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In the Treatment of Schizophrenia and Depression, New Atypical Antipsychotics

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Abstract

Depression and schizophrenia are distinct mental illnesses.Due to the intricate pathomechanisms of the diseases, patients may respond differently to medication.Although there are numerous psychotropic medications on the market, achieving the best therapeutic effect can be difficult.New atypical antipsychotic medications may be effective against the affective symptoms of depression as well as the negative and cognitive symptoms of schizophrenia based on their strong correlation with clinical observations.Aripiprazole, cariprazine, lurasidone, asenapine, brexpiprazole, lumateperone, and pimavanserin—new antipsychotics of the second and third generations—are used to treat depression and schizophrenia. The purpose of this review is to provide background information as well as evidence for these medications.We have initially briefly discussed the major neurobiological causes of schizophrenia and depression. The benefits, drawbacks, and dangers of continuing pharmacotherapy for depression and schizophrenia are then briefly discussed.The primary focus of this review was on the current therapeutic potential of new atypical antipsychotic medications for the treatment of psychotic and affective disorders.

Keywords: Schizophrenia; Depression; Aripiprazole; Cariprazine; Lurasidone; Asenapine; Brexpiprazole; Lumateperone; Pimavanserin

Introduction

In 1951, chlorpromazine, the first antipsychotic, was discovered. At first, it was developed as an antihistamine to lessen the autoimmune stress caused by surgery [**1**].The first-generation antipsychotics, also referred to as neuroleptics or typical antipsychotics, are represented by chlorpromazine.Clozapine, the initial atypical antipsychotic, was made available to patients in clinics in 1990 [**2**].The positive symptoms of psychosis, such as hallucinations and delusions, are thought to be treated by typical medications by inhibiting dopamine 2 (D2) receptors.Atypical antipsychotics treat both positive and negative schizophrenia symptoms, the latter of which includes withdrawal from social settings and diminished motivation and pleasure perception. As a outcomes, atypical antipsychotics are known to alleviate the fundamental and affective symptoms of schizophrenia as well as depression in schizophrenic patients.It is currently common practice to use antipsychotic medications alone or in conjunction with antidepressants and mood-stabilizing medications for mood disorders that are not necessarily associated with psychosis [**3,4**]. Depression and schizophrenia, two severe mental illnesses, contribute to the global burden of disease and are a major public health concern.

Schizophrenia is a mental illness that affects about 1% of the world's population and lasts a long time.There are three main categories of symptoms that make up the disease's diagnostic criteria:Positive and negative symptoms, cognitive impairment, as well as positive symptoms of the patient's mental disorders and hallucinations, frequently cause the patient to engage in risky and aggressive behavior. In addition, a significant number of patients have persistent negative symptoms (deficits) like difficulty speaking, feelings of isolation, a lack of pleasure and emotion, and avolition [**5-8**]. Cognitive dysfunction can be characterized by deficits in verbal and working memory, as well as difficulties with reasoning and attention. It is estimated that 40% of patients have negative symptoms, and up to 80% may have marked cognitive impairment.

One of the most prevalent mental illnesses, depression has a complicated etiology.It is a disease with recurring symptoms over time. It can show up as a gradual decline in happiness, depressive thoughts, anxiety, a sense that life has no purpose, trouble sleeping, decreased libido, and menstrual problems [**9**].Although there has been a lot of focus on depression treatment, the underlying causes are still poorly understood.Environmental, epigenetic, and genetic factors may all play a role in the disease.The development of new, more effective treatments may be significantly facilitated by a deeper comprehension of the pathophysiology of depression.

The purpose of this review is to provide background information and evidence regarding the use of new antipsychotics of the second and third generations to treat schizophrenia and depression.The major neurobiological factors that contribute to schizophrenia and depression have first been briefly discussed [**10-12**].The benefits, drawbacks, and dangers of continuing pharmacotherapy for depression and schizophrenia are then briefly discussed.The primary focus of this review was on the current therapeutic potential of new atypical antipsychotic medications for the treatment of psychotic and affective disorders.

Neurobiology of Schizophrenia

Dysregulation of the Dopaminergic System [13]

The dopaminergic system affects cognitive function, emotional behavior, and motor performance.Dopaminergic dysfunction is the root cause of mental illnesses like schizophrenia and depression.In schizophrenia patients who were studied after death, dopamine (DA) and its metabolites, as well as an increased number of DA receptors in the ventral striatum, were found.Overstimulation of the D2 receptors may be the cause of positive schizophrenia symptoms.Amphetamine,

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a DA-releasing drug, and levodopa, a DA precursor, were also found to exacerbate schizophrenic symptoms.After amphetamine induction, patients with schizophrenia release more dopamine (DA) in the ventral striatum than a control group, according to neuroimaging studies.The dopaminergic system might be more sensitive because of this.The onset of negative symptoms is linked to a reduction in the stimulation of the D1, D3, and D4 receptors in the prefrontal cortex and a decrease in the dopaminergic activity of the mesocortical pathway.

Glutamatergic Transmission Disorder [14-15]

It has been demonstrated that cognitive dysfunction and both positive and negative symptoms can be indirectly attributed to dysfunctions in the regulation of glutamatergic transmission.The well-known glutamatergic hypothesis was founded on the altered sensitivity of the N-methyl-D-aspartate receptor (NMDAR) to GABA receptors in the cerebral cortex.Secondary glutamatergic neurons, which are inhibited, directly stimulate dopaminergic neurons in the mesolimbic pathway.The overactivity of the dopaminergic system can lead to positive symptoms.NMDA receptor deficiency may also indirectly inhibit dopaminergic transmission in the mesocortical pathway, whose hypoactivity is linked to the onset of negative symptoms and cognitive dysfunction.Both phencyclidine and ketamine, which are glutamatergic receptor antagonists, can make healthy people feel like they have schizophrenia.The amplified, more pronounced DA release that occurs after the drug is administered to schizophrenia patients suggests a correlation between glutamatergic and dopaminergic transmission.In some postmortem studies, the NMDA receptor's GluN1 subunit was found to be expressed less in prefrontal cortex patients.However, other postmortem studies of human brain tissue have revealed reduced signal transduction despite an increase in NMDA receptor expression.However, the outcomes of these studies suggest that the glutamatergic system is not working as well as it could. There may be a connection between the causes and the dysfunction of NMDA receptors and receptor modulators.Natural antagonists like kynurenic acid and N-acetylaspartylglutamic acid (NAAG) and endogenous NMDA receptor agonist D-serine, as well as antagonist-regulating enzyme glutamate carboxypeptidase II (GCP-II), are found in higher concentrations in patient tissues after death.Genetic variants related to glutamatergic transmission have also been identified.DNA copy number variation (CNV) demonstrated that de novo mutations in NMDAR proteins and genes affected postsynaptic receptor density.

Neurobiology of Depression

The Monoaminergic Hypothesis

The observation that antidepressants raise neurotransmission tone in response to one or more of these neurotransmitters led to the development of this hypothesis.The most common explanation for depression's pathophysiology is this.There are three monoamines involved in impaired monoaminergic transmission:5-HT, dopamine A, and noradrenaline (NE). DA was also linked to depression and neurodegenerative diseases of the basal ganglia like Parkinson's and Huntington's. Impaired monoaminergic transmission can be caused by a number of things, such as altered excitability or expression of the receptors, impaired monoamine synthesis, impaired regulation of monoamine activity (neurotransmitter reuptake by the specific transporter), or depletion of monoamine.Monoaminergic neurons are functionally connected because different types of receptors interact with autoreceptors and heteroreceptors to facilitate direct and indirect connections between 5-HT, NE, and DA neurons.Both the 5-HT2A and 5-HT2C receptor-mediated mechanisms demonstrated that the 5-HT systems have a particularly intricate effect on NE and DA neurotransmission.Adrenergic receptors, on the other hand, control both the complex positive and negative effects of the NE system on 5-HT neurotransmission.The treatment of safe despondency appears to be viable due to the multimodal effect on focal monoamine neurotransmission that includes the effect on reuptake carriers and the various monoamine auto/hetreroreceptors.

According to postmortem and imaging studies, depressed patients typically have a lower density of postsynaptic 5-HT1A receptors.The length of time required to desensitize cell body 5-HT1A autoreceptors may also be reflected in the delayed onset of action of selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-noradrenaline reuptake inhibitors (SNRIs).5-HT1A autoreceptor desensitization finding from chronic drug administration inactivates this negative feedback mechanism, allowing for a significant increase in extracellular 5-HT and the activation of postsynaptic 5-HT receptors. The 5-HT1A autoreceptors may initially reduce 5-HT release from serotonergic neurons as a means of compensating for inhibited 5-HT reuptake .Consequently; 5-HT transmission does not change, especially at the nerve terminal level.

New Atypical Antipsychotics in the Treatment of Schizophrenia

Antipsychotics play a significant role in both acute schizophrenia treatment and maintenance pharmacotherapy.The dopaminergic hypothesis was demonstrated by the first psychostimulant medications that inhibited the D2 receptor.The subsequent development of medications with distinct chemical structures but comparable pharmacological effects was sparked by this discovery.The drugs' low selectivity for the site of action is one drawback.They not only antagonize receptors in the other dopaminergic pathways but also inhibit receptors at the target site.This generation is prone to numerous side effects because of its high affinity and non-selectivity, such as significant extrapyramidal disturbances, hyperprolactinemia, and cognitive decline.Typical antipsychotics, which are also linked to an increase in deficit symptoms, block the nigrostriatal pathway.Sedation and cardiovascular issues caused by blocking the one adrenergic receptor are additional significant side effects.

Among the second-generation "atypical" neuroleptics are risperidone and clozapine.They oppose 5HT2A receptors and inhibit D2 receptors in the mesolimbic pathway, assisting in the partial alleviation of negative symptoms.Dopaminergic neurons' tone may be altered by antagonistic 5-HT2A receptors, finding in antipsychotic effects.The atypical neuroleptics' less noticeable side effects may be due to a lower affinity for D2 receptors or a high degree of dissociation.Additionally, it has been hypothesized that atypical neuroleptics favor mesolimbic pathway receptors over nigrostriatal ones, reducing the likelihood of extrapyramidal disorders.Through a decrease in glutamate release in the VTA, blocking 5HT2A receptors also reduces dopaminergic transmission in the mesolimbic pathway. However, their use is linked to weight gain in patients.

The most recent medications are sometimes referred to as antipsychotics of the third generation.They have a wide range of receptors, including subtypes of the DA and 5-HT receptors, as well as a significant partial antagonistic effect on the D2/D3 and 5-HT1A receptors.Prefrontal 5-HT1A receptor levels were higher in schizophrenia patients than in healthy controls, according to a meta-analysis of postmortem studies.Negative symptoms of schizophrenia are brought on by a decrease in DA in the prefrontal cortex.Similar

to how atypical antipsychotics reduce negative symptoms, it has been hypothesized that partial agonism of the 5HT1A receptor may raise DA levels in the prefrontal cortex.5HT6 and 5HT7 receptors are additional promising molecular targets, and it has also been hypothesized that partial agonism of the 5HT2C receptor may produce antipsychotic effects without causing extrapyramidal symptoms. As an autoreceptor, stimulation of the 5HT1A receptor inhibits 5-HT release and subsequent inhibition of DA release in the prefrontal cortex.

New Atypical Antipsychotics in the Treatment of Depression

The discovery that agents that alter monoamine metabolism, particularly that of 5-HT and NE, could alleviate depressive symptoms had a significant impact on research in the second half of the 20th century.Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), both nonspecific medications, have numerous adverse effects despite their therapeutic benefits.With the assistance of SSRIs and noradrenaline reuptake inhibitors (NRIs), two medications that are more recent and more focused, a significant number of patients are able to experience relief from symptoms.SSRIs are typically chosen. The next class of first-choice medications are SNRIs.Postsynaptic stimulation of 5-HT receptors on the surface of nerve cells is made possible by increasing the concentration of this neurotransmitter in the synaptic gap when 5-HT reuptake is inhibited.Patients tolerate these medications well and they are not cardiotoxic or affect cognitive function in any way.The fact that SSRIs take time to work is a drawback; It will probably take several weeks for the treatment to work.When it comes to treating depression, TCAs come in second place.Due to their serious side effects, they are not considered first-line treatments for depressive symptoms. Aggression, drowsiness, ADHD, paraesthesia, weight gain, QT prolongation, constipation, and nausea are all possible symptoms.When depression is accompanied by anxiety disorders, medication that also treats generalized anxiety is recommended. SSRIs, duloxetine, and venlafaxine are a few examples. Trazadone, mirtazapine, and agomelatine are prescribed for insomnia-related depression.

People with major depressive disorder (MDD) whose symptoms have persisted despite treatment are referred to as "treatment-resistant depression."Additionally, it is believed that mixed components are to blame for one third of major depressive episodes.Psychomotor agitation, irritability, and distractibility are the most common symptoms of mixed depression. Risky behaviors like impulsive attempts at suicide are frequently linked to mixed depression.As a outcomes, these unstable conditions need to be found and treated right away. Altering to a different class of antidepressants or using an augmenting medication like lithium, anticonvulsants, or atypical antipsychotics are examples of pharmacological treatment options. The clinical efficacy of two atypical neuroleptics, olanzapine and quetiapine, has already been demonstrated by numerous meta-analyses. On the other hand, taking olanzapine and quetiapine has been linked to increased weight and the possibility of akathisia, parkinsonism, or insomnia. Patients with treatment-resistant depression now have hope thanks to a new class of atypical neuroleptics. The medications are safer for the patient and have a lower risk of motor side effects because of their unique mechanism of action.

Conclusions

Depression and schizophrenia are distinct mental illnesses.Due to the intricate pathomechanisms of the diseases, patients may respond differently to medication.Although there are numerous psychotropic medications on the market, achieving the best therapeutic effect can be difficult. As a outcomes, there are a lot of good reasons to look into ways to make current pharmacotherapy work better.

New atypical antipsychotic medications may be effective against the affective symptoms of depression as well as the negative and cognitive symptoms of schizophrenia based on their strong correlation with clinical observations. As a outcomes, a significant advancement in the treatment of schizophrenia and depression can be seen in the development of new antipsychotic medications that are more effective, have a greater impact on functional impairment, and have fewer side effects.

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