should not be considered a failure until the patient has had 3 weeks of therapy at a serum level of 0.7 mEq/L (0.7 mmol/L) or higher.[27]

The patient in this case successfully discontinued therapy after an initial 9 months of treatment with both medications. About 9 months after discontinuing the medications, he experienced a relapse that again was successfully treated with nortriptyline and lithium. After a second treatment period of 9 months, he elected to remain on both medications as maintenance therapy, and as of this report 15 months later, he was still asymptomatic on maintenance therapy.

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