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Snips from the journals

The role of lithium in the treatment of bipolar disorder

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An oldie but goodie: Lithium in the treatment of bipolar disorder through neuroprotective and neurotrophic mechanisms (1)

The exact mechanism whereby lithium exerts its therapeutic effects is still unclear. This review article focuses on the use of lithium in bipolar disorder, as well as highlighting the neuroprotective and the neurotrophic effects of lithium. A comprehensive literature search of peer-reviewed publications was conducted using PubMed, and relevant articles were identified using keywords.

When compared to other mood stabilizers and atypical antipsychotics, lithium has been shown to have a similar treatment efficacy to valproate, olanzapine, risperidone and haloperidol in the management of acute manic and mixed episodes. Lithium was also suggested to be more effective in patients with mania, compared to valproate and olanzapine. However, lithium has a reported slower onset of action compared to antipsychotics, i.e., 6-10 days for lithium, compared to 2-6 days for antipsychotics. Previous work suggests that lithium has less efficacy in the treatment of bipolar depression compared to quetiapine, and antidepressants such as venlafaxine. However, the antidepressant effect of lithium has been reported to have a delayed onset of 6-8 weeks. In clinical practice, a combination of lithium with other agents is considered to be effective in the treatment of bipolar depression, is more likely to be administered, and despite limited evidence, lithium remains important in the treatment of bipolar depression.

Earlier studies have reported that risks of completed and attempted suicide, and suicidal acts in patients with bipolar disorder and major depression is significantly lower during periods of treatment with lithium. A later study reports that lithium is more effective than placebo in reducing the number of suicides in patients with mood disorders, although no clear benefits were observed for lithium in preventing deliberate self-harm.

The specific therapeutic mechanisms of lithium in mood regulation has not been clarified, but it has been suggested that lithium causes a mood stabilizing effects by acting on cellular targets and exerting neuroprotective effects. Lithium is also considered to influence numerous neuroprotective pathways, by increasing phosphorylated GSK3 and inhibiting its action. The response to lithium can be predicted by GSK3b gene expression and phosphorylation, and lithium induced increases in phosphorylated GSK3 is reported to be correlated with symptom improvement.

There have been increased findings regarding the effect of lithium on circadian rhythms and the HPA axis, both of which are considered to be associated with the pathophysiology of bipolar disorder.

Numerous studies have reported the positive effects of lithium on gray matter volume and white matter integrity. Patients treated with lithium show significantly greater grey matter density in diffuse cortical regions, compared to healthy controls. Lithium has also been shown to attenuate the decrease in both grey and white matter in patients with bipolar disorder.

Prophylactic lithium treatment and cognitive performance in patients with a long history of bipolar illness: no simple answers in complex disease-treatment interplay (2).

Cognitive impairment in patients with bipolar disorder (BD) is seen not only during the symptomatic phases, but also in euthymia. There is evidence of differences in the brain structure between bipolar patients and healthy individuals, as well as changes over time, amongst patients. There seems to be a correlation between the duration of illness (DOI) as well as the number of illness episodes (especially depressive ones) and the degree of impairment. Data on the latter, however, are conflicting and even the causal direction is not yet clear.

Lithium constitutes the gold standard in long-term prophylactic treatment. Appropriate therapy that prevents new episodes improves the disease course and reduces the frequency of harmful outcomes, including substantial reduction of neurocognitive impairment. Interestingly, preclinical data suggest that lithium has an additional neuroprotective effect.

In this multi-center cross-sectional study from the International Group for the Study of Lithium-treated Patients (IGSLi), the authors compared three groups: bipolar patients without long-term lithium treatment,

bipolar patients with long-term lithium treatment, and healthy subjects. A total of 142 subjects were included, 31 in the non-lithium and 58 in the lithium group, as well as 53 healthy controls.

Patients with long-standing BD who had been treated, did not differ significantly from controls, with regards to overall cognitive functioning and verbal learning, recall, and recognition; this was seen regardless of whether lithium had been part of the treatment. Patients, however, demonstrated poorer early visual information processing than healthy controls, with the lithium-treated patients performing worse than those without.

The data suggest that bipolar patients with a long illness history and effective prophylactic treatment do not reveal significantly impaired general cognitive functioning or verbal learning and memory. However, they are worse at processing early visual information. Accompanying volumetric and spectroscopic data suggest cell loss in patients not treated with lithium that may be counter-balanced by long-term lithium treatment.

Lithium for prevention of mood episodes in bipolar disorder: A systematic review and meta-analysis (3)

Previous meta-analysis of randomized controlled trials comparing lithium with placebo have shown that lithium clearly prevents manic episodes in the long-term treatment of bipolar affective disorder. However, the effect appears to be equivocal with regards to depressive episodes. In this recent systematic review, the authors present the data on efficacy of lithium in comparison to alternative drug treatments.

Randomized controlled trials (RCTs) comparing lithium with placebo and lithium with an alternative treatment in bipolar disorder, where the stated intent of treatment was prevention of mood episodes, was considered for this review. Searches were conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), reference lists relevant papers and major textbooks of mood disorders were examined, and authors, experts in the field, and pharmaceutical companies were contacted for knowledge of suitable trials, published or unpublished.

Based on the results of the seven studies comparing lithium and placebo included in the review, lithium was more effective than placebo in preventing overall mood episodes, manic episodes, and, dependent on the type of analyses applied, depressive episodes.

Seven trials comparing lithium and anticonvulsants were included in the study. For the prevention of manic episodes, lithium was superior to anticonvulsants. However, there was no significant difference between the two groups of medication, regarding the prevention of overall mood episodes, depressive episodes, dropping-out due to reasons other than a mood episode, or study completion.

In summary, this review found that treatment with lithium decreases the probability of mood episodes compared to placebo for up to 2 years in patients with bipolar disorders. The treatment effect is present for prevention of both manic relapse/recurrence and depressive relapse/recurrence, with the statistical significance of the latter finding being dependent on the type of analysis performed.

With respect to the comparison with anticonvulsants, lithium was superior for prevention of manic episodes; however there was no significant difference regarding the overall number of mood episodes, depressive episodes, drop-out due to reasons other than a mood episode, or study completion.

Overall, given that no other drug has such ample and consistent evidence for its efficacy in the long-term treatment of bipolar disorder, lithium remains one of the most useful treatment options for this disorder.

Starting lithium prophylaxis early versus late in bipolar disorder (4)

Bipolar disorder (BD) is associated with a high risk of relapse, and with each relapse the risk of further relapse increases, leading to cognitive and functional deterioration of affected individuals. Various mechanisms have been suggested to explain this deterioration. There is wealth of evidence to suggest that lithium may facilitate neural plasticity, suggesting early treatment with lithium might be associated with a more favourable outcome in the prognosis of BD.

The aim of the study was to compare non-response rates among patients with bipolar disorder, comparing those who were prescribed lithium early, versus those who were prescribed this medication late. The authors hypothesis that starting lithium early is associated with an increased probability of good response to lithium.

Early versus late intervention with lithium was decided in two ways, as follows: Patients with a diagnosis of a single manic episode/bipolar disorder who started lithium following their first contact versus patients who started lithium following later contacts; and patients who started lithium following a diagnosis of a single manic episode versus those who started lithium following a diagnosis of bipolar disorder.

The study included 4714 patients with BD. According to the first definition of early versus late intervention with lithium, 715 patients (15.2%) started lithium following their first contact ever and 3999 patients (84.8%) started

lithium at later contacts. The probability of still being an excellent responder for patients starting lithium following first contact at 5 year follow up and at 10 year follow-up were 13.3% and 8.7% respectively. The corresponding probabilities for patients starting lithium at later contacts were 6.3% at 5 year follow-up and 4.0% at 10 year follow-up. In a Cox regression model, patients who were started on lithium following their first contact had a significantly decreased rate of non-response to lithium.

According to the second definition of early versus late intervention with lithium, 410 patients (8.7%) were included in early intervention with lithium and 4304 patients (91.3%) were included in the late intervention group. In the early intervention group, excellent responders at 5 year and 10 year follow up were 13.2% and 10.1% respectively. The corresponding probabilities for late intervention group were 6.7% at 5-year follow-up and 4.2% at 10-year follow-up. Thus, patients who were started on lithium following a diagnosis of a single manic/mixed episode had a significantly decreased rate of non-response to lithium compared with patients who started lithium following a diagnosis of bipolar disorder.

The study included a 16-year follow up of 4714 patients with bipolar disorder. Regardless of the definition used, early intervention with lithium showed significantly less rates of non-response to lithium compared to late intervention.

The authors identified several confounding factors; patients who were given lithium early might have had 'typical BD', who may have a better prognosis than 'atypical BD'. The early intervention group also might have had severe BD, prompting the clinicians to start lithium early.

In conclusion, even after considering these factors the results clearly suggest that early prophylactic intervention with lithium following first psychiatric hospital contact or following the first manic/mixed episode is associated with improved long-term response to lithium.

Effects of lithium on inflammation (5)

Since John Cade introduced lithium as an effective treatment for mania in1949, its efficacy as an anti-manic prophylactic in bipolar disorder (BD) and an anti-suicidal agent has been well established. The mode of action of lithium is not fully understood. With regards to pathophysiology of BD, there is ample evidence to suggest that patients with bipolar disorder have altered inflammatory markers in brain. The review summarized the effect of lithium on inflammatory markers.

Prostaglandins are very important mediators of tissue homeostasis. Synthesis of PGs involves several enzymes, and amongst them COX-2 is mostly associated with inflammatory and mitogenic conditions. Prostaglandins and the arachidonic pathway has been extensively linked to brain inflammation and the treatment of bipolar disorder. Long term treatment with lithium has shown to reduce COX 2 activity. Experiments have shown that lithium reduces the production of nitric oxide, a substance produced in glial cells in inflammatory conditions of the brain. Long term treatment with lithium has also been shown to inhibit TNF- α production in the brain, which is a proinflammatory cytokine.

Glial cells play a major role in maintaining brain homeostasis and function by secreting growth factors and inflammatory mediators, by supporting and protecting neurons, and by regulating neuroplasticity. In BD the function and cell expression of glial cells are altered. In vitro models using lithium have shown encouraging results with regards to glial cells.

Despite these findings, the authors overall conclusion is that due to different study designs/methods used, it is difficult to come to a definitive conclusion as to how lithium exerts its anti-inflammatory effects; and suggest that future studies should focus on anti-inflammatory action of all mood stabilizing medications.

Conflicts of interest

None declared

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