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Authors

Tadros, Emile
Keerthana, Shirley
Padder, Samar
et al.

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REVIEW

Anxiety disorders, PTSD and OCD: systematic review of approved psychiatric medications (2008–2024) and pipeline phase III medications

Emile Tadros[1,2], Shirley Keerthana[1], Samar Padder[1], Jayant Totlani[3], Drew Hirsch[1], Daniel N Kaidbay[1], Lorena Contreras[4], Aasim Naqvi[1], Samuel Miles[1], Krista Mercado[5], Ashley Meyer[6], Sabrina Renteria[1], Robert N Pechnick[7], Itai Danovitch[1], Waguih William IsHak[1,8]

[1]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [2]Corewell Health East, Dearborn, MI, USA; [3]Virginia Commonwealth University Health System, Richmond, VA, USA; [4]Keck Medicine of University of Southern California, Los Angeles, CA, USA; [5]University of Cincinnati College of Medicine, Cincinnati, OH, USA; [6]University of California Irvine School of Medicine, Irvine, CA, USA; [7]Western University of Health Sciences, Pomona, CA, USA; [8]David Geffen School of Medicine at UCLA, Los Angeles, CA, USASchool of Medicine, New Haven, CT, USA

Abstract

Objective: This systematic review examines psychiatric medications approved by the FDA for anxiety disorders, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) from 2008 to 2024 and describes the mechanism of action, indications for both labelled and off-label uses, evidence for efficacy, dosing and adverse effects for each medication.

Methods: The methodology involved a literature search of the PubMed database for studies published from 1 January 2008 to 31 December 2024 on FDA-approved psychiatric medications and phase III pipeline medications, using the keywords: "anxiety" OR "PTSD" OR "OCD" AND "psychopharm*" OR "medic*" OR "pharm*". The authors conducted independent assessments of the resulting articles and reached a consensus on eligible studies to include in this systematic review.

Results: Our review revealed that, in the past 16 years, the FDA approved only two medications for anxiety disorders (a delayed-release form of duloxetine for generalized anxiety disorder and an extended-release form of lorazepam) and none for PTSD or OCD. We also identified 14 pipeline medications for anxiety disorders, eight for PTSD and one for OCD, all of which are currently in phase III clinical trials.

Conclusion: Our results showed a paucity of new medications for anxiety disorders and none for PTSD and OCD in the past 16 years. However, phase III psychiatric medications for anxiety disorders, PTSD and OCD seem to show several agents with novel mechanisms of action, various modes of administration, and improved side-effect profiles.

Keywords: anxiety disorders, FDA-approved, OCD, psychiatric disorders, psychiatric medications, PTSD.

Citation

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Introduction

Anxiety disorders, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) are amongst the most prevalent psychiatric conditions, contributing significantly to the global burden of disease. The DSM-5 separated trauma-related and stressor-related disorders (such as PTSD) and obsessive-compulsive conditions (such as OCD) from anxiety disorders, which include generalized anxiety disorder (GAD), panic disorder with or without agoraphobia, specific phobias, agoraphobia, social anxiety disorder (SAD), separation anxiety disorder, and selective mutism.[1] Anxiety disorders are estimated to affect approximately 301 million people globally.[2] The chronic

nature of anxiety disorders, coupled with their high rates of comorbidity, particularly with depression and substance use disorders, complicates treatment and places a great strain on individuals and healthcare systems.

PTSD is estimated to affect approximately 8.3% of the population of the USA throughout their lifetime, with higher rates observed in populations such as military veterans and survivors of assault or natural disasters.[3] The disorder can manifest as debilitating symptoms, including flashbacks, nightmares and anxiety, that impair daily functioning. PTSD is also associated with increased risks of developing other psychiatric conditions as well as with physical health issues such as cardiovascular disease. Despite these challenges, no new medications have been approved by the FDA for PTSD in recent years, leaving a paucity of available treatment options.

OCD, a disorder characterised by intrusive thoughts and repetitive behaviours, affects about 2% of the general population.[4] The condition can severely disrupt daily life, as compulsions can interfere with personal and professional responsibilities. The ability to function effectively can be further compromised by the frequent comorbidity of OCD with mood disorders, anxiety disorders and other mental health conditions. Similarly to PTSD, treatments for OCD have stagnated, with no new FDA-approved medications in the past decade.

These disorders are associated with considerable morbidity, including impaired social and occupational functioning, and increased risk of comorbid psychiatric and physical conditions. Developing treatments for these disorders has evolved over the past decades, with a focus on effective pharmacological interventions and manageable side-effect profiles. This systematic review aims to provide a comprehensive overview of psychiatric medications approved by the FDA for anxiety disorders, PTSD and OCD between 2008 and 2024. Additionally, the review explores medications currently in phase III clinical trials that hold promise for expanding the therapeutic options for these conditions. By examining the mechanisms of action, indications, efficacy, dosing and adverse effects of these medications, this review seeks to evaluate the progress and future directions in the pharmacological treatment of these anxiety-related disorders.

Methods

The methodology involved a literature search of the PubMed database for studies published from 1 January 2008 to 31 December 2024 on FDA-approved psychiatric medications and phase III pipeline medications, using the keywords: "anxiety" OR "PTSD" OR "OCD" AND "psychopharm*" OR "medic*" OR "pharm*". The authors independently assessed the studies and collected relevant information to include in this systematic review. A PRISMA flow diagram is presented in Figure 1.

Results

Our review revealed that, in the past 16 years (1 January 2008 to 31 December 2024), the FDA approved only two medications for anxiety disorders: duloxetine for GAD and an extended-release (XR) form of lorazepam (Table 1), and none for PTSD or OCD. We also identified 14 pipeline medications for anxiety disorders, eight for PTSD and one for OCD, all of which are currently in phase III clinical trials (Table 2).

Detailed descriptions of each medication are provided below, including the medication class, mechanism of action, indications, evidence for efficacy, practical implementation issues (cost, special procedures or restrictions), and reported adverse effects for each psychiatric medication.

Approved medications for anxiety disorders: 2008–2024

Detailed descriptions of approved medications for anxiety disorders: 2008–2024 are provided below and in Table 3.

Duloxetine delayed-release (Drizalma Sprinkle)

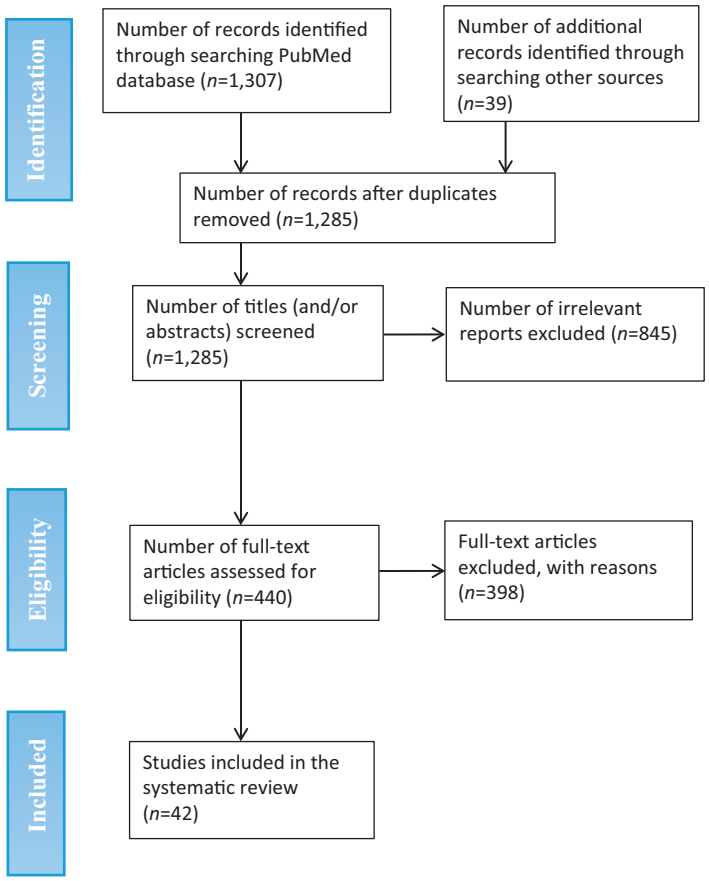
Overview: Duloxetine delayed-release (Drizalma Sprinkle) is an orally administered selective serotonin-norepinephrine reuptake inhibitor (SNRI) that was approved in 2019 by the FDA for GAD in adults and paediatric patients from 7 to 17 years old and for treatment of major depressive disorder (MDD) in adults.

Dose and route: Oral dose of a capsule formulation dosed at 30–60 mg once daily.

Evidence: Duloxetine delayed-release capsules demonstrated efficacy in reducing anxiety symptoms in several clinical trials. According to the FDA (2023),[5] three studies were conducted, one fixed-dose randomized, double-blind over a 9-week treatment period (Study 1), and two flexible-dose randomized, double-blind, placebo-controlled trials at doses of 60 mg/day and 120 mg/day over a 10-week treatment period (Study 2 and Study 3). In all three studies, greater improvement in the Hamilton Anxiety Rating Scale (HAM-A) total score and the Sheehan Disability Scale global functional impairment score was seen for treatment groups compared to placebo.[6]

Adverse events: Sedation, nausea, constipation.

Figure 1. PRISMA flow diagram.



Lorazepam extended-release (Loreev XR)

Overview: Lorazepam XR is a benzodiazepine commonly used for the treatment of anxiety disorders. It binds allosterically to benzodiazepine receptors on post-synaptic GABA-A, ligand-gated chloride ion channels on neurons in the central nervous system. The XR formulation, marketed as Loreev XR, is designed to provide a stable release of lorazepam over 24 hours and was approved in 2021 by the FDA.[7,8]

Table 1. Approved medications for anxiety disorders: 2008–2024.

Disorder	*n*	Generic name	Trade name	Approval year
Anxiety disorders	2	Duloxetine	Drizalma Sprinkle	2019
		Lorazepam Extended-Release	Loreev XR	2021

Dose and Route: Oral dose of a capsule formulation. It is typically administered as 1–10 mg daily.

Evidence: Lorazepam has long been used to treat anxiety, receiving FDA approval in 1977 as an immediate-release (IR) formulation. Its XR formulation received approval in 2021 based on pharmacokinetic data in healthy volunteers. A phase I study assessing the pharmacokinetics of XR lorazepam compared 3 mg of XR lorazepam taken once daily to 1 mg of IR lorazepam taken three times a day (TID; every 8 hours).[8] A total of 43 participants completed this study. The 90% confidence intervals for maximum concentration, minimum concentration and area under the curve for once-daily ER lorazepam compared to IR lorazepam taken TID confirmed steady-state bioequivalence. Maximum mean concentrations of lorazepam were reached at 11 hours for XR compared to 1 hour for IR lorazepam. The bioequivalent pharmacokinetic profiles between once-daily XR lorazepam and IR lorazepam given TID suggest that XR lorazepam is a viable alternative to IR lorazepam.

Adverse events: Sedation, high risk of misuse, dizziness, headache, nausea, vomiting.

Table 2. Pipeline medications for anxiety disorders in phase III as of 31 December 2024.

Disorder	*n*	Generic name	Other name(s)	Year entered phase III
Anxiety disorders	14	ABIO-08/01	BTG 1640	2006
		Agomelatine	Thymanax	2004
		Aloradine	Fasedienol, PH94B	2021
		BNC210	IW-2143	2024
		Buagafuran	AF-5	2023
		Cannabidiol	CBD, Epidiolex	2021
		Pregabalin	Lyrica	2004
		Quetiapine	Seroquel XR, Seroquel	2005
		Shugan Jieyu	SGJYC	2023
		SR58611A	Amibegron	2005
		SEP-363856	Ulotaront	2021
		Toludesvenlafaxine	Ansofaxine, LY03005, LPM570065	2018
		Vilazodone	Viibryd	2012
		Vortioxetine	Trintellix	2008
		Brexpiprazole	Rexulti	2019
		Cyclobenzaprine	Flexeril, Amrix, Fexmid, TNX-102 SL	2017
Post-traumatic stress disorder	8	Glecaprevir/Pibrentasvir	Mavyret, Maviret	2023
		Ketamine	Ketalar	2015
		MDMA	3,4-Methylenedioxymethamphetamine	2020
		Prazosin	Minipress	2009
		Propranolol	Inderal LA, Inderal XL, Hemangeol	2023
		Silexan	Lasea	2024
Obsessive-compulsive disorder	1	Troriluzole	Trigriluzole	2020

Table 3. Summary descriptions of the newly approved medications in anxiety disorders: 2008–2024.

Name, year approved	Mechanism of action	Route and dose	Notes to clinicians including effects on sedation, weight/lipids, sexual dysfunction and QTc
Duloxetine (Drizalma Sprinkle), 2019 for generalized anxiety disorder	Serotonin-norepinephrine reuptake inhibitor	Oral 30–60 mg daily	Sedation, nausea and constipation
Lorazepam extended-release (Loreev XR)	Positive allosteric modulator of GABA-A receptors	Oral 1–10 mg daily	Sedation, nausea, dizziness, headache, vomiting, high risk of misuse (Schedule IV controlled substance) and additive effects with ethanol

Detailed descriptions of pipeline medications

Pipeline medications for anxiety disorders as of 31 December 2024

Detailed descriptions of pipeline medications for anxiety disorders as of 31 December 2024 are discussed below and in Table 4.

ABIO-08/01

Overview: ABIO-08/01 (BTG 1640) is a selective inhibitor of GABA-gated and glutamate-gated chloride channels that is undergoing phase III investigation for the treatment of GAD (clinical trial identifier: EU2006-003643-23).[9–11]

Dose and route: Oral dose of a tablet formulation, dosed at 10–40 mg once daily.

Preliminary findings: Effects of ABIO-08/01 on regional electric brain generators were studied in phase I 3-dimensional electroencephalography (EEG) tomography study.[9] In a double-blind, placebo-controlled, multiple-ascending-dose study, healthy male volunteers (*n*=16) received three oral drug doses of 10 mg, 20 mg, and 40 mg, and a placebo over 7 days, with an 8-day washout period. EEG mapping and psychometric tests were conducted at hours 0, 1, and 6 on day 1 (acute effects) and on day 5 (sub-acute and combined effects). Using EEG, the study found significant central nervous effects of ABIO-08/01 compared to placebo across all doses. Higher doses (40 mg) showed activating effects in the resting EEG, whilst lower doses (10 mg) were sedative in the eyes-open EEG. The highest dose (40 mg) improved concentration and activated the EEG in vigilance-controlled conditions, whilst the lowest dose (10 mg) improved reaction time and psychomotor activity but reduced well-being. ABIO-08/01 was well tolerated and shows potential for the treatment of anxiety disorders.

Adverse events: None reported.

Agomelatine (Thymanax)

Overview: Agomelatine is a melatonin receptor agonist and serotonin 5HT-2C receptor antagonist that is already approved for the treatment of MDD and has been shown to reduce anxiety symptoms. It is being tested in phase III trials for the treatment of GAD and relapse prevention of GAD (clinical trial identifier: ISRCTN38094599).[12–14]

Dose and route: Agomelatine is administered orally. Two short-term randomized controlled trials (RCTs) and a phase II study showed significant improvement in patients receiving 25–50 mg daily.[12]

Preliminary findings: Agomelatine was effective in a phase II trial at reducing anxiety symptoms and reducing relapse rate in GAD. Previous studies have shown that agomelatine was extremely effective in treating symptoms of anxiety compared to placebo, as measured by the HAM-A, and indicated remission on the Clinical Global Impression–Severity scale.[13]

Adverse events: Agomelatine is contraindicated in patients with high liver enzymes or liver impairment.

Aloradine (Fasedienol)

Overview: Aloradine is an isomer of androstadienol and is currently undergoing investigation in phase III for SAD (clinical trial identifier: NCT06615557).[15,16] Participants who self-administered aloradine nasal spray were found to have decreased anxiety in fearful situations. Whilst its exact mechanism of action is unknown, aloradine is hypothesised to act at the GABA-A receptor.[16]

Dose and route: Aloradine is administered via intranasal spray. Trials have shown a reduction in social anxiety after receiving two puffs in each nostril.

Preliminary findings: A phase II multicentre trial observed the effectiveness of PH94B (fasedienol) on the treatment of symptoms of SAD. Participants diagnosed with generalized SAD were administered a single dose of fasedienol, a few minutes before exposure to simulated social interaction challenges. Effectiveness was measured using Subjective Unit of Distress scores. Results showed that, after two separate administrations, fasedienol was significantly more effective in decreasing social distress and related symptoms compared to participants given only one administration or placebo.[16]

Adverse effects: Commonly reported adverse effects were headache and gastrointestinal discomfort.

BNC210

Overview: BNC210 is a negative allosteric modulator of the α7-nicotinic acetylcholine receptor and is currently being explored in a phase III clinical trial for the treatment of anxiety in adults with SAD (clinical trial identifier: NCT06510504).[17,18]

Dose and route: Oral dose of a tablet formulation, dosed at 900 mg twice daily.

Preliminary findings: A phase II clinical trial examined the effects of oral administration of BNC210 on brain activity changes in adults with GAD.[17] Twenty-four volunteers with GAD received either low-dose BNC210 (300 mg), high-dose (2000 mg), placebo, or lorazepam as a positive control. Effects on anxiety-relevant neural circuits were observed using functional MRI. The results found that the low dose of BNC210 decreased

amygdala activity in response to fearful faces and reduced task-related functional connectivity in the anterior cingulate in individuals with GAD, providing evidence that drug targeting of this system may be useful in the treatment of anxiety disorders.

Adverse effects: Headache, nausea, fatigue and hepatic enzyme increases.

Buagafuran (AF-5)

Overview: Buagafuran is an α-agarofuran derivative that acts as an inhibitor of neuronal delayed rectifier potassium channels and modulates central monoamine neurotransmitters.[19,20] It is currently being explored in phase III clinical trials as a treatment for GAD (clinical trial identifiers: NCT06243640, NCT06243614).[21,22]

Dose and route: Oral dose of a tablet formulation dosed at 30–120 mg daily.

Preliminary findings: *In vitro* studies of buagafuran have found that CYP3A and CYP2E were the major enzymes involved in its metabolism.[19,20] Phase I clinical trials have been completed and found that buagafuran was well tolerated in healthy volunteers at doses up to 120 mg twice daily.[15] Another study estimated an effective human dose of 30 mg taken TID, using physiologically based pharmacokinetic (PBPK)/pharmacodynamic modelling.[23] The GastroPlus™ software developed a PBPK/pharmacodynamic model in rats, linking buagafuran brain concentrations with behavioural responses in an elevated plus-maze test. The human PBPK model successfully predicted plasma and brain concentrations of buagafuran, supporting its clinical use. Validation of PBPK models for rats and humans was achieved with observed data, and the pharmacodynamic model was extrapolated from rats to humans, assuming similar pharmacological effects.

Adverse effects: Drowsiness.

Cannabidiol (CBD, Epidiolex)

Overview: Cannabidiol (CBD) is a phytocannabinoid found in cannabis plants that is currently approved by the FDA to treat seizures associated with Lennox–Gastaut syndrome or Dravet syndrome in patients 2 years of age or older. It is currently undergoing a placebo-controlled phase III RCT for the treatment of anxiety disorders (clinical trial identifier: CTRI/2023/01/049110).[24–28]

Dose and route: Oral capsule, CBD oil 200–800 mg daily.

Preliminary findings: A systematic review and meta-analysis found that CBD significantly reduced anxiety with a considerable effect size (Hedges g = −0.92) in various anxiety disorders, including GAD, SAD and PTSD.[25] However, the authors cautioned that the limited size of the clinical sample necessitates further trials to confirm these findings.

Adverse effects: Frequently reported adverse effects of CBD include hepatic abnormalities, diarrhoea, fatigue, vomiting and somnolence.[26]

Pregabalin (Lyrica) (as an adjunct and as monotherapy)

Overview: Pregabalin is approved by the FDA for the treatment of fibromyalgia and neuropathic pain. It is a GABA analogue and a voltage-gated calcium channel modulator that has been investigated in phase III RCTs for the treatment of anxiety disorders (clinical trial identifiers: NCT00413010, NCT00368745).[29–31]

Dose and route: Pregabalin is taken orally and initially dosed at 150 mg/day in two to three divided doses. Providers may increase the dose at weekly intervals of 150 mg/day up to 300 mg/day.[32] May further increase up to 600 mg/day. However, additional benefits >300 mg/day are unclear.[33]

Preliminary findings: In a phase III double-blind RCT assessing the efficacy of pregabalin in GAD as adjunctive to serotonergic antidepressants, the mean change in HAM-A scores was significantly greater for pregabalin relative to placebo ($p<0.05$). Additionally, response rates were significantly higher for pregabalin relative to placebo.[29]

Adverse effects: Somnolence, dizziness, dry mouth.

Quetiapine XR (Seroquel XR)

Overview: Quetiapine is an atypical antipsychotic drug that is also used in the treatment of bipolar disorder. This XR formulation of quetiapine demonstrated efficacy in reducing anxiety symptoms and relapse rate.[34]

Dose and route: IR: initial oral dose is 50 mg once daily; may gradually increase the dose based on response and patient tolerability every ≥7 days to a dose of 50–200 mg daily in a single dose. The maximum recommended dose is 300 mg/day.

Preliminary findings: Systematic reviews revealed efficacy in GAD.[34] In a phase III RCT, (clinical trial identifier: NCT00534599) quetiapine XR, when used alongside serotonergic antidepressants, did not show a significant benefit over placebo in reducing generalized anxiety symptoms, as measured by the HAM-A total score.[35]

Adverse effects: Somnolence, dry mouth, headache and dizziness.

Shugan Jieyu capsules

Overview: Shugan Jieyu capsule is a herbal medicine composed of *Acanthopanax senticosus* and *Hypericum perforatum* that has been used in China for the treatment of depression and anxiety. Shugan Jieyu promotes the secretion of dopamine and 5-HT and is currently undergoing a phase III clinical trial for treating GAD (clinical trial identifier: NCT05772104).[36,37]

Dose and route: Oral administration of own or two capsules taken twice daily, with the specification of approximately 0.36 g/capsule.

Preliminary findings: A randomized, double-blind, placebo-controlled trial was conducted on the efficacy of Shugan Jieyu in improving sleep and emotional disorders in patients convalescing from COVID-19.[36] Patients (n=200) were treated with either Shugan Jieyu or placebo over 6 weeks, and differences between the two groups before and after treatment for HAM-A were measured, along with other measures related to depression and insomnia. After 6 weeks of treatment, there were statistically significantly different reduction rates and efficiency in HAM-A total scores from baseline in the experimental and control groups. Four adverse events were reported in the experimental group. Clinical studies are being continued to assess the effectiveness of Shugan Jieyu alone or in combination with Western medicine in improving symptoms of depression and anxiety.

Adverse effects: Dizziness, drowsiness, nausea, fatigue, dry mouth, headache, constipation and decreased lipid metabolism.

SR58611A (Amibegron)

Overview: SR58611A is a selective β3-adrenoceptor agonist that has been investigated in phase III trials for the treatment of GAD (clinical trial identifiers: NCT00332891, NCT00266747, NCT00252343).[37–41]

Dose and route: Oral administration in tablet form administered as 60–180 mg/day TID. Intraperitoneal injection of 0.1–0.3 mg/kg in rodents.

Preliminary findings: Results from clinical trials in humans investigating the anxiolytic efficacy of SR58611A were not identified. Previous studies on animal models show that SR58611A was effective in exerting anxiolytic effects, whilst simultaneously improving symptoms of depression.[42] The study investigated the role of β3-adrenoceptors in the antidepressant-like effects of amibegron, a β3-adrenoceptor agonist, using adrenergic β3-receptor knockout (*Adrb3*) mice in a chronic mild stress model of depression. Amibegron was administered intraperitoneally for 33 days at 3 mg/kg/day. Amibegron exhibited both anxiolytic and antidepressant-like effects, which were shown to be blocked by serotonin antagonists or β3 antagonists in previous studies. This suggests that amibegron has anxiolytic effects that are mediated through β3-adrenoceptors.

Adverse effects: SR58611A appears to be well tolerated in mammals; however, side-effects in humans are unclear.

SEP-363856 (Ulotaront)

Overview: Ulotaront (SEP-363856) is an agonist of trace amine-associated receptor 1 (TAAR1) and serotonin 5-HT1A receptors that is in phase III clinical trials for the treatment of GAD (clinical trial identifier: NCT05729373).[43,44]

Dose and route: Oral administration in a tablet formulation dosed at 25–75 mg daily.

Preliminary findings: A review of existing data from preclinical and clinical investigations of ulotaront as a treatment for schizophrenia, depression, GAD and other neuropsychiatric disorders highlights the key features of ulotaront.[43] In preclinical studies, ulotaront showed potential antipsychotic effects across various animal models. It was well tolerated in both 4-week and 26-week oral administration. In a phase II clinical trial, ulotaront effectively treated both positive and negative symptoms of schizophrenia, with minimal extrapyramidal and metabolic side-effects.[45] Notably, ulotaront is the first TAAR1 agonist to complete phase II clinical trials for schizophrenia. Beyond schizophrenia, ulotaront has shown potential efficacy in preliminary clinical trials for Parkinson disease psychosis, depression and anxiety.

Adverse effects: Worsening schizophrenia, headaches and insomnia.

Toludesvenlafaxine (Ansofaxine, LY03005, LPM570065)

Overview: Toludesvenlafaxine (ansofaxine, LY03005, LPM570065) is a potential triple monoamine reuptake inhibitor that blocks the reuptake of serotonin, dopamine and norepinephrine in the central nervous system. It is being explored in phase III clinical trials as a treatment for GAD (clinical trial identifier: NCT05970510). [46,47]

Dose and route: Oral administration in tablet formulation dosed at 80–160 mg daily.

Preliminary findings: The efficacy and safety of ansofaxine were assessed in a multicentre, double-blind, randomized, placebo-controlled phase III clinical trial in patients with MDD in China.[46] Patients with MDD (n=588) were randomly assigned to treatment with

ansofaxine 80 mg/day, ansofaxine 160 mg/day or placebo over an 8-week treatment period. Ansofaxine significantly improved anxiety symptoms in patients with MDD compared to placebo, as evidenced by a reduction in the HAM-A total score of 11.5 (80 mg/day) and 11.1 (160 mg/day) over an 8-week treatment period (compared to 8.1 with placebo). This outcome indicates the anxiolytic effectiveness of ansofaxine, which is currently being explored in phase III clinical trials for the treatment of GAD.

Adverse effects: Nausea, vomiting, headache and drowsiness.

Vilazodone (Viibryd)

Overview Vilazodone (Viibryd) is an orally administered antidepressant that is a selective serotonin reuptake inhibitor (SSRI) as well as a 5-HT1 receptor partial agonist. It has been found to be efficacious in the treatment of MDD and GAD in adults (clinical trial identifier: NCT01766401).[48,49]

Dose and route: Immediate-release tablet. Initial 10 mg/day; increase to 20 mg/day after 1 week; can increase to 40 mg/day after another week; should be taken with food.

Preliminary findings: In a multicentre, double-blind RCT in patients with GAD, the least squares mean difference in the change from baseline in HAM-A total score (using MMRM) showed a statistically significant improvement for vilazodone 40 mg/day compared to placebo (−1.80 (−3.26 to −0.34); p=0.0312, adjusted for multiple comparisons). However, vilazodone 20 mg/day did not show a significant difference from placebo.[48]

Adverse effects: Diarrhoea, nausea, vomiting and insomnia.

Vortioxetine (Trintellix)

Overview: Vortioxetine inhibits the reuptake of serotonin, is an antagonist at serotonin 5-HT3, 5-HT1D and 5-HT7 receptors, an agonist at 5-HT1A receptors, and a 5-HT1B receptor partial agonist. It is approved by the FDA for the treatment of MDD and has been investigated in phase III clinical trials for the treatment of GAD (clinical trial identifiers: NCT00788034, NCT00744627).[50–54]

Dose and route: Oral administration in tablet formulation dosed at 5–10 mg taken once daily. Preliminary studies of vortioxetine in GAD used a dose of 5 mg over 8 weeks, which appeared to yield relevant results.[55]

Preliminary findings: A preliminary study observed the efficacy of vortioxetine on the treatment of symptoms of GAD in 304 participants in total. Participants were randomly assigned to be administered 5 mg of vortioxetine (n=152) or placebo (n=152). The effectiveness of vortioxetine was assessed using scores from HAM-A. Results showed that there was no significant difference in symptom alleviation between 5 mg and placebo.[50] However, studies show that slightly higher doses of vortioxetine (10–20 mg/day) for 12 weeks showed great improvement in alleviating symptoms of MDD and comorbid GAD,[51] and in a phase IV study, an earlier increase of vortioxetine to a dose of 20 mg/day for 8 weeks led to significant improvement in both depressive and anxiety-related symptoms in participants with comorbid GAD and MDD.[52]

Adverse effects: Dizziness, nausea and headaches dry mouth.

Pipeline medications for PTSD as of 31 December 2024

Detailed descriptions of pipeline medications for PTSD as of 31 December 2024 are discussed later and in Table 5.

Brexpiprazole (Rexulti) (as adjunctive therapy)

Overview: Brexpiprazole (Rexulti) is an orally administered partial agonist at serotonin 5-HT1A and dopamine D2 receptors and an antagonist at serotonin 5-HT2A receptors.[56] It is approved for treating schizophrenia, as an add-on therapy in MDD, and for managing agitation in patients with dementia. Brexpiprazole recently underwent phase III trials for the treatment of PTSD as an adjunct to sertraline (clinical trial identifier: NCT04174170), and a supplemental new drug application was submitted to the FDA for this indication in 2024.[57–59]

Dose and route: Oral tablet. Initial 0.5–1 mg once daily; increase in weekly intervals up to 1 mg once daily and then up to 2 mg once daily; maximum dose 3 mg once daily.

Preliminary findings: In a phase III RCT, combination therapy of brexpiprazole and sertraline resulted in a significant reduction in PTSD symptoms compared to sertraline plus placebo.[57] By week 10, the combination of brexpiprazole and sertraline was associated with significantly greater reduction in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score than sertraline and placebo.

Adverse events: Akathisia, somnolence, headache, weight gain and tremor.[60]

Cyclorbenzaprine (Flexeril)

Overview: Cyclobenzaprine is a sublingual serotonin 2A receptor antagonist used to relax muscles and relieve pain and discomfort caused by strains, sprains and other muscle injuries. It is already approved as a muscle relaxant (oral Flexeril) and has been investigated for the treatment of PTSD in phase III trials (clinical trial identifier: NCT02277704).[61,62]

Table 4. Summary descriptions of medications in the pipeline for anxiety disorders as of 31 December 2024.

Name	Mechanism of action	Indications being tested in phase III	Route and dose	Notes to clinicians (including effects on sedation, weight/lipids, sexual dysfunction and QTc)
ABIO-08/01	Inhibition of GABA and glutamate-gated chloride channels	Symptoms of generalized anxiety disorder	Oral, 10–40 mg daily	No significant risk of adverse effects. Administration of ABIO-08/01 showed improvement in cognitive functioning (concentration, mental well-being), as well as overall psychomotor activity in previous studies[9]
Agomelatine (Thymanax)	Melatonin receptor agonist and serotonin 5HT-2C receptor antagonist	Treatment and relapse prevention in generalized anxiety disorder	Oral, 25–50 mg daily	No concerns with weight gain, sexual dysfunction, or sedation and, though overall QTc impact is not concerning, one case study observed prolonged QTc intervals after agomelatine administration[121]
Aloradine (Fasedienol)	Unknown, potential GABA receptor action	Social anxiety disorder	Intranasal (spray), as needed, maximum of four doses daily	Side-effects seen in clinical trials were similar to placebo
BNC210	α7 nicotinic acetylcholine receptor-negative allosteric modulator	Social anxiety disorder	Oral, 900 mg twice daily	Headache, nausea, fatigue and hepatic enzyme increases were the most common side-effects
Buagafuran (AF-5)	Modulates central monoamine neurotransmitters; inhibition of neuronal delayed rectifier potassium channels	Treatment of generalized anxiety disorder	Oral, 30–120 mg daily	Undergoes extensive CYP3A and CYP2E metabolism. Most common side-effect in phase I trials was dizziness
Cannabidiol (CBD, Epidiolex)	Modulates endocannabinoid system; precise mechanism is unclear[17]	Generalized anxiety disorder, social anxiety disorder, panic disorder, and agoraphobia	Oral, 200–800 mg daily	Frequently reported adverse effects of CBD include hepatic abnormalities, diarrhoea, fatigue, vomiting and somnolence[26]
Pregabalin (Lyrica)	GABA analogue and a voltage-gated calcium channel modulator	Adjunctive and monotherapy in the treatment of generalized anxiety disorder	Oral, 300–600 mg daily	Sedation and weight gain were detected. Previous studies have also found that pregabalin may lead to loss of libido, erectile dysfunction and anorgasmia[122]
Quetiapine extended release (Seroquel XR)	Atypical antipsychotic, binds to histamine, dopamine, 5HT and norepinephrine receptors; multimodal agent	Generalized anxiety disorder	Oral, 50–300 mg daily	Sedation is significant. Less effects on weight/lipids, extrapyramidal tract, prolactin and QTc
Shugan Jieyu capsules	Promote secretion of dopamine and 5-HT	Generalized anxiety disorder	Oral, four capsules twice daily	Dry mouth, dizziness, insomnia, constipation, nausea/vomiting, anorexia can occur.[123] Decreased lipid metabolism,[124] improved sexual dysfunction. No observed cardiovascular harm[125]

(*Continued*)

Table 4. (Continued)

Name	Mechanism of action	Indications being tested in phase III	Route and dose	Notes to clinicians (including effects on sedation, weight/lipids, sexual dysfunction and QTc)
SR58611A (Amibegron)	Selective β3 adrenoceptor agonist	Generalized anxiety disorder	Oral, 0.3–10 mg/kg daily	Previous studies found no adverse effects reported regarding cognitive functioning or risks relating to dependence and alcohol interaction[42]
SEP-363856 (Ulotaront)	Trace amine-associated receptor 1 (TAAR1) and serotonin 5-HT1A receptors agonist	Generalized anxiety disorder	Oral, 2,575 mg daily	Somnolence, headaches, insomnia, anxiety and gastrointestinal symptoms. No significant differences in extrapyramidal symptoms, lipid levels, glycated haemoglobin or prolactin between groups. No QTc interval prolongation[45]
Toludesvenlafaxine (Ansofaxine, LY03005, or LPM570065)	First-in-class triple monoaminergic reuptake inhibitor that blocks the reuptake of serotonin, dopamine and norepinephrine in the central nervous system	Generalized anxiety disorder	Oral, 80–160 mg daily	Common adverse events: nausea, vomiting, headache and drowsiness.[113] Sexual functioning should be monitored due to detected changes in prolactin and testosterone levels in preclinical studies[113]
Vilazodone (Viibryd)	Selective serotonin reuptake inhibitor and 5-HT1A receptor partial agonist	Generalized anxiety disorder	Oral, 10–40 mg daily	Fatigue was reported as an adverse effect of vilazodone; however, it was not associated with weight gain, sexual dysfunction or QTc prolongation[48]
Vortioxetine (Trintellix)	5-HT multimodal agent	Relapse prevention in generalized anxiety disorder	Oral, 10–20 mg daily	Dose dependent sexual dysfunction ranging from 16% to 34% *versus* 14% to 20% on placebo[52]

Dose and route: Patients receive cyclobenzaprine in a sublingual formulation. Studies in patients with PTSD utilised sublingual doses of 2.8 mg and 5.6 mg taken once at bedtime.[61,62]

Preliminary findings: Cyclobenzaprine demonstrated efficacy in improving sleep, psychosocial function and PTSD symptoms compared to placebo in a phase II trial at 5.6 mg, but not 2.8 mg, as measured by change from baseline in CAPS-5 score, as well as secondary outcome measures.[61]

Adverse events: Somnolence, dry mouth, headache, sedation and oral hypoesthesia.

Glecaprevir/Pibrentasvir (GLE/PIB; Mavyret)

Overview: Glecaprevir is an NS3/4A protease inhibitor, and pibrentasvir is a NS5A protein inhibitor. GLE/PIB is an FDA-approved antiviral used to treat hepatitis C viral (HCV) infections and is being explored in phase III clinical trials as a PTSD therapeutic in the absence of HCV (clinical trial identifiers: NCT05446857, NCT05637879).[63–65]

Dose and route: Oral administration in tablet formulation dosed as a tablet containing 100 mg of glecaprevir and 40 mg of pibrentasvir.

Preliminary findings: A study published in the *American Journal of Epidemiology* investigated the potential of the direct-acting antivirals glecaprevir and pibrentasvir in improving PTSD symptoms amongst US Department of Veterans Affairs patients with HCV infection.[63] The findings revealed that patients receiving GLE/PIB experienced significantly greater improvement in PTSD symptoms compared to those receiving ledipasvir/sofosbuvir, with an average improvement of approximately 15 points on the PTSD Checklist. This level of improvement is notably

Table 5. Summary descriptions of medications in the pipeline for post-traumatic stress disorder (PTSD) as of 31 December 2024.

Name	Mechanism of action	Indications being tested in phase III	Route and dose	Notes to clinicians (including effects on sedation, weight/lipids, sexual dysfunction and QTc)
Brexpiprazole (Rexulti)	D2 and 5-HT1A partial agonist, and 5-HT2A receptor antagonist	Post-traumatic stress disorder	Oral 1–3 mg daily	Reported adverse effects include akathisia, somnolence and weight gain
Cyclorbenzaprine (Flexeril)	α1-adrenergic, H1-histaminergic, M1-muscarinic and 5-HT2A receptor antagonist	Sleep disturbance associated with PTSD sleep-dependent memory consolidation	Sublingual, 5–6 mg daily	Muscle relaxant utilised for sudden-onset and acute muscle spasms. Sedation was reported during clinical trials
Glecaprevir/ Pibrentasvir (Mavyret)	Glecaprevir is a NS3/4A protease inhibitor whilst pibrentasvir is a NS5A protein inhibitor	PTSD in patients with hepatitis C virus infection	Oral, glecaprevir 100 mg + pibrentasvir 40 mg, three tablets once daily	Headache and fatigue were noted
Ketamine (Ketalar)	NMDA receptor antagonist	Chronic PTSD	Intravenous, 0.5 mg/kg	Blurred vision, dizziness, fatigue, headache and nausea/vomiting were reported[66]
MDMA	5HT, dopamine, noradrenaline releaser	PTSD	Oral, 75–125 mg daily	Granted breakthrough therapy designation as assisted therapy in treatment of PTSD in 2017 Risk of dependence, neurotoxicity and cardiovascular toxicity have been described, but not in recent PTSD trials.[70] In August 2024, the FDA declined MDMA approval citing the need for an additional phase III trial to further evaluate safety and efficacy[106]
Prazosin (Minipress)	α1-adrenergic receptor antagonist	PTSD	Oral, 1–20 mg daily	Common adverse reactions include dizziness (10%), headache (8%), drowsiness (8%), lack of energy (7%), weakness (7%), palpitations (5%) and nausea (5%)[116,117]
Propranolol (Inderal)	β-adrenergic receptor blocker	PTSD in children	Oral, 20–120 mg daily	Bradycardia, sedation, thrombocytopenic purpura and bronchospasm were commonly reported adverse effects.[119] Sex differences in PTSD symptom reduction has been noted[126]
Silexan (Lasea)	Suggested mechanism of action includes mediation of 5-HT1A receptor	PTSD	Oral, 80 mg daily	Gastrointestinal disturbances including constipation, diarrhoea and nausea

higher than that typically observed with standard PTSD treatments, such as antidepressants or trauma-focused psychotherapies.[63] The study suggests that GLE/PIB may have off-target effects on PTSD, potentially due to its anti-inflammatory properties and ability to inhibit pro-inflammatory cytokines associated with PTSD pathophysiology. These findings support further investigation into GLE/PIB as a potential treatment for PTSD, indicating potential beyond its primary use for HCV.

Adverse events: Headache and fatigue.

Ketamine (Ketalar)

Overview: Ketamine is an intravenously or intranasally administered NMDA antagonist and anaesthetic that underwent a small phase III clinical trial for the treatment of PTSD (clinical trial identifier: NCT02397889).[66,67]

Dose and route: Intravenous injection of ketamine 0.5 mg/kg.

Preliminary findings: In a phase III RCT, individuals with chronic PTSD (n=30) received either six intravenous ketamine infusions (0.5 mg/kg) or midazolam (0.045 mg/kg) over 2 weeks.[66] The ketamine group had significantly greater reductions in PTSD symptom severity, with a CAPS-5 score decrease of 11.88 points lower than the midazolam group (d=1.13, 95% CI 0.36–1.91). Additionally, treatment response was noted in 67% of the ketamine group *versus* 20% in the placebo group. Intravenous ketamine was well tolerated overall, with no serious adverse events.

Adverse events: The most commonly reported adverse effects of ketamine included blurred vision, dizziness, fatigue, headache and nausea/vomiting.[66]

3,4-Methylenedioxy-methamphetamine (MDMA)

Overview: MDMA is an orally administered amphetamine derivative that leads to increased release of serotonin, norepinephrine and dopamine. It was investigated in a phase III trial and demonstrated superiority compared to placebo in the treatment of PTSD in several phase II studies that were questioned as detailed below (clinical trial identifiers: NCT03537014, NCT04077437).[68–73]

Dose and route: Orally administered, typically as 75–125 mg spaced 3–5 weeks apart.

Preliminary findings: MDMA demonstrated superiority compared to placebo in the treatment of PTSD. The previous longitudinal study observed the effectiveness of MDMA-adjunctive therapy with psychotherapy.[68] Participants received two to three doses of MDMA during psychotherapy sessions, and the effectiveness of MDMA-adjunctive therapy on PTSD symptoms was measured using the Clinician-Administered PTSD Scale for DSM-IV. Results showed that months after the last active-dose MDMA session, PTSD symptoms were significantly improved and baseline scores were significantly decreased, with continued symptomatic improvement more than 12 months after treatment.[68,69] In June 2024, the FDA Psychopharmacologic Drugs Advisory Committee declared the efficacy data unconvincing due to trial design and conduct concerns such as past MDMA use amongst participants, unreported adverse events, concerns about blinding and missing information on misuse.[70] In August 2024, the FDA declined the approval of MDMA-assisted therapy, requesting an additional phase III trial to examine the safety and efficacy of MDMA.[70]

Adverse events: Euphoria, altered sense of self and dilated pupils. Risk of dependence, neurotoxicity and cardiovascular toxicity have been described though not in recent PTSD trials.[71]

Prazosin (Minipress)

Overview: Prazosin is an α1-adrenergic receptor antagonist approved by the FDA as a medication for hypertension. It has shown potential to treat nightmares related to PTSD and is in phase III clinical trials (clinical trial identifier: NCT00532493).[74–76]

Dose and route: Oral administration in tablet formulation dosed at 1–20 mg daily in divided doses.

Preliminary findings: A randomized, double-blind, placebo-controlled trial conducted over 26 weeks assessed the efficacy of prazosin in reducing trauma-related nightmares in military veterans with chronic PTSD.[74] Participants were randomly assigned to receive either prazosin or placebo, with the primary outcomes measured at 10 weeks. Results showed no significant difference between the prazosin and placebo groups in reducing the frequency and intensity of nightmares, thus prazosin did not provide a significant benefit over placebo in treating PTSD symptoms in this population. A meta-analysis later conducted examined the effectiveness of prazosin in treating PTSD-related sleep disturbances and overall PTSD symptoms.[75] It included six randomized placebo-controlled trials, with a total of 429 patients. The analysis aimed to pool data from various studies to assess the overall effect of prazosin compared to placebo on PTSD outcomes such as nightmares and sleep quality. Results indicated that prazosin significantly improved overall PTSD symptoms, reduced nightmares and enhanced sleep quality. However, in the largest trial included, the placebo effect was notably large, particularly concerning nightmares, which diminished the observable treatment differences. Despite the

mixed findings from individual trials, the meta-analysis concluded that prazosin offers statistically significant benefits for managing PTSD symptoms and sleep disturbances.

Adverse events: Dizziness, headache, drowsiness, lack of energy, weakness, palpitations and nausea.

Propranolol (Inderal)

Overview: Propranolol is a non-selective β-adrenergic receptor antagonist and a hypertensive medication that has shown therapeutic potential in PTSD. Its efficacy is being explored in phase III clinical trials (clinical trial identifiers: NCT04985344, NCT01127568).[77–79]

Dose and route: Oral administration in tablet formulation as 20–120 mg daily.

Preliminary findings: A review of propranolol examined the clinical evidence of the drug's effectiveness in treating and preventing PTSD.[77] It included four systematic reviews, three RCTs and one non-randomized study. In total, these studies reviewed the use of propranolol both before trauma memory reactivation and following trauma as a preventative measure. Propranolol, administered before trauma memory reactivation, has been found to decrease PTSD symptom severity, reduce physiological responses (e.g. heart rate, skin conductance), and improve cognitive performance compared to placebo in all studies but one. As a preventative treatment after trauma, propranolol did not significantly reduce the risk of developing PTSD or acute stress disorder compared to placebo or no treatment. The review has limitations such as methodological differences and lack of long-term follow-up data.

Adverse events: Headache, dizziness, nausea, fatigue, bradycardia, sedation, thrombocytopenic purpura and bronchospasm.

Silexan (Lasea)

Overview: Silexan is an oral lavender oil preparation with a mechanism of action which has not yet been fully elucidated. It has been investigated in a phase III trial for the treatment of PTSD (clinical trial identifier: NCT06412757).[80–83]

Dose and route: Oral capsules, typically administered as a single dose of 80–160 mg daily.

Preliminary findings: Silexan, authorised in Germany for anxiety symptoms, has shown efficacy in treating GAD and other anxiety-related conditions, and is now being explored for PTSD.[82] A meta-analysis of five randomized controlled trials involving 1,320 participants found that Silexan (160 mg/day) outperformed paroxetine and lorazepam in reducing anxiety symptoms.[80] Participants were randomized to receive either 80 mg of Silexan or a placebo daily for 10 weeks. Efficacy was assessed using the HAM-A, anxiety self-rating scales, the Clinical Global Impression scale and the Short Form-36 health status questionnaire. After 10 weeks, Silexan was found to be significantly more effective than placebo in reducing HAM-A scores, including both psychic and somatic anxiety sub-scores. The responder rate ratio for a ≥50% reduction in HAM-A total score was 1.34, favouring Silexan. Preliminary evidence also supports its potential use in PTSD. A phase II trial administering 80 mg daily of Silexan over 6 weeks in patients with PTSD or somatization disorder saw a decrease in the Zerssen Depression Scale and a decrease in the Symptom Checklist-90-Revised Global Severity Index compared to baseline.[81]

Adverse events: Nausea, eructation, diarrhoea and other gastrointestinal issues.

Pipeline medications for OCD as of 31 December 2024

Detailed descriptions of pipeline medications for OCD as of 31 December 2024 are discussed below and in Table 6.

Troriluzole (Trigriluzole)

Overview: Troriluzole is being investigated as an adjunctive therapy for OCD. It is a prodrug formulation of riluzole that inhibits voltage-dependent sodium channels and reduces synaptic glutamate by increasing its uptake and inhibiting its release. It has been investigated in phase III trials for the treatment of OCD (clinical trial identifiers: NCT04641143, NCT04693351, NCT03299166).[84–88]

Dose and route: Oral administration in a tablet formulation dosed at 200–280 mg daily.

Preliminary findings: Troriluzole is a conjugate of riluzole, which has previously been observed in the treatment of OCD. A previous study found that riluzole, as an adjunctive medication to psychotherapy, was significantly effective in treating obsessive symptoms alongside depressive and anxiety-related symptoms in patients with treatment-resistant OCD, measured by improved scores on the Yale-Brown Compulsive Scale, Hamilton Depression Rating Scale and HAM-A.[84] However, riluzole has been shown to produce rare yet serious adverse effects, including pancreatitis and affected liver function due to increased transaminase levels.[88] As a result, troriluzole is being investigated for the same indications due to its ability to bypass the first-pass metabolic properties of riluzole.

Table 6. Summary descriptions of medications in the pipeline for obsessive-compulsive disorder as of 31 December 2024.

Name	Mechanism of action	Indications being tested in phase III	Route and dose	Notes to clinicians (including effects on sedation, weight/lipids, sexual dysfunction and QTc)
Troriluzole (Trigriluzole)	Glutamate release inhibitor and glutamate glial uptake stimulator	Obsessive-compulsive disorder	Oral, 200–280 mg daily	No significant concerns regarding sedation, weight gain, sexual dysfunction or QTc interval change

Adverse effects: Low reports of adverse effects; however, of those reports, the most common include headache, diarrhoea, dizziness and somnolence.

Discussion

Summary of the findings

Over the 16 years covered by this review, two medications were approved by the FDA specifically for anxiety disorders: duloxetine (Drizalma Sprinkle) and lorazepam XR (Loreev XR). Duloxetine, approved in 2019 as a delayed-release sprinkle capsule, functions as an SNRI and has been shown to effectively reduce symptoms of GAD and MDD.[89] Clinical trials have demonstrated significant improvements in anxiety symptoms as measured by the HAM-A and the Sheehan Disability Scale compared to placebo.[90,91] Lorazepam XR, approved in 2021, provides prolonged action of the established benzodiazepine lorazepam, allowing for stable drug levels over 24 hours and continuous anxiety symptom relief.[8] However, the potential for misuse due to its sedative nature remains a concern as well as the risks associated with the long-term use of benzodiazepines.[92]

Notably, no new medications were approved for PTSD or OCD during this period. However, 14 compounds progressed to phase III clinical trials for the treatment of anxiety disorders, along with eight for PTSD and one for OCD. These investigational drugs offer innovative approaches to the treatment of anxiety disorders, amongst other conditions, and represent a significant step towards addressing unmet psychiatric needs.

Current state of treatment of anxiety disorders, OCD and PTSD

Clinical guidelines, such as those provided by the American Psychiatric Association, the National Institute for Health and Care Excellence (NICE) and the World Health Organization, frequently influence the selection of treatment. These guidelines stress the importance of considering patient history, comorbid conditions and side-effect profiles when choosing the best course of action. The World Health Organization's 2021 guidelines endorse cognitive behavioural therapy (CBT) and SSRIs as effective treatments for anxiety disorders and PTSD, with an emphasis on the need for accessible psychological interventions globally.[62,63] For anxiety disorders, NICE recommends SSRIs as first-line pharmacological treatments for GAD and panic disorder, with a focus on patient-centred care.[93] When first-line treatments are ineffective or not tolerated, second-line therapies, such as SNRIs, tricyclic antidepressants, pregabalin or benzodiazepines, can be considered.[94,95] However, most guidelines generally advise against the use of benzodiazepines in anxiety disorders due to their potential adverse effects, including sedation, withdrawal and dependence. With this in mind, benzodiazepines can sometimes be prescribed to patients for short-term use if their symptoms are severe.[95] In these cases, the newly approved daily XR lorazepam presents a promising, more convenient alternative to the IR formulation, which is taken TID. The selection of second-line treatments should be tailored to medication characteristics, side-effect profiles and the specific needs of the patient. The same is suggested for children and adolescents who suffer from anxiety disorders.[96]

The American Psychiatric Association updated its clinical practice guideline for the treatment of PTSD in 2017 to emphasize evidence-based psychotherapies as first-line treatment in addition to pharmacotherapy, particularly the SSRIs fluoxetine, paroxetine, and sertraline and the SNRI venlafaxine, as alternatives when therapy is not available or preferred by the patient.[97] Similarly, NICE updated its guidelines in 2018 for PTSD and in 2021 for anxiety disorders. For PTSD, NICE recommends trauma-focused CBT and eye movement desensitization and reprocessing (EMDR) as first-line treatments and recommends pharmacotherapy with SSRIs, such as sertraline or paroxetine, when psychotherapy is

ineffective or declined.[93] The 2023 US Veterans Health Administration/Department of Defence guidelines recommend prolonged exposure, cognitive processing therapy or EMDR as well as SSRI/SNRIs, such as paroxetine, sertraline and venlafaxine, based on meta-analyses.[98] For OCD, the first line is CBT/exposure and response prevention or SSRIs, such as fluoxetine, fluvoxamine, paroxetine or sertraline, which are already approved by the FDA for OCD. Second-line options include clomipramine (FDA-approved for OCD), adjunctive agents such as ondansetron and aripiprazole, and deep transcranial magnetic stimulation.[99]

It is becoming clearer to clinicians and researchers that both PTSD and OCD might be multidimensional disorders, each having various neurobiological underpinnings and several pharmacological targets. Efficacy, limitations and side-effect profiles for the first-line pharmacological agents have opened new avenues for further research. Research findings have shown increased noradrenergic activity in patients with PTSD, and meta-analysis findings revealed the efficacy of α1 adrenoreceptor antagonists, such as prazosin, in reducing nightmares in the treatment of PTSD.[100] Recent studies have shown that augmenting agents can be used along with first-line medications in treatment-resistant PTSD[101] and OCD.[102]

Unique characteristics of newly approved and pipeline medications

The recently approved medications for anxiety disorders showcase a focus on enhancing efficacy and safety. Drizalma Sprinkle (duloxetine) is unique in its delayed-release formulation designed for the treatment of anxiety disorders, particularly GAD. This formulation allows for the capsule's contents to be taken once daily and/or sprinkled on food, such as applesauce, which can be particularly beneficial for patients who have difficulty swallowing pills or with medication adherence. Peak plasma concentrations of Drizalma Sprinkle are achieved approximately 5 hours post-administration, with steady-state concentrations typically reached after 3 days of dosing.[5] As an SNRI, duloxetine exerts a dual mechanism of action that broadens its therapeutic profile in anxiety disorders, most especially when accompanied by neuropathic pain, fibromyalgia or musculoskeletal pain. Its recent extension of approval for paediatric use additionally enhances its clinical applicability in younger populations. Per the American Academy of Child and Adolescent Psychiatry, duloxetine is the only SNRI with an FDA indication for the treatment of GAD in children and adolescents aged 7–17 years.[96]

Lorazepam XR, with its XR formulation, improves adherence and reduces dosing frequency, catering to those requiring longer-term anxiety management. With duration of action of around 6–8 hours, lorazepam (IR) is already a relatively longer-acting benzodiazepine; however, for consistent management of symptoms, lorazepam requires a TID dosing schedule.[8] Many patients struggle with adherence to prescribed medications, leading to a growing trend in the production of XR formulations to help address this issue.[103] In addition, this shift towards once-daily dosing helps to improve tolerability by minimizing fluctuations in drug concentrations throughout the day, reducing the occurrence of pharmacokinetic peaks and troughs often associated with IR formulations.

With this in mind, clinicians must remain vigilant regarding potential dependence on benzodiazepines, which represent a major obstacle to their use.[8] However, XR benzodiazepines seem to carry a lower potential for abuse than their IR counterparts due to a slower release rate.[8,104] Whilst further research regarding the long-term tolerability and abuse liability of XR benzodiazepines in clinical populations is warranted, drugs such as Loreev XR may offer a more favourable risk–benefit profile for patients requiring long-term treatment for anxiety disorders.[8]

Pipeline medications introduce novel mechanisms and delivery systems that may influence future treatment guidelines. For example, clinical trials are investigating MDMA-assisted therapy as a potentially groundbreaking approach for treatment-resistant PTSD. A phase III trial demonstrated that MDMA-assisted psychotherapy significantly reduced PTSD symptoms compared to psychotherapy with placebo, with 67% of participants no longer meeting diagnostic criteria for PTSD after treatment.[105] However, these analyses and studies have been retracted due to significant protocol violations, including undisclosed ethical misconduct at one of the study sites and failure to disclose conflicts of interest by certain researchers.[70,106] These issues raise concerns about the validity and reliability of these findings, underscoring the need for further research conducted with rigorous ethical oversight. However, despite these promising results, the FDA expressed concerns regarding the safety profile of MDMA and methodological issues in the study design, including the potential for abuse, neurotoxicity and the need for additional evidence to confirm long-term efficacy and safety. As a result, the agency has requested an additional phase III trial to further evaluate safety and efficacy.[106] Despite setbacks in MDMA-assisted therapy, these studies reflect the continued interest in psychedelics as potential treatments for PTSD. Research into the potential of other psychedelics, such as psilocybin-assisted psychotherapy, is ongoing, with studies being conducted at institutions like Johns Hopkins University and Ohio State University to explore their efficacy in treating PTSD.[107,108]

Emerging pharmacological treatments for PTSD are under investigation, reflecting a concerted effort to expand the therapeutic options for this challenging condition. BNC210, a negative allosteric modulator of the α7 nicotinic acetylcholine receptor, has received Fast Track designation from the FDA and is entering phase III trials after demonstrating potential efficacy in reducing PTSD symptoms without sedative side-effects.[17] Additionally, the combination of sertraline and brexpiprazole has shown promise in recent phase II and III trials, achieving statistically significant reductions in PTSD symptoms compared to sertraline plus placebo, without supplemental psychotherapy.[57,109] The FDA has accepted the new drug application for this combination therapy, with a decision expected in February 2025.[59]

Furthermore, the US Department of Veterans Affairs and the Department of Defence continue to invest in PTSD research, for example, on the use of methylphenidate for neurocognitive complaints and PTSD symptoms.[98] Likewise, through programmes such as the PTSD Psychopharmacology Initiative, they continue to explore novel therapeutic approaches to the treatment of PTSD.[110]

The expansion of agents with dual mechanisms, like agomelatine, which affects melatonergic and serotonergic receptors, has made them particularly suitable for managing comorbid conditions or symptoms such as when anxiety is accompanied by sleep disturbances.[11,111] Approved medications, such as vortioxetine, primarily indicated for depression, have also shown effectiveness in treating GAD, offering a novel option that works on serotonin receptors to improve cognitive function and alleviate anxiety symptoms.[55] Additionally, the emergence of ulotaront (SEP-363856), targeting trace amine-associated receptor 1 (TAAR1) and serotonin receptors, reflects the exploration of unconventional pathways for therapeutic benefits.[45] Such approaches reflect ongoing efforts to target multiple receptor systems, potentially enhancing efficacy and addressing comorbid conditions such as schizophrenia and anxiety.

New trends

Current trends in anxiety disorders, PTSD and OCD management include the development of drugs that aim to minimize adverse effects and emphasize patient quality of life. Pharmacological agents in development include those that do not directly target serotonin and norepinephrine receptors. Potential categories of novel mechanisms of action include GABA and glutamate modulation, melatonin receptor agonism, TAAR1 agonism, glutamate release inhibitors, glutamate glial uptake stimulators, and NS3/4A protease inhibitors. New treatments differ from the usual anxiolytic sedatives, which, in contrast to the sedative effect, have cognition-enhancing abilities.

Several agents are demonstrating efficacy in phase II and III clinical trials whilst minimizing adverse effects such as sedation, reflecting a shift towards treatments that emphasize patient quality of life. These novel medications may provide clinicians with additional tools to treat anxiety disorders, allowing them to more confidently switch medications or augment current treatment regimens.

Recent developments in psychiatric medications emphasize personalized treatment strategies, aiming to maximize efficacy whilst minimizing adverse effects.[112] Multi-receptor agents like toludesvenlafaxine, which target serotonin, dopamine and norepinephrine pathways, illustrate a comprehensive approach to combat treatment-resistant anxiety and depressive disorders.[113] Emerging delivery methods, such as intranasal sprays, offer rapid onset and improved patient compliance. For example, aloradine, administered via intranasal spray for SAD, provides a convenient alternative to oral medications, potentially increasing adherence and patient satisfaction.[114]

There is a continued effort to repurpose medications originally approved for other conditions. Antihypertensives, including prazosin and propranolol, are being explored for their efficacy in managing PTSD symptoms.[75,115] The role of prazosin in mitigating nightmares associated with PTSD exemplifies the innovative use of existing drugs to address specific symptoms, enhancing overall patient management; studies have shown that prazosin significantly reduces the frequency and severity of nightmares in patients with PTSD.[116,117] The potential of propranolol in modulating physiological responses to stress also illustrates the evolving landscape of PTSD treatment.

Early-stage agents, such as buagafuran, a potent anxiety-reducing medication with promising results in preclinical studies, have shown unique pharmacokinetic properties, suggesting potential for the future treatment of anxiety disorders.[23] Additionally, the Shugan Jieyu capsule offers a unique method to address anxiety symptoms and enhance sleep quality, suggesting its relevance in integrative and complementary medicine.[118] These advancements reflect a broader shift towards precision medicine, where treatments are tailored to individual patient profiles, including genetic predispositions, specific symptoms and comorbidities. This approach holds promise for improving therapeutic outcomes and reducing the trial-and-error process often associated with psychiatric medication management whilst minimizing adverse effects.

Progress in the development and evaluation of numerous pharmacological interventions for anxiety disorders

in paediatric and adult populations has underscored the growing need for clear guidelines to aid clinicians in selecting the most appropriate medication for individual patient care. SSRIs and SNRIs, such as duloxetine, are considered first-line pharmacological options for the treatment of GAD in adults.[119] In paediatric patients with GAD, SSRIs are also considered the first-line pharmacotherapy.[95] When these first-line treatments are ineffective, second-line therapies, such as benzodiazepines, buspirone or pregabalin, can be considered.[94,95] The selection of second-line treatments should be individualised based on medication characteristics, side-effect profiles and the specific needs of the patient.

As the field advances, the integration of new medications promises to offer more comprehensive and tailored treatment strategies, enhancing patient outcomes and potentially transforming the treatment paradigms for anxiety disorders, PTSD and OCD. The advancement of new pharmacotherapies, such as BNC210 and the sertraline-brexpiprazole combination, holds the potential to improve outcomes for patients who do not respond to existing treatments.[120] These developments reflect ongoing efforts to expand therapeutic options, moving beyond traditional treatments and exploring novel mechanisms of action that may address treatment-resistant cases and specific symptom clusters.

Limitations

This review is subject to several limitations. All compounds were retrieved from publicly available databases, which might miss medications such as those in trials outside the USA. Moreover, clinical trials with negative or inconclusive results tend to be underreported or selectively published, contributing to publication bias. Additionally, the underrepresentation of trials reporting negative outcomes skews our findings towards more favourable results. Lastly, the variability in clinical trial designs, including differences in study populations, outcome measures and duration, complicates direct comparisons of their findings. More research is essential to assess and compare the efficacy of novel drugs for the treatment of anxiety disorders, PTSD and OCD across diverse populations.

Recommendations

Based on meta-analyses comparing psychotherapy to pharmacotherapy, several guidelines support the use of psychotherapies, such as CBT, cognitive processing therapy, EMDR and CBT/exposure and response prevention as the first line in the treatment of anxiety disorders, PTSD and OCD. Psychopharmacological interventions are highly utilised and are supported by evidence as first-line or in combination with psychotherapy. Newer psychopharmacological agents add to the armamentarium of front-line clinicians. These advancements reflect a broader shift towards precision medicine and hold promise for improving therapeutic outcomes and reducing the trial-and-error process often associated with psychiatric medication management whilst minimizing adverse effects. Real-world clinical practice and medicine consider the various aspects of each condition, the several neurobiological underpinnings and the diverse pharmacological targets available to each clinician. Therefore, the most supported approach remains that of tailoring the treatment plan according to the individual patient profile and need.

Conclusion

This review encapsulates a dynamic era in the treatment of anxiety disorders, PTSD and OCD from 2008 to 2024, which includes the FDA approval of only two medications for anxiety disorders and phase III trials now involving 14 medications for anxiety disorders, eight for PTSD and one for OCD. The emergence of diverse formulations and phase III pipeline medications indicates a pivotal shift towards more tailored and potentially more effective treatment modalities. These developments not only promise to enhance patient care and quality of life but also signify major progress in personalizing the management of anxiety disorders, PTSD and OCD. Continued research and the clinical application of these findings will be vital in achieving the full potential of such promising therapeutic advances.

Innovations in multi-receptor targeting, novel delivery methods and personalized treatment strategies are transforming the field of psychiatric care. These developments aim to provide more effective, safer and patient-centred treatments, addressing both symptom management and underlying mechanisms. However, despite the exciting progress, several limitations need to be acknowledged. First, many of the identified pipeline medications remain in the early stages of clinical trials, meaning that their safety, efficacy and long-term outcomes are not yet fully validated. Moreover, the generalization of the results from these trials is uncertain, particularly for underrepresented populations, as clinical trials often have limited diversity in patient demographics. Additionally, whilst these emerging therapies hold promise, access to them may be limited by factors such as cost, regulatory approval processes and healthcare infrastructure constraints. The real-world effectiveness of these medications, once implemented, could also be affected by adherence challenges and potential side-effects not fully captured in controlled clinical environments.

As research progresses, the potential for pipeline medications to reshape treatment paradigms for anxiety disorders, PTSD and OCD remain promising. Ongoing clinical trials will be crucial in validating these innovations and ensuring their safe integration into practice. Ultimately, these advancements hold the potential to significantly enhance the quality of life of individuals with these debilitating conditions, offering hope for a future with more effective and targeted psychiatric interventions.

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Correspondence: Waguih William IsHak, Cedars-Sinai Health System, Clinical Professor of Psychiatry at UCLA, 8700 Beverly Blvd Drive, Los Angeles, CA 90048, USA. Email: waguih.ishak@cshs.org

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