BREXPIPRAZOLE

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Topic Overview

Brexpiprazole is an atypical antipsychotic indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults, as well as the treatment of schizophrenia in patients ages 13 years and older. Brexpiprazole can be used off-label to treat severe behavioral or psychological symptoms of dementia (BPSD) and agitation in patients with Alzheimer's disease. Brexpiprazole may also have promise in the treatment of unipolar and bipolar patients with treatment-resistant depression when used in combination with other drugs. The combination drugs that have been studied are maintenance doses of esketamine or intravenous ketamine. Notable adverse effects include akathisia and weight gain. Data is limited comparing brexpiprazole to other antipsychotics, but it should be considered in patients who have not tolerated other antipsychotics well.

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Credits: 1 hour of continuing education credit

Type of Activity: Knowledge

Media: Internet **Fee Information:** $4.99

Estimated time to complete activity: 1 hour, including Course Test and course evaluation

Release Date: October 18, 2022 **Expiration Date:** October 18, 2025

Target Audience: This educational activity is for pharmacists.

How to Earn Credit: From October 18, 2022, through October 18, 2025, participants must:

1) Read the "learning objectives" and "author and planning team disclosures;"
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Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Describe** the basic pharmacological profile, use, and clinical outcomes of brexpiprazole treatment
2. **Identify** the uses for brexpiprazole
3. **Compare** the benefits and risks of brexpiprazole use for patients with chronic mental illness compared to other antipsychotics
4. **Identify** the contraindications and potential side effects of brexpiprazole

Disclosures

The following individuals were involved in the development of this activity: Angel A. Rodriguez, PharmD, BCACP, and Susan DePasquale, MSN. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

Introduction

Brexpiprazole is an atypical antipsychotic currently indicated for use as an adjunctive therapy for the treatment of major depressive disorder in adults, as well as the treatment of schizophrenia in patients ages 13 and older. This drug has also been used off-label for the treatment of severe behavioral or psychological symptoms of dementia, and agitation in patients with Alzheimer's disease. Brexpiprazole is currently being explored as a possible treatment for unipolar and bipolar patients with treatment-resistant depression when used in combination with other drugs.

History of Brexpiprazole

Brexpiprazole was approved by the Food and Drug Administration in 2015.[1,2] It is marketed under the brand name Rexulti®. It is approved for the treatment of major depressive disorder (MDD) in adults, as well as the treatment of schizophrenia in patients ages 13 and older. It is used off-label for the treatment of severe behavioral or psychological symptoms of dementia (BPSD).[1,2]

Compared with some of the newer second-generation antipsychotics, brexpiprazole is reported to have a more balanced serotonin/dopamine receptor binding profile leading to fewer neuromotor adverse effects. There is also less sedation and less weight gain reported with brexpiprazole. Clinical studies on the benefit and risk profile of brexpiprazole are discussed in later sections.

Brexpiprazole and other similar drugs are referred to as second-generation or atypical antipsychotics because they were developed 20-30 years after the first antipsychotics, such as haloperidol and thioridazine, had been in use. Atypical antipsychotics are less likely to cause adverse effects like extrapyramidal symptoms (EPS) that are relatively common for *typical* antipsychotics like haloperidol and thioridazine.

Aside from when they were developed and the comparative risk for EPS, atypical antipsychotics are also distinct from typical antipsychotics in their pharmacologic actions, and these differences influence their adverse effect profile and clinical effectiveness. The primary mechanism of action of the typical antipsychotics is dopamine$_2$ receptor antagonism. Atypical antipsychotics have this effect, as well, but to a lesser degree; the binding of the atypical antipsychotics to dopamine receptors may not be as strong or as lasting as for the typical antipsychotics, and this may explain the decreased risk for EPS compared to the typical antipsychotics.[3-5] In addition, atypical antipsychotics are powerful serotonin receptor antagonists, and their ability to act as serotonin receptor antagonists is often stronger than their dopamine$_2$ receptor blockade.[3-5]

Pharmacological Profile

Brexpiprazole is an atypical, second-generation antipsychotic that exhibits its main mechanism of action as a partial agonist of the D_2 and 5-HT_{1A} receptors as well as antagonistic activity at 5-HT_{2A} receptors. Brexpiprazole also has partial agonist activity at D_3 and 5-HT_{1A} receptors, antagonist activity at 5-HT_{2B}, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors, and affinity for H_1 receptor and M_1 receptors.[1,2] The partial agonism of D_2 receptors theoretically reduces dopamine output when the dopamine concentrations are high and increases dopamine output when dopamine concentrations are low. These two actions are thought to improve the positive and negative symptoms of schizophrenia. The partial agonist activity at 5-HT_{1A} receptors is what is responsible for mood, anxiety, and cognitive changes. The agonistic activity at 5-HT_{2A} receptors is responsible for the enhancement of dopamine release in certain brain regions, which reduces motor side effects. Lastly, blockade of receptor α_{1B} may reduce agitation associated with dementia and reduce motor side effects such as akathisia.[1,2]

The mean half-life of brexpiprazole is 91 hours, with its major metabolite having a half-life of 86 hours. The major metabolite of DM-3411 is not considered to contribute to the therapeutic effects of brexpiprazole. After a single-dose administration, the peak plasma concentration was observed at 4

hours post-administration with 95% bioavailability. A steady state was achieved within 10-12 days of dosing. Brexpiprazole is 99% protein-bound, and the protein binding is not affected by renal or hepatic impairment. Nearly half of metabolized brexpiprazole will be eliminated through the GI tract, and one-fourth will be renally eliminated.

Brexpiprazole was first approved for the primary treatment of schizophrenia but may also be used as an adjunctive therapy for the treatment of MDD. Off-labeled uses of brexpiprazole include the treatment of psychosis and/or agitation associated with dementia.[1,2]

Brexpiprazole Uses

Brexpiprazole is available under the brand name Rexulti in tablet strengths of 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg. Dosing is typically once daily, with or without food. Dosing for schizophrenia, and MDD may be obtained from the package inserts or drug summary.[1,2]

Labeled Uses

For adult patients diagnosed with schizophrenia, the treatment goal is a reduction in positive and negative symptoms, with the patient recognizing that the symptoms may not be eliminated completely. If brexpiprazole does not work as monotherapy, additional add-on therapies include valproic acid, mood-stabilizing anticonvulsants, lithium, topiramate, and benzodiazepines.[1,2]

For the adjunctive treatment of MDD, treatment should continue until symptoms are significantly reduced or gone, and treatment should continue for 1 year if it is the first episode of depression but may need to be indefinite in the second or subsequent episodes.[1,2]

Unlabeled Uses

Brexpiprazole's package insert states that it is not an approved treatment for patients with dementia-related psychosis; however, it has been used as an off-label treatment for BPSD. The treatment of severe BPSD does not have an established dosing regimen. The FDA has required a boxed warning noting increased death in geriatric patients being treated for BPSD. In 2019, there were two phase III clinical trials that reported brexpiprazole 2mg/day had the potential to be efficacious. These clinical trials included nearly 700 adult patients with Alzheimer's disease (AD) and showed that brexpiprazole has the potential to be well-tolerated, safe, and efficacious in the treatment of agitation in patients with AD.[6] Brexpiprazole is noted to be used as a short-term adjunctive treatment to help while addressing the underlying causes of severe symptoms. Grossberg, *et al.* (2020) suggest a dosing schedule of 0.25 mg once daily for 3 days, then 0.5 mg once daily for 10 days, then 1 mg once daily for 2 weeks with a target dose of 2 mg once daily.[7]

Dosing Adjustments

Several dosing adjustments need to be taken into consideration involving CYP2D6 and CYP3A4 enzymes. In patients with decreased activity of the CYP2D6 enzyme, half of the normal dose of brexpiprazole is recommended. If a patient has decreased CYP2D6 activity and is also taking a drug that is a strong CYP3A4 inhibitor, one-fourth of the normal dose should be used. In a patient taking a strong inhibitor of CYP2D6 *or* CYP3A4, one-half of the normal dose should be used. When patients are taking a strong inhibitor of CYP2D6 *and* a strong inhibitor of CPY3A4, one-quarter of the normal dose should be used. Patients taking drugs that are strong CYP3A4 inducers will need the dose doubled over two weeks.[2]

Brexpiprazole is metabolized by the liver, and the area under the curve (AUC) of brexpiprazole is increased in patients who have moderate to severe hepatic impairment.[1] For patients with moderate to severe hepatic impairment, Child-Pugh category B or C, the maximum daily dose is 2 mg for

the treatment of MDD and 3 mg for the treatment of schizophrenia.[1,2] Liver test abnormalities reportedly occurred in ~ 1% of patients on long-term therapy with brexpiprazole, but the risk for this was equivalent to patients taking a placebo. There is no published information on acute liver injury caused by brexpiprazole.[8]

Renal impairment increases the AUC of brexpiprazole when the creatinine clearance (CrCL) is < 60 mL/minute. The maximum daily dose should be adjusted to 2 mg for MDD and 3 mg for schizophrenia.[1,2]

Contraindications, Adverse Effects, Warnings, and Precautions

Brexpiprazole's drug summary and package inserts state that it is contraindicated in patients who have a hypersensitivity to brexpiprazole, or any of the components of the drug.[1,2] A patient taking brexpiprazole may present with a rash, facial swelling, or urticaria; and, anaphylaxis has been reported with brexpiprazole use.[1,2]

The package inserts for brexpiprazole list a number of warnings and precautions. Many of these adverse effects have not been reported with the use of brexpiprazole, but it is structurally and pharmacologically similar to other atypical antipsychotics.[9,16] Moreover, because it is comparatively new, it is possible that with more clinical use, some of the listed, potential adverse effects may be reported with the use of brexpiprazole. A prudent clinician should evaluate a patient for risk factors that are associated with these effects prior to prescribing brexpiprazole, and then monitor the patient during the therapeutic period.

The most common adverse reactions seen with the use of brexpiprazole are weight gain and akathisia. These adverse effects are also linked to metabolic changes, such as dyslipidemia and hyperglycemia.[9] Adverse effects from brexpiprazole, such as dose-related akathisia, increased serum triglycerides, and weight gain, have reported incidence rates of >10%.[1,2]

Other warnings and precautions that should be considered when prescribing brexpiprazole are "cerebrovascular adverse reactions in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, leukopenia, orthostatic hypotension, and seizures."[9] There are boxed warnings and precautions listed for pregnant women.[1,2,9] As a consequence, precautions should be taken in individuals with the following health conditions or a history of a prior adverse response to brexpiprazole.[1,2,9]

Central Nervous System

Brexpiprazole may cause central nervous system (CNS) depression. Additionally, EPS, acute dystonia, akathisia, Parkinsonism, and tardive dyskinesia, are well-known adverse effects of the atypical antipsychotic.[1,6,7] No published information on brexpiprazole and acute dystonia, Parkinsonism, and tardive dyskinesia was found. Akathisia has been reported to occur in 4.0% - 14% of patients. The dose of brexpiprazole and the incidence of akathisia are correlated; as the dose increases, the incidence of akathisia increases as well. Because of the dose/risk relationship, treatment of brexpiprazole-induced akathisia may begin with a dose reduction.[2,10,11]

Akathisia typically starts several days after the patient begins taking an antipsychotic, with 50% of cases developing within a month, and 90% developing within three months after the first dose.[12] However, Stroup and Gray (2018) stated that while akathisia usually develops gradually during the days to weeks after treatment begins, it can present more acutely.[13] Beta-blockers, benzodiazepines, or 5-HT_{2A} antagonists can be used for the treatment of akathisia. Drug-induced parkinsonism can be treated with benztropine, trihexyphenidyl, or amantadine. Lastly, tardive dyskinesia can be treated with valbenazine or deutetrabenazine,[12] but Stroup and Gray reported that the clinical utility of valbenazine and deutetrabenazine in treating tardive dyskinesia is unclear.[13]

Hyperglycemia and Weight Gain

Hyperglycemia has been reported as an adverse effect of atypical antipsychotics, including brexpiprazole, and severe cases of hyperglycemia causing hyperosmolar coma, ketoacidosis, and death have occurred with the use of the atypical antipsychotics.[1,2] Patients who have diabetes or who are prediabetic are more likely to develop hyperglycemia from an atypical antipsychotic.[14] Hyperglycemia can resolve after discontinuing the use of the drug, with some patients requiring treatment of diabetes after discontinuation of therapy.[14] The prescribing information for brexpiprazole states that there have been reports of hyperglycemia in patients treated with brexpiprazole, but no other published information on the topic was located.[1,2]

During clinical trials of patients who had MDD, a weight gain of ≥ 7% of body weight was reported in 2%-5% of patients taking brexpiprazole and in 2% of patients receiving a placebo.[2] During clinical trials of patients who had schizophrenia, a weight gain of ≥ 7% of body weight was reported in 10%-11% of patients taking the drug and in 4% of patients receiving a placebo.[2] In open-label studies, 30% of patients who had MDD and 20% of patients who had schizophrenia had a weight gain of ≥ 7% of body weight.[2]

Schizophrenia and MDD patients treated with brexpiprazole have experienced weight gain; however, Weiss, *et al.* (2018) reported that brexpiprazole may be grouped among antipsychotics with "the lowest propensity to induce weight increase in schizophrenia and in MDD."[15]

Metformin is a common strategy used to help prevent or reverse antipsychotic-induced weight gain. Lifestyle modifications should also be a focus for patients with the potential for medication-related weight gain.

Cardiovascular

The risk for orthostatic hypotension from brexpiprazole appears to be greatest at treatment initiating or when the dose is increased.[2] Brexpiprazole should be used cautiously in patients who cannot tolerate a sudden drop in

blood pressure, who have cardiovascular disease, have a cerebrovascular disease, are chronically dehydrated, or are taking blood pressure-lowering drugs.[1]

The clinical trials for MDD observed a 0.1% incidence of orthostatic hypotension for the brexpiprazole group compared to 0.0% for the placebo group.[2] The clinical trials for schizophrenia observed a 0.4% incidence of orthostatic hypotension for the brexpiprazole group compared to 0.2% of the placebo group.[2] The overall incidence of syncope was 0.1% for brexpiprazole compared to 0% in all placebo groups.[2]
Falls

Brexpiprazole and other atypical antipsychotics can cause orthostatic hypotension, CNS depression, motor instability, and sensory instability. These adverse effects increase the risk for falls, particularly in elderly patients.[1,2] Fall risk assessments should be completed upon initiation of brexpiprazole and reevaluated for long-term use.

Gastrointestinal

Antipsychotics have been associated with esophageal dysmotility and aspiration. Brexpiprazole should be used cautiously in patients who are at risk for aspiration, who have AD or dementia, or patients > 75 years old.[1,2]

Dyslipidemia

Atypical antipsychotics, including brexpiprazole, can significantly increase serum triglyceride levels.[1,2,4] Unlike some of the other atypical antipsychotics, brexpiprazole does not cause significant increases in fasting serum cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol.[1,2]

Seizure Disorder

Atypical antipsychotics may lower the seizure threshold, and seizures associated with the use of brexpiprazole have been reported.[2,4] Brexpiprazole should be used cautiously in patients who have a seizure disorder or may be at risk for seizures or are taking a medication that causes seizures or lowers the seizure threshold.[2]

Hematologic

Agranulocytosis, leukopenia, and neutropenia have been reported to be temporally associated with the use of antipsychotics.[1,2,4] Possible risk factors for hematologic adverse effects include a pre-existing low white blood cell (WBC) count or absolute neutrophil count (ANC), and drug-induced leukopenia or neutropenia.[1,2] Blood counts should be periodically measured if the patient has risk factors for these dyscrasias.[2] If the patient has signs of blood dyscrasia or if the ANC is <1,000/mm^3, drug use should be discontinued.[2] For patients who have had drug-induced leukopenia or have a low ANC or WBC, the complete blood count (CBC) should be checked at baseline and frequently during the first few months of therapy.[1,2]

Neuroleptic Malignant Syndrome

Atypical antipsychotics can cause neuroleptic malignant syndrome (NMS), a rare and potentially fatal adverse drug reaction characterized by autonomic instability, hyperthermia, muscle rigidity, and neurological changes.[1,2] Neuroleptic malignant syndrome may occur after rapid dose titration, or because of a higher total daily drug dose, but it *usually* occurs within the typical therapeutic dosage range of antipsychotics.[14] There is currently no data available to determine the propensity for brexpiprazole causing NMS; however, due to its mechanistic similarity to aripiprazole, clinicians should continue to monitor their patients for NMS when they are taking brexpiprazole.[16]

The onset of signs and symptoms usually begin within two weeks of starting therapy with an antipsychotic, and almost all cases of NMS occur within 30 days of the first dose, but NMS can occur after the first dose or after years of taking the same drug at the same dose and can even happen when the use of the drug is discontinued.[16,17] If NMS occurs, the use of the antipsychotic drug should be discontinued immediately.[14]

Temperature Regulation

Antipsychotics have been associated with altered thermoregulation and can have anticholinergic effects, both of which can put the patient at risk for an elevated temperature.[1,2] Dehydration, high ambient temperature, the concurrent use of anticholinergic drugs, and strenuous exercise may increase this risk.[1,2] No specific information has been reported with Rexulti, but this is something that should be monitored with all atypical antipsychotics.

Geriatric Patients and Beers Criteria

US Boxed warnings for brexpiprazole include an increased risk for mortality in elderly patients with dementia-related psychosis.[9] The Beers Criteria consider antipsychotics inappropriate for use in patients 65 years and old who have dementia as their use in this population may cause stroke, cognitive decline, and an increase in mortality.[1] For the atypical antipsychotics, the Beers Criteria warns that their use in elderly patients who have dementia increases the risk for serious adverse effects, and they should only be used to treat behavioral problems in this patient population when non-pharmacological interventions have not worked, and the patient is a danger to self or to others.[18]

Suicidal Ideation and Behavior

The prescribing information for brexpiprazole includes a US Boxed Warning that states that antidepressants increase the risk of suicidal behavior and ideation in patients 24 years of age and younger.[1,2,9] Brexpiprazole is not categorized as an antidepressant; however, atypical antipsychotics are often

prescribed for patients who have unipolar major depression. Although the FDA data analysis that was the basis for the US Boxed Warning about antidepressants and suicide did not include information about the atypical antipsychotics, the prescribing information for brexpiprazole and the other atypical antipsychotics is required to include the US Boxed Warning about suicide.

Pregnancy and Breastfeeding

Brexpiprazole has not been assigned to a pregnancy category of the Food and Drug Administration, and there are no well-controlled studies that have examined the risks of taking brexpiprazole during pregnancy.[2] The use of atypical antipsychotics during the third trimester has been associated with neonatal EPS and withdrawal signs and symptoms.[1,2,9]

There is a national exposure registry that collects information about atypical antipsychotics and pregnancy: National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388. There is no relevant published information about brexpiprazole and breastfeeding.[19] If a woman chooses to breastfeed while on medication, the infant should be monitored for possible adverse effects of the medication.

Other Warnings and Precautions

Warnings about drug-induced QT prolongation, dysphagia and aspiration, hematologic abnormalities, and elevated prolactin level are included in the prescribing information for brexpiprazole.[1,2,20]

Brexpiprazole Overdose

Atypical antipsychotics are relatively well tolerated, even if a patient overdoses.[17,21] Fatalities are rare with atypical antipsychotics, but there is an increased risk of sudden cardiac death.[1,13] Atypical antipsychotics usually cause anticholinergic effects, orthostatic hypotension, and sedation.[1,13] Although serious cases can present with coma, QTC, and (occasionally) QRS

prolongation, seizures, and respiratory depression, these are uncommon.[1,9,13,19] The onset of effects usually is within one to two hours after ingestion, and the peak effects occur within six hours.[9,13] No published cases of injury from brexpiprazole overdose were located, and the toxic doses of brexpiprazole are not known. Ware, *et al.* (2019), and Forbes, *et al.* (2018) reported on an overdose case during their respective study, but the participant did not suffer any lasting effects from the overdose.[11,16]

Treatment of brexpiprazole overdose should be symptomatic and supportive; there is no antidote.[17,22] Activated charcoal is recommended if its use would be appropriate and safe; gastric lavage should not be used.[23] Atypical antipsychotics are highly protein bound, have a high volume of distribution, and have low blood levels, so extracorporeal removal would be unlikely to be effective.[17]

Drug Interactions

Brexpiprazole is primarily metabolized by CYP2D6 and CYP3A4. Concurrent use of brexpiprazole and the drugs that have strong effects on CYP3A4 and CYP2D6 may be contraindicated, or concurrent use should be done very cautiously and with dosing adjustment and close monitoring.[2]

Significant CYP3A4 inducers include phenytoin, rifampicin, St. John's wort, carbamazepine, and barbiturates, while significant CYP3A4 inhibitors include clarithromycin, ketoconazole, and grapefruit juice.[24]

While not an extensive list, some significant CYP2D6 inhibitors include diphenhydramine, fluoxetine, haloperidol, and paroxetine. CYP2D6 is not as susceptible to being induced, so only CYP2D6 inhibitors may require dose adjustments.[24]

Some medications that are CYP inhibitors and inducers do not require dose adjustments for brexpiprazole. These include dextromethorphan (CYP2D6), lovastatin (CYP3A4), bupropion (CYP2D6 and 2B6), fexofenadine (P-gp), and gastric pH modifiers such as omeprazole.[2]

Studies Reviewing the Uses of Brexpiprazole

As mentioned above, brexpiprazole is approved to treat schizophrenia, and as an adjunctive treatment for MDD. Brexpiprazole can be used off-label to treat BPSD and agitation in patients with AD. The following sections discuss study findings for these uses.

Major Depressive Disorder

Atypical antipsychotics are recommended as an adjunctive treatment for the treatment of MDD. The FDA approved this indication of brexpiprazole based on the results of two phase-3 trials.[25,26] Patients who were unresponsive to therapy to at least one previous antidepressant were randomized to receive brexpiprazole (3 mg, 213 patients; 2 mg, 175 patients; 1 mg, 211 patients) plus an antidepressant, or an antidepressant plus a placebo (381 patients). After six weeks, the patients who were given 2 mg or 3 mg of brexpiprazole had significant improvement compared to the placebo-treated patients; the patients given 1 mg of brexpiprazole did not.[25,26] The most commonly reported adverse effects in both trials were akathisia and weight increases, with some reports of headaches as well.[25,26] Subsequent research has confirmed the effectiveness of brexpiprazole as an adjunctive therapy for treating MDD, but several reviews and meta-analyses have concluded that the evidence for its effectiveness is limited and based on a small amount of data from short-term trials.[27-29]

There are no studies that have directly compared the effectiveness of brexpiprazole to other atypical antipsychotics as an adjunctive treatment for MDD.[29] The review by Diefenderfer, *et al.* (2018) found that there was no difference between aripiprazole, brexpiprazole, cariprazine, olanzapine, or risperidone in their effectiveness as an adjunctive treatment for MDD.[28]

Schizophrenia

Antipsychotics are the first-choice drug for acute and maintenance treatment of schizophrenia, and the efficacy of brexpiprazole as a treatment

for schizophrenia was first established in two phase-3 clinical trials (VECTOR and BEACON trials).[30-34] A third clinical trial, the LIGHTHOUSE trial, followed.[30,34]

In the VECTOR trial, patients who were having an acute exacerbation of psychotic symptoms of schizophrenia were randomized to receive brexpiprazole 0.25 mg, 2 mg, or 4 mg or placebo; 445 patients received brexpiprazole, and 178 received a placebo. After six weeks, the scores of the Positive and Negative Symptom Scale (PANSS) and the Clinical Global Impressions scale (CGI) were compared, and the PANSS and CGI scores for the patients who had taken 2 mg or 4 mg of brexpiprazole were significantly improved compared to the placebo-treated group.[31]

Further, patients who were having an acute exacerbation of psychotic symptoms of schizophrenia were randomized to receive brexpiprazole 0.25 mg, 2 mg, or 4 mg or placebo; 490 patients received brexpiprazole, and 184 received a placebo. After six weeks, the scores of the Positive and Negative Symptom Scale (PANSS) and the Clinical Global Impressions scale (CGI) were compared, and the PANSS and CGI scores for the patients who had taken 4 mg of brexpiprazole were significantly improved compared to the placebo-treated group. The PANSS and CGI scores of patients who had taken 1 mg or 2 mg of brexpiprazole were numerically improved compared to the placebo-treated group, but the differences were not clinically significant.[32]

These trials were limited, but recent reviews suggest that short-term and long-term treatment plans using brexpiprazole may treat the symptoms of schizophrenia throughout the changes and phases that characterize this disorder.[34,35]

Behavioral and Psychological Symptoms of Dementia

For AD patients with agitation and psychosis, second-generation antipsychotics are only recommended as a treatment after first-line non-pharmacological interventions, and treatment duration should be no longer than 12 weeks. The prescribing information for many of the atypical

antipsychotics has a US Boxed Warning as long-term use of antipsychotics in elderly patients with dementia is associated with an increased risk of death and also an increased risk of cerebrovascular events.[1,2] Reduction of agitation is the major goal of the treatment of BPSD in patients with AD while not inducing sedation.[6] Two distinct phase III clinical trials conducted in 2019 (NCT01862640 and NCT01922258) with nearly 700 participants with AD reported that brexpiprazole 2mg/day had the potential to be safe, efficacious, and well-tolerated in this population. The primary endpoint in these studies was the change from baseline to week 12 in the Cohen-Mansfield Agitation Inventory (CMAI). In the first study with a fixed dose of 1 mg or 2 mg/day, patients with 2mg/day showed a statistically significant improvement, whereas in the second study with flexible dosing of 0.5-2 mg/day, only patients who were titrated to 2mg/day at week 4 demonstrated significant improvement. There are currently three phase III clinical trials underway evaluating the long-term safety and clinical efficacy in this patient population, which may help gain FDA approval for the treatment of agitation in AD.[6]

Atypical antipsychotics can be used to treat serious behavioral and emotional problems in patients who have dementia, but their use should be restricted to situations in which other treatments have been unsuccessful, and the patient's health or the safety of others is at risk.[18]

Brexpiprazole v. Aripiprazole and Cariprazine

Brexpiprazole and aripiprazole are both dopamine partial agonists.[36-38] Brexpiprazole has less intrinsic activity at D_2 receptors than aripiprazole, which may induce fewer activating adverse events. Brexpiprazole is also more potent at 5-HT_{1A} partial agonist, 5-HT_{2A} antagonist, and α_{1B} antagonist than aripiprazole which may reduce akathisia, EPS, and hyperprolactinemia. Brexpiprazole is a more potent H_1 receptor antagonist than aripiprazole, but it has a more than 50 times lower affinity for H_1 receptors relative to D_2/5-HT_{1A} receptors which may limit the risk for weight gain and sedating adverse effects.[36] Citrome, *et al.* (2016) revealed that brexpiprazole (3 mg) had similar efficacy to aripiprazole (15 mg) for treatment in acute schizophrenia measured by a reduction in PANSS scores; however, brexpiprazole was associated with a

lower incidence of akathisia (9.4%) compared to aripiprazole (21.2%), and similar rates of weight gain from baseline to week 6.[37]

There are few open-label trials comparing brexpiprazole and aripiprazole. Mohr, *et al.* (2022) provided a comparative study between aripiprazole, brexpiprazole, and cariprazine.[39] The authors acknowledge the "clinical efficacy of aripiprazole, brexpiprazole, and cariprazine in the treatment of various psychiatric disorders," but they highlight the lack of "head-to-head comparisons between them."[39] This is important because "there are clinically meaningful differences in their effects that can be attributed to their specific pharmacological profiles."[39]

Potential Future Uses for Brexpiprazole

Brexpiprazole may have promise in the treatment of unipolar and bipolar patients with treatment-resistant depression when used in combination with other drugs.[40] Chan, *et al.* (2022) reported on a drug treatment that combines brexpiprazole with maintenance esketamine or intravenous ketamine for unipolar and bipolar patients with treatment-resistant depression.[40] The authors highlighted a possible connection between a reduction in suicidal behavior and improvements in cognition and patients' abilities to function.[40]

Some challenges will need to be overcome, such as patients experiencing "overlapping adverse events" from the combination of drugs, cost, and availability. More research is needed before this treatment regimen may be regarded as a treatment option for unipolar and bipolar patients with treatment-resistant depression.[40]

Summary

Brexpiprazole is an atypical, second-generation antipsychotic with its main mechanism of action as a dopamine partial agonist. Brexpiprazole is considered to be the primary treatment for schizophrenia and may be used as adjunctive therapy along with antidepressants to treat MDD.

Brexpiprazole can be used off-label to treat severe behavioral or psychological symptoms of dementia (BPSD) and agitation in patients with Alzheimer's disease.

Brexpiprazole may also have promise in the treatment of unipolar and bipolar patients with treatment-resistant depression when used in combination with other drugs. The combination drugs that have been studied are maintenance doses of esketamine or intravenous ketamine.

Notable adverse effects include akathisia and weight gain. Data is limited comparing brexpiprazole to other antipsychotics, but it should be considered in patients who have not tolerated other antipsychotics well.

Course Test

1. **Brexpiprazole is categorized as a second-generation,**

    a. anticonvulsant.
    b. atypical antipsychotic.
    c. mood stabilizer.
    d. typical antipsychotic.

2. **Brexpiprazole has an unlabeled use for the treatment of**

    a. behavioral disturbances in dementia.
    b. major depressive disorder (MDD).
    c. schizophrenia.
    d. hypertension.

3. **Which of the following is not an adverse effect of brexpiprazole?**

    a. Akathisia
    b. Acne
    c. Weight gain
    d. Hyperglycemia

4. **If neuroleptic malignant syndrome (NMS) occurs with the use of an atypical antipsychotics**

    a. the antipsychotic should be discontinued immediately.
    b. the dosage of the drug(s) should be tapered.
    c. the drug(s) may be continued but at reduced dosage(s).
    d. the patient may continue the use of the drug(s) but should be monitored carefully.

5. **The maximum daily dosage for the treatment of schizophrenia is**

    a. 6 mg.
    b. 2 mg.
    c. 4 mg.
    d. 1 mg.

6. **A mother who is taking brexpiprazole and who plans to breastfeed her newborn should know that**

    a. brexpiprazole is NOT excreted in breast milk.
    b. brexpiprazole is contraindicated in women who are breastfeeding.
    c. there is no relevant, published information on brexpiprazole and breastfeeding.
    d. brexpiprazole has an RID of > 10%.

7. **The incidence of akathisia increases with**

    a. an increase in the dose of brexpiprazole.
    b. a reduction in the dose of brexpiprazole.
    c. the concomitant administration of brexpiprazole and a benzodiazepine.
    d. the concomitant administration of brexpiprazole and a beta-blocker.

8. **Treatment of brexpiprazole overdose may include**

    a. after administration of the recommended antidote.
    b. extracorporeal removal.
    c. gastric lavage.
    d. activated charcoal, if safe and appropriate.

9. **True or False: Brexpiprazole is considered a first-line treatment for Major Depressive Disorder.**

    a. True
    b. False

10. **The prescribing information for brexpiprazole includes a US Boxed Warning that states antidepressants increase the risk of suicidal behavior and ideation in patients**

    a. 24 years of age and younger
    b. ages 50-65
    c. adults >65.
    d. ages 25-30.

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