

Graylands Hospital Drug Bulletin

Brexpiprazole

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Introduction

There are now three dopamine receptor partial agonists, aripiprazole, brexpiprazole and cariprazine available around the world. All have been approved for schizophrenia and some other disorders in various countries.¹ Brexpiprazole is the second, partial agonist antipsychotic to be released into the Australian market. It was approved in May 2017 by the Therapeutic Goods Administration for the treatment of schizophrenia. Brexpiprazole was discovered in 2007 and was developed and marketed by Otsuka and Lundbeck. Brexpiprazole was synthesised by Otsuka Pharmaceutical Co and development was based on structural modifications of aripiprazole with the aim of an improved side effect profile.²

Mechanism of Action

It has become commonplace for articles about antipsychotics to begin with a statement along the lines of “all antipsychotics are postsynaptic D₂ receptor antagonists”. While D₂ antagonism has been one of the main strategies in development of antipsychotic medications, the statement is inaccurate in that clozapine, the most effective antipsychotic, has very little effect on D₂ receptors.

Because of side effects, strong dopamine antagonists are often not the optimal treatment for psychoses and various strategies have been used to minimise the dopamine side effects from antipsychotics. One strategy has been to use D₂ receptor partial agonists to achieve “stabilisation” of dopamine activity and improved tolerability.^{3,4}

The effects of partial agonists are believed to vary depending on the area of the brain. According to this theory, in areas where there is an abundance of dopamine e.g. the mesolimbic area, a partial agonist will have more of an antagonist effect by blocking access to the dopamine receptors. Where there are low levels of dopamine activity e.g. mesocortical areas, a partial agonist will tend to have more of an agonist effect.^{4,5}

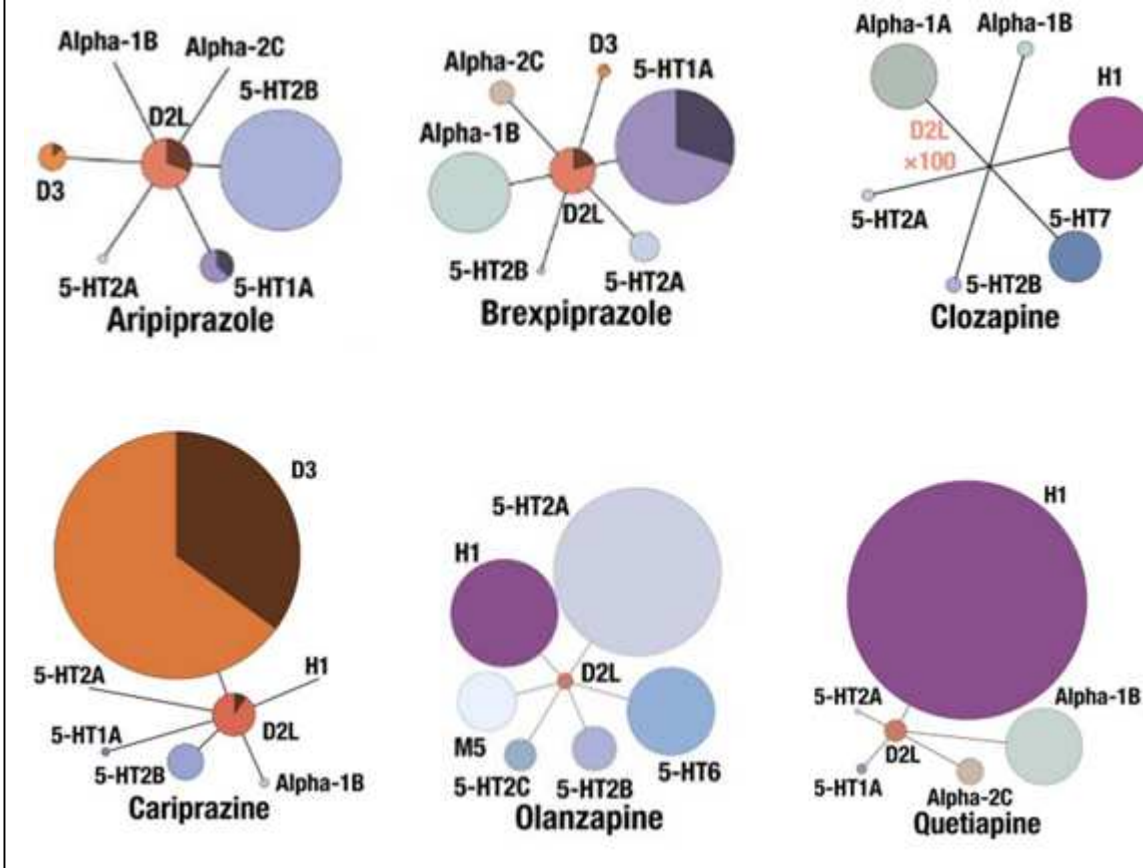
Before considering the binding properties of brexpiprazole, it is important to understand that the pharmacological effects of a drug are a result of a number of factors which have been summarised by de Bartolomeis et al⁶

1. Affinity to the receptor
2. Intrinsic activity
3. Selectivity
4. Mode of Interaction
5. Residence time

The affinity is the ability of the drug to bind to the receptor while the intrinsic activity describes the degree of response the drug makes when it binds to the receptor. The potency of a drug is a product of a combination of these factors. A high potency drug can have high affinity for the receptor or have high intrinsic activity or both.⁶

Figure 1 shows the relative affinity and functional activity at the main receptors for brexpiprazole and aripiprazole in Saklad diagrams. The functional activity is represented by shading the binding disk like a pie chart. For comparison, diagrams for clozapine, cariprazine, olanzapine and quetiapine have been included.

Figure 1 Saklad graphic representation of receptor binding affinity. [Reproduced with permission from Saklad SR. Graphic representation of pharmacology: Development of an alternative model. *Mental Health Clinician* 2017;7:201-206.]



Aripiprazole has very high affinity for D_2 , α_{1B} and $5-HT_{1A}$ and high affinity for D_3 and $5-HT_{2A}$ receptors.⁶ Brexpiprazole has higher affinity than aripiprazole to D_2 receptors⁷ but has lower intrinsic activity at D_2 .¹ Brexpiprazole has ten times the affinity at $5-HT_{1A}$, $5-HT_{2A}$ ¹ and α_{1B} receptors⁷ than aripiprazole. As depicted in Figure 1 by the partially shaded disks, both brexpiprazole and aripiprazole are partial agonists at $5-HT_{1A}$. They are antagonists at $5-HT_{2A}$ ⁵, $5-HT_7$ and $\alpha_{1b/2c}$ receptors⁵. They have very low activity at H_1 and no anticholinergic activity.⁵

By contrast, it can be seen that cariprazine has higher affinity for D_3 receptors and quetiapine is virtually only an antihistamine.

Adverse Effects

Brexpiprazole appears to be well tolerated. The Rexulti® Product Information (PI) proudly states that “there are no common adverse reactions that meet the criteria incidence $\geq 5\%$ and at least twice the rate of placebo”⁸ While this statement was limited to the selected trials in the PI, reviews of the safety of brexpiprazole tend to support the low

incidence of adverse effects. The rate of discontinuations from clinical trials because of adverse effects has been higher in placebo groups than in brexpiprazole treated patients.^{9, 10}

Patients reported low rates of sedation and activation. Akathisia was seen at a rate slightly higher than placebo in both long term and short-term studies.⁹

Adverse reactions reported at $\geq 2\%$ and at a greater incidence than placebo: dyspepsia, weight gain, CK increase, pain in extremity, tremor and sedation, toothache, reduced appetite, muscle spasms, musculoskeletal pain, tremor and pruritus. Akathisia was reported at 5.5% as compared to 4.6% in placebo treated patients. This is approximately half the rate of aripiprazole. In the stabilisation phase, the most common adverse effects were insomnia, akathisia, agitation, schizophrenia, increased weight, and headache.¹⁰ In the maintenance phase no patients had an incidence of adverse effects $\geq 5\%$.

Precautions

There seems to have been a trend for the PI for new psychotropic drugs to include many precautions that are based on “class effects” of antipsychotics. The PI for Latuda® is a case in point, as discussed in a previous drug bulletin.¹¹ The inclusion of “class effects” becomes even more illogical when it is considered that the pharmacological profiles of most of the atypical antipsychotics differ so widely in their receptor affinities that the concept of grouping them under a single heading of “atypical antipsychotics” has been called into question.¹²

The Australian version of the Rexulti® PI includes an extensive list of precautions but many of these appear to be effects attributed to antipsychotics generally. Table 1 breaks the precautions into three groups. Those where there is evidence that they have occurred with brexpiprazole, those with theoretical evidence and those with no evidence at all. This is not to say that the precautions listed in the third group are not possible, only that with the limited experience with brexpiprazole so far, they have not been reported.

| Precautions with Brexpiprazole | | |
|-------------------------------------|--|---|
| With Evidence | Theoretical Evidence | No Evidence |
| Weight Gain and Dyslipidaemia | Neuroleptic Malignant Syndrome (NMS) | Hyperglycaemia and Diabetes Mellitus |
| Orthostatic Hypotension and Syncope | Tardive Dyskinesia | QT interval prolongation |
| | Dysphagia | Seizures |
| | Effects on Fertility based on animal studies at high doses | Body Temperature Dysregulation |
| | Venous Thromboembolism | Neutropenia and Agranulocytosis |
| | | Suicidal Risk |
| | | Increased Mortality in Elderly Patients with Dementia-related Psychosis |
| | | Cerebrovascular Adverse Reactions |

Weight Gain and Metabolic Parameters

In short term studies, brexpiprazole caused clinically relevant weight increases ($\geq 7\%$) at about twice the rate of placebo.⁹ In longer term studies, 18% of patients had $\geq 7\%$ weight increase. The mean increase was 1.1kg for patients treated with brexpiprazole group.⁹

Metabolic syndrome was reported in patients treated with brexpiprazole at a rate of 3% in long term studies.⁹ More

specifically, LDL cholesterol showed an average increase of 0.91 mg/dL (0.02 mmol/L) in patients treated with brexpiprazole compared to a reduction in LDL of 1.82mg/dL (0.04 mmol/L) in the placebo group. There were virtually no changes in HbA1c.

The data presented in the review by Kane et al⁹ indicates that there is evidence that brexpiprazole can cause weight gain and deranged metabolic parameters.

Suicidality

In reviews, the incidence of suicidality was no different to placebo and this was very low.⁹

Pharmacokinetics

Brexpiprazole is well absorbed after oral administration with peak plasma levels seen at about 4 hours. The absolute bioavailability is 95% and brexpiprazole can be administered with or without food. Brexpiprazole is highly protein bound (>99%) to serum albumin and α 1 acid glycoprotein. The terminal elimination half-life of brexpiprazole is 91 hours, predicting achievement of steady state levels after dose change at 19 days (i.e. 5 half-lives).

Metabolism

Brexpiprazole is metabolised by Cytochrome (CYP) 3A4 and CYP2D6 enzymes. The major metabolite of Brexpiprazole is DM-3411 which, in pre-clinical studies, does not produce a detectable brain concentration, therefore, DM-3411 is considered not to contribute to the therapeutic effects of brexpiprazole.

The PI makes the same recommendation for both hepatic and renal impairment: the recommended maximum dose should be reduced, however no guidance as to the amount of reduction is made. Micromedex makes the recommendation to reduce the maximum dose to 3mg daily for schizophrenia in renal impairment and to 2mg daily in severe hepatic impairment.

Therapy is advised to be initiated at the low end of the scale for geriatric use.¹³

Clinical Efficacy

Schizophrenia

The phase 3 study of brexpiprazole demonstrated that 4mg brexpiprazole was superior to placebo with a 6.47 point reduction in Positive and Negative Syndrome Scale (PANSS) score ($p < 0.01$) in 6 weeks.¹⁴ The reduction of PANSS score for brexpiprazole 1mg and 2mg were not statistically significant.¹⁴

A multicentre, 6-week randomised, double-blind, placebo-controlled study by Correll *et al* has shown that brexpiprazole at 2mg and 4mg had an 8.72 and 7.64 reduction in PANSS score respectively and a 0.33 and 0.38 reduction in Clinical Global Impression (CGI) severity score respectively compared to placebo in acute schizophrenia.¹⁵

In the longer term, brexpiprazole is efficacious by reducing the risk of relapse in patients with schizophrenia. Fleischhacker *et al* found that 13.5% of patients on brexpiprazole are at risk of relapse compared to 38.5% of patients on placebo at 52 weeks.¹⁰

An exploratory study including both brexpiprazole 3mg and aripiprazole 15mg demonstrated brexpiprazole is comparable to aripiprazole in terms of efficacy but superior in reducing impulsivity and has significantly lower rates of akathisia.¹⁶

Depression

Brexpiprazole is only approved for schizophrenia in Australia but the U S Food and Drug Administration also approved brexpiprazole as adjunctive treatment of major depressive disorder in 2015. A meta-analysis for four randomised-controlled trials found that brexpiprazole 1-3mg is superior to placebo in the treatment of major depressive disorder.¹⁷ The authors also compared their study with previous meta-analysis of adjunctive atypical antipsychotics in the treatment of depression and found brexpiprazole's efficacy is comparable to aripiprazole, olanzapine and quetiapine.¹⁷

The onset of action with adjunct brexpiprazole on depressive symptoms is rapid. A post hoc analysis of two clinical studies by Nelson *et al* shows statistically significant improvement in five out of six Montgomery-Åsberg Depression Rating Scale (MADRS) core symptoms subscale in two weeks of initiation of adjunct brexpiprazole compared to antidepressant treatment alone.¹⁸ The size of improvement was even greater at Week 6 of the study.¹⁸

Adjunct brexpiprazole has also demonstrated comparable efficacy in improving depressive symptoms of depressed patients with or without irritability.¹⁹ It has also been shown to improve sleep disturbances in depressed patients.²⁰ A small open-labelled study by Krystal *et al* observed improved sleep efficiency, total sleep time, sleep onset latency and wake-time after sleep onset and latency to persistent sleep.²⁰

Interactions

Brexpiprazole is unlikely to significantly affect other drugs by CYP enzyme changes or P-glycoprotein transporter effects.⁸

Dose adjustments to half the dose are recommended when brexpiprazole is used with strong CYP2D6 and CYP3A4 inhibitors e.g. clarithromycin, erythromycin, ketoconazole, paroxetine and fluoxetine.⁸

Place in Therapy

Brexpiprazole appears to be a promising antipsychotic. To date, there have been a number of placebo controlled trials published and one trial using quetiapine in an active control arm. If the early promise of brexpiprazole as an antipsychotic is realised, it will be a welcome addition to the repertoire of antipsychotics available in Australia. Given the favourable side effect profile, brexpiprazole appears to be a good choice in early episode psychosis where aripiprazole is frequently prescribed.

It appears useful for patients where sedation is an issue with other antipsychotics and in patients sensitive to extra-pyramidal side effects due to its lower intrinsic D₂ receptor activity and its 5HT_{2A}, 5HT_{1A} and α_{1B} activity. One down side of brexpiprazole as an antipsychotic is the lack of a depot formulation.

There is mounting evidence for the use of brexpiprazole in antidepressant

augmentation.^{17, 18, 21} Unfortunately, it is only licensed in Australia for the treatment of schizophrenia but it could be one of the better choices of antipsychotics for antidepressant augmentation due to the minimal risk of metabolic syndrome and lack of daytime sedation compared to quetiapine and olanzapine.

Dosage Recommendations

It is recommended that the target dose range is 2 to 4mg, once daily.⁸ The manufacturer, Lundbeck, suggest that the following dosage titration be followed:

- 1mg daily from days 1 to 4
- 2mg daily on day 5 to 7
- 4mg daily on Day 8 if required

Presentation

Brexpiprazole is available in Australia as tablets in strengths of 1mg, 2mg, 3mg and 4mg. There are 0.25mg and 0.5mg strengths but these are not marketed in Australia. Tablets are film-coated and should be swallowed whole. They may be taken with or without food.

Accessibility and Availability

Brexpiprazole is listed on the Pharmaceutical Benefits Scheme (PBS) as a streamlined authority for schizophrenia (4246). The Western Australian Drug Evaluation panel (WADEP) has also approved brexpiprazole for schizophrenia.

A non-PBS prescription for any strength of brexpiprazole is expected to cost approximately \$142 for 30 tablets.



This Drug Bulletin was written by Darren Schwartz and Hun Oon. It was reviewed by the North Metropolitan Health Service Mental Health Drugs and Therapeutics Committee

Comments are welcome at the email address:

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