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HYPOTHESIS

Clozapine As Transformative Treatment In Bipolar Patients

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Abstract: Clozapine is an atypical antipsychotic used in treatment-resistant bipolar disorder. There is evidence for its anti-suicidal, anti-aggressive properties and efficacy in substance use comorbidities. Despite guidelines, the drug is used in 1.5% of bipolar patients only. Considering its effectiveness in treatment-resistant cases as well as its epigenetic effects it may become transformative treatment in bipolar disorder impacting the clinical course and psychosocial burden of the disease.

Keywords: clozapine, transformative treatment, bipolar disorder, treatment resistance

Introduction

Bipolar disorder is a chronic and severe mental disorder, characterized by irregular acute episodes of depressed, elevated, and mixed mood states often accompanied by comorbidities and suicidality-associated symptomatology.[1] Bipolar disorder is a disabling illness due to its early onset, severity and chronicity. Current trends in growth and aging are leading to an increase in the burden of bipolar disorder over time. It is important that resources be directed towards more effective treatments.[2]

The Hypothesis

Clozapine is effective in treatment resistant and severe cases of bipolar disorder. There is growing evidence that it has impact on course modifying processes which can change the course of disease leading to significant improvement, reducing the disease burden and become a transformative treatment in psychiatry.

Clozapine In Bipolar Disorder

Clozapine has been used in treatment-resistant bipolar disorder (TRBD) for almost 30 years.[3] It reduces symptom severity in manic and mixed episodes and decreases the need for use of concomitant psychotropic drugs.[3,4]

The treatment with clozapine in bipolar disorder is associated with the reduction in psychiatric admissions, number of psychotropic concomitant medications, and hospital contact for self-harm and overdose,[3] all suggesting that clozapine exhibits strong mood-stabilizing properties. Clozapine has been shown to be useful in treatment of TRBD, decreasing the number of hospitalizations and improving symptomatic and functional improvement.[5] It has anti-manic and possibly an antidepressant effect described in one case report.[6–8] There is also evidence for use of clozapine in rapid-cycling bipolar disorder.[9,10]

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According to the contemporary guidelines, clozapine is worth considering as a treatment option in cases of resistant bipolar I disorder, including rapid cycling.[11] It is recommended for treatment-resistant BD,[12] as the third-line treatment for acute mania and treatment-resistant mania and also as an additional agent for the maintenance treatment of BD I.[13] Despite all that clozapine lacks official regulatory approval for use in any phase of bipolar disorder which is probably due to the very small number of studies on clozapine in bipolar disorder.[14]

Antisuicidal And Antiaggressive Effects Of Clozapine

Clozapine has been shown to have specific anti-suicidal properties in patients with schizophrenia.[15–17] Some authors suggest that clozapine may exhibit anti-suicidal properties that extend beyond schizophrenia into bipolar disorder.[18,19] This effect was described in one case report and our recent case series.[20,21] Suicide accounts for 15% to 20% of deaths among bipolar disorder patients.[22,23] For today there are no approved pharmacological interventions for suicidality in bipolar disorder.

Another interesting effect of clozapine is the reduction of violence and aggression in patients with schizophrenia and other psychiatric disorders.[24] This also applies to patients with comorbid substance use disorder. There is evidence that clozapine reduces aggressive behavior in patients with bipolar disorder with psychotic symptoms[25] as well as substance abuse. It may limit the use of cannabis,[26] alcohol,[27] both combined[28] and poly-substance abuse including cocaine[29] in comparison to FGA (first-generation antipsychotics) and other SGA (second-generation antipsychotics). Some authors suggest that clozapine should be evaluated for reducing abuse of alcohol and other substances in bipolar disorder patients.[30] It may be hypothesized that clozapine impacts the disease itself along with the specific symptom domains like suicidality, aggression and substance use.

The Unique Properties Of Clozapine

Clozapine has complex binding receptor profile.[31] The mechanisms employed in the anti-suicidal effect of clozapine probably involve the simultaneous modulation of dopamine, norepinephrine, and serotonin,[18] regulation of the endocrine system (pregnenolone, cortisol)[32] and intracellular systems-dependent modulation of N-methyl-D-aspartate (NMDA) receptor expression, brain-derived neurotrophic factor up-regulation, and regulation of the arachidonic acid cascade.[33,34] Animal studies suggest that clozapine has an impact on glutamatergic transmission. Fukuyama et al found that clozapine prevents thalamocortical hyperglutamatergic transmission via activation of mPFC presynaptic III-mGluR and by the activation of astroglial l-glutamate release. The authors suggest that these actions may contribute to the unique clinical profile of clozapine.[35]

Clozapine is a known 5-HT_{2A} antagonist, but it can also act as an agonist at this receptor. These mixed properties of the drug can be explained through "biased agonism." Clozapine is an antagonist on 5-HT_{2A} serotonin receptor in relation to the G protein activation but it is an agonist on the same receptor if AKT (protein kinase B) activation is measured. In addition, clozapine, more than other second-generation antipsychotics, activates ERK1/2 (extracellular signal-regulated kinases), which may explain, in part, the therapeutic superiority of this drug on many aspects of mental disorders. Actually, activation of ERK1/2 pathway that is involved in transcriptional regulation might contribute in improving synaptic plasticity, connectivity and neurogenesis. It might also be associated in enhancing the expression of neurotrophic factors, such as BDNF.[36,37] Clozapine is the powerful drug activating ERK1/2 and part of this effect is due to the novel mechanism of 5-HT_{2A} receptor activation. This evidence might be relevant to explain, at least in part, the superiority of clozapine among the SGAs.[38]

Epigenetic Effects Of Clozapine – Animal Studies

The unique properties of clozapine seem to be related to its epigenetic effects. There is growing evidence published during last few years, suggesting an important role of clozapine in epigenetic mechanisms.

Guidotti et al[39] used prenatally stressed mice (PRS) model to study potential efficacy of antipsychotic drugs acting on altered epigenetic mechanisms, reducing hypermethylation which causes reduced gene expression and behavioral endophenotypes. PRS mice model turned out to be insensitive to haloperidol, but sensitive to drugs like clozapine and valproate[40,41] that modulate chromatin function. Another study using this model also found that clozapine, but not haloperidol nor risperidone corrected behavioral endophenotype. In a study conducted with use of the prenatally stressed mice brains clozapine, unlike

haloperidol and risperidone limited methylation in reelin, BDNF and glutamic acid decarboxylase 67 promoter regions and normalized mice behavior in the form of their social interaction.[42]

Ayoama et al[43] suggest that the antipsychotic effect of clozapine develops, at least in part, through histone modification and this process is mediated by activation of the dopamine D1 receptor in the prefrontal cortex of PCP (Phencyclidine)-treated mice.

Epigenetic Effects Of Clozapine – Human Studies

Human studies like the one by Kinoshita et al[44] investigated gene methylation in peripheral leukocytes from patients with treatment-resistant schizophrenia following 12 months clozapine treatment. Genes with clozapine-induced changes in DNA methylation were associated with cell substrate adhesion and cell matrix adhesion. The authors also observed DNA methylation changes in the CREBBP (cAMP response element-binding protein) gene, acting as a transcription factor. These changes were significantly correlated with the clinical improvements. Kouter et al[45] in their recent study conducted on human suicide victims present significant differences in brain DNA methylation suggesting that this process may be involved in the pathophysiology of suicide.

Nakazawa et al,[46] using induced pluripotent stem (iPS) cell-based technology, investigated a pair of monozygotic twins with treatment-resistant schizophrenia. One twin responded well to clozapine treatment and the other twin did not. Although these iPS cells similarly differentiated into neurons, several genes encoding homophilic cell adhesion molecules showed differential expression patterns between these two patients. Long-term treatment with antipsychotics is often necessary for the improvement of schizophrenic symptoms[47,48] and these improvements probably involve epigenetic changes. The evidence is mounting however, the molecular and epigenetic mechanisms underlying the therapeutic efficacy of clozapine in bipolar disorder have not yet been fully elucidated.

Neuroplasticity – Animal Studies

Clozapine is hypothesized to promote synaptic remodeling or synaptic reorganization in the hippocampus.[49] In the clozapine vs haloperidol comparison study on neuroplasticity, the authors found that clozapine increases dendritic spine formation, postsynaptic spinophilin expression and up-regulates the number of post-synaptic density (PSD) sites, as indicators of synaptogenesis and synaptic maturation.[49] The study describing the effects of clozapine administration on levels of SNAP-25 and synaptophysin in the hippocampus in rodents revealed changes in these proteins levels that may be related to hippocampal synaptic remodeling. Interestingly, haloperidol did not induce similar synaptic changes suggests that the exceptional effect of clozapine could be related to changes in hippocampal plasticity.[50] There is also evidence for clozapine-mediated significant changes in cell composition in white matter of primates, which could lead to a partial rewiring of prefrontal circuitry.[51] According to Maletic and Raison,[52] morphological changes like gray matter volume reduction and its hypofunction present in bipolar patients provide strong support for the hypothetical impairment of neuroplasticity in bipolar disorder. The authors also suggest the significant role of BDNF in regulating neuroplastic processes in this disorder.

Concept Of Transformative Treatment

Clozapine is used in complicated cases of BP I disorder including treatment-resistant mania and depression, mixed episodes, rapid cycling, cases with suicidality, aggression and substance use disorders. It seems that the effect of clozapine is more pronounced in severe forms of this neuropsychiatric disorder. The great burden of this disease with highest risk of suicide among psychiatric disorders, common psychiatric and somatic comorbidities, treatment resistance and devastating psychosocial consequences calls for more effective treatments.[53] Clozapine with its unique pharmacology and epigenetic and neuroplastic effects can become a transformative treatment similarly to antiviral transformative treatments for AIDS or HCV, cell therapies in oncology or gene therapies[54] or ketamine in the treatment of depression. It can significantly reduce the great burden of BP I and may modify the course of the disease.

Consequences

Clozapine may be associated with long-term prognosis, course and anti-suicidal effect in BP I patients impacting the course of the disease particularly in treatment-resistant, rapid cycling, suicidal subpopulations and patients with comorbidities. Transformation of the global burden of the disease may exemplify for the observed clinical improvement.

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Disclosure

The authors report no conflicts of interest in this work.

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