A review of Efficacy and Safety of Brexpiprazole for Treatment of Schizophrenia

Andhale Komal K., Homkar Prajakta G., Pawar P.Y.

Dr Vitthalrov Vikhe Patil Foundations College of Pharmacy Ahmednagar

Abstract: Brexpiprazole has US Food and Drug Administration approval on July 10, 2015 monotherapy treatment of schizophrenia and adjunctive treatment to antidepressants for major depressive disorder. It is an Antipsychotic drug. Brexpiprazole is a serotonin-dopamine activity modulator that acts as a partial agonist at serotonin 5-HT1A and dopamine D2 receptors at similar potencies and as an antagonist at 5-HT2A and noradrenaline alpha1B/2 receptors. These all lead to a favorable antipsychotic profile in terms of improvement of cognitive performance and sleep patterns, as well as effects on affective states and potential to treat core symptoms in Schizophrenia and major depressive disorder, including cognitive deficits with a low risk of adverse effects. Schizophrenia is a serious mental illness that interferes with a person’s ability to think clearly, make decisions, manage emotions and relate to others. It is a complex, long-term medical illness.

Keywords: brexpiprazole, schizophrenia, Major Depressive Disorder, atypical Antipsychotic.

1. Introduction

(BREX) is an atypical antipsychotic medication. It works by changing the action of Chemicals in the brain.[1] It is a dopamine D2 receptor partial agonist and has been described as a “Serotonin Dopamine Activity Modulator” (SDAM). The drug received FDA approval on July 10, 2015 for the treatment of Schizophrenia, and as an adjunctive treatment for depression. Partial agonists have both blocking properties and stimulating properties at the receptor they bind to. The ratio of blocking activity to stimulating activity determines a portion of its clinical effects. BREX has more blocking and less stimulating activity than its predecessor, aripiprazole, which may decrease its risk for agitation and restlessness. It is also an antagonist of the serotonin 5-HT2A, 5-HT7 and the α1A, α1B, α1D, and α2C-adrenergic Receptors. The drug has negligible affinity for the muscarinic Acetylcholine receptors, and hence has no anticholinergic effects.[2]

Characterized by its hallmark symptoms (ie, hallucination and delusion), schizophrenias represents one of the most debilitating mental disorders, with its prevalence being as high as 0.1% to 0.4%.1–3 It is regarded as a progressive Disease, it occurs initially during adolescence and young adulthood and follows a chronic course as it manifests highly variable mental Symptoms and recurs repeatedly. [3] Aripiprazole affects the same receptors but to a lesser extent. This may give brexpiprazole advantage over aripiprazole. Brexpiprazole has a lower Side effect like akathisia and extra pyramidal symptoms than aripiprazole and other class of antipsychotic drug[4]

2. Chemistry

Brexpiprazole is chemically designated as 7-[4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy]-1,2-dihydroquinolin-2-one. Its molecular Formula is C25H27N3O2S, and its molecular weight Is 433.57. Brexpiprazole is a white-to-off white Powder. It is freely soluble in methanol and Practically insoluble in water.[5-10]
### Metabolism

Based on in vitro metabolism studies using recombinant human cytochrome P450, the metabolism of Brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6 leading to formation of oxidative metabolites. Based on in vitro data, brexpiprazole showed little to no inhibition of other CYP450 isozymes. In vivo, the metabolism of brexpiprazole is mainly mediated by CYP3A4 and CYP2D6 leading to formation of oxidative metabolites with only one metabolite, DM-3411, present in plasma.

### Excretion

Following a single oral dose of [14C]-labeled brexpiprazole, approximately 25% and 46% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged brexpiprazole was excreted in the urine and approximately 14% of the oral dose was recovered unchanged in the feces. Apparent oral clearance of brexpiprazole oral tablet after once daily administration is 19.8 (±11.4) mL/h/kg. After multiple once daily administration of brexpiprazole, the terminal elimination half-life of brexpiprazole and its major metabolite, DM-3411, is 91.4 hours and 85.7 hours, respectively.[13-15]
6. Efficacy and Safety

6.1. Efficacy:

1) Short-term Studies:

Two Phase III RCTs comparing brexpiprazole 2 mg/day, 4 mg/day and placebo were it included in a pooled analyses conducted by Correll et al,[16] which demonstrated that The mean change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score was significantly different at −18.79 and −20.01 (P = 0.0004 and P < 0.0001), respectively, in those receiving brexpiprazole 2 mg/day (n = 359) and 4 mg/day (n = 359), compared to −13.3 in those receiving placebo (n = 358).

It is a pooled analysis conducted by Marder et al,[17] which included a further randomized controlled trial for analysis and demonstrated that the PANSS total score was significantly improved at week 6 at 20.1 in those receiving Brexpiprazole, irrespective of its dose (n = 868), compared to 14.3 in those receiving placebo (n = 517) (P < 0.0001). Another study of interest, pending validation of its results, is a randomized, double-blind, placebo-controlled study conducted to evaluate brexpiprazole 1, 2 and 4 mg/day in Japanese patients with schizophrenia requiring hospitalizations for acute relapse of disease (n = 459).[18]

2) Long-term Studies:

It is a randomized, double-blind trial, Fleischhacker et al assigned patients with schizophrenia to brexpiprazole (at a flexible dose ranging from 1 to 4 mg/day; mean dosage, 3.6 mg/day) or to placebo to evaluate the efficacy of brexpiprazole in preventing relapses.[23] In a 52-week, open-label study, Forbes et al included a total of 1072 patients who had participated in 3 short-term, randomized, double-blind, placebo-controlled trials, as well as de novo patients who had not been part of these trials, to evaluate the safety and tolerability of brexpiprazole.[25] In this study, the efficacy assessment was also conducted as a secondary endpoint in 410 patients, and demonstrated that the PANSS total score improved by 12.2 points.

In a 52-week, open-label study conducted by Ishigooka et al included patients with schizophrenia rolled over from previous short-term studies conducted in Japan. As well as new (de novo) patients with schizophrenia switching to brexpiprazole from previous antipsychotics, To evaluate the safety and tolerability of brexpiprazole (with its dose allowed to be flexible and range from 1 to 4 mg/day).[26]

6.2. Safety

1) Short-term Study:

Kane et al conducted a pooled analysis of randomized, double-blind, placebo-controlled studies of brexpiprazole published to date with a focus on its adverse effect profile.[28] which demonstrated that, of all the treatment emergent adverse events (TEAEs) reported in ≥5% of patients receiving brexpiprazole ≤4 mg/day (n = 1163), none occurred twice or more often in those receiving placebo (n = 463) and that akathisia occurred in a small proportion (5.8%) of those receiving brexpiprazole (compared to 4.5% of those receiving placebo) early with its incidence shown to peak 8–11 days after initiation of brexpiprazole.

It is also of interest that Ivkovic et al conducted a pooled analysis of the effect of brexpiprazole on prolactin,[9] demonstrating, among those with normal prolactin levels at baseline, a mean change in prolactin levels at week 6 of 6.72 ng/mL and 2.35 ng/mL in women (n = 195) and men (n = 267) receiving brexpiprazole 2–4 mg/day, respectively, as compared to 0.08 ng/mL in women (n = 98) and 0.66 ng/mL in men (n = 158) receiving placebo, respectively. Among those whose prolactin levels were shown to be above the upper limit of normal at baseline, The study revealed a mean change in prolactin levels at week 6 of −33.41 and −12.64 ng/mL in women (n = 47) and men (n = 95) receiving brexpiprazole 2–4 mg/day, respectively, as compared to −38.79 and −11.29 ng/mL in women (n = 26) and men (n = 49) receiving placebo, concluding that brexpiprazole affects prolactin levels only minimally.[29]

2) Long-term Studies:

In the relapse prevention trial conducted by Fleischhacker et al described [17], the incidence of TEAEs was shown to be 43.3% in those receiving brexpiprazole 1–4 mg/day (n = 97) as compared to 55.8% in those receiving placebo (n = 104), with the incidence of TEAEs leading to treatment discontinuation being 5.2% in those receiving brexpiprazole compared to 11.5% in those receiving placebo; No TEAEs, including akathisia and weight gain, occurred twice or more frequently in those receiving brexpiprazole than in those receiving placebo. Again, in the maintenance phase of treatment, the study revealed a mean change in body weight of −0.3 kg in those receiving brexpiprazole, as compared to 2.2 kg in those receiving placebo, while the two groups were shown to be comparable with regard to the extrapyramidal symptoms, glucose/lipid metabolism, and heart rate-corrected QT interval parameters, with no tardive dyskinesia seen in those receiving brexpiprazole.

In the prospective, open-label study conducted by Forbes et al,[25] the incidence of TEAEs was shown to be 60.4% in those receiving brexpiprazole at flexible doses ranging between 1 and 4 mg (n = 1031), with the incidence of TEAEs leading to study not continuing being 14.6%. The TEAEs reported in ≥5% of patients receiving BRX included worsening of schizophrenia (11.6%), insomnia (8.6%), weight gain (7.8%), headache (6.4%), and agitation (5.4%), with the change in body weight from baseline being 1.3 kg at week 26 (n = 611) and 2.1 kg at week 52 (n = 408). Thus, the authors concluded that no unforeseeable safety or tolerability issues were found and that brexpiprazole has highly favorable tolerability profile.

During the course of this prospective, open-label, long-term study,[25] Newcomer et al focused attention on fasting metabolic parameters and investigated how the 52-week treatment with brexpiprazole might affect the trial subjects classified into normal, borderline, and high lipid/glucose categories,[24] demonstrating that those exhibiting an unfavorable shift ("normal to borderline or high" or "borderlines to high") accounted for a smaller proportion than those exhibiting a favorable shift ("borderline or high to Normal" or "high to normal").
Thus, both short- and long-term safety results shows that BRX is associated with a low incidence of akathisia and affects lipid metabolism only. Brexpiprazole is also shown to have minimal effect on QTc. In conclusion, brexpiprazole is deemed a safe antipsychotic, consistently with the results of the above-mentioned network meta-analysis.[25]

<table>
<thead>
<tr>
<th>Authors [Reference]</th>
<th>Duration [Week]</th>
<th>Disease Type</th>
<th>N Randomized</th>
<th>Brexpiprazole Dose [n]</th>
<th>Comparator [n]</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Pooled Analysis</td>
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<tr>
<td>Correll et al[16]</td>
<td>6</td>
<td>Acute Schizophrenia</td>
<td>-</td>
<td>0.25 mg (90), 1 mg (120), 2 mg (368), 4 mg (364)</td>
<td>Placebo [368]</td>
<td>Pooled analysis of 3 randomized, double-blind, placebo-controlled studies. BRX 2 mg and 4 mg were superior to placebo in efficacy.</td>
</tr>
<tr>
<td>Marder et al[17]</td>
<td>6</td>
<td>Acute Schizophrenia</td>
<td>Fixed Dose[868]</td>
<td>Placebo [517]</td>
<td></td>
<td>Meta-analysis of 4 short- and long term studies showed a clinically change in PANSS total score of −20.0 in those receiving BRX, compared to 14.3 in those receiving placebo.</td>
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</table>

<p>| Short term studies  |                 |              |              |                        |               |          |
| Ishigooka et al[18] | 6               | Acute Schizophrenia | 459          | 1 mg (115), 2 mg (115), 4 mg (113) | Placebo [116] | Phase III multicenter, randomized, double-blind, placebo-controlled study in Japan BRX at 2 mg/day showed statistically significant efficacy compared to placebo with the most common TEAE being worsening of schizophrenia. Correll et al20 6 Acute schizophrenia. |
| Correll et al [19]  | 6               | Acute Schizophrenia | 636          | 0.25 mg (90), 2 mg (182), 4 mg (180) | Placebo [184] | Phase III multicenter, randomized, double-blind, placebo-controlled study. BRX at 2 and 4 mg/day demonstrated statistically significant efficacy (as assessed by PANSS total score and CGI-S) compared to placebo with the most common TEAE being akathisia. |
| Citrome et al [20]  | 6               | Acute Schizophrenia | 97           | Target Dose 3mg | Aripiprazole Target dose 15 mg (10–20 mg) | Phase IIIb, multicenter, randomized, open-label, exploratory study. BRX showed significant improvement in PANSS total score. BRX demonstrated a slightly greater numerical improvement. |</p>
<table>
<thead>
<tr>
<th>Study (Author)</th>
<th>Sample Size</th>
<th>Study Design</th>
<th>Treatment</th>
<th>comparator</th>
<th>Conclusion</th>
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<tr>
<td>Van Erp et al [21]</td>
<td>6</td>
<td>Stable Schizophrenia</td>
<td>38</td>
<td>2mg[19] 4mg[19]</td>
<td>compared with aripiprazole in symptoms and function (CGI-S, SLOF, BIS-11). The incidence of akathisia was lower in brexpiprazole (9.4%) than aripiprazole (21.2%).</td>
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<tr>
<td>Malla et al [22]</td>
<td>16</td>
<td>Early episode schizophrenia</td>
<td>49</td>
<td>3mg[1-4mg] [49]</td>
<td>Exploratory, multicenter, randomized, double-blind, functional magnetic resonance imaging study. BRX showed a significant decrease in right VLPFC BOLD activation during the stop-signal task, and was associated with significantly improved stop-signal reaction time.</td>
</tr>
<tr>
<td>Kane et al [23]</td>
<td>6</td>
<td>Acute schizophrenia</td>
<td>673</td>
<td>1 mg (110), 2 mg (185), 4 mg (185)</td>
<td>Phase III multicenter, randomized, double-blind, placebo-controlled study. BRX 4 mg showed statistically significant efficacy compared to placebo. The most common TEAEs were headache, insomnia and restlessness.</td>
</tr>
<tr>
<td>Fleischhacke r et al[24]</td>
<td>52</td>
<td>Maintenance treatment in schizophrenia</td>
<td>201</td>
<td>1-4 mg [96]</td>
<td>Phase III, multicenter, randomized, double-blind, placebo-controlled relapse prevention study. BRX significantly delayed the time to impending relapse compared to placebo (relapse rates: BRX, 13.5%; placebo, 38.5%) with the most common TEAEs being headache, and insomnia.</td>
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<tr>
<td>Study</td>
<td>N</td>
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<td>NNT</td>
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<tr>
<td>Forbes et al [25]</td>
<td>52</td>
<td>Maintenance treatment in schizophrenia</td>
<td>282: 184 de novo 98 rollover</td>
<td>1–4 mg (282)</td>
<td>Phase III multicenter, long-term, open-label study, 53.2% of patients completed the study. It is common TEAEs were nasopharyngitis, worsening of schizophrenia. PANSS total and CGI-S remained stable until week 52.</td>
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<tr>
<td>Yan et al [26]</td>
<td>&gt;52</td>
<td>Schizophrenia</td>
<td>6255</td>
<td>175</td>
<td>Retrospective cohort study. BRX users had the lowest mean psychiatric costs among all oral atypical antipsychotic users ($12,013). The compared with BRX users, paliperidone and quetiapine users had much psychiatric hospitalization per year. Paliperidone had higher psychiatric costs than BRX. Psychiatric medical costs were also higher in olanzapine users than in BRX users.</td>
</tr>
<tr>
<td>Yoshimura Et al [27]</td>
<td>16</td>
<td>Schizophrenia</td>
<td>119</td>
<td>LAT [99] HAT [21]</td>
<td>A retrospective survey of all inpatients and outpatients. At the start high-dose antipsychotic therapy is not depend a risk factor for BRX discontinuation in patients with schizophrenia.</td>
</tr>
</tbody>
</table>

Table 2: Clinical trails of Brexpiprazole in Schizophrenia

[Abbreviations :PAANSS-Positive and Negative Syndrome Scale; NNT-Number Need to Treatment; CGI-S-Clinical Globle Impression Severity; TEAE-Treatment Emergent Adverse Event; ; HR, hazard ratio; SLOF, Specific Levels of Functioning Scale; BIS, Barratt Impulsiveness Scale; PSP, Personal and Social Performance Scale; PSQI, Pittsburgh Sleep Quality Index; VLPFC, ventrolateral prefrontal cortex; BOLD, blood oxygen level-dependent; LAT, previous low-dose antipsychotic therapy; HAT, previous high-dose antipsychotic therapy,BRX:Brexpiprazole]

7. Conclusion:
Brexpiprazole is an antipsychotic drug and it works by changing the action of hormones in the brain. The treatment is both short and long term studies. The brexpiprazole shows favourable safety, tolerability and efficacy. Brexpiprazole shows more effective drug as compare to Aripiprazole because it shows low side effect.

8. Acknowledgments:
Authors are heartly thankful to pharmaceutical chemistry department of Dr. Vithalrov Vikhe Patil Foundations, College of Pharmacy, Ahmednagar for providing support.
Reference:


[14]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4927015/

[15]. https://www.drugs.com/monograph/brexpiprazole.html


