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Original article

A single-blind, randomised controlled trial on the effects of lithium and quetiapine monotherapy on the trajectory of cognitive functioning in first episode mania: A 12-month follow-up study

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ABSTRACT

Background: Cognitive deficits have been reported during the early stages of bipolar disorder; however, the role of medication on such deficits remains unclear. The aim of this study was to compare the effects of lithium and quetiapine monotherapy on cognitive performance in people following first episode mania.
Methods: The design was a single-blind, randomised controlled trial on a cohort of 61 participants following first episode mania. Participants received either lithium or quetiapine monotherapy as maintenance treatment over a 12-month follow-up period. The groups were compared on performance outcomes using an extensive cognitive assessment battery conducted at baseline, month 3 and month 12 follow-up time-points.
Results: There was a significant interaction between group and time in phonemic fluency at the 3-month and 12-month endpoints, reflecting greater improvements in performance in lithium-treated participants relative to quetiapine-treated participants. After controlling for multiple comparisons, there were no other significant interactions between group and time for other measures of cognition.
Conclusion: Although the effects of lithium and quetiapine treatment were similar for most cognitive domains, the findings imply that early initiation of lithium treatment may benefit the trajectory of cognition, specifically verbal fluency in young people with bipolar disorder. Given that cognition is a major symptomatic domain of bipolar disorder and has substantive effects on general functioning, the ability to influence the trajectory of cognitive change is of considerable clinical importance.

1. Introduction

Widespread cognitive impairments have been identified during inter-episode euthymia in people with bipolar disorder (BD), implying that cognitive dysfunction may be a trait marker of the illness [10]. A recent meta-analysis that included several mental states of BD as a first episode (i.e., depression, hypomania, mania,

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or a psychotic mood episode) found a range of cognitive deficits early in the course of the disorder [25]. However, a recent systematic review focusing on first episode mania (FEM) highlighted that findings for most cognitive domains were equivocal, with the exception of a relatively consistent deficit in working memory, and preserved verbal fluency and visual memory [13]. The inconsistency between study findings in the latter review may have been influenced by the effect of medication on cognition, which has seldom been reported. For example, only three of seven studies in the systematic review controlled for the effect of medication in their analyses of FEM [13], and medication was not included as a moderating factor in the previous meta-analysis [25].

According to recommended treatment guidelines, people experiencing a severe manic or mixed episode can be treated with a mood stabiliser and/or an antipsychotic [3]. Lithium carbonate (lithium) is considered the gold-standard mood stabiliser in the treatment of BD [1], and has been shown to reduce suicidal behaviour [11], and the risk of relapse by 40–61% [17]. Antipsychotics are often necessary for individuals with the most severe symptoms, especially when there are associated psychotic features. The atypical antipsychotic quetiapine fumurate (quetiapine) in particular has established efficacy in the treatment of acute mania [11], and bipolar depression, without exacerbating the risk of relapse [12].

Given the actions of these drugs in the brain, lithium and quetiapine may benefit cognition. There is evidence that lithium may have neuroprotective and neurotrophic effects, which could conceivably act upon the biological mechanisms and pathways involved in the neuroprogression of BD [7]. For example, lithium has been found to increase levels of brain-derived neurotrophic factor (BDNF) as well as the neuroprotective marker n-acetylaspartate (NAA) in people with BD [16,15], and individuals at risk for psychoses that include BD [6]. Furthermore, greater hippocampal and amygdala volumes have been found in lithium-treated patients with BD compared to patients not on lithium treatment and healthy controls [20].

Despite the generally positive clinical and neurobiological profile of lithium, its role in modifying the cognitive trajectory in people with BD is unclear. In fact, lithium has been associated with either no significant effects on cognition [28,30], or adverse effects in relation to verbal learning and memory, psychomotor speed, and creativity in healthy volunteers and people with BD [40]. However, there is evidence from non-randomised studies suggesting that lithium responders have preserved cognitive function [33,34]. Thus, the evidence regarding the cognitive effects of lithium remains uncertain.

It is also suggested that some atypical antipsychotics may be involved in neuroprotection. For example, quetiapine has been linked to increased BDNF [31], and decreased apoptosis through its role in the inhibition of tumour necrosis factors in microglial cells [8]. Whilst some literature suggests a positive effect of quetiapine on cognitive functioning in schizophrenia [32], research on the impact of quetiapine on cognition in BD is scarce. Of the limited research conducted, quetiapine does not appear to have an effect on cognition when added as an adjunctive to mood stabilising therapy [23], and may have deleterious effects on some cognitive domains relative to untreated patients with BD [39].

Protecting cognitive functioning early in the course of BD is a key treatment priority, as cognitive impairment is associated with poorer functional outcomes in people with BD [38]. To date there is a paucity of literature comparing the effect of treatment medication on cognitive functioning in BD, highlighting the need for further investigation, particularly in the early stages of the illness. This is the first study to conduct a randomised comparison of quetiapine and lithium on cognitive functioning following FEM. These agents were chosen due to their neuroprotective properties, and their efficacy in the treatment of both mania and bipolar depression, without increasing the risk of relapse [29]. As there is diagnostic instability during the early stages of psychiatric illnesses [35], and that a diagnosis of bipolar disorder may be delayed on average for 7.5 years [18], any presentation of FEM will be under investigation in this study. The aim of the study was to compare the effects of lithium and quetiapine monotherapy on cognitive functioning over the 12-month period following FEM. As the literature on the cognitive effects of lithium and quetiapine are inconclusive, it was hypothesised that lithium- and quetiapine-treated participants would perform similarly across cognitive domains, including: processing speed, attention, sustained attention, verbal learning and memory, visual learning and memory, working memory, verbal fluency and executive functions.

2. Method

2.1. Design

This was a longitudinal, single-blind, randomised controlled trial (RCT) conducted at Orygen, The National Centre of Excellence in Youth Mental Health. The primary purpose of this study was to compare the effects of quetiapine and lithium monotherapy on neuroanatomical changes in FEM over a 12-month follow-up period. This paper focuses on the secondary neuropsychological outcomes of the trial. This trial was registered with the Australian and New Zealand Clinical Trials Registry ACTRN12607000639426.

2.2. Sample and setting

Participants were recruited between 2006 and 2013 from outpatient clinics of the Orygen Youth Health – Clinical Program (OYH-CP) and Monash Health, located within the Western, North Western and South Eastern suburbs of Melbourne. To satisfy inclusion criteria for the RCT, participants were required to have:

- met Diagnostic and Statistical Manual of Mental Disorders – Fourth edition–Text Revision (DSM-IV-TR) criteria for bipolar I disorder, schizoaffective disorder - bipolar type, or a substance-induced mood disorder;
- scored a minimum of 20 on the Young Mania Rating Scale (YMRS) during their first acute manic episode;
- been aged 15 to 25 years at the time of recruitment;
- have symptomatically stabilised on a combination of lithium and quetiapine for at least one month prior to randomisation.

The use of other agents in addition to lithium and quetiapine that were considered necessary for the safety and well-being of the participants by their treating team, were permitted; though the use of potent cytochrome P450 inhibitors and inducers were prohibited during the trial. Optima serum lithium levels in the acute phase were between 0.8 and 1.0. Lower lithium levels (0.6–0.8) were targeted in the maintenance phase, with dose flexibility according to tolerability.

Participants were excluded if they had a clinically relevant systemic medical disorder, biochemical or haematological abnormalities or unstable diabetes mellitus, were pregnant or lactating, had a sensitivity or allergy to components of lithium or quetiapine, were non-fluent in English, had a history of epilepsy, were at immediate risk of self-harm or risk to others, or had an organic mental disease, including intellectual disability (IQ < 70).

2.3. Measures

2.3.1. Neuropsychological measures

Administration of the neuropsychological battery was standardised and consisted of psychometrically robust tests. The