REVIEW

Brexpiprazole: A New Treatment Option for Schizophrenia

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ABSTRACT

Schizophrenia occurs in approximately 0.3 to 0.7 percent of the world's population and is associated with significant morbidity and mortality. Although atypical antipsychotics reduce positive and negative symptoms, they are associated with varying degrees of metabolic adverse effects. This necessitates continued development of efficacious yet metabolically favorable treatments. This article reviews brexpiprazole, a medication recently approved to treat patients with schizophrenia. Brexpiprazole was well-tolerated, and adverse reactions were statistically insignificant. They included nausea; insomnia; headache; agitation; akathisia; and weight gain or changes in lipid, creatine phosphokinase, glucose, or prolactin levels. Brexpiprazole is taken once daily without regard to food, and the dose should be adjusted in patients who receive moderate or strong CYP450 inhibitors or inducers and in patients with hepatic or renal disease.

INTRODUCTION

Schizophrenia occurs in approximately 0.3 to 0.7 percent of individuals worldwide and is characterized by at least two of the following symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, or negative symptoms.[1,2] It is associated with decreased functioning in work, interpersonal relationships, and/or self-care.[2] Second-generation or atypical antipsychotics reduce positive and negative symptoms and are recommended first-line treatments. However, they are associated with adverse effects such as weight gain, dyslipidemia, and hyperglycemia, which may worsen comorbid cardiovascular conditions.[3,4] This necessitates continued development of effective, tolerable, and metabolically favorable antipsychotics. In July 2015, brexpiprazole was approved to treat schizophrenia and major depressive disorder (as adjunct with antidepressant therapy). However, a discussion of brexpiprazole for both conditions is beyond the scope of this article. This review will highlight efficacy, tolerability, dosing, and precautions for brexpiprazole in patients with schizophrenia.

MECHANISMS OF ACTION

Similar to aripiprazole, brexpiprazole is a partial agonist at 5-HT_{1A}, D_2, and D_3 receptors and an antagonist at 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors.[5,6] Compared to antipsychotics that exert antagonism of dopamine receptors, partial agonism suggests lower risk of akathisia, tardive

TABLE 1. Studies of brexpiprazole for schizophrenia

STUDY	STUDY DESIGN	DURATION	*N*	DOSES
Phase 2 trial[13]	Randomized, double-blind, placebo-controlled	6 weeks	459	0.5–1.5mg, 2–3mg, or 4–6mg range groups; aripiprazole 10–20mg/day
Phase 2 trial[14]	Randomized, open-label	6 weeks	97	Brexpiprazole 1–4mg/day or aripiprazole 10–20mg/day
Phase 3 trial[15]	Randomized, double-blind, placebo-controlled	6 weeks with 1 month follow-up	674	1mg, 2mg, or 4mg
Phase 3 trial[16]	Randomized, double-blind, placebo-controlled	6 weeks with 1 month follow-up phase	636	0.25mg, 2mg, or 4mg
Phase 3 trial[17]	Randomized, single-blind, placebo-controlled	Up to 52 weeks; study was terminated early because efficacy was determined at first interim analysis	202	1–4mg

dyskinesia, extrapyramidal symptoms, and abnormal prolactin levels. Lack of significant histamine receptor antagonism decreases risk for sedation and weight gain. Although brexpiprazole shares a similar mechanism of action with aripiprazole, it exerts greater partial agonism of $5HT_{1A}$ receptors, greater antagonism of $5HT_{2A}$ receptors, and less partial agonism of D_2 receptors.[7] Due to greater modulation of $5HT_{1A}$ and 5-HT_{2A} receptors, rats receiving brexpiprazole exhibited less cognitive impairment compared to those receiving aripiprazole.[8] This modulation led to improvements in social recognition in mice, with no such improvement noted in mice receiving olanzapine or risperidone.[9]

EFFICACY

Given their similar mechanism of action, brexpiprazole was compared to aripiprazole in two studies; two additional trials assessed efficacy of varying doses for reducing acute symptoms, and one maintenance study evaluated efficacy for preventing exacerbation or relapse.[13–17] Details for each study are provided in Table 1. The primary endpoint in all studies was the total change in the Positive and Negative Syndrome Scale (PANSS).[10] The main secondary endpoint was change in the Clinical Global Impressions—Severity scale (CGI-S) and/or the Personal and Social Performance Scale.[11,12]

Both aripiprazole comparison studies used flexible doses, and the first study noted that decreases in PANSS scores were significant for placebo, brexpiprazole, and aripiprazole groups.[13] In the second study, both brexpiprazole and aripiprazole resulted in significant reductions in PANSS scores.[14] Results are not available for a trial comparing brexpiprazole to extended-release quetiapine.

In the first varying-dose study, the 4mg dose of brexpiprazole was statistically superior to placebo on both primary and secondary endpoints.[15] The second study found that 2mg and 4mg doses significantly reduced PANSS and CGI-S scores, but only the 2mg group experienced a significant change on the Personal and Social Performance Scale.[16] In the maintenance study, patients stabilized on brexpiprazole were randomized to placebo or continued brexpiprazole treatment.[17] Patients in the treatment group experienced fewer relapses compared to placebo.

TOLERABILITY

Brexpiprazole was well-tolerated in acute and maintenance studies. Less than five percent of patients reported adverse effects, which were mild or moderate and included dyspepsia, insomnia, headache, and agitation.[15,16,18] The discontinuation rate was higher in the placebo group and was attributed to adverse effects, withdrawal of consent, or lack of efficacy with emergent symptoms of schizophrenia. Brexpiprazole was associated with statistically insignificant increases in weight and levels of glucose, triglyceride, creatine phosphokinase, and changes (increases or decreases) in prolactin.[15,16] Kane et al[15] reported akathisia more frequently in the placebo group, but Correll et al[16] noted akathisia more commonly in patients receiving 2mg and 4mg doses of brexpiprazole. Occurring within the first three weeks of treatment, akathisia tended to be mild and did not lead to discontinuation. In the second comparison study with aripiprazole, patients receiving brexpiprazole reported fewer extrapyramidal symptoms and akathisia.[14]

DOSING

Brexpiprazole is available in 0.25mg, 0.5mg, 1mg, 2mg, 3mg, and 4mg tablets, given once daily without regard to food.[6] The recommended daily dose is 2 to 4mg, starting with 1mg for four days, then 2mg for

three days, then 4mg if indicated. For patients who are CYP2D6 poor metabolizers or who are receiving a moderate or strong CYP3A4 and/or CYP2D6 inhibitor, the dose should be reduced by 50 to 75 percent of the usual dose.[6] The dose should be slowly doubled over 1 to 2 weeks in patients receiving a strong CYP3A4 inducer.[6] The maximum dosage is 3mg/day in patients with moderate or severe hepatic or renal impairment or with end-stage renal disease.

Following oral administration, brexpiprazole reaches peak concentrations within four hours and steady-state within 10 to 12 days, with a half-life of 91 hours. It has a high volume of distribution and is highly protein bound in plasma.[6] It is largely metabolized by CYP3A4 and CYP2D6 isozymes, with the metabolite being primarily excreted in feces.[6]

CONTRAINDICATIONS

Brexpiprazole is contraindicated in patients with known hypersensitivity to brexpiprazole or its formulation components. As with other atypical antipsychotics, brexpiprazole carries the risk of seizure, tardive dyskinesia, neuroleptic malignant syndrome, orthostatic hypotension, white blood cell count and metabolic abnormalities, cerebrovascular adverse reactions in elderly patients, and a "black box" warning for increased mortality in elderly patients with dementia-related psychosis.[6] Brexpiprazole is not yet assigned a Pregnancy Category, but neonates exposed to brexpiprazole in the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms.[6] While no data are available regarding safety in breastfeeding mothers, the manufacturer recommends prescribers and their patients consider the benefits of breastfeeding and the mother's need for brexpiprazole and the potential adverse effects on the infant from brexpiprazole or the underlying mental illness.[6]

CONCLUSION

Schizophrenia is a debilitating condition with significant morbidity and mortality. Many atypical antipsychotics improve functioning, but they carry risks for adverse effects. Brexpiprazole reduced symptoms of acute schizophrenia and prevented relapse with minimal adverse effects. It is an additional option for clinicians who treat patients with schizophrenia, and ongoing trials are assessing its efficacy as an adjunctive treatment for patients with posttraumatic stress disorder or behavioral disturbances associated with dementia.

DISCLAIMER

The views expressed in this article are those of the author and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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