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REVIEW

Preclinical Evidence for the Use of Brexpiprazole + Antidepressant Treatment for Major Depressive Disorder and Post-Traumatic Stress Disorder: A Systematic Review

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Purpose: Brexpiprazole, when administered with antidepressant therapy, may provide additional benefits due to complementary actions on noradrenaline (norepinephrine), serotonin, and dopamine neurotransmitter systems. This review addressed the question: what information can preclinical studies provide on the use of brexpiprazole + antidepressant treatment?

Methods: A systematic literature review was conducted to search for preclinical studies of brexpiprazole + antidepressant therapy that included a behavioral test relating to any psychiatric disorder. Ovid MEDLINE, Ovid Embase, and conference abstracts were searched (January 1, 2011–July 5, 2021). The statistically significant ($p<0.05$) findings for brexpiprazole + antidepressant were extracted.

Results: Of 296 records screened, nine articles were eligible, describing seven unique studies. In rodent models, including three models of depression (unpredictable chronic mild stress, social defeat stress, and lipopolysaccharide-induced depression), brexpiprazole + selective serotonin reuptake inhibitor (SSRI) or serotonin–noradrenaline reuptake inhibitor (SNRI) consistently showed statistically significant benefits over vehicle on depression-like behaviors (forced swim test, tail suspension test, sucrose preference), whereas brexpiprazole and antidepressant monotherapies did not. In the predator scent stress model of post-traumatic stress disorder (PTSD), brexpiprazole + SSRI (escitalopram) showed a significant benefit over vehicle and/or monotherapy on anxiety-like behaviors (elevated plus-maze) and hyperalertness (acoustic startle response), whereas brexpiprazole and escitalopram monotherapies did not significantly differ from vehicle. In the fear conditioning model of PTSD, brexpiprazole showed significant improvements whether administered as monotherapy or in combination with escitalopram.

Conclusion: Based on a small number of studies, the administration of brexpiprazole with an antidepressant appears to have a greater treatment effect than either brexpiprazole or antidepressant monotherapies in preclinical studies of depression- and PTSD-like behaviors. Thus, preclinical studies support evidence from randomized clinical trials for the therapeutic effects of adjunctive brexpiprazole in the treatment of major depressive disorder, and brexpiprazole in combination with sertraline in the treatment of PTSD. Funding: Otsuka/Lundbeck.

Plain Language Summary: Studies of medications in animals can provide additional information to complement studies in humans. This review investigates what can be learned from animal studies of brexpiprazole (a medication known as an "atypical antipsychotic") given together with an antidepressant medication. Seven animal studies that assess brexpiprazole + antidepressant treatment in rat or mouse models of depression and post-traumatic stress disorder were identified. Overall, these animal studies provide support for the observed benefits of brexpiprazole added to antidepressant treatment in major depressive disorder, and the ongoing development of brexpiprazole + antidepressant as a potential combination treatment for post-traumatic stress disorder.

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Introduction

Major depressive disorder (MDD) remains a challenging psychiatric condition to treat, with a considerable proportion of patients experiencing inadequate response to standard antidepressant therapies.[1] Among such patients, multiple clinical trials show that augmentation with brexpiprazole (and certain other atypical antipsychotics) provides greater efficacy than antidepressant monotherapy.[2–6] Similarly, many patients with post-traumatic stress disorder (PTSD) do not respond to selective serotonin reuptake inhibitors (SSRIs; the most common first-line pharmacotherapy for PTSD).[7,8] Recent clinical trials suggest that the combination of brexpiprazole with the SSRI, sertraline, may be more efficacious than sertraline monotherapy in PTSD.[9,10] Brexpiprazole is approved in various countries for the adjunctive treatment of MDD, and is under investigation in combination with sertraline for the treatment of PTSD.[9,11]

MDD and PTSD are each associated with dysfunction of the three major monoamine neurotransmitter systems: noradrenergic (norepinephrinergic), serotonergic, and dopaminergic.[12–15] Many symptoms of MDD and PTSD overlap, including hyperarousal, irritability, agitation/aggression, and insomnia.[16,17] Thus, similar pharmacological treatment strategies may be appropriate for MDD and PTSD.

It may be hypothesized that the clinical benefits of administering antidepressants and brexpiprazole together may be due to complementary actions on the noradrenergic, serotonergic, and dopaminergic monoamine systems.[18] The most commonly prescribed antidepressant classes (SSRIs, serotonin–noradrenaline reuptake inhibitors [SNRIs], and noradrenaline–dopamine reuptake inhibitors [NDRIs][19]) act primarily on one or two monoamine systems.[12] The majority of atypical antipsychotics also act primarily on two monoaminergic systems, through a combination of dopamine D_2 and serotonin 5-HT_{2A} receptor antagonism.[12] Brexpiprazole is the only antipsychotic that targets receptors in all three monoamine neurotransmitter systems with similarly high binding affinity for noradrenergic α_{1B} and α_{2C} receptors, serotonergic 5-HT_{1A} and 5-HT_{2A} receptors, and dopaminergic D_2 receptors.[20] Of these targets, brexpiprazole shows antagonistic activity at α_{1B}, α_{2C} and 5-HT_{2A} receptors, and partial agonistic activity at 5-HT_{1A}, D_2, and D_3 receptors.[20]

Additional insights into the effects of brexpiprazole + antidepressant therapy in the treatment of psychiatric disorders may be obtained from preclinical studies. Animal models of psychiatric disorders do not directly translate into clinical relevance, since psychiatric disorders are complex and heterogeneous, with diverse symptoms and a subjective experience.[21,22] However, animal models of psychiatric disorders allow new drugs to be tested for specific hypotheses in a diverse array of disease models and behavioral tests, under highly controlled conditions, and with options for experimental design that are not possible in human trials.[23] Thus, preclinical studies are valuable to complement information from clinical studies.

A review of the preclinical studies of brexpiprazole as a monotherapy (including in models of schizophrenia-like behavior) is available elsewhere.[24] The aim of the present review was to identify, describe, and appraise animal behavioral studies in order to address the question: what information can preclinical studies provide on the use of brexpiprazole + antidepressant treatment?

Methods

A systematic literature review was conducted to search for preclinical studies of brexpiprazole + antidepressant therapy that included a behavioral test relating to a psychiatric disorder. The eligibility criteria and search strategy were specified in advance and documented in a brief protocol (provided in the online supplement); the review was not registered. PRISMA reporting guidelines were followed.[25]

Eligibility Criteria

Studies were eligible if experiments were performed in animals; studies in humans and in vitro studies were excluded. The required study intervention was brexpiprazole + antidepressant (any class), with or without a comparator. The study outcomes must have included a behavioral test relating to any psychiatric disorder; studies with no behavioral test, or

behavioral tests that did not relate to a psychiatric disorder (eg, tests for drug adverse effects) were excluded. No restrictions were placed on study design. Primary study reports were considered; reviews were also included provided they contained information on relevant but otherwise unidentified studies (ie, unpublished studies or those missed by the database search). Articles could be in any language and published from January 1, 2011, onwards (the first brexpiprazole publication was in 2011).

Search Strategy

Two databases were searched via Ovid: MEDLINE (which covers the period 1966–present, and does not generally contain abstracts of papers or posters presented at national or international meetings) and Embase (which covers the period 1947–present, and includes journal supplements that routinely contain abstracts of papers or posters presented at some national and international meetings). The following search terms were used, reflecting the generic, developmental, and brand names of brexpiprazole: brexpiprazole[title] OR OPC-34712[title] OR Rexulti[title] OR Rxulti[title]. All article types were eligible. In addition, abstract books from the American Psychiatric Association Annual Meeting were manually searched, as this meeting is not covered by Embase. Abstract books were available for 2011–2019; the regular annual meeting did not take place in 2020 or 2021. All searches were performed on July 5, 2021, by CPW.

Study Selection

After removal of duplicate records, titles and abstracts were screened to exclude records that described a study in humans or an in vitro study, or a study on a topic other than behavioral tests relating to a psychiatric disorder.

Next, full-text articles were retrieved (for poster abstracts, the full posters were obtained from the study sponsor) and assessed for eligibility based on the criteria listed in the 'Eligibility criteria' section. Eligibility assessment was performed by a single reviewer (CPW).

Data Extraction

The following data were extracted from eligible studies: the animal model used; the behavioral test used; sample size; the antidepressant, its dose, duration, and method of administration; the brexpiprazole dose, duration, and method of administration; the effects in the behavioral test of antidepressant monotherapy, brexpiprazole monotherapy, and brexpiprazole + antidepressant, with statistical significance; and funding source. Data were extracted by a single reviewer (CPW).

Data are presented for individual studies and were not combined or re-analyzed. P-values <0.05 were considered statistically significant.

Risk of bias is difficult to assess in animal studies because design aspects such as randomization and blinding are not standard practice, and there is no central, publicly accessible database of protocols.[26,27] Where possible, risk of bias in individual studies was assessed by a single reviewer (CPW) based on descriptions of the randomization and blinding process, animal characteristics at baseline, and animal attrition rates.

Results

Study Characteristics

A total of 296 records were screened, and nine articles were eligible for inclusion (Figure 1). Eight of the nine eligible articles were primary reports of an animal study.[28–35] The other eligible article was a published review[36] that described a relevant but otherwise unidentified study in the pharmacology review of the FDA New Drug Application for brexpiprazole, which was subsequently downloaded from the FDA website.[37]

The nine eligible articles described seven unique studies (Table 1). Studies 1–5 were of treatment effects on depression-like behaviors in rodent models; and Studies 6 and 7 were of treatment effects on PTSD-like behaviors in rodent models. Study 1, which was included based on abstracts, has been published (in part) since the present review was conducted.[38]

All seven studies were funded by the commercial developers of brexpiprazole, Lundbeck and Otsuka.

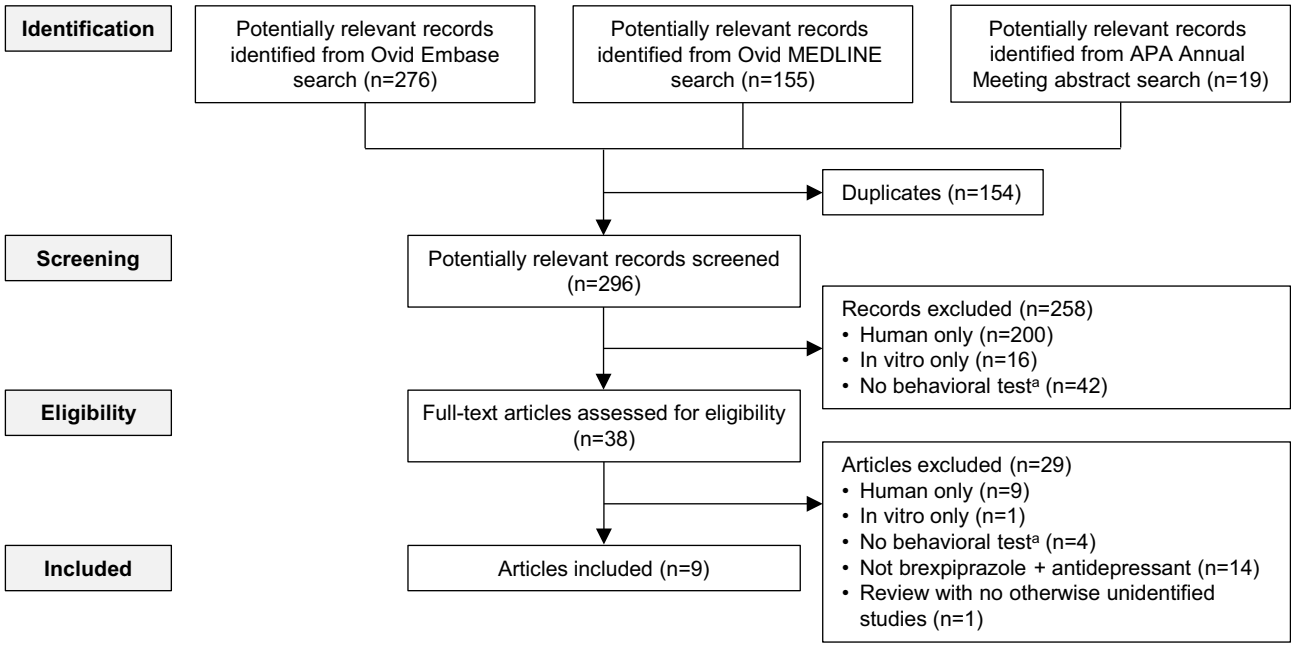

Figure 1 PRISMA flow diagram.
Notes: [a]Relating to a psychiatric disorder.
Abbreviation: APA, American Psychiatric Association.

Considering the risk of bias, Studies 1–5 did not report if they were randomized or blinded, whereas Studies 6 and 7 stated that they were randomized and blinded but did not give specific details. None of the studies compared treatment groups at baseline. While most of the studies reported a sample size (with the exception of Study 3), attrition could not be determined as the number of animals excluded from analyses was not reported.

Studies Assessing Effects on Depression-Like Behaviors

The animal models and behavioral tests used in Studies 1–5 (depression-like behaviors) are briefly described below, followed by descriptions of the treatment effects.

Description of Animal Models of Depression

Although behavioral tests can be performed on 'healthy' rodents, it can be more informative to use rodent models of depression. Examples described here are the unpredictable chronic mild stress (UCMS), social defeat stress (SDS), and lipopolysaccharide (LPS)-induced depression models.

In the UCMS model, rodents are exposed over several weeks or months to a sequence of mild stressors, such as removal or wetting of bedding, tilting the cage, exposure to the cage of another rodent, and changing the light/dark cycle.[39,40] This is thought to produce depression-like behavioral alterations, including anhedonia and apathy, which can be reversed by chronic administration of antidepressant drugs.[39,40]

In the SDS model, C57BL/6 mice are repeatedly exposed to larger CD1 mice that have been screened for aggressive behavior.[41] Among 'susceptible' C57BL/6 mice, this results in depression- and anxiety-like behaviors, such as social avoidance, which can be reversed by chronic administration of antidepressant drugs.[41]

It is hypothesized that inflammation can lead to symptoms of depression in vulnerable individuals; this can be modeled in rodents by peripheral administration of the bacterial endotoxin, LPS, which induces depression-like behaviors such as loss of appetite and reduced motor activity.[42] Treatment with certain antidepressants prior to administration of LPS has been shown to mitigate these depression-like behaviors.[43,44]

Table 1 Summary of Methodology for Preclinical Behavioral Studies of Brexpiprazole + Antidepressant

Study #	Reference	Animal Model	Behavioral Test	Sample[a]	Antidepressant Dose[b]	Brexpiprazole Dose[b]	Duration
1	[28,29,37,38]	Mouse (ddY)[c]	Forced swim test	7–10	SSRIs: Fluoxetine 75 mg/kg, sertraline 15 mg/kg, escitalopram 60 mg/kg, paroxetine 10 mg/kg, fluvoxamine 10/75[d] mg/kg SNRIs: Duloxetine 10 mg/kg, venlafaxine 15 mg/kg, milnacipran 30 mg/kg, desvenlafaxine 20 mg/kg sc	0.001, 0.003 mg/kg ip	Single dose
			Marble burying behavior	10	SSRIs: Fluoxetine 10 mg/kg, sertraline 10 mg/kg, paroxetine 10 mg/kg, fluvoxamine 15 mg/kg	0.1 mg/kg	Single dose
2	[30,31,37]	Rat (Wistar)[c]	Forced swim test	10	SSRI: Fluoxetine 16, 32, 64 mg/kg ip	0.3, 1, 3 mg/kg	2–3 doses over 1 day
			Vogel conflict test	10	SSRI: Fluoxetine 4, 8, 16, 32 mg/kg ip	0.3, 1, 3 mg/kg	Single dose
3	[37]	Depression-like mouse (UCMS)	Coat state	Not stated	SSRI: Fluoxetine 5, 10 mg/kg ip	0.03, 0.1 mg/kg	5 weeks
4	[32]	Depression-like mouse (SDS-exposed C57BL/6)	Locomotion Tail suspension test Forced swim test Sucrose preference test	6–9	SSRI: Fluoxetine 10 mg/kg	0.1 mg/kg	Single dose
5	[33]	Depression-like mouse (LPS-injected C57BL/6)	Locomotion Tail suspension test Forced swim test	7–9	SSRI: Fluoxetine 10 mg/kg	0.1 mg/kg	Single dose
6	[34]	PTSD-like rat (PSS-exposed Sprague Dawley)	Elevated plus-maze Acoustic startle response	30–31	SSRI: Escitalopram 5 mg/kg ip	3 mg/kg	14 days BID
7	[35]	PTSD-like mouse (fear conditioned and corticosterone-injected C57BL/6)	Fear response	10	SSRI: Escitalopram 0.3 mg/kg sc SSRI: Escitalopram 15 mg/kg sc	0.03, 0.1, 0.3 mg/kg 0.1, 0.3, 1 mg/kg sc	Single dose 7 days

Notes: [a]Number of animals per treatment group. [b]Drugs were administered orally unless otherwise stated. [c]Not a model of a psychiatric disorder. [d]References are inconsistent regarding fluvoxamine dose.

Abbreviations: BID, twice per day; ip, intraperitoneal; LPS, lipopolysaccharide; PSS, predator scent stress; PTSD, post-traumatic stress disorder; sc, subcutaneous; SDS, social defeat stress; SNRI, serotonin–noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; UCMS, unpredictable chronic mild stress.

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Description of Behavioral Tests

The potential effects of treatment on depression-like behaviors were assessed using the forced swim test, tail suspension test, coat state, sucrose preference test, and locomotor activity level.

In the forced swim test, a rodent is placed in a narrow, water-filled, vertical cylinder, from which it cannot escape.[45,46] In this scenario, rodents undergo a period of vigorous swimming, followed by a floating, immobile posture that indicates behavioral despair (thought to reflect lowered mood or hopelessness).[45,46] Antidepressants have been shown to reduce the amount of time that rodents spend immobile.[47] In Studies 1, 2, 4 and 5 (where this information was provided), forced swim test immobility time was determined over a 4–6 minute test period using an infrared system to detect motion.[28–33,38] The tail suspension test is an alternative, 'dry' measure of behavioral despair, in which immobility is induced by suspending the mouse by its tail.[48] In Studies 4 and 5, tail suspension test immobility time was recorded over a 10-minute test period.[32,33]

The condition of a mouse's coat reflects its grooming behavior and thus is a measure of the animal's motivation toward self-centered activities.[40] Exposure to stress leads to worsened coat state, and this effect is reversed by chronic administration of antidepressants.[40] A coat state score can be determined from visual inspection of seven body areas, with the total score ranging from 0 (good) to 7 (bad).[40] Coat state score was determined in Study 3.[37]

In the sucrose preference test, rodents are provided with a choice of two drinking bottles, one containing water and the other containing a sucrose solution.[49,50] Healthy rodents have a natural preference for the sucrose solution; a reduction in sucrose preference is indicative of anhedonia, and can be reversed by chronic administration of antidepressants.[49,50] In Study 4, the two drinking bottles were weighed before and after a 1-hour test period, and sucrose preference was calculated as a percentage.[32]

When a rodent is placed in a new environment, its locomotor activity indicates its interest in the situation; rodents subject to SDS show reduced locomotor activity, implying a deficit in motivation.[51] In Studies 4 and 5, mice were placed in experimental cages, and locomotor activity over 60 minutes was automatically counted using an infrared system.[32,33]

In addition to tests of treatment effects on depression-like behaviors, Studies 1 and 2 used the marble burying behavior test and the Vogel conflict test to assess treatment effects on anxiety-like behaviors in rodent models.

Mice, when placed in a cage with marbles, will naturally bury the marbles – a behavior that is reduced by antidepressant and anxiolytic agents.[52–55] In Study 1, 25 marbles were evenly spaced on a layer of sawdust in a cage, and the number of marbles more than two thirds covered by sawdust after 30 minutes was counted,[28,29] where a lower number of buried marbles indicates a stronger therapeutic effect.

In the Vogel conflict test, water-deprived rats are periodically administered electric shocks ('punishment') when they drink water via a drinking tube.[56,57] This reduces the amount of time that the rats spend drinking – an effect that is reversed by anxiolytic agents (results are inconsistent for antidepressants).[56–58] In Study 2, the number of punished licks was measured (ie, the number of shocks taken, which corresponds to the amount of time spent drinking), where a greater number of punished licks indicates a stronger anxiolytic-like effect.[30,31]

Effect of Brexpiprazole + Antidepressant Administration

Table 2 summarizes the outcomes from studies assessing potential treatment effects on depression-like behaviors. Three of the five studies included a specific rodent model of depression.

Four studies used the forced swim test and/or the tail suspension test to assess treatment effects on depression-like behaviors. In general, brexpiprazole + antidepressant significantly reduced immobility time versus vehicle, indicating reduced behavioral despair, whereas brexpiprazole monotherapy and antidepressant monotherapy did not significantly affect immobility time. Specifically, in mice (Study 1), brexpiprazole monotherapy, SSRI monotherapy (fluoxetine, sertraline, escitalopram, paroxetine, fluvoxamine), and SNRI monotherapy (duloxetine, venlafaxine, milnacipran, desvenlafaxine) did not significantly change immobility time at the doses tested.[28,29,37,38] However, brexpiprazole + SSRI/SNRI (every combination, as well as pooled data) produced a statistically significant reduction in immobility time versus vehicle. A similar pattern was observed in rats (Study 2), where brexpiprazole monotherapy and fluoxetine monotherapy did not significantly change immobility time (except in one of five fluoxetine experiments), whereas brexpiprazole + fluoxetine at the highest dose tested had a statistically significant benefit versus vehicle and versus fluoxetine monotherapy.[30,31,37] Finally, in mice susceptible to SDS (Study 4) and in the LPS model (Study 5), brexpiprazole

Table 2 Effects of Brexpiprazole + Antidepressant in Preclinical Studies of Depression-Like Behaviors

Outcome	Study #	SSRI	Brexpiprazole		Brexpiprazole + SSRI		
		vs vehicle	vs vehicle	vs SSRI	vs vehicle	vs SSRI	vs Brex
In rodent model							
FST: immobility time	1[a]	×	×	–	✓	–	–
	2	✓	×	–	✓	✓	–
MBB: number of buried marbles	1	–	–	–	✓	✓	✓
VCT: number of punished licks	2	✓	✓	–	×	–	–
In rodent model of depression							
FST: immobility time	4	×	×	–	✓	–	–
	5	×	×	–	✓	–	–
TST: immobility time	4	×	×	–	✓	–	–
	5	×	×	–	✓	–	–
Coat state score	3	✓	–	–	✓	✓	–
Sucrose preference	4	×	×	–	✓	–	–
Locomotion over 60 minutes	4	×	×	×	×	×	×
	5	×	×	×	×	×	×

Notes: [a]SNRIs were also tested in Study 1, with the same pattern of results. ✓=statistically significant benefit ($p<0.05$) for at least one dose tested. ×=no statistically significant benefit for any dose tested. –=statistical comparison not performed/reported, or experiment to make this comparison not performed.

Abbreviations: Brex, brexpiprazole; FST, forced swim test; MBB, marble burying behavior; SNRI, serotonin–noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TST, tail suspension test; VCT, Vogel conflict test.

monotherapy and fluoxetine monotherapy did not significantly change immobility time versus vehicle, whereas brexpiprazole + fluoxetine produced a statistically significant reduction in immobility time versus vehicle.[32,33]

In the UCMS model (Study 3), fluoxetine monotherapy produced a statistically significant improvement in mouse coat state score versus vehicle after 1–2 weeks of treatment, which lasted until the end of the 5-week treatment period.[37] Brexpiprazole + fluoxetine produced greater improvement, with statistically significant benefits over fluoxetine monotherapy after 3 weeks of treatment and lasting until the end of the study, indicating enhanced motivation. The effect of brexpiprazole alone was not determined.

In the sucrose preference test, among mice susceptible to SDS (Study 4), brexpiprazole + fluoxetine produced a statistically significant increase in sucrose preference, indicating reduced anhedonia, whereas brexpiprazole monotherapy and fluoxetine monotherapy did not significantly change sucrose preference.[32]

In the locomotion test, among mice susceptible to SDS (Study 4) and in the LPS model (Study 5), there were no statistically significant effects of any treatment.[32,33]

In mice (Study 1), brexpiprazole + SSRI (fluoxetine, paroxetine, sertraline, and fluvoxamine) produced a statistically significant reduction in the number of marbles buried versus vehicle.[28,29] Brexpiprazole + SSRI (fluoxetine, sertraline, and fluvoxamine) also produced a statistically significant reduction versus brexpiprazole monotherapy, and brexpiprazole + fluoxetine/fluvoxamine produced a statistically significant reduction versus the corresponding SSRI monotherapies.[28,29] Statistical tests were not performed for monotherapies versus vehicle.

In rats (Study 2), at the highest doses tested, brexpiprazole monotherapy and fluoxetine monotherapy produced a statistically significant increase in the number of punished licks versus vehicle in the Vogel conflict test, indicating a reduction of anxiety-like behaviors.[30,31] Brexpiprazole + fluoxetine did not significantly increase punished drinking compared to vehicle, with large error bars. In a separate control experiment, brexpiprazole monotherapy and fluoxetine monotherapy had no significant effect on time spent drinking in an unpunished session, whereas brexpiprazole + fluoxetine produced a statistically significant reduction in unpunished drinking.

Studies Assessing Effects on PTSD-Like Behaviors

The animal models and behavioral tests used in Studies 6 and 7 (PTSD-like behaviors) are briefly described below, followed by descriptions of the treatment effects.

Description of Animal Models of PTSD

Two rodent models of PTSD were utilized: exposure to predator scent stress (PSS), and fear conditioning followed by a corticosterone injection.

In the PSS model, rodents are exposed to the odor of predators, such as cats or foxes, for a short but inescapable period.[59,60] This induces fear and stress, with long-lasting behavioral responses such as freezing and avoidance, and physiological responses such as the release of stress hormones.[59,60] In susceptible animals, these same responses may be triggered by a situational reminder of the trauma, which resembles aspects of PTSD in humans.[59,60] In Study 6, rats were exposed to used cat litter as the trauma, and unused cat litter as a reminder of the trauma.[34]

People with PTSD have memory impairments that make them unable to restrict fear to the correct predictors of their trauma, as opposed to peritraumatic contextual cues.[61,62] In mice, this memory impairment can be replicated by a corticosterone injection after fear conditioning.[62] Mice are given an electric foot shock when placed in a conditioning cage (correct predictor), and a tone is played at different times to the shock (incorrect predictor).[62] Control mice develop a fear response to the cage more than the tone, whereas corticosterone-injected mice show a fear response to the tone more than the cage.[62]

Description of Behavioral Tests

The potential effects of treatment on PTSD-like behaviors were assessed using the elevated plus-maze, acoustic startle response, and fear response tests.

The elevated plus-maze comprises two raised, narrow platforms, one of which is walled and the other of which is open, meeting in the middle to form a "+" shape.[63] Rodents have an innate aversion to heights and open spaces, and the proportion of time spent in each arm can be used to measure anxiogenic- and anxiolytic-like responses.[60,63] In Study 6, rats were placed in the maze for 5 minutes and the following outcomes were determined: time spent in the open arms; number of times entering the open arms; overall activity (number of times entering the open arms + closed arms); and overall anxiety index, which is calculated from the above outcomes, and ranges from 0 to 1, with higher values reflecting more anxiety-like behavior.[34]

The acoustic startle response is a reflex muscle contraction that occurs in response to a sharp noise, and which has a greater amplitude among patients with PTSD compared with controls, reflecting hyperalertness.[60,64,65] Failure to habituate to startle stimuli is also a marker for PTSD.[66] In Study 6, rats were exposed to 30 acoustic pulses, and the amplitude of the startle reflex was measured in arbitrary units using a piezoelectric accelerometer under the test chamber (averaged over all 30 trials).[34] In addition, startle habituation to repeated acoustic pulses was calculated as the percent change in startle reflex amplitude between the first six pulses and the last six pulses.

In the fear response test, mice that have undergone fear conditioning as described in the previous section are firstly re-exposed to the tone (incorrect predictor) in a safe, familiar chamber, and secondly re-exposed to the conditioning cage (correct predictor) with no tone.[62] In Study 7, fear response was measured by the percentage of time spent 'freezing' in each scenario (defined as a lack of all movement except for respiratory-related movement), and by the ratio of freezing increase to the tone relative to baseline freezing.[35]

Effect of Brexpiprazole + Antidepressant Administration

Table 3 summarizes the outcomes from studies assessing potential treatment effects on PTSD-like behaviors. Both of the studies used specific rodent models of PTSD.

In the elevated plus-maze (Study 6), 2 weeks of treatment with brexpiprazole monotherapy and escitalopram monotherapy did not significantly decrease anxiety-like behaviors following PSS exposure.[34] In contrast, PSS-exposed rats treated with brexpiprazole + escitalopram spent significantly more time in open arms and had a significantly lower anxiety index than rats administered vehicle (with no change in overall activity, ie, total arm entries) – thereby indicating a reduction in anxiety-like behavior.

Table 3 Effects of Brexpiprazole + Antidepressant in Preclinical Studies of PTSD-Like Behaviors

Outcome	Study #	SSRI	Brexpiprazole		Brexpiprazole + SSRI		
		vs vehicle	vs vehicle	vs SSRI	vs vehicle	vs SSRI	vs Brex
In rodent model of PTSD							
EPM: time in open arms	6	×	×	×	✓	✓	×
EPM: open arm entries	6	×	×	×	×	✓	×
EPM: total arm entries	6	×	×	×	×	×	×
EPM: anxiety index	6	×	×	×	✓	✓	✓
ASR: startle amplitude	6	×	×	×	×	✓	×
ASR: startle habituation	6	×	×	×	×	×	×
FR: freezing to the tone (ratio)	7	✓	✓	✓	✓	–	–
FR: freezing to the context	7	×	✓	✓	✓	–	–

Notes: ✓=statistically significant benefit ($p<0.05$) for at least one dose tested. ×=no statistically significant benefit for any dose tested. –=experiment to make this comparison not performed.
Abbreviations: ASR, acoustic startle response; Brex, brexpiprazole; EPM, elevated plus-maze; FR, fear response; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor.

There was no significant effect of brexpiprazole monotherapy or escitalopram monotherapy on the acoustic startle response in PSS-exposed rats (Study 6).[34] Brexpiprazole + escitalopram treatment reduced startle amplitude compared with vehicle and both monotherapies; however, this benefit was only statistically significant versus escitalopram monotherapy. There was no significant effect of brexpiprazole + escitalopram or either monotherapy on startle habituation.

In the fear response test, in corticosterone-injected animals (Study 7), brexpiprazole monotherapy (acute and subchronic administration) completely suppressed the abnormally high fear response to the tone (incorrect predictor) at all doses tested, and increased the abnormally low fear response to the conditioning cage (correct predictor) in a dose-dependent manner.[35] The same result occurred when brexpiprazole was administered with escitalopram, indicating that escitalopram did not influence the effect of brexpiprazole. In a separate experiment, escitalopram monotherapy (acute administration) had no significant effect on fear response to the tone (incorrect predictor) or to the conditioning cage (correct predictor) in corticosterone-injected animals immediately following a single dose, but did show a significant benefit on fear response to the tone after 7 days.

Discussion

This systematic literature review identified seven preclinical studies that were considered suitable to assess the effects of brexpiprazole + antidepressant therapy on animal behaviors relevant to a psychiatric disorder. Overall, the identified preclinical studies support a greater effect of brexpiprazole + antidepressant therapy versus the respective monotherapies in various validated (with regard to etiology, symptomatology, and treatment response[67–69]) behavioral models and tests of treatment effects on depression- and PTSD-like behaviors.

In rodent models of depression, brexpiprazole + SSRI therapy consistently showed significant benefits over vehicle on almost all tests of depression-like behaviors, indicating improvements in behavioral despair, motivation, and anhedonia. The only exception was locomotor activity, which is a simplistic measure influenced by natural variations in activity and stress levels between animals, especially in small samples.[65] Brexpiprazole monotherapy and SSRI monotherapy showed no significant benefits over vehicle in any rodent model of depression (except SSRI on coat state). Thus, in models of depression, the administration of brexpiprazole + SSRI was superior to either monotherapy. In clinical practice, adjunctive brexpiprazole may be added to existing antidepressant treatment for patients with MDD and unresolved symptoms on antidepressants alone.[11] For these patients, brexpiprazole + antidepressant has demonstrated significantly greater improvement than placebo + antidepressant on overall and specific depressive symptoms, notably anxiety and irritability symptoms.[70–75]

In rodent models (not of psychiatric disorders), brexpiprazole + SSRI showed mixed results in tests of anxiety-like behaviors. On the marble burying test, brexpiprazole + SSRI showed improvement versus vehicle, versus brexpiprazole monotherapy and versus SSRI monotherapy. In contrast, on the Vogel conflict test, brexpiprazole + fluoxetine did not significantly increase the number of punished licks versus vehicle, whereas both monotherapies showed a benefit. However, this result must be considered in the context of the control experiment, in which brexpiprazole + fluoxetine showed an inhibitory effect on unpunished drinking that may have masked a possible treatment effect on punished licks.[30,31] Brexpiprazole has not been studied in randomized clinical trials in people with anxiety disorders and is not approved for such use. However, data from clinical trials in MDD have demonstrated the efficacy of adjunctive brexpiprazole in patients with anxious distress and anxious depression.[73–75]

In the PSS model of PTSD, brexpiprazole + SSRI (escitalopram) showed a significant improvement over vehicle and/or monotherapy on the elevated plus-maze and on acoustic startle amplitude, indicating benefits on anxiety-like behaviors and hyperalertness, respectively. In the fear conditioning model of PTSD, brexpiprazole improved fear response metrics whether administered as monotherapy or with escitalopram. Overall, across PTSD models, the administration of brexpiprazole + SSRI produced greater improvements than SSRI monotherapy. In randomized clinical trials in people with PTSD, combination treatment with brexpiprazole + sertraline has demonstrated significantly greater improvement than placebo + sertraline on overall PTSD symptoms in two flexible-dose trials, with a similar (non-significant) improvement in a fixed-dose trial.[9,10,76] Brexpiprazole + sertraline combination treatment is currently in development as a potential pharmacotherapy for PTSD.

With regard to why SSRI monotherapy generally failed to show an effect in the above models of depression and PTSD, the results of animal tests are known to vary between studies depending on experimental design factors such as the strain of mouse/rat, the duration of drug administration (acute or chronic), the dose and route of administration, and the specific test conditions.[21,58,77,78] Furthermore, the authors of Study 1 stated that ineffective doses were intentionally selected in order to investigate a potential synergistic effect of brexpiprazole + SSRI.[38]

This review focused on statistically significant effects rather than magnitudes of effect, which reflects the presentation of data in the primary publications. Translation of animal models to humans remains a challenge,[21,22] and rather than attempting to interpret clinical relevance, these results should be considered as hypothesis generating. This is especially pertinent given the differences in animal strain, dose, and treatment duration between studies, meaning that results cannot be amalgamated. However, given that brexpiprazole + antidepressant has also shown efficacy in clinical trials,[3–6,9,10] this allows for reverse translation, thereby supporting this set of behavioral tests (except for locomotor activity) as tools in the development of new treatments for MDD and PTSD.[21]

The observed benefits of treatment with brexpiprazole + SSRI/SNRI antidepressants can be attributed to a complex and likely complementary interaction of the noradrenaline, serotonin, and dopamine neurotransmitter systems, with SSRIs/SNRIs increasing the availability of monoamines at the synapse, and brexpiprazole directly acting on the monoaminergic receptors via antagonism or partial agonism.[13,18,20,79–81] The majority of monoamine release is non-synaptic, meaning that drugs which directly interact with monoamine receptors may provide greater improvement of depressive symptoms than drugs that inhibit reuptake.[82] Considering specific symptoms, a hyperactive noradrenaline system is associated with the MDD/PTSD symptoms of hyperarousal, irritability, agitation/aggression, and insomnia,[16,83] whereas a hypoactive noradrenaline system is associated with the MDD symptoms of low energy and concentration difficulties.[16,84] Of note, serotonergic antidepressants may sometimes cause emotional blunting, apathy, and anhedonia, which is attributed to dampening of dopaminergic and noradrenergic activity.[85–87] Unlike most other antipsychotics, brexpiprazole has high affinity (K_i <1 nM), as an antagonist, for noradrenergic α_{1B} and α_{2C} receptors,[20] which may help to modulate noradrenaline activity, as follows. In a hyperactive system, antagonism of α_1 receptors may prevent the negative effects of excessive noradrenaline and thereby improve hyperarousal, irritability, agitation/aggression, and insomnia, whereas, in a hypoactive system, selective antagonism of α_{2C} receptors may increase noradrenaline levels and thereby improve symptoms of low energy and concentration difficulties.[83,88–90] Brexpiprazole also shows high affinity (K_i <1 nM) serotonin 5-HT_{1A} receptor partial agonism and 5-HT_{2A} receptor antagonism,[20] actions with established antidepressant effects.[91–93] Serotonin 5-HT_{1A} receptor partial agonism is also associated with improvement of anxiety symptoms.[94] Serotonergic activity may reduce generalized fear (relating to PTSD) by inhibiting glucocorticoid

receptors and restoring γ-aminobutyric acid (GABA)/glutamate balance.[95] Finally, the clinically demonstrated efficacy of brexpiprazole as monotherapy for agitation associated with Alzheimer's dementia, as well as for schizophrenia, may be linked to modulatory effects on noradrenaline, serotonin, and dopamine monoamine neurotransmitter systems.[20,96–102] Further research into the clinical implications of the mechanism of action of brexpiprazole + antidepressant would be valuable.

This review is limited in that it considered published studies (including abstracts) only. It has been estimated that up to 40% of animal studies are never published,[103,104] and such selective publication could lead to bias if, say, positive studies are more likely to be published than inconclusive studies. All seven studies included in the review were supported by the commercial developers of brexpiprazole; independent replication of the studies would increase confidence in the results. A single reviewer selected articles for the review, which may increase the risk of rejecting relevant articles. Only seven small studies were identified, some of which were single-dose studies, limiting the strength of the evidence. Finally, minimal risk of bias assessment was possible for the individual studies due to lack of clarity in the articles regarding aspects such as randomization, blinding, and attrition.

Conclusion

In conclusion, the available evidence from published preclinical behavioral studies indicates that the administration of brexpiprazole with an antidepressant has a greater treatment effect than the respective monotherapies in various animal models and tests of depression- and PTSD-like behaviors. Thus, preclinical studies support evidence from randomized clinical trials for the antidepressant effects of adjunctive brexpiprazole in MDD,[3–6] and the efficacy of brexpiprazole in combination with the SSRI, sertraline, in PTSD.[9,10] Furthermore, the preclinical evidence from this review highlights the value of this combination of behavioral tests in drug development to help evaluate potential new treatments for MDD and PTSD.

Abbreviations

FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; LPS, lipopolysaccharide; MDD, major depressive disorder; NDRI, noradrenaline–dopamine reuptake inhibitor; PSS, predator scent stress; PTSD, post-traumatic stress disorder; SDS, social defeat stress; SNRI, serotonin–noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; UCMS, unpredictable chronic mild stress.

Data Sharing Statement

All data extracted or analyzed during this study are included in this published article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Vladimir Maletic died on December 11, 2024, prior to resubmission after peer review. Dr. Maletic was involved throughout the development of this article, from conceptualization to submission, and provided input during the peer review process.

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Disclosure

Malaak Brubaker, Shivani Kapadia and Jessie S Chambers are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc. Vladimir Maletic was a consultant for AbbVie/Allergan, Acadia Pharmaceuticals, Inc., Alfasigma, USA, Inc., Alkermes, Inc., Biogen, Boehringer Ingelheim, Cerevel Therapeutics, LLC, Corium, H. Lundbeck A/S, Intra-Cellular Therapies, Ironshore, Janssen, Jazz Pharmaceuticals, LivaNova, Neurelis, Neumora, Noven Pharmaceuticals Inc, Otsuka America Pharmaceutical, Inc., Pax Medica, Relmada Therapeutics, Sage Pharmaceuticals, Sunovion Pharmaceuticals Inc., Supernus Pharmaceuticals, Inc., Takeda Pharmaceutical Company Limited, and Tris Pharma; and was part of a speakers bureau for AbbVie, Acadia, Alfasigma, Alkermes, Inc., Axsome, Corium, Eisai, Ironshore, Intra-Cellular, Janssen, H. Lundbeck A/S, Otsuka America Pharmaceutical, Inc., Sunovion, Supernus Pharmaceuticals Inc., and Takeda Pharmaceutical Company Limited. Christopher P Watling is an employee of Cambridge (a division of Prime), which received funding from Otsuka Pharmaceutical Development & Commercialization Inc. and Lundbeck LLC for this work. Leslie Citrome has acted as a consultant for AbbVie/Allergan, Acadia, Adamas, Alkermes, Angelini, Astellas, Avanir, Axsome, Biogen, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Delpor, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, INmune Bio, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Luye, Lyndra, MapLight, Marvin, Medavante-ProPhase, Merck, Mitsubishi-Tanabe Pharma, Neumora, Neurocrine, Neurelis, Noema, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sumitomo/Sunovion, Supernus, Teva, University of Arizona, Vanda, and Wells Fargo, and has performed one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; has acted as a speaker for AbbVie/Allergan, Acadia, Alkermes, Angelini, Axsome, BioXcel, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and universities and professional organizations/societies; owns stocks (small number of shares of common stock) in Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer (purchased >10 years ago), and has stock options for Reviva; and has received royalties/publishing income from Taylor & Francis (Editor-in-Chief, Current Medical Research and Opinion, 2022–date), Wiley (Editor-in-Chief, International Journal of Clinical Practice, through end 2019), UpToDate (reviewer), Springer Healthcare (book), and Elsevier (Topic Editor, Psychiatry, Clinical Therapeutics). The authors report no other conflicts of interest in this work.

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