Unipolar depression in adults: Treatment with lithium

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INTRODUCTION

Lithium is mainly used to treat bipolar disorder, which is characterized by recurrent episodes of depression, mania, and hypomania. However, lithium is also used as an adjunctive medication in patients who have inadequately responded to an antidepressant for treatment of unipolar depression (ie, depression with no lifetime history of mania or hypomania) [1]. In addition, lithium is used as monotherapy to treat acute episodes of unipolar depression and as maintenance treatment to prevent recurrence of unipolar depressive episodes.

Lithium was first used by psychiatrists in the mid-1800s [2]. The first controlled trial of lithium for unipolar depression was in 1968.

This topic reviews the use of lithium as adjunctive treatment and as monotherapy for acute episodes and maintenance treatment of unipolar depression. Treatment-resistant depression and the use of lithium to treat bipolar disorder are discussed separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression" and "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Lithium'.)

ADD-ON LITHIUM FOR TREATMENT-RESISTANT DEPRESSION

The most common use of lithium in patients with unipolar depression is to augment an antidepressant that does not adequately treat a depressive syndrome. Lithium or an alternative adjunctive agent is often necessary because remission with antidepressant monotherapy occurs

in only 28 to 47 percent of patients, even with an optimal trial [3-5]. It is commonly thought that augmentation is more effective for patients who initially have a partial response to antidepressant monotherapy, compared with patients who do not respond at all, but this is not established [6].

Efficacy — Results from high-quality studies consistently support using add-on lithium for acutely depressed patients who do not fully respond to an antidepressant [7]. As an example, four meta-analyses of randomized trials have compared lithium with placebo as an adjunct to antidepressants in patients with treatment-resistant depression (pooled sample sizes ranging from approximately 250 to 650) [8-11]. Lithium was commonly administered at a dose of 800 or 900 mg/day, in trials that lasted on average three weeks. Results from the meta-analyses included the following:

- Response (reduction of baseline symptoms ≥50 percent) was generally three times more likely to occur with adjunctive lithium than placebo (odds ratio 3) [8-10].
- Lithium provided one more response than placebo for every five patients treated with each regimen (number needed to treat of five) [8,11].
- Subgroup analyses found that lithium was efficacious for augmenting either first-generation antidepressants (eg, tricyclics) or second-generation antidepressants (eg, selective serotonin reuptake inhibitors [SSRIs]) [8].
- Tolerability varied across studies, such that discontinuation of treatment due to adverse effects was:
  - Comparable with lithium and placebo [8]
  - Greater with lithium than placebo (odds ratio 2) [9]

There are no established predictors of response to adjunctive lithium in patients with unipolar depression. One study suggests a more robust response to adjunctive lithium in geriatric versus nongeriatric depressed patients [12]. Although it is generally thought that adjunctive lithium is equally effective with all antidepressants, one small study suggests that lithium is more effective when it is added to venlafaxine, rather than imipramine [13].

Lithium augmentation may reduce the risk of completed suicide in patients with unipolar depression. (See "Suicidal ideation and behavior in adults", section on 'Pharmacotherapy'.)

Compared directly with other drugs — Only a few head-to-head, randomized trials have compared the efficacy of lithium with other drugs for augmenting an antidepressant that has

inadequately treated a depressive syndrome. The limited data suggest that lithium is comparable to T3 (triiodothyronine) or a second antidepressant.

Other medications are used more often than lithium as augmentation, despite the robust evidence supporting adjunctive lithium. A study examined a pharmacy database that included nearly 250,000 patients with unipolar depression and found that more patients received a second antidepressant, an antipsychotic, or an anticonvulsant as augmentation compared with lithium (10.9 versus 7.3 versus 3.7 versus 0.5 percent of all patients) [14]. This may reflect the perception that lithium often causes side effects and long-term toxicity. In addition, clinicians must monitor serum lithium levels, renal function tests, and thyroid function tests. (See "Renal toxicity of lithium" and "Lithium and the thyroid".)

Use of second-generation antipsychotics as add-on therapy to treat unipolar, nonpsychotic major depression that is unresponsive to an antidepressant is discussed separately. (See "Unipolar depression in adults: Treatment with second-generation antipsychotics".)

Triiodothyronine (T3) — Two head-to-head randomized trials found that lithium was comparable to triiodothyronine (T3) for augmenting a tricyclic antidepressant, citalopram, sertraline, bupropion, or venlafaxine in patients with unipolar major depression [15,16]. One trial compared lithium, T3, and placebo in 50 patients who did not respond to desipramine or imipramine and found that response (improvement from baseline on the depression rating scale ≥ 50 percent) occurred in significantly more patients who received adjunctive lithium or T3, compared with placebo (53 and 59 versus 19 percent); there was no significant difference between lithium and T3 [16]. The second trial was open label and compared lithium with T3 in 73 patients who prospectively failed antidepressant monotherapy; there was no significant difference in the proportion of patients who remitted with either adjunctive lithium or T3 (16 versus 25 percent) nor in time to remission [15]. However, withdrawal from treatment because of side effects was significantly greater for patients who received lithium compared with patients who received T3 (23 versus 10 percent).

Use of T3 as add-on therapy to treat unipolar, nonpsychotic major depression that is unresponsive to an antidepressant is discussed separately. (See "Unipolar depression in adults: Augmentation of antidepressants with thyroid hormone".)

Antidepressants — For patients with unipolar major depression, it is not clear if add-on treatment with lithium is comparable or inferior to add-on treatment with a second antidepressant due to the limited evidence:

- Two head-to-head randomized trials found that low-dose lithium (300 to 600 mg per day) was comparable to low-dose desipramine (25 to 50 mg per day) as augmentation [17,18].

In each trial, patients who had a partial response or no response to eight weeks of treatment with fluoxetine (20 mg per day) were assigned to lithium plus fluoxetine or to desipramine plus fluoxetine for four weeks. The proportion of patients who remitted in the two trials was similar in the groups who received lithium augmentation compared with the groups who received desipramine augmentation (29 and 24 versus 25 and 29 percent). Trials comparing therapeutic doses of these medications have not been conducted.

- A 10-week, open-label randomized trial compared add-on lithium with add-on citalopram in patients (n = 104) who did not respond to initial treatment with imipramine [19]. Lithium target serum levels were 0.6 to 0.8 mEq/L and citalopram was titrated up to 30 mg/day. Remission occurred in fewer patients who received lithium than citalopram than lithium (21 versus 40 percent).

Dose and serum level — We suggest clinicians initially prescribe adjunctive lithium 300 or 600 mg once per day. The dose should be increased every one to five days depending on how well it is tolerated, to an eventual target dose of 600 to 1200 mg per day, or a dose sufficient to achieve 12-hour serum levels of 0.6 to 0.9 mEq/L (0.6 to 0.9 mmol/L) [20-22].

One study compared lithium 750 mg per day versus 250 mg per day as adjunctive treatment in 34 patients with unipolar major depression who did not respond to treatment with a tricyclic antidepressant [23]. Significantly more patients responded (50 percent or more decrease in the depression rating scale score) with 750 mg per day (44 versus 18 percent).

A meta-analysis of nine controlled trials (234 patients) found no evidence for a dose response relationship beyond 800 mg daily [24]. A second meta-analysis of 10 controlled trials (269 patients) found that lithium augmentation was significantly more efficacious compared with placebo, with lithium generally prescribed at a dose of 900 mg/day [7]. Serum levels generally ranged from 0.6 to 1.0 mEq/L (0.6 to 1.0 mmol/L). In a subsequent controlled trial, adjunctive lithium was started at 225 or 450 mg per day for one week and titrated up to a target dose of 900 mg per day; the final mean daily dose was 860 mg and the median serum level was 0.6 mEq/L (0.6 mmol/L) [15].

Duration — We suggest clinicians prescribe adjunctive lithium for at least four weeks before deciding whether it is helpful [13,20]. Remission may occur as soon as one week.

Evidence related to the duration of an adequate trial of add-on lithium includes a review of 27 open-label studies or randomized trials (803 depressed patients, >90 percent unipolar), which estimated that 50 percent of patients responded within two to six weeks of lithium augmentation [25,26]. In a meta-analysis that included 12 randomized trials (n = 541 depressed patients), the mean duration of treatment was four weeks [10]. In one trial, patients with

unipolar major depression were treated with adjunctive lithium for up to 14 weeks and a mean of nine weeks [15]. Among the nine patients who eventually remitted:

- Two remitted after 2 weeks of treatment
- Three after 3 to 4 weeks
- One after 5 to 6 weeks
- One after 7 to 12 weeks
- Two after 13 to 14 weeks

Another study found that depression rating scale scores began to decline in week one of treatment with adjunctive lithium and steadily decreased during six weeks of treatment [23].

Patients who respond to lithium augmentation should be maintained on the lithium-antidepressant combination for at least one year [25,27]. The largest controlled trial that examined this issue studied 29 patients with unipolar major depression who initially did not respond to antidepressant monotherapy (primarily tricyclics), but subsequently remitted with adjunctive lithium [28]. All patients then continued their antidepressant and were randomly assigned to continue adjunctive lithium or to receive placebo for four months. Relapse occurred in significantly fewer patients who received lithium compared with placebo (0 versus 46 percent). Afterwards, the 14 patients who had received lithium plus an antidepressant were tapered off all their medication, which led to recurrence of depression in five patients during six months of follow-up [29].

Contraindications — Lithium is contraindicated in patients with:

- Significant renal impairment
- Sodium depletion
- Dehydration
- Significant cardiovascular disease

Contraindications and precautions are discussed in greater detail elsewhere. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Lithium'.)

Drug interactions — Lithium interacts with many drugs. Medications that decrease renal lithium excretion and are particularly prone to increase serum levels with possible toxicity are:

- Thiazide diuretics
- Nonsteroidal anti-inflammatory drugs
- Angiotensin converting enzyme inhibitors

Drug interactions with lithium are discussed in greater depth elsewhere. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Lithium'.)

Laboratory monitoring — Clinicians must monitor serum lithium levels, renal function tests, and thyroid function tests. Laboratory monitoring is discussed elsewhere. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Laboratory tests and monitoring'.)

Side effects with lithium augmentation — The combination of lithium and an antidepressant is often well tolerated. Although most controlled studies have examined lithium augmentation of tricyclic antidepressants, there is more information available about side effects that occur during lithium augmentation of an SSRI.

Acute side effects of lithium augmentation are reviewed here. Side effects of lithium monotherapy and longer-term toxicity are discussed elsewhere. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Lithium' and "Renal toxicity of lithium" and "Lithium and the thyroid".)

Added onto selective serotonin reuptake inhibitors — An observational study compared 110 patients receiving fluoxetine monotherapy with a matched group of 110 patients receiving fluoxetine plus lithium and found no significant differences in the number and type of adverse events during seven weeks of treatment [30]. In addition, a review of reports with a total of 503 patients, who were treated with lithium plus an SSRI, found none of the patients suffered a serious or life-threatening adverse event [31]. The side effects that occur most frequently during lithium augmentation of an SSRI are [17,30,31]:

- Gastrointestinal distress (nausea, diarrhea)
- Sedation
- Tremor
- Anxiety and nervousness
- Insomnia
- Headache
- Dry mouth

Added onto tricyclic and tetracyclic drugs — The side effects that occur most frequently during lithium augmentation of a cyclic antidepressant are [32]:

- Nausea
- Tremor
- Polyuria

- Dry mouth

Mechanism of action — The benefit of lithium augmentation for treating unipolar major depression may be due to synergy between lithium and the antidepressant, or to the antidepressant effect of lithium itself [33]. In either case, the mechanism of action is unclear. Most hypotheses suggest lithium enhances serotonergic function [27]. Pharmacogenetic studies suggest that several single nucleotide polymorphisms are involved [33].

LITHIUM MONOTHERAPY FOR ACUTE DEPRESSION

Lithium monotherapy may effectively treat acute unipolar depression, but there is far less evidence than there is for antidepressants [34-36]. We do not use lithium as first-, second-, or third-line treatment for acute unipolar depression. When lithium is used to treat acute depression, we suggest it be prescribed to achieve a serum level of 0.6 to 1.2 mEq/L (0.6 to 1.2 mmol/L) based upon our clinical experience.

Evidence supporting the use of lithium for acute unipolar depression includes the following:

- A six-week controlled trial assigned 27 patients with major depression to lithium or placebo. Fewer patients who received lithium withdrew from the study as treatment failures and among patients who remained in the study, depression rating scale scores were lower at weeks four and five in patients who received lithium compared with patients who received placebo [34].

- A meta-analysis of four controlled studies, in which 148 patients were treated for three weeks with either lithium at a serum level of 0.4 to 1.5 mEq/L (0.4 to 1.5 mmol/L) or with an antidepressant, found a moderate clinical effect favoring lithium [35]. A subsequent randomized trial compared lithium with clomipramine in patients with depression and found that efficacy was comparable [36]. However, the lack of a placebo arm makes it more difficult to interpret the treatment effects observed in these studies. In addition, no randomized trials have compared lithium with selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, mirtazapine, or bupropion for treating acute unipolar depression.

There are no established predictors for lithium's acute antidepressant effect. Lithium may be more effective for bipolar depression compared with unipolar depression, thus, a family history of bipolar depression may possibly predict a better outcome for lithium's efficacy in acute unipolar depression [37,38].

However, the recurrent or cyclical nature of the mood disorder may be associated with a positive response to lithium, rather than polarity. In a prospective observational study of 30 patients with acute unipolar major depression who were treated for four weeks, response (reduction of baseline symptoms ≥50 percent) occurred in more patients with a recurrent episode than patients with a first lifetime episode (15 of 22 versus 0 of 8 patients [68 versus 0 percent]) [39].

LITHIUM MONOTHERAPY AS MAINTENANCE TREATMENT

Lithium prevents recurrence of unipolar depression.

Three meta-analyses of randomized trials have established that lithium monotherapy is more efficacious than placebo as maintenance treatment:

- One meta-analysis of eight trials (263 patients with unipolar depression) found that recurrence of depression occurred in fewer patients who received lithium compared with patients who received placebo (34 versus 67 percent) [35].
- A subsequent meta-analysis of a nine trials (229 patients with unipolar depression) also found that recurrence of depression occurred in fewer patients who received lithium compared with patients who received placebo (36 versus 75 percent) [40].
- In the third meta-analysis, which included seven trials that lasted 15 to 112 weeks (n = 233 patients with unipolar major depression), the likelihood of remaining euthymic was greater with lithium than placebo (odds ratio 4.5, 95% CI 1.4-14.5) [10].

Three meta-analyses have compared the efficacy of lithium monotherapy with an antidepressant as maintenance treatment:

- One meta-analysis of seven randomized trials (298 patients with unipolar depression) found that recurrence of depression occurred in a similar number of patients who received lithium compared with patients who received a tricyclic antidepressant (48 versus 56 percent) [35].
- A subsequent meta-analysis of eight trials (475 patients, the large majority had unipolar depression) also compared the efficacy of lithium with antidepressants in preventing recurrence [41]. One analysis that defined recurrence as admission to the hospital (three studies with 152 patients) found recurrence of depression occurred in significantly fewer patients who received lithium compared with patients who received an antidepressant (7 versus 22 percent). Analyses that used different definitions of recurrence found that the

rate of recurrence was comparable for patients who received lithium and patients who received an antidepressant. In addition, there were no significant differences between lithium and antidepressants in the overall drop-out rate (as a proxy measure of overall acceptability of treatment), drop-out due to side effects, and number of patients who reported at least one side effect. The lack of a placebo arm makes it more difficult to interpret the treatment effects observed in these studies.

- In the third meta-analysis, which included five trials that lasted 56 to 130 weeks (n = 224 patients with unipolar major depression), the likelihood of remaining euthymic was comparable in patients who received lithium or antidepressants (odds ratio 2.2, 95% CI 0.7-7.1) [10].

Using lithium to prevent recurrence of unipolar depression is consistent with the American Psychiatric Association Practice Guidelines for Major Depressive Disorder [42] and treatment guidelines from the British Association for Psychopharmacology [43].

Based upon the serum levels used in randomized trials and our clinical experience, we suggest clinicians prescribe lithium to achieve a serum level of 0.6 to 1.2 mEq/L (0.6 to 1.2 mmol/L). There are no established factors that predict response to maintenance treatment with lithium monotherapy.

PREVENTING SUICIDE

Lithium may reduce the risk of suicide in patients with mood disorders, including recurrent unipolar major depression. (See "Suicidal ideation and behavior in adults", section on 'Pharmacotherapy'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

SUMMARY

- **Add-on lithium for treatment-resistant depression** – Lithium is superior to placebo as augmentation for an antidepressant that does not adequately treat a depressive syndrome. Clinicians should initially prescribe adjunctive lithium 300 mg per day or 300

mg twice per day. The dose should be increased every one or two days depending on how well it is tolerated, to an eventual target dose of 900 mg per day, or a dose to achieve 12-hour serum levels of 0.6 to 0.9 mEq/L (0.6 to 0.9 mmol/L).

Only a few controlled trials have compared the efficacy of lithium with other drugs for augmenting an antidepressant that has inadequately treated a depressive syndrome, but the limited data suggest that lithium is comparable to T3 (triiodothyronine) or a second antidepressant. (See 'Add-on lithium for treatment-resistant depression' above.)

- **Lithium monotherapy**
  - **Acute depression** – Lithium monotherapy may effectively treat acute unipolar depression, but the evidence is limited. (See 'Lithium monotherapy for acute depression' above.)
  - **Maintenance treatment** – Lithium monotherapy prevents recurrent episodes of unipolar depression. Lithium maintenance treatment generally requires a serum level of 0.6 to 1.2 mEq/L (0.6 to 1.2 mmol/L). (See 'Lithium monotherapy as maintenance treatment' above.)
- **Preventing suicide** – Lithium may reduce the risk of suicide in patients with recurrent unipolar major depression. (See "Suicidal ideation and behavior in adults", section on 'Pharmacotherapy'.)

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