

Spotlight on brexpiprazole and its potential in the treatment of schizophrenia and as adjunctive therapy for the treatment of major depression

Dawn Bruijnzeel
Rajiv Tandon

Department of Psychiatry, University of Florida College of Medicine, Gainesville, FL, USA

Abstract: Antipsychotic agents, utilized for the treatment of a range of psychiatric disorders, differ substantially in terms of their pharmacology and adverse effect profiles. Incomplete and variable efficacy, differences in safety–tolerability, and highly heterogeneous response across individuals prompt development of new agents. Brexpiprazole is one of the two most recently introduced antipsychotic agents approved for the treatment of schizophrenia and as an adjunct for treatment of major depressive disorder. Its pharmacology, clinical trial data, and efficacy and side effects in comparison with other antipsychotic agents are discussed. Brexpiprazole is a dopamine D-2 partial agonist with potent activity at the serotonin 5HT_{1A} and 5HT_{2A} and noradrenergic alpha-1B and alpha-2C receptors. Placebo-controlled clinical trials in persons with schizophrenia support its efficacy in treating psychosis and preventing relapse. Short-term clinical trials also support its efficacy as an adjunct to antidepressants in treating major depressive disorder in individuals inadequately responsive to antidepressant treatment alone. Adverse effects include akathisia, gastrointestinal side effects, and moderate weight gain. The recommended oral dose of brexpiprazole is 2–4 mg/day in schizophrenia and 2–3 mg/day as adjunctive treatment in major depression. It must be titrated up to its target dose over 1–2 weeks and is effective in once-daily dosing. How brexpiprazole’s unique pharmacological profile will translate into clinically meaningful differences from other antipsychotic agents is unclear. Its place in our antipsychotic armamentarium and potential role in the treatment of schizophrenia and major depressive disorder will be determined by additional clinical data and experience.

Keywords: brexpiprazole, partial agonist, schizophrenia, major depression, treatment, pharmacology, dopamine

Introduction

Twenty antipsychotic medications are currently approved for clinical use in the US (Figure 1) with brexpiprazole (Rexulti®) being one of the most recent agents to become available. Despite the availability of a number of antipsychotic medications, many patients either do not benefit from or develop significant side effects to currently available agents.¹ In this article, we review the pharmacological profile of brexpiprazole, summarize clinical trial data that pertain to its efficacy and safety–tolerability, discuss its optimal clinical utilization, compare its clinical profile to that of other commonly used antipsychotic agents, and critically evaluate its potential role in the treatment of schizophrenia and major depressive disorder.

Correspondence: Dawn Bruijnzeel
Department of Psychiatry, University of Florida College of Medicine, 1601 SW Archer Rd, 116A, Gainesville, FL 32608, USA
Tel +1 352 376 1611 ext 4381
Email dheron@ufl.edu



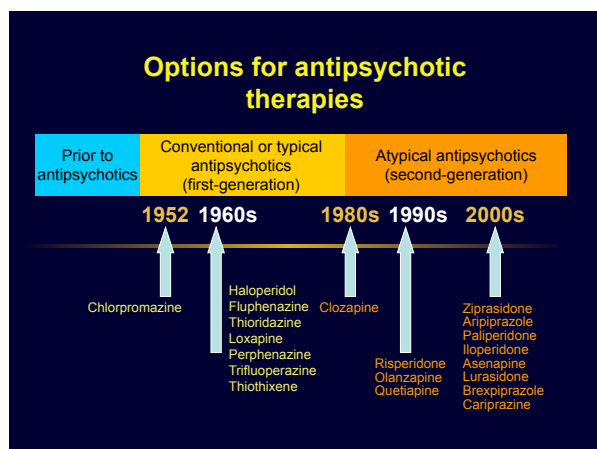


Figure 1 Antipsychotic agents in the USA.

Receptor pharmacology

Brexpiprazole is a phenylpiperazine derivative whose unique chemical structure most closely resembles aripiprazole among currently available antipsychotic agents.² In the scheme of broadly classifying antipsychotic agents into first-generation and second-generation antipsychotics (SGAs), brexpiprazole is an SGA.³ Like other antipsychotic agents, the precise mechanism of antipsychotic action of brexpiprazole is currently unknown, although it appears to be related to its activity at the dopamine D₂ receptor.⁴ Brexpiprazole is a partial agonist at the dopamine D₂ receptor, similar to aripiprazole and cariprazine. It also shares the additional attribute shared by all currently available SGAs – the ability to potently block the serotonin 5HT_{2A} receptor.^{2,5} Additionally, brexpiprazole has potent activity at the serotonin 5HT_{1A} (partial agonist) and noradrenergic alpha-1 and alpha-2 (antagonist) receptors.² It exhibits moderate antagonist activity at the serotonin 5HT₇ and 5HT_{2C} and histamine H₁ receptors and negligible activity at the muscarinic cholinergic M₁ receptor.

A comparison of brexpiprazole's receptor binding profile with that of aripiprazole is instructive. Whereas both aripiprazole and brexpiprazole are high-affinity, partial agonists at the dopamine D₂ receptor, brexpiprazole has twice the affinity and approximately half the intrinsic activity of aripiprazole at this receptor. Brexpiprazole has higher affinity to and greater intrinsic activity than aripiprazole at the serotonin 5HT_{1A} receptor, where both agents are partial agonists. In contrast to aripiprazole, brexpiprazole has significantly greater antagonist activity at alpha-1a and alpha-2 noradrenergic receptors.

Although the precise clinical implications of this pharmacological profile are not fully known, current understanding of potential efficacy and side effect consequences of relevant neurotransmitter receptor modulation is summarized in

Table 1.⁶ The potent D₂ affinity with low intrinsic activity (likely functional antagonism in the mesolimbic dopamine system) along with potent 5HT_{2A} antagonism might appear to confer upon brexpiprazole the attribute of a potent antipsychotic with low liability to cause extrapyramidal side effects – as with other SGAs. The lower intrinsic activity at the dopamine D₂ receptor, in comparison to aripiprazole, positions brexpiprazole in between that agent and other antipsychotics (which are D₂ antagonists with 0% intrinsic activity) in this regard. The potent 5HT_{1A} partial agonism and moderate 5HT₇ antagonism could potentially be associated with improved cognition and antidepressant benefits;^{7–10} whereas the potent alpha-1 and alpha-2 noradrenergic antagonism could contribute to hypotension and necessitate gradual titration to a target dose. The enhancement of noradrenergic neurotransmission in conjunction with 5HT_{2A} antagonism may contribute to its antidepressant effects. The absence of significant affinity to the M₁ receptors suggests a low liability for this agent to cause peripheral and central anticholinergic side effects,¹¹ whereas the low affinity at the H₁ and 5HT_{2C} receptors suggests a modest potential for weight gain and other metabolic side effects. Data from preclinical studies with brexpiprazole have generally been consistent with this profile.

Pharmacokinetics

The activity of brexpiprazole is almost exclusively due to the parent drug. The pharmacokinetics of brexpiprazole is dose-proportional within a total daily dose of 1–8 mg and steady-state concentrations are reached within 2 weeks. The mean half-life at steady-state is ~91 hours.¹² Brexpiprazole is rapidly absorbed after oral administration, reaching peak serum concentrations in 4 hours. Approximately 95% is absorbed without any notable impact of food. Brexpiprazole is highly protein-bound (over 99%), with high affinity for alpha-1 glycoprotein and albumin. Protein binding is not affected by hepatic or renal impairment. Brexpiprazole is eliminated largely by hepatic metabolism, principally via cytochrome P450 (CYP)-3A4 and -2D6. Thus, drugs that induce or inhibit the CYP-3A4 enzyme system may have profound effects on its bioavailability. In contrast, brexpiprazole is neither an inducer nor inhibitor of CYP enzymes. It has one major inactive metabolite (DM-3411). Less than 1% is excreted unchanged in the urine.

Clinical trials in schizophrenia

Focus on efficacy

Data on the short-term efficacy and safety of brexpiprazole in the treatment of schizophrenia are available from three

Table 1 Clinical implications of agonism and antagonism at various neurotransmitter receptors

Receptor and activity	Benefits	Side effects
Dopamine receptors		
D ₂ receptor (antagonist)	Antipsychotic effects Efficacious for positive symptoms	Extrapyramidal side effects (EPS): Dystonia Parkinsonism Tardive dyskinesia Prolactin elevation: Galactorrhea Gynecomastia Menstrual changes Sexual dysfunction Negative symptoms Cognitive dysfunction Dysphoria
Serotonin receptors		
5HT _{1A} (agonist)	Possible improved mood Possible improved cognition	Not known
5HT _{2A} (antagonist)	Reduced EPS	Not known
5HT _{2C} (antagonist)	Not known	Weight gain
5HT ₇ (antagonist)	Possible efficacy in improving mood Possible efficacy in improving cognition	Not known
Adrenergic receptors		
α ₁ (antagonist)	Not known	Postural hypotension Dizziness
α _{2A} (antagonist)	Not known	Changes in blood pressure Possible hyperalgesia
Histamine receptors		
H ₁ (antagonist)	Not known	Sedation Weight gain
Acetylcholine receptors		
Muscarinic	Not known	Blurred vision Xerostomia Constipation Urinary retention Sinus tachycardia Cognitive dysfunction

6-week, Phase II or Phase III double-blind, randomized, placebo-controlled multinational, multicenter clinical trials in 1,769 patients (Table 2).^{13–15} The average age of patients in these studies was 40 years, with two-thirds being male, and patients had a moderately severe illness burden at baseline on average. One of these three studies also included an active antipsychotic comparator (ie, aripiprazole).¹³ This particular study was a failed study in that neither brexpiprazole (0.25, 1, 2.5, and 5 mg/day) nor aripiprazole (15 mg/day) was found to be more effective than placebo.¹³ In the other two studies, 2–4 mg of brexpiprazole was found to be more effective than placebo. While preliminary data suggest that the 4 mg/day dose may be more efficacious than the 2 mg daily dose, this is not definitive.^{14,15} Consequently,

it is recommended that 2 mg/day be the initial target dose of brexpiprazole with gradual titration up to this dose and 4 mg/day the maximum recommended dose.¹² In these studies, brexpiprazole was found to be effective across multiple dimensions of schizophrenia.¹⁶

Brexipiprazole (up to 4 mg/day) has also been compared to quetiapine extended release (up to 800 mg/day) and placebo in 465 patients with an acute exacerbation of schizophrenia in a 6-week randomized clinical trial (NCT01810380), but results of this study are currently unavailable.

The long-term efficacy of brexpiprazole has been evaluated in a 1-year double-blind, placebo-controlled maintenance study of 202 schizophrenia patients.¹⁷ The stabilization and medication-withdrawal study design is currently the

Table 2 Acute placebo-controlled clinical trials of brexpiprazole in the treatment of schizophrenia

Study	Study duration number of patients	Daily dose of brexpiprazole	Comparator	Findings
McQuade et al ¹³	6 weeks 459 patients	0.25 mg 1 mg 2.5 mg 5 mg	Placebo aripiprazole 15 mg	Failed study Neither aripiprazole nor any dose of brexpiprazole found to be more effective than placebo
Correll et al ¹⁴	6 weeks 353 patients	0.25 mg 2 mg 4 mg	Placebo	Both 2 and 4 mg of brexpiprazole found significantly more effective than placebo in overall psychopathology (PANSS and CGI), positive, and negative symptoms
Kane et al ¹⁵	6 weeks 674 patients	1 mg 2 mg 4 mg	Placebo	4 mg brexpiprazole, but not 1 or 2 mg, was significantly more effective than placebo in overall psychopathology (PANSS and CGI), positive, and negative symptoms
Hobart et al ¹⁷	52 weeks 202 patients	1–4 mg/day	Placebo	Brexpiprazole more effective than placebo in relapse prevention with significantly delayed time to relapse and lower rate of relapse

Abbreviations: PANSS, positive and negative syndrome scale; CGI, clinical global impression.

standard for the evaluation of the effectiveness of treatments in preventing relapse in schizophrenia.¹⁸ Brexpiprazole was found to be significantly more effective than placebo in preventing relapse, with a significantly lower proportion of schizophrenia patients relapsing in the brexpiprazole versus placebo group (13.5% vs 38.5%, $P < 0.01$) over the 1-year period.

Brexpiprazole at doses between 2 and 4 mg/day has thus far been efficacious in the treatment of schizophrenia in several short-term studies. How its efficacy compares to that of other antipsychotic agents is unclear. Only limited data are currently available from head-to-head clinical trials, and final results of the completed study comparing brexpiprazole to quetiapine are not yet available. The hope that brexpiprazole might offer advantages in treating the cognitive symptoms of schizophrenia, based on its potent serotonin 5HT_{1A} partial agonism and 5HT_{2A} and 5HT₇ antagonism, awaits confirmation in clinical trials – current data are inadequate to support the claim.^{19,20} Similarly, the promise that brexpiprazole might more effectively treat the mood symptoms of schizophrenia (again based on its distinctive pharmacological profile) awaits confirmation in clinical trials.

Adverse events and safety–tolerability

Data on the safety–tolerability of brexpiprazole in the treatment of schizophrenia were also compiled from the studies discussed earlier. Dose-dependent side effects of brexpiprazole include nausea, akathisia, headache, and modest weight gain. In contrast to aripiprazole that reduces prolactin levels, modest dose-dependent increases in prolactin levels are observed with brexpiprazole. This difference is likely

explained by the lower intrinsic activity of brexpiprazole versus aripiprazole at the dopamine D₂ receptor, rendering brexpiprazole intermediate between aripiprazole and other antipsychotic agents in this regard. Although a modestly greater weight gain was also observed, no significant differences from placebo were observed with regard to changes in serum glucose or lipids. Lastly, this agent appears to have little effect on the corrected QT interval on electrocardiogram.

There are several class level warnings included in the product label for brexpiprazole. These include increased mortality in elderly patients with dementia-related psychosis (black box), cerebrovascular adverse reactions, including stroke, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia, dyslipidemia, hyperprolactinemia, leukopenia, seizures, orthostatic hypotension, potential for cognitive impairment, disrupted body temperature regulation, and dysphagia.

In the absence of direct head-to-head trials versus other antipsychotic agents, it is difficult to precisely place brexpiprazole in the context of other available antipsychotic agents in terms of its adverse effect profile. It appears intermediate between aripiprazole and other SGAs, with a relatively low occurrence of metabolic side effects and modest rates of akathisia. Results of the comparator trials should provide greater clarity.

Clinical trials in major depressive disorder

Focus on efficacy

The short-term efficacy and safety of brexpiprazole in the treatment of major depressive disorder have been assessed in

Table 3 Acute placebo-controlled clinical trials of adjunctive brexpiprazole in the treatment of major depressive disorder inadequately responsive to antidepressant alone

Study	Study duration number of patients	Daily dose of brexpiprazole antidepressant	Comparator antidepressant	Findings
Thase et al ²¹	6 weeks 429 patients	0.15 mg 0.5 mg 1.5 mg	Placebo	1.5 mg, but not other doses of brexpiprazole found to be more effective than placebo in antidepressant response
Thase et al ²²	6 weeks 379 patients	2 mg	Placebo	2 mg of brexpiprazole found significantly more effective than placebo as adjunctive treatment to antidepressant
Thase et al ²³	6 weeks 677 patients	1 mg 3 mg	Placebo	3 mg, but not 1 mg, brexpiprazole, significantly more effective than placebo in improving depression

three 6-week, Phase II or Phase III double-blind, randomized, placebo-controlled multinational, multicenter clinical trials in ~1,500 patients (Table 3).^{21–23} The average age of patients in these studies was 45 years, with approximately a third being male, and study participants had moderately severe illness burden at baseline (average Montgomery-Asberg Depression Rating Scale total score =26).²⁴ In all three studies, patients with major depressive disorder with inadequate response to one to three trials of standard antidepressant medications were selected and received an 8-week prospective trial of a standard antidepressant + placebo. Those who did not respond to such treatment were then randomized to receive adjunctive brexpiprazole or placebo for 6 weeks. In these studies, treatment with 1.5–3 mg of adjunctive brexpiprazole/day was found to produce significantly greater reduction in total Montgomery-Asberg Depression Rating Scale scores (the primary outcome measure)²⁵ and a greater proportion of improved patients than adjunctive placebo. Consequently, it is recommended that 1.5–2 mg/day be the initial target dose of adjunctive brexpiprazole with gradual titration up to this dose and 3 mg/day is the maximum recommended dose for this indication.¹²

The extent of improvement observed with brexpiprazole augmentation of antidepressant is similar in magnitude to that observed in studies of aripiprazole^{25,26} and quetiapine²⁷ augmentation.

Adverse events and safety–tolerability

Data on the safety–tolerability of brexpiprazole as an adjunctive treatment of major depressive disorder were also compiled from the studies discussed earlier. Short-term side effects of brexpiprazole include nausea, diarrhea, akathisia, and modest weight gain. Long-term safety–tolerability data were derived from over 2,000 patients with major depressive disorder who received brexpiprazole augmentation.²⁸ Moderate weight gain was noted as the major adverse effect.

Clinical use

Brexipiprazole is currently approved by the US Food and Drug Administration for the treatment of schizophrenia and as adjunctive treatment of major depressive disorder.

The recommended starting dose for major depressive disorder is 0.5 mg/day to be titrated up to 1.0 mg/day and then to the target dose of 2 mg/day with dosage increases to occur at weekly intervals based on patient response and tolerability (hypotension is the main side effect that necessitates gradual titration). The maximum recommended dose for adjunctive treatment of major depressive disorder is 3 mg/day.

The recommended starting dose for schizophrenia is 1 mg/day to be increased to the target dose of 2 mg/day over a week based on patient response and ability to tolerate the drug. The maximum daily dose is 4 mg/day.

Brexipiprazole can be administered once a day and taken with or without food. Dose adjustments are likely unnecessary on the basis of age, sex, or race. Dose adjustment is recommended in the presence of moderate–severe hepatic impairment or moderate–severe renal impairment; in both instances, the daily dose should not exceed 3 mg/day. If brexpiprazole is administered along with strong CYP-2D6 or -3A4 inhibitors, lower doses should be utilized (approximately half the usual dosage); alternatively, if it is administered with strong CYP-3A4 inducers, higher doses should be utilized.

Summary

Brexipiprazole appears to be a useful addition to our current armamentarium of antipsychotic medications for the treatment of schizophrenia and adjunctive treatment for major depressive disorder that is inadequately responsive to antidepressants alone. It seems comparable to currently available SGAs (ie, similar efficacy, reduced but some extrapyramidal side effect liability) with a relatively low risk of metabolic adverse effects. It should be emphasized, however, that

long-term data on the use of brexpiprazole in the treatment of schizophrenia and major depressive disorder are sparse at this time. Furthermore, available data directly comparing brexpiprazole to other available antipsychotic agents in head-to-head clinical trials are limited. The putative clinical benefits of brexpiprazole relative to other SGA agents need to be demonstrated in well designed and appropriately powered studies and direct comparative studies have thus far not been conducted. The therapeutic place of brexpiprazole in the treatment of schizophrenia and manic disorder and as an adjunct in major depressive disorder will be determined by additional clinical data and clinical experience.

Disclosure

The authors report no conflicts of interest in this work.

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