

Cambridge University Press & Assessment  
978-1-009-22505-2 — The Lithium Handbook: Stahl's Handbooks  
Jonathan M. Meyer , Stephen M. Stahl  
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# The Lithium Handbook

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Meyer and Stahl's *Lithium Handbook* accomplishes a rare feat - a book for clinicians that is comprehensive, scientifically sophisticated, data-based and clinically wise - all at once! It can be read as an overall review or used as a reference book to explore specific questions. The sections reviewing the renal effects of lithium are particularly detailed and thoughtful. The book covers the use of lithium in all clinical areas imaginable, from bipolar disorder to depression to dementia; provides concrete recommendations in pediatric populations, geriatric populations and pregnant women. Overall, a tour de force!

**Michael Gitlin, M.D.**

Distinguished Professor of Clinical Psychiatry; Director, Adult Division of Psychiatry;  
 Director, Mood Disorders Clinic, Geffen School of Medicine at UCLA

Dr. Meyer has provided a masterpiece for the field by synthesizing and translating the literature as it relates to Lithium for psychiatric and medical disorders that integrates basic and translational research with accessible clinical application; a must-have for clinicians, academics, researchers, and all persons interested in the best of care of persons living with bipolar disorder.

**Roger S. McIntyre, M.D., FRCPC**

Professor of Psychiatry and Pharmacology, University of Toronto, Canada

What a timely appearance of this excellent publication! This year, we observe the 60th anniversary of Geoffrey Hartigan's article, which first discovered the prophylactic activity of lithium in mood disorders. In the following years, lithium became a gold standard for preventing affective episodes in bipolar illness. Furthermore, many beneficial psychiatric properties of lithium have been established, such as the augmentation of antidepressant drugs and the great benefits of long-term treatment, including antisuicidal, neuroprotective, and antiviral effects. Yet in recent years, the art of lithium treatment has deteriorated, and the use of this valuable drug decreased, probably due to the introduction of other mood-stabilizing medications and a reluctance to employ lithium by psychiatrists, simply uninformed in this respect. And here comes Stahl's book, with its rectifying and educational message for psychiatrists. The book is bringing hope that, after its careful reading, more patients will become the beneficiaries of lithium therapy.

**Janusz Rybakowski**

Professor Emeritus and previous Head, Department of Adult Psychiatry, Poznan University of Medical Sciences; Corresponding member of the Polish Academy of Sciences

This is the most authoritative and comprehensive exposition of lithium to date. Lithium is the only medication in psychiatric practice that could be reasonably considered as disease-modifying, and so is worthy of a dedicated exposition of its chemistry, physiological impact, clinical efficacy and safety. Drs Meyer and Stahl deftly explain putative mechanisms of lithium action with both accessibility and nuance. This is a must have for any practitioner prescribing in the mental health space.

**Manpreet Kaur Singh, MD MS**

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## Stahl's Handbooks

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## Foreword

There is no single medication for mood disorder treatment such as lithium, which has an abundance of clinical and scientific evidence supporting its unique features but which is grossly underutilized [1]. The conclusions of recent reviews reiterate that lithium is the gold standard for long-term treatment of bipolar I disorder (BD-1) [2–4], that it is no less effective than other agents when used in rapid cycling or mixed episode BD patients [1], and that it possesses unparalleled effects on the risk for completed suicide [5, 6] and the incidence of dementia [7, 8]. Sadly, many clinicians are dissuaded from prescribing lithium due to overestimation of its risks and underestimation of its efficacy, misperceptions that are often reinforced by their peers [9]. Stoking these anxieties have been years of counterdetailing by manufacturers of anticonvulsant mood stabilizers and second generation antipsychotics (SGAs) that caused both a decline in lithium use and the loss of a shared cultural memory within the psychiatric profession about lithium's efficacy across the BD spectrum, and its generally favorable risk–benefit profile when prescribed and monitored using the latest recommendations [10, 11].

The net result is that patients suffer. As papers on naturalistic outcomes slowly appear in the literature, it has become apparent that in long-term real world usage BD-1 patients have comparatively high rates of treatment failure on SGA monotherapy compared with lithium monotherapy [12]. Certain anticonvulsants touted as potential mood stabilizers (e.g. gabapentin, oxcarbazepine, topiramate) have no maintenance data to support ongoing use in BD, and have failed to demonstrate efficacy in placebo-controlled acute mania trials [13, 14]; moreover, within-subject mirror image studies also note no anti-suicide effect during periods of valproate treatment [15]. Older BD patients suffer in a different manner when unnecessarily deprived of lithium therapy, specifically because long-term lithium use reduces dementia risk nearly 50% while non-lithium therapies exhibit no impact on dementia risk [7, 16]. Women of childbearing age also suffer greatly when decisions to routinely discontinue lithium are made based on outdated estimates of lithium related risks during pregnancy and lactation [17, 18].

Excellent papers and books have been devoted to educating clinicians about lithium [19, 20], yet there have been dramatic and rapid advances in many areas

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related to lithium in recent years including: revised estimates of lithium related risks during pregnancy and lactation; new data informing how one alters the frequency and type of laboratory monitoring based not on age but on estimated glomerular filtration rate (eGFR) and the presence of medical comorbidities. There are also newer understandings regarding the mechanisms and early signs of lithium's renal effects, the implementation of monitoring tools to track polyuria, and the use of amiloride and acetazolamide to manage this condition. Outside of renally focused topics, there are recent data indicating a general lack of effects on cardiac conduction, papers reporting nonsurgical options to manage hyperparathyroidism, and evidence based actions that minimize the risk of lithium toxicity from kinetically interacting medications.

In the end, the only way to combat the disconnect between lithium's efficacy and its underuse is through education. Knowledge is indeed power, and once clinicians develop a comfort level with anxiety-inducing topics, such as lithium's journey through the kidney, they are ideally situated to offer the advantages of lithium treatment without undue trepidation. The purpose of the present volume is to provide prescribers with a clinically oriented handbook that gives evidence based and rational approaches to situations commonly encountered during lithium treatment, and that dispels misguided notions regarding lithium's safety and efficacy. Meyer and Stahl have established the standard for such handbooks [21, 22], and have employed the same eye for detail in creating this comprehensive book that covers all aspects of lithium treatment, and, most importantly, leads the clinician through the reasoning process that underlies all of the ideas and recommendations. As both a researcher and a clinician, it is my hope that this handbook will serve as the cornerstone of any clinician's library on mood disorder treatment, and thereby help reverse the trend of lithium underprescribing. Lithium is not a medication to be feared but one which should be used frequently in the management of BD spectrum and other mood disorder patients. This handbook is one of many efforts to facilitate increased lithium use, and arrives at an opportune moment to support those clinicians who want to practice based on knowledge, not on fear, and thus offer their patients the most optimal care by confidently employing the gold standard for BD treatment: lithium.

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FOREWORD

- 20. **Malhi, G. S., Masson, M. and Bellivier, F., eds. (2017).** *The Science and Practice of Lithium Therapy*. Basle, Switzerland: Springer International Publishing AG.
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## Preface: How to Use This Handbook

Most clinicians are aware of lithium's unparalleled efficacy data in bipolar disorder (BD), and evidence pointing to its anti-suicide and neuroprotective properties [1, 2]; however, some may be less familiar with recent long-term observational studies indicating that lithium's renal impact is more modest than previously thought [3–6]. There are many hypotheses surrounding the disconnect between the data supporting lithium as the gold standard mood stabilizer and its low utilization, but the leading contender very much parallels the lack of widespread clozapine use for treatment resistant schizophrenia: clinician fear [7, 8]. Lithium shares a laboratory monitoring burden with anticonvulsant mood stabilizers, but it is those short-term adverse effects unique to lithium (e.g. hypothyroidism, hyperparathyroidism, polyuria) combined with concerns about lithium toxicity and lithium's long-term renal impact which dissuade clinicians from lithium prescribing despite knowledge that it is the superior mood stabilizing option for many BD spectrum patients. (Chapter 4 also documents that this may be compounded by patient fear of lithium derived from a variety of sources and rumors [9].)

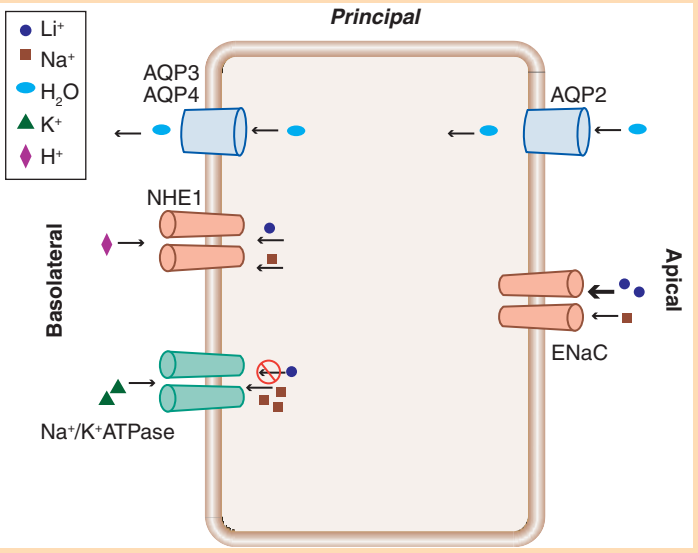
**With those thoughts in mind, the core element of this text is Chapter 2, devoted to a detailed explanation of lithium's renal clearance. To understand lithium is to understand how lithium moves through the kidney (Figure P1)** [6, 10]. The short- and long-term renal adverse effects, potential for drug interactions, monitoring scheme, and treatment approaches derive from the physiology of lithium's clearance, and an understanding of how lithium enters collecting duct principal cells via the epithelial sodium channel (ENaC) and interferes with urine concentrating ability. That polyuria represents the earliest sign of lithium's renal effects, and that it can be easily tracked with a simple test of urine osmolality and treated with the ENaC inhibitor amiloride is welcome news for many clinicians. This knowledge transforms the inchoate mass of kidney related fears into discrete actionable monitoring and treatment related tasks, with Chapter 2 also reinforcing that use of appropriate maintenance lithium levels, once daily dosing, and management of chronic kidney disease (CKD) risks (e.g. hypertension, diabetes mellitus [DM]) are all central to preserving renal health. The subsequent chapters on kinetic and drug interactions (Chapter 3), laboratory monitoring (Chapter 4), lithium

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toxicity (Chapter 5) and lithium's use in a variety of patient populations (e.g. older individuals, pregnant women) (Chapter 7) relate to this newfound appreciation of lithium's renal journey. Once this information is assimilated, it becomes clear how to use the estimated glomerular filtration rate (eGFR) to track renal function, why one adjusts the monitoring frequency based on eGFR and not age, why one should add the urine albumin-to-creatinine ratio to the laboratory monitoring scheme to track CKD pathology from non-lithium-related comorbidities (e.g. hypertension, DM), and how to employ urine osmolality and the 24h fluid intake record (FIR) to manage polyuria complaints.



**Figure P1** Detailed view of collecting duct principal cells illustrating how lithium enters via the epithelial sodium channel (ENaC) [11]



**Legend** AQP: aquaporin channel; ENaC: epithelial sodium channel; NHE1: sodium-hydrogen exchanger type 1 (Adapted from: J. P. Grünfeld and B. C. Rossier [2009]. Lithium nephrotoxicity revisited. *Nat Rev Nephrol*, 5, 270–276.)

Despite 70 years of literature comprising contributions from numerous scientists and clinical investigators around the world, the sources of renal related consternation among clinicians are readily apparent. Certain important questions

are often indirectly addressed in reviews or treatment guidelines, but represent significant clinical decision points. For example:

1. Is there a minimum eGFR to initiate lithium?
2. What is the lowest eGFR to continue lithium and what clinical factors play a role in this decision?
3. What laboratory measures other than eGFR can be used to track changes in renal function from systemic illnesses associated with CKD?
4. Can the prophylactic use of amiloride mitigate lithium's renal related risks by blocking lithium entry into collecting duct principal cells via ENaC?

Although there is a lack of consensus on these topics, by building a foundation of knowledge on lithium's renal profile and how to mitigate risks related to low eGFR, drug interactions and the presence of CKD comorbidities, one can approach the first three decisions with the necessary monitoring tools to manage more challenging situations. The latter question about prophylactic amiloride use is an important research topic. While prophylactic use is not endorsed by any study or guideline presently, amiloride is a strongly evidence based method for treating polyuria, and should be employed as early as possible when this complaint arises during lithium treatment [12].

The purpose of this handbook is to provide a level of detail about lithium prescribing that builds on modern understanding of dosing, lithium kinetics and safety data covering renal and other adverse effects. While the primary use of lithium is for BD spectrum patients, this is not a volume dedicated to covering the natural history and diagnostic dilemmas clinicians encounter with BD patients, nor a compendium of the wide-ranging and extensive preclinical and human research about lithium, or the history of its discovery for mood disorder treatment. Those topics are eloquently covered by other volumes that psychiatric professionals should include in their library [13–16], with the first two chapters of the 2016 book entitled *The Essential Guide to Lithium Treatment* by longstanding mood researchers Professor Michael Bauer (Technische Universität, Dresden, German) and Professor Michael Gitlin (Geffen School of Medicine, University of California, Los Angeles) providing a clear description of mood disorder classification, the natural history of bipolar disorder and implications for treatment [17]. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders is a thoughtful and beautifully illustrated document that covers the course and subtypes of BD, and how to utilize this information in managing the spectrum of BD patients with the evidence-based biological and non-biological

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therapies [18]. While the pressing clinical question at times can be “Does this patient have a BD spectrum disorder?”, the more angst-riddled consideration for many prescribers is not the diagnostic dilemma, but: “Is it safe to use lithium?” Reading Chapter 2 before digesting the later chapters of this handbook will help the reader master the latest information about lithium, and hopefully bolster the confidence of those who want to give their patients the benefits of lithium therapy but did not feel comfortable about their knowledge of its renal issues to use lithium to the fullest extent possible.



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