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A potential treatment of schizophrenia through mitigating the neurotransmitter imbalance: ADX71149

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Abstract. Schizophrenia has been characterized with positive symptoms and negative symptoms. The cardinal symptoms of schizophrenia were described to be the presence of delusions and hallucination as well as sensation associated with psychosis, the general loss of touch with reality. There are several known causes or general trends that lead to schizophrenia. Schizophrenia has heavy ties with genetic factors. Its causes are linked to genetic factors, with candidate genes like COMT and DISC1 being studied for their impact on symptom severity. Substance-induced psychosis, particularly from cannabis, increases the risk of transitioning to schizophrenia spectrum disorder by 30-40% within three years. New discovery displays that the positive and negative symptoms associated with schizophrenia have been correlated with an imbalance in interactive dopamine-glutamate circuitry between the striatum and the prefrontal cortex. Newly developed metabotropic glutamate receptor modulators such as ADX71149, regulate glutamate and dopamine release, showing better results for both positive and negative symptoms compared to older dopamine antagonist medications. ADX71149 holds several advantages over the previously developed antipsychotic medication as previous medication mainly revolves around the mechanism of being a dopamine antagonist. Previous psychotic medication, although effective against positive symptoms of schizophrenia, can potentially worsen the severity of negative symptoms, ADX71149, being able to regulate both pathways and subsequently mitigate this issue. ADX71149 may also enhance combination therapies with cognitive behavioral therapy and other patient-professional interactions.

Keywords: Schizophrenia, Glutamate, Dopamine.

1. Introduction

Schizophrenia has been traditionally associated with both positive symptoms, including hallucination and delusion, and negative symptoms, such as disorganized speech, grossly disorganized motor action, and other absent functions such as anhedonia and avolition [1]. In terms of diagnosis, hallucination and delusion has been identified as the main attributes towards schizophrenia according to Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM5) [2]. Patients being diagnosed with schizophrenia generally have difficulty separating reality from fiction, due to the influence of hallucination of psychosis, which result in over 10 percent of patients committing suicide after enduring the symptoms for over a year [3]. In terms of the causes of schizophrenia, generally combined factors of nature and nurture contributes greatly for the contraction of schizophrenia. Although not fully penetrant, the cause of schizophrenia is widely known to be heavily influenced by genetics [4]. Studies

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of family aggregation further support the influence of genetics as described that Monozygous twin have a 50 percent of risk of being diagnosed if the other twin is contracted, while dizygous twin has a 13 to 15 percent risk; genetic has heavy influence, however does not display complete penetrant as described in classical mendelian genetics [5]. In terms of environmental influence, cannabidiol usage in underage teens of been linked to greater risk of contracting schizophrenia as the individual ages. The usage of cannabidiol in underage teens results in cortex thinning and shrinkage of the hippocampus, two conditions that have been linked to the development of schizophrenia. In current studies, a discovery in terms of the interaction between dopamine-glutamate circuitry within the striatum and the prefrontal cortex has marked a new direction for the medication treatment for schizophrenia. Neurotransmitter imbalance within the frontal lobe and striatal has been linked to negative and positive symptoms of schizophrenia respectfully. New waves of medication, specifically the metabotropic glutamate receptor modulators, have been shown to be tremendous results in terms of the regulation of neurotransmitter imbalance between the striatal and the prefrontal lobe.

ADX71149, a specific metabotropic glutamate receptor modulator for the glutamate-dopamine pathway, holds several advantages over previously discovered antipsychotic medication through the regulation of both pathways of schizophrenia. Previous medication such as chlorpromazine, specifically blocking the receptor in the binding for dopamine, has seen effective results in treating positive symptoms like hallucination, however, the pathway to treat positive symptoms further worsens the symptoms of the negative symptoms. ADX71149 corrected this mistake by highlighting two different pathways for the two types of symptoms and has shown results that yielded for the degradation of both types of symptoms. In addition, ADX71149 has shown it has the ability to combine with therapeutic intervention, similar to previous antipsychotic medication. ADX71149, through working through both pathways, is predicted to yield greater results when combined with therapies such as cognitive behavior therapy due to its further yield in suppressing negative symptoms and drastically decreasing the patient's willingness to carry out the treatment. The purpose of this article is to explore the potential advantages of ADX71149 with its mechanism and compare the new generation of schizophrenia treatment with previous generation of antipsychotic medication.

2. Schizophrenia Brain Circuit and potential targets of drug discovery

Schizophrenia symptoms are divided into two categories, each linked to different brain circuit deficiencies. Positive symptoms (delusions, hallucinations, disorganized thinking/behavior) are linked to overactive D2 receptors and dopamine imbalance [6]. The discovery of the relation between dopamine and schizophrenia stems from the study of antipsychotic medication, through stimulating a increase activation, release and retention of dopamine within the neuron junction, similar effects positive symptoms of schizophrenia, including Euphoria, irrational behavior and hallucination at high dosage. Clinical trials showed that antipsychotic drugs, which block D2 receptors, reduce these symptoms by decreasing dopamine activity in the striatal region of the basal ganglia [7]. The mesolimbic system functioning through the basal ganglia are involved in the neurological pathway that results in reward processing, motivation, and emotional response. Overexpression of D2 receptors have been found, through the testing of antipsychotic medication, to be directly associated with positive symptoms of schizophrenia through the dysregulation of dopamine expression [8].

In contrast to positive symptoms of schizophrenia, negative symptoms, such as anhedonia, avolition, and alogia, have been found through clinical trials to be correlated with under expression of dopamine within the prefrontal cortex [9]. The prefrontal cortex functions through operating through higher cognitive executive functions, attention and emotional regulation. Neuroimaging as shown hypoactivity and irregular structure within the prefrontal cortex in patients with schizophrenia. In addition, dysfunction in the under expression of dopamine within the dorsolateral prefrontal cortex, which results in deficiency in executive function, social cognition, emotion expression, and motivation, key aspects of negative symptoms of schizophrenia [10]. In terms of the connection between negative and positive symptoms, the opposite running brain circuit has resulted in the treatment of one symptom yielding negligible or the opposite effect in the other symptoms. Through trials testing for the effect of

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antipsychotic medication on positive symptoms of schizophrenia, the decrease in the expression of dopamine has exacerbated the negative symptoms [11].

In spite of the positive and negative symptoms of schizophrenia being regulated in opposite directions by the same neurotransmitter and being located in different areas of the brain, there are potential targets for medication intervention that may induce changes in dopamine level to different areas of the brain. In clinical experiments, the consumption of phencyclidine(PCP) can initiate symptoms that resemble the entire spectrum of schizophrenia rather than the symptoms that occur when increasing or decreasing dopamine levels alone, in addition, despite being known for increasing stimulation of dopamine within the mesolimbic system, chronic exposure to PCP causes a decrease in dopamine release into the prefrontal cortex: the positive and negative brain circuits may be complementary rather than oppositional [12]. The observation of the effect of PCP may lead to a potential target for antipsychotic medication through targeting the interactive dopamine-glutamate circuitry between striatal and prefrontal cortex. Repeated PCP exposure within the body lowers levels of glutamate throughout the brain in which directly results in the lower prefrontal dopamine expression, as seen in cognitive deficits associated with negative symptoms, and higher striatal dopamine, which is linked to psychosis in positive symptoms [13]. A potential medication that increases levels of glutamate levels which alleviate neurotransmitter imbalance in both dopamine brain circuit, may result in better result in improving in both symptoms and prevent the aggravation of the counter process.

3. ADX71149 effect on the body and advantage over previous medication

ADX71149 is an antipsychotic medication that acts as a selective positive allosteric modulator of the metabotropic glutamate receptor (mGluR2). mGluR2 receptors are located primarily in the presynaptic neurons and control the release of glutamate, inhibition of mGluR2 receptors leads to dysregulation of glutamate release, which correlates with the effect of PCP and result in both positive and negative symptoms of schizophrenia. ADX71149 specifically regulates the level of glutamate by enhancing the function of mGluR2 receptors and controls the glutamate level to an optum level. In relation to dopamine release in both pathways for the two types of symptoms, by regulating the level of glutamate release, the ADX71149 acts specifically based on the interactive dopamine-glutamate circuitry. ADX71149 has been found to normalize the glutamate transmission through interaction specifically acting on the linkage of dopamine and glutamate levels in the striatal and prefrontal cortex. By modulating glutamate transmission, ADX71149 has been found to mediate both the negative and positive symptoms of schizophrenia by restoring a higher prefrontal dopamine level and a lower striatal dopamine through the release of glutamate that normalizes the levels dopamine, through the dopamine-glutamate circuitry [14]. Through clinical research, ADX71149 has been applied through animal models of schizophrenia and have demonstrated the attenuation of negative behavior and cognitive deficits associated with both positive and negative symptoms [15]. Thought data for the application of ADX 71149 on human subjects are scarce, ADX71149 has shown results in terms of regulating the release of glutamate and alleviating both negative and positive symptoms of schizophrenia.

ADX71149 offers several advantages over previous antipsychotic medication, specifically in terms of the mechanism targets for a balanced treatment for both symptom pathways and significant reduced side effects. Traditional antipsychotic medication mechanisms generally target D2 receptors in which inhibits the binding of dopamine to the receptors on the basal ganglia striatal. This mechanism pathway, while useful for preventing psychotic symptoms within bipolar and severe depression, falls short when treating schizophrenia due to the dual pathway of positive and negative symptoms that result in opposing levels of dopamine levels and expression. ADX71149 medication offers a regulation within the glutamate pathway, which when the level of glutamate is regulated to an optum level, targets and regulates both pathways of dopamine expression. Subsequently ADX71149 medication reduces the side effects of intaking the medication compared to previous generations of antipsychotic medication. Conventional antipsychotic medication inhibits the release of dopamine throughout the brain, this results in decrease in dopamine binding to the already lower levels of dopamine expression within the prefrontal cortex. This results in the worsening of negative symptoms as greater induction of social withdrawal

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and anhedonia is observed within patients under traditional antipsychotic treatments [16]. In contrast, by regulating both pathways of dopamine expression, ADX71149 avoids the regression of mental function present in traditional treatments, which only treats one circuit of the brain.

4. Limitation of ADX71149

While ADX71149 showed promising mechanisms and results in simultaneously treating the positive and negative symptoms, ADX71149 has displayed shortcomings that mostly concern the contemporary invention and ramification of the medication. Although the effect of ADX71149 on the mGluR2 is measurable, the exact impact on the brain circuit is unknown. While the regulation control over the expression of glutamate release by the mGluR2 and ADX71149 has resulted in desirable results, without proper experiment on the impact of the regulation on the brain circuit and subsequently the symptoms of schizophrenia, the medication cannot account for individual difference and may vary in the specific nature of glutamatergic dysregulation [17]. In addition, due to the novelty in the development of ADX71149, the long term efficacy of the drug is still under investigation. The prolonged effect of taking ADX71149 draws significant uncertainties regarding the drug's long-term effect on the body, specifically, if the prolonged activation of mGluR2 receptors may have side effects on the release of any neurotransmitter [18]. Lastly, the complexity of the glutamate and glutamatergic system may result in unforeseen effects of the novel medication on other aspects of brain circuitry regulated through glutamate. While ADX71149 has shown great promises in terms regulating the glutamatergic neurological pathway regarding the symptoms of schizophrenia, the regulation of glutamate level by the drug may also affect the other neurological pathways such as cortico-limbic pathway which regulates emotion and memory formation or nigrostriatal pathway which regulates motor control. The novelty of ADX71149 medication yields numerous concerns in terms of its long-term impact on the body as well as uncertainties regarding the drug's interaction with other brain regions and neural pathways.

5. Combination of ADX71149 and cognitive behavioral therapy

The emergence of ADX71149 medication as a potentially superseding option compared to traditional drug treatment has offered additional, potentially superior, options for multidimensional approach when combining ADX71149 medication with therapeutic treatment, such as cognitive behavioral therapy. Psychological therapy, specifically cognitive behavior therapy, helps individuals identify and change dysfunctional thought patterns and behavior. Through an algorithmic interaction session between the patient and the therapist, the cognitive behavior therapy focuses on managing symptoms, improving coping strategies and enhancing daily functions. In terms of specific applications of ADX71149 to cognitive behavior therapy, ADX71149 targets glutamate imbalance, which offers an gradual decrease in terms of the severity of both aspect of symptoms in schizophrenia, this sets the stage for cognitive behavior therapy in addressing and modifying the cognitive and behavior symptoms, delusion and hallucination, that the patients are sensing and provide a coping or managing strategy for the patient to follow. This dual approach provided by combination therapy initiated additional options for patients and supplied a more comprehensive symptom relief in both positive and negative symptoms for the patient. Through clinical trials, it has been found that combination therapies, where medication and therapeutic sessions are working in tandem, significantly increases the success rate of alleviating the symptoms. In addition, combination therapy has been found to reduce withdrawal symptoms from the medications and improve coping strategies provided by therapeutic sessions [19]. In terms of reducing the withdrawal symptoms, Cognitive behavior therapy can help patients understand the principles of intaking medications and act of a source of information to assist the patient in managing psychological triggers and cravings associated with withdrawal. In terms of clinical experiment, through the usage of cognitive restructuring to challenge negative thought patterns associated with intaking medication, the combination approach substantially increased the effectiveness of medication, a success rate to over 70% when comparing patient's response to the medication with or without therapeutic intervention, and decreased the patient's reliance and craving for the medication after the treatment sessions [20]. In addition, the combination therapy between improve implemented strategies from cognitive behavior

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therapy. A major setback for cognitive behavior therapy is the incentive for patients to follow through the coping and managing strategies prescribed by the clinician, most patients forbid the follow through with therapist's techniques due to the substantial amounts of adversities that comes with the neurotransmitter imbalance, and patients often revert to unprescribed medication without supervision. ADX71149 reduces the symptoms of both positive and negative symptoms. Through using ADX71149 in amalgamation with therapy, patients may find greater ease in applying and benefitting from coping techniques from cognitive behavior therapy.

The usage of ADX71149 medication over previous generations of antipsychotic medications offers several advantages, including a more targeted approach with fewer side effects and potential enhancement of cognitive function through the regulation of glutamate levels. ADX71149 are substantially more specific compared to the broad targeting antipsychotics in terms of specifically targeting only the mGluR2 receptors, this result in ADX71149 to be more regulated in terms of its mechanism and results in less potential side effects through seldomly influencing other major pathways of the brain. In addition, ADX71149's regulation on the glutamate levels could potentially improve cognitive functions such as memory and executive function through improving glutamate signaling and reducing dysregulation. The increase in excitatory signaling playing in unity with cognitive behavior therapy as the enhancement in cognitive and physical functions make it easier for patients to engage in cognitive restructuring and other therapeutic activities.20 The usage of ADX71149 supersedes the traditional medications as older antipsychotic, through regulating dopamine levels, does not directly address cognitive deficits. As proposed prior, this may limit the function of cognitive behavior therapy as it relies on the cognitive function and engagement of the patient. In addition, through the regulation of both positive and negative symptoms of schizophrenia, ADX71149 addresses both concerning symptoms of schizophrenia; this results in greater cognitive functioning and attention in Cognitive behavior therapy for patients with both positive and negative symptoms. In contrast, older generation antipsychotic medication serves to decrease the level of dopamine expression throughout the brain. Rather than improving the cognitive function of the patient, the decrease in the level of dopamine decreases the cognitive functioning as negative symptoms are worsened under the exposure from antipsychotic medications, which in terms makes patients less likely to follow through with cognitive behavior therapy [21].

6. Conclusion

Schizophrenia is a multifaceted mental illness characterized by severe symptoms like delusions and hallucinations, often leading to a disconnection from reality. Genetic factors, particularly certain genes like COMT and DISC1, and substance use, notably cannabis, significantly influence the risk of developing the disorder. Recent research has shed light on the role of imbalances in brain chemistry and structural brain changes in schizophrenia. A promising advancement in treatment is the development of ADX71149, a new drug that regulates both dopamine and glutamate, offering potential benefits over traditional treatments. This could not only help manage symptoms more effectively but also work well in combination with therapies like cognitive behavioral therapy, offering new hope for a more comprehensive approach to treating schizophrenia.

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