

Lithium: The Case for Earlier Use

a disease-modifying medication

Why the most extensively studied treatment in bipolar disorder is prescribed less often than agents with weaker evidence, and what the research says about starting it sooner.

In a 2002 to 2003 U.S. claims analysis of 7,760 patients with bipolar diagnoses, lithium was the first medication prescribed for only 8 percent, while antidepressants were first for 50 percent. Antidepressants were chosen first twice as often as all mood stabilizers combined.

A disease-modifying medication changes the trajectory of an illness rather than only suppressing its current symptoms. In multiple sclerosis and rheumatoid arthritis, these medications are standard of care and are started early, after the first diagnosis rather than after accumulated damage.

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

CMHRC's role is not to prescribe or advise on individual treatment plans, but to provide education on how medications work, what the research shows, and what questions are worth asking, so that families can engage as fully informed partners in the decisions that matter most.

A Guide to Lithium and Mood Disorders

Lithium's use has declined across the industrialized world over three decades while its evidence base expanded. None of the usual explanations for that decline is a challenge to its efficacy. Lithium is an element, so no company funds trials of it, sends representatives to discuss it, or runs continuing-education programs about it.

Dr. Robert Post's framing 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.

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

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.

Post describes lithium as "pathetically" underused in adults, and more so in children.



Is lithium a medication of last resort for the severely ill?

NO

Response is better when lithium is started early. Among 4,714 patients in Denmark, starting lithium after a first psychiatric contact, or after a single manic or mixed episode, predicted significantly lower rates of non-response than starting later.

Does lithium prevent both manic and depressive recurrence?

YES

Lithium prevents recurrence of both poles, and it is the only maintenance agent with positive randomized evidence obtained under non-enriched conditions, meaning in patients not pre-selected for having already tolerated and responded to the study medication.

Does lithium cause end-stage kidney disease?

NO

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. Bipolar disorder also damages renal function independently.

Is hypothyroidism a reason to stop lithium?

NO

Hypothyroidism is readily treated with thyroid replacement and is not a reason to stop lithium. Check TSH at baseline and periodically, along with lithium levels, serum creatinine and eGFR, and calcium.

Is lithium best used on its own, as a monotherapy?

NOT REALLY

Post's practice position is to give as much lithium as a patient will tolerate and no more. When the response at a tolerated dose is partial, the gap is filled by adding another agent rather than by raising lithium into toxicity.

Can lithium be taken during pregnancy?

YES

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

Is stopping lithium a reversible trial?

NOT REALLY

Post reports more than a dozen long-term good responders who discontinued lithium after many years, relapsed, resumed it, and did not regain their previous response. This is a reason to treat the decision to stop as a significant one.

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.

THE RISK LEFT OUT OF THE CALCULATION

Every risk of lithium is weighed, in practice, against an implicit alternative of no lithium. That alternative carries its own risks: continued episodes, cumulative cognitive and functional loss, and the elevated mortality of poorly controlled bipolar disorder, which is associated with roughly a decade of reduced life expectancy.

If cognition recovers only when no further episode follows, then each prevented episode in the first year is not a deferred episode. It is a preserved capacity.

ON ACTING EARLY

Why the Trial Tables Understate Lithium

An **enriched** trial treats everyone openly with the study medication first, waits for remission, and only then randomizes the survivors to continue it or switch to placebo. A **non-enriched** trial randomizes patients without that pre-selection.

WHAT A HEAD-TO-HEAD LOSS MEANS

Most modern comparator trials tested the sponsor's medication under enriched conditions and lithium under non-enriched conditions in the same study. When lithium loses that comparison, the result is not "quetiapine beats lithium." It is "continuing a medication that already worked beats starting a medication that might not."

Graded separately under the two 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, a lack of evidence, under non-enriched conditions.

- Criteria 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.

Effects That Carry the Disease-Modification Claim

The case for lithium as a disease-modifying agent does not rest on mood symptoms alone. Several of its reported effects reach into structure, cognition, and survival.

- What the research reports:
- Dementia: among 16,238 people in Danish national registers, patients who continued lithium had their rate of dementia fall to the level of the general population
 - Brain structure: attenuated white matter volume reduction on lithium relative to quetiapine over twelve months after a first episode of mania, in a 26-patient imaging substudy
 - Suicide: a meta-analysis of randomized trials found lithium more protective against suicide than placebo, with an odds ratio of 0.13
 - Early initiation: among 4,714 Danish patients, early starters had significantly lower rates of non-response
 - Children: in cohort work from Pittsburgh and from Barbara Geller's St. Louis group, children who received lithium in the community fared best, with fewer mood episodes and fewer suicide attempts

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.

FOR FAMILIES

Treat the decision not to offer lithium as one requiring a reason. The question at the point of maintenance initiation is not whether a patient has failed enough medications to justify lithium, but whether there is a specific contraindication, a documented prior failure, or an inability to monitor.