

Executive Summary

This white paper outlines the safety, efficacy, and arguments for a more robust use of lithium as a mood stabilizing agent. It is based on a series of recorded interviews conducted by Children's Mental Health Resource Center (CMHRC) with Dr. Robert Post, as well as on Dr. Post's presentation on lithium at the 28th Annual Conference of the International Society for Bipolar Disorders (ISBD), September 2026.

Lithium is the most extensively studied treatment in bipolar disorder, and it is prescribed less often than agents with weaker evidence. In a 2002–2003 U.S. claims analysis of 7,760 patients with bipolar diagnoses, lithium was the first medication prescribed for only 8%, while antidepressants were first for 50% (Baldessarini et al., 2007). That gap between evidence and practice is the subject of this paper.

The argument advanced here, following Post, Li, Berk and Yatham (2025), is that lithium functions as a disease-modifying medication, an agent that changes the trajectory of an illness rather than only suppressing its current symptoms. That is a strong claim, which rests on four independent lines of evidence:

1. **Efficacy.** Lithium prevents both manic and depressive recurrence, and it is the only maintenance agent with positive randomized evidence obtained under non-enriched conditions (that is, in patients not pre-selected for having already tolerated and responded to the study medication).
2. **Timing.** Response is better when lithium is started early. In a Danish national cohort of 4,714 patients, starting lithium after a first contact or single manic/mixed episode predicted lower non-response than starting later (Kessing, Vradi, & Andersen, 2014).
3. **Effects beyond mood.** Lithium is associated with reduced dementia incidence, attenuated white matter loss after a first mania, and reduced suicidality.
4. **A tolerable risk profile under monitoring.** The renal risk that drives most clinical avoidance is smaller and more manageable than its reputation. In a Danish population study of over 1.5 million people, lithium was associated with chronic kidney disease but not with end-stage chronic kidney disease; anticonvulsants were associated with both (Kessing et al., 2015).

This paper provides evidence to support the position taken by Dr. Post and colleagues that **current low rates of lithium prescribing cannot be justified by the evidence, and the burden of proof has shifted to those who avoid it.**

About Robert M. Post, MD

Dr. Post spent 36 years at the National Institute of Mental Health, serving for roughly two decades as Chief of the Biological Psychiatry Branch, where his research focused on treatment-resistant unipolar and bipolar illness. He graduated from Yale University in 1964 and

the University of Pennsylvania School of Medicine in 1968, interned at the Albert Einstein College of Medicine, and completed psychiatric residency training at Massachusetts General Hospital, NIMH, and George Washington University.

He founded The Stanley Foundation Bipolar Network, now the Bipolar Collaborative Network, which he continues to head. He is Professor of Psychiatry at the George Washington University School of Medicine, and he helped pioneer the use of carbamazepine in lithium-resistant bipolar disorder. He has published more than 1,000 manuscripts, edits the Bipolar Network News, and has received awards from the Society of Biological Psychiatry, the American Psychiatric Association, the American College of Neuropsychopharmacology, NARSAD, NAMI and others. He is in private practice, where he consults on difficult-to-treat mood disorders including childhood-onset bipolar illness.

The disease-modification paper is co-authored with Michael Berk and Lakshmi N. Yatham, and the broader argument for earlier and greater lithium use has been made independently by Gin S. Malhi and Michael Bauer (2023), and by Lars Vedel Kessing's Copenhagen group.

Introduction

The Paradox: The Evidence Rose, The Prescribing Fell

Lithium's use has declined across the industrialized world over three decades while its evidence base expanded. Baldessarini and colleagues (2007) analyzed national MarketScan data on 7,760 patients with ICD-9 bipolar diagnoses in 2002–2003. Antidepressants were the first-prescribed class for 50% of patients, anticonvulsants for 17%, sedatives 15%, antipsychotics 11%, and lithium 8%. Antidepressants were chosen first twice as often as all mood stabilizers combined. The same analysis found lithium was sustained longer before any change than any other monotherapy, 29 weeks to change for 25% of patients, against 13 weeks for antidepressants, anticonvulsants and antipsychotics, demonstrating that *the medication clinicians were least likely to start was the one patients were most likely to stay on*.

Why the Decline is Not an Evidence Story

Four explanations for the decline recur, and none of them is a challenge to lithium's efficacy.

- **No commercial sponsor.** Lithium is an element. No company funds trials of it, sends representatives to discuss it, or runs continuing-education programs about it. Every comparator in the maintenance literature (olanzapine, quetiapine, lamotrigine, aripiprazole) arrived with a marketing budget.
- **Asymmetric evidence generation.** Because industry designs the trials, the trials are designed to favor the sponsor's molecule.
- **Reputation lag.** Perceptions of lithium's safety are outdated and widely based on understandings from the 1970s and 1980s. That data was collected before routine level monitoring became the norm, before the recognition that bipolar disorder *independently* damages renal function, and before comparison against the anticonvulsant alternatives.

- **Perceived management burden.** Blood draws, level monitoring, medication interactions and a narrow therapeutic index must be considered when prescribing lithium to a patient. These are also not extreme or unusual burdens to care considering they are the ordinary conditions of managing most areas of internal medicine as well as medications such as warfarin, insulin, and lithium's oncology equivalents.

Post's framing in his interviews is blunt: **lithium's efficacy is underestimated by physicians and its side effects are overestimated by physicians and the public alike, while more expensive and less effective medications are advertised.**

What "Disease-Modifying" Means, and Why the Term is Meaningful

In multiple sclerosis and rheumatoid arthritis, disease-modifying medications are standard of care and are started early, after the first diagnosis rather than after additional accumulated damage. They are given not to relieve today's symptoms but to prevent the lesions, the joint destruction and the disability that otherwise accrue. No rheumatologist waits for a third erosion before starting a Disease-Modifying Anti-Rheumatic Drug.

Post, Li, Berk and Yatham (2025) argue in *The Lancet Psychiatry* that lithium meets the same description in bipolar disorder. Their case is that bipolar disorder is a progressive condition in which each episode worsens and accelerates the next, and that lithium acts on that progression rather than only on the current episode.

Criterion for a Disease-Modifying Agent

1. Prevents recurrence of the core illness
2. Works better when given earlier
3. Slows or prevents structural damage
4. Slows functional and cognitive decline
5. Reduces mortality attributable to the illness
6. Benefit persists as a changed trajectory

Lithium satisfies the first criterion on randomized evidence, the middle criteria on a mix of randomized and observational evidence, and the last on inference. Lithium retains a considerably stronger position as a disease modifying agent than any other agent used in bipolar disorder treatment.

The dilemma for prescribers: If lithium is a symptomatic treatment, reserving it until two or three other agents have failed costs the patient nothing but time. However, if it is disease-modifying, that delay is itself the harm.

Post's clinical mantra states: **prevent episodes, protect the brain.**

The Design Problem: Why the Evidence Tables Understate Lithium

There are two types of maintenance trials: An **enriched** trial recruits patients in an acute

episode, treats them all openly with the study medication, waits for remission and stability, and only then randomizes the survivors to continue the medication or switch to placebo. Patients who did not respond, or could not tolerate the medication, are gone before randomization.

A **non-enriched** trial randomizes patients without that pre-selection.

An enriched positive result tells you that a patient already known to respond to and tolerate medication X should stay on medication X. It cannot tell you whether to start medication X in a patient whose acute response is unknown, or whose acute medication must be replaced because of intolerance. However, these are the two situations clinicians routinely face when choosing maintenance treatment.

Enrichment also inflates effect size. Selecting responders raises the observed separation from placebo, and the placebo arm additionally suffers discontinuation effects from a medication it had been taking. Everyone who did not respond to medication X, or could not tolerate it, is gone before randomization, so the trial can only speak about patients already known to do well on it.

Most of the modern comparator literature tested the sponsor's medication under enriched conditions and lithium under non-enriched conditions in the same trial. The arm patients were frequently switched to involved receiving lithium, without any evidence they would respond to it, while the sponsor's medication was the arm responders were kept on when they had already responded to it.

When lithium loses a head-to-head comparison in that configuration, the result is not, for example, "quetiapine beats lithium." It is "continuing a medication that already worked beats starting a medication that might not."

Grading maintenance agents separately under enriched and non-enriched conditions, **lithium is the only agent carrying category A evidence for prevention of any mood episode under non-enriched conditions**. Aripiprazole, lamotrigine and quetiapine carry category A under enriched conditions and category F (lack of evidence) under non-enriched conditions.

The practical question: "Which maintenance medication should I start in a patient whose long-term response I do not yet know?" **Answer:** Lithium is the only agent with an affirmative randomized answer. For the question "should I continue the medication that just worked," several agents qualify, lithium among them.

Beyond Mood: The Effects that Carry the Disease-Modification Claim

Dementia: Kessing, Søndergård, Forman and Andersen (2008) followed 16,238 people in Danish national registers. Patients who continued lithium had their rate of dementia fall to the level of the general population. Continued treatment with anticonvulsants, antidepressants or

antipsychotics showed no such association. Notably, the reduction was not incremental with prescription count, it appeared once treatment was continued at all.

Brain structure: The first-episode mania imaging substudy found attenuated white matter volume reduction on lithium relative to quetiapine over twelve months (Berk et al., 2017b). The sample was 26 patients. While this randomized finding was in a very small cohort, it is consistent with a larger observational literature reporting greater hippocampal and cortical grey matter volume in lithium-treated patients.

Suicide: Cipriani, Hawton, Stockton and Geddes (2013) meta-analyzed randomized trials and found lithium more protective against suicide than placebo (odds ratio 0.13, 95% CI 0.03–0.66, $n = 485$ across four trials). That analysis has been the basis of guideline statements for a decade.

Alzheimer's: Aron and colleagues (2025) reported in *Nature* that lithium is present endogenously in the brain, that brain lithium is depleted in mild cognitive impairment and further in Alzheimer's disease while serum lithium is unchanged, and that amyloid plaques sequester lithium. In mouse models, lithium orotate, which binds amyloid far less than lithium carbonate, prevented amyloid and tau accumulation and reversed cognitive deficits; lithium carbonate did not. Post does encourage appropriate caution for clinicians to watch the developing literature.

Mortality: Bipolar disorder is associated with roughly a decade of reduced life expectancy from mixed causes. The observational mortality literature is consistent with a lithium benefit.

Early versus late initiation: Kessing, Vradi and Andersen (2014) identified all 4,714 patients in Denmark prescribed lithium for bipolar disorder in psychiatric settings between 1995 and 2012. Early initiation was defined two ways: lithium started after the first psychiatric contact rather than later, and lithium started after a single manic or mixed episode rather than after an established bipolar diagnosis. On both definitions, early starters had significantly lower rates of non-response ($p < 0.0001$; hazard ratio 0.75, 95% CI reported in the paper, for the single-episode definition).

Episodes are the mechanism: Post reports that episodes, stressors, and substance use each leave epigenetic marks, and that accumulated marks drive treatment resistance, cognitive decline, and somatic comorbidity. He draws the analogy to cancer: the point of early intervention is to act before the process multiplies. More prior episodes predict worse response to most treatments, lithium included.

Post cites Yatham's Vancouver work indicating that cognition declines after a first manic episode and recovers only if no further episode occurs in the following year. If that is right, each prevented episode in the first year is not a deferred episode but a preserved capacity.

Safety Reconsidered

Hypothyroidism: Readily treated with thyroid replacement; not a reason to stop lithium. Check TSH at baseline and periodically.

Tremor, GI upset, polyuria: Largely dose-related. The dosing approach below is designed around them.

Toxicity: Toxicity episodes, associated with the narrow therapeutic index, are a common argument against lithium use, however they are an argument for avoiding unnecessarily high doses and dehydration, not for avoiding the medication itself.

Weight gain: Among mood stabilizers lithium has a lower weight gain profile than the others. It compares favorably to olanzapine, whose weight gain does not plateau with duration.

Pregnancy: Considered safe, without impacts on the fetus, throughout pregnancy, including during the first trimester at levels of 900mg QD or less. Higher levels during second and third trimesters are considered safe.

Medication interactions: NSAIDs, thiazides, ACE inhibitors and dehydration raise levels. Patient education on this is non-optional.

The Risk That is Routinely Left Out of the Calculation

Every risk above is compared, in practice, against an implicit alternative of no lithium. That alternative has its own risks: continued episodes, cumulative cognitive and functional loss, and the elevated mortality of poorly controlled bipolar disorder.

One specific risk of stopping: Post reports more than a dozen long-term good responders who discontinued lithium after many years, relapsed, resumed lithium, and did not regain their previous response. This phenomenon, discontinuation-induced refractoriness, is described in the literature and is **a reason to treat the decision to stop lithium as a significant one rather than a reversible trial.**

Dosing: Post's clinical practice position is to give patients as much lithium as they will tolerate, and no more, and not to use lithium as a monotherapy. When the response at a tolerated dose is partial, the gap is filled by adding another agent rather than by raising lithium into toxicity. Post's stated rationale is that lithium potentiates essentially every other psychotropic used in bipolar disorder, including anticonvulsants and atypical antipsychotics, where he reports combination outperforming either agent alone.

Monitoring, at minimum: Serum lithium levels, serum creatinine and eGFR, TSH, and calcium, checked at baseline and then three to six month intervals. Patients need explicit education on

dehydration, NSAIDs, and diuretics. Monitoring, according to the Kessing data, supports lithium as a medication that is far safer than its reputation leads clinicians to believe.

Children and Adolescents

The use of lithium in pediatric and adolescent populations is described by Post as one of systematic undertreatment. **Roughly two thirds of bipolar disorder in the United States begins before age 19. Earlier onset predicts a worse adult course, and earlier onset is also associated with a longer delay to first treatment, which is independently associated with worse adult outcome.** He describes lithium as "pathetically" underused in adults and more so in children.

Post cites cohort work from Pittsburgh and from Barbara Geller's St. Louis group in which children who received lithium in the community fared best, with fewer mood episodes and fewer suicide attempts. Children with bipolar disorder not otherwise specified (BD-NOS), who cycle rapidly and sometimes multiple times within a day, are the hardest to stabilize and Post is specific about what to avoid.

Olanzapine: Weight gain from olanzapine does not plateau with duration, and the resulting inflammation has consequences for the brain.

Antidepressants: Antidepressant monotherapy in a bipolar-vulnerable child risks activation or a switch into mania. Post reports that in his network's adult data, more prior antidepressant trials predicted worse outcomes. Sidor and MacQueen's (2011) meta-analysis of fifteen trials and 2,373 patients found antidepressants not statistically superior to placebo or standard treatment for acute bipolar depression, and concluded their lack of efficacy may limit their clinical utility.

SSRI + Stimulant: The pattern Post describes: a child with bipolar disorder misdiagnosed with ADHD and depression is given a stimulant and an SSRI. This is precisely the combination the evidence least supports and clinical practice most often produces.

Lithium prevents recurrence of both poles; it is the only maintenance agent with positive randomized evidence under non-enriched conditions; in the one evenly designed head-to-head trial after a first manic episode it outperformed quetiapine (Berk et al., 2017a); it is not associated with end-stage renal disease in a monitored population where anticonvulsants are; and it is prescribed first to roughly one in twelve American patients with the diagnosis.

Conclusions

Bipolar disorder appears to be progressive, lithium is the only widely available agent with a credible claim to altering that progression, and it is currently reserved for patients who have already sustained the damage it might have prevented.

For prescribers. Treat the decision *not* to offer lithium as one requiring a reason. The relevant question at the point of maintenance initiation is not "has this patient failed enough medications

to justify lithium" but "is there a specific contraindication, a documented prior failure, or an inability to monitor." After a first manic episode in particular, the cited literature favors lithium.

For families. The two misperceptions that most often keep lithium out of a treatment plan are that it is uniquely damaging to the kidney and that it is a medication of last resort for the severely ill. The first is contradicted by the comparative data. The second is contradicted by the timing data. Families are entitled to be offered lithium, while being warned that lithium may not be a monotherapy and that it requires regular blood work indefinitely.

With thanks to Robert M. Post, MD, for the interviews on which much of this paper draws.

References

- Aron, L., Ngian, Z. K., Qiu, C., Choi, J., Liang, M., Drake, D. M., et al. (2025). Lithium deficiency and the onset of Alzheimer's disease. *Nature*, 645(8081), 712–721.
<https://doi.org/10.1038/s41586-025-09335-x>
- Baldessarini, R. J., Leahy, L., Arcona, S., Gause, D., Zhang, W., & Hennen, J. (2007). Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders. *Psychiatric Services*, 58(1), 85–91. <https://doi.org/10.1176/ps.2007.58.1.85>
- Berk, M., Daglas, R., Dandash, O., et al. (2017a). Quetiapine v. lithium in the maintenance phase following a first episode of mania: Randomised controlled trial. *The British Journal of Psychiatry*, 210(6), 413–421. <https://doi.org/10.1192/bjp.bp.116.186833>
- Berk, M., Dandash, O., Daglas, R., et al. (2017b). Neuroprotection after a first episode of mania: A randomized controlled maintenance trial comparing the effects of lithium and quetiapine on grey and white matter volume. *Translational Psychiatry*, 7(2), e1041.
<https://doi.org/10.1038/tp.2017.13>
- Cipriani, A., Hawton, K., Stockton, S., & Geddes, J. R. (2013). Lithium in the prevention of suicide in mood disorders: Updated systematic review and meta-analysis. *BMJ*, 346, f3646.
<https://doi.org/10.1136/bmj.f3646>
- Kessing, L. V., Søndergård, L., Forman, J. L., & Andersen, P. K. (2008). Lithium treatment and risk of dementia. *Archives of General Psychiatry*, 65(11), 1331–1335.
<https://doi.org/10.1001/archpsyc.65.11.1331>
- Kessing, L. V., Hansen, H. V., Hvenegaard, A., Christensen, E. M., Dam, H., Gluud, C., & Wetterslev, J. (2013). Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: Randomised clinical trial. *The British Journal of Psychiatry*, 202(3), 212–219. <https://doi.org/10.1192/bjp.bp.112.113548>
- Kessing, L. V., Vradi, E., & Andersen, P. K. (2014). Starting lithium prophylaxis early v. late in bipolar disorder. *The British Journal of Psychiatry*, 205(3), 214–220.
<https://doi.org/10.1192/bjp.bp.113.142802>
- Kessing, L. V., Gerds, T. A., Feldt-Rasmussen, B., Andersen, P. K., & Licht, R. W. (2015). Use of lithium and anticonvulsants and the rate of chronic kidney disease: A nationwide population-based study. *JAMA Psychiatry*, 72(12), 1182–1191.
<https://doi.org/10.1001/jamapsychiatry.2015.1834>
- Malhi, G. S., & Bauer, M. (2023). Lithium first: Not merely first line. *Bipolar Disorders*, 25(1), 7–8.

<https://doi.org/10.1111/bdi.13299>

Post, R. M., Li, V. W., Berk, M., & Yatham, L. N. (2025). Lithium as a disease-modifying drug for bipolar disorder. *The Lancet Psychiatry*, 12(11), 863–868.

[https://doi.org/10.1016/S2215-0366\(25\)00097-5](https://doi.org/10.1016/S2215-0366(25)00097-5)

Sidor, M. M., & MacQueen, G. M. (2011). Antidepressants for the acute treatment of bipolar depression: A systematic review and meta-analysis. *The Journal of Clinical Psychiatry*, 72(2), 156–167. <https://doi.org/10.4088/JCP.09r05385gre>

Unpublished Source Material

Post, R. M. (2026). *Lithium as a disease modifying drug: Mandating earlier and greater use* [ISBD September 27, 2026 conference presentation].

Post, R. M. (2025, October 7 and October 14). *Interviews conducted by E. Errico* [Recorded interviews]. Children's Mental Health Resource Center. Transcripts on file.