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Advances and Limitations on the Current Treatment for Schizophrenia and its Future Prospect

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Abstract. Schizophrenia is a challenging mental disorder marked by recurring psychosis. This article provides an in-depth overview of the current status of research and treatment techniques for schizophrenia. The introductory part gives a thorough explanation of the illness, including all of its many phases and symptoms. The review analyzes the genes involved in cell signaling and neurotransmission, including NRG1, DTNBP1, DISC1, and RGS4, which are important contributors to schizophrenia susceptibility. The article discusses the limitations and challenges associated with existing treatment modalities, including antipsychotic drugs (both typical and atypical), transcranial magnetic stimulation, deep brain stimulation, virtual reality, electroconvulsive therapy, and the ketogenic diet. These approaches have demonstrated efficacy in managing different aspects of schizophrenia symptoms, but they also come with limitations such as side effects, individual variability in response, and ethical concerns. To overcome these limitations, the study offers CRISPR gene editing as a viable future therapeutic option. To improve the efficacy and safety of schizophrenia therapies, the conclusion underlines the need for tailored treatment planning, continuous research, and creative approaches. The changing landscape of schizophrenia research and therapy gives promise for better results and quality of life for people living with the condition.

Keywords: Schizophrenia; Therapies; AAPDs; Typical APDs; Gene.

1. Introduction

Schizophrenia is a psychiatric issue characterized by recurrent psychosis, affecting about 0.32% of the population. Schizophrenia was translated from Greek roots, skhizein and phrēn, which refers to a person's perception and thinking being distorted or fractured. Generally, the symptoms of schizophrenia can be classified into 3 main types: positive, negative, and cognitive. Patients with positive symptoms usually suffer hallucinations, delusions, and disorganized behaviors. A patient may firmly hold a false belief, see or hear things that are not there, or be unable to maintain normal conversations or behave reasonably. Patients with negative symptoms would lose interest or motivation, and will have reduced emotional responses. Cognitive symptoms refer to a loss in ability to remember or understand information. The exact causes of this mental illness have not yet been found, yet researchers suggested many factors that could play a role in making someone more susceptible to developing Schizophrenia. Genetically, the disease showed heritability. Several genes were identified to be related to the susceptibility of Schizophrenia. Meanwhile, psychological and environmental factors such as prenatal nutrition, stress, drug use, or traumatic experiences can also contribute to the development of this disease [1].

Treatment utilizes both medications and therapy to relieve psychosis, but they also come with side effects. Many of the medicines focus on lowering Dopamine and Serotonin levels by blocking D2 and serotonergic receptors. These medicines are called antipsychotic drugs (APDs) and can be categorized into typical and atypical depending on the system they act on. While typical APDs like Chlorpromazine, Haloperidol, and Fluphenazine act on the dopaminergic system; atypical APDs, including Clozapine, Risperidone, and Olanzapine, affects the Serotonin system . Transcranial magnetic stimulation and deep brain stimulation are another two ways of treating schizophrenia, each

using a magnetic field above the skull and electrodes implanted in the deep brain. VR serves as a treatment to relieve hallucinations if used properly. Electroconvulsive Therapy (ECT) applies electroshock on brains to relieve severe symptoms. Ketogenic Diet treatment tackles the disease by changing metabolism. However, side effects in these treatments continue to limit its application on patients. Less production of Dopamine relieves hallucinations on the cost of pleasure and emotional response, while safety remains an issue in both TMS and DBS. Brain damages and memory losses have been noted in ECT, high individuality and insufficient practice limits the use of VR, and Ketogenic Diet has been questioned of its effectiveness.

Although Schizophrenia remains difficult to treat, more studies were conducted on gene variations and pathways. This review focuses on explaining the functionality of current treatment options, covering from APDs to TMS and DBS, while exploring their benefits and limitations. In addition, the review evaluates the potential for gene modification with CRISPR to be an option for treatment. Using one of the genes that have been previously identified to be associated with Schizophrenia, an analysis was done to understand the possible pathway for the mutant gene to affect the disease. The review of current treatments and the analysis on CRISPR will help evaluate and identify the pathways for future development of schizophrenia treatment.

2. Genes associated to schizophrenia

A lot work has been done on the genetic causes of schizophrenia, leading to the identification of important susceptibility genes including Neuregulin 1 (NRG1), Dysbindin (DTNBP1), Disrupted in Schizophrenia 1 (DISC1), and Regulator of G-Protein Signaling 4 (RGS4).

Schizophrenia has been linked to abnormal neurotransmission and NRG1, which is located on chromosome 8p21. The pathogenesis of the condition is thought to include regulating synaptic plasticity, glutamatergic neurotransmission, and dopaminergic signaling, all of which have been the subject of recent investigations [2]. Dysbindin, a protein involved in synaptic function, is encoded by the gene DTNBP1, which is found on chromosome 6p22.3. Recent studies have illuminated the probable pathways through which DTNBP1 affects schizophrenia. According to studies, genetic variants in DTNBP1 may have a role in the cognitive abnormalities seen in people with schizophrenia, highlighting the disorder's importance to cognitive impairment [3]. The significance of DISC1 in neurodevelopment and synaptic dysfunction was first recognized by its link with a translocation co-segregating with schizophrenia in a Scottish family. Recent research has dug into the molecular mechanisms through which DISC1 affects synaptic plasticity and neurodevelopmental processes, shedding light on how it participates in the risk of schizophrenia [3]. RGS4 controls G-protein signaling and modifies dopaminergic neurotransmission; it is found on chromosome 1q23. The genetic variants in RGS4 and their effects on dopamine-related pathways in schizophrenia have been studied in recent years. These investigations highlight the importance of RGS4 in dopaminergic dysregulation, a key feature of the pathogenesis of the illness [4]. The fact that schizophrenia is a polygenic condition impacted by a variety of hereditary and environmental variables must be understood. Further investigation into the particular processes by which these genes play a role in schizophrenia will deepen our understanding of the condition and may eventually result in brand-new treatment approaches.

3. Current treatments of schizophrenia

3.1. Atypical antipsychotic drugs (AAPDs)

The FDA has approved the atypical antipsychotic clozapine to treat schizophrenia with treatment resistance. However, due to a number of side effects that make compliance challenging for many patients, it is not the optimal medication to use. It does, however, offer certain benefits, including fewer relapses and a decreased risk of suicide and tardive dyskinesia. Studies have shown that clozapine helps persons with schizophrenia who are resistant to treatment by reducing their suicidal

tendencies. This exercise looks at the clozapine mechanism of action, the profile of adverse events, toxicity, dosing, pharmacodynamics, and monitoring in relation to the interprofessional team members who should be monitoring the medication [5]. Risperidone functions by inhibiting receptors for serotonin like 5HT2A more so than D2, which it does to a lesser extent. It's important to highlight that risperidone has no inhibitory properties, which may be helpful for some patient populations, including elderly people with dementia [6]. Olanzapine is a second-generation atypical antipsychotic drug that mainly impacts dopamine and serotonin receptors, acting as an antagonist at the mesolimbic pathway's dopamine D2 receptors and preventing any possible impact of dopamine on postsynaptic receptors. Olanzapine has a weak binding capacity and easily detaches from the receptor, permitting regular dopamine neurotransmission. In patients, positive symptoms such as hallucinations, delusions, and difficulties with speech, cognition, and behavior, are lessened by effects on D2 receptors. Olanzapine functions similarly to a serotonin 5HT2A receptor antagonist in the frontal brain. Because of how olanzapine affects serotonin, it lessens undesirable symptoms such anhedonia, a depressed mood, aphasia, weak will, and inattentiveness [7].

3.2. Typical APDs

Chlorpromazine is suspected to produce antipsychotic effects via inhibiting D2 receptors in the mesolimbic post synaptic pathway, while its specific mode of action is unknown. However, the nigrostriatal pathway's suppression of D2 receptors is what causes its extrapyramidal adverse effects. Haloperidol inhibits the brain's dopamine D2 receptors, acting as an antipsychotic. The drug works best when 72% of dopamine receptors are inhibited. Haloperidol has no selectivity for D2 receptors. Furthermore, it possesses histaminergic, cholinergic, and noradrenergic inhibiting properties. Several negative medication responses have been linked to blocking these receptors. Fluphenazine predominantly affects mesolimbic and nigrostriatal neuronal circuits by inhibiting postsynaptic dopamine-2 receptors. The mesolimbic pathway's postsynaptic receptors for dopamine-2 are blocked to treat positive symptoms of schizophrenia like hallucinations, delusions, and slurred speech. It is well known to have antagonistic actions on alpha-1 adrenergic receptors, which accounts for its adverse effects on the heart and orthostatic tachycardia. Fluphenazine is a strong antagonist of both muscarinic-1 and histamine-1 receptors, just like the majority of other antipsychotics [8].

3.3. Transcranial Magnetic Stimulation

TMS is a stimulation that temporarily deactivate specific areas of the brain’s cortex using a magnetic field. The magnetic field is generated by a coil positioned above the skull. Despite some concerns about safety, magnitude of effects, and mechanisms of neurological disturbances, TMS is often used in brain imaging studies to establish causality. Clinically, TMS achieves therapeutic purposes through the use of different frequencies, having high frequencies (>1Hz) being mainly excitatory and low frequencies (≤1Hz) being more inhibitory. TMS has the physical characteristics of being either painful or non-traumatic. Some research suggests that TMS can be used as a therapy to treat schizophrenia [9].

3.4. Deep Brain Stimulus (DBS)

A DBS device consists of electrodes implanted near specific deep brain structures, which are then connected by subcutaneous wires to a pulse generator implanted in the chest wall. Then, the stimuli parameters are forwarded by the computer to the pulse generator with appropriate amplitude, frequency and pulse width. Study has shown that targeting the NAcc with DBS can significantly improve symptoms of delusions and hallucinations [5].

3.5. Virtual Reality (VR)

VR (Virtual Reality) is an immersive experience that simulates a completely fictional or real-world environment through computer technology and perception equipment. In virtual reality, users experience environments and situations that appear to be there, and the feel of virtual worlds is often

more realistic and immersive than traditional computer interfaces. Some studies have shown that VR can alleviate positive symptoms of schizophrenia [10].

3.6. Electroconvulsive Therapy (ECT)

Electroconvulsive Therapy is a treatment method used in the field of psychiatry to induce generalized convulsions by applying electrical stimulation, and is used to treat some serious mental illnesses, especially depression and in some cases schizophrenia. ECT is often used in combination with drugs to intensify treatment. It can be used to treat catatonia and treat resistance [5].

3.7. Ketogenic Diet

The ketogenic diet tries to switch the body's energy metabolic route from primarily depending on carbohydrate metabolism to relying on fat metabolism. It follows a high-fat, moderate protein, and low-carbohydrate diet. The diet is frequently used to manage weight, stabilize energy levels, and improve cognitive function, in addition to treating epilepsy and a variety of other disorders. According to research, neurometabolic illnesses including schizophrenia, bipolar disorder, depression, and binge eating disorder can all be treated with the ketogenic diet. According to the current theory, a ketogenic diet promotes GABA by changing the ratio of GABA to glutamate by decreasing catabolism and boosting GABA synthesis as well as glutamate metabolism, which may assist to make up for the schizophrenia-related brain blockage [11].

4. Limitations and future development

4.1. AAPDs

AAPDS have a tendency to cause metabolic side effects, including as considerable weight gain, an increased chance of developing diabetes, and dyslipidemia, which can have detrimental long-term repercussions on patients' health. The recurrence of extrapyramidal side effects, such as akathisia and dystonia, while at a lower incidence than with conventional antipsychotic medications, is another negative. A few AAPDs are also related to cardiovascular problems, such as the QTc prolongation, which raises the possibility of arrhythmias and sudden cardiac death [8]. These restrictions highlight the necessity of meticulous monitoring and individualized treatment choices while utilizing AAPDs in people with mental health issues.

4.2. Typical APDs

Traditional antipsychotic medications (APDs) have a variety of disadvantages. Their potential for extrapyramidal side effects, which can be upsetting or adversely impair a patient's quality of daily life, is a serious drawback. Examples include severe dystonia, akathisia, parkinsonism, and tardive dyskinesia. Additionally, there is a risk of over-blocking dopamine D2 receptors in the mesolimbic pathway because standard APDs primarily target these receptors, which might have negative side effects and impair cognitive performance [8]. The disadvantages of standard APDs emphasize the need for careful consideration when using them to mental therapy, especially when evaluating their potential benefits against these severe side effects.

4.3. TMS

Transcranial magnetic stimulation (TMS) has showed promise in treating a number of mental disorders, including schizophrenia. TMS has limitations, though. The variation in treatment response across individuals is one of the major problems. While TMS may significantly relieve some patients' symptoms, it may have only a minimal impact on others. The TMS effects' hazy persistence is another downside. To keep their symptoms under control, some patients might need continuous and recurrent TMS treatments. Patients may feel burdened by this, which may affect how useful TMS is as a long-term therapeutic choice [9].

4.4. DBS

Surgical risk is a significant limitation. Risks associated with the implantation process include infection, bleeding, and adverse reactions to anesthesia. Furthermore, DBS may only be appropriate for a specific patient population with severe drug-resistant schizophrenia. Its use is limited to patients who have not responded well to other therapies. The long-term effects of DBS on schizophrenia remain unclear. More research is needed [5].

4.5. VR

Individual differences in responses to VR experiences can be a challenge. Some patients may find VR environments discomforting or even exacerbating their symptoms, which might hinder its widespread applicability. Accessibility issues are also a concern. Implementing VR therapy requires specialized equipment and technology, which might limit its use in clinical settings. The cost and technical requirements might pose barriers to its adoption. Furthermore, while VR offers an immersive and controlled environment for exposure therapy or cognitive interventions, its long-term therapeutic effects still need more rigorous research and validation.

4.6. ECT

Memory problems are a common problem with ECT. Patients receiving ECT may experience short-term memory problems during and after treatment. This can be distressing for the individual and affect their overall cognitive function. ECT is associated with temporary cognitive impairment, affecting attention, focus, and processing speed. These cognitive effects can affect patients' daily activities and health [5]. Social ethics remains a major challenge. Despite its effectiveness, ECT is often stigmatized in society, causing patients and their families to hesitate to consider it as a treatment option.

4.7. Ketogenic Diet

First of all, due to the food limitations included with ketogenic diets, which can be tough to stick to over longer periods of time and may even result in cessation, the long-term sustainability of these diets for people with schizophrenia may be problematic. Second, the effectiveness and security of ketogenic diets as a first-line therapy for schizophrenia lack empirical support. Larger, more thorough clinical practices are required to determine the efficacy of ketogenic diets in treating schizophrenia [11], even if a few small studies have suggested possible advantages in terms of symptom reduction. Furthermore, the effects of ketogenic diets on metabolic health and any possible long-term effects for people with schizophrenia are yet unknown, underscoring the necessity for additional study and clinical assessment in this field.

5. CRISPR

CRISPR can be used to modify specific genes, potentially helping correct mutations or abnormal genes associated with schizophrenia. This may provide individualized treatment options for specific patients [12]. A single guide RNA was found on the NRG1 gene, which could help modify specific mutation sites, develop specific treatments, and carry them out for individual cases. Although the mutation site is not located within the coding sequence, indicating that the mutation pathway couldn’t be hypothesized through protein domains, further research on gene modification by CRISPR may provide a clearer understanding. Based on the data, human NRG1 and mouse NRG1 have high similarity in their NRG1 sequences, making mouse a very suitable animal to perform experiments on. NRG1_399_0 was identified to be a suitable gRNA for CRISPR.

6. Conclusion

In conclusion, treating schizophrenia is a difficult task that requires a diverse strategy. Although improvements in therapy have greatly enhanced the lives of many people with schizophrenia, each kind of treatment has its own restrictions and possible downsides. The importance of creating tailored treatment plans cannot be stressed since it is crucial to properly take into account each patient's particular needs, preferences, and risk factors. The discipline is set for new breakthroughs despite the obstacles faced by side effects, inconsistent treatment responses, surgical risks, and societal stigma. With continuous research and innovative strategies providing fresh opportunities for improving treatment results, the management of schizophrenia has a bright future. Notably, gene editing methods like CRISPR provide an attractive chance to address the genetic variables underlying schizophrenia susceptibility, maybe resulting in customized and focused treatments. As these technologies develop, thorough validation and ethical issues will be crucial. Collaboration between scientists, doctors, patients, and their families will be essential in developing the next wave of schizophrenia therapies as we move forward. We may strive to enhance the lives of those impacted by this difficult condition and open the door for a more promising future in schizophrenia management by addressing the shortcomings of present techniques and adopting alternative strategies.

Author contribution

All the authors contributed equally and their names were listed in alphabetical order.

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