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Efficacy and Effectiveness of Lithium in the Long-Term Treatment of Bipolar Disorders: An Update 2018

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ABSTRACT

For more than 40 years, lithium has been the gold standard in the long-term treatment of bipolar disorders. In the course of the last 15 years, other drugs have been approved in this indication and are widely used in clinical practice at the expense of lithium. New research from the last few years, however, indicates that lithium is still the first-line treatment in this indication. Against this background and lithium's proven acute antimanic efficacy, we should perhaps be using lithium more regularly (in combination with an atypical antipsychotic, if necessary) right from the start for the acute treatment of a manic episode and, once remission has been achieved and euthymia maintained during continuation treatment, to regularly taper off the atypical antipsychotic, if possible, and continue with lithium as monotherapy for prophylactic treatment. This might lead to lithium being used more consistently with the scientific evidence in the long-term treatment of bipolar disorders. It remains uncertain, however, to predict who will respond to and tolerate lithium prophylactically, and more research is needed to deliver the best possible individualized care to our patients.

Introduction

For more than 40 years, lithium has been the gold standard in the long-term treatment of bipolar disorders [1]. In the course of the last 15 years, other drugs have been approved in this indication (e. g., valproic acid, lamotrigine, olanzapine, quetiapine, aripiprazole) and are widely used in clinical practice at the expense of lithium [2, 3].

Methods

We set out to selectively review the recent scientific evidence (Medline search on March 17, 2018, using the MESH terms "lithium" AND "bipolar disorders," considering publications from 2014 onwards) regarding the efficacy and effectiveness of lithium in the long-term treatment of bipolar disorders in comparison to placebo as well as other treatment options.

Results

To have a reliable estimate of how the available treatment options compare to placebo and between each other (comparative efficacy), 2 meta-analyses have been recently performed [4, 5], with 1 of them being a network analysis [5] to also allow for comparisons between treatments for which no direct comparison within 1 or more randomized controlled trial (RCT) is available. The outcome criteria chosen were as follows: prevention of any mood episode,

prevention of a manic episode (including hypomanic episode), prevention of a depressive episode, tolerability (dropout due to reasons other than a mood episode), and acceptability (completion of study: no mood episode and no dropout due to reasons other than a mood episode). Acceptability was selected for both its clinical relevance and its robustness against methodological bias [4, 6]. In both meta-analyses, lithium was superior to placebo in the prevention of overall mood episodes, manic episodes, acceptability, and (dependent on the type of analyses performed [4]) depressive episodes, while placebo was superior to lithium for tolerability [7–9]. Lithium and quetiapine were the only drugs that outperformed placebo in the prevention of overall mood episodes, depressive episodes, manic episodes, and acceptability [4, 5]. However, the confidence in the relative risk for any mood episode prevention compared to placebo was "low" for quetiapine (downgraded by 2 levels using the GRADE system due to study limitations and heterogeneity) compared to "moderate" for lithium (downgraded by 1 level due to study limitations) [5]. In the head-to-head comparison for prevention of mood episodes ("low evidence") in the network analysis, there was no significant difference between lithium and quetiapine. In spite of this, given that lithium is the only drug with evidence of efficacy in the prevention of both manic and depressive episodes in nonenriched study designs [10], the authors of both meta-analyses and accompanying commentaries [11, 12] concluded that lithium should remain the standard treatment in the long-term management of bipolar disorders [4, 5]. The evidence for lithium's unique antisuicidal properties as well as lithium's ability to control for subsyndromal symptoms further strengthen this view [13–17].

Nevertheless, some uncertainties remain [4, 12]. For example, an enrichment design that selectively recruits patients with a positive acute response to the investigational drug is obviously likely to favor that drug for acceptability (e. g., for lithium vs. quetiapine) [18, 19]. The impact on efficacy is believed to be similar [20], though the evidence is less conclusive [21, 22] and may even be dependent on the type of study/analysis performed (e. g., meta-analysis vs. survival analysis of an individual RCT [4]). In addition, the polarity of the index episode may differentially affect the power to prove efficacy for depressive and manic recurrences [23, 24]. Furthermore, much of the primary data included in the meta-analyses was obtained from phase III trials for new compounds in which patients were naive to the new drug to be tested while the majority of the study participants had previously been treated with lithium, the active comparator [25, 26]. As previous lifetime use of lithium has been found to be a risk factor for depressive recurrence in 1 study [27], it would be desirable to only include patients naive to both the new compound to be tested and lithium, if used as active comparator, to get an unbiased picture of relative efficacy. Furthermore, differentiating between relapse and recurrence [28] may prove difficult when using the time to a new episode as the outcome criterion. In addition, time to relapse/recurrence may not be the ideal outcome measure; often it is an improvement in the overall morbidity during the treatment that counts [29]. Finally, high target lithium levels may impact tolerability and thereby influence outcome by increasing study withdrawal [22].

In this context, a recently published single-blind randomized controlled parallel group design trial comparing the efficacy of lithium versus quetiapine in the maintenance phase following a first episode of mania is of particular interest—this is a trial in which many of the above problems were avoided [30]. In this real-world study, young patients aged 15–25 years with a severe first-episode mania, with psychotic features in the majority of cases (n = 286 assessed for eligibility), were openly treated with a combination of lithium (target lithium level 0.8–1.0 mmol/L) and quetiapine (dose was determined by the treating clinician). Those who could be stabilized on this combination were subsequently randomized (n = 61) to lithium (target lithium level 0.6–0.8 mmol/L) or quetiapine monotherapy (up to 800 mg/day, with the individual dose determined by the treating clinician) and followed up for 1 year. Depressive symptoms (MADRS, BDRS, CGI-BD), mania (YMRS, CGI-BD), psychotic symptoms (BPRS), general functioning (GAF, SOFAS), global illness severity (BPRS, CGI-BD), and quality of life (Quality of Life Scale) were measured criteria over 12 months. After randomization, discontinuation of either lithium or quetiapine occurred very gradually over weeks or months at the discretion of the treating clinicians. Lithium proved superior to quetiapine with regard to psychotic symptoms, global psychopathology, and general functioning at the 9 and 12 months' time points (mixed-model repeated measures analyses). In addition, lithium was superior to quetiapine regarding planned and post hoc comparisons (baseline to 12 months) on depression, psychotic symptoms, overall psychopathology, and general functioning. The mean lithium level in the lithium group was 0.6 mmol/L, and the mean quetiapine dose was 437.5 mg/day. On one hand, given the small number of patients randomized and the existing literature [18, 19], this was a surprising finding. However, crucially, it may point to the importance of prior treatment on comparative outcomes (no participants had received lithium, although a small number may have had atypicals for anxiety or depression before [Michael Berk, personal communication, January 15, 2018]) and combination treatment with both drugs during the acute manic episode, resulting in, among other issues, only a small proportion of the study sample having adverse events during the randomization period.

There are some limitations to this study, with the small number of individuals randomized limiting the robustness of the results. In addition, as the study was not powered for recurrence/relapse but for imaging [31], continuous outcomes were used instead of "time to a new episode" as the primary outcome, therefore making it difficult to compare the results of this study to the large approval-seeking trials included in the meta-analyses [4, 5]. However, the results are strikingly consistent with a recent population-based UK cohort study [32], a nationwide cohort study from Finland [33], and a systematic review of evidence from observational studies [34] that also found lithium to be superior to quetiapine and other atypical antipsychotics in the long-term treatment of bipolar disorders.

Discussion

During the last few years, new research indicates that lithium is still the gold standard in the long-term treatment of bipolar disorders and should be prescribed accordingly [2, 3, 35]. Given the results of Berk et al. [30] and lithium's proven acute antimanic efficacy [36], even in combination with quetiapine [37], we should perhaps

be using lithium more regularly (in combination with an atypical antipsychotic, if necessary) right from the start for the acute treatment of a manic episode and, once remission has been achieved and euthymia maintained during continuation treatment, to regularly taper off the atypical antipsychotic, if possible, and continue with lithium as monotherapy for prophylactic treatment [10]. This might lead to lithium being used more often in the evidence-based long-term treatment of bipolar disorders [10, 38]. It remains uncertain, however, to predict reliably who will respond to and tolerate lithium [39–43], and more research is needed to deliver best possible individualized care to our patients in the long-term treatment of bipolar disorders.

Conflict of Interest

Dr. Severus declares that he has received speaker honoraria from Servier and Roche in the past 3 years. In addition Dr. Severus is Co-Chair of the joint ISBD-IGSLI lithium task force.
Dr. Bauer has received grants from Deutsche Forschungsgemeinschaft (DFG), and from Bundesministerium für Bildung und Forschung (BMBF). Dr. Bauer has received personal fees on advisory board employments or speaker honoraria from Allergan, Aristo, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Janssen, Lilly, personal Lundbeck, neuraxpharm, Otsuka, Sandoz, and Servier, outside the submitted work within the last 3 years.
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