



Overview of Psychiatric Medications in the Pipeline in Phase III Trials as of June 1, 2024: A Systematic Review

ABSTRACT

Objective: This systematic review provides an overview of psychiatric medications in the late stages of development (Phase III clinical trials) as of June 1, 2024. It details the mechanisms of action, efficacy, dosing, and adverse effects of these medications. **Methods:** We searched the PubMed database for Phase III studies of psychiatric medications published until June 1, 2024, using the keywords “psychiatric” OR “psychopharm*” AND “medic*” OR “pharm*”. Our review encompassed medications currently undergoing Phase III clinical trials and those that have completed Phase III but are awaiting approval from the United States Food and Drug Administration (FDA). We independently analyzed the identified studies and reached a consensus on the medications to be included in this systematic review. **Results:** As of June 1, 2024, a total of 89 pipeline drug trials were identified, including nine for schizophrenia, five for bipolar disorders, 25 for depressive disorders, 11 for anxiety disorders, five for post-traumatic stress disorder (PTSD), one for obsessive compulsive disorder (OCD), two for eating disorders, two for sleep-wake disorders, three for sexual dysfunctions, one for substance-related and addictive disorders, 22 for neurocognitive disorders, and three for neurodevelopmental disorders, specifically attention deficit hyperactivity disorder (ADHD). **Conclusion:** The psychiatric medications in the pipeline as of June 1, 2024, demonstrate significant promise in treating psychiatric disorders.

KEYWORDS: Psychiatric medications, Phase III clinical trials, schizophrenia, bipolar disorder, depression, anxiety, psychiatric disorders, FDA

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Psychiatric medications undergoing United States Food and Drug Administration (FDA) evaluation progress through three distinct clinical trial phases. Phase I aims to establish safety profiles and determine appropriate dosages and typically involves 20 to 100 healthy volunteers or individuals with the target disease/condition over a study duration of several months. Phase II assesses efficacy and side effects and typically extends to several hundred participants with the target condition over several months to years. Phase III determines efficacy and safety in a larger population, typically 300 to 3,000 participants diagnosed with the condition, over 1 to 4 years.¹ The purpose of this systematic review is to examine the psychiatric medications in Phase III clinical trials up to June 1, 2024, delineating their mechanisms of action, evidence of efficacy, dosing protocols, and adverse effects. Our goal is to offer clinicians a comprehensive and user-friendly review of these emerging psychiatric medications, equipping them with valuable insights to prepare for potential new treatment options upon regulatory approval.

METHODS

Studies of Phase III psychiatric medications published until June 1, 2024, were identified from the PubMed database using the keywords: “psychiatric” OR “psychopharm*” AND “medic*” OR “pharm*”. The authors independently conducted a focused analysis and reached a consensus on the medications to include in this systematic review. Key findings were extracted and summarized from the full text and tables of the selected studies.

RESULTS

Overview. Psychiatric medications undergoing development in Phase III trials were fully described. Medications currently in Phase III studies and those that have completed Phase III and are awaiting FDA approval were included (Table 1). We organized the list of psychiatric medications by psychiatric disorder according to the nomenclature of the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5). An overview of medications for each psychiatric disorder grouped by characteristics and indications is accompanied by an alphabetically

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TABLE 1. List of the pipeline psychiatric medications in Phase III trials

DISORDER	NUMBER OF MEDICATIONS	PHASE III MEDICATION
Schizophrenia	9	Brilaroxazine (oxaripiprazole, RP-5063), iclepertin (BI425809), lumateperone (Caplyta), olanzapine subcutaneous (TEV-749), raloxifene (Evista), roluperidone (MIN-101), ulotaront (SEP-363856), vortioxetine (Trintellix), xanomeline + trospium (KarXT)
Bipolar disorders	5	Amisulpride/esamisulpride (SEP-4199), armodafinil (Nuvigil), brexpiprazole (Rexulti), cycloserine + lurasidone (Cyclurad), lumateperone (Caplyta)
Depressive disorders	25	Aticaprant (JNJ-67953964), buprenorphine + samidorphan (ALKS 5461), cariprazine (Vraylar), celecoxib (Celebrex), esmethadone (REL-1017), estradiol + progesterone, ezogabine (retigabine), lumateperone (Caplyta), lurasidone (Latuda), minocycline (Minocin, CoreMino [DSC], Minolira, Solodyn, Ximino), mitozodone, NMRA-335140, navacprant (BTRX-335140, NMRA-140), pimavanserin (Nuplazid), pioglitazone + citalopram + chlorthalidopoxide, pramipexole (Mirapex), psilocybin (COMP360), racemic ketamine (Wafertime), racemic ketamine subcutaneous, rapastinel (GLYX-13), seltorexant (MIN-202, JNJ-4u2847922), solriamfetol (Sunosi), toludesvenlafaxine (ansofaxine), ulotaront (SEP-363856), zuranolone (Zurzuvae)
Anxiety disorders	11	ABIO-08/01, agomelatine (Valdoxan, Thymanax), amibegron (SR58611A), buagafuran, fasedienol (Aloradine, PH94B), pregabalin (Lyrica), quetiapine (Seroquel), toludesvenlafaxine (ansofaxine, LY03005, LPM570065), ulotaront (SEP-363856), vortioxetine (Trintellix)
Post-traumatic stress disorder (PTSD)	5	Cyclobenzaprine (Flexeril, Amrix), glecaprevir/pibrentasvir (Mavyret), MDMA (3,4-methylenedioxyamphetamine), prazosin (Minipress), propranolol (Inderal)
Obsessive compulsive disorder (OCD)	1	Troriluzole
Eating disorders	2	Naltrexone-bupropion (Contrave), solriamfetol (Sunosi)
Sleep-wake disorders	2	Mazindol ER (Quilience), sodium oxybate (FT218, Lumryz)
Sexual dysfunctions	3	Dutasteride-tamsulosin (Jalyn), onabotulinumtoxinA (Botox), sildenafil oral film (CURE film Blue)
Substance use disorders	1	Baclofen (Lioresal)
Neurocognitive disorders	22	ACP-204, AR1001, dextromethorphan-bupropion (Auvelity, AXS-05), dapagliflozin (Forxiga), latrepirdine (DMB-I, Dimebon), donanemab, gantenerumab (RO4909832), GV1001, levetiracetam low dose (AGB101, Keppra), masitinib (Masivet), masupirdine, metformin extended release, nabilone (Cesamet), nilotinib (Tasigna), pimavanserin (Nuplazid), remtetterug, sabirnetug (ACU193), simufilam (PTI-125), suvorexant (Belsomra), tricaprilin (CER-0001), valiltramiprosate (ALZ-801), xanomeline (Lumeron)
Neurodevelopmental disorders (attention deficit hyperactivity disorder)	3	Centanafadine (EB-1020), NRCT-101SR, solriamfetol (Sunosi)

organized summary table containing the medication's generic, as well as other, names, mechanism of action, indication(s) being tested in Phase III, route and dosage, and notes for clinicians, including effects on sedation, weight/lipids, extrapyramidal tract, prolactin, sexual dysfunction, and QTc.

Schizophrenia. Recent Phase III trials have showcased promising investigational medications

targeting cognitive and psychotic symptoms in schizophrenia, each with distinct mechanisms of action and pharmacological profiles.

Brilaroxazine (oxaripiprazole, RP-5063), administered at dosages ranging from 5 to 100mg daily, acts as a partial agonist at dopamine D2, D3, D4, and serotonin receptors (5-HT1A, 5-HT2A, 5-HT2B), also blocking 5-HT6 and 5-HT7 receptors. It is being studied for its

potential to treat both cognitive and psychotic symptoms, showing minimal impact on weight, lipids, prolactin levels, blood pressure, or electrocardiogram (EKG). The most commonly reported side effects include somnolence and akathisia.^{2,3}

Iclepertin (BI-425809), a potent glycine transporter 1 (GlyT1) inhibitor, has demonstrated safety and good tolerance in both healthy volunteers and patients with schizophrenia. By inhibiting GlyT1, iclepertin raises glycine levels in the cerebrospinal fluid, thereby enhancing N-methyl-D-aspartate (NMDA) receptor activity and improving glutamatergic signaling. This is crucial for neural synchrony and synaptic plasticity, which are often impaired in schizophrenia due to NMDA receptor hypofunction.^{4,5} Early studies indicate that it improves memory performance and electroencephalogram (EEG) parameters, with clinical trials showing significant cognitive improvements at daily doses of 10mg and 25mg, and it was well tolerated at doses up to 75mg. Phase III trials are now assessing its long-term effects on daily functioning.^{3,6}

Xanomeline plus trospium (KarXT) is a promising treatment for schizophrenia, combining the effects of xanomeline and trospium to target psychotic symptoms effectively while minimizing common side effects. Xanomeline, an M1/M4 muscarinic agonist, can readily cross the blood-brain barrier (BBB) and stimulate muscarinic receptors in the brain, addressing both negative and potentially positive symptoms of schizophrenia. Trospium, a peripheral and nonselective muscarinic antagonist, cannot cross the BBB and thus acts primarily outside the brain. By blocking peripheral muscarinic receptors, trospium reduces side effects that xanomeline might cause in other organs. Clinical trials have demonstrated that KarXT significantly improves outcomes in patients with schizophrenia, including marked improvements in the Positive and Negative Syndrome Scale (PANSS) total score and cognitive function, compared to placebo. Additionally, KarXT enhances working memory and linguistic cognition without causing sedation, weight gain, or extrapyramidal side effects often associated with other antipsychotic medications.^{7,8}

Ulotaront (SEP-363856), a trace amine-associated receptor 1 (TAAR1) and serotonin

TABLE 2. Summary descriptions of Phase III medications for schizophrenia

MEDICATION	MECHANISM OF ACTION	INDICATIONS BEING TESTED IN PHASE III	ROUTE AND DOSE	NOTES TO CLINICIANS (INCLUDING EFFECTS ON SEDATION, WEIGHT/LIPIDS, EXTRAPYRAMIDAL TRACT, PROLACTIN, AND QTc)
Brilroxazine (oxaripiprazole, RP-5063)	Partial agonist at dopamine D2, D3, and D4; partial agonist at serotonin 5-HT1A, 5-HT2A, and 5-HT2B receptors; and antagonist at serotonin 5-HT6 and 5-HT7 receptors. ^{2,3}	Cognitive dysfunction and psychotic symptoms in schizophrenia	Oral, 5–100mg daily ³	Somnolence and akathisia were detected, but there were no reported changes in weight, lipid or prolactin levels, or electrocardiogram (EKG). ³
Iclepertin (BI-425809)	Glycine transporter 1 inhibitor. ^{3,4}	Cognitive dysfunction in schizophrenia ⁴	Oral, 2–25mg daily ⁴	Did not demonstrate improvements on the Schizophrenia Cognition Rating Scale (SCoRS), which is a requirement for approval. ^{3–6}
Lumateperone (Caplyta)	Serotonin 5-HT2A antagonist and postsynaptic D2 receptor antagonist. ^{14,15}	Schizophrenia and bipolar disorder in pediatric patients (10–17 years of age). ¹⁴	Oral, 42mg daily ¹⁵	Most common side effects include dizziness, nausea, sleepiness, and dry mouth. ^{14,16}
Olanzapine extended release subcutaneous (TEV-749)	Dopamine D2 and serotonin 5-HT2A antagonist ¹⁷	Schizophrenia ¹⁷	Subcutaneous, monthly, 3 doses compared, exact mg not yet published ¹⁷	Safety and side effects data not yet published. ¹⁷
Raloxifene (Evista)	Estrogen receptor modulator ¹⁸	Adjunctive therapy for psychotic and cognitive symptoms for postmenopausal women with schizophrenia ¹⁸	Oral, 120mg daily ¹⁹	Weight gain was detected. ¹⁹
Roluperidone (MIN-101)	Serotonin 5-HTA and alpha 1-a adrenergic receptor antagonist ²⁰	Negative symptoms in schizophrenia ²⁰	Oral, 32–64mg daily ²⁰	No extrapyramidal side effects, no weight or metabolic effects, and no changes in prolactin levels were reported. ^{20,21}
Ulotaront (SEP-363856)	Trace amine-associated receptor 1 (TAAR1) agonist ^{9,10}	Psychotic symptoms in schizophrenia ^{9,10}	Oral, 25–75mg daily ¹¹	No extrapyramidal side effects, low weight and metabolic effects, and no changes in prolactin levels were reported. ^{11–13}
Vortioxetine (Trintellix)	5-HT multimodal agent: agonist at 5-HT1A; antagonist at 5-HT3, 5-HT7, and 5-HT1D; partial agonism at 5-HT1B; and inhibitor of the 5-HT transporter (SERT) ^{22,23}	Cognitive functioning and negative symptoms in early-stage schizophrenia ^{22,23}	Oral, 5–20mg daily ²³	Common side effects include nausea, constipation, and vomiting. Risk of activation of mania, bleeding, fragility fractures, hyponatremia, serotonin syndrome, sexual dysfunction, suicidal thinking/behavior, and withdrawal syndrome were reported. Might require dose adjustment with CYP2D6 inducers (e.g., carbamazepine, phenytoin, barbiturates) or inhibitors (e.g., bupropion, fluoxetine, paroxetine). ^{22–27}
Xanomeline + trospium (KarXT)	Muscarinic M1/M4 agonist and peripheral muscarinic antagonist ^{7,8}	Psychotic symptoms in schizophrenia and Alzheimer's disease ⁷	Oral, 50mg xanomeline + 20mg trospium twice per day ⁷	No sedation, weight gain, or extrapyramidal side effects were reported. Improved working memory and linguistic cognition were reported in previous trials of xanomeline. ^{7,8}

5-HT1A receptor agonist administered in 25 to 75mg daily doses, has been noted for its lack of extrapyramidal side effects and minimal impact on weight and metabolism, maintaining stable prolactin levels.^{9–12} Over 92 percent of the drug is excreted in urine, with no clinically meaningful drug interactions involving ulotaront or its metabolites and cytochrome P450 (CYP) enzymes or transporters.¹³

Lumateperone is already FDA-approved for treating adult schizophrenia and bipolar disorder, either as monotherapy or adjunctive therapy with lithium or valproate. Currently, it is under investigation for pediatric use.

This antipsychotic targets dopaminergic, serotonergic, and glutamatergic pathways. It acts as a presynaptic partial agonist and postsynaptic antagonist at dopamine D2 receptors, reducing dopamine in the synaptic cleft while blocking postsynaptic D2 receptors. It requires only 40-percent D2 receptor occupancy, which results in a lower risk of extrapyramidal side effects. Lumateperone also antagonizes 5-HT2A receptors and augments NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activity in the prefrontal cortex, contributing to its antipsychotic and antidepressant effects. Clinical trials have shown its efficacy in treating

acute schizophrenia with minimal metabolic side effects and potential benefits for negative symptoms. For pediatric use, it is usually taken at 42mg daily, with the most common side effects being dizziness, nausea, and dry mouth.^{14–16}

The extended-release subcutaneous formulation of olanzapine (TEV-749) is currently being studied as a potential treatment for schizophrenia. This medication acts as an antagonist for dopamine D2 and serotonin 5-HT2A and is administered via subcutaneous injection once a month. The study is comparing three different doses, but the specific milligram amounts have not been

TABLE 3. Summary descriptions of medications in the pipeline for bipolar disorders

MEDICATION	MECHANISM OF ACTION	INDICATIONS BEING TESTED IN PHASE III	ROUTE AND DOSE	NOTES TO CLINICIANS (INCLUDING EFFECTS ON SEDATION, WEIGHT/LIPIDS, EXTRAPYRAMIDAL TRACT, PROLACTIN, AND QTc)
Amisulpride + esamisulpride (SEP-4199)	Dopamine D2 and serotonin 5-HT7 antagonist ²⁸	Bipolar I depression ²⁸	Oral, 200–400mg daily ²⁸	Somnolence and extrapyramidal effects, such as akathisia, were detected. Minimal changes were reported in weight, lipids, prolactin elevation, and QTc prolongation. ²⁸
Armodafinil (Nuvigil)	Sympathomimetic dopamine reuptake inhibitor ²⁹	Adjunctive therapy for depressive symptoms in bipolar disorder ²⁹	Oral, 150mg daily ²⁹	No sedation, extrapyramidal symptoms, weight, lipids, or electrocardiogram (EKG) changes were reported. ^{29,30}
Brexiprazole (Rexulti)	D2 and 5-HT1A receptor partial agonist, 5-HT2A receptor antagonist ¹⁴	Bipolar I depression ^{14,31}	Oral, 2–4mg daily ^{14,31}	Akathisia, somnolence, and weight gain were reported. ^{14,31}
Cycloserine + lurasidone (NRX-101, Cyclurad)	Antagonist at the glycine coreceptor of the N-methyl-D-aspartate (NMDA) receptor plus antagonist at D2, 5-HT2A, and 5-HT7 ³²	Maintenance of remission in bipolar depression with suicidal ideation ³²	Oral, 950mg (D-cycloserine) + 66mg (lurasidone) daily ³²	Low-to-moderate sedation was reported. Elevated prolactin levels and extrapyramidal effects were detected, with minimal changes in weight and lipids. No clinically relevant QTc prolongation was reported. ³²
Lumateperone (Caplyta)	Serotonin 5-HT2A antagonist and postsynaptic D2 receptor antagonist ¹⁴	Major depressive episodes associated with bipolar I or bipolar II disorder (bipolar depression) in pediatric patients (10–17 years of age). ^{14,33}	Oral, 42mg daily ¹⁴	Most common side effects include dizziness, nausea, sleepiness, and dry mouth. ^{14,33}

disclosed yet. Safety and side effect data for this treatment are still awaiting publication.¹⁷

Raloxifene, an estrogen receptor modulator, is under investigation for its potential to alleviate negative symptoms in postmenopausal women with schizophrenia. Studies have indicated cognitive benefits, particularly in working memory, with a daily oral dose of 120mg. However, weight gain has been noted as a potential side effect of this treatment.^{18,19}

Roluperidone (MIN-101) acts on serotonin 5-HT2A and alpha-1A adrenergic receptors and is known for its lack of extrapyramidal side effects and its negligible impact on weight, metabolic function, and prolactin levels. Administered at doses of 32 to 64mg per day, this medication has exhibited significant efficacy in addressing negative symptoms in schizophrenia.^{20,21}

Vortioxetine, a 5-HT multimodal agent, has been approved for major depressive disorder (MDD) since 2013. It is being investigated for cognitive enhancement and action on negative symptoms in patients with schizophrenia at doses of 5 to 20mg daily. Animal studies have shown it improves cognitive and social behaviors, and clinical studies indicate it improves social and physical anhedonia, particularly when combined with olanzapine. Adverse effects include nausea, constipation, potential mania activation, and serotonin syndrome.^{22–27}

This condensed overview provides a grouped perspective on investigational medications,

offering insight into their shared characteristics and potential applications in schizophrenia. For further details, Table 2 presents comprehensive information on each medication.

Bipolar disorders. Pipeline medications for the treatment of bipolar disorders were found to have both traditional and novel mechanisms.

Amisulpride plus esamisulpride (SEP-4199) combines a dopamine D2 and serotonin 5-HT7 antagonism to target bipolar I depression. Administered orally in dosages ranging from 200 to 400mg daily, clinical trials report somnolence and extrapyramidal effects, such as akathisia, minimal changes in weight and lipids, elevated prolactin levels, and QTc prolongation.²⁸

Armodafinil (Nuvigil), a sympathomimetic and dopamine reuptake inhibitor, is also being studied as an adjunctive therapy for depressive symptoms in bipolar disorder with a daily dose of 150mg. The medication is generally well tolerated, with common side effects being headache and nausea.^{29,30}

Brexiprazole (Rexulti) is being investigated for bipolar I depression at dosages of 2 to 4mg daily. It is a partial agonist at D2 and 5-HT1A receptors and an antagonist at 5-HT2A receptors. This medication offers potential benefits with reduced risks of extrapyramidal symptoms and hyperprolactinemia, compared to other antipsychotics. Clinical trials have shown its effectiveness in reducing depressive symptoms in bipolar I disorder, with potential side effects including weight gain, somnolence, and akathisia. Brexiprazole has a long half-

life and stable pharmacokinetics, making it easier for patients to adhere to the treatment regimen. The drug is metabolized by CYP2D6 and CYP3A4, necessitating monitoring for potential interactions.^{14,31}

The combination of cycloserine plus lurasidone (NRX-101, Cyclurad), acting as an antagonist at the glycine coreceptor of the NMDA receptor plus antagonist at D2, 5-HT2A, and 5-HT7 receptors, is being explored for the maintenance of remission in bipolar depression with suicidal ideation. Administered at a daily combined dose of 950mg (D-cycloserine) and 66mg (lurasidone), it has shown low-to-moderate sedation, elevated prolactin levels, and extrapyramidal effects, with minimal impact on weight and lipids and no clinically relevant QTc prolongation.³²

Lastly, lumateperone is being investigated for its effectiveness in treating major depressive episodes associated with bipolar I or II disorder in pediatric patients aged 10 to 17 years. It is taken orally at a dosage of 42mg daily and generally causes side effects such as dizziness, nausea, sleepiness, and dry mouth.^{14,33}

For further details on each medication, refer to Table 3.

Depressive disorders. As of June 1, 2024, 25 medications were in the pipeline for approval for the treatment of depressive disorders and their associated symptoms. Many of the medications reviewed showed similar mechanisms of action, notably 5-HT serotonin agonism and antagonism and kappa-opioid receptor antagonism. However,

several medications introduce novel or distinct mechanisms of action.

Adjunctive therapy involving a combination of citalopram, chlordiazepoxide, and pioglitazone (used for Type 2 diabetes) has been evaluated for significant depression treatment at a daily dose of 15mg. However, the tolerability and safety of this combination remains a concern. This medication combines a peroxisome proliferator-activated receptor gamma (PPAR- γ) agonist (pioglitazone) with a selective serotonin reuptake inhibitor (citalopram) and a benzodiazepine (chlordiazepoxide). Pioglitazone might cause weight gain in patients with diabetes and increase the risk of heart failure and edema, while chlordiazepoxide has shown similar effects in animal models.^{34–37}

Medications such as rapastinel, seltorexant, toludessvenlafaxine, psilocybin, racemic ketamine, and zuranolone introduce distinct mechanisms of action.

Rapastinel (GLYX-13) is an NMDA receptor modulator with partial agonist properties at the glycine site. It is administered intravenously at doses of 225mg, 450mg, or 900mg on a weekly or biweekly basis. Early trials demonstrated rapid and sustained antidepressant effects in individuals with treatment-resistant depression (TRD) without causing psychotomimetic effects. However, it failed to meet primary or secondary endpoints in subsequent Phase III trials. Ongoing studies are evaluating its long-term antidepressant effects in individuals with MDD, both as an additional treatment and as a standalone therapy. The drug has been shown to have no sedative effects or significant impact on QTc interval, and in animal studies, it has exhibited the potential to alleviate memory deficits.^{38–41}

Seltorexant (MIN-202, JNJ-42847922) antagonizes orexin-2 receptors, which regulate wakefulness and arousal. It is being investigated for the treatment of MDD and insomnia with daily doses of 10 to 40mg. Common adverse events included somnolence, headache, and nausea, with some participants experiencing elevated liver enzymes and sleep issues, leading to discontinuation.^{42,43}

Toludessvenlafaxine (ansofaxine), a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI), is being evaluated for MDD at oral doses ranging from 40 to 160mg daily. Past studies have shown potential impacts

on liver function with elevated bilirubin and alanine transferase levels.^{44,45}

Psilocybin, a 5-HT1A/5-HT2A receptor agonist, is presently under investigation for MDD. The compound is typically administered orally in doses ranging from 20 to 30mg. Notably, studies have demonstrated the efficacy of psilocybin in reducing weight gain and altering the trajectory of obesity in animal models.^{46–48}

Two formulations of racemic ketamine, an NMDA receptor antagonist, are currently under study for the treatment of MDD and TRD: Wafermine, a sublingual racemic ketamine, and subcutaneous racemic ketamine. Wafermine is administered sublingually at doses of 300 to 450mg/kg at various frequencies. It shows promise in treating MDD but is associated with elevated blood pressure and the potential to induce hypertension.⁴⁹ Subcutaneous racemic ketamine is administered at doses of 0.5 to 1mg/kg for TRD. Possible side effects might include hallucinations, dissociation, sedation, disorientation, and insomnia.⁵⁰

Pramipexole, a full dopamine agonist FDA-approved for Parkinson's disease and restless legs syndrome, demonstrates marked selectivity for D3 receptors. It is implicated in mood regulation and has shown neuroprotective and anti-inflammatory properties, suggesting utility in depression treatment, specifically for anhedonia.^{51,52} It is taken orally at 0.125mg twice daily and might cause side effects, such as nausea, dizziness, headache, fatigue, insomnia, constipation, hallucinations, orthostatic hypotension, impulse control disorders, and daytime sleepiness.^{51–54}

Kappa opioid receptors are targeted by aticaprant and navacaprant, acting as antagonists. Aticaprant (JNJ-67953964) is being studied as an adjunctive therapy for MDD with moderate-to-severe anhedonia. It is taken orally at a 10mg daily dose and has no significant effects on sedation, sexual dysfunction, weight gain, or QTc interval activity.^{55,56} Navacaprant (BTRX-335140, NMRA-140) is under investigation as a monotherapy for MDD, administered orally at 80mg daily. In Phase II trials for mild-to-moderate MDD, significant improvements were noted at four weeks, but not sustained at eight weeks, compared to placebo. This compound

also improved working memory and executive functioning in animal models.⁵⁷

Buprenorphine plus samidorphan (ALKS 5461) combines a kappa opioid receptor agonist with a mu opioid receptor partial agonist. It is being explored for TRD, taken sublingually in doses ranging from 4mg plus 4mg to 8mg plus 8mg daily. Previous studies on opioid dependence treatment suggest possible adverse effects, including sexual dysfunction and premature ejaculation in more than 80 percent of participants.^{58,59}

Cariprazine and lurasidone offer promising results in monotherapy for MDD through antagonism at D2 and 5-HT receptors. Cariprazine (Vraylar) is being studied at daily doses of 1 to 4.5mg. It is a partial agonist at central D2 and 5-HT1A receptors, with antagonist activity at the 5-HT2A receptor. It is already FDA-approved for schizophrenia and bipolar disorder, and it was also approved in December 2022 as adjunctive therapy for MDD.^{14,60} Lurasidone (Latuda), which antagonizes 5-HT2A/D2 receptors with additional 5-HT7 antagonism, is being tested at doses ranging from 20 to 60mg daily, with infrequent mild sedation reported.^{14,32}

Solriamfetol and ulotaront both target MDD by acting as agonists at TAAR1. Solriamfetol (Sunosi), a dopamine and norepinephrine reuptake inhibitor and TAAR1 agonist, is being tested at an oral dose of 300mg for MDD. It is approved for managing excessive daytime sleepiness due to obstructive sleep apnea (OSA) or narcolepsy, with common side effects including headache, nausea, and decreased appetite.^{61,62} Ulotaront (SEP-363856), a TAAR1 agonist with additional agonism at 5-HT1A, has been studied for treating psychotic symptoms in schizophrenia and as an adjunctive therapy in MDD, with a daily dose of 25 to 75mg and no significant side effects.^{10–12}

Several novel therapies are under investigation, primarily focusing on modulating the serotonin system. Pimavanserin (Nuplazid), an inverse agonist at serotonin 5-HT2A and 5-HT2C receptors, is being studied for MDD, dementia-related psychotic symptoms, and residual psychotic symptoms in schizophrenia. The recommended daily dose is 20mg. It is already FDA-approved for Parkinson's disease-related psychosis and might affect QTc interval.^{63–67} Lumateperone tosylate (Caplyta) is a 5-HT2A antagonist being investigated

TABLE 4. Summary descriptions of medications in the pipeline for depressive disorders

MEDICATION	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)
Aticaprant (JNJ-67953964)	Selective kappa opioid receptor antagonist ⁵⁵	Adjunctive therapy for major depressive disorder (MDD) with moderate-to-severe anhedonia ⁵⁶	Oral, 10mg daily ⁵⁵	There were no reports on sedation, sexual dysfunction, weight gain, or QTc interval activity. ⁵⁵
Buprenorphine + samidorphan (ALKS 5461)	Kappa opioid receptor agonist and mu opioid receptor partial agonist ^{58,59}	Adjunctive therapy for treatment-resistant depression (TRD) ^{58,59}	Sublingual, 4mg+4mg to 8mg+8mg daily ^{58,59}	Studies investigating buprenorphine for treatment of opioid dependence reported sexual dysfunction and premature ejaculation as adverse effects in more than 80% of participants. ^{58,59}
Cariprazine (Vraylar)	Partial agonist at central D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptor ¹⁴	Monotherapy for MDD ⁶⁰	Oral, 1–4.5mg daily ⁶⁰	United States Food and Drug Administration (FDA)-approved for the treatment of schizophrenia and bipolar disorder mania, mixed, and depression, as monotherapy or adjunctive therapy. Approved in December 2022 as adjunctive therapy for MDD ¹⁴
Celecoxib (Celebrex, Elyxyb)	Inhibition of cyclooxygenase-2 (COX-2) ^{77,78}	Monotherapy and adjunctive therapy for MDD ^{78–80}	Oral, 200–400mg daily ^{78–80}	Risks of cardiovascular events (myocardial infarctions at doses >200mg daily) and gastrointestinal (GI) bleeding, as well as potential renal and hepatic toxicity, were reported. Avoid or use with caution in patients with pre-existing conditions. Consider administering with proton pump inhibitor in patients with GI bleeding risk. Celecoxib inhibits CYP2D6 and is metabolized by CYP2C9, interacting with enzyme inhibitors. ^{77,78}
Esmethadone	N-methyl-D-aspartate (NMDA) receptor antagonist ⁷¹	TRD ⁷⁰	Oral, 25–50mg daily ⁷⁰	Methadone has previously been observed to contribute to weight gain. ⁷¹ Further evaluation of esmethadone on weight gain should be observed.
Estradiol + progesterone	Estrogen receptor agonist, progesterone receptor agonist ⁷²	Prevention of depressive symptoms in peri- and postmenopausal female patients ⁷²	Oral, estrogen 0.45mg + progesterone, 200mg daily ⁷²	Nausea, changes in bleeding levels, musculoskeletal pain, weight gain, and headaches were reported. ^{72,73}
Ezogabine (retigabine)	Positive allosteric modulator for KCNQ2 and KCNQ3 potassium channels ⁷⁴	Anhedonia and other associated depressive symptoms ⁷⁴	Oral, titrated to up to 900mg/day (3 doses of 300mg daily) ⁷⁴	Anticonvulsant approved by the FDA to treat focal onset seizures. Commonly reported adverse effects for treatment of depression were dizziness, confusion, and headaches. ⁷⁴
Lumateperone tosylate (Caplyta)	5-HT2A antagonist ¹⁴	Monotherapy and adjunctive for MDD ³³	Oral, 42mg daily ¹⁴	Low frequency of sedation, extrapyramidal symptoms, weight gain, prolactin changes, and QTc prolongation were reported. ¹⁴
Lurasidone (Latuda)	5HT2A/D2 receptor antagonist with 5-HT7 antagonism ^{14,32}	Monotherapy for MDD. ^{14,32}	Oral, 20–60mg daily ¹⁴	There were infrequent reports of potential mild sedation. ^{14,32}
Minocycline (Minocin, CoreMino [DSC], Minolira, Solodyn, Ximino)	Tetracycline antibiotic inhibits bacterial protein synthesis by binding with the 30S and possibly the 50S ribosomal subunit(s), a with pleiotropic antineuroinflammatory properties. ^{82,83}	Adjunctive treatment for MDD ^{82,83}	Oral, 200mg daily ⁸²	GI effects (nausea, vomiting, diarrhea), photosensitivity, skin reactions (pruritus, urticaria), dizziness, vertigo, pseudotumor cerebri autoimmune reactions (drug-induced lupus-like syndrome, autoimmune hepatitis), teeth and bone discoloration, liver toxicity, and renal toxicity were reported. Good penetration through the blood-brain barrier was reported, which accounts for its neuroprotective ability. ^{82,83}
Mitizodone	5-HT receptor antagonist and 5-HT1A receptor partial agonists ⁶⁹	Monotherapy for MDD ⁶⁹	Oral, 10–40mg daily ⁶⁹	Additional studies are needed to fully assess the adverse effects of this medication. ⁶⁹
NMRA-335140	Selective kappa opioid receptor antagonist ⁶⁴	MDD ⁶⁴	Oral, 80mg daily ⁶⁴	Information not yet available.
Navacaprant (BTRX-335140, NMRA-140)	Kappa opioid receptor antagonist ⁵⁷	Monotherapy for major depressive disorder (MDD) ⁵⁷	Oral, 80mg daily ⁵⁷	NMRA-140 improves working memory and executive functioning in animal models via benzodiazepine inverse agonists. ⁶⁶ In Phase II trials for mild-to-moderate MDD, improvement was significant at 4 weeks, but not at 8 weeks, compared to placebo. ⁵⁷
Pimavanserin (Nuplazid)	Inverse agonist at serotonin 5-HT2A and 5-HT2C receptors ⁶³	MDD, dementia-related psychotic symptoms relapse prevention, and residual psychotic symptoms in schizophrenia ^{63–66}	Oral, 20mg daily ⁶⁶	United States Food and Drug Administration (FDA)-approved for psychosis related to Parkinson's disease. Studies report that it might prolong QTc intervals by 5–8ms. ⁶⁷

TABLE 4, CONT. Summary descriptions of medications in the pipeline for depressive disorders

MEDICATION	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)
Pioglitazone + citalopram + chlordiazepoxide	Peroxisome proliferator-activated receptor gamma (PPAR- γ) agonist ³⁴	MDD ³⁴	Oral, 15mg daily ³⁴	Pioglitazone can cause weight gain in patients with diabetes and increase the risk of heart failure and edema. Chlordiazepoxide also contributes to weight gain in animal models. ^{34–37}
Pramipexole	Full dopamine agonist with higher affinity for D3 receptor than D1, D2, and D4 receptors ⁵¹	Adjunctive treatment of MDD, especially anhedonia ^{51–54}	Oral, 0.125mg twice per day ⁵¹	Nausea, dizziness, headache, fatigue, insomnia, constipation, hallucinations, orthostatic hypotension, impulse control disorders (might be less common than in patients with Parkinson's disease), and daytime sleepiness were reported. ^{51–54}
Psilocybin (COMP360)	5-HT1A/5-HT2A receptor agonist ⁴⁶	MDD ^{46,47}	Oral, 20–30mg, single dose ⁴⁶	Studies have shown that psilocybin was effective in decreasing weight gain and obesity trajectory in animal models. ⁴⁸
Racemic ketamine (Wafertime)	N-methyl-D-aspartate (NMDA) receptor antagonist ⁴⁹	MDD ⁴⁹	Sublingual, 300–450 mg/kg, variable frequency (not established) ⁴⁹	Use of racemic ketamine has been shown to affect blood pressure and induce hypertension. ⁴⁹
Racemic ketamine subcutaneous	NMDA receptor antagonist ⁵⁰	Treatment-resistant depression (TRD) ⁵⁰	Subcutaneous, 0.5–1mg/kg twice weekly ⁵⁰	Side effects include hallucinations, dissociation, sedation, disorientation, insomnia. ⁵⁰
Rapastinel (GLYX-13)	NMDA receptor modulator with glycine-site partial agonist properties ³⁸	MDD ^{39,40}	Intravenous, 225mg, 450mg, or 900mg weekly or biweekly ^{39–41}	There were no reports of sedation or affected QTc intervals. Rapastinel was found to restore memory deficits in studies utilizing animal models. ³⁸
Seltorexant (MIN-202, JNJ-42847922)	Selective orexin-2 receptor antagonist ⁴²	Adjunctive therapy for MDD and insomnia ⁴²	Oral, 10–40mg daily ⁴²	Reports of elevated alanine and aspartate aminotransferase (i.e., affected liver function), as well as insomnia and sleep paralysis, have led to discontinuation of participant involvement in some studies. ⁴²
Solriamfetol (Sunosi)	Dopamine and norepinephrine reuptake inhibitor and trace amine-associated receptor 1 (TAAR1) agonist ^{61,62}	MDD ⁶¹	Oral, 300mg daily ^{61,62}	Schedule IV drug that is already approved for excessive daytime sleepiness due to obstructive sleep apnea or narcolepsy. Side effects include headache, nausea, and decreased appetite. ^{61,62}
Toludesvenlafaxine (ansofaxine)	Serotonin, norepinephrine, and dopamine reuptake inhibitor ⁴⁴	MDD ⁴⁴	Oral, 40–160mg daily ⁴⁴	Administration might affect liver function, as indicated by elevated levels of bilirubin and alanine transferase in previous studies. ⁴⁴
Ulotaront (SEP-363856)	TAAR1 agonist with additional agonism at 5-HT1A ¹⁰	Psychotic symptoms in schizophrenia and adjunctive therapy in MDD ^{10,11}	Oral, 25–75mg daily ^{10,11}	No extrapyramidal side effects, weight changes, metabolic effects, alterations in prolactin levels, or changes in QT interval were observed. ^{10–12}
Zuranolone (Zurzuvae)	GABA _A receptor agonist ⁷⁵	Adjunctive therapy for MDD ⁷⁵	Oral, 30–50mg daily ⁷⁵	FDA approved for treatment of postpartum depression in August 2023. Clinical trials showed that sedation was reported in more than 5% of participants who experienced adverse events. ⁷⁵

for use in MDD. Administered at 42mg daily, it has a low risk of sedation, extrapyramidal side effects, weight gain, prolactin changes, and QTc prolongation.^{14,33,68} Mitizodone is a 5-HT receptor antagonist and a 5-HT1A receptor partial agonist being investigated as a monotherapy for MDD and is administered orally at doses ranging from 10 to 40mg daily. Additional research is needed to fully assess the adverse effects of this medication.⁶⁹

Esmethadone, estradiol plus progesterone, ezogabine, and zuranolone represent innovative approaches targeting complex symptoms of depression, including treatment resistance and anhedonia, through unique mechanisms of action.

Esmethadone, an NMDA receptor antagonist, is being studied for TRD with a recommended daily oral dose of 25 to 50mg. Its predecessor, methadone, was known to contribute to weight gain, so further observation of esmethadone for similar effects is warranted.^{70,71}

Estradiol plus progesterone, acting as an estrogen receptor agonist and progesterone receptor agonist, is being investigated for the prevention of depressive symptoms in peri- and postmenopausal female patients. It is administered orally with a dosage of 0.45mg of estrogen and 200mg of progesterone daily. Reported side effects include nausea, changes in bleeding levels, musculoskeletal pain, weight gain, and headaches.^{72,73}

Ezogabine (retigabine), a positive allosteric modulator of KCNQ2 and KCNQ3 potassium channels, is being assessed for anhedonia and other depressive symptoms, with an oral dosing regimen titrated up to 900mg/day. Previously approved for focal onset seizures, ezogabine use has been associated with dizziness, confusion, and headaches.⁷⁴ Zuranolone, a GABA_A receptor agonist, is being tested as an adjunctive therapy for MDD at a daily oral dose of 30 to 50mg. It was recently FDA-approved for postpartum depression. Sedation was a frequent side effect in over five percent of participants in clinical trials.⁷⁵

Extensive studies confirm the proinflammatory status in depression,

TABLE 5. Summary descriptions of medications in the pipeline for anxiety disorders

MEDICATION	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 ⁹²	Symptoms of generalized anxiety disorder (GAD) ⁹²	Oral, 10–40mg daily ⁹²	No significant risk of adverse effects were reported. Administration of ABIO-08/01 showed improvement in cognitive functioning (concentration, mental wellbeing), as well as overall psychomotor activity in previous studies. ⁹²
Agomelatine (Valdoxan, Thymanax)	Melatonin receptor agonist and serotonin 5-HT _{2C} receptor antagonist. ⁸⁴	Treatment and relapse prevention in GAD ⁸⁴	Oral, 25–50mg daily ⁸⁴	No concerns with weight gain, sexual dysfunction, or sedation were reported. Although overall QTc impact is not concerning, one case study observed prolonged QTc intervals after agomelatine administration. ⁸⁵
Buagafuran	Modulates central monoamine neurotransmitters, inhibition of neuronal delayed rectifier potassium channels ⁹³	Treatment of GAD ⁹³	Oral, 30–120mg daily ⁹³	Buagafuran undergoes extensive CYP3A and CYP2E metabolism. The most common side effect in Phase I trials was dizziness. ⁹³
Fasedienol (Aloradine or PH94B)	Unknown, potential GABA receptor action ⁹⁰	Acute anxiety in patients with social anxiety disorder. ^{90,91}	Intranasal (spray), as needed, maximum of 4 doses daily. ⁹⁰	Side effects seen in clinical trials were similar to placebo. ⁹⁰
Pregabalin (Lyrica)	GABA analogue and a voltage-gated calcium channel modulator ⁸⁶	Adjunctive and monotherapy in the treatment of GAD ⁸⁶	Oral, 300–600mg daily ⁸⁶	Sedation and weight gain were detected. Previous studies have also found that pregabalin might lead to loss of libido, erectile dysfunction, and anorgasmia. ⁸⁷
Quetiapine extended release (Seroquel XR)	Histamine, dopamine, 5-HT, and norepinephrine multimodal agent ⁸⁸	GAD ^{88,89}	Oral, 50–300mg daily ^{88,89}	Sedation is significant. Less effects on weight/lipids, extrapyramidal tract, prolactin, and QTc were reported. ⁸⁸
SRS8611A (Amibegaron)	Selective beta-3 adrenoceptor agonist ⁹⁴	GAD ⁹⁴	Oral, 0.3–10mg/kg daily ⁹⁴	Previous studies found no adverse effects reported regarding cognitive functioning, or risks relating to dependence and alcohol interaction. ⁹⁴
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 ^{44,45}	GAD ^{44,45}	Oral, 80–160mg daily ^{44,45}	Common adverse events include nausea, vomiting, headache, and drowsiness. ⁴⁴ Sexual functioning should be monitored due to detected changes in prolactin and testosterone levels in preclinical studies. Enhanced dopamine neurotransmission might benefit patients with major depressive disorder, substance use disorders, hyposexual desire disorder, or serotonin-induced sexual dysfunctions. ⁴⁵
Ulotaront (SEP-363856)	Trace amine-associated receptor 1 (TAAR1) and serotonin 5-HT _{1A} receptor agonist ⁹	GAD ¹⁰³	Oral, 25–75mg daily ¹⁰³	In the initial trial, somnolence and gastrointestinal symptoms were observed. No extrapyramidal side effects, low weight and metabolic effects, no changes in prolactin levels, and no QTc interval prolongation were reported. ⁹
Vortioxetine (Trintellix)	5-HT multimodal agent. ^{22,23,27}	Relapse prevention in GAD ⁹⁶	Oral, 10–20mg daily ^{23,96}	Dose dependent sexual dysfunction ranging from 16–34% versus 14–20% on placebo. ^{22,23,27,96}

with causal links to neurotransmitter dysregulation.⁷⁶ Some clinical studies have demonstrated the positive benefits of celecoxib and minocycline in improving depressive symptoms. Celecoxib inhibits cyclooxygenase-2 (COX-2) and is currently being investigated as a potential monotherapy or adjunctive therapy for MDD. It is typically prescribed at a daily oral dose of 200 to 400mg and increases the risk of cardiovascular events and gastrointestinal bleeding, with potential renal and hepatic toxicity.^{77–81} Minocycline, a tetracycline antibiotic with antineuroinflammatory properties, is being studied as an adjunctive treatment for MDD at 200mg daily. It can penetrate the BBB, contributing to its

neuroprotective potential. However, its use is associated with gastrointestinal effects, photosensitivity, and potentially severe autoimmune reactions.^{82,83}

For more detailed information on each medication, refer to Table 4.

Anxiety disorders. As of June 1, 2024, there were 11 medications in the pipeline for approval in the treatment of anxiety disorders. While the majority are being investigated for generalized anxiety disorder (GAD), some also target symptoms associated with social anxiety disorder.

Several medications under investigation focus on modulating the serotonin system and GABA receptors. Pregabalin and fasedienol

work on or modulate GABA receptors, while vortioxetine, quetiapine, and agomelatine act on serotonin (5-HT) family receptors, among others.

Agomelatine, a melatonin receptor agonist and serotonin 5-HT_{2C} receptor antagonist, is being studied for the treatment and relapse prevention of GAD. Administered orally at doses of 25 to 50mg daily, it has shown no effects on weight gain, sexual dysfunction, or sedation, although a single case study observed prolonged QTc intervals.^{84,85}

Pregabalin (Lyrica), a GABA analogue and voltage-gated calcium channel modulator, is being explored both as an adjunctive therapy and monotherapy for GAD at doses of 300 to

TABLE 6. Summary descriptions of medications in the pipeline for post-traumatic stress disorder (PTSD)

MEDICATION	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)
3,4-methylenedioxy-methamphetamine (MDMA)	5HT, dopamine, noradrenaline releaser. ¹⁰⁴	PTSD ¹⁰⁴	Oral, 75–125mg daily ¹⁰⁴	MDMA was 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. ^{104,105}
Glecaprevir/pibrentasvir (Mavyret)	Glecaprevir is a NS3/4A protease inhibitor while pibrentasvir is a NS5A protein inhibitor. ^{102,103}	PTSD in patients with hepatitis C. ¹⁰²	Oral, glecaprevir 100mg + pibrentasvir 40mg, 3 tablets once daily ¹⁰²	Headache and fatigue were noted. ^{102,103}
Cyclobenzaprine sublingual (Flexeril, Amrix)	Alpha-1 adrenergic, H1-histaminergic, M1-muscarinic, and 5-HT2A receptor antagonist ⁹⁷	Sleep disturbance associated with PTSD and sleep-dependent memory consolidation ⁹⁷	Sublingual, 5–6mg daily ⁹⁷	Cyclobenzaprine is a muscle relaxant utilized for sudden-onset and acute muscle spasms. Sedation was reported during clinical trials. ⁹⁷
Prazosin (Minipress)	Alpha-1 adrenergic receptor antagonist ⁹⁸	PTSD ^{98,99,110}	Oral, 1–20mg daily ^{98,99}	Common adverse reactions include dizziness (10%), headache (8%), drowsiness (8%), lack of energy (7%), weakness (7%), palpitations (5%), and nausea (5%). ^{98,99}
Propranolol (Inderal)	Beta-adrenergic receptor blocker ¹⁰⁰	PTSD in children ¹⁰⁰	Oral, 20–120mg daily ¹⁰⁰	Bradycardia, sedation, thrombocytopenic purpura, and bronchospasm were commonly reported adverse effects. ¹⁰¹ Sex differences in PTSD symptom reduction have been noted. ¹⁰⁰

600mg daily. Side effects include sedation, weight gain, and potential sexual dysfunction, such as loss of libido, erectile dysfunction, and anorgasmia.^{86,87}

Quetiapine extended release (Seroquel XR), a multimodal agent affecting histamine, dopamine, 5-HT, and norepinephrine receptors, is being evaluated for GAD. The typical dose ranges from 50 to 300mg daily. Significant sedation is noted, but it has less of an impact on weight, lipids, extrapyramidal symptoms, prolactin, and QTc intervals.^{88,89}

Fasedienol (Aloradine, PH94B), which potentially acts on GABA receptors, is being assessed for acute anxiety in patients with social anxiety disorder. It is administered intranasally as needed, up to four doses daily, with side effects similar to placebo.^{90,91}

Other medications, including ABIO-08/01, buagafuran, SR58611A (Amibegron), toludessvenlafaxine (ansofaxine), ulotaront (SEP-363856), and vortioxetine (Trintellix), focus on specific neurotransmitter pathways.

ABIO-08/01, which inhibits GABA and glutamate-gated chloride channels, is being tested for GAD symptoms. Administered orally at doses of 10 to 40mg daily, it has shown improvements in cognitive functioning and psychomotor activity without significant adverse effects.⁹²

Buagafuran, which modulates central monoamine neurotransmitters and inhibits neuronal delayed rectifier potassium channels, is being studied for GAD treatment at doses of

30 to 120mg daily. Extensive CYP3A and CYP2E metabolism is noted, with dizziness being the most common side effect in early trials.⁹³

SR58611A (Amibegron) introduces a distinct mechanism of action through selective beta-3 adrenoceptor agonism and is administered orally at doses of 0.3 to 10mg/kg daily for the treatment of GAD. Previous studies have reported no adverse effects on cognitive functioning, dependence, or alcohol interaction.⁹⁴

Toludessvenlafaxine (ansofaxine), a first-in-class triple monoaminergic reuptake inhibitor (TRI) blocking the reuptake of serotonin, dopamine, and norepinephrine, is being evaluated for GAD at doses of 80 to 160mg daily. Common adverse events include nausea, vomiting, headache, and drowsiness. Sexual functioning should be monitored due to changes in prolactin and testosterone levels observed in preclinical studies.^{44,45}

Ulotaront (SEP-363856), a TAAR1 and serotonin 5-HT1A receptor agonist, is being studied for GAD at doses of 25 to 75mg daily. Initial trials have reported somnolence and gastrointestinal symptoms, but no extrapyramidal side effects, changes in weight, metabolic effects, prolactin changes, or QTc interval prolongation were reported.^{10,95}

Vortioxetine (Trintellix), a 5-HT multimodal agent, is being investigated for relapse prevention in GAD. It is administered orally at 10 to 20mg daily. Dose-dependent sexual dysfunction has been reported, ranging from 16 to 34 percent, compared to 14 to 20 percent with

placebo.^{22,23,27,96}

For more detailed information on each medication, refer to Table 5.

Post-traumatic stress disorder (PTSD).

Five medications for PTSD were in the approval pipeline as of June 1, 2024, targeting various mechanisms to address symptoms of PTSD, including sleep disturbances and comorbid conditions, such as hepatitis C infection.

Cyclobenzaprine (TNX-102 SL) is an alpha-1 adrenergic, H1-histaminergic, M1-muscarinic, and 5-HT2A receptor antagonist being studied for its potential to address sleep disturbances related to PTSD, especially those affecting sleep-dependent memory consolidation. This substance is administered sublingually at doses of 5 to 6mg daily and is primarily recognized as a muscle relaxant for sudden-onset and acute muscle spasms. Clinical trials have reported sedative effects associated with its use.⁹⁷

Prazosin, an alpha-1 adrenergic receptor antagonist, is under investigation for its efficacy in treating PTSD, especially nightmares and sleep disturbances, and PTSD associated with alcohol use disorder. It is administered orally at 1 to 20mg daily, and common side effects include dizziness, headache, drowsiness, lack of energy, weakness, palpitations, and nausea.^{98,99}

Propranolol, a beta-adrenergic receptor blocker, is under investigation for the treatment of PTSD in children. It is taken orally at doses ranging from 20 to 120mg daily. Commonly reported adverse effects include bradycardia, sedation, thrombocytopenic purpura, and

TABLE 7. Summary descriptions of medication in the pipeline for obsessive compulsive disorder (OCD)

MEDICATION	MECHANISM OF ACTION	INDICATION BEING TESTED IN PHASE III	ROUTE AND DOSE	NOTES TO CLINICIANS (INCLUDING EFFECTS ON SEDATION, WEIGHT/LIPIDS, SEXUAL DYSFUNCTION, AND QTc)
Troriluzole	Glutamate release inhibitor and glutamate glial uptake stimulator ^{106,107}	OCD ^{106,107}	Oral, 200–280mg daily ^{106,107}	No significant concerns regarding sedation, weight gain, sexual dysfunction, or QTc interval change were reported. ^{106,107}

TABLE 8. Summary descriptions of medications in the pipeline for eating disorders

MEDICATION	MECHANISM OF ACTION	INDICATION BEING TESTED IN PHASE III	ROUTE AND DOSE	NOTES TO CLINICIANS (INCLUDING EFFECTS ON DAYTIME SEDATION, DEPENDENCE RISK, AND OTHERS)
Naltrexone-bupropion (Contrave)	The combination has a leptin excitatory activity. Naltrexone is mu opioid receptor antagonist, and bupropion is a norepinephrine and dopamine reuptake inhibitor. ¹⁰⁸	Binge eating disorder ¹⁰⁸	Oral naltrexone 16mg and bupropion 180mg daily ¹⁰⁸	United States Food and Drug Administration (FDA)-approved for obesity. Side effects include nausea, vomiting, constipation, dizziness, and headache. Serious side effects include seizures and elevation of blood pressure and heart rate. ¹⁰⁸
Solriamfetol (Sunosi)	Dopamine and norepinephrine reuptake inhibitor and trace amine-associated receptor 1 (TAAR1) agonist. ^{109,110}	Binge eating disorder ^{109,110}	Oral, 150mg or 300mg daily ^{109,110}	Solriamfetol is a schedule IV drug that is already approved for excessive daytime sleepiness due to obstructive sleep apnea or narcolepsy. Side effects include headache, nausea, and decreased appetite. ¹⁰⁹

bronchospasm. Notably, a trial has observed sex differences in the reduction of PTSD symptoms, with male patients showing more reduction in symptoms compared to female patients.¹⁰¹

Glecaprevir/pibrentasvir is a combination of a NS3/4A protease inhibitor (glecaprevir) and a NS5A protein inhibitor (pibrentasvir), being tested for PTSD in patients infected with hepatitis C. Administered orally as three tablets once daily (glecaprevir 100mg + pibrentasvir 40mg), headache and fatigue are the primary noted side effects.^{102,103}

3,4-methylenedioxy-methamphetamine (MDMA), known for its action as a releaser of serotonin, dopamine, and noradrenaline, is being evaluated for PTSD treatment. Administered orally at doses of 75 to 125mg daily, it was granted breakthrough therapy designation as assisted therapy for PTSD in 2017. Although risks of dependence, neurotoxicity, and cardiovascular toxicity have been described, recent PTSD trials have not reported these issues.^{104,105}

For more details on these medications, refer to Table 6.

Obsessive compulsive disorder. As of June 1, 2024, only one medication has advanced to Phase III clinical trials for treating obsessive compulsive disorder (OCD). Troriluzole functions as a glutamate release inhibitor and a glutamate glial uptake stimulator taken orally at 200 to 280mg daily doses. Clinical trials have not reported significant concerns about sedation, weight gain, sexual dysfunction, or QTc interval changes, making it a promising treatment for OCD without notable adverse effects.^{106,107} See Table 7 for more details.

Feeding and eating disorders. Two medications currently in Phase III trials target binge eating disorder by utilizing different mechanisms of action.

Naltrexone plus bupropion is an FDA-approved medication for obesity. Early results show potential therapeutic use in treating binge eating disorder. It combines naltrexone, an opioid receptor blocker, and bupropion, a drug that affects norepinephrine and dopamine levels. The medication is taken orally in doses of naltrexone 16mg and bupropion 180mg daily. Common side effects include nausea, vomiting, constipation, dizziness, and headache. Serious side effects might include seizures, high blood pressure, and increased heart rate.¹⁰⁸

Solriamfetol (Sunosi) is FDA-approved for excessive daytime sleepiness due to OSA or narcolepsy and is under Phase III investigation for binge eating disorder in adults. It is a dopamine and norepinephrine reuptake inhibitor and TAAR1 agonist, taken orally once per day at 150mg or 300mg doses. Common side effects include headache, nausea, and decreased appetite.^{109,110}

For a comprehensive overview, please refer to Table 8.

Sleep-wake disorders. As of June 1, 2024, only two medications were identified in the pipeline for approval in the treatment of sleep-wake disorders.

Sodium oxybate (FT218, Lumryz), which acts as a GABA_B receptor agonist, is under investigation for treating cataplexy and narcolepsy symptoms. It is taken orally at 6 to 9g nightly doses. However, it is under FDA review due to concerns about adverse effects,

including the risk of dependence, leading to its classification as a Schedule III controlled substance with a restricted safety program for prescription.^{111,112}

Quilience (Mazindol ER), a triple-reuptake inhibitor (SNDRI) and partial agonist for orexin (hypocretin)-II receptors, is also being studied for narcolepsy and comorbid cataplexy. Mazindol has shown improvements in narcolepsy symptoms when taken orally at a dose of 3mg nightly. However, it did not demonstrate improvements in cataplexy or sleep paralysis at this dose. At a higher dose of 6mg, it exhibited similar efficacy to dextroamphetamine 50mg for treating narcolepsy, with fewer adverse effects.¹¹³

For further details, refer to Table 9.

Sexual dysfunctions. Three medications are currently in Phase 3 trials for the treatment of sexual dysfunction, specifically erectile disorder. These medications utilize different mechanisms of action to address this condition.

Dutasteride-tamsulosin combines two active components: dutasteride, which blocks the conversion of testosterone to dihydrotestosterone (DHT), a key androgen involved in prostate gland development and growth, and tamsulosin, an alpha-blocker that relaxes the muscles in the bladder and prostate. This combination is administered orally at 0.5mg dutasteride and 0.4mg tamsulosin once daily. Common side effects include dizziness, abnormal ejaculation, decreased libido, and impotence.^{114,115}

OnabotulinumtoxinA works by blocking the presynaptic release of the neurotransmitter acetylcholine at the neuromuscular junction.

TABLE 9. Summary descriptions of medications in the pipeline for sleep-wake disorders

MEDICATION	MECHANISM OF ACTION	INDICATIONS BEING TESTED IN PHASE III	ROUTE AND DOSE	NOTES TO CLINICIANS (INCLUDING EFFECTS ON DAYTIME SEDATION, DEPENDENCE RISK, AND OTHERS)
Sodium oxybate (FT218, Lumryz)	GABA _B receptor agonist activity ¹¹¹	Cataplexy and excessive daytime tiredness associated with narcolepsy ¹¹¹	Oral, 6–9g nightly ¹¹¹	Risk of dependence led to its classification as Schedule III drug, as well as the implementation of a restricted safety program for its prescription to patients. ¹¹²
Mazindol extended release (Quilience)	Triple-reuptake inhibitor (serotonin-norepinephrine-dopamine reuptake inhibitor), partial agonist for orexin (hypocretin)-II receptors ¹¹³	Narcolepsy and comorbid cataplexy ¹¹³	Oral, 3mg nightly ¹¹³	Mazindol improved narcolepsy symptoms but not cataplexy or sleep paralysis. At 6mg, it showed similar efficacy to dextroamphetamine (50mg) for narcolepsy with fewer adverse effects. ¹¹³

TABLE 10. Summary descriptions of medications in the pipeline for sexual dysfunctions

MEDICATION	MECHANISM OF ACTION	INDICATIONS BEING TESTED IN PHASE III	ROUTE AND DOSE	NOTES TO CLINICIANS (INCLUDING EFFECTS ON SEDATION, DEPENDENCE RISK, LIVER EFFECTS, AND OTHERS)
Dutasteride-tamsulosin (Jalyn)	Dutasteride blocks the conversion of testosterone to dihydrotestosterone (DHT), a key androgen involved in prostate gland development and growth. Tamsulosin acts as an alpha-blocker, relaxing the muscles in the bladder and prostate. ¹¹⁴	Erectile disorder ¹¹⁵	Oral, dutasteride 0.5mg + tamsulosin 0.4mg once daily ¹¹⁵	The proportion of patients experiencing any adverse events, serious adverse events, and drug-related adverse events was significantly higher in the active treatment group compared to the placebo group. ¹¹⁴
OnabotulinumtoxinA (Botox)	Blocks presynaptic release of the neurotransmitter (acetylcholine) at the neuromuscular junction ¹¹⁶	Erectile disorder ^{116,117}	Intracavernous injection, 100 units once daily ¹¹⁶	Mild penile pain on injection and mild penile pain for 3 days following injection were reported; no systemic effects were reported. ^{116,117}
Sildenafil oral film (CURE film Blue)	Selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase (PDE-5). ¹¹⁸	Erectile disorder ¹¹⁹	Oral, 25–100mg daily ¹¹⁸	Sildenafil oral film as a high solubility, rapid onset of action, and enhanced systemic bioavailability. Mild-to-moderate headache (33.3% of subjects) and vomiting (8.3%) were reported in a healthy volunteer study. ^{118,119}

It is being tested for erectile disorder through intracavernous injections of 100 units once daily. Reported side effects include mild penile pain on injection and mild penile pain for three days following injection, with no systemic effects noted.^{116,117}

Sildenafil oral film, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase 5 (PDE5), is also under investigation for erectile disorder. This medication is taken orally at daily doses of 25 to 100mg. In trials involving healthy volunteers, a small number of patients experienced mild-to-moderate headaches and vomiting.^{118,119}

For more detailed information about these medications, refer to Table 10.

Substance use disorder. As of June 1, 2024, only one medication was in the approval pipeline for the treatment of substance use disorder. Baclofen (Lioresal), a GABA_B receptor agonist, is being investigated for the treatment of alcohol use disorder. Administered orally at a dose of 30mg daily, baclofen is notable for its limited liver metabolism, which makes it a promising option for patients with liver damage. Clinical trials have reported somnolence as a common side effect. Previous

studies have shown that in patients with kidney disease, adverse effects, such as delirium and symptoms of mania, might occur.¹²⁰ Refer to Table 11 for additional details on baclofen.

Neurocognitive disorders. Twenty-two new medications have been investigated for the treatment of neurocognitive disorders in Phase III trials. These medications are generally indicated for the treatment of Alzheimer’s disease and associated agitation and the clinical syndrome of dementia, which is typically operationally defined as a decline in cognition and functional abilities relative to an individual’s baseline level of function. However, such medications are diverse in their unique mechanisms of action.

A significant focus of current research involves targeting amyloid beta, a protein that accumulates abnormally in the brains of individuals with Alzheimer’s disease, contributing to neurodegeneration. These medications aim to reduce or neutralize amyloid beta to slow disease progression and alleviate symptoms.¹²¹

The monoclonal antibody sabirnetug (ACU193) targets soluble amyloid beta oligomers implicated in Alzheimer’s disease

progression and neurodegeneration. This medication is delivered through intravenous infusion, with an initial dosage of 35mg/kg for the first two administrations, followed by a maintenance dose of 50mg/kg every four weeks.^{122,123}

Donanemab is an antibody designed to target the buildup of amyloid beta peptides (N3pG). It is given intravenously at doses of 700 to 1,400mg every four weeks. Clinical trials have not revealed significant concerns regarding fall risk, change in QTc interval, weight fluctuation, sedation, or vital signs. However, there have been observations of potential amyloid-related cerebral edema.^{124,125}

Gantenerumab, a monoclonal antibody, specifically targets amyloid plaques by promoting their breakdown through microglial recruitment and phagocytosis. It is administered subcutaneously at different doses (120–1,200mg at minimum 1-week intervals). The FDA has recognized its potential by granting it a breakthrough designation.¹²⁶

Simufilam (PTI-125) modulates the conformation and activity of filamin A, a structural protein that undergoes abnormal changes in Alzheimer’s disease, leading to the

TABLE 11. Summary descriptions of medications in the pipeline for substance use disorders

MEDICATION	MECHANISM OF ACTION	INDICATION BEING TESTED IN PHASE III	ROUTE AND DOSE	NOTES TO CLINICIANS (INCLUDING EFFECTS ON SEDATION, DEPENDENCE RISK, LIVER EFFECTS, AND OTHERS)
Baclofen (Lioresal)	GABA _B receptor agonist ¹²⁰	Alcohol use disorder ¹²⁰	Oral, 30mg daily ¹²⁰	With limited liver metabolism and emphasis on renal metabolism, it holds promise for patients with liver damage. Clinical trials reported somnolence, while previous studies noted adverse effects in patients with kidney disease, including delirium and symptoms of mania. ¹²⁰

development and persistence of amyloid beta plaques. It acts as a filamin alpha-7 nicotinic acetylcholine receptor antagonist and is currently under investigation for the treatment of Alzheimer's disease, with and without accompanying dementia. The recommended dosage is 100mg orally twice daily. While the drug has advanced to Phase III trials, concerns have been raised about the integrity of results. No serious adverse effects on health have been reported.^{127,128}

Valiltramiprosate (ALZ-801) inhibits the aggregation of amyloid beta-42 through a mechanism involving 3-sulfopropanoic acid (3-SPA) metabolism. In early trials, oral administration of 265mg twice daily resulted in adverse effects, including nausea, dizziness, and vomiting.¹²⁹

Other medications focus on modulating neurotransmitter systems, such as serotonin, GABA, and dopamine, which play crucial roles in cognitive function and psychiatric symptoms.¹²⁹

ACP-204, an inverse agonist at 5-HT_{2A} receptors, is being studied for Alzheimer's disease-associated psychosis. Administered orally at 30 to 60mg daily, it does not cause QTc prolongation, unlike similar treatments.^{130,131}

Pimavanserin (Nuplazid), a 5-HT_{2A} and 5-HT_{2C} inverse agonist, is being investigated for preventing relapse in dementia-related psychotic symptoms, residual psychotic symptoms in schizophrenia, and MDD. It is administered orally at 20mg daily and might prolong QTc intervals by 5 to 8ms. Currently, it is approved for Parkinson's disease psychosis.¹³²⁻¹³⁴

Masupirdine, a 5-HT₆ receptor selective antagonist, is being tested for Alzheimer's disease. Commonly reported adverse effects include agitation, falls, and atrial fibrillation when administered orally at doses of 50 to 100mg daily.¹³⁵

Suvorexant, an orexin-1 and orexin-2 receptor antagonist, was FDA-approved in 2014 for the treatment of insomnia and is being tested for the treatment of dementia. It is taken orally at night at a dose of 10mg, and

somnolence is a commonly reported adverse effect.^{136,137}

Latrepirdine (DMB-1, Dimebon), an H1 histamine receptor antagonist and NMDA receptor antagonist, is being studied for Alzheimer's disease. Administered orally at doses of 10 to 60mg daily, it shows no significant risk of QTc prolongation, sedation, or falls.¹³⁸

Levetiracetam (AGB101, Keppra), a synaptic vesicle glycoprotein 2A (SV2A) inhibitor, is being studied for mild cognitive impairment due to Alzheimer's disease at low doses. Administered orally at 220mg daily, it showed no significant risk of QTc interval change or weight gain in Phase II trials, but falls were a common adverse effect.^{139,140}

AR1001, a PDE5 inhibitor, is being investigated for mild cognitive impairment and early Alzheimer's disease. The daily dosage is 30mg, taken orally. There are no significant risks related to QTc prolongation or weight gain, but fainting might increase the risk of falls.¹⁴¹

Dextromethorphan-bupropion (Auvelity, AXS-05) is being researched for treating agitation in Alzheimer's disease and has been approved by the FDA for MDD. The medication combines dextromethorphan, which acts as an NMDA receptor antagonist and sigma-1 receptor agonist, with bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI) that competitively inhibits CYP2D6, resulting in a prolonged half-life of dextromethorphan to 22 hours. The recommended initial dosage is 45mg of dextromethorphan and 105mg of bupropion taken orally once daily, with a subsequent increase to twice daily after three days. Common side effects can include dizziness, headache, diarrhea, drowsiness, dry mouth, sexual dysfunction, and excessive sweating.^{142,143}

Nabilone, a partial agonist at CB-1 and CB-2 cannabinoid receptors, is being studied for potential use in treating dementia. It is taken orally in doses ranging from 0.5 to 1.5mg daily and might cause sedation and drowsiness, increasing the risk of falls.^{144,145}

Certain medications target mild cognitive impairment, early-stage Alzheimer's disease, and related symptoms by affecting metabolic pathways and providing energy supplementation.

Tricaprilin, a medium-chain triglyceride metabolized to act as a ketogenic energy source, is being studied for Alzheimer's disease. It is administered orally at 20g twice daily, and typical side effects include gastrointestinal discomfort and nausea.¹⁴⁶

GV1001, a gonadotropin-releasing hormone receptor (GnRHR) activator, is being investigated for Alzheimer's disease. When administered subcutaneously at doses ranging from 0.56 to 1.12mg weekly or biweekly, no notable adverse effects associated with QTc intervals, weight change, or fall risk were observed.^{147,148}

Masitinib, a tyrosine kinase inhibitor, is currently under investigation for its potential to treat Alzheimer's disease. In clinical studies, oral daily doses of 3 to 4.5mg/kg did not show significant risk in terms of changes to QTc interval and vital signs. However, notable adverse effects included neutropenia, hypoalbuminemia, and rash.¹⁴⁹

Metformin extended release is being studied for its potential influence on cognitive function through the gut-brain axis. It regulates insulin levels, thus helping to prevent hyperinsulinemia, which has been associated with neuroinflammation and the accumulation of amyloid beta plaques. It is administered orally at doses ranging from 500 to 2,000mg daily. Some studies suggest a potential risk of cognitive decline in patients with Type 2 diabetes.^{150,151}

Dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, decreases glucose reabsorption in blood and is being studied for cognitive impairment and dementia symptoms in patients with Type 2 diabetes. It is FDA-approved for Type 2 diabetes, heart failure, and chronic kidney disease and is administered at 10mg daily. Serious adverse effects include diabetic ketoacidosis and urinary tract infections.¹⁵²

Nilotinib, a c-Abl tyrosine kinase receptor inhibitor, is being investigated for Alzheimer's disease. When taken orally at 84 to 112mg daily, common side effects include mood swings, pain, and gastrointestinal discomfort. There are no reports of QTc prolongation, weight gain, or fall risk.^{153,154}

Xanomeline (Lumeron), a muscarinic receptor agonist selectively targeting M1 and M4 receptors, is being studied for Alzheimer's disease and related cognitive deterioration. The daily oral dose ranges from 75 to 225mg, and it has been associated with weight gain and increased QTc interval at lower doses.^{155,156}

Additional research is investigating the use of nanoparticles for the diagnosis and treatment of Alzheimer's disease.¹⁵⁷ Other potential treatments in earlier stages of clinical development remain focused on investigating disease-modifying therapies for various conditions (i.e., multiple sclerosis).¹⁵⁸ See Table 12 for more details on each medication in the approval pipeline for neurocognitive disorders.

Neurodevelopmental disorders (attention deficit hyperactivity disorder [ADHD]). As of June 1, 2024, three pharmaceuticals had advanced to Phase III clinical trials for the treatment of neurodevelopmental disorders, specifically ADHD.

Centanafadine (EB-1020) is a SNDRI being studied for ADHD. It is administered orally at doses of 200 to 400mg daily and is well tolerated, with no significant risk of dependence, liver function issues, or sedation.¹⁵⁹

NRCT-101SR exerts its effects on glutamatergic synapses to augment synaptic plasticity and neurotransmission. It is orally administered at doses ranging from 1,500 to 2,000mg per day, and it is well tolerated, with no significant adverse effects in clinical trials.¹⁶⁰

Solriamfetol (Sunosi) is a dopamine and norepinephrine reuptake inhibitor and TAAR1 agonist approved for excessive daytime sleepiness due to OSA or narcolepsy. It is administered orally at doses of 150mg or 300mg daily. Common side effects include headache, nausea, and decreased appetite.¹⁶¹

Table 13 provides more detailed information on the medications in the pipeline for ADHD.

DISCUSSION

This systematic review identified numerous psychiatric medications of potential interest

that were in the late stages of development on the path to FDA approval as of June 1, 2024. A total of 90 pipeline drug trials were identified, including nine for schizophrenia, five for bipolar disorders, 25 for depressive disorders, 11 for anxiety disorders, five for PTSD, one for OCD, two for eating disorders, two for sleep-wake disorders, five for sexual dysfunctions, one for substance-related and addictive disorders, 22 for neurocognitive disorders, and three for neurodevelopmental disorders, specifically ADHD.

Significant activity is observed in the development of new medications for neurocognitive disorders. However, several agents were not reviewed in this manuscript, and some innovative mechanisms of action did not translate into significant clinical effects. For example, solanezumab, which is an intravenous monoclonal immunoglobulin G1 (IgG1) antibody targeting the mid-domain of the amyloid beta peptide for Alzheimer's disease, did not meet its expected endpoint, leading to the discontinuation of its Phase III trials.¹⁶² Additionally, clinical trials on pimavanserin for schizophrenia were discontinued after they failed to demonstrate significant improvement in negative symptoms.¹⁶³ Similarly, deudextromethorphan plus quinidine (AVP-786), which is an NMDA antagonist and sigma 1 receptor agonist and is FDA-approved for pseudobulbar affect, was studied in Phase III for agitation in dementia due to Alzheimer's disease; it did not show significant difference from placebo and was thus terminated.¹⁶⁴

Research on medications classified as psychedelic agents expanded to new indications, with several studies now in Phase III, and many others completing Phase II and approaching Phase III, such as ketamine for PTSD; psilocybin for alcohol use disorder, TRD, PTSD, GAD, OCD, fibromyalgia, and anorexia nervosa; and 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) for TRD, bipolar II disorder, postpartum depression, and alcohol use disorder.¹⁶⁵ Most recently, lysergic acid diethylamide (LSD) was granted an FDA breakthrough designation for GAD; the Phase IIb trials of MM120 (lysergide d-tartrate) showed 65 percent response and 48 percent remission of GAD after 12 weeks of a single dose.¹⁶⁶

Nutriband has partnered with Kindeva Drug Delivery to scale up the production of a new

substance use medication that incorporates Nutriband's AVERSA™ abuse-deterrent transdermal technology into Kindeva's FDA-approved transdermal fentanyl patch system. The medication, AVERSA™ Fentanyl, aims to be the first abuse-deterrent patch of its kind and is currently in the process of obtaining FDA approval. Notably, the development has already completed a Phase I study, bypassing the need for Phase II and III trials.¹⁶⁷ More progress is still being made with long-acting injectable antipsychotics, with subcutaneous monthly forms, such as olanzapine, being tested for efficacy.¹⁶⁸

The field of psychiatry is in urgent need of innovation to effectively address the alarming rise of mental health disorders worldwide.¹⁶⁹ The lack of effective psychiatric treatments and alternatives is reflected in the relatively high prevalence of treatment-resistant conditions. More research is needed to better understand the biopsychosocial mechanisms underlying mental disorders and the effects of medications.^{170,171} Historically, psychiatric disorders have been classified based on symptoms and diagnostic criteria. This poses a challenge, as patients diagnosed with the same disorder might present with a broad spectrum of phenotypes and clinical presentations. To address this challenge, biomarkers in psychiatry are a promising tool to help guide treatment for heterogeneous and complex mental disorders, as patients with the same diagnosis might respond differently to medications based on several mediating and moderating factors that continue to be identified at increasing rates. Several potential biomarkers have been identified and linked to certain neuropsychiatric conditions and neurodegenerative diseases.¹⁷¹ However, few have demonstrated to be useful in clinical practice to date.

Further exploration of the neurochemical pathways and associated biomarkers, in conjunction with comprehensive pharmaceutical reviews such as the present one, might consequently improve and optimize the clinical practice of pharmacotherapy. Many medications under development utilize well-established mechanisms of action. While innovative combinations, formulations, and applications could add significant value, there is also a pressing need for novel medications that achieve breakthroughs on our intolerably long list of refractory psychiatric conditions.

TABLE 12. Summary descriptions of medications in the pipeline for neurocognitive disorders

MEDICATION	MECHANISM OF ACTION	INDICATIONS BEING TESTED IN PHASE III	ROUTE AND DOSE	NOTES TO CLINICIANS (INCLUDING EFFECTS ON SEDATION, VITAL SIGNS, FALL RISK, AND QTc)
ACP-204	Inverse agonist at 5-HT _{2A} receptors. ^{130,131}	Alzheimer's disease-associated psychosis. ^{130,131}	Oral, 30–60mg daily ^{130,131}	Unlike pimavanserin, ACP-204 does not cause QTc prolongation. ^{130,131}
AR1001	Phosphodiesterase 5 (PDE5) inhibitor ¹⁴¹	Mild cognitive impairment and early Alzheimer's disease ¹⁴¹	Oral, 30mg daily ¹⁴¹	No significant risk related to QTc prolongation and weight gain was reported. However, reports of fainting might increase fall risk. ¹⁴¹
Dextromethorphan-bupropion (Auvelity, AXS-05)	Dextromethorphan is an N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist. Bupropion is a norepinephrine-dopamine reuptake inhibitor that competitively inhibits CYP2D6, prolonging dextromethorphan half-life. ¹⁴³	Agitation in Alzheimer's disease; already approved in major depressive disorder ^{142,143}	Oral 45mg dextromethorphan + 105mg bupropion once daily, then increase to twice daily after 3 days ¹⁴²	Dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis were reported. ^{142,143}
Dapagliflozin (Farxiga)	Sodium-glucose co-transporter 2 (SGLT2) inhibitor, decreasing glucose reabsorption in blood ¹⁵²	Cognitive impairment; symptoms of dementia and Alzheimer's disease in patients with Type 2 diabetes ¹⁵²	Oral, 10mg daily ¹⁵²	United States Food and Drug Administration (FDA)-approved for treatment of Type 2 diabetes, heart failure, and symptoms of chronic kidney disease. Serious adverse effects (especially for those with Type 1 diabetes) include diabetic ketoacidosis, urinary tract infections, and genital yeast infections. ¹⁵²
Donanemab	Antibody that targets accumulated deposits of amyloid beta peptides (N3pG) ^{124,125}	Early stages of Alzheimer's disease ^{124,125}	Intravenous, 700–1,400mg every 4 weeks ^{124,125}	No major concerns regarding fall risk, QTc interval change, weight change, sedation, or vital signs were noted. However, patients should be aware of potential adverse effects related to amyloid imaging. Cases of possible cerebral edema (amyloid-related) were observed with donanemab administration. ^{124,125}
Gantenerumab (RO4909832)	Monoclonal antibody that targets amyloid plaques and degrades them through microglial recruitment and phagocytosis ¹²⁶	Alzheimer's disease ¹²⁶	Subcutaneous, 120–1,200mg at varying intervals (minimum of 1 week) ¹²⁶	Gantenerumab was granted breakthrough designation by the FDA in 2021. No significant concerns regarding weight loss, sedation, or fall risk were reported. ¹²⁶
GV1001	Gonadotropin releasing hormone receptor (GnRHR) activator ^{147,148}	Alzheimer's disease ¹⁴⁷	Subcutaneous, 0.56–1.12mg weekly or every 2 weeks ¹⁴⁸	No significant adverse effects related to QTc intervals, weight change, or fall risk were reported. ^{147,148}
Latrepirdine (DMB-I, Dimebon)	H1 histamine receptor antagonist, NMDA receptor antagonist ¹³⁸	Alzheimer's disease ¹³⁸	Oral, 10–60mg daily ¹³⁸	No significant risk of QTc prolongation, sedation, or falls were reported. ¹³⁸
Levetiracetam low dose (AGB101, Keppra)	Synaptic vesicle glycoprotein 2A (SV2A) inhibitor ^{139,140}	Mild cognitive impairment due to Alzheimer's disease ^{139,140}	Oral, 220mg daily ^{139,140}	Levetiracetam is FDA-approved to treat partial seizures and epilepsy. In a Phase IIb trial, AGB101 did not statistically slow Alzheimer's disease progression. Yet, its inhibitory effects on SV2A proteins hold promise, hypothesized to influence amyloid plaque formation. Phase II trials showed no significant risk of QTc interval change or weight gain, but falls were a common adverse effect. ^{139,140}
Masitinib (Masivet)	Tyrosine kinase inhibitor ¹⁵⁷	Alzheimer's disease ¹⁵⁷	Oral, 3–4.5mg/kg daily ¹⁵⁷	No significant risk in QTc interval changes and vitals were reported. However, distinct adverse effects reported were neutropenia, hypoalbuminemia, and rash. ¹⁵⁷
Masupirdine	5-HT ₆ receptor selective antagonist ¹³⁵	Alzheimer's disease ¹³⁵	Oral, 50–100mg daily ¹³⁵	Commonly reported adverse effects to note include agitation, falls, and cases of atrial fibrillation. ¹³⁵
Metformin extended release (metformin XR)	Acts on cognitive functioning using the gut-brain axis and regulates insulin levels by activating AMP protein kinase to avoid hyperinsulinemia, linked to neuroinflammation and amyloid beta plaque accumulation ¹⁵⁰	Neurocognitive decline and dementia ¹⁵⁰	Oral, 500–2,000mg daily ¹⁵⁰	Previous studies have observed that metformin combats QTc prolongation and is able to reduce dispersion in low-to-medium doses. ¹⁵⁰ Some studies have observed insignificance or even risk of cognitive deterioration in patients with Type 2 diabetes. ¹⁵¹
Nabilone	Partial agonist at CB-1 and CB-2 cannabinoid receptors ^{144,145}	Dementia ¹⁴⁴	Oral, 0.5–1.5mg daily ^{144,145}	Sedative effects after administration in some participants were observed. Furthermore, common reports of drowsiness might cause further fall risk. ¹⁴⁴

TABLE 12, CONT. Summary descriptions of medications in the pipeline for neurocognitive disorders

MEDICATION	MECHANISM OF ACTION	INDICATIONS BEING TESTED IN PHASE III	ROUTE AND DOSE	NOTES TO CLINICIANS (INCLUDING EFFECTS ON SEDATION, VITAL SIGNS, FALL RISK, AND QTc)
Nilotinib (Tasigna)	c-Abl tyrosine kinase receptor inhibitor ¹⁵³	Alzheimer's disease ¹⁵³	Oral, 84–112mg daily ¹⁵³	There were no reports of QTc prolongation, weight change, or fall risk. Common adverse effects included mood swings, pain, and gastrointestinal discomfort. ^{153,154}
Pimavanserin (Nuplazid)	5-HT2A and 5-HT2C inverse agonist ^{132,133}	Relapse prevention in dementia-related psychotic symptoms, residual psychotic symptoms in schizophrenia, and major depressive disorder ¹³²	Oral, 20mg daily ¹³²	Pimavanserin might prolong QTc intervals by 5–8ms. ⁷¹ No significant concerns regarding weight gain, sedation, or fall risk were reported. It is currently approved for Parkinson's disease psychosis only. ^{132,133}
Remternetug	Antibody recognition of the pyroglutamated amyloid beta aggregated in amyloid plaques ¹⁶⁶	Alzheimer's disease	Subcutaneous, 700–2,800mg every 4 weeks	Higher than average amyloid-related imaging abnormalities were reported in early trials. No other significant adverse events were reported. ¹⁶⁶
Sabirnetug (ACU193)	Monoclonal antibody developed to be selective for soluble amyloid beta oligomers, which accumulate in Alzheimer's disease and cause neurodegeneration ^{122,123}	Alzheimer's disease ^{122,123}	Intravenous infusion, 35mg/kg for the first 2 doses, followed by 50 mg/kg every 4 weeks ^{122,123}	Phase I INTERCEPT-AD trial (NCT04931459) showed sabirnetug to be well tolerated with a favorable overall safety profile. Study results included statistically significant, dose-related amyloid plaque reduction similar to approved and in-review amyloid-directed therapies at similar time points, low overall levels of amyloid-related imaging artifacts (ARIA-E), and pharmacokinetic data confirming proof-of-mechanism. ^{122,123}
Simufilam (PTI-125)	Filamin alpha-7 nicotinic acetylcholine receptor antagonist ¹²⁷	Alzheimer's disease (with and without dementia) ¹²⁷	Oral, 100mg twice daily ^{127,128}	While the drug is entering Phase III trials, there have been significant setbacks due to integrity of results, which is under investigation. No serious adverse health effects have been reported. ¹²⁷
Suvorexant (Belsomra)	Antagonist at orexin-1 and orexin-2 receptors. ^{136,137}	Dementia ¹³⁷	Oral, 10mg nightly ¹³⁷	Received United States Food and Drug Administration (FDA) approval in 2014 for the treatment of insomnia. Somnolence is a commonly reported adverse effect. ^{136,137}
Tricaprilin (CER-0001)	Medium-chain triglyceride metabolized to act as ketogenic energy source for neural and physiological processes ¹⁴⁶	Mild-to-moderate Alzheimer's disease ¹⁴⁶	Oral, 20g twice daily. ¹⁴⁶	Commonly reported adverse effects included gastrointestinal discomfort and nausea. ¹⁴⁶
Valiltramiprosate (ALZ-801)	Amyloid beta-42 aggregation inhibition through 3-SPA metabolism ¹²⁹	Alzheimer's disease ¹²⁹	Oral, 265mg twice daily ¹²⁹	Early trials showed adverse effects, such as nausea, dizziness (fall risk), and vomiting. ¹²⁹
Xanomeline (Lumeron)	Muscarinic receptor agonist, selectively M1 and M4 receptors ¹⁵⁵	Alzheimer's disease and related cognitive deterioration ¹⁵⁵	Oral, 75–225mg daily ¹⁵⁵	Use of xanomeline was linked to weight gain in a limited number of individuals during clinical studies. Limited cases of increased QTc interval were reported after low dosage administration. ^{155,156}

However, without rigorous clinical trials, it is challenging to determine the efficacy of medications, their associated risks, and the most suitable treatments for each individual, which is crucial for achieving personalized medicine.

Strengths and limitations. This review's strengths include a broad search strategy and the inclusion of multiple medication classes, which were systematically organized by psychiatric disorder. It identified medications for a wide range of psychiatric indications. This review also provides concise information for each medication, resulting in a practical resource. In addition, by highlighting

mechanisms of action and dosing, this review reflects new trends and developments within the field.

Regarding limitations, this systematic review is limited by the available information and data made public by the agents behind these therapies. It is acknowledged that new medications are continuously being developed, and this review might not have captured all the upcoming developments.

CONCLUSION

We are entering a new era of psychiatry, which is reflected in the new and innovative treatments included in this review. To continue

to advance the field and make a significant impact on the current worldwide burden of mental health conditions, it is critical to continue efforts in promoting innovation, development, and acceptance of new treatments. In this time of need, without efforts promoting research of new medications, there might be a significant delay in the development of new treatments and their impact on the general population.

REFERENCES

1. United States Food and Drug Administration. FDA drug approval process infographic (vertical). Current as of 26 Feb 2016. Accessed

TABLE 13. Summary descriptions of medications in the pipeline for neurodevelopmental disorders

MEDICATION	MECHANISM OF ACTION	INDICATIONS BEING TESTED IN PHASE III	ROUTE AND DOSE	NOTES TO CLINICIANS (INCLUDING EFFECTS ON SEDATION, DEPENDENCE RISK, LIVER EFFECTS, AND OTHERS)
Centanafadine	Serotonin-norepinephrine-dopamine reuptake inhibitor ¹⁵⁹	Attention deficit hyperactivity disorder (ADHD) ¹⁵⁹	Oral 200–400mg daily ¹⁵⁹	Centanafadine was well tolerated in multiple studies, posing no significant risk of dependence development or adverse effects on liver function or sedation. ¹⁵⁹
NRCT-101SR	Acts on glutamatergic synapses ¹⁶⁰	ADHD ¹⁶⁰	Oral, 1,500–2,000mg daily ¹⁶⁰	NRCT-101SR was well tolerated, with no significant adverse effects reported. ¹⁶⁰
Solriamfetol (Sunosi)	Dopamine and norepinephrine reuptake inhibitor and trace amine-associated receptor 1 (TAAR1) agonist ¹⁶¹	ADHD ¹⁶¹	Oral, 150mg or 300mg daily ¹⁶¹	Solriamfetol is a schedule IV drug that is already approved for excessive daytime sleepiness due to obstructive sleep apnea or narcolepsy. Side effects include headache, nausea, and decreased appetite. ¹⁶¹

1 May 2024. <https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fda-drug-approval-process-infographic-vertical>

- Pahwa M, Sleem A, Elsayed OH, et al. New antipsychotic medications in the last decade. *Curr Psychiatry Rep.* 2021;23(12):87.
- Tsapakis EM, Diakaki K, Miliaras A, Fountoulakis KN. Novel compounds in the treatment of schizophrenia—a selective review. *Brain Sci.* 2023;13(8):1193.
- Greenwood LM, Leung S, Michie PT, et al. The effects of glycine on auditory mismatch negativity in schizophrenia. *Schizophr Res.* 2018;191:61–69.
- Kantrowitz JT, Epstein ML, Lee M, et al. Improvement in mismatch negativity generation during d-serine treatment in schizophrenia: correlation with symptoms. *Schizophr Res.* 2018;191:70–79.
- Rosenbrock H, Desch M, Wunderlich G. Development of the novel GlyT1 inhibitor, iclepertin (BI 425809), for the treatment of cognitive impairment associated with schizophrenia. *Eur Arch Psychiatry Clin Neurosci.* 2023;273(7):1557–1566.
- Kaul I, Sawchak S, Correll CU, et al. Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose Phase 3 trial. *Lancet.* 2024;403(10422):160–170.
- Brannan SK, Sawchak S, Miller AC, et al. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. *N Engl J Med.* 2021;384(8):717–726.
- Højlund M, Correll CU. Ulotaront: a TAAR1/5-HT1A agonist in clinical development for the treatment of schizophrenia. *Expert Opin Investig Drugs.* 2022;31(12):1279–1290.
- Kuvarzin SR, Sukhanov I, Onokhin K, et al. Unlocking the therapeutic potential of ulotaront as a trace amine-associated receptor 1 agonist for neuropsychiatric disorders. *Biomedicines.* 2023;11(7):1977.
- Correll CU, Koblansky KS, Hopkins SC, et al. Safety and effectiveness of ulotaront (SEP-363856) in schizophrenia: results of a 6-month, open-label extension study. *NPJ Schizophr.* 2021;7(1):63.
- Howes OD, Dawkins E, Lobo MC, et al. New drug treatments for schizophrenia: a review of approaches to target circuit dysfunction. *Biol Psychiatry.* 2024;S0006-3223(24)01349-0. Epub ahead of print.
- Achtyes ED, Hopkins SC, Dedic N, et al. Ulotaront: review of preliminary evidence for the efficacy and safety of a TAAR1 agonist in schizophrenia. *Eur Arch Psychiatry Clin Neurosci.* 2023;273(7):1543–1556.
- Corponi F, Fabbri C, Bitter I, et al. Novel antipsychotics specificity profile: a clinically oriented review of lurasidone, brexpiprazole, cariprazine and lumateperone. *Eur Neuropsychopharmacol.* 2019;29(9):971–985.
- ClinicalTrials.gov. Safety and tolerability trial of lumateperone in pediatric patients with schizophrenia or bipolar disorder. ClinicalTrials.gov Identifier: NCT06229210. Updated 30 Jan 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT06229210>
- Longo G, Cicolini A, Orsolini L, Volpe U. The novel antipsychotic lumateperone (ITI-007) in the treatment of schizophrenia: a systematic review. *Brain Sci.* 2023;13(12):1641.
- Kunz L. Phase 3 SOLARIS trial demonstrates potential of TEV-749 in schizophrenia. *Psychiatric Times.* 9 May 2024. Accessed 6 Aug 2024. <https://www.psychiatrictimes.com/view/phase-3-solaris-trial-demonstrates-potential-of-tev-749-in-schizophrenia>
- Brand BA, de Boer JN, Marcelis MC, et al. The direct and long-term effects of raloxifene as adjunctive treatment for schizophrenia-spectrum disorders: a double-blind, randomized clinical trial. *Schizophr Bull.* 2023;49(6):1579–1590.
- Brand BA, de Boer JN, Oude Ophuis SBJ, et al. Raloxifene augmentation in men and women with a schizophrenia spectrum disorder: a study protocol. *Contemp Clin Trials Commun.* 2020;20:100681.
- Rabinowitz J, Staner C, Saoud J, et al. Long-term effects of roluperidone on negative symptoms of schizophrenia. *Schizophr Res.* 2023;255:9–13.
- Harvey PD, Saoud JB, Luthringer R, et al. Effects of Roluperidone (MIN-101) on two dimensions of the negative symptoms factor score: reduced emotional experience and reduced emotional expression. *Schizophr Res.* 2020;215:352–356.
- Moazen-Zadeh E, Bayanati S, Ziafat K, et al. Vortioxetine as adjunctive therapy to risperidone for treatment of patients with chronic schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. *J Psychopharmacol.* 2020;34(5):506–513.
- Chen G, Højer AM, Areberg J, Nomikos G. Vortioxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet.* 2018;57(6):673–686.
- ClinicalTrials.gov. Adjunctive vortioxetine in schizophrenia (AVIS). ClinicalTrials.gov Identifier: NCT02357797. Updated 8 Feb 2024. Accessed 2 Jun 2024. <https://www.clinicaltrials.gov/study/NCT02357797>
- ClinicalTrials.gov. Cognitive effects of adjuvant vortioxetine in early schizophrenia (CAVES). ClinicalTrials.gov Identifier: NCT04895488. Updated 26 Feb 2024. Accessed 2 Jun 2024. <https://www.clinicaltrials.gov/study/NCT04895488>
- Takeda Pharmaceuticals America, Inc. Trintellix (vortioxetine) tablets, for oral

- use: US prescribing information. Accessed 25 Mar 2024. <https://content.takeda.com/?contenttype=PI&product=TRI&language=ENG&country=GBL&documentnumber=1>
27. Chen G, Lee R, Højer AM, et al. Pharmacokinetic drug interactions involving vortioxetine (Lu AA21004), a multimodal antidepressant. *Clin Drug Investig.* 2013;33(10):727–736.
 28. Loebel A, Koblan KS, Tsai J, et al. A randomized, double-blind, placebo-controlled proof-of-concept trial to evaluate the efficacy and safety of non-racemic amisulpride (SEP-4199) for the treatment of bipolar I depression. *J Affect Disord.* 2022;296:549–558.
 29. Calabrese JR, Ketter TA, Youakim JM, et al. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. *J Clin Psychiatry.* 2010;71(10):1363–1370.
 30. Ketter TA, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder. *J Affect Disord.* 2015;181:87–91.
 31. Siwek M, Wojtasik-Bakalarz K, Krupa AJ, Chrobak AA. Brexpiprazole-pharmacologic properties and use in schizophrenia and mood disorders. *Brain Sci.* 2023;13(3):397.
 32. Nierenberg A, Lavin P, Javitt DC, et al. NRX-101 (D-cycloserine plus lurasidone) vs. lurasidone for the maintenance of initial stabilization after ketamine in patients with severe bipolar depression with acute suicidal ideation and behavior: a randomized prospective Phase 2 trial. *Int J Bipolar Disord.* 2023;11(1):28.
 33. ClinicalTrials.gov. Multicenter study of lumateperone for the treatment of bipolar depression in pediatric patients. ClinicalTrials.gov Identifier: NCT06372964. Updated 29 Jul 2024. Accessed 2 Jun 2024. <https://clinicaltrials.gov/study/NCT06372964>
 34. Sepanjnia K, Modabbernia A, Ashrafi M, et al. Pioglitazone adjunctive therapy for moderate-to-severe major depressive disorder: randomized double-blind placebo-controlled trial. *Neuropsychopharmacology.* 2012;37(9):2093–2100.
 35. Panikar V, Kale NJ, Hoskote SS, et al. Effect of low (7.5 mg/day), standard (15 mg/day) and high (30 mg/day) dose pioglitazone therapy on glycemic control and weight gain in recently-diagnosed Type 2 diabetes patients. *J Assoc Physicians India.* 2015;63(11):36–39.
 36. Lett BT, Grant VL, Koh MT, Parsons JF. Chlordiazepoxide attenuates activity-induced anorexia and weight loss in rats. *Exp Clin Psychopharmacol.* 1998;6(4):360–366.
 37. Colle R, de Larminat D, Rotenberg S, et al. Pioglitazone could induce remission in major depression: a meta-analysis. *Neuropsychiatr Dis Treat.* 2016;13:9–16.
 38. Rajagopal L, Huang M, He W, et al. Repeated administration of rapastinel produces exceptionally prolonged rescue of memory deficits in phencyclidine-treated mice. *Behav Brain Res.* 2022;432:113964.
 39. Moskal JR, Burgdorf JS, Stanton PK, et al. The development of rapastinel (Formerly GLYX-13); a rapid acting and long lasting antidepressant. *Curr Neuropharmacol.* 2017;15(1):47–56.
 40. ClinicalTrials.gov. Study of rapastinel as monotherapy in patients with major depressive disorder (MDD). ClinicalTrials.gov Identifier: NCT03675776. Updated 28 Jul 2020. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT03675776>
 41. ClinicalTrials.gov. Study of adjunctive or monotherapy rapastinel treatment in patients with major depressive disorder (MDD). ClinicalTrials.gov Identifier: NCT03668600. Updated 17 Jul 2020. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT03668600>
 42. Savitz A, Wajs E, Zhang Y, et al. Efficacy and safety of seltorexant as adjunctive therapy in major depressive disorder: a Phase 2b, randomized, placebo-controlled, adaptive dose-finding study. *Int J Neuropsychopharmacol.* 2021;24(12):965–976.
 43. Recourt K, de Boer P, Zuiker R, et al. The selective orexin-2 antagonist seltorexant (JNJ-42847922/MIN-202) shows antidepressant and sleep-promoting effects in patients with major depressive disorder. *Transl Psychiatry.* 2019;9(1):216.
 44. Vasiliiu O. Efficacy, tolerability, and safety of toludenesvenlafaxine for the treatment of major depressive disorder—a narrative review. *Pharmaceuticals (Basel).* 2023;16(3):411.
 45. Li C, Jiang W, Gao Y, et al. Acute, subchronic oral toxicity, and genotoxicity evaluations of LPM570065, a new potent triple reuptake inhibitor. *Regul Toxicol Pharmacol.* 2018;98:129–139.
 46. Goodwin GM, Croal M, Feifel D, et al. Psilocybin for treatment resistant depression in patients taking a concomitant SSRI medication. *Neuropsychopharmacology.* 2023;48(10):1492–1499.
 47. ClinicalTrials.gov. Psilocybin-assisted therapy in treatment-resistant depression. ClinicalTrials.gov Identifier: NCT06303739. Updated 23 Jul 2024. Accessed 3 Jun 2024. <https://classic.clinicaltrials.gov/ct2/show/record/NCT06303739>
 48. Huang J, Pham M, Panenka WJ, et al. Chronic treatment with psilocybin decreases changes in body weight in a rodent model of obesity. *Front Psychiatry.* 2022;13:891512.
 49. Ekstrand J, Fattah C, Persson M, et al. Racemic ketamine as an alternative to electroconvulsive therapy for unipolar depression: a randomized, open-label, non-inferiority trial (KetECT). *Int J Neuropsychopharmacol.* 2022;25(5):339–349.
 50. Loo C, Glozier N, Barton D, et al. Efficacy and safety of a 4-week course of repeated subcutaneous ketamine injections for treatment-resistant depression (KADS study): randomised double-blind active-controlled trial. *Br J Psychiatry.* 2023;223(6):533–541.
 51. Tundo A, de Filippis R, De Crescenzo F. Pramipexole in the treatment of unipolar and bipolar depression. A systematic review and meta-analysis. *Acta Psychiatr Scand.* 2019;140(2):116–125.
 52. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry.* 2004;161(3):564–566.
 53. Hori H, Kunugi H. The efficacy of pramipexole, a dopamine receptor agonist, as an adjunctive treatment in treatment-resistant depression: an open-label trial. *ScientificWorldJournal.* 2012;2012:372474.
 54. Martens MAG, Kaltenboeck A, Halahakoon DC, et al. An experimental medicine investigation of the effects of subacute pramipexole treatment on emotional information processing in healthy volunteers. *Pharmaceuticals (Basel).* 2021;14(8):800.
 55. Hampsey E, Jelen L, Young AH. Aticaprant: (a κ -opioid receptor antagonist) for major depressive disorder. *Expert Opin Emerg Drugs.* 2024;1–12. Epub ahead of print.
 56. ClinicalTrials.gov. A study of aticaprant as adjunctive therapy in adult participants with major depressive disorder (MDD) with moderate-to-severe anhedonia and

- inadequate response to current antidepressant therapy (VENTURA-1). ClinicalTrials.gov Identifier: NCT05455684. Updated 17 Jul 2024. Accessed 2 Jun 2024. <https://clinicaltrials.gov/study/NCT05455684>
57. ClinicalTrials.gov. Study to assess the effects of oral NMRA-335140 in participants with major depressive disorder. ClinicalTrials.gov Identifier: NCT06058039. Updated 18 Jul 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT06058039>
 58. Namchuk AB, Lucki I, Browne CA. Buprenorphine as a treatment for major depression and opioid use disorder. *Adv Drug Alcohol Res.* 2022;2:10254.
 59. Peckham AM, De La Cruz A, Dufresne RL. Kappa opioid receptor antagonism: are opioids the answer for treatment resistant depression? *Ment Health Clin.* 2018;8(4):175–183.
 60. ClinicalTrials.gov. Effectiveness of cariprazine monotherapy for treatment of major depressive disorder. ClinicalTrials.gov Identifier: NCT05933538. Updated 7 Jul 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/ct2/show/NCT05933538>
 61. Thorpy MJ, Shapiro C, Mayer G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. *Ann Neurol.* 2019;85(3):359–370. Erratum in: *Ann Neurol.* 2020;87(1):157.
 62. ClinicalTrials.gov. Progressing TAAR-1, dopamine, and norepinephrine in depression using solriamfetol (PARADIGM). ClinicalTrials.gov Identifier: NCT06360419. Updated 11 Apr 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT06360419>
 63. Bugarski-Kirola D, Arango C, Fava M, et al. Pimavanserin for negative symptoms of schizophrenia: results from the ADVANCE Phase 2 randomised, placebo-controlled trial in North America and Europe. *Lancet Psychiatry.* 2022;9(1):46–58.
 64. ClinicalTrials.gov. Adjunctive pimavanserin in subjects with major depressive disorder and inadequate response to antidepressant treatment. ClinicalTrials.gov Identifier: NCT03968159. Updated 17 Nov 2021. Accessed 3 Jun 2024. <https://www.clinicaltrials.gov/study/NCT03968159>
 65. ClinicalTrials.gov. Efficacy and safety of pimavanserin as adjunctive treatment for the negative symptoms of schizophrenia (ADVANCE-2). ClinicalTrials.gov Identifier: NCT04531982. Updated 16 Aug 2023. Accessed 3 Jun 2024. <https://www.clinicaltrials.gov/study/NCT04531982>
 66. Nasrallah HA, Fedora R, Morton R. Successful treatment of clozapine-nonresponsive refractory hallucinations and delusions with pimavanserin, a serotonin 5HT-2A receptor inverse agonist. *Schizophr Res.* 2019;208:217–220.
 67. Torres-Yaghi Y, Carwin A, Carolan J, et al. QTc interval prolongation with therapies used to treat patients with Parkinson's disease psychosis: a narrative review. *Neuropsychiatr Dis Treat.* 2021;17:3791–3818.
 68. Tarzian M, Ndrio M, Chique B, et al. Illuminating hope for mental health: a drug review on lumateperone. *Cureus.* 2023;15(9):e46143.
 69. ClinicalTrials.gov. The efficacy and safety of mitozodone phosphate tablets in the treatment of patient with major depressive disorder. ClinicalTrials.gov Identifier: NCT04984512. Accessed 3 Jun 2024. <https://www.clinicaltrials.gov/study/NCT04984512>
 70. Fava M, Stahl SM, De Martin S, et al. Esmethadone-HCl (REL-1017): a promising rapid antidepressant. *Eur Arch Psychiatry Clin Neurosci.* 2023;273(7):1463–1476.
 71. Carr MM, Lou R, Macdonald-Gagnon G, et al. Weight change among patients engaged in medication treatment for opioid use disorder: a scoping review. *Am J Drug Alcohol Abuse.* 2023;49(5):551–565.
 72. Gordon JL, Rubinow DR, Eisenlohr-Moul TA, et al. Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: a randomized clinical trial. *JAMA Psychiatry.* 2018;75(2):149–157.
 73. Mayo Clinic. Estradiol (vaginal route). Updated 1 Jul 2024. Accessed 3 Jun 2024. <https://www.mayoclinic.org/drugs-supplements/estradiol-vaginal-route/side-effects/drg-20075648?p=1>
 74. Costi S, Morris LS, Kirkwood KA, et al. Impact of the KCNQ2/3 channel opener ezogabine on reward circuit activity and clinical symptoms in depression: results from a randomized controlled trial. *Am J Psychiatry.* 2021;178(5):437–446.
 75. Clayton AH, Lasser R, Nandy I, et al. Zuranolone in major depressive disorder: results from MOUNTAIN-a Phase 3, multicenter, double-blind, randomized, placebo-controlled trial. *J Clin Psychiatry.* 2023;84(2):22m14445.
 76. Halaris A. Inflammation and depression but where does the inflammation come from? *Curr Opin Psychiatry.* 2019;32(5):422–428.
 77. Gędek A, Szular Z, Antosik AZ, et al. Celecoxib for mood disorders: a systematic review and meta-analysis of randomized controlled trials. *J Clin Med.* 2023;12(10):3497.
 78. Wu KJ, Wang YS, Hung TW, et al. Effect of celecoxib on improving depression: a systematic review and meta-analysis. *World J Clin Cases.* 2022;10(22):7872–7882.
 79. ClinicalTrials.gov. Treating immuno-metabolic depression with anti-inflammatory drugs (INFLAMED). ClinicalTrials.gov Identifier: NCT05415397. Updated 25 Sep 2023. Accessed 2 Jun 2024. <https://www.clinicaltrials.gov/study/NCT05415397>
 80. ClinicalTrials.gov. Inflammation-based stratification for immune-targeted augmentation in major depressive disorder (INSTA-MD). Updated 9 Dec 2022. ClinicalTrials.gov Identifier: NCT05644301. Accessed 2 Jun 2024. <https://www.clinicaltrials.gov/study/NCT05644301>
 81. ClinicalTrials.gov. The effect of celecoxib on neuroinflammation in MDD. ClinicalTrials.gov Identifier: NCT04814355. Updated 22 Nov 2023. Accessed 2 Jun 2024. <https://www.clinicaltrials.gov/study/NCT04814355>
 82. Avari JN, Kanellopoulos D, Solomonov N, et al. Minocycline augmentation in older adults with persistent depression: an open label proof of concept study. *Int Psychogeriatr.* 2020;32(7):881–884.
 83. Soczynska JK, Kennedy SH, Alsuwaidan M, et al. A pilot, open-label, 8-week study evaluating the efficacy, safety and tolerability of adjunctive minocycline for the treatment of bipolar I/II depression. *Bipolar Disord.* 2017;19(3):198–213.
 84. Stein DJ, Ahokas A, Márquez MS, et al. Agomelatine in generalized anxiety disorder: an active comparator and placebo-controlled study. *J Clin Psychiatry.* 2014;75(4):362–368.
 85. Koziar R, Syrbe G. QTc-Zeit-Verlängerung unter Therapie mit Agomelatin [QTc prolongation during treatment with agomelatine]. *Psychiatr Prax.* 2010;37(8):405–407. German.
 86. ClinicalTrials.gov. Safety and Efficacy evaluation of pregabalin (Lyrica) with patients with generalized anxiety disorder. ClinicalTrials.gov Identifier: NCT00624780. Updated 28 Jan 2021. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT00624780>

87. Hamed SA. Sexual dysfunctions induced by pregabalin. *Clin Neuropharmacol*. 2018;41(4):116–122.
88. Maneeton N, Maneeton B, Woottitluk P, et al. Quetiapine monotherapy in acute treatment of generalized anxiety disorder: a systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther*. 2016;10:259–276.
89. Katzman MA, Brawman-Mintzer O, Reyes EB, et al. Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disorder: a long-term, randomized, placebo-controlled trial. *Int Clin Psychopharmacol*. 2011;26(1):11–24.
90. Liebowitz MR, Salman E, Nicolini H, et al. Effect of an acute intranasal aerosol dose of PH94B on social and performance anxiety in women with social anxiety disorder. *Am J Psychiatry*. 2014;171(6):675–682.
91. ClinicalTrials.gov. Fasedienol nasal spray for the acute treatment of anxiety in adults with social anxiety disorder (PALISADE-3) (PALISADE-3). ClinicalTrials.gov Identifier: NCT06358651. Updated 24 Jul 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT06358651>
92. Saletu-Zyharz GM, Anderer P, Wolzt M, et al. Double-blind, placebo-controlled, multiple-ascending-dose study on the pharmacodynamics of ABIO-08/01, a new CNS drug with potential anxiolytic activity. 1. EEG mapping, psychometric and tolerability findings. *Neuropsychobiology*. 2009;59(2):100–109.
93. Yang F, Wang B, Liu Z, et al. Prediction of a therapeutic dose for buagafuran, a potent anxiolytic agent by physiologically based pharmacokinetic/pharmacodynamic modeling starting from pharmacokinetics in rats and human. *Front Pharmacol*. 2017;8:683.
94. Stemmelin J, Cohen C, Terranova JP, et al. Stimulation of the beta3-adrenoceptor as a novel treatment strategy for anxiety and depressive disorders. *Neuropsychopharmacology*. 2008;33(3):574–587.
95. ClinicalTrials.gov. A clinical study that will measure how well SEP-363856 works and how safe it is in adults with generalized anxiety disorder. ClinicalTrials.gov Identifier: NCT05729373. Updated 26 Jun 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT05729373>
96. ClinicalTrials.gov. Relapse-prevention study with Lu AA21004 (vortioxetine) in patients with generalized anxiety disorder. ClinicalTrials.gov Identifier: NCT00788034. Updated 23 Jun 2015. Accessed 3 Jun 2024. <https://classic.clinicaltrials.gov/ct2/show/NCT00788034>
97. Parmenter ME, Lederman S, Weathers FW, et al. A Phase 3, randomized, placebo-controlled, trial to evaluate the efficacy and safety of bedtime sublingual cyclobenzaprine (TNX-102 SL) in military-related posttraumatic stress disorder. *Psychiatry Res*. 2024;334:115764.
98. Togno J, Eaton S. Is there a role for prazosin in the treatment of post-traumatic stress disorder? *Aust Fam Physician*. 2015;44(9):647–649.
99. Paiva HS, Filho IJZ, Cais CFDS. Using prazosin to treat posttraumatic stress disorder and associations: a systematic review. *Psychiatry Investig*. 2021;18(5):365–372.
100. Nugent NR, Christopher NC, Crow JP, et al. The efficacy of early propranolol administration at reducing PTSD symptoms in pediatric injury patients: a pilot study. *J Trauma Stress*. 2010;23(2):282–287.
101. Strawn JR, Keeshin BR, DeBello MP, et al. Psychopharmacologic treatment of posttraumatic stress disorder in children and adolescents: a review. *J Clin Psychiatry*. 2010;71(7):932–941.
102. Shiner B, Huybrechts K, Gui J, et al. Comparative effectiveness of direct-acting antivirals for posttraumatic stress disorder in Veterans Affairs patients with hepatitis C virus infection. *Am J Epidemiol*. 2022;191(9):1614–1625.
103. AbbVie. Common side effects of Mavyret. Accessed 6 Aug 2024. <https://www.mavyret.com/side-effects>
104. Tedesco S, Gajaram G, Chida S, et al. The efficacy of MDMA (3,4-methylenedioxymethamphetamine) for post-traumatic stress disorder in humans: a systematic review and meta-analysis. *Cureus*. 2021;13(5):e15070.
105. Kalant H. The pharmacology and toxicology of “ecstasy” (MDMA) and related drugs. *CMAJ*. 2001;165(7):917–928.
106. Pittenger C. Glutamatergic agents for OCD and related disorders. *Curr Treat Options Psychiatry*. 2015;2(3):271–283.
107. ClinicalTrials.gov. Efficacy and safety study of adjunctive trilorizole in obsessive compulsive disorder. ClinicalTrials.gov Identifier: NCT04641143. Updated 19 Apr 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT04641143>
108. Grilo CM, Lydecker JA, Jastreboff AM, et al. Naltrexone/bupropion for binge-eating disorder: a randomized, double-blind, placebo-controlled trial. *Obesity (Silver Spring)*. 2023;31(11):2762–2773.
109. Krystal AD, Benca RM, Rosenberg R, et al. Solriamfetol treatment of excessive daytime sleepiness in participants with narcolepsy or obstructive sleep apnea with a history of depression. *J Psychiatr Res*. 2022;155:202–210.
110. ClinicalTrials.gov. Elucidating TAAR-1, dopamine, and norepinephrine in binge eating disorder using solriamfetol (ENGAGE). ClinicalTrials.gov Identifier: NCT06413433. Updated 14 May 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT06413433>
111. Roth T, Thorpy MJ, Kushida CA, et al. Once-nightly sodium oxybate (FT218) improved symptoms of disrupted nighttime sleep in people with narcolepsy: a plain language summary. *J Comp Eff Res*. 2023;12(12):e230133.
112. Avadel CNS Pharmaceuticals, LLC. MED-US-LUM-2100001 Risk Evaluation and Mitigation Strategy (REMS) Document LUMRYZ TM (sodium oxybate extended-release) REMS Program. 2023. Accessed 3 Jun 2024. https://www.accessdata.fda.gov/drugsatfda_docs/REMS/2147550orig1s000REMS.pdf
113. Parkes JD, Schachter M. Mazindol in the treatment of narcolepsy. *Acta Neurol Scand*. 1979;60(4):250–254.
114. Roehrborn CG, Manyak MJ, Palacios-Moreno JM, et al. A prospective randomised placebo-controlled study of the impact of dutasteride/tamsulosin combination therapy on sexual function domains in sexually active men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). *BJU Int*. 2018;121(4):647–658.
115. ClinicalTrials.gov. Prospective sexual function study for BPH subjects. ClinicalTrials.gov Identifier: NCT01777269. Updated 20 Aug 2018. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT01777269>
116. Giuliano F, Jousain C, Denys P. Long-term effectiveness and safety of intracavernosal botulinum toxin A as an add-on therapy

- to phosphodiesterase type 5 inhibitors or prostaglandin E1 injections for erectile dysfunction. *J Sex Med.* 2022;19(1):83–89.
117. Abdelrahman IFS, Raheem AA, Elkhayat Y, et al. Safety and efficacy of botulinum neurotoxin in the treatment of erectile dysfunction refractory to phosphodiesterase inhibitors: results of a randomized controlled trial. *Andrology.* 2022;10(2):254–261.
 118. Hosny KM, El-Say KM, Ahmed OA. Optimized sildenafil citrate fast orodispersible film: a promising formula for overcoming the barriers hindering erectile dysfunction treatment. *Drug Deliv.* 2016;23(1):355–361.
 119. Loprete L, Leuratti C, Frangione V, Radicioni M. Pharmacokinetics of a novel sildenafil orodispersible film administered by the supralingual and the sublingual route to healthy men. *Clin Drug Investig.* 2018;38(8):765–772.
 120. de Beaupre R, Sinclair JMA, Heydtmann M, et al. The use of baclofen as a treatment for alcohol use disorder: a clinical practice perspective. *Front Psychiatry.* 2019;9:708.
 121. Zhang Y, Chen H, Li R, et al. Amyloid β -based therapy for Alzheimer's disease: challenges, successes and future. *Signal Transduct Target Ther.* 2023;8(1):248.
 122. Acumen Pharmaceuticals. Acumen Pharmaceuticals announces first patient Dosed in ALTITUDE-AD, a Phase 2 clinical trial of sabinetug (ACU193) in early Alzheimer's disease. 8 May 2024. Accessed 3 Jun 2024. <https://investors.acumenpharm.com/news-releases/news-release-details/acumen-pharmaceuticals-announces-first-patient-dosed-altitude-ad>
 123. ClinicalTrials.gov. A study to evaluate efficacy and safety of intravenous ACU193 in oarticipants with early Alzheimer's disease (ALTITUDE-AD) (ALTITUDE-AD). ClinicalTrials.gov Identifier: NCT06335173. Updated 6 Aug 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT06335173>
 124. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *N Engl J Med.* 2021;384(18):1691–1704.
 125. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA.* 2023;330(6):512–527.
 126. Klein G, Delmar P, Voyle N, et al. Gantenerumab reduces amyloid- β plaques in patients with prodromal to moderate Alzheimer's disease: a PET substudy interim analysis. *Alzheimers Res Ther.* 2019;11(1):101.
 127. Wang HY, Cecon E, Dam J, et al. Simufilam reverses aberrant receptor interactions of filamin A in Alzheimer's disease. *Int J Mol Sci.* 2023;24(18):13927.
 128. Wang HY, Pei Z, Lee KC, et al. PTI-125 reduces biomarkers of Alzheimer's disease in patients. *J Prev Alzheimers Dis.* 2020;7(4):256–264.
 129. Hey JA, Kocis P, Hort J, et al. Discovery and identification of an endogenous metabolite of tramiprosate and its prodrug ALZ-801 that inhibits beta amyloid oligomer formation in the human brain. *CNS Drugs.* 2018;32(9):849–861. Erratum in: *CNS Drugs.* 2018;32(12):1185.
 130. ClinicalTrials.gov. ACP-204 in adults with Alzheimer's disease psychosis. ClinicalTrials.gov Identifier: NCT06159673. Updated 1 Aug 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT06159673>
 131. ClinicalTrials.gov. ACP-204 in adults with Alzheimer's disease psychosis open label extension study. ClinicalTrials.gov Identifier: NCT06194799. Updated 2 Aug 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT06194799>
 132. Cummings J, Ballard C, Tariot P, et al. Pimavanserin: Potential treatment for dementia-related psychosis. *J Prev Alzheimers Dis.* 2018;5(4):253–258.
 133. Tariot PN, Cummings JL, Soto-Martin ME, et al. Trial of pimavanserin in dementia-related psychosis. *N Engl J Med.* 2021;385(4):309–319.
 134. ClinicalTrials.gov. Relapse prevention study of pimavanserin in dementia-related psychosis. ClinicalTrials.gov Identifier: NCT03325556. Updated 21 Jun 2021. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT03325556>
 135. Nirogi R, Ieni J, Goyal VK, et al. Effect of masupirdine (SUVN-502) on cognition in patients with moderate Alzheimer's disease: a randomized, double-blind, Phase 2, proof-of-concept study. *Alzheimers Dement (N Y).* 2022;8(1):e12307.
 136. Herring WJ, Ceesay P, Snyder E, et al. Polysomnographic assessment of suvorexant in patients with probable Alzheimer's disease dementia and insomnia: a randomized trial. *Alzheimers Dement.* 2020;16(3):541–551.
 137. Owen RT. Suvorexant: efficacy and safety profile of a dual orexin receptor antagonist in treating insomnia. *Drugs Today (Barc).* 2016;52(1):29–40.
 138. Bezprozvanny I. The rise and fall of Dimebon. *Drug News Perspect.* 2010;23(8):518–523.
 139. ClinicalTrials.gov. AGB101 for mild cognitive impairment. ClinicalTrials.gov Identifier: NCT05986721. Updated 20 Jun 2024. Accessed 20 Jun 2024. <https://clinicaltrials.gov/study/NCT05986721>
 140. Mohs R, Bakker A, Rosenzweig-Lipson S, et al. The HOPE4MCI study: a randomized double-blind assessment of AGB101 for the treatment of MCI due to AD. *Alzheimers Dement (N Y).* 2024;10(1):e12446.
 141. Kang BW, Kim F, Choi YP, et al. AR1001 ameliorates Alzheimer's disease pathology and symptoms by multi-mechanisms. *Alzheimers Dement.* 2020;16:e047266.
 142. Putka S. Alzheimer's agitation relapse delayed with dextromethorphan-bupropion. MedPage Today. Updated 18 Apr 2024. Accessed 7 Aug 2024. <https://www.medpagetoday.com/meetingcoverage/aan/109714>
 143. McCarthy B, Bunn H, Santalucia M, et al. Dextromethorphan-bupropion (Auvelity) for the treatment of major depressive disorder. *Clin Psychopharmacol Neurosci.* 2023;21(4):609–616.
 144. Bajtel Á, Kiss T, Tóth B, et al. The safety of dronabinol and nabilone: a systematic review and meta-analysis of clinical trials. *Pharmaceuticals (Basel).* 2022;15(1):100.
 145. Herrmann N, Ruthirakuhan M, Gallagher D, et al. Randomized placebo-controlled trial of nabilone for agitation in Alzheimer's disease. *Am J Geriatr Psychiatry.* 2019;27(11):1161–1173.
 146. Li Z, Ramirez G, Tang R, et al. Modeling digestion, absorption, and ketogenesis after administration of tricaprillin formulations to humans. *Eur J Pharm Biopharm.* 2023;182:41–52.
 147. Koh SH, Kwon HS, Choi SH, et al. Efficacy and safety of GV1001 in patients with moderate-to-severe Alzheimer's disease already receiving donepezil: a Phase 2 randomized, double-blind, placebo-controlled, multicenter clinical trial. *Alzheimers Res Ther.* 2021;13(1):66.
 148. Park H, Kwon HS, Lee KY, et al. GV1001 modulates neuroinflammation and improves memory and behavior through the activation of gonadotropin-releasing hormone receptors in a triple transgenic Alzheimer's disease mouse model. *Brain Behav Immun.* 2024;115:295–307.
 149. Dubois B, López-Arrieta J, Lipschitz S, et al.

- Masitinib for mild-to-moderate Alzheimer's disease: results from a randomized, placebo-controlled, Phase 3, clinical trial. *Alzheimers Res Ther.* 2023;15(1):39. Erratum in: *Alzheimers Res Ther.* 2023;15(1):85.
150. Campbell JM, Stephenson MD, de Courten B, et al. Metformin use associated with reduced risk of dementia in patients with diabetes: a systematic review and meta-analysis. *J Alzheimers Dis.* 2018;65(4):1225–1236.
 151. Rosell-Díaz M, Fernández-Real JM. Metformin, cognitive function, and changes in the gut microbiome. *Endocr Rev.* 2024;45(2):210–226.
 152. Samman WA, Selim SM, El Fayoumi HM, et al. Dapagliflozin ameliorates cognitive impairment in aluminum-chloride-induced Alzheimer's disease via modulation of AMPK/mTOR, oxidative stress and glucose metabolism. *Pharmaceuticals (Basel).* 2023;16(5):753.
 153. Turner RS, Hebron ML, Lawler A, et al. Nilotinib effects on safety, tolerability, and biomarkers in Alzheimer's disease. *Ann Neurol.* 2020;88(1):183–194.
 154. Nobili A, D'Amelio M, Viscomi MT. Nilotinib: from animal-based studies to clinical investigation in Alzheimer's disease patients. *Neural Regen Res.* 2023;18(4):803–804.
 155. Mirza NR, Peters D, Sparks RG. Xanomeline and the antipsychotic potential of muscarinic receptor subtype selective agonists. *CNS Drug Rev.* 2003;9(2):159–186.
 156. Brannan SK, Sawchak S, Miller AC, et al. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. *N Engl J Med.* 2021;384(8):717–726.
 157. Puranik N, Yadav D, Song M. Advancements in the application of nanomedicine in Alzheimer's disease: a therapeutic perspective. *Int J Mol Sci.* 2023;24(18):14044.
 158. Morató X, Pytel V, Jofresa S, et al. Symptomatic and disease-modifying therapy pipeline for Alzheimer's disease: towards a personalized polypharmacology patient-centered approach. *Int J Mol Sci.* 2022;23(16):9305.
 159. Adler LA, Adams J, Madera-McDonough J, et al. Efficacy, safety, and tolerability of centanafadine sustained-release tablets in adults with attention-deficit/hyperactivity disorder: results of 2 Phase 3, randomized, double-blind, multicenter, placebo-controlled trials. *J Clin Psychopharmacol.* 2022;42(5):429–439.
 160. ClinicalTrials.gov. Study to evaluate NRCT-101SR in pediatric subjects with ADHD (ADHD). ClinicalTrials.gov Identifier: NCT06215144. Updated 20 Mar 2024. Accessed 3 Jun 2024. <https://clinicaltrials.gov/study/NCT06215144>
 161. Surman CBH, Walsh DM, Horick N, et al. Solriamfetol for attention-deficit/hyperactivity disorder in adults: a double-blind placebo-controlled pilot study. *J Clin Psychiatry.* 2023;84(6):23m14934.
 162. Sperling RA, Donohue MC, Raman R, et al. Trial of solanezumab in preclinical Alzheimer's disease. *N Engl J Med.* 2023;389(12):1096–1107.
 163. Medscape. Acadia to stop trials of antipsychotic drug after it fails schizophrenia study. 11 Mar 2024. Accessed 3 Jun 2024. <https://www.medscape.com/s/viewarticle/acadia-stop-trials-antipsychotic-drug-after-it-fails-2024a10004m5>
 164. Lobo A. Otsuka stops developing AVP-786 therapy for Alzheimer's agitation. *Alzheimer's News Today.* 23 May 2024. Accessed 3 Jun 2024. <https://alzheimersnewstoday.com/news/otsuka-stops-development-avp-786-agitation-alzheimers/>
 165. Psychedelic Alpha. Psychedelic drug development tracker. Accessed 3 Jun 2024. <https://psychedelicalpha.com/data/psychedelic-drug-development-tracker>
 166. MindMed. MindMed receives FDA breakthrough therapy designation and announces positive 12-week durability data from Phase 2B study of MM120 for generalized anxiety disorder. 7 Mar 2024. Accessed 3 Jun 2024. <https://ir.mindmed.co/news-events/press-releases/detail/137/mindmed-receives-fda-breakthrough-therapy-designation-and-announces-positive-12-week-durability-data-from-phase-2b-study-of-mm120-for-generalized-anxiety-disorder>
 167. BioSpace. Nutriband provides clinical and regulatory path overview for lead product – AVERSA® Fentanyl transdermal patch. 27 Mar 2024. Accessed 3 Jun 2024. <https://www.biospace.com/article/releases/nutriband-provides-clinical-and-regulatory-path-overview-for-lead-product-aversa-r-fentanyl-transdermal-patch/>
 168. Kunz L. Phase 3 SOLARIS trial demonstrates potential of TEV-'749 in schizophrenia. *Psychiatric Times.* 9 May 2024. Accessed 7 Aug 2024. <https://www.psychiatrictimes.com/view/phase-3-solaris-trial-demonstrates-potential-of-tev-749-in-schizophrenia>
 169. Sarris J. Disruptive innovation in psychiatry. *Ann N Y Acad Sci.* 2022;1512(1):5–9.
 170. Markowitz JC. Supportive evidence: brief supportive psychotherapy as active control and clinical intervention. *Am J Psychother.* 2022;75(3):122–128.
 171. García-Gutiérrez MS, Navarrete F, Sala F, et al. Biomarkers in psychiatry: concept, definition, types and relevance to the clinical reality. *Front Psychiatry.* 2020;11:432. **ICNS**