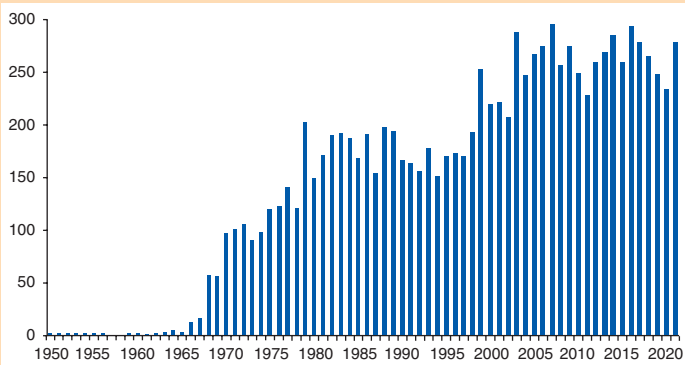
Introduction

As reflected in the number of citations per year, the initial golden age of lithium discovery was indeed 1965–1990. Yet interest in lithium has not waned, and a renaissance in lithium related publications has occurred over the past 20 years (Figure 0.1). This literature is fueled by ongoing exploration of lithium's unique mood stabilizing, anti-suicide and neuroprotective properties, a constellation of activities not seen in any single molecule [1–10]. Delving into how a simple ion conveys such benefits has opened important avenues of research into the neurobiology of both mood and degenerative brain disorders, and the molecular neuropharmacology of intracellular G-protein dependent and G-protein independent 2nd messenger systems [11, 12].

Unfortunately, this recent explosion of scientific interest occurs in the context of low lithium utilization despite the abundant evidence of lithium's advantages [13, 14]. However, rumors of lithium's demise are greatly exaggerated – as seen in Figure 0.2, the declining trend in US lithium use stabilized in 2009, a finding reflected in data sets from European sites [13, 15]. Factors underlying this reversal include: (1) the realization that certain non-lithium therapies have significant efficacy limitations (e.g. lamotrigine, second generation antipsychotics [SGAs]) or may be largely ineffective as mood stabilizers (e.g. gabapentin, oxcarbazepine, topiramate) [16–20]; (2) a greater appreciation for the risk of treatment failure when SGAs are used as maintenance monotherapy for bipolar I disorder (BD-1) [21]; (3) a renewed focus on the cognitive effects of mood disorders and emerging data supporting lithium's neuroprotective effects in older bipolar patients [22–26]; (4) the realization that the negative perception of lithium may be based on misconceptions regarding efficacy and safety that have been dispelled by newer data (Table 0.1) [27, 28]; (5) recent bans on prescribing valproate/divalproex (VPA) to women of reproductive age due to the risk for polycystic ovary syndrome (PCOS), congenital malformations and fetal valproate syndrome; and (6) recently revised lower estimates of the lithium related risk for Ebstein's and other cardiovascular anomalies following 1st trimester exposure [29–33].

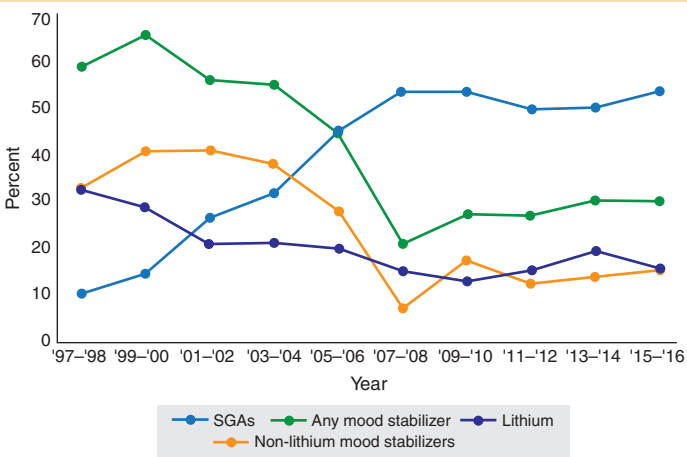
A 2021 meta-analysis and critical review of clinical guidelines with derived practice algorithms concluded that lithium remained the gold standard for treatment of BD-1 patients based on its clear efficacy in treating mania and in preventing manic episodes [28]. The clinical course of bipolar II disorder (BD-2) is dominated by the time spent in a depressive phase (50.3%), with very little time spent in a hypomanic or mixed phase (3.6%) [34]. While some BD-2 patients may respond to and tolerate antidepressants for extended periods without undue switch rates [35], there is increasing evidence that the number of prior antidepressant treatment trials decreases likelihood of response, increases the odds of depressive relapse, and shortens the time to relapse in those with BD-2 disorder who previously were antidepressant responders, and in whom antidepressants are used as maintenance therapy [36]. Many BD-2 patients need mood stabilization, and lithium has proven efficacy in preventing mood episodes, although the data are not compelling for lithium as a treatment for acute bipolar depression [37]. Schizoaffective disorder, bipolar type (SAD-BT) patients also experience acute mania, but there is a paucity of prospective data in this patient group compared with other bipolar diatheses or mood disorders. Nonetheless, the available data make the compelling argument that SAD-BT patients also benefit from lithium therapy, and that this group has suboptimal stability on antipsychotic monotherapy [38].

Figure 0.1 70-year trend in lithium references on mood disorders and neuroprotection



(Data from PubMed search conducted May 1, 2022. Search terms: lithium AND [manic OR mania OR neuroprotection OR major depression OR bipolar disorder].)

Figure 0.2 US trends 1997–2016 in different medication categories prescribed during outpatient visits for bipolar disorder



(Adapted from: T. G. Rhee, M. Olfson, A. A. Nierenberg, et al. [2020]. 20-year trends in the pharmacologic treatment of bipolar disorder by psychiatrists in outpatient care settings. *Am J Psychiatry*, 177, 706–715.)

A Dispelling the Misconceptions

This disconnect between the evidence base supporting lithium and its underutilization has not gone unnoticed, with concerted efforts undertaken by leading psychopharmacologists to help clinicians appreciate that current practice is not in line with new insights about lithium's safety and efficacy profile. Among the leading champions is Professor Janusz K. Rybakowski, a Polish researcher from the Department of Adult Psychiatry, Poznań University of Medical Sciences, who has been publishing on lithium for over 50 years [39]. His 2022 mini-review on lithium lamented the dissociation between practice patterns and data, provided a concise summary of lithium's unique features, and called on the mental health profession worldwide to simultaneously promote the long-term use of lithium in mood disorders, and challenge the negative perception that lithium is not suitable as a first-line candidate for BD prophylaxis [40]. Another leading psychopharmacologist and lithium proponent who has been instrumental in shaping BD treatment guidelines is Professor Gin Malhi (Psychiatry Chair at The University of Sydney,

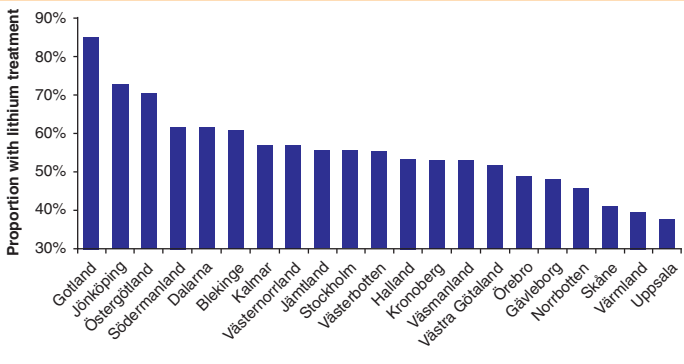
Executive and Clinical Director of the CADE Clinic at the Northern Clinical School, and Head of the Academic Department of Psychiatry at the Royal North Shore Hospital). Crucial to increasing use of lithium is the need to dispel outdated ideas, and Professor Malhi's 2021 editorial "Lithium mythology" provides a list of seven statements frequently elaborated as reasons to avoid prescribing lithium [41]:

1. ***Lithium is an old drug; it has nothing new to offer***
2. ***Lithium seldom works***
3. ***Lithium is not suitable first line***
4. ***Lithium is complicated to prescribe and manage***
5. ***Lithium is a dirty drug and difficult to tolerate***
6. ***Lithium destroys thyroid function***
7. ***Lithium ruins kidney function and eventuates in kidney failure***

While Professor Malhi's wording is deliberately provocative, his passion to "make lithium great again" is part of a collective effort to disseminate cutting-edge information, and thereby inspire clinicians to practice psychiatry based on evidence based concepts, and not on anxiety and fear [42]. Underlying these educational efforts is the overarching idea that certain medications such as clozapine and lithium offer distinct efficacy advantages, that the knowledge to prescribe such molecules is easily assimilated, and that depriving patients of such treatments is below the standard of care [42–44]. The tremendous regional variation in Swedish lithium use (Figure 0.3) very much parallels findings related to clozapine prescribing in the United Kingdom and in the United States [45–47], and reflects how local culture either promotes best practices, or sustains a climate where fear, uncertainty and doubt are acceptable reasons for not using pharmacological tools that are inarguably in the patient's best interest [48]. The Swedish data also present a compelling picture of the clinical outcomes associated with variations in lithium use for BD: higher prescription rates were significantly associated with a lower rate of mood recurrence, an association that was even more robust when analyzed separately for the BD-1 cohort [48].

To rectify the underuse of clozapine, governmental entities established resource centers to provide clinicians with data, education and decision support [49, 50]. Education is also the key to rectifying the inequities in lithium use and addressing those areas of greatest concern and misinformation that interfere with evidence based practice. Professor Malhi's use of the term "myth" reflects that certain exaggerated and inexact beliefs *not supported by the latest data* still hold sway in many corners of the mental health profession. While not intended to supplant the

Figure 0.3 Regional variation in proportion of lithium treated bipolar patients by county in Sweden [48]



(Adapted from: M. Sköld, S. Rolstad, E. Joas, et al. [2021]. Regional lithium prescription rates and recurrence in bipolar disorder. *Int J Bipolar Disord*, 9, 18–27.)

list above, in the spirit of cooperativity with all efforts to promote accurate language about lithium, I present a list of misconceptions encountered when discussing lithium with trainees and clinicians throughout the spectrum of care delivery: medical students, physician assistants, pharmacists, nurses, psychiatric nurse practitioners and physicians (Table 0.1). The items largely overlap many of the concerns enumerated in Professor Malhi's list, and the "Modern evidence" column provides the busy reader with some quick rejoinders to erroneous statements made by colleagues or to misperceptions voiced by patients and caregivers.

Table 0.1 A selected list of misconceptions and modern evidence regarding lithium treatment

Efficacy misconceptions	Modern evidence
1. Second generation antipsychotic (SGA) monotherapy is as effective as lithium monotherapy for maintenance treatment of bipolar I disorder	• Naturalistic data indicate that bipolar I patients on SGA monotherapy have higher rates of treatment failure than those on lithium monotherapy [21].

Efficacy misconceptions	Modern evidence
2. Rapid cycling bipolar disorder (RC-BD) patients respond poorly to lithium in general, and lithium is inferior to other options such as divalproex in this patient cohort	• The hallmark of RC-BD (when not iatrogenically induced by use of traditional antidepressant molecules) is frequent, but comparatively shorter, depressive episodes than non-rapid cycling patients [51]. • The number of prospective controlled studies in general is very sparse for this diagnosis. Clinical decisions must be made based on the few prospective and retrospective studies available [52]. • RC-BD patients respond comparably to non-RC-BD patients during lithium treatment in terms of time spent ill. RC-BD patients continue to have a greater number of depressive episodes during lithium treatment than non-RC-BD patients but not greater total time spent depressed [53, 54]. • The prospective studies indicate that lithium is not inferior to divalproex for management of RC-BD [55]. Use of a 2nd agent to treat the depressive phase of the disorder will likely be necessary regardless of mood stabilizer choice [53].
3. Lithium should be avoided in older bipolar disorder patients due to the lack of efficacy data and concerns about safety	• Lithium is as effective as divalproex in acutely manic older bipolar I (BD-1) patients and its tolerability is comparable [56]. • A 1-year follow-up study of 1388 older BD-1 patients (age ≥ 66 years) found that, after discharge from an acute psychiatric hospitalization for mania, there were no significant differences between lithium- and VPA-treated individuals in the proportion with medical admissions or nonpsychiatric emergency room visits, or in the time to medical admission [57]. • Older BD patients can be safely maintained on lithium with appropriate eGFR monitoring, and oversight of medications with potential kinetic interactions [58–63]. • Due to a number of factors (e.g. lifestyle, cardiometabolic comorbidities), BD is associated with a 3-fold increased risk of dementia; treatment with lithium decreases the risk of dementia in BD by almost 50% [22, 26].
Safety misconceptions	**Modern evidence**
4. Use of lithium is associated with high risk for end-stage renal disease or renal failure	• Using modern monitoring principles, and practices that minimize risks for renal insufficiency (e.g. once daily lithium use, keeping maintenance levels < 1.2 mEq/l), no patient should develop severe chronic kidney disease (eGFR 15–29 ml/min) or renal failure (eGFR < 15 ml/min) on lithium therapy [64, 65].

Efficacy misconceptions	Modern evidence
5. There is no easy way to monitor for or manage lithium related polyuria (defined as daily urine output > 3 liters)	• Patients may underreport the inconvenience of polyuria – all patients on lithium should be asked at each visit urinary frequency and volume, and the functional impact [66]. • The 24h fluid intake recollection (FIR) is an evidence based office screening tool [67]. • Early morning urine osmolality (EMUO) is an easily obtained laboratory measure to quantify the extent of any concentrating defect [67]. • Amiloride has emerged as an effective treatment for lithium related nephrogenic diabetes insipidus (NDI), and should be started as soon as any problems are detected [68].
6. Lithium should not be used in women of reproductive age due to an estimated 400-fold increased relative risk for Ebstein's anomaly.	• Using modern statistical methods (e.g. propensity score matching), analysis of the largest data set available revealed three important conclusions regarding risks from 1st trimester lithium exposure [29]: a. The adjusted risk ratio (ARR) for non-cardiac defects among infants exposed to lithium was not significantly different than among unexposed infants. b. No cases of Ebstein's anomaly were seen among 663 lithium-exposed pregnancies examined. c. There was a dose dependent increased risk for any cardiac malformation: **Dose ≤ 600 mg/d:** **RR 1.11** (95% CI 0.46–2.64) **Dose 601–900 mg/d:** **RR 1.60** (95% CI 0.67–3.80) **Dose > 900 mg/d:** **RR 3.22** (95% CI 1.47–7.02) d. **Meta-analysis findings:** The number needed to harm (NNH) for any cardiovascular malformation across all lithium doses is 83 when comparing rates between lithium users and non-users with bipolar disorder [69].
7. Other mood stabilizer options (e.g. valproate) are safer and should be routinely used in female bipolar disorder patients of reproductive age in lieu of lithium	• 1st trimester valproate/divalproex (VPA) exposure is associated with unacceptably high rates of congenital malformations and fetal valproate syndrome and should be avoided in women of reproductive age, or only prescribed if a woman understands the risks and uses adequate contraception [70]. • A meta-analysis of VPA related reproductive adverse effects in bipolar patients revealed statistically significant differences between the VPA treated and non-VPA treated groups in PCOS (odds ratio [OR]: **6.74**), any menstrual disorder (OR **1.81**) and hyperandrogenism (OR **2.02**) [71].

Efficacy misconceptions	Modern evidence
8. Lithium related hypothyroidism is highly prevalent, difficult to screen for and to manage, and often leads to treatment discontinuation	• Prevalence estimates vary, but overt hypothyroidism is only thought to occur in 8%–19% [72], and is easily screened for with TSH added to routine monitoring labs. • In large studies, hypothyroidism is not among the 10 leading somatic causes of lithium discontinuation, with a rate of only 2.0% in a recent surveillance study [73]. • Lithium use is not associated with development of antithyroid antibodies [74, 75]. • Hypothyroidism never justifies lithium discontinuation [72] but, should discontinuation be necessary for other reasons, hypothyroidism is often reversible [76]. • The sensitivity of depressive symptoms to TSH values at the upper limit of the normal range in bipolar patients provides important guidance about when thyroid replacement therapy might be initiated when hypothyroidism is not present by TSH or somatic symptom criteria [77, 78, 79].

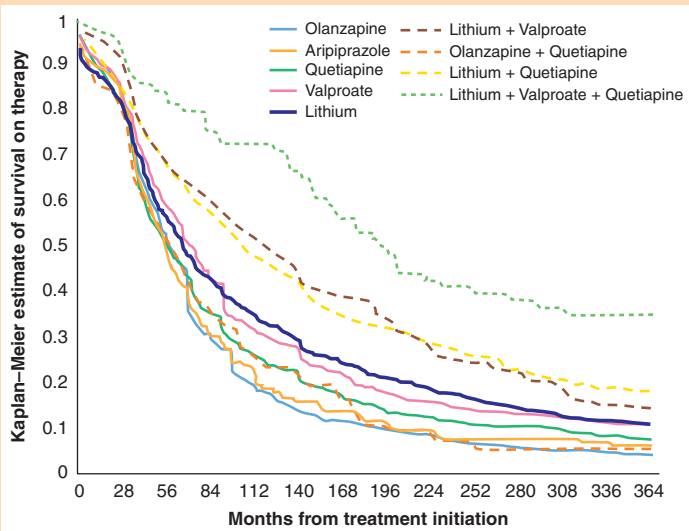
B The Efficacy Misconceptions

Broadly speaking, the misconceptions about lithium fall into one of two categories: those which minimize efficacy, or those which exaggerate safety issues. Many of the safety concerns were reinforced by the pharmaceutical industry in promoting VPA and SGAs for BD [40]. As seen in the upward trends toward SGA use and the simultaneous decline in lithium prescriptions, the unopposed message of lithium's harms and management burdens not only led clinicians to eschew lithium, but often to avoid mood stabilization altogether, even in BD-1 patients [13, 21]. Although aripiprazole, olanzapine and long-acting injectable risperidone microspheres have indications for BD-1 maintenance as monotherapy [80], the design of monotherapy maintenance trials is to prove that stable patients who have previously responded to that treatment have lower relapse rates than those on placebo. Importantly, neither aripiprazole, olanzapine or risperidone have demonstrable efficacy for the depressive pole of the disorder. Among the SGAs, only cariprazine and quetiapine have US approvals for acute mania and bipolar depression, but cariprazine has no registrational data for adjunctive use with lithium or VPA, no maintenance indication for BD-1 in the US, and is only approved for schizophrenia by the European Medicines Agency [81].

The results of the naturalistic experiment that unfolded over the past 15 years is becoming apparent, with data indicating that BD-1 patients have

higher rates of treatment failure on SGA monotherapy compared with lithium monotherapy [21]. One Swedish group examined treatment failure rates (defined as: treatment discontinuation, switch or rehospitalization) with mood stabilizer and SGA therapies, alone or in combination among 3772 adults discharged from psychiatric inpatient care for mania from July 1, 2006 to December 31, 2014. After excluding those with schizophrenia, SAD-BT, or dementia diagnoses from the analysis, and after adjusting for an extensive list of potential confounding variables related to sociodemographics, severity of the index hospitalization for mania and prior psychiatric history, the investigators found that, compared with lithium monotherapy, VPA monotherapy had a higher rate of medication discontinuation, and that SGA monotherapies (aripiprazole, olanzapine or quetiapine) were associated with the highest rates of all-cause treatment failure and failure due to medication switching (Figure 0.4) [21]. Prospective randomized studies corroborate

Figure 0.4 Time to treatment failure after hospitalization for mania among various treatment options for bipolar I disorder using lithium (dark blue line) as the comparator treatment [21]



(Adapted from: L. Wingård, L. Brandt, R. Bodén, et al. [2019]. Monotherapy vs. combination therapy for post mania maintenance treatment: A population based cohort study. *Eur Neuropsychopharmacol*, 29, 691–700.)

this naturalistic finding. In a 1-year randomized trial of patients with first episode mania, lithium was more effective than quetiapine during follow-up on every outcome measure, including mood, functioning, cognition, and brain imaging changes, with large differences emerging during the second half of the year [82].

In addition to short-term clinical outcomes when BD patients receive suboptimal treatment (e.g. mood relapse), recent papers have advanced a more nuanced argument that failure to adequately manage this disorder may itself be a disease-modifying event that portends lower long-term treatment response [83]. This argument has been made extensively in the schizophrenia literature as multiple analyses have demonstrated higher response rates when clozapine is initiated earlier for treatment resistant patients [84]. Multiple studies in BD-1 patients substantiate that earlier treatment with lithium is met with higher response rates, and that patients who receive more intensive treatment for just two years following a first manic episode have a longer time to rehospitalization than those randomized to usual care, an effect that persisted and increased during the next six years [85]. The underlying hypothesis for schizophrenia and BD is that failure to minimize symptom severity and recurrence, through treatment delay or suboptimal treatment, may result in epigenetic changes that have long-term impact on neurochemistry and medication response [83]. It is for this reason that treatment guidelines and expert recommendations are substantially in agreement that one must preferentially use lithium as the gold standard core treatment in the maintenance therapy of BD-1 patients and possibly BD-2 individuals, while acknowledging that additional medications may be necessary to manage mood recurrence, especially to the depressive pole [28, 30, 53, 86–88].

Improved characterization of the clinical course of rapid cycling bipolar disorder (RC-BD) has also been helpful in reframing the misguided notion that lithium is either ineffective in this cohort, or less effective than non-lithium options, especially VPA [86]. The hallmark of RC-BD is frequent, brief depressive episodes (by definition ≥ 4 mood episodes in a 12-month period), although total illness duration may not differ from non-RC patients [51]. Papers on lithium response often note that the presence of RC-BD diminishes rates of good clinical outcomes [89, 90]; however, a 2020 meta-analysis on predictors of long-term lithium response came to two important conclusions: (1) there is marked heterogeneity in the quality of outcomes data in this area; (2) among the 4 predictors of poor lithium outcome initially identified in the 31 relevant data sets (alcohol use disorder, personality disorders, higher lifetime number of hospital admissions, rapid cycling), when the analysis was confined to data from the high-quality studies (11 trials,