Lithium Therapy, Bipolar Disorder— and Neurocognition

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Functional mood stability can be attained with lithium therapy, but guidelines on how to get there have become increasingly sophisticated.

Lithium has a global history—discovered initially by Danish siblings (Carl and James Lange) in the 19th century and then rediscovered as a treatment for manic-depressive illness in the mid-20th century by John Cade, an Australian. Sometime later, following publication of the first clinical trials, lithium was introduced to clinical practice in the US and across Europe.

In clinical practice, functional mood stability—which can on occasion be achieved with optimum lithium therapy—is the gold standard that both clinicians and patients strive to attain. To facilitate this endeavor, guidelines on lithium therapy have become increasingly sophisticated; they not only provide therapeutic indications and plasma levels with respect to efficacy, but also inform practitioners about how potential adverse effects can be minimized or avoided.

CASE VIGNETTE
Margaret, a 36-year-old with bipolar I disorder, is referred for an appraisal of treatment strategies following the resolution of an episode of depression. Although the episode was relatively moderate in severity and she did not require hospitalization, suicidality featured strongly during the episode. She currently takes 1000 mg of lithium and 400 mg of lamotrigine daily.

She reports that her mood is better but says that she has been “slowing down at work.” She is finding it difficult to perform mental arithmetic, something she had previously been very adept at doing. She is assessed for cognitive symptoms using the Lithium Battery—Clinical; in addition, a battery of cognitive tests reveals scores in the normal range. Her plasma lithium level (0.7 mmol/L) is within the normal range for maintenance therapy.

Given the presence of manic-mixed features and a recent episode occurrence, as well as subjective chronic cognitive impairment, it is recommended that valproate be substituted for the lamotrigine. Once the transition takes place, the dose of lithium is gradually decreased to achieve a plasma level of 0.5 mmol/L. During this period, Margaret regularly visits her primary physician for clinical assessment and monitoring. She is understandably anxious about the changes to her medication regimen but maintains mood stability and only reports anticipated adverse effects.

When re-evaluated by her regular psychiatrist after 2 weeks, Margaret reports noticeable improvement in her cognitive symptoms. Twelve months later, Margaret remains well and continues to work full time. She is monitored regularly and comprehensively every 3 months.

This case highlights the fact that maintenance monotherapy is not always possible in the treatment of bipolar disorder and that therapy must always be tailored to individual needs. The most important component is patient engagement in the therapeutic process and clinical decision-making. This is best achieved by understanding the patient’s concerns and informing her fully of risks and benefits while ensuring regular follow-up.

A common complaint made by those who take lithium, but one which may easily be overlooked, is cognitive compromise. Clinically, patients describe this as “brain fog”—an elusive admixture of complaints regarding attention, concentration, and memory occurring in conjunction with a slowing of thought processes. Clinicians usually regard these as symptoms of the illness, whereas patients are more inclined to attribute them to the effects of medications. In reality, both the illness and its treatment likely contribute to these symptoms, which makes disentangling the various causes extremely difficult. It is an important clinical issue because patients are likely to discontinue treatment on the basis of such concerns and the cognitive adverse effects do in reality limit patients’ ability to function—both occupationally and socially.

Although lithium provides a promising opportunity to attain long-term mood stability, it sometimes comes at considerable cost and forces psychiatrists and their patients to constantly balance remaining well on the one hand by preventing symptoms of illness and remaining functional on the other by addressing tolerability.

Stabilizing mood and improving cognition
In addition to its effects on mood, lithium is known to alter neurocognition—improving some functions while impairing others. These opposing and complex actions likely occur both acutely and
long term and are probably subject to changes in plasma levels. Lithium has profound effects on wellness in a significant proportion of patients with bipolar disorder, who remain episode-free and highly functioning for many years solely with lithium monotherapy. Lithium treatment response is helped by the ability to optimize its impact and tolerability with the use of plasma lithium concentrations to guide dosage adjustments. With this in mind, the Lithiumeter (Figure 1), a tool for balancing efficacy and tolerability in clinical practice, has recently been updated with the inclusion of additional guidance based on new evidence (version 2.0).

In recent years, there has been a resurgence of interest in lithium therapy that has increased awareness of its benefits and debunked some of the myths tarnishing its tolerability profile. In fact, key new studies have shown that severe problems are relatively rare and that assiduous monitoring of lithium plasma levels minimizes the likelihood of lithium toxicity and the potential risk of renal and thyroid dysfunction.

While lithium monotherapy is the ideal, for most patients who have bipolar disorder, satisfactory prophylaxis with lithium is only possible when it is used in combination with other agents. In patients with predominantly manic episodes, lithium in combination with valproate is a useful option. Similarly, lamotrigine can be used in conjunction with lithium in cases with predominantly depressive episodes. In both scenarios, lithium combination therapy may also enable the use of lower doses of individual agents—thus maintaining efficacy while achieving greater tolerability. In this context, atypical antipsychotics and antidepressants can be conceptualized as rescue treatments that should be used mainly during manic and depressive episodes, respectively. Longer-term use poses considerable physical health risks and the possibility of a treatment-emergent affective switch.

Hence, it is widely recommended that once the acute symptoms of an episode resolve in response to rescue treatments, dosages are reduced as quickly as possible. Lithium also appears to have neuroprotective effects that are thought to be achieved by initiating and then maintaining a cascade of cellular processes, among which glycogen synthase kinase 3β inhibition appears to be key. Lithium’s many intracellular actions are thought to underpin its diverse therapeutic effects. When treating bipolar disorder with lithium, it is difficult to parcel out the effects of the agent from those of the illness, especially since lithium also seems to have positive effects on maintaining cognitive function over the long term. Hence, alongside its use in mood disorders, lithium is being studied in neurodegenerative disorders such as Alzheimer and Parkinson diseases, in an attempt to harness its potential neuroprotective properties.

Intriguingly, independent of its effects on mood stability, lithium is a highly effective anti-suicidal agent, and much lower plasma concentrations than necessary for treating mood disorders may serve to reduce the risk of suicide. This means that lithium can be used to tackle suicidality, but in practice its use needs to be tempered against the individual’s conviction to commit suicide. Lithium’s anti-suicidal action is likely to be in part a consequence of its moderating effects on impulsivity and irritability.

**Altered neurocognition**

Lithium has a complicated neurocognitive profile. It produces impairment across some domains, while preserving others—with these effects seemingly more apparent in those more vulnerable to the deleterious effects of bipolar disorder. A recent review concluded that lithium administration alters specific aspects of neurocognition and that these effects are perhaps cumulative—increasing with the duration of treatment. The effects are likely to occur via direct and indirect mechanisms (eg, via altering mood) and may be the product of low-level chronic toxicity or repeated episodes of acute toxicity.

In 2007, we examined 25 patients with bipolar I disorder over a period of 30 months in order to capture depressed and hypomanic mood episodes as well as periods of euthymia. Patients were compared with healthy cohorts on neurocognitive tests over time. This study provided the first indications that some neurocognitive impairments are mood-state–related, while others are more chronic and remain with patients even when they are relatively well.

Specifically, when patients were depressed, total recall scores on the Rey Auditory Verbal Learning Test (RAVLT) were lower than during periods of euthymia or hypomania. This suggests that verbal memory ability is impaired during episodes of depression. Compared with healthy controls, depressed and hypomanic patients had relatively impaired executive function, memory and attention, and motor abilities. When patients were relatively well, they continued to show subtle impairments in attention and memory relative to healthy controls; this suggests that these impairments are chronic and do not necessarily recover with symptom improvement. Since this early study, a number of trials have produced similar results, which suggest that the neurocognitive profile

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of bipolar disorder is dynamic and subject to further modification with the use of medications.\textsuperscript{13,15} The impact of lithium therapy on neurocognition adds an additional layer of complexity for researchers, but in practice the broad range of effects is concordant with the experience of patients and clinicians. In research settings, lithium appears to have virtually no effect on concentration or on short- or long-term memory, but it does have modest effects on psychomotor speed, verbal memory, and verbal fluency.\textsuperscript{13} Therefore, lithium may be acting—at least in part—on the impairments displayed when patients are experiencing an episode. However, the effects of the disorder and lithium therapy are subtle, and in a clinical setting, they may not always be detectable.

To map the neurocognitive changes that occur in patients with bipolar disorder who undergo lithium treatment, we propose that clinicians use the Lithium Battery–Clinical (\textbf{Figure 2}) to assess the neurocognitive effects of lithium.\textsuperscript{13} This tool allows clinical complaints to be correlated with changes to the illness profile and, in particular, to changes in treatment. The adoption of such a tool automatically enhances the attention paid to neurocognition in clinical settings and provides a richer understanding of contributing factors in patient illness. In turn, this should assist in formulating treatment strategies that focus on improving neurocognition as well as on normalizing mood—and thereby enhance overall functioning. Specifically, lithium dose and plasma blood levels should be modified and monitored with neurocognitive components in mind, as part of an overarching clinical strategy to attenuate adverse effects and identify an optimal therapeutic level that is effective and safe and facilitates functioning.

\textbf{Untangling neurocognitive domains}

Untangling the domains of neurocognition that are modulated by lithium in the context of a fluctuating and complex illness such as bipolar disorder is a significant challenge. The Lithium Battery–\textit{Clinical} offers a systematic approach for clinical practice settings, but to elucidate the causes and develop better treatments, a detailed scientific understanding is required. Until such a time that specific neurocognitive profiles can be mapped out, and the illness and the effects of treatment can be targeted and easily discernible, clinicians will have to rely on their judgment to provide advice and make treatment decisions on the basis of bedside tests. Guidance based on evidence is urgently needed, and a useful first step is recognition of the problem. Even simple acknowledgment of neurocognitive compromise, as well as engagement with patients regarding their concerns, is likely to reassure them that the problems they sense are indeed real and in many cases can be ameliorated by optimizing therapy.

\textbf{Clinical recommendation}

Historically, neurocognitive outcomes and deficits have not been viable areas for treatment or for quantifying neurocognitive changes in patients. To understand the neurocognitive effects of bipolar disorder and its treatment, we propose that future research employ a more sophisticated research version of the Lithium Battery that includes specific neuropsychological tests. Over time, this approach is likely to reveal which medications are better suited to improving mood while preserving neurocognition. In the meantime, clinicians can employ the Lithium Battery–\textit{Clinical} for noting and managing neurocognitive concerns as part of routine clinical practice during lithium treatment, and should do so regularly.

Neurocognition plays a significant role in functioning, and treatment effects and patient concerns affect compliance. Effective and more specific treatment strategies are urgently needed to improve outcomes and ameliorate this aspect of illness burden in bipolar disorder. Moreover, a better understanding is needed of the tolerability of lithium in patients for whom this treatment can be highly beneficial.
SIGNIFICANCE FOR THE PRACTICING PSYCHIATRIST

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Note: The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the American Foundation for Suicide Prevention.

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