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Letter to Editor

# Lithium Chloride, Ketogenic Diet and Stem Cell Transplantation in Treatment of Bipolar Disorder

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## Dear Editor

Bipolar disorder (BPD), with a high risk of recurrence, is one of the most burdensome severe mental disorders presented by high levels of personal and social disabilities including cardiovascular diseases, diabetes mellitus, and neurological disorders, especially dementia and Parkinson's disease (1). Patients with BPD often need an integrated personalized pharmacological and non-pharmacological approach. Medications for BPD include antidepressants (duloxetine, sertraline, fluoxetine, desvenlafaxine, venlafaxine, and escitalopram), atypical antipsychotics (aripiprazole, clozapine, risperidone, ziprasidone, olanzapine, quetiapine, and paliperidone), or mood stabilizers (gabapentin lamotrigine, divalproex, topiramate, carbamazepine, and lithium). Lithium chloride (LiCl), as a mood stabilizer, has been used as a gold standard in the treatment of BPD (1). When non-pharmacological approach is targeted, it is necessary to know that individuals with BPD encounter a decreased intake in polyunsaturated fatty acids (PUFA), including docosahexaenoic acid (DHA), arachidonic acid (AA), eicosapentaenoic acid (EPA); decreased PUFA concentration of plasma EPA, and linoleic acid (LA) (2). So a ketogenic diet together with LiCl therapy can help treatment of BPD, because a ketogenic diet can impact glutamate metabolism and nerve cell metabolism by applying ketone bodies as energy sources and the ketogenic diet is a dietary therapy with high-fat, adequate-protein, and low-carbohydrate forcing the body to burn fats rather than carbohydrates (2).

Patients with BPD often need an integrated personalized pharmacological and non-pharmacological approach. Pharmacological approach for BPD include antidepressants (duloxetine, sertraline, fluoxetine, desvenlafaxine, venlafaxine, and escitalopram), atypical antipsychotics

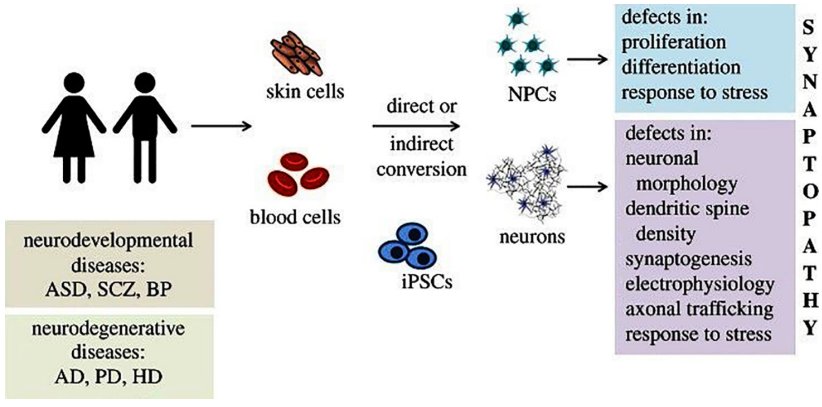


**Figure 1: Sc**heme of modeling neurological diseases using cell reprogramming technology. ASD: Autism spectrum disorders, SCZ: Schizophrenia, BP: Bipolar disorder, AD: Alzheimer's disease, PD: Parkinson's disease, HD: Huntington's disease, iPSCs: induced pluripotent stem cells, NPCs: neural progenitor cells (5).

(aripiprazole, clozapine, risperidone, ziprasidone, olanzapine, quetiapine, and paliperidone), or mood stabilizers (gabapentin lamotrigine, divalproex, topiramate, carbamazepine, and lithium). Lithium chloride (LiCl), as a mood stabilizer, has been used as a gold standard in the treatment of BPD (3). Implications of LiCl as neuroprotective activity in mood stabilizing and in the treatment of BPD have received approval from Food and Drug Administration (4). It is an essential trace element and the smallest alkali metal with an atomic weight of 6.9 that is found in vegetables, grains, and supplemented drinking water sources. Recent advances in regenerative medicine employing stem cell technology, such as induced pluripotent stem cells (iPSCs), have resulted in the use of new methods for psychiatric diseases including BPD. iPSCs have been shown to be easily derived from human somatic cells, with a high capacity for growth, and are differentiated into several cell types such as neurons, oligodendrocytes, astrocytes, microglia, etc. (Figure 1) (5). Accordingly, the study of BPD using iPSC-related technologies has been on the rise in recent years (4). In addition to iPSCs, mesenchymal stem cells (MSCs), with plasticity and high self-renewal capacity, have been used as a promising therapeutic strategy for psychiatric disorders, because they can promote neurogenesis and increase the expression of neurotrophic factors such as brain derived neurotrophic factor (BDNF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1) that enhance the survival and differentiation of neurons (6). MSCs were shown to have immunomodulatory properties, prevent apoptosis and decrease inflammatory responses. They can release membrane derived extracellular microvesicles that can deliver mRNA, miRNA, and functional proteins to target cells, thereby, improving cell survival and proliferation (7). Tfilin *et al.* demonstrated that intracerebroventricular use of MSCs could promote depressive-like behavior and increased hippocampal neurogenesis in an animal model of depression (8). Shwartz *et al.* have also found that the administration of MSCs could attenuate depressive-like behaviors (9) (Figure 2). To sum up, in addition to LiCl intake in treatment

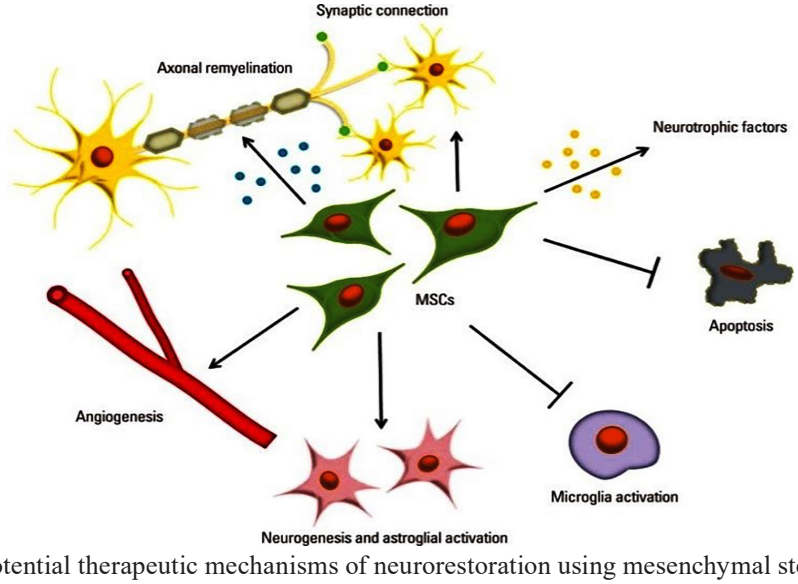


**Figure 2:** Potential therapeutic mechanisms of neurorestoration using mesenchymal stem cells (10).

of BPD as a gold standard (10), a ketogenic diet (2) and transplantation of stem cells (7) can be beneficial and promising therapeutic options to promote neurogenesis.

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## Authors' Contribution

Concept and search: AH, MH, and AM; Writing the draft: DM and SJM. All authors approved the final version of the manuscript.

## Conflict of Interest

None declared.

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