Executive Summary

This white paper explores the use of lithium in the treatment of bipolar disorders in the pediatric population. We recognize that a diagnosis of bipolar disorder for a child is still considered controversial by some, causing skepticism regarding identification and uncertainty on how to begin treatment. However, it is important to provide appropriate treatment for symptoms of bipolar disorder as soon as possible. Early intervention is essential to prevent the development of more severe symptom presentation later in life. Effective management can prevent long-term negative outcomes.

This paper contains details on best practice recommendations for the use of lithium carbonate, which is a proven mood stabilizer and the gold standard treatment in adult bipolar disorder. References to published book content and peer reviewed research papers outlining lithium use are listed. Additional information on other mood stabilizers and contraindicated medications for bipolar disorder are also included.

Introduction

Lithium is a medication recognized throughout the research and academic communities as a safe, effective, and disease modifying medication in the treatment of bipolar disorder. Dr. Robert Post, a practicing psychiatrist who spent 35 years at the National Institute of Mental Health, with 20 of those years as the Chief of the Biological Psychiatry Branch, has focused on bettering the understanding and treatment of bipolar disorder, emphasizing the importance of early, long-term treatment to prevent progressive episode recurrence and treatment resistance. Dr. Post is the editor of Bipolar Network News, and author of *Treatment of Bipolar Illness: A Casebook for Clinicians and Patients.* When asked about the use of lithium in pediatric bipolar cases his response was, **"we need to think about it early and more continuously to avoid disability."** He went on to tell our team, **"*Using lithium is not only about getting patients better, but it's about keeping them better.* *If you have more episodes after the first one, you have more cognitive dysfunction. The more episodes, the more cognitive dysfunction*. ***It's another reason for getting lithium in there early and often."*** [1]

There is a mounting body of research suggesting that Lithium may fulfil criteria of a *disease-modifying* treatment in bipolar disorder (i.e., altering illness trajectory, protecting brain structures and functions, and reducing progressive decline), rather than simply suppressing symptoms. In 2025, Post and colleagues asserted that lithium "acts like a disease-modifying drug"[2] because it affects mechanisms at a cellular level, and at the levels of brain structure and function, and systemic body systems. This built upon prior research demonstrating that lithium is associated with neuroprotective changes such as cortical thickening and hippocampal volume preservation that could underlie disease-modification.[3] Additionally, lithium has been shown to ameliorate abnormal brian function in regions implicated in emotional regulation and cognition functioning, going beyond mere symptom relief. This is consistent with the modification of underlying disease processes.[4]

Lithium has also been shown to lengthen telomeres[5] and decrease incidence of dementia,[6] improving physical and cognitive health.

A 2025 study by Oliva and colleagues shows that people who are treated with insufficient or intermittent lithium do not have as good of a response. Continuity of lithium exposure, or sustained lithium exposure, significantly lowers risk of all-cause mortality compared to no use of lithium.[7] Notably, patients with *partial or intermittent* lithium exposure did *not* show the same protective effect,[7] making it essential to begin lithium treatment early and maintain it consistently in the treatment of bipolar disorder.

Lithium as Gold Standard Medication

For bipolar disorder treatment in adults, mood stabilizers have long been accepted as the first line of treatment in symptom management, with lithium carbonate considered to be the gold standard. Other mood stabilizers are often used in a secondary or supplementary role to support lithium's effectiveness, or may be used instead of lithium if it is not tolerated by the patient. In the pediatric population, symptoms such as the rapid cycling of mood from depression and irritability to mania and hypomania can be treated through the application of lithium.

Concerns about the use of lithium: many practitioners are concerned about the safety of lithium and erroneously think of it as toxic. Yet, there are only a small few contraindications to lithium treatment: severe cardiovascular or renal disease, severe debilitation, severe dehydration, severe sodium depletion, and concurrent use with diuretics. The fears of toxicity stem in part from concerns about what's known as "lithium toxicity." Because lithium is a salt, it can be exchanged by the body for sodium, so "if a person is salt-depleted, it competes with sodium and rises to toxic levels in the body and brain."[14(p.78)] However, lithium toxicity is entirely avoidable, regardless of dose or duration of treatment, provided that the patient stays hydrated and maintains necessary levels of sodium. This involves maintaining hydration in terms of both drinking enough water and consuming enough electrolytes. With attention to hydration and sodium, lithium toxicity need never occur.

Additional concerns may stem from the laboratory testing required to obtain serum blood levels. Many providers have concerns that pediatric patients will not be able to tolerate these blood draws and they will therefore be at risk while taking lithium. Expressing these concerns to the family, explaining the importance of blood testing, and allowing the family to take these concerns into consideration during their decision making process is an important part of partnering with families in a child's care. However, clinical practice shows that as stability improves blood draws become more tolerable, allowing for regular monitoring of serum blood levels.

Standard Treatment Protocol for Lithium Titration

This commonly followed, conservative titration protocol, is most often successful for those who tolerate lithium and is recommended by child and adolescent psychiatrists who specialize in treating juvenile onset bipolar disorder:

Prescriber Points to Remember

- The slower the titration the less likely the patient will experience negative side effects.
- Use the *extended release* lithium carbonate tablets for more consistent levels of lithium.
- Increase by no more than 150mg every 6-11 days.
- Use 300mg ER tablets and 450mg ER tablets in combination to keep dose increases to *no more than* 150mg of extended release per dose increase.
- Continue on the below schedule until desired clinical response is reached, or maximum tolerated dose is reached, whichever comes first.
- If maximum tolerated dose is reached and clinical response has shown improvement but the lithium appears to be insufficient as a singular medicinal intervention, consider secondary mood stabilizers listed above.

1. **Begin with one 300mg ER** tablet in the morning.
    a. Hold for a minimum of 5-10 days
    b. Maintain proper hydration and electrolytes, especially sodium (salt)
    c. Monitor for side effects
    d. Monitor for clinical improvement
    e. Have serum blood levels drawn between days 6-11.
    f. Hold dose until serum level results have been read
    g. Continue titration provided there are no intolerable side effects, blood levels are *below* 1.5, *and* symptoms have not resolved
2. **Increase by 150mg** by switching to one 450mg ER tablet in the morning.
    a. Hold for a minimum of 5-10 days
    b. Maintain proper hydration and electrolytes, especially sodium (salt)
    c. Monitor for side effects
    d. Monitor for clinical improvement
    e. Have serum blood levels drawn between 6-11 days *after the most recent dose increase*
    f. Hold dose until serum level results have been read
    g. Continue titration provided there are no intolerable side effects, blood levels are *below* 1.5, *and* symptoms have not resolved
3. **Increase by 150mg** by switching to one 300mg ER tablet in the morning and adding one 300mg ER tablet in the evening.
    a. Hold for a minimum of 5-10 days
    b. Maintain proper hydration and electrolytes, especially sodium (salt)
    c. Monitor for side effects
    d. Monitor for clinical improvement
    e. Have serum blood levels drawn between 6-11 days *after the most recent dose increase*
    f. Hold dose until serum level results have been read
    g. Continue titration provided there are no intolerable side effects, blood levels are *below* 1.5, *and* symptoms have not resolved

4. **Continue titration** on this schedule until clinical response is sufficient
5. **Once therapeutic levels have been reached**, routine lab work for serum levels should be done quarterly (every 3 months), with continuous hydration and symptom monitoring

Patient Points to Remember

- When possible, take the larger of the two doses in the AM until side effects can be assessed.
- If a dose is missed, do not double the next dose. It's safer to skip a dose than to double a dose.
- Consider taking lithium with foods high in calcium and protein such as yogurt to ease GI upset.
- If using extended release tablets, do not crush, cut, or chew tablets.[9] They must be swallowed whole. If swallowing with water is difficult try a spoonful of applesauce, ice cream, or pudding.
- All laboratory testing for serum blood levels *must* be drawn 12 hours after the most recent dose in order to get an accurate level.
- 10% to 26% increases of 12-hour serum concentrations can be expected in once-daily dosing compared to 12-hour serum concentrations of an equal dose given twice daily.[9]

Lithium Blood Levels

In order for lithium to be effective, its concentration in the blood must be held within a specific range. **Many providers are under the false impression that the normal range, reported on lithium serum level laboratory reports, is the same thing as the medication's therapeutic range. It is not.** In *The Bipolar Child* Dr. Papolos reports, "maintenance therapeutic levels for children typically range from 0.8 to 1.2 mEq/liter."[14(p.81)] Importantly, provided no negative side effects are reported, titration should not be calibrated to a predetermined blood level, rather it should be titrated to clinical response, meaning that symptoms have been reduced or eliminated.

Giadli and colleagues concur advising, "[f]or the treatment of acute manic or hypomanic episodes and recurrent depressive disorders, a higher target range of 0.8–1.2 mmol/L (up to a maximum of 1.5 mmol/L) is generally recommended."[24] In a 2025 paper Papolos and colleagues[25] concur and specify the following, "Mood Stabilization: Lithium titrated to clinical response; Usually requires levels 1.0-1.2 mEq/l; Oxcarbazepine, if lithium not tolerated."

Side Effects

All medications have potential side effects, lithium included. With attenuation to a child or teen's symptoms, parents are quick to identify when undesirable side effects occur. Partnering with parents as citizen scientists in monitoring their child's response to a medication can facilitate successful titration. As the body adjusts to lithium the child may experience some gastrointestinal distress, headaches, and/or excessive thirst.[9] More severe presentations of side effects can often be resolved by returning to the previous dose (when side effects were not present), holding until the body has adjusted and is ready to begin further titration. Luckily, **the most common side effects of**

lithium titration can be avoided by the low and slow approach to introducing the medication, and maintaining hydration.

It is also important to to avoid combining lithium with other agents that increase serum levels including: nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. ibuprofen (Advil, Motrin), acetylsalicylic acid (Asprin), naproxen (Aleve, Naprosyn), ketorolac (Toradol), angiotensin-converting enzyme inhibitors (ACE inhibitors) (e.g. benazepril (Lotensin), captopril, enalapril (Vasotec), lisinopril (Zestril), quinapril (Accupril), ramipril (Altace), angiotensin II receptor antagonists (ARBs) (e.g. azilsartan (Edarbi), candesartan (Atacand), losartan (Cozaar)m olmesartan (Benicar), valsartan (Diovan), or diuretics (e.g. hydrochlorothiazide, spironolactone (Aldactone), bumetanide (Bumex), furosemide (Lasix), amiloride (Midamor).[9]

Other Proven Mood Stabilizers

1. **Trileptal (Oxcarbazepine):** an anti-seizure medication used to stabilize mood in psychiatric conditions.
    a. Oxcarbazepine may be considered an effective adjunctive therapy for mania in bipolar disorder,[15] but should not be seen as a first-line, well-established, evidence-based therapy in the way that lithium is.
    b. In the treatment of Bipolar I, oxcarbazepine is most effectively used as a *secondary* mood stabilizer with lithium as the *primary* mood stabilizer.[16]
    c. Oxcarbazepine is most often used in patients who have more frequent manic or hypomanic episodes than depressive ones.
2. **Tegretol (Carbamazepine):** Similar to Oxcarbazepine, Carbamazepine is also an anti-seizure medication that is used to stabilize mood in psychiatric conditions. However, Carbamazepine is used less frequently that Oxcarbazepine for the following reasons:
    a. Carbamazepine is generally less well-tolerated than Oxcarbazepine, and has more side effects such as drowsiness, dizziness, nausea, vomiting, ataxia, and rash.[17,18]
    b. Carbamazepine has a higher risk of serious side effects, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hyponatremia.[17,19]
    c. There is a box warning for patients with an increased likelihood of carrying the HLA-B allele, especially those of Asian descent, and should be screened for the allele prior to starting therapy since those with the allele have a significantly greater risk of developing Stevens-Johnson syndrome or toxic epidermal necrolysis and is an absolute contraindication.[17]
    d. Carbamazepine has a risk of anemia or agranulocytosis, so regular complete blood count testing is recommended.[17]
    e. Carbamazepine is metabolized in the liver, while Oxcarbazepine is metabolized in the kidneys, making Carbamazepine more likely to interact with other drugs metabolized by the liver.
3. **Lamictal (Lamotrigine)**
    a. Lamotrigine is a mood stabilizer with antidepressant characteristics and that has been shown to have little to no efficacy in treating acute mania.[18]

b. In a 2024 metaanalysis, Haenen and colleagues found substantial evidence for lamotrigine's efficacy for acute depressive episodes in bipolar disorder, and for maintenance and relapse prevention.[20] But this analysis showed little or no strong evidence for lamotrigine's effectiveness in treating acute mania/hypomania.
c. Lamotrigine is typically used in the treatment of Bipolar II, which includes only hypomania, not mania. (The diagnosis shifts from Bipolar I to Bipolar II with the presence of a manic episode.)
d. In the case of Bipolar II, lamotrigine may be used as a primary mood stabilizer.[21]
e. In the case of Bipolar I, lamotrigine is more effectively used as a *secondary* mood stabilizer with lithium as the primary mood stabilizer, and is used in patients who have more frequent depressive episodes than manic ones.
f. If used alone to treat Bipolar I, lamotrigine is often insufficient to curb manic symptoms.[22]
g. Lamotrigine must be titrated extremely slowly because of the risk of life-threatening Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).[23] Generally these will occur between 5 days and 8 weeks of initiating treatment.[23] Risk factors in addition to high initial doses and rapid titration include, age under 13 years, concurrent treatment with valproate, and prior rash with any other antiseizure medication.[23]

Contraindicated Medications in Bipolar Treatment

Antidepressants - SSRIs and SNRIs: adverse reactions are considered to be clinical indicators that a diagnosis of unipolar depression is incorrect and that the correct diagnosis is likely bipolar. Due to their reported anxiolytic properties, some SSRIs and/or other types of antidepressants (such as SNRIs) are mistakenly given in bipolar disorder treatment in an attempt to address elevated anxiety. Unfortunately, this use case can cause the antidepressants to trigger mania, or switches to hypomania/mania. A 2020 meta-analysis showed that in bipolar disorder individuals on antidepressants may experience antidepressant associated mania (AAM) within weeks, with increased risk to those who are younger in age or have a history of rapid cycling.[8] If bipolar disorder is suspected in either its full or prodromal presentations, or if a first-degree relative has a diagnosis of bipolar disorder or other mood disorder, antidepressants should be avoided. In addition, there is a risk of serotonin syndrome when other serotonin modifying agents (e.g. SSRIs, SNRIs, tricyclic antidepressants, MAOIs, buspirone, or SAM-E) are used concurrently, requiring extremely vigilant monitoring.[9]

Stimulant Medications (often used to treat ADHD): adverse reactions, including mood destabilization, increases in aggression and irritability, and sleep disruptions are considered to be clinical indicators that a diagnosis of ADHD is incorrect and that the correct diagnosis is likely bipolar. A large 2016 review showed that adults with bipolar disorder who initiated treatment with methylphenidate experienced a markedly increased risk of manic episodes, and that use of stimulants appear to be a risk for inducing mania, especially in those with lower levels of overall mood stabilization.[10] If bipolar disorder is suspected in either its full or prodromal presentations, or if

a first-degree relative has a diagnosis of bipolar disorder or other mood disorder, stimulant medications should be avoided.

Antipsychotic Medications: while often used as a first line treatment for children with mood disorders and bipolar disorder, antipsychotic medications, both first and second generations, are not shown to stabilize mood over long term periods on their own. Overall, the research suggests that while antipsychotics may be helpful in treating acute mania and/or psychosis, their *long-term mood-stabilizing* effects (especially in preventing both mania and depression) are less robustly supported compared to established mood-stabilizers like lithium. Smith and colleagues[11] reported that while mood stabilizers showed evidence of efficacy in preventing relapses of both mania and depression, antipsychotic medications are more effective as adjunctive treatments used in combination with mood stabilizers if required after titration to therapeutic levels of mood stabilizers has occurred. Additionally, Kusamaker[12] reported that in an 8 year study antipsychotic medications found reductions in mania but increased depressive episodes. Antipsychotic medications also have significant metabolic impacts including being associated with major metabolic changes that contribute to the onset of metabolic syndrome, leading to medical morbidity and a significantly shortened life span.[13] In some instances, the combination of antipsychotics and lithium may result in increased CNS effects including drowsiness, sedated state, ataxia, abnormal gait, concussion, disorientation, lethargy, memory impairment, slurred speech and headache. Decreasing, discontinuing, or restricting to as-needed use of the antipsychotic can limit this risk and decrease these side effects.[9]

Conclusion

Lithium is a safe, effective, and easy to tolerate medication that can be used successfully to not only treat bipolar disorder symptoms in childhood, but to facilitate positive lasting impacts on psychiatric as well as general health. While care does need to be taken to titrate slowly, and to monitor hydration, sufficient electrolyte intake, side effects, and serum blood levels, these are not concerns that need to preclude the use of this life saving medication.

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