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].

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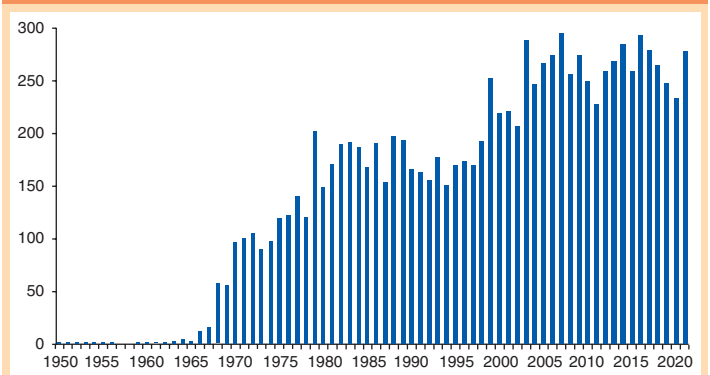
A 2021 meta-analysis and critical review of clinical guidelines with derived practice algorithms concluded that lithium remained the gold standard for treatment of BD-1 patients based on its clear efficacy in treating mania and in preventing manic episodes [28]. The clinical course of bipolar II disorder (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].)

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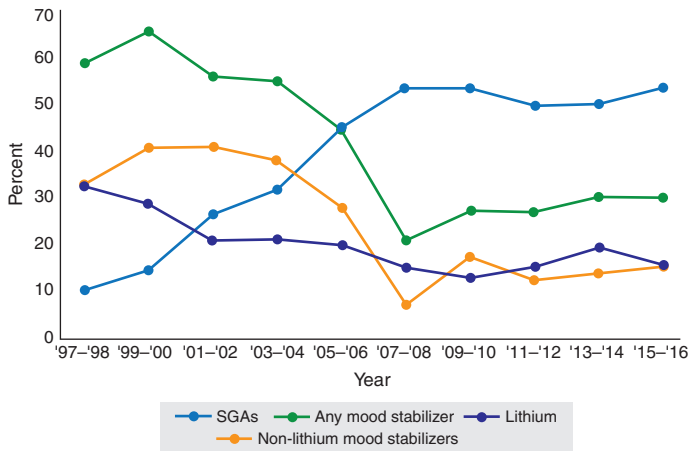
Figure 0.2 US trends 1997–2016 in different medication categories prescribed during outpatient visits for bipolar disorder



(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,

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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

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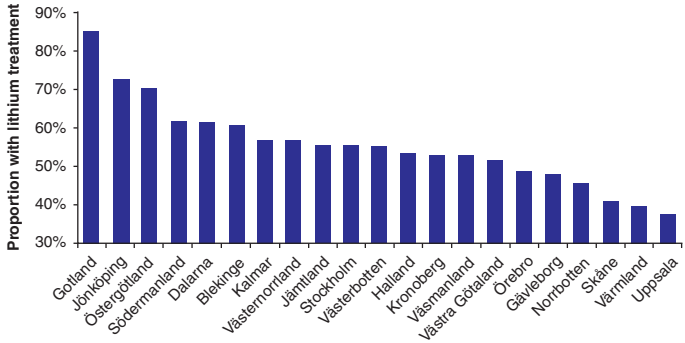
Figure 0.3 Regional variation in proportion of lithium treated bipolar patients by county in Sweden [48]



(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].

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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].

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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].

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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

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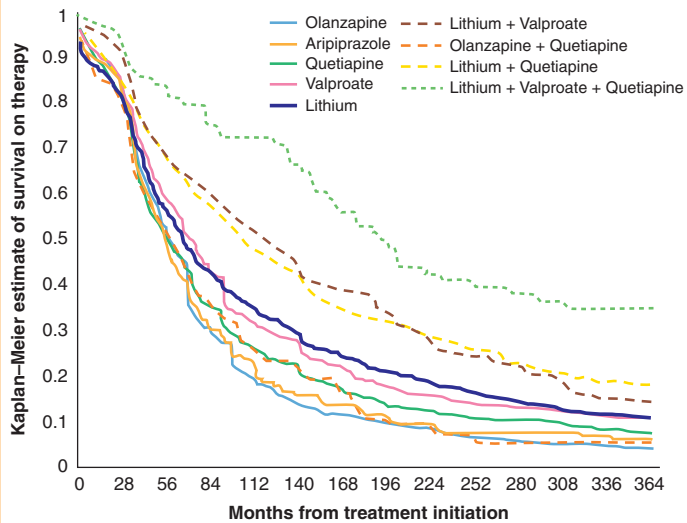
higher rates of treatment failure on SGA monotherapy compared with lithium monotherapy [21]. One Swedish group examined treatment failure rates (defined as: treatment discontinuation, switch or rehospitalization) with mood stabilizer and SGA therapies, alone or in combination among 3772 adults discharged 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.)

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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,

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n = 9981), only higher lifetime number of hospitalization admissions remained [91]. Importantly, when studies compare lithium to non-lithium treatments, both retrospective analyses and prospective trials note that RC-BD patients have high substance use comorbidity rates and high rates of mood recurrence, yet lithium treated RC-BD patients respond at rates that are comparable to patients on other therapies, including VPA [54, 55, 92]. The refined message from two decades of research is that the limitations of lithium relate to the neurobiology of RC-BD itself and not a failure of lithium per se, and that no mood stabilizer monotherapy will be sufficient to manage mood recurrence in many of these individuals [53]. Eschewing traditional antidepressants (e.g. selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, etc.), and use of evidence based medications for acute and maintenance treatment of bipolar depression (e.g. lurasidone, cariprazine, quetiapine, lamotrigine), is now understood to be the optimal approach in RC-BD [53].

Another patient cohort in which use of lithium has been unnecessarily avoided is older bipolar patients. While age-related declines in estimated glomerular filtration rate (eGFR) diminish the margin of error for older individuals [93], assumptions that lithium use is inherently poorly tolerated, ineffective or unsafe in this population are largely disproven. Prospective, randomized, double-blind acute mania trials document that lithium is as effective and tolerable as divalproex [56]; moreover, the recent literature documents that long-term lithium use in older BD patients is associated with a close to 50% reduction in dementia risk, a finding not seen with non-lithium therapies [22, 26]. One investigator in particular, Dr. Soham Rej of McGill University Department of Psychiatry, Montréal, Canada, has contributed numerous analyses substantiating that use of lithium is not associated with undue risk for medical complications in comparison to other options such as VPA, and that, with appropriate eGFR monitoring and attention to use of medications with kinetic interactions, lithium is generally well tolerated in patients older than 65 years of age [57–61, 94–96].

C The Safety Misconceptions

The early recognition that use of certain SGAs was associated with inordinate rates of metabolic adverse effects had one important outcome: it focused clinical attention and research on medical comorbidity in patients with serious mental illnesses such as schizophrenia and BD [80, 87]. The high prevalence of cardiometabolic disorders in BD patients is likely a significant contributor to the 3-fold increased dementia risk in this diagnostic group [97, 98]. While

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lithium is associated with renal adverse effects, some of the long-term risk of renal insufficiency previously ascribed solely to lithium exposure is contributed by chronic kidney disease (CKD) risk factors, such as hypertension, metabolic syndrome, diabetes and smoking, that disproportionately affect BD patients [99]. Echoing the findings for dementia, having a diagnosis of BD is associated with a 3-fold increased risk of CKD *independent of drug treatment* [99]. Not only is the independent effect of lithium on chronic eGFR changes lower than previously suspected [100], with the use of modern monitoring protocols, once daily lithium dosing and modest outpatient 12h serum levels (e.g. < 1.00 mEq/l), the risk of developing end-stage CKD attributable to lithium has been essentially eliminated in many countries [64, 65, 99]. (See Chapter 2 for a more complete discussion of renal issues related to lithium use.)

Although the potential effects of lithium on CKD risk demand routine monitoring, performing that task is relatively easy as laboratories report eGFR calculated from serum creatinine (and now cystatin C) values [101]. Moreover, changes in eGFR were typically a longer-term issue for the treating clinician, and not an immediate source of patient complaints. The more vexing clinical problem, and one that patients may notice early in therapy, is the development of polyuria (defined as 24h urinary output > 3 liters) [73]. Often patients will complain bitterly about the inconvenience of polyuria, but many clinicians appreciate that some underreport the functional impact of these problems, and actively query lithium treated patients about urinary frequency and thirst [66]. The goal of early recognition is to employ evidence based options for managing lithium related nephrogenic diabetes insipidus (NDI) such as amiloride, and forestall patient demands to discontinue lithium [68, 73]. The use of amiloride for lithium related NDI is well established, so statements that switching from lithium is the only option are simply untrue [68, 101, 102]. Unfortunately, the literature often recommends only one option for assessing the severity of a patient's concentration defect and for tracking changes to an intervention: the 24h urine collection [101]. While the gold standard for quantifying urine output [67], the impracticality of obtaining a valid 24h urine collection in many circumstances can preclude its use as a diagnostic tool and as a tool to track urine osmolality during amiloride treatment. Fortunately, a solution to this problem was provided a decade ago by the ambitious work of a group in Ireland who subjected a cohort of 179 lithium treated patients to a battery of subjective and laboratory tests, including the 24h urine collection [67]. This comprehensive study yielded two important clinical conclusions: (1) the 24h FIR is a useful method for office screening and for patients to easily monitor changes in polyuria; (2) EMUO is a valid method for estimating NDI severity [67]. How these are utilized is discussed

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extensively in Chapter 2, but the important message is that ongoing research has provided answers to help manage these important adverse effects, and that lithium related NDI should now be viewed as a problem with well-defined monitoring tools and a treatment pathway.

The pharmacological management of mental disorders for women of childbearing age demands nuanced and individualized decisions based not only on the literature, but on the prior history of stability with and without certain medications, and, importantly, patient values [69, 103]. The greatest area of concern is always 1st trimester exposure, and the impact of any medication on organogenesis. For lithium, the early focus was on cardiovascular malformations broadly, and Ebstein's anomaly specifically, based on spontaneous reports [80]. Unfortunately, the nature of these data led to risk estimates that were wildly inaccurate (e.g. 400-fold higher risk), but that continued to be cited in the absence of more systematic analyses [29]. As in other areas of research, more advanced statistical methods using propensity score matching and covariate balancing have been developed to analyze data sets retrospectively and remove many of the biases inherent to prescribing practices and to confounding factors in the population receiving a particular treatment [104]. Employing these robust statistical techniques, we can now estimate that the maximal increased risk for any cardiovascular malformation from lithium exposure is 1.8-fold higher than in non-exposed infants, which generates a number needed to harm of **83** [29, 69]. (See Chapter 7.) Whether this risk is acceptable to any individual depends on all of the factors mentioned above, but knowledge of this revised estimate, and the method by which this adjusted risk ratio was calculated, should inform any discussion about risk:benefit considerations around 1st trimester lithium exposure. Absolutist statements that lithium always presents an unacceptable risk for cardiovascular malformations are indeed based on misconceptions rooted in outdated risk estimates and do a disservice to the many women who must remain on lithium to preserve psychiatric stability [29].

As the reproductive risk associated with lithium has been reevaluated, that related to VPA has been subjected to increased scrutiny due to the known high rates of congenital malformations and neural tube defects from 1st trimester exposure, combined with the increased risk for polycystic ovary syndrome (PCOS) [105]. The 2017 British Association for Psychopharmacology (BAP) consensus guidance on the use of psychotropic medication during preconception, pregnancy and the postpartum period notes that VPA exposure increases the risk for any major congenital malformation 3-fold, and for spina bifida 13-fold, a risk that is

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not mitigated by the use of folate [105]. It is for that reason the BAP included the following language regarding VPA (p. 527):

- There is a particular concern around the use of anticonvulsant mood stabilisers, such as valproate or carbamazepine, whose adverse effects may have occurred before confirmation of pregnancy.
- **Valproate is the only psychotropic contraindicated in women of childbearing potential when used for psychiatric indications, although even here there can be very rare exceptions.**

The European Medicines Agency (EMA) subsequently issued a statement on March 23, 2018, endorsing new measures to avoid VPA exposure in pregnancy related to these concerns (www.ema.europa.eu/en/documents/press-release/new-measures-avoid-valproate-exposure-pregnancy-endorsed_en.pdf). Such warnings were deemed necessary as 2018 audit data indicated that VPA prescribing in BD women of reproductive age continued to fall short of best practice in developed countries such as the UK, particularly with regard to provision of information regarding the risks associated with VPA exposure during pregnancy, and the need for contraception to manage such risks [70]. While acknowledging the complexity of managing BD, a panel of experts convened in March 2019 and issued recommendations on use of VPA in women of childbearing age, including [30]:

1. Bipolar disorder childbearing women treated with VPA must be managed on a personalized basis according to the clinical situation.
2. It is mandatory to stop VPA during pregnancy. The duration of the discontinuation/switch process depends on different clinical variables.
3. Lithium, lamotrigine, quetiapine, olanzapine or aripiprazole are good options for switch in stable BD patients in planned/unplanned pregnancy.

The impact of these and earlier recommendations was slowly seen in declining rates of VPA use among BD women of childbearing age (Figure 0.5) [106]; moreover, statements in the literature suggesting that VPA is a reasonable option for this patient population have come under strong attack by reproductive psychiatric specialists. One group from Johns Hopkins University (Baltimore, Maryland) stated that "reproductive psychiatry has shifted away from considering valproate as a 'reasonable alternative' in women of reproductive age and toward viewing valproate as a last resort, not justifiable unless it is the only option for treating severe illness"

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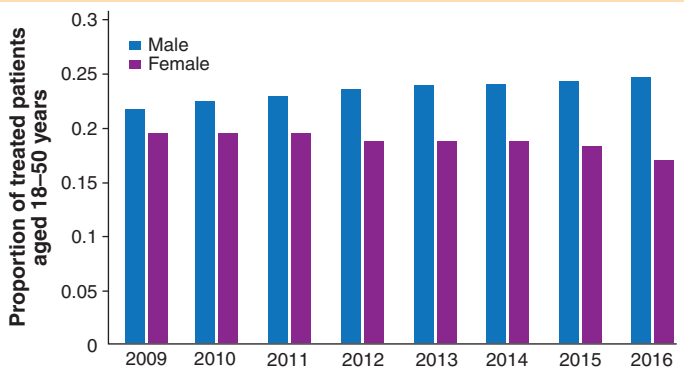
[31]. Should any clinician choose to use VPA in women of reproductive potential they were advised to document: (1) why there are no acceptable alternatives to VPA for a particular patient; (2) that the patient is using a highly reliable method of birth control; (3) that there has been a discussion of VPA's risks for both the patient and fetus, especially the high rates of fetal valproate syndrome; and (4) that the patient has been recommended to take 4 mg of folic acid daily to reduce the risks of congenital malformations in an unplanned pregnancy [31]. Starting in 2023, the UK banned VPA in women under age 55 unless two independent consultants certified there were no options and the patient was enrolled in a pregnancy prevention program.

Figure 0.5 Declining use of valproic acid (VPA) in Scotland for female bipolar disorder patients aged 18–50 years compared with males aged 18–50 years [106]



(Adapted from: L. M. Lyall, N. Penades and D. J. Smith [2019]. Changes in prescribing for bipolar disorder between 2009 and 2016: National-level data linkage study in Scotland. *Br J Psychiatry*, 215, 415–421.)

If the above concerns were not sufficiently sobering, the association between VPA exposure and PCOS became another important issue for managing bipolar women of childbearing age [71]. The primary features of PCOS include irregular menstrual cycles and hyperandrogenism (Figure 0.6), with insulin resistance also commonly seen as an independent finding, but one which is exacerbated by obesity [32]. The estimated PCOS prevalence worldwide was 6%–10% in 2016 [32], but a meta-analysis published that same year covering studies of VPA related reproductive and metabolic abnormalities in women with BD found that the risks of PCOS were almost 7-fold higher (OR 6.74), and the risk of hyperandrogenism 2-fold greater (OR 2.02) among VPA exposed patients [71].

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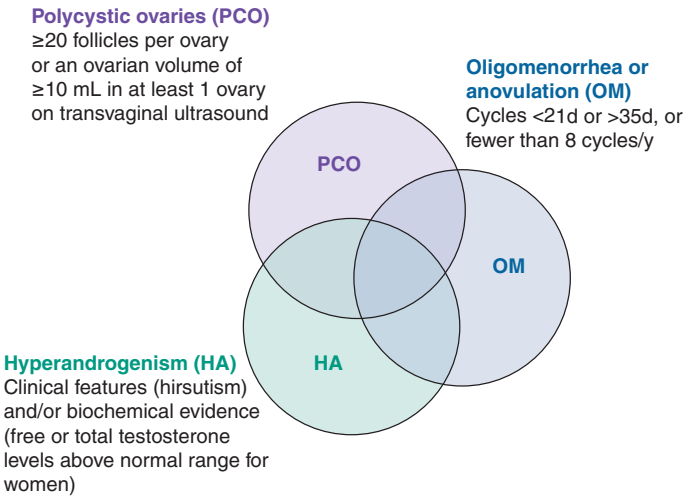
Figure 0.6 Diagnosis of polycystic ovary syndrome (PCOS) [32]



(Adapted from: H. G. Huddleston and A. Dokras [2022]. Diagnosis and treatment of polycystic ovary syndrome. *JAMA*, 327, 274–275.)

While hypothyroidism is not among the 10 leading causes of lithium discontinuation, clinicians may cite a prior history of hypothyroidism as a reason to eschew lithium therapy, and still, occasionally, stop lithium in the face of rising TSH [73]. While perhaps less compelling to prescribers than fears surrounding renal and reproductive risks, the unfortunate persistence of lithium discontinuation for what is putatively a manageable problem is a source of consternation to mood disorder experts. Professor Michael Gitlin of the University California, Los Angeles School of Medicine has been publishing on lithium for nearly 40 years [107], and in his 2016 review on management strategies for adverse effects flatly stated: "The most important clinical rule is that hypothyroidism never justifies lithium discontinuation" [72]. While stopping lithium is not necessary to manage hypothyroidism, the effect of lithium on thyroid function is often reversible, and use of lithium is not associated with development of antithyroid antibodies [74–76]. The prevalence of overt hypothyroidism is in the range of 8%–19%, and easily screened for employing high sensitivity TSH levels that are obtainable at most laboratories [72].

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Grade 1 subclinical hypothyroidism occurs when TSH levels are between the upper limit of the reference range (typically 4.5 or 5.0 mU/L) and 9.9 mU/L, and in the general population is rarely associated with somatic, cognitive or mood effects [108]. However, the threshold for thyroid supplementation may be different in BD patients as studies have shown that TSH levels that are otherwise in the upper limit of the normal range may be associated with more depressive relapse [77, 78]. A 2022 review noted that, since the use of thyroid extract was superseded by levothyroxine in the 1970s, "no major innovation has emerged for the treatment of hypothyroidism" [109]. The point is that most patients respond to L-thyroxine supplementation, although consultation with an endocrinologist may be helpful when cognitive and energy complaints persist that do not appear attributable to depressive mood symptoms [109].

D Conclusions

Dissemination of new knowledge is central to dispelling outdated ideas regarding lithium and allowing patients access to its unique constellation of therapeutic properties. Professor Malhi's 2021 editorial on lithium mythology opens with a quote from former US President John F. Kennedy that aptly describes why certain ideas take root and are difficult to eradicate [41]:

> The great enemy of truth is very often not the lie – deliberate, contrived and dishonest – but the myth – persistent, persuasive and unrealistic. Too often we hold fast to the cliches of our forebears. We subject all facts to a prefabricated set of interpretations. We enjoy the comfort of opinion without the discomfort of thought.
>
> (Commencement address at Yale University, June 11, 1962)

As research continues to expand our frontiers about lithium's efficacy and tolerability profile, it is incumbent upon all mental health practitioners to reinforce new insights with colleagues, patients and caregivers, thereby changing the culture surrounding the use of lithium. Lessons from initiatives designed to stimulate clozapine prescribing are instructive in this regard – education can change attitudes.

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