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Research paper

The use of lithium for the treatment of bipolar disorder: Recommendations from clinical practice guidelines

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ABSTRACT

Background: Lithium is an effective mood stabilizer that is used principally for the management of bipolar disorder (BD). Its administration is complex and often requires sophisticated management and assiduous monitoring. When considering the use of lithium therapy for bipolar disorder, clinicians are advised to refer to recommendations outlined in clinical practice guidelines (CPGs); but because of varying emphases placed by different international CPGs, recommendations addressing the practical use of lithium lack consistency.

Method: In order to inform clinicians of optimal lithium therapy for bipolar disorder, we compared and synthesized recommendations for the treatment of bipolar disorder made by recognized CPGs internationally. We conducted a search of the literature and extracted guidance across multiple clinical issues, including clinical indications, disorder subtypes, additional uses, special populations, practical aspects, and side effects.

Results: Collectively, CPGs consider lithium most robustly as a first-line intervention for maintenance treatment of bipolar disorder and strongly for the treatment of mania, with relatively modest support for the management of acute bipolar depression. Additionally, there is consensus across the CPGs that lithium tangibly reduces the risk of suicide. Generally, CPGs provide guidance on the many facets of initiating and maintaining patients on lithium therapy, but individually the CPGs varied in terms of depth and practical guidance they provide across these areas. However, consensus was established across many key areas of practice such as the ideal lithium plasma concentration for maintenance and monitoring (0.6–0.8 mmol/L), along with the need for regular monitoring of renal and endocrine function. However, with more complex aspects (e.g., atypical presentations) and in special populations (e.g., youth; pregnancy and post-partum; older adults), guidance varied considerably and clear consensus recommendations were more difficult to achieve. In younger adults desirable plasma lithium levels of 0.6–0.8 mmol/L can perhaps be achieved with comparatively lower doses and in the very elderly it may be prudent to target lower plasma levels in the first instance. These are important practical points for consideration that, along with many others offered throughout the article, should assist clinicians in dissecting the more complex aspects of management with greater precision.

Limitations: This review was limited to CPGs written in English. CPGs are themselves limited by reliance on evidence that often has little resemblance to real-world presentations. An important area that is not sufficiently addressed in the CPGs is clear guidance on the cessation of lithium therapy.

Conclusions: Further research is needed on many aspects of lithium therapy and this alongside existing knowledge needs to be used more consistently to inform CPGs, which should also incorporate empirical evidence and clinical experience. The recommendations in this paper provide a useful synthesis of guidance available currently.

1. Introduction

Lithium is a mood-stabilising agent used for the treatment of bipolar disorder (BD). The latter is a chronic and recurrent condition that confers substantial functional impairment and suicide risk over time. The specific therapeutic actions of lithium remain somewhat of a mystery, and the full extent of properties are yet to be fully exploited, even though its use in manic-depressive illness was first described by Cade (1949) over sixty years ago. Since then it has been used for prophylaxis in generations of patients with bipolar disorder, and has

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Table 1
Current international guidelines that recommend lithium in the treatment of bipolar disorder.

Guideline	Country	Abbreviation
American Psychiatric Association, Hirschfeld et al. (2002)	USA	APA
British Association for Psychopharmacology, Goodwin et al. (2016)	UK	BAP
Canadian Network for Mood and Anxiety Treatments, Yatham et al. (2013)	Canada	CANMAT
National Institute for Health and Care Excellence, NICE (2014)	UK	NICE
The International Society for Bipolar Disorders, Ng et al. (2009)	Worldwide	ISBD
The Japanese Society of Mood Disorders, Kanba et al. (2013)	Japan	JSMD
The Korean Medication Algorithm for Bipolar Disorder, Jeong et al. (2015)	Korea	KMAP-BP
The Maudsley Prescribing Guidelines in Psychiatry, Taylor, Paton and Kapur (2015)	UK	Maudsley
The Ministry of Health, Mok et al. (2011)	Singapore	MOH
Royal Australian and New Zealand College of Psychiatrists, Malhi et al. (2016a)	Australia	RANZCP
The South African Society of Psychiatrists, Emsley et al. (2013)	South Africa	SASOP
The Taiwanese Society of Biological Psychiatry and Neuro-psychopharmacology, Bai et al. (2013)	Taiwan	TSBPN
The World Federation of Societies of Biological Psychiatry, Grunze et al. (2013)	Worldwide	WFSBP

withstood displacement by a continual influx of newer/novel pharmacotherapeutic options.

Lithium's suitability for bipolar disorder stems essentially from its efficacy in maintaining periods of remission and this positions it prominently across all international clinical practice guidelines (CPGs) for the treatment of bipolar disorder. This is because though bipolar disorder requires prompt treatment of acute manic and depressive symptoms from time to time, it is effective long-term prophylactic management that ensures the prevention of recurrences and functional mood stability. Nevertheless lithium is also widely recommended by CPGs for the treatment of acute illness episodes – especially mania.

In practice, lithium therapy is adopted somewhat variably despite its efficacy. Part of the reason is that lithium therapy requires clinicians to negotiate additional psychological and physical assessments and institute assiduous monitoring and optimisation, and also consider additional practical aspects at all stages of therapy. Due to these additional considerations, clinicians often seek recommendations from CPGs; but variable reporting within international CPGs means that advice is not always consistent and clear. Therefore, consistency in guidance across practical issues for lithium therapy is imperative. Hence, this article aims to provide consistent recommendations for lithium therapy by comparing and synthesizing the advice contained within international CPGs so as to inform clinicians of optimal practice regarding the treatment of bipolar disorder.

2. Methods

A clinical overview of international CPGs for the treatment of bipolar disorder was conducted and recommendations specific to the use of lithium were extracted. CPGs published since 2000 by recognized international bodies were selected provided they 1) made evidence-based treatment recommendations but also 2) examined grey literature and were 3) available in English.

Lithium-specific recommendations in the treatment of bipolar disorder were extracted and collated in terms of clinical indication, disorder subtypes, additional considerations, special populations, practical aspects and side effects. Recent handbooks and guides, known to the authors, providing practice recommendations were also consulted in order to inform the recommendations made in this article.

To standardize the recommendations, where there was a consensus within CPG recommendations (over 50% agreement), a “green” rating was assigned. For guidance with poor consensus (less than 50% agreement), an “amber” rating was assigned.

3. Results

3.1. Current status in clinical practice guidelines

Twenty-three international treatment guidelines were identified, of which thirteen met inclusion criteria. The thirteen guidelines that were included in this review are listed in Table 1. Publication dates ranged from 2002 to 2016; with 11 of the 13 international guidelines providing updates within the last five years. Given that lithium is included as a treatment option for bipolar disorder within all the reviewed guidelines, its status as a key pharmacotherapeutic agent in the treatment of bipolar disorder is evident.

3.1.1. Mania

The use of lithium in the treatment of acute mania has received strong support across guidelines, and was endorsed as first-line monotherapy by the Canadian Network for Mood and Anxiety Treatments (CANMAT; Yatham et al., 2013), the International Society for Bipolar Disorders (ISBD; Ng et al., 2009), The Korean Medication Algorithm for Bipolar Disorder (KMAP-BP; Jeong et al., 2015), The Maudsley Prescribing Guidelines in Psychiatry (Maudsley; Taylor et al., 2015), The Ministry of Health (MOH; Mok et al., 2011), Royal Australian and New Zealand College of Psychiatrists (RANZCP; Malhi et al., 2015), and The South African Society of Psychiatrists (SASOP; Emsley et al., 2013) treatment guidelines. In addition, lithium was recommended as monotherapy for the treatment of *less acute* mania according to American Psychiatric Association (APA; Hirschfeld et al., 2002), British Association for Psychopharmacology (BAP; Goodwin et al., 2016), and The Japanese Society of Mood Disorders (JSMD; Kanba et al., 2013) guidelines.

Many recommendations noted the superior efficacy of short-term combination strategies such as the commencement of lithium alongside an antipsychotic as a first-line approach by APA, CANMAT, JSMD, KMAP-BP, SASOP, The Taiwanese Society of Biological Psychiatry and Neuro-psychopharmacology (TSBPN; Bai et al., 2013) and RANZCP. The latter also recommended short-term first-line combination therapy alongside a benzodiazepine (RANZCP), and TSBPN also recommended combination lithium and valproate therapy for acute mania.

Partial support for lithium in the treatment of acute mania treatment was given by The World Federation of Societies of Biological Psychiatry (WFSBP; Grunze et al., 2013),[1] whereas the National Institute for Health and Care Excellence (NICE, 2014) guidelines have recommended lithium as a second-line approach, to be administered adjunctive to antipsychotic treatment, following the trialling of antipsychotic monotherapy. BAP and TSBPN guidelines specified serum concentrations for acute mania as higher than the maintenance target range, at 0.8–1.0 mmol/L and 0.8–1.3 mmol/L respectively.

Lithium remains a first-line recommendation for acute mania treatment in bipolar disorder. While first-line monotherapy is supported by a strong

[1] Lithium received a Category A: full evidence for treatment in acute mania for efficacy in preventing treatment-emergent episodes, and separately manic episodes in non-enriched study samples; and Category B: limited positive evidence for efficacy in preventing treatment-emergent episodes of any polarity, and separately manic episodes in study samples enriched for acute response and/or acute tolerability of this medication (Grunze et al., 2013).