REVIEW ARTICLE

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Brexpiprazole for the Treatment of Schizophrenia and Major Depressive Disorder: A Comprehensive Review of Pharmacological Considerations in Clinical Practice

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ABSTRACT *~ Mood and psychotic disorders are a group of illnesses that affect behavior and cognition. Schizophrenia is characterized by positive symptoms, such as delusions and hallucinations, as well as negative symptoms. Major depressive disorder (MDD) is a mood disorder that affects the patient's emotions, energy, and motivation. Brexpiprazole works as a partial agonist at serotonin 5-hydroxytryptamine1A and dopamine D2 receptors and an antagonist at serotonin 5-hydroxytryptamine2A. Schizophrenia and MDD have a wide range of risk factors, both biological and environmental. Third generation antipsychotics, which include brexpiprazole, are the latest group of drugs to reach the market, demonstrating efficacy and tolerability. Patients with acute schizophrenia have responded well to brexpiprazole. In this regard, in patients who have MDD plus anxiety symptoms, brexpiprazole can be effective as an adjunctive therapy and can reduce anxiety symptoms. In summary, brexpiprazole has proved to be an effective alternative to typical or first and second-generation atypical antipsychotics.* Psychopharmacology Bulletin. *2021;51(2):69–95.*

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Introduction

Major depressive disorder (MDD) is a debilitating disease that is characterized by at least one discrete depressive episode lasting at least two weeks and involving clear-cut changes in mood, interests, and pleasure, changes in cognition such as decreased concentration, decreased energy, and changes in sleep.[1] Studies have shown that those with MDD demonstrated a decreased interest in social interactions, which can lead to difficulties in initiating, establishing, and maintaining satisfying relationships with other people.[2] Although significant advances have been made in medicine, the etiology and understanding of the pathology are not clear. Studies have also suggested women are 1.7 times more likely to develop an episode of major depressive disorder than men, and the difference in prevalence is not influenced by socioeconomic status or country of origin.[3] Among all medical conditions, MDD is the second leading contributor to chronic disease burden as measured by "years lived with disability".[1]

Schizophrenia, a unique and continuously evolving disease, has affected many individuals and the diverse clinical presentation continues to cause ambiguity in clearly defining its etiology and pathophysiology. Schizophrenia, among other mood disorders or psychiatric illnesses, has a significant association with suicide. A 5-year follow-up study of 1065 patients with psychotic disorders conducted by the World Health Organization (WHO) found that "the risk for suicide in schizophrenia is as great, if not greater, than the risk of suicide associated with affective disorders".[4] Related to the close relationship between the two disorders, treatment of MDD and schizophrenia are similar and involve a variety of antipsychotics or antidepressants to manage positive and/or negative symptoms, preventing relapses of psychotic symptoms and augmentation of antidepressants in MDD. Antipsychotics are classified as either atypical or typical based on their affinity towards D2 receptors. Of those drugs, brexpiprazole, an FDA approved atypical antipsychotic for the use of treating schizophrenia and MDD. Brexpiprazole works as a partial agonist at serotonin 5-hydroxytryptamine1A and dopamine D2 receptors and an antagonist at serotonin 5-hydroxytryptamine2A.[5] Recent studies have shown its viability in the treatment of acute exacerbations of MDD and schizophrenia. Although antipsychotics, in general, have a tendency to cause extrapyramidal symptoms and movement disorders, its side effect profile is preferable to most typical antipsychotics. In this review, MDD and schizophrenia, current treatment, and the role of brexpiprazole in the management of these disorders will be explained in detail.

Schizophrenia and Major Depressive Disorder

Presentation

Schizophrenia is characterized by three categories of symptoms—positive (e.g., hallucinations, delusions, abnormal motor behavior), negative (e.g., avolition, anhedonia, alogia), and cognitive (e.g., disorganized thought and speech, attention deficits). Generally, positive symptoms are easier to identify compared to negative symptoms, although negative symptoms are associated with higher morbidity.[6–8] According to the *Diagnostic and Statistical Manual of Mental Disorders* Fifth Edition (DSM-V), the diagnostic criteria for schizophrenia include the persistence of two or more of the following active-phase symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms; at least one of the qualifying symptoms must be delusions, hallucinations, or disorganized speech. Additionally, the patient must exhibit some form of decreased functioning with respect to interpersonal relationships, work, or self-care, and the patient must exhibit signs of schizophrenia for at least six months, including the month of active-phase symptoms.[8] Presentations of schizophrenia vary widely, but schizophrenia can be distinguished from other conditions (schizoaffective disorder, a major depressive disorder with psychotic features, schizophreniform disorder, etc.) through careful examination of the duration, timing, and severity of symptoms.[7,8]

Pathophysiology

Although much progress has been made in relating altered neurobiology to aspects of schizophrenia, the exact mechanisms underlying its development are not fully known. Most theories on the pathophysiology of schizophrenia focus on abnormal levels of dopamine, glutamate, and/or serotonin.[7,9,10] The dopaminergic hypothesis posits that abnormal activity at dopamine receptors (D_2) in the nigrostriatal, mesolimbic, and mesocortical pathways plays a large role in the development of symptoms.[7,11,12]

Low dopamine levels in the nigrostriatal and mesocortical pathways have been associated with motor symptoms and cognitive deficits, respectively, whereas excess dopamine in the mesolimbic pathway is thought to contribute to positive symptoms.[7] Glutamatergic dysfunction was first implicated in the development of schizophrenia when psychotic effects were noticed in patients taking

N-methyl-D-aspartate (NMDA) receptor/glutamate antagonists, such as ketamine and phencyclidine.[13] NMDA receptor dysfunction in the cerebral cortex is believed to contribute to cognitive deficits typical of schizophrenia.[9,11,14] Little is known about serotonin's involvement in schizophrenia, but the administration of serotonin-dopamine antagonists has been shown to improve both positive and negative symptoms of schizophrenia to a greater degree than dopamine receptor antagonists alone.[7,12,15]

Risk Factors

Schizophrenia has a wide range of risk factors, both biological and environmental. Genetics plays quite a large role in the development of the disorder; a relatively recent meta-analysis of genome-wide association studies has identified 108 schizophrenia-associated loci.[16] Its heritability is estimated to be anywhere between 66% and 83%.[17,18] Family history of the disorder in a first-degree relative is the most widely replicated risk factor, and twin and adoption studies have ruled out the family environment as a confounding factor.[17,19] Other nonhereditary risk factors include complications during pregnancy (e.g., fetal malnutrition, prematurity, ischemic events, and maternal infections), advanced parental age, social adversity during childhood and adolescence, brain structural abnormalities, and cannabis and psychostimulant use.[20] None of these environmental risk factors alone is necessary or sufficient for developing schizophrenia. Studies have reported that multiple risk factors seem to have an additive effect on a patient's risk of developing schizophrenia, and genes interact with each other and with environmental factors to heighten the risk of developing symptoms.[17,20]

Epidemiology

It is estimated that the lifetime prevalence of schizophrenia is around 0.87%.[21] Rates of incidence vary by location, but rates range from 7.7 to 43.0 per 100,000 per year. Long-term trends in the incidence of schizophrenia have not been extensively studied. Males generally experience an onset of symptoms at an earlier age than females, with the peak incidence for males occurring in the late teens to early twenties and the peak incidence for females in the late twenties to early thirties.[17] A recent systematic review of mortality studies reports that the standardized mortality ratio for schizophrenia is currently 2.6, which has unfortunately been rising over the past several decades.[22]

Major Depressive Disorder—Background

Presentation

Major depressive disorder (MDD) can present with a wide range of mental, emotional, and physical symptoms. The most common symptoms include persistent feelings of despair or depressed mood, anhedonia, significant weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness, impaired ability to concentrate, and recurrent suicidal ideation.[8,23] For a diagnosis of MDD, the DSM-V requires five or more of the above symptoms to be present and cause discernible functional changes in the patient for at least a two-week period, with at least one of the symptoms being either depressed mood or anhedonia.[8]

Given the broad range of possible symptoms of MDD and given that the symptoms often overlap with those of other disorders, misdiagnosing other psychiatric illnesses as MDD is common. Bipolar disorder is especially prone to misdiagnosis, as the clinical presentation of bipolar disorder during depressive phases is often indistinguishable from the clinical presentation of MDD.[24,25] As another example, dementia and delirium can present with negative moods and cognitive deficits that mimic the symptoms of MDD.[23] Conversely, numerous non-psychiatric disorders can cause depressive symptoms, which can easily be mistaken for MDD. For instance, anemia, hypothyroidism, Parkinson's disease, sleep apnea, some vitamin deficiencies, and several infectious diseases can all cause depressive symptoms, and in many cases treating these underlying conditions will alleviate the depressive symptoms.[23]

Pathophysiology

The pathophysiology of MDD is not yet fully understood, as several biological, genetic, environmental, and social factors impact the development and progression of the disease; however, significant evidence points to serotonin (5-HT) dysfunction as the main underlying mechanism.[26,27] The two major players in 5-HT neurotransmission are the group of neuronal 5-HT receptors and the serotonin membrane transporter (5-HTT).

In animal models, direct alterations of 5-HT receptor function can produce long-lasting anti-depressive effects through varied mechanisms.[27,28] The 5-HT_{1A} receptor is found on presynaptic serotonergic neurons as an autoreceptor and as a heteroreceptor on post-synaptic neurons. Activation of the 5-HT_{1A} autoreceptor inhibits the release of 5-HT from the neuron and results in rapid desensitization of the neuron to 5-HT, whereas the heteroreceptor mediates the inhibition of non-serotonergic

pathways.[27,29] Selective suppression of 5-HT_{1A} heteroreceptors in animal models causes depressive symptoms, while suppression of autoreceptors induces anxiety-like symptoms but no depressive symptoms. Further, 5-HT_{1A} knockout mice displayed higher rates of 5-HT firing.[30]

5-HT_{1B} and 5-HT_{2A} autoreceptors have also been implicated in the pathophysiology of MDD, although the direct link between their functioning and the development of MDD is not as well understood. Administration of 5-HT_{1B} agonists produces anti-depressive effects in animal models, although it has also been shown that 5-HT_{1B} antagonists produce anxiolytic effects.[30] Antidepressant drugs have the effect of reducing levels of 5-HT_{1B} mRNA in the dorsal raphe nucleus, leading to increased 5-HT and a reduction in depressive symptoms.[30,31] Selective serotonin reuptake inhibitors (SSRIs) have a similar downregulating effect on 5-HT_{2A} receptors with a subsequent increase in 5-HT levels.[32]

The main target for most antidepressants is the neuronal serotonin membrane transporter (5-HTT), which facilitates the reuptake of 5-HT into the presynaptic neuron following an action potential.[27] Studies have shown that patients with functional polymorphisms in the 5-HTT gene promoter experience a greater number of depressive symptoms in response to stress.[33] Inhibitory ligands that bind preferentially to 5-HTTs act as antagonists that block the function of these transporters, thereby increasing 5-HT levels.[27,34]

Risk Factors

In contrast to schizophrenia, which has been shown to have a large genetic component, MDD has an estimated heritability of only 37%.[26]Most studies on the heritability of MDD focus on the gene encoding 5-HTT and its relation to how individuals react to stress. These studies emphasize that polymorphisms in the gene encoding 5-HTT predispose an individual to depressive episodes but are not the sole cause of MDD.[26,33] Rather, a multitude of social, environmental, and epigenetic factors interact with genes to heighten or lower the risk of developing MDD. Social and environmental factors that may increase one's risk of developing MDD include childhood maltreatment during the first decade of life, experiencing activity limitations, having limited contact with family members, having less than high school education, and having physical chronic diseases.[26,35]

Epidemiology

While the prevalence of MDD varies widely with location, other aspects of its epidemiology (age of onset, the persistence of symptoms)

are surprisingly consistent across different countries. The lifetime prevalence of MDD ranges from 1.0% to 16.9%, with the United States having the highest lifetime prevalence among countries for which there is available data.[36] This wide variation is due in part to cultural and environmental factors that can directly affect rates of MDD, but a large portion of the variation can be attributed to measurement and reporting

Current Treatment of Schizophrenia and Major Depressive Disorder

Goal and Limitations of Schizophrenia Treatment

The goal of pharmacological treatment for schizophrenia is mainly to reduce the severity of positive symptoms, lessen their impact on the patient, and enable the patient to function better.[37] Often long-term prophylactic treatment is indicated in order to decrease the number and severity of future relapses.[38] A systematic review of six studies was done to examine the relapse risk in patients who had recovered from their first non-affective episode of psychosis, and they concluded a weighted mean one-year recurrence rate of 77%. After two years, this recurrence rate increased to over 90%.[39] This high risk of relapse emphasizes the need for long-term treatment.

It is worth noting that standard antipsychotic treatment has no effect on 20% of patients with schizophrenia. 30%–40% will show improvement but still experience some symptoms. This is one of several factors that makes this disorder difficult to treat. Treatment adherence is another substantial problem. Approximately 50% of patients do not follow short-term treatment, and long-term treatment is much more difficult to maintain.[40] One workaround for this is to use long-acting depot injections of the drugs. The key takeaway of drug delivery in this fashion is that there is a long-lasting drug deposit that will slowly release over time. It is important to note that these long-acting injections require patients to utilize oral forms of the medication at first to support the tolerance to a long-acting depot. According to a prospective cohort study involving 29,823 patients that focused on the effectiveness of various antipsychotics to treat schizophrenia, those who had the least number of relapses were treated with clozapine and long-acting injectable antipsychotic medications. When administering the medication with the depot injection route instead of using their oral counterparts, the study showed that patients were 20%–30% less likely to be re-hospitalized.[41]

Other limitations of antipsychotics include the fact that while they treat positive symptoms well, negative symptoms and cognitive symptoms

often fail to resolve.[42] Second-generation antipsychotics, which will be discussed later, typically do the best with alleviating them, particularly during an acute episode. If negative symptoms still persist, typically, an antidepressant is considered for add-on therapy.[43] A systematic review and meta-analysis of 23 randomized controlled trials (22 publications, n = 819) was performed to assess how beneficial selective serotonin reuptake inhibitors were as an add-on therapy to antipsychotics compared to monotherapy with antipsychotics. The results showed an overall standardized mean difference of −0.48, which the authors of the review evaluated as significant in favor of antidepressant add-on therapy.[44]

Antipsychotics

Antipsychotics divided into first, second, and third generations have a wide range of debilitating side effects. These side effects can be broken down into three categories, which are metabolic effects, cardiac effects, and extrapyramidal symptoms/tardive dyskinesia. These side effects are one of the contributing factors for low treatment adherence.[10] Therefore, benefits and risks must be carefully weighed before initiation of treatment.

First-Generation Antipsychotics

This group is divided into two categories: low potency and high potency drugs. An example of a low potency drug would be chlorpromazine, and examples of high potency drugs would be haloperidol and fluphenazine.[45] First-generation antipsychotics act by blocking dopamine D_2 receptors located in the brain. However, these drugs are not selective, so they act on many dopamine pathways indiscriminately and therefore exhibit a multitude of side effects. Of note are extrapyramidal side effects (tardive dyskinesia, dystonia, akathisia, etc.), hyperprolactinemia, and metabolic syndrome. Cardiac side effects are especially prominent with first-generation antipsychotics, which notably includes QTc elongation. The greatest risk of QTc prolongation is seen in thioridazine, haloperidol, and chlorpromazine. Thioridazine increased the *QTc* interval from baseline by 30.1 ms, and haloperidol increased it by 7.1 ms.[46] Side effects are particularly of concern when too high a dosage is given to the patient. Another adverse effect includes the worsening of negative symptoms due to the medication interfering with central reward pathways.[37,47]

Second-Generation Antipsychotics

Some examples of this group include clozapine, olanzapine, quetiapine, risperidone, paliperidone, iloperidone, lurasidone, and

ziprasidone.[10] This category of antipsychotics tends to block serotonin 5-HT_{2A} receptors more than dopamine D_2 receptors. Their D_2 receptor antagonism is weaker than the first generation antipsychotics; this has the useful effect of fewer incidences of extrapyramidal side effects.[48] Ziprasidone has a high risk of QTc prolongation, so it should not be given with other medications that could also cause QTc prolongation, which could be citalopram, escitalopram, methadone, and amiodarone. Of note, clozapine is a highly effective antipsychotic that can also decrease suicidality, but it is generally recommended only for treatment-resistant cases because of its potentially fatal side effect, agranulocytosis.[49]

Third-Generation Antipsychotics

This category constitutes the latest group of drugs to reach the market and includes the drug of interest for this review. It includes aripiprazole, brexpiprazole, and cariprazine.[10] These are different from the prior two generations: they are D_2 partial agonists that also have actions on 5-HT_{1A} and 5-HT_{2A} receptors. This means that depending on the dopamine levels in the brain; partial agonists also have the ability to function as antagonists, allowing them some flexibility on whether to act as an agonist or antagonist.[50] These act as functionally selective D_2 ligands; depending on the D_2 receptor's location and signaling environment, they have a varying spectrum of intrinsic activity. This property allows them to have a therapeutic antipsychotic effect without putting the patient at risk for extrapyramidal side effects.[51,52]

Psychosocial Support as a Facet of Schizophrenia Treatment

It is important not to forget psychosocial support for this patient population. This can include encouragement and aid in social activities, help with activities of daily living, and restoring their prior productivity levels. Case management and psychotherapy are imperative to include, especially for newly diagnosed patients who might deny their condition and reject treatment.[53]

Limitations of MDD Treatment

MDD is another difficult illness to treat. One reason that makes it difficult is the presence of lingering depressive symptoms during remission periods, which can increase the risk of relapse into another depressive episode. A three-year prospective study found that three symptoms in particular (cognitive deficits, lack of energy, and sleeping problems)

were present for 85%–94% of the depressive episodes and 39%–44% of the remission periods.[54]

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are the first-line antidepressants for the treatment of MDD, so these will be examined. Some examples of this class of drugs include sertraline, fluoxetine, and citalopram. These drugs block the presynaptic serotonin transporter (SERT), thereby precipitating a rise in extracellular serotonin levels in the synapse.[55–57] Common side effects of this drug class are nausea and sexual dysfunction.[57] QTc prolongation can also be a concern with some SSRIs such as citalopram and escitalopram, so caution should be used if any other medications known to prolong the QTc interval are also being prescribed.

Non-SSRI Treatment or Augmentation for MDD

Pharmacological treatment is not the only option to treat MDD. Clinical guidelines by the American College of Physicians strongly recommended either cognitive behavioral therapy (CBT) or second-generation antidepressants (SSRIs or serotonin-norepinephrine reuptake inhibitors).[58] The use of CBT, along with antidepressant therapy, was showed to be more effective than either treatment on its own.[59,60]

Augmentation involves the addition of a medication that has a different mechanism of action that can boost the action of the original medication. It is common that a combination of SSRIs or serotonin-norepinephrine reuptake inhibitors is often used for augmentation. In the treatment of treatment, resistant MDD, medications that can be used for augmentation is lithium, thyroid replacement hormone, and atypical antipsychotics.[61] These atypical antipsychotics can include risperidone, olanzapine, aripiprazole, and ziprasidone. Risperidone antagonizes the serotonin 5-HT2A receptor, which is thought to enhance the SSRI antidepressant effect at the serotonin 5HT1A receptor.[61] All other listed antipsychotics work in a similar fashion on the serotonin receptor system. The use of atypical antipsychotics is not without risks. Results from a population-based cohort study showed that among middle-aged adults with depression taking an antidepressant, those who also took a second-generation antipsychotic were at increased mortality risk compared with their peers who instead took a second antidepressant.[62] This risk should be discussed with the patient when augmentation of current treatment is considered. A recent study suggests that physicians should consider prescribing antipsychotics to adults with depression carefully, and the results emphasized: "the importance of considering

newer antipsychotics only after nonresponse to less risky, evidence-based treatment options has been established".[62]

Brexpiprazole

Brexpiprazole is an atypical antipsychotic approved by the FDA in July 2015 for the treatment of schizophrenia and as an adjunct therapy for the management of MDD. It is a partial agonist at 5-HT1A and D2 neuroreceptors and also has activity at noradrenergic receptors, although the clinical significance of this is unclear.[63] The safety and efficacy of brexpiprazole were studied in four completed placebo-controlled clinical phase III studies—two studies as adjunctive therapy to antidepressants in MDD and two studies in schizophrenia and was demonstrated to be superior to placebo for both conditions at specific dosages.[64] It is available as a tablet in several strengths (mg): 0.25, 0.5, 1, 2, 3, and 4. For schizophrenia, it is recommended for initiation, to start at 1 mg once daily and to titrate to a target dose of 2 mg to 4 mg once daily. As an adjunct therapy for MDD, dose initiation is recommended at 0.5 mg or 1 mg once daily, increasing weekly to a target dose of 2 mg. It is contraindicated in individuals with prior hypersensitivity reactions to medications of the same class. The most common adverse reactions seen are weight gain and akathisia but are also linked with other metabolic changes such as dyslipidemia and hyperglycemia. Warnings and precautions to the use of brexpiprazole include but are not limited to cerebrovascular adverse reactions in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, leukopenia, orthostatic hypotension, and seizures. There is also a black box warning for increased mortality in elderly patients with dementia-related psychosis and suicidal thoughts and behaviors in children, adolescents, and young adults.[5] Also, when used in pregnancy, there is a risk of extrapyramidal and/or withdrawal symptoms in neonates with third-trimester exposure. Hepatic enzymes metabolize brexpiprazole, and doses should be adjusted if the CYP2D6 or CYP3A4 superfamilies of enzymes are affected.

Mechanism of Action

Brexpiprazole acts as a partial agonist at dopamine D2 and serotonin 5-HT1A receptor and potent antagonist at serotonin 5-HT2A and α1B, 2C adrenergic receptors. In the comparison of brexpiprazole to aripiprazole, brexpiprazole has much greater potency at each of these three receptors, i.e., at the 5HT2A receptor, at 5HT1A receptor, and at the alpha 1B receptor.[65] Although EPS and akathisia is a commonly

reported side effect, its strong affinity to these receptors may play a role in less activity of these symptoms. It has greater intrinsic activity at the serotonin 5HT2A receptor and displays lower intrinsic activity at the dopamine D2 receptor and a stronger affinity for the norepinephrine transporter. Hyperprolactinemia is an undesirable effect of most antipsychotics, considered to primarily be due to dopamine D2-receptor blockade, which causes loss of the dopaminergic inhibitory effect on prolactin secretion.[66] Comprehensively, brexpiprazole exhibits moderate antagonist activity at the dopamine D3, serotonin 5-HT2B, 5-HT7 and α1A, 1D receptors, and moderate affinity for histamine H1 and low affinity for muscarinic cholinergic M1 receptors. This pharmacodynamic profile allows brexpiprazole to not only be more efficacious but may be a preferable alternative depending on the patient's tolerability and goals of therapy.

Pharmacokinetics/Dynamics

Absorption and Distribution

Peak serum concentration (C_{max}) occurs approximately 4.1 hours (t_{max}) after a single-dose oral administration of brexpiprazole. Both C_{max} and the area under the plasma concentration-time curve (AUC_{24h}) have been shown to increase proportionally with the administered dose.[67–69] Neither eating a high-fat meal nor fasting before administration of the dose has an appreciable effect on C_{max} or AUC. Following intravenous administration, the volume of distribution of brexpiprazole is 1.56 ± 0.42 L/kg, suggesting a high degree of extravascular distribution. The absolute oral availability is around 95%. In plasma, brexpiprazole is almost completely (>99%) bound to albumin and a1-acid glycoprotein.[68,69] In pharmacokinetic studies involving multiple once-daily oral dosing of brexpiprazole, steady-state plasma concentration is reached around day 10. After day 14, C_{max} and AUC_{24h} show a 2.5- to 5.5-fold increase compared with day 1, indicating the accumulation of the drug.[67,69]

Metabolism

Brexpiprazole is mainly metabolized by the enzymes CYP3A4 and CYP2D6. Its major metabolite, DM-3411, represents between 23% and 48% of brexpiprazole's exposure at steady state, although DM-3411 has not been shown to contribute to any antipsychotic effects.[69,70] Several factors affect brexpiprazole's rate of metabolism, which in turn affects its overall exposure (AUC). Patients taking strong CYP3A4

inhibitors (e.g., erythromycin, itraconazole) or strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine) are likely to experience increased exposure. Exposure is similarly increased in patients who are poor CYP2D6 metabolizers. Conversely, co-administration of strong CYP2D6 inducers (e.g., rifampicin, glucocorticoids) is likely to decrease the exposure of brexpiprazole. Patients with moderate-to-severe hepatic impairment (Child-Pugh Class B or C) and moderate-to-severe renal impairment (creatinine clearance rate of 60 mL/min) experience greater exposure relative to patients with normal hepatic and renal function, and dosages should be adjusted accordingly.[67,69,70]

Elimination

When taken orally, approximately 25% of a single oral dose of ^{14}C-radiolabelled brexpiprazole was recovered in the urine, and 46% was recovered in the feces. The urine contained less than 1% of unchanged brexpiprazole, and approximately 14% of the dose remained unchanged in the feces. The terminal elimination half-lives of brexpiprazole and DM-3411 were 91 and 86 hours, respectively, following multiple once-daily administration.[69,70]

Clinical Studies

Phase I Study

A summary of the studies discussed can be found in table 1. In a phase I, 14-day, multiple-dose administration study, brexpiprazole was given in 1, 4, and 6 mg/day (n = 7, 8, and 6 respectively) doses. The objective of this study was to assess the pharmacokinetics and safety of brexpiprazole in Japanese patients with schizophrenia. The authors examined plasma concentrations, PK parameters, the effect that CYP2D6 polymorphisms had on metabolizing the drug, and treatment-emergent adverse effects (TEAE). The half-life was found to be 52–92 hours, reinforcing the clinical guidelines of prescribing it once per day. After 10 days, steady-state concentrations were achieved for all three dosage groups. C_{max} and AUC_{24h} showed dose-proportionality. CYP2D6 was found to participate in the metabolism, which is something to be aware of if the patient is taking other drugs that affect CYP2D6. Overall, adverse effects were noted to be mild to moderate, and the most frequently seen effect was temporarily increased serum prolactin. The authors concluded that in Japanese patients with schizophrenia, brexpiprazole was safe and well-tolerated.[67]

TABLE 1

Clinical Safety and Efficacy

AUTHOR (YEAR)	GROUPS STUDIED AND INTERVENTION	RESULTS AND FINDINGS	CONCLUSIONS
Ishigooka J. et al. (2018)[67]	Phase I, 14-day, multiple-dose administration study. Brexpiprazole was given in 1, 4, and 6 mg/day doses. The authors examined plasma concentrations, PK parameters, the effect that CYP2D6 polymorphisms had on metabolizing the drug, and TEAE.	The half-life of brexpiprazole was found to be 52–92 hours, which reinforces the clinical guidelines of prescribing it once per day. C_{max} and AUC_{24h} showed dose-proportionality. CYP2D6 participated in the metabolism. Adverse effects were mild to moderate, the most frequently seen being increased serum prolactin.	Brexpiprazole was safe, well-tolerated, and a once-daily dosing frequency was supported.
Ishigooka J. et al. (2018)[71]	Phase II/III, multicenter, randomized, double-blind, placebo-controlled, 6-week study in Japan. Patients diagnosed with acute SCZ were given brexpiprazole 1 mg, 2 mg, 4 mg, or placebo once daily. The primary endpoint was to see a difference from the start of treatment to week 6 in PANSS total scores.	Significant improvement over placebo was observed in the 2 mg group (treatment difference: −7.32, $p = 0.0124$). The TEAEs with the highest incidence were vomiting, hyperprolactinemia, diarrhea, nausea, and dental caries; these were all mild to moderate.	Brexpiprazole showed improvement in Japanese adult patients with acute schizophrenia and was well-tolerated. 2 mg/d appeared to offer the most benefit.
Forbes A. et al. (2018)[72]	Phase III, multicenter, open-label, flexible-dose (1–4 mg/d) 52-week study to elucidate the safety, tolerability, and efficacy of administering brexpiprazole over a long time. The primary endpoint was to examine the occurrence rate and gauge the seriousness of TEAEs. The secondary endpoint was to quantify efficacy using PANSS and the Personal and Social Performance scale.	The incidences of TEAEs that were above 5% were schizophrenia, insomnia, weight gain, headache, and agitation; most of these were mild to moderate. The mean weight increase from the beginning of the study to week 52 was 2.1 kg. Patients steadily improved with regards to their symptoms.	For schizophrenia, brexpiprazole is mostly well tolerated at doses of 1–4 mg/d for up to 52 weeks.

Fleischhacker W. et al. (2016)[73]	Phase III, randomized, double-blind, placebo-controlled study to ascertain efficacy, safety, and tolerability of brexpiprazole maintenance treatment for adults with schizophrenia. After stabilizing on brexpiprazole (1–4 mg/d), patients were then double-blind randomized to a maintenance treatment of brexpiprazole or placebo for up to 52 weeks. The primary efficacy endpoint was to measure time until relapse.	Time until relapse was statistically significantly delayed when using brexpiprazole compared to placebo ($p < 0.0001$). 13.5% of the brexpiprazole group and 38.5% of the placebo group met criteria for an approaching relapse. The rate at which adverse events occurred was similar between brexpiprazole and placebo.	Maintenance brexpiprazole treatment for schizophrenia was more effective than placebo and was well-tolerated.
Thase M. et al. (2015)[74]	Phase III, randomized, double-blind study to assess efficacy, safety, and tolerability of brexpiprazole as an add-on therapy with ADTs in treatment-resistant MDD. Patients were given 8 weeks of an ADT and subsequently double-blind randomized for 6 weeks to one of three groups: brexpiprazole 3 mg/day, 1 mg/day, or placebo. The primary efficacy end point was to observe a difference in MADRS total score, and the secondary efficacy end point was to see a change in SDS mean score.	The brexpiprazole 3 mg group showed a statistically significant improvement in MADRS total score over placebo (-8.29 vs -6.33; $p = 0.0079$). The 1 mg dosage did not show significant improvement. When looking at the SDS score, the two brexpiprazole groups both showed a similar level of improvement compared to placebo. Akathisia, headache, and weight gain were the most common TEAEs.	Brexpiprazole 3 mg was efficacious in treating treatment-resistant MDD patients compared to placebo. Both the 1 mg and 3 mg dosages were well tolerated.
Weisler R. et al. (2016)[75]	Phase IIIb, open-label, 12-week study performed to examine how effective brexpiprazole was as an add-on therapy for treatment-resistant MDD in young adults (18–35 years old) who were currently studying or working. Patients were given	Brexpiprazole improved depressive symptoms as measured by MADRS ($p < 0.0001$). The SDS score and the Work Limitations Questionnaire showed improvements by the end of the study (both $p < 0.0001$), signifying improved functioning in various spheres (work or school, social	Brexpiprazole could improve functioning in work/school and increase quality of life for young adults

(Continued)

TABLE 1 (*Continued*)

Clinical Safety and Efficacy

AUTHOR (YEAR)	GROUPS STUDIED AND INTERVENTION	RESULTS AND FINDINGS	CONCLUSIONS
	adjunctive brexpiprazole 1–3 mg/day (target dose: 2 mg/day).	interactions, and responsibilities at home). Common TEAEs included headache, weight gain, and somnolence.	with MDD who are working or studying.
Davis L. et al. (2016)[76]	Phase IIIb, open-label, exploratory, 6-week study with the goal of assessing efficacy, safety, and tolerability of brexpiprazole as an add-on therapy in patients who had treatment-resistant MDD with anxious symptoms. They were given open-label brexpiprazole 1–3 mg/day (target dose: 2 mg/day) adjunctively for a time period of 6 weeks. The endpoints were to observe a change in MADRS total score, HAM-A total score, and SDS score.	Compared to participants' baseline, there was significant improvement in symptoms. The least squares mean change in MARS total score was −19.6 ($p < 0.0001$), HAM-A total score was −17.8 ($p < 0.0001$), and mean SDS score was −3.6. Increased hunger, diarrhea, dry mouth, and dizziness were the most commonly reported TEAEs noted.	Brexpiprazole as an adjunctive therapy to ADT can be used to treat both depressive and anxious symptoms in MDD.
Krystal A. et al. (2016)[77]	Phase III, interventional, open-label, flexible-dose, 8-week, exploratory study to examine the effect that brexpiprazole had on alleviating sleep disturbances in treatment-resistant MDD. Patients were given open-label treatment of their ADT with brexpiprazole (target dose: 3 mg/d). Data was compared from the beginning and end using PSG and rankings for insomnia severity, depressive symptoms, and daytime attentiveness.	Brexpiprazole adjunct therapy resulted in improvements in sleep efficiency, increased time asleep, insomnia, fatigue, and morning sleepiness. MADRS showed improvement in depressive symptoms of −16.0, and the Massachusetts General Hospital-Cognitive and Physical Functioning Questionnaire (all $p < 0.05$) showed an improvement in functioning of −8.4. Depressive symptoms were improved by increasing quality and length of sleep.	Brexpiprazole as an add-on therapy to ADT improved sleeping problems in patients with treatment-resistant MDD.

Citrome L. et al. (2016)[78]	Randomized, multicenter, open-label, 6-week, exploratory study to compare brexpiprazole's and aripiprazole's efficacy, effects on cognition, and safety in acute schizophrenia. Patients were randomized into two groups: brexpiprazole 3 mg/d and aripiprazole 15 mg/d. Results were measured using PANSS, Barratt Impulsiveness Scale 11-item score, and Cogstate computerized cognitive test battery scores.	Both brexpiprazole and aripiprazole showed significant reduction in symptoms. A modest reduction in impulsivity was seen with brexpiprazole but not aripiprazole. Neither treatment showed improvement in cognition. A lower incidence of akathisia was observed in the brexpiprazole group compared to the aripiprazole group.	When comparing brexpiprazole to aripiprazole, brexpiprazole was at least similar in efficacy, resulted in fewer cases of akathisia, and may show improvement in impulsive symptoms.
Weiss C. et al. (2018)[79]	Analysis of short-term and long-term clinical studies that set out to examine the adverse effect of body weight gain for brexpiprazole and aripiprazole when used in patients for schizophrenia and as an add-on therapy to ADT for MDD. Their goal was to quantify the weight gain and evaluate how often clinically relevant body weight change happened, which they defined as ⩾7% change.	In short-term studies of brexpiprazole, the mean weight gain was 1.2 kg for schizophrenia, and 1.5 kg for MDD. In short-term studies of aripiprazole, the mean weight gain was 0.6 kg for schizophrenia and 1.6 kg for MDD. In long-term studies for brexpiprazole, the mean weight gain was 2.1 kg for schizophrenia and 3.2 kg for MDD. In long-term studies for aripiprazole, the mean weight gain was 3.0 kg for schizophrenia and 4.0 kg for MDD.	Brexpiprazole and aripiprazole had a similar effect on weight gain over the time period of one year.
Citrome L. et al. (2019)[80]	Post hoc analysis of data from two 6-week, randomized, double-blind, placebo-controlled studies and a 52 week, open-label, extension study to examine the effectiveness of brexpiprazole in alleviating hostility and agitation in schizophrenia. The PANSS Excited Component (EC) and PANNS hostility item (P7) were used to quantify change in agitation and hostility.	After 6 weeks of treatment, there was improvement in agitation and hostility. A greater improvement was seen in the 4 mg/d group than the 2 mg/d group. These improvements persisted after 58 weeks. The TEAE of akathisia was noted to be higher in the 4 mg group than the 2 mg group, possibly indicating a relationship between dose and risk of TEAEs.	Brexpiprazole could treat hostility and agitation in patients with schizophrenia and was well-tolerated. The incidence of akathisia may have a relationship with dosage.

Phase II/III study

A phase II/III, multicenter, randomized, double-blind, placebo-controlled study (n = 459) was performed over the course of 6 weeks in Japan with patients diagnosed with acute schizophrenia (SCZ). The purpose was to elucidate the efficacy, safety, and tolerability of brexpiprazole over placebo in this patient population. The participants were given brexpiprazole 1 mg, 2 mg, 4 mg, or placebo once daily. The primary endpoint was to see a difference from the beginning of treatment to week 6 in Positive and Negative Syndrome Scale (PANSS). Significant improvement over placebo was observed in the 2 mg group (treatment difference: −7.32, p = 0.0124), numerical improvement was observed in the 4 mg group (treatment difference: −3.86, p = 0.8330), and only a slight improvement was observed in the 1 mg group (treatment difference: −0.63, p = 0.8330). Vomiting, hyperprolactinemia, diarrhea, nausea, and dental caries were the TEAEs that occurred with an incidence of 5% and ⩾2 times the placebo rate. These were deemed to be mild to moderate adverse effects. The conclusions drawn were that Japanese adult patients with acute schizophrenia responded well to brexpiprazole, and it did not cause severe TEAEs.[71]

Phase III studies

A phase III, multicenter, open-label, flexible-dose (1–4 mg/d) 52-week study (some participated for 26 weeks) was performed to elucidate the safety, tolerability, and efficacy of administering brexpiprazole over a long period of time. Most of the participants of this study were transferred from 3 randomized, double-blind, placebo-controlled, phase III studies, but some were new patients. The primary endpoint was to examine the occurrence rate and gauge the seriousness of TEAEs. The secondary endpoint was to quantify efficacy using PANSS and the Personal and Social Performance scale. The authors found that 14.6% of patients who took at least one dose of brexpiprazole ended the treatment due to TEAEs; schizophrenia was the most frequent (8.8%), and psychotic disorder was next (1.5%). The incidences of TEAEs that were above 5% were schizophrenia (11.6%), insomnia (8.6%), weight gain (7.8%), headache (6.4%), and agitation (5.4%); most of these were judged to be mild to moderate. In terms of weight gain, the mean increase from the beginning of the study to week 26 was 1.3 kg, and when comparing the beginning to week 52, it was 2.1 kg. In terms of efficacy, patients steadily improved with regard to their symptoms. As a treatment for schizophrenia, brexpiprazole is well tolerated at doses of 1–4 mg/d for up to 52 weeks.[72]

A randomized, double-blind, placebo-controlled study was performed to ascertain the efficacy, safety, and tolerability of brexpiprazole maintenance treatment in adult patients who had been diagnosed with schizophrenia. Patients who presented with acute psychotic symptoms were switched to brexpiprazole (1–4 mg/day) over the course of 1–4 weeks and stabilized single-blind for 12 weeks. These patients (n = 202) were then double-blind randomized to maintenance treatment of brexpiprazole (using their stabilization dose) or placebo for as long as 52 weeks. The primary efficacy endpoint was to measure the time it took for patients to relapse after the double-blind randomization began. The trial was ended early because the treatment was shown to be efficacious after 45 events (a predetermined time to perform analysis). Time until relapse was statistically significantly delayed when using brexpiprazole compared to placebo ($p < 0.0001$, log-rank test). The hazard ratio was 0.292 (95% confidence interval: 0.156, 0.548), and during the last visit, the mean dose recorded was 3.6 mg. 13.5% of the brexpiprazole group and 38.5% of the placebo group met the criteria for an approaching relapse. The rate at which adverse events occurred was similar between brexpiprazole and placebo during maintenance treatment. The authors concluded that brexpiprazole as a maintenance treatment for schizophrenia was more effective than a placebo and well-tolerated.[73]

A phase III, randomized, double-blind study was performed with patients whose depression persisted after 1–3 previous antidepressant treatments (ADTs). The goal of this study was to assess efficacy, safety, and tolerability of brexpiprazole as an add-on therapy with ADTs in patients diagnosed with MDD (using DSM-IV-TR criteria) who experienced treatment failure. The patients were given eight weeks of prospective, physician-determined, open-label ADT and subsequently double-blind randomized for six weeks to one of three groups: brexpiprazole 3 mg/day, 1 mg/day, or placebo. The primary efficacy endpoint was to observe a difference in Montgomery-Asberg Depression Rating Scale (MADRS) total score from the beginning of treatment to the end, and the secondary efficacy endpoint was to see a change in Sheehan Disability Scale (SDS) mean score. For the brexpiprazole 3 mg group (n = 213), there was a statistically significant improvement in MADRS total score over placebo (n = 203; −8.29 vs −6.33; p = 0.0079). The 1 mg dosage did not show significant improvement (n = 211; −7.64 vs −6.33; p = 0.0737). When looking at the SDS score, the two brexpiprazole groups both showed a similar level of improvement compared to the placebo. Akathisia, headache, and weight gain were the most common TEAEs. This study concluded that brexpiprazole 3 mg was efficacious in treating treatment-resistant MDD patients compared to placebo, and both the 3 mg and 1 mg dosages were well tolerated.[74]

A phase IIIb, open-label, 12-week study was performed to examine how effective brexpiprazole was as an add-on therapy for MDD in young adults (defined as 18–35 years old) who were currently studying or working. Patients who did not adequately respond to 1–3 ADTs were given adjunctive brexpiprazole 1–3 mg/day; the target dose was 2 mg/day. Brexpiprazole was shown to improve depressive symptoms, which was measured by MADRS total score as −18.1 ($p < 0.0001$). The Sheehan Disability Scale Score showed a mean change of −11.2 ($p < 0.0001$), and the Work Limitations Questionnaire also showed improvements by the end of the study ($p < 0.0001$). Reductions in these two scores signified improved functioning in various spheres (work or school, social interactions, and responsibilities at home). Common TEAEs included headache (21.3%), weight gain (17.0%), and somnolence (17.0%). The authors concluded that young adults with MDD who are in work or study responded well to brexpiprazole as an add-on treatment, and it could improve functioning in work/school and increase the quality of life.[75]

A phase IIIb, open-label, exploratory, 6-week study was done with the goal of assessing efficacy, safety, and tolerability of brexpiprazole as add-on therapy in patients who had MDD with anxiety symptoms. The participants selected had a diagnosis of MDD, Hamilton Anxiety Rating Scale (HAM-A) total score ⩾20, and were not responding adequately to their current ADT. In addition to their current ADT, they were given open-label brexpiprazole 1–3 mg/day (target dose of 2 mg/day) for a time period of 6 weeks. The endpoints were to observe a change in MADRS total score, HAM-A total score, and Sheehan Disability Scale (SDS) after six weeks. Compared to the participants' baseline, there was a significant improvement in symptoms. The least-squares mean change in MARS total score was −19.6 ($p < 0.0001$), HAM-A total score was −17.8 ($p < 0.0001$), and the mean SDS score was −3.6. Increased hunger (13.5%), diarrhea, dry mouth, and dizziness (10.8% for the last 3) were the most commonly reported TEAEs noted. The conclusions drawn were that for patients who had MDD plus anxiety symptoms, brexpiprazole can be effective as an adjunctive therapy and can reduce anxiety symptoms as well.[76]

A phase III, interventional, open-label, flexible-dose, 8-week, exploratory study ($n = 44$) aimed to examine the effect that brexpiprazole had on alleviating sleep disturbances in patients with treatment-resistant MDD (diagnosed with DSM-IV-TR criteria). The selected participants in the study failed to respond to an ADT and had lower than 85% sleep efficiency, which was quantified by baseline polysomnography

(PSG). They were given open-label treatment of their ADT with brexpiprazole (target dose: 3 mg/d) added for a time period of 8 weeks. Results were measured by comparing data from the beginning and end of the study using PSG and rankings for insomnia severity, depressive symptoms, and attentiveness during the day. Brexpiprazole adjunct therapy resulted in improvements ($p < 0.05$), assessed by PSG and Consensus Sleep Diary for Morning, in the efficiency of sleep (10.4 and 15.4%), total time spent sleeping (49.0 and 84.5 min), time until falling asleep (−19.7 and −42.6 min), time spent awake through the night after falling asleep (−26.4 and −48.9 min), and time until continued sleep (−24.9 min, PSG only). The Insomnia Severity Index showed an improved score (−9.2), the Epworth Sleepiness Scale showed less fatigue during the day (−2.1), and the Bond-Lader Visual Analog Scale showed less sleepiness in the morning (−9.2; $p < 0.05$ for all three measurements above). Treatment caused reaction time to fall marginally ($-0.2\ sec^{-1}$; $p < 0.05$). MADRS showed improvement in depressive symptoms of −16.0, and the Massachusetts General Hospital-Cognitive and Physical Functioning Questionnaire (all $p < 0.05$) showed an improvement in functioning, −8.4. The ISI showed that depressive symptoms were influenced by sleep ($p < 0.0001$), and increased alertness throughout the day depended on the ISI improving ($p = 0.009$). The authors concluded that brexpiprazole as an add-on therapy to ADT improved sleeping problems in treatment-resistant MDD patients.[77]

Other Clinical Studies

A randomized, multicenter, open-label, 6-week, exploratory study was done to elucidate and compare brexpiprazole's and aripiprazole's efficacies, effects on cognitive functioning, and safety in patients diagnosed with acute schizophrenia. The authors identified patients with schizophrenia who were experiencing an acute psychotic episode and would benefit from hospitalization. They randomized the patients into two groups: one received a target dose of brexpiprazole 3 mg/d, and the other received a target dose of aripiprazole 15 mg/d over the course of 6 weeks. Results would be measured using PANSS, Barratt Impulsiveness Scale 11-item score, and Cogstate computerized cognitive test battery scores. Using PANSS for reduction of symptoms, brexpiprazole showed −22.9 reduction, and aripiprazole showed −19.4 reduction. Using the Barratt Impulsiveness Scale 11-item total score, brexpiprazole showed a modest reduction in impulsivity (−2.7), but aripiprazole did not (0.1). Neither of the treatment groups showed improvement in

Cogstate scores. With regards to TEAEs, a lower incidence of akathisia was observed in the brexpiprazole group (9.4%) compared to the aripiprazole group (21.2%). Clinical improvements were observed with both treatments. The study concluded that brexpiprazole was at least similar in efficacy to aripiprazole, was well-tolerated, resulted in fewer cases of akathisia than aripiprazole, and may show improvement in impulsive symptoms, whereas aripiprazole does not.[78]

Analyses of Clinical Trials

One of the most commonly reported TEAEs is weight gain. An analysis of various short-term and long-term clinical studies set out to examine the adverse effect of body weight gain for brexpiprazole and aripiprazole when used in patients for schizophrenia and as an add-on therapy to ADT for MDD. Their goal was to quantify the weight gain and evaluate how often clinically relevant body weight change happened, which they defined as ⩾7% change. In short-term studies (4–6 weeks) of brexpiprazole, the mean weight gain was 1.2 kg for schizophrenia and 1.5 kg for MDD. In short-term studies of aripiprazole, the mean weight gain was 0.6 kg for schizophrenia and 1.6 kg for MDD. In long-term studies (52 weeks) for brexpiprazole, the mean weight gain was 2.1 kg for schizophrenia and 3.2 kg for MDD. In long-term studies for aripiprazole, the mean weight gain was 3.0 kg for schizophrenia and 4.0 kg for MDD. The conclusions drawn were that after one year, brexpiprazole and aripiprazole have a similar effect on body weight in the treatment of schizophrenia and MDD.[79]

A post hoc analysis of data from two 6-week, randomized, double-blind, placebo-controlled studies and a 52 week, open-label, extension study was done to examine the effectiveness of brexpiprazole in alleviating hostility and agitation in patients with schizophrenia. The PANSS Excited Component (EC) and PANNS hostility item (P7) were used to quantify the change in agitation and hostility. After 6 weeks of brexpiprazole treatment, there was an improved PANSS-EC score; the least-squares mean differences versus placebo showed reduction in symptoms (2 mg/d: -0.69, $p = 0.020$; 4 mg/d dose: -1.11, $p = 0.0002$). In the hostile subgroup, their PANSS-EC least-squares mean differences versus placebo at week 6 showed improvement (2 mg/d: -0.63, $p = 0.18$; 4 mg/d: -1.03, $p = 0.024$). For P7, they showed some improvement (2 mg/d: -0.27, $p = 0.038$; 4 mg/d: -0.34, $p = 0.0080$). Over the course of 58 weeks, these improvements persisted. The TEAE of akathisia was noted to be higher in the 4 mg group (8.6%) than the 2 mg group (5.2%), possibly indicating a relationship between increased dose and increased risk of TEAEs. Brexpiprazole was concluded to have the

ability to treat hostility and agitation in patients with schizophrenia and was well-tolerated.[80]

Conclusion

Regardless of the progress made in determining the neurobiology to aspects of schizophrenia or MDD, the exact pathology is not fully understood. Most theories on the pathophysiology focus on abnormal levels of dopamine, glutamate, and/or serotonin, which have been targets of interest for therapies. Schizophrenia and MDD have a wide range of risk factors, both biological and environmental. The close relationship between the two disorders involve similar treatments which includes a variety of antipsychotics or antidepressants mainly to reduce the severity of positive symptoms, which have the largest impact on improving patient function, as well as preventing relapses of psychotic symptoms. As mentioned, a recent systematic review of mortality studies reports that the standardized mortality ratio for schizophrenia is currently 2.6, which has unfortunately been rising over the past several decades. Third generation antipsychotics, which include brexpiprazole, are the latest group of drugs to reach the market and includes the drug of interest for this review. These are different from the prior two generations: they are D2 partial agonists that also have actions on 5-HT1A and 5-HT2A receptors. Brexpiprazole is an atypical antipsychotic approved by the FDA in July 2015 for the treatment of schizophrenia and as an adjunct therapy for management of MDD. In pharmacokinetic studies involving multiple once-daily oral dosing of brexpiprazole, steady state plasma concentration is reached around day 10. Overall, adverse effects were noted to be mild to moderate, and the most frequently seen effect was temporarily increased serum prolactin, which is common in most antipsychotic medications. Studies mentioned above concluded that patients with schizophrenia who took brexpiprazole were safe and well tolerated. Patients with acute schizophrenia responded well to brexpiprazole, and it did not cause severe treatment emergent adverse events. Also, patients who had MDD plus anxiety symptoms, brexpiprazole can be effective as an adjunctive therapy and can reduce anxiety symptoms as well. Risk should be discussed of adding brexpiprazole such as adverse metabolic effects, QT prolongation, sedation and falls when considering the addition of an atypical antipsychotics. Baseline labs such as a lipid panel, A1c as well as an EKG should be obtained prior to the addition of this medication for augmentation. In conclusion, brexpiprazole has proved to be an effective alternative to typical or first and second-generation atypical antipsychotics with a favorable side effect profile depending on the patient's tolerance. ✤

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