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A Psychopharmacology Review of Brexpiprazole

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Introduction

Brexpiprazole (Rexulti) is a second-generation drug, sometimes referred to as an atypical antipsychotic. Brexpiprazole (BRX) is a derived altered version of the second-generation drug aripiprazole. These two drugs are related due to their structure, chemistry, and their pharmacology (Frampton, 2019). Although very similar to aripiprazole, brexpiprazole appears to have fewer aversive effects. It is currently recommended that second-generation drugs are used as the first-line antipsychotic treatment due to the reduced side effects (Stummer et al. 2020). In an effort to make antipsychotics more efficient by having the favorable characteristics of dopamine-system stabilizers (such as drugs like aripiprazole) and serotonin-dopamine antagonists (such as riperidone); Ostsuka Pharmaceutical Co., Ltd began to research second-generations drugs in 1999 until H. Lundbeck A/S successfully developed brexpiprazole (Kikuchi et al., 2021). Brexpiprazole is classified as a serotonin-dopamine activity modulator as it has favorable characteristics of a serotonin-dopamine antagonist and a dopamine-system stabilizer (Kikuchi et al., 2021). Shortly after its development, the United States approved brexpiprazole as a treatment for schizophrenia and an adjunctive treatment for major depressive disorder in 2015 (Kikuchi et al., 2021). To date, it is now approved in Canada, Australia, Japan, and Europe for schizophrenia (Kikuchis et al., 2021). It is also approved in Canada as an adjunctive treatment for major depressive disorder (Kikuchis et al., 2021).

In an attempt to create a better understanding of the second-generation antipsychotic drug brexpiprazole, this review will summarize its pharmaceutical properties starting with a general overview of its uses and history before exploring into its pharmacodynamics and

pharmacokinetics. It will finish with the pharmacological effects and toxicology.

Indication/manner of use

Brexpiprazole was FDA approved for usage in 2015 (Kikuchis et al., 2021) and is prescribed for schizophrenia and is commonly prescribed as an adjunctive treatment for major depressive disorder. There has also been some research for using this drug for treating Alzheimer's disease and post-traumatic stress disorder (Ishima et al., 2015), as well as bipolar depressive disorder (Milienne-Petiot et al., 2017). The recommended dosage for brexpiprazole is between 1.0 – 4.0mg once per day, and if the higher dose is needed it should slowly be increased over a period of at least eight days (Frampton, 2019). As a treatment for schizophrenia it is recommended the maximum dose be 4.0mg a day, where as a treatment for major depressive disorder the maximum recommended dose is 3.0mg a day (Greig, 2015). Despite the recommended dosage stated above some research has shown that the dosage should be adjusted for patients with metabolism differences or impairments. Patients who are CYP2D6 poor metabolizers should be advised to take halve the recommended dosage (Elmokadem et al., 2022; Greig, 2015). CYP2D6 poor metabolizers who are taking CYP3A4 inhibitors should take a quarter of the recommended dose (Greig, 2015). There have been no reports of brexpiprazole being used recreationally and there have been no reports of abuse concerns.

History of development

Aripiprazole can be classified as a second-generation antipsychotic that commonly used to treat schizophrenia. Aripiprazole was developed by Ostsuka Pharmaceutical Co., Ltd in 1987

and has the ability to act as a presynaptic dopamine agonist and as a postsynaptic dopamine D2 antagonist (Kikuchi et al., 2021). Although it is different from other antipsychotics it still has a number of aversive effects which led to the development of brexpiprazole. Starting in 1999, Ostsuka Pharmaceutical Co., Ltd continued to research and develop aripiprazole to create another second-generation molecule in hopes to improve tolerability (Kikuchi et al., 2021). Through this research, brexpiprazole was developed with H. Lundbeck A/S as a serotonin-dopamine activity modulator (this type of modulator takes the favorable characteristics of dopamine-system stabilizer and serotonin-dopamine antagonists) (Kikuchi et al., 2021). Aripiprazole is sometimes described as a third-generation drug instead of a second-generation drug due to its mechanism of action, as it could fall into both first- and second-generation antipsychotic (Prus, 2021). This begs the question if brexpiprazole should be described as a third-generation antipsychotic, as it shares similar characteristics of aripiprazole. Both drugs are partial agonist to D2 receptors and antagonists to 5-HT2a receptors with low potential for extrapyramidal side effects. Given the research done, most scientist continue to refer to brexpiprazole as a second-generation antipsychotic.

It was not until 2015 that brexpiprazole was FDA approved in the United States as a schizophrenia treatment and as an adjunctive major depressive disorder treatment (Kikuchi et al., 2021). Following its approval in the United States other countries started to approve the drug as a treatment for schizophrenia with approval beginning in Australia and Canada in 2017, then Japan and Europe in 2018, Canada then approved its use as an adjunctive treatment for major depressive disorder in 2019 (Kikuchi et al., 2021).

Pharmacokinetics

The only administration route mentioned for human participants is oral administration. There are some studies such as one by Oosterhof and colleagues (2016) which the drug was administered via injection, this was only seen in rodent studies. Comparing the results from Oosterhof et al., (2016) injection administration to Maeda et al., (2014a) oral administration there were no striking differences, as the plasma concentration were similar between the two studies. Due to the common positive symptom paranoia seen in schizophrenia patients, drug administration can pose as a challenge, which results in few antipsychotics using injection as the administrative route. It is likely for the reason previously stated that most research conducted with brexpiprazole is through oral administration. Said research has found that brexpiprazole has a 95% oral bioavailability and can be taken with or without food (Garnock-Jones et al., 2016).

Despite the good bioavailability by oral administration, not having other administration routes is a limitation. It would be worth exploring other routes of administration such as a nasal spray. As mentioned earlier, getting schizophrenic patients to take medication can be difficult due to paranoia. Although it can be better to give patients an oral administration rather than an injection, it can still pose a problem. A nasal spray may be easier to administer for some patients, although, given that its properties are similar to aripiprazole this may not be possible.

Like many other drugs it takes time for brexpiprazole to reach its steady state to have its full effect. It takes between 10-12 days to reach its steady state, after it is reached the peak plasma concentration occurs within four hours of administration (Markovic et al., 2017;

Garnock-Jones et al., 2016). Compared to other antipsychotic medication (Markovic et al, 2017), the half-life of brexpiprazole significantly longer as it is at about 91 hours and its metabolite at DM-3411 is 86 hours (Markovic et al, 2017; Garnock-Jones et al., 2016). Brexpiprazole has an oral clearance of about 19.8ml/h/kg (Garnock-Jones et al., 2016). This drug is eliminated through urine and feces, with 25% eliminating through urine, 46% eliminating through feces (Markovic 2017).

Brexpiprazole is metabolized by members of cytochrome P450, (CPY)3A4 and CYP2D6 (Garnock-Jones et al., 2016; Chen et al., 2020). These enzymes break brexpiprazole down into the metabolite DM-3411 (Garnock-Jones et al., 2016). DM-3411 seemingly has little (if any) contribution to the therapeutic effects observed by brexpiprazole (Garnock-Jones et al., 2016; Markovic et al, 2017). The area under the plasma concentration-time curve shows DM-3411 to represent 23-48% of the concentration (Greig, 2015) and as mentioned above the half-life is shorter for DM-3411 than brexpiprazole (Garnock-Jones et al., 2016), these results suggest that the metabolite does little to promote the drug's effects compared to the compound prior to breakdown.

As any other drug, individuals can metabolize brexpiprazole differently. It has been shown those with CYP3A4 genetic polymorphisms leads to different drug effects and potentially high toxicity (Chen et al., 2020). Specifically, patients with decreased CYP3A4 activity present with higher risks of adverse effects, thus it would be recommended for these patients to take a higher dose (Chen et al., 2020). It has also been seen that CYP2D6 poor metabolizers are at greater risk of adverse effects without adjusted dosing (Elmokadem et al., 2022). Elmokadem and colleagues (2022) found that CYP2D6 poor metabolizers have a delay in the time-to-

effective concentration. Due to these results it has been recommended for poor metabolizers to reduce the dose by 50%, but this results in a steady state of 88.7ng/mg which compared to the normal steady state of 90.9ng/ml is a difference that needs to be improved (Elmokadem et al., 2022). Thus, Elmokadem and colleagues (2022), suggest an alternative dosing regiment for CYP2D6 poor metabolizers which requires a gradual increase in dosing from 0.5mg twice a day to 2mg (50% normal dosing) once a day which provides a more desirable effect with a reduced risk for side effects.

Oosterhof and colleagues (2016) investigated the discharge activity of a number of brain regions, specifically, systems with high dopamine activity. They investigated the ventral tegmental area, the locus coeruleus for both dopamine and norepinephrine activity, and the dorsal raphe nucleus serotonin neurons. Oosterhof and colleagues (2016) administered brexpiprazole by an injection for 2 or 14 days following by the electrophysiological recordings (using a single-barrel glass micropipette loaded with 2M NaCl) and taking a blood sample. Their results showed that brexpiprazole effects D2 autoreceptors but leaves dopamine neurons within the ventral tegmental area unchanged, this suggests brexpiprazole has a stabilizing effect. This was concluded as they found increased firing in the locus coeruleus norepinephrine and serotonin neurons but no change in the hippocampus and ventral tegmental areas neurons, and alpha2-adrenergic autoreceptors were not blocked. Maeda and colleagues (2014a), found that there was increased dopamine metabolite levels within the prefrontal cortex when treating rats with 3 and 10mg/kg of brexpiprazole.

As mentioned earlier, patients can have effected distribution if they have genetic differences involving various metabolites, such as, CYP3A4 or those who are CYP2D6 poor metabolizers (Chen et al., 2020; Elmokadem et al., 2022). Mentioned later in this review absorption of brexpiprazole is affected by certain juices due to their effect on important metabolites (Thakkar et al., 2021).

Pharmacodynamics

Compared to aripiprazole, brexpiprazole tends to hold a higher affinity for a number of receptors. Brexpiprazole has a 3-fold higher affinity to dopamine D2 receptors, 10-fold higher affinity to 5-HT1a and 5-HT2a receptors, about a 200-fold higher affinity to alpha1b adrenoceptors, and about a 65-fold affinity to alpa2c adrenoceptors (Garnock-Jones et al., 2016; Greig, 2015). Likely linked to the D2 affinity, there is significant improvement of cognitive impairments compared to aripiprazole (Garnock-Jones et al, 2016). According to an in vitro study done by Ishima (2015), brexpiprazole is associated with neural growth factor – induced neurite outgrowths, seemingly through activation of 5-HT1a and antagonism of 5-HT2a; the activation of these receptors leads to downstream effects of calcium signaling through IP3 receptors. It also seems that brexpiprazole increases the level of Hsp90alpha protein which plays a role in the neurite outgrowths (Ishima et al., 2015). Maeda and colleagues (2014a), found the effects of brexpiprazole worked through D2 agonism by inhibiting the reserpine-induced increase in DOPA accumulation, although it was not as effective as aripiprazole. They also found an increase in extracellular histamine within the prefrontal cortex (at 10 and 30mg/kg) but with lower intrinsic activity than aripiprazole. The lower activity of these

receptors contributes to the less adverse side effects of brexpiprazole compared to aripiprazole. With lower affinity, brexpiprazole also acts on D3, 5-HT2b, 5-HT7 and alpha1a receptors (Greig, 2015). From the findings stated above, it can be seen that brexpiprazole mainly interacts with dopamine D2 receptors and 5-HT2a receptors.

Pharmacological effects

Schizophrenia has many symptoms which fall into one of the following categories positive, negative, or cognitive. Most antipsychotics help to treat the positive symptoms. Although it has strongest effects on positive symptoms, brexpiprazole seems to have some effect on all categories. Specifically, when compared to its predecessor aripiprazole. A common symptom of schizophrenia is cognitive deficits. Using phencyclidine (PCP) Yoshimi and colleagues (2014) induced cognitive deficits and other schizophrenia like symptoms in mice. Following treatment with brexpiprazole the mice seemed to have a decrease in the cognitive deficits caused by phencyclidine compared to mice without the brexpiprazole treatment; they measured cognitive ability using a novel object recognition task (Yoshimi et al., 2014). Maeda et al. (2014b), also found similar results as 1-3mg/kg of brexpiprazole could reverse subPCP-induced impairments in rats which showing an improvement of positive and cognitive symptoms.

In a six-week clinical trial by Kane and colleagues (2015), patients treated with 4mg of brexpiprazole showed a significantly improved score on the Positive and Negative Syndrome Scale (PANSS), as well as a number of secondary measurements including but not limited to PANSS sub-scale, CGI-I, and PEC scores. In a similar experiment Correll et al. (2015), through a

six-week double-blind study, showed improved PANSS scores within 2-4mg dosage. Although they found little effect on anxiety and depression. When testing QT, it was seen that brexpiprazole was lower than the placebo (Correll et al., 2015). The results stated above are promising as they show an improvement in symptoms that other antipsychotics have little effect on.

Toxicology/safety

Brexpiprazole is being investigated as it has less aversive effects when compared to aripiprazole (Frampton et al., 2019). The most common effected is akathisia (or the inability to stay still), with weight gain following close behind (Markovic et al., 2017; Correll et al, 2015; Garnock-Jones et al, 2016). According to Correll et al. (2015), akathisia is likely to occur during the first three weeks of treatment. More serious side effects such as psychiatric disorders and suicidal ideation are observed (Correll et al., 2015) more common in adolescence than adults (Stummer et al., 2020). Within elderly patients there is an increased risk of mortality (Stummer et al., 2020). Other effects can be sedation, anxiety, or insomnia which are less common (Garnock-Jones et al, 2016; Correll et al., 2015; Stummer et al., 2020). Due to the more severe side effects there is a Blackbox warning on this substance to warn uses of the potential risk of suicidal ideation and mortality, specifically for patients within the age range its more likely to affect.

It is also advised to avoid grape fruit juice and pomegranate juice (or adjust dosage of brexpiprazole), because these particular juices raise the absorption of brexpiprazole (Thakkar et al., 2021). According to the study done by Thakkar et al., (2021) grape fruit juice and

pomegranate juice increases inhibition of intestinal CYP3A4 enzyme when mice were orally treated with brexpiprazole. This raise in absorbance can cause more serious adverse effects stated above.

It is also good to note that brexpiprazole has shown no evidence of abuse potential as research has shown through self-administration tasks (Otsuka Pharmaceutical Co Ltd., 2015).

Summary

Brexpiprazole is as recently developed second-generation antipsychotic. This drug is approved for treating schizophrenia and major depressive disorder, gaining its approval in 2015 within the United States. The development of brexpiprazole stemmed from another second-generation antipsychotic aripiprazole (Kikuchi et al., 2021). Although similar in many ways, the key difference is that brexpiprazole is classified as a serotonin-dopamine activity modular whereas aripiprazole is a dopamine-system stabilizer (Kikuchi et al., 2021). This antipsychotic is administered orally with a strong bioavailability (Garnock-Jones et al., 2016). After 10-12 days of treatment the steady state is reached allowing for peak plasma concentration to hit 4hr after administration (Markovic et al., 2017). Lots of research has shown that patients who are CYP2D6 poor metabolizers should have an adjusted dose compared to the recommended dose between 1-4mg once per day (Frampton, 2019; Elmokadem et al., 2022). Dosage also seems to depend on what brexpiprazole is being used to treat. The recommended maximum dose is lower for treating major depressive disorder than schizophrenia (Greig, 2015).

Brexpiprazole is found to be a partial agonist for D2 and 5-HT1A receptors and an antagonist for 5-HT2A receptors (Markovic 2017). Mainly through these receptors this

antipsychotic produces its unique effects. This drug reduces positive symptoms and cognitive symptoms, as well as a small effect on negative symptoms of schizophrenia. It has also been shown that brexpiprazole has fewer side effects compared to its predecessor aripiprazole (Frampton et al., 2019). The main side effects seen with brexpiprazole are weight gain and akathisia (Correll et al., 2015; Stummer et al., 2020). From the data presented above it can be seen that brexpiprazole is a good novel treatment for patients suffering from schizophrenia as well as major depressive disorder. Although more research needs to be done to further expand what is known about this antipsychotic medication. Future research should observe the long-term effects of this drug as well as look into the other implications for this medication.

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