

Why is not Lithium Prescribed More Often? Here are the Reasons

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INTRODUCTION

One of the current conundrums in the psychopharmacology of bipolar disorder is usually phrased as: Why isn't lithium prescribed more often, especially as a maintenance treatment? After all: 1) It is our oldest and most well established agent; its efficacy has been established in many studies and verified in a recent meta-analysis (1); 2) multiple Practice Guidelines from a variety of countries and regions have consistently deemed lithium as the first line, "gold standard" of mood stabilizers; 3) befitting a gold standard treatment, it is frequently utilized as an active comparator when testing new mood stabilizers (2-4); 4) since it has been prescribed for over 50 years, there is little worry that new long term toxicities or side effects will emerge; 5) equally, there is an astonishing amount of clinical experience with lithium's use (including mine, having prescribed lithium for 40 years, during over 30 years of which I have directed an academic Mood Disorders Clinic).

Despite these compelling reasons to prescribe lithium, evidence from multiple studies in both bipolar disorder and when it is used as an adjunctive antidepressant treatment demonstrate declining and/or lower prescribing rates of lithium than would be anticipated (5-7). Frequently, this issue is reviewed

with the conclusion that we should prescribe lithium more often (as in Professor Nolen's (8) thoughtful and wise review in this Journal recently). Yet, when a phenomenon-the decreased use of lithium-is repeatedly observed, it may be wise to consider the reasons for the observation instead of simply exhorting our colleagues to act differently. In this article, despite my gratitude for the availability of, experience with, and academic interest in lithium (9), I will present the counter argument, suggesting answers to the question of why lithium is not prescribed more often.

How are Clinical Decisions in Psychopharmacology Made?

Clinical decisions, made (hopefully) collaboratively by physicians and patients, are constructed by using informal algorithms that combine four factors: perceived efficacy, perceived tolerability (i.e., side effect burden), potential toxicity and the burdensomeness of treatment-e.g. need for ongoing blood tests and so forth. (For the sake of the discussion, I am ignoring nonclinical factors such as cost, which is relevant in some countries but not others). In psychopharmacology, the various options for treatment are then compared, either explicitly or

implicitly with all four factors being considered by both physicians and patients. Of course, physicians and patients may weigh these factors somewhat differently. One might assume that physicians would be more oriented towards efficacy whereas patients might consider burdensomeness and side effects more highly than do physicians. However, ironically, some data suggest psychiatrists consider side effects as more relevant in explaining nonadherence than do patients (10).

With these four factors in mind, let us consider how lithium may be perceived by patients and psychiatrists that explain its declining use.

Efficacy of Lithium

As confirmed in the recent meta-analysis (1), lithium robustly prevents mood episodes and specifically mania. Yet, depression is the dominant pole in bipolar disorder with the average bipolar patient spending three times as much time depressed as manic/hypomanic (11). One large naturalistic study found that bipolar II individuals had a 37:1 ratio of depressed vs. hypomanic weeks (12). Lithium's efficacy is more robust against mania than depression. In the Severus et al. meta-analysis (1), lithium's efficacy prevented depression at only a trend level ($p=0.08$; $RR=0.78$, $CI=0.59-1.03$). Thus, for the typical bipolar patient for whom depression dominates the course of illness, lithium may be perceived as only a weakly effective agent.

Similarly, in comparing lithium to other mood stabilizers, lithium is not always necessarily more effective and, in some studies, is less effective than active comparators. In the combined analysis of the two registrational lamotrigine studies, lithium and lamotrigine were equally effective mood stabilizers but lamotrigine statistically separated from placebo in preventing depression while lithium did not (2), a finding that was replicated (albeit only numerically, not statistically) by Licht et al. (3). Similarly, in the quetiapine/lithium/placebo maintenance treatment study, quetiapine was more effective than lithium in preventing depression (4). Olanzapine was more

effective than lithium in preventing manias in another study (13). Some of these studies (2,4) were enriched for the non-lithium comparator medication, which may have given the comparators an advantage. Other studies, however (4,13) did not employ an enriched design. Still, other studies demonstrated lithium's robust efficacy (14). The overall conclusion, however, is that lithium does not routinely stand out as the most effective mood stabilizer and, in depression-predominant patients, may not even be the most effective mood stabilizer we have.

Tolerability of Lithium

Most lithium treated patients, estimated between 67-90%, experience side effects (15). Additionally, the majority of lithium treated patients experience more than one side effect. The most common side effects are nausea and/or diarrhea, tremor, polyuria/polydipsia, cognitive impairment and weight gain. Some side effects are more associated with treatment nonadherence (e.g., weight gain, cognitive impairment) than others (16). Thus, side effect burden with lithium is nontrivial.

Comparing rates of side effects of lithium with those of other mood stabilizers is rather difficult given the different methodologies of the studies. As examples, in enriched designs, the medication being tested-e.g., quetiapine or lamotrigine- is given openly before random assignment to either continuing that medication or switching to lithium as an active comparator or to placebo (2,4). This design therefore selects for subjects who can tolerate the experimental medication before the controlled phase of the study, thereby biasing the side effect data against lithium. In a study using a non-enriched design, lithium was associated with a numerically higher discontinuation rate compared to olanzapine (26% vs 19%) but olanzapine was associated with significantly more weight gain (13). In two studies using non-enriched designs, lithium was associated with a higher premature termination rate for intolerance (35% vs. 22%) compared to valproate in one (17), whereas no significant differences in side effects leading to

treatment termination were seen between lithium and valproate in the other study (14). Lithium was associated with more side effects than lamotrigine in the one non-enriched maintenance study (3). In the most recent, non-enriched study, quetiapine was associated with more side effect burden compared to lithium but no differences in discontinuation rates were observed (18).

For now, then, it would be difficult to consistently distinguish between lithium and many other mood stabilizers on side effect burden. Clinically, lamotrigine is associated with the fewest side effects, consistent with the results of the study conducted by Licht et al. (3).

Toxicity of Lithium

It has long been known that lithium has toxic effects on the thyroid gland and the kidneys. The thyroid toxicity, caused primarily by lithium's interference with thyroid hormones' release from the gland (19) affects up to 19% of treated patients (20). Although easily monitored and treated, lithium-induced hypothyroidism is a relevant clinical concern. No other mood stabilizer causes hypothyroidism.

Of greater concern is lithium's effects on renal function. Although controversy remains as to the extent of the renal toxicity, there is little doubt that lithium adversely affects renal tubular function by causing permanent structural changes with long term treatment (21,22). Additionally, although not all studies agree (23), compelling evidence suggests that lithium treated patients are at significantly higher risk compared to a control population to develop end stage renal disease (24,25).

More recently, lithium has additionally been associated with the development of hypercalcemia due to hyperparathyroidism (26,27).

To be sure, other mood stabilizers confer risks for other toxicities. Lamotrigine is associated with the risk for a high grade immunological rash, Stevens Johnson syndrome, at least within the first few months of treatment. Valproate is (rarely) associated with fulminant hepatitis. All antipsychotics can cause

tardive dyskinesia which, at times, is irreversible while metabolic syndrome is a major risk with some agents such as quetiapine, olanzapine and clozapine.

Of course, we have no mood stabilizers that are devoid of any health risks. Yet, the long term worries with lithium treatment, especially the concern about renal damage are legitimate concerns when treating bipolar patients for long time periods as is inherent for a lifetime disorder.

Lithium and Burdensomeness of Treatment

More than any other mood stabilizer, lithium requires regular, albeit infrequent venipuncture to monitor lithium levels and parameters associated with the potential toxicities noted above-thyroid, renal and calcium/PTH measures. Usual recommendations suggest monitoring between every three months to yearly (9). Although not particularly frequent, these tests are mandatory elements of lithium treatment and are burdensome to many patients. Monitoring of metabolic parameters is also necessary when treating with second generation antipsychotics, but somewhat less frequently than lithium monitoring. Valproate treatment requires yearly liver function tests. In contrast, lamotrigine requires no ongoing monitoring at all.

Personal Preferences

Of course, each person/patient is differentially sensitive to the concerns described above. For one person, the lithium's long term record of efficacy may be more important than any other factor. For another person, the burden of regular venipuncture might push the decision towards another mood stabilizer. As treating psychiatrists, it may be helpful to occasionally ask the question: if I had the disorder I am treating, what treatment would I want? For me, I would rather be on lamotrigine monotherapy than lithium monotherapy unless I was mania-predominant bipolar I in which case I would want to be on lithium plus lamotrigine (to effectively protect against both mania and depression).

CONCLUSION

Lithium is a remarkable mood stabilizer that has added immeasurably to our ability to treat bipolar disorder. Furthermore, as discussed elsewhere, lithium has other impressive clinical efficacies, such as its antisuicidal effects, as discussed in more detail elsewhere (28,29). Nonetheless, there are many

legitimate reasons why patients would rather take and psychiatrists would rather prescribe other mood stabilizers. Thus, the answer to the question: why do not more psychiatrists prescribe lithium seems self-evident. We should simply be grateful that we and our patients have a number of effective mood stabilizers available to us, both for monotherapy and in combination.

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