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CURRENT AND EMERGING TREATMENTS FOR SCHIZOPHRENIA: A CONCISE REVIEW

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ABSTRACT

Schizophrenia is a complicated psychiatric illness characterized by the presence of positive (e.g. hallucinations and delusions), negative (e.g. emotional withdrawal and avolition), and cognitive symptoms (e.g. memory and attention deficits). While there have been developments in first- and second-generation antipsychotic medications, there remain large treatment gaps, notably for negative symptoms and cognitive impairment, as well as restrictions associated with antipsychotic medications such as metabolic syndrome and tardive dyskinesia. This article will review the current and emerging treatments for schizophrenia, including pharmacological, non-pharmacological and emerging class of agents. First-generation antipsychotics can provide effective acute management of psychosis but can present neurological risk, while second-generation antipsychotics reduce risk but present metabolic risk. Pharmacological assistances and advancements in pharmacogenetics may lead to more personalized and precise treatment. Non-pharmacological treatment approaches have the potential to address cognitive and functional impairments experienced in schizophrenia, with neuroimaging studies confirming neuroplasticity in the frontal lobes. Emerging therapies, suggest a transformative therapeutic approach to schizophrenia. It is likely that despite advances in addressing the balance of efficacy, tolerability, and accessibility, there will always be a need for work in this area. The path forward is to consider hybrid models - comprising biological and technology-enhanced innovations - with safety considerations for psychedelics, as well as scalable digital

technologies. This review highlights the importance of multi-dimensional, personalized approaches to improve outcomes for individuals diagnosed with schizophrenia.

KEYWORDS: schizophrenia, antipsychotics, cognitive behavioral therapy, glutamate modulators, psychedelic-assisted therapy.

INTRODUCTION

Schizophrenia is a heterogenic psychiatric disorder that alters a patient's psychological function primarily in perception, emotion, and cognition. The disorder is typically organized into three categories of symptoms: positive symptoms (including hallucination and delusions), negative symptoms (emotional withdrawal, and reduced motivation), and cognitive impairment (impaired ability to recall and concentrate).[1] The World Health Organization estimates that the global prevalence of schizophrenia is approximately 1 in 300 people, typical onset being early adulthood, with all symptoms likely associated with significant lifelong disability.[2] The root causes of schizophrenia consist of a wide range, especially implicating the brain's neurotransmitter imbalance i.e. dopamine (responsible for positive and negative symptoms) and glutamate (responsible for cognitive impairments).[3] Treatment has shifted substantially in the past few decades and while there have been positive gains, the limitations are significant. The current anti-psychotic drugs do not alleviate negative symptoms adequately, and cognitive dysfunctions poorly.[4] In addition to overcoming negative symptoms and cognitive dysfunctions, anti-psychotic medications deliver unwanted side effects, which include obesity, movement disorders, and in some resistance to treatment.[5] The gaps in schizophrenia care have redirected an increasing focus towards ensuring better treatment approaches. Some scientists have already begun developing new medications that target the glutamate containing systems, carefully controlled psychedelic-assisted therapies with reduced psychotomimetic risks, and incorporating technological support along with traditional treatment.[6] Emphasizing their mechanisms, effectiveness and adaptability in addressing the current gaps in schizophrenia care the review seeks to consider the existing and emerging treatment responses systematically considering their adaptations, mechanisms, effectiveness and potential to address the gaps in schizophrenia care.

PHARMACOLOGICAL TREATMENTS

1. First generation (Typical) antipsychotics

The emergence of chlorpromazine in 1952 revolutionized the field of psychiatric treatment and served as the first pharmacological evidence that psychosis could be managed chemically.[7] These early antipsychotic medications such as haloperidol and fluphenazine function primarily by antagonizing the dopamine D2 receptor in the brain. A prospective study published in 2023 assessed the effectiveness of intramuscular (IM) haloperidol in treating acute undifferentiated agitation in emergency departments. The study found that IM haloperidol 5 mg effectively sedated many patients within 20 minutes demonstrating effectiveness quickly.[8] Unfortunately, the benefits have a significant neurological cost. In addition to extrapyramidal symptoms and the well-known muscle stiffness, long-term consequences arise from the use of first-generation antipsychotics. There is now a growing body of evidence to suggest that after 5 years of continuous treatment with a first-generation antipsychotic, about one-quarter of patients develop tardive dyskinesia, a likely irreversible condition characterized by involuntary facial movement.[9] Perhaps even more significant is the cognitive cost at times. While medication may reduce hallucinations with dopamine blockade in individuals, cognitive executive functioning may decay as individuals describe their thought process feeling "thick and slow, like moving through molasses." The duality of an improvement in symptoms and cognition leads clinicians to face difficult treatment decisions, especially in chronic situations.

2. Second-Generation (Atypical) Antipsychotics

Since the introduction of the second-generation antipsychotic medications in the 1990s there has been hope that we could begin a new era of treatments with less risk of neurological side effects. Medications such as olanzapine and risperidone work by targeting both serotonin and dopamine receptors to provide similar management of symptoms while avoiding some movement disorders. For treatment-resistant individuals clozapine has resulted in amazing outcomes.[10] Nonetheless these medications brought about a separate array of difficulties. The metabolic impacts can be severe. Furthermore, the incidence of diabetes is raised to 3.5 times the incidence than that of the general population. Newer medications in this class are attempting to mitigate these complications.[11] Cariprazine shows almost unique promise in reducing negative symptoms as well as providing cognitive benefit.[12] However, the issue is not being solved- rather, one set of side effects is simply being exchanged for another. This leaves an appeal for an even better treatment.

3. Adjunctive Medications (e.g. Mood stabilizers, antidepressants)

There is an increasing trend in the treatment of schizophrenia that favours strategic combinations of medications to manage the shortcomings of antipsychotics used on their own. One approach to managing significant weight gain induced by many antipsychotic medications is the addition of metformin, a met analysis found that on average patients lost 3.27 kilograms.[13] Additionally, researchers are testing newer combinations such as low-dose amisulpride with aripiprazole, which appear to have a synergistic effect in improving symptoms while minimizing adverse effects. Perhaps most interesting is the area of personalized medicine. A study in pharmacogenomics found specific gene variants that predict individual risk of metabolic side effects as a stepping stone toward truly personalized plans.[14]

NON-PHARMACOLOGICAL TREATMENTS

In the management of schizophrenia, non-pharmacological interventions are essential in treating the multiaxial complexities of the disorder, particularly in addressing residual symptoms, cognitive deficits, and functional recovery. Several meta-analyses have proved Cognitive Behavioural Therapy for psychosis (CBTp) to be very effective in reducing positive symptoms and its association with increased rates of improvement in mental state.[15] Neuroimaging studies demonstrate that CBTp enhances activation of the prefrontal cortex which would help in increasing cognition, hypothetically through the process of neuroplasticity.[16] In patients with severe treatment resistance and where there is a need for stabilization and symptom control, electroconvulsive therapy (ECT), again, is an option with caution. In a study of 81 patients with schizophrenia who had acute psychotic exacerbation, there was a greater response rate when augmenting antipsychotic treatment with ECT compared with antipsychotics alone (95% versus 75%). Response was defined as a 25% reduction on the Positive and Negative Symptom Scale (PANSS) scores.[17] New brain stimulation techniques such as transcranial magnetic stimulation (TMS) act similar to ECT but perhaps less evasively. In a recent trial for example, participants had significant decrease in auditory hallucination after high frequency TMS applied to the temporoparietal cortex.[18]

Psychosocial interventions are critical. Social Skills Training (SST) enhances real-world functioning by teaching communication skills, problem-solving skills, and skills specific to work in people's lives. A controlled clinical trial involving 28 male patients with schizophrenia showed that patients receiving intensive SST were able to substantially acquire

and maintain social skills, summed as an overall improvement on social adjustment, and exhibited significantly fewer relapses and rehospitalizations over a 24-month follow-up.[19] Family psychoeducation comprises an additional essential element of psychosocial care. A randomized controlled trial discovered that involvement of family members in monthly sessions focused on medication compliance and coping with stress may lead to significant reduction in the relapse risk.[20] For younger population, early intervention may be through CBTp, family therapy, and/or case management to delay the onset of psychosis that is at high risk for developing psychosis.[21]

The delivery of care is increasingly influenced by technology. Virtual Reality (VR) therapy exposes patients to social situations in a contained environment as a means for reducing paranoia. In 2018, a RCT based in the Netherlands aimed to investigate how efficacious virtual reality based cognitive behavioral therapy (VR-CBT) is in reducing paranoid ideation in patients with psychotic disorders. A total of 116 participants aged between 18 - 65 years, all diagnosed with a DSM-IV psychotic disorder, and had experienced paranoid ideation in the past month, were included in the study. Study participants were randomly assigned to either the VR-CBT group (n = 58) or the waiting list control group that received usual treatment (n = 58). Compared to the control group at post-treatment assessment, there were significant reductions in momentary paranoid ideation (b=-0.331 [95% CI -0.432 to -0.230], p<0.0001; effect size -1.49) and momentary anxiety (-0.288 [-0.438 to -0.1394]; p=0.0002; -0.75) in the VR-CBT group.[22] Mobile health applications offer patients an opportunity to track their symptoms in real-time.[23] Finally, consideration of physical health monitoring within psychiatric care is pivotal for increasing the life expectancy in individuals with schizophrenia, and is supported by consensus guidelines recommending regular metabolic and cardiovascular screening.[24]

EMERGING AND FUTURE THERAPIES: The therapeutic shortcomings of traditional antipsychotic medications have led to the initiation of research studies into three innovative therapeutic areas: novel glutamatergic agents, cautiously-delivered psychedelic-assisted therapies, and software-based AI digital solutions. Each therapeutic area attempts to identify distinct elements of the pathophysiology of schizophrenia while also enhancing functionality.

1. **Novel pharmacological agents (e.g. glutamate modulators):** The investigation of options other than dopamine D2 antagonists has produced promising glutamatergic modulators. For example, glycine transporter-1 (GlyT1) inhibition (e.g. bitopertin) has

been associated with improvements in negative symptoms, demonstrating significance for the negative symptom assessment scale in a phase II trial where GlyT1 inhibition was adjunctive to antipsychotics.[25] In addition, metabotropic glutamate receptor (mGluR2/3) was identified as a treatment with cognitive benefits, having fMRI studies that demonstrated a normalization of prefrontal-parietal connectivity during working memory.[26] Both treatment opportunities could assuage the metabolic and extrapyramidal side effects associated with commonly employed treatments.

2. **Psychedelic-Assisted Therapy:** Research endeavors concerning the utilization of psychedelic substances in the contemporary treatment of schizophrenia are emerging after proceeding through careful investigation of the safety protocols associated with the substance. For clinical research studies, the typical dosage of psilocybin used to evoke discernible perceptual, cognitive, and mood effects in healthy adults is between 20–25 mg per 70 kg. However, it is possible that a much smaller amount, called a microdose, has therapeutic effects that are clinically relevant without inducing any psychotic symptoms. A psychedelic microdose is approximately 10% of the psychedelic effect dose, which for psilocybin is about 2.0–2.5 mg. The fact that microdosing psilocybin might improve symptoms of schizophrenia without increasing the symptoms of psychosis is an intriguing prospect.[27] MDMA may be able to lessen negative symptoms in schizophrenia by increasing social motivation, emotional responsiveness and social engagement, notably by promoting the release of serotonin, dopamine, and oxytocin.[28] The study indicates that these methodologies require further research and involve: careful patient selection (excluding individuals with active psychosis), supervised administration settings, and the incorporation of psychotherapy sessions.

3. **Digital and AI-Based Interventions**: The incorporation of digital technologies and artificial intelligence are changing the treatment of schizophrenia by filling in gaps of monitoring, intervention and personalized treatment. Virtual reality (VR) therapies have emerged as useful modalities. In the 2022 randomized controlled trial, patients with schizophrenia who participated in VR-based Social Cognition and Interaction Training (VR-SCIT) showed statistically significant changes. Emotion perception and metacognition increased with large effect sizes (Cohen's d = 1.66), and social functioning changed significantly (d = 1.09) with decreases in hostile attributional bias. The VR group also experienced higher levels of engagement and completion rates; participants

reported no adverse events. These results indicate that VR-SCIT is a promising avenue for enhancing social cognition in schizophrenia.[29] VR provides immersive environments, giving patients a safe space to practice social interactions while giving the clinician the unique opportunity to observe any physiological stress responses in real-time.

On the diagnostic side, AI-based predictive models are achieving unprecedented success in relapse prevention. Studies have indicated that an analysis of narrative speech could accurately predict the relapse of psychosis within a two- to four-week period, although, further large-scale validation would be appropriate.[30] Another study showed that a combination of low semantic density and an increase in the references to voices and sounds in the speech predicted conversion to psychosis with 93% accuracy in the training set and 90% accuracy in the holdout dataset. This suggests that machine learning for speech analysis for early detection provides a viable methodology to consider.[31]

The study examined the impact of tDCS (transcranial direct current stimulation) on cognitive functions through a randomized double-blind sham-controlled trial, which enrolled 173 outpatients with schizophrenia. Results showed a statistically significant improvement in working memory and neurocognition as measured by the MATRICS Consensus Cognitive Battery (MCCB). The estimated marginal mean difference in working memory was 2.716 ($p < .001$) and in neurocognition was 1.289 ($p = .007$). Therefore, tDCS has been found effective in improving cognition in patients with schizophrenia.[32] Various artificial intelligence chatbots have integrated cognitive behavioral therapy (CBT) techniques to boost self-efficacy and support behaviour change. For example, chatbots Tess and Woebot have used a variety of CBT, motivational interviewing, and dialectical behaviour therapy to offer emotional support and personalized psychoeducation, which can aid in medication adherence.[33]

CONCLUSION

The treatment of schizophrenia over the past 70 years has remarkably changed. Nevertheless, significant barriers remain in the treatment of negative symptoms, cognitive impairment, and side effects of medications. Though antipsychotic medications in the current therapeutics are effective for treating positive symptoms of schizophrenia, new treatment options (glutamatergic agents, psychedelic-assisted therapy, and machine-learning and AI treatments) offer potential strategies to address more complex, customized, multidimensional care for patients with schizophrenia. Counseling therapy (CBTp) and neuromodulation offer two non-

pharmacological strategies for managing schizophrenia that target functional recovery. This said, whether effect size, tolerability, or access would impact upon the efficacy of cognitive therapists refers to the quality-of-life of patients. Future strategies will need to concentrate on hybrid models of care having viable biological and technological features, robust monitoring of safety and improving the delivery process will need to be a focus. The shift from a patient-centered approach incorporating precision and aspect of psychosocial features of patients, will be the key to improving the treatment of patients with schizophrenia in a bid to improve overall long-term quality of life.

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