# Lithium for bipolar disorder: Which patients will respond?

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Though Cade discovered it 70 years ago, lithium is still considered the gold standard treatment for preventing manic and depressive phases of bipolar disorder (BD). In addition to its primary indication as a mood stabilizer, lithium has demonstrated efficacy as an augmenting medication for unipolar major depressive disorder.[1] While lithium is a first-line agent for BD, it does not improve symptoms in every patient. In a 2004 meta-analysis of 5 randomized controlled trials of patients with BD, Geddes et al[2] found lithium was more effective than placebo in preventing the recurrence of mania, with 60% in the lithium group remaining stable compared to 40% in the placebo group. Being able to predict which patients will respond to lithium is crucial to prevent unnecessary exposure to lithium, which can produce significant adverse effects, including somnolence, nausea, diarrhea, and hypothyroidism.[2]

Several studies have investigated various clinical factors that might predict which patients with BD will respond to lithium. In a review, Kleindienst et al[3] highlighted 3 factors that predicted a positive response to lithium:

- fewer hospitalizations prior to treatment

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**Table**

## Factors that predict response to lithium in patients with bipolar disorder

| Predictors of good response to lithium | | Predictors of poor response to lithium | |
|---|---|---|---|
| **Probable predictors** | **Possible predictors** | **Probable predictors** | **Possible predictors** |
| Older age (>50) at illness onset | Classic (euphoric) mania | Rapid cycling | Mixed episode |
| Mania/depression/ euthymia pattern | Episodic frequency | Depression/mania/ euthymia pattern | Baseline anxiety symptoms |
| Family history of bipolar disorder | Female sex | Continuous cycling | Functional impairments |
| Shorter duration of illness before receiving lithium | Lower body mass index | Higher number of previous hospitalizations | Childhood trauma/PTSD |
| | Early response to lithium (within first 2 weeks) | Comorbid personality disorder | Suicide ideation/attempt |
| | Early use of lithium after bipolar disorder diagnosis | Mood-incongruent psychotic features | Migraine |
| | Good social support | | Longer duration of illness before receiving lithium |
| | Depressive polarity at onset of bipolar disorder | | Male sex |
| | Family history of response to lithium | | Higher number of lifetime mood episodes |
| | | | Comorbid alcohol/ substance use |
| | | | Higher body mass index |
| | | | Learning disability |
| | | | No response to lithium within first week of therapy |
| | | | Delayed use of lithium after diagnosis |
| | | | Discontinuing and then restarting lithium |

PTSD: posttraumatic stress disorder

**Source**: References 3-6

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• an episodic course characterized sequentially by mania, depression, and then euthymia

• a later age (>50) at onset of BD.

Recent studies and reviews have isolated additional positive predictors, including having a family history of BD and a shorter duration of illness before receiving lithium, as well as negative predictors, such as rapid cycling, a large number of previous hospitalizations, a depression/mania/euthymia pattern, mood-incongruent psychotic features, and the presence of residual symptoms between mood episodes.[3,4]

The ***Table*** (***page 37***) provides a list of probable and possible positive and negative predictors for therapeutic response to lithium in patients with BD.[3-6] While relevant, the factors listed as possible predictors may not carry as much influence on lithium responsivity as those categorized as probable predictors.

Because of heterogeneity among studies, clinicians should consider their patient's presentation as a whole, rather than basing medication choice on independent factors. Ultimately, more studies are required to fully determine the most relevant clinical parameters for lithium response. Overall, however, it appears these clinical factors could be extremely useful to guide psychiatrists in the optimal use of lithium while caring for patients with BD.

**Predicting which patients with BD are likely to respond can help prevent unnecessary lithium exposure**

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