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

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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

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), mitizodone, NMRA-335140, navacaprant (BTRX-335140, NMRA-140), pimavanserin (Nuplazid), pioglitazone + citalopram + chlordiazepoxide, pramipexole (Mirapex), psilocybin (COMP360), racemic ketamine (Wafermine), 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), ulotorant (SEP-363856), vortioxetine (Trintellix)
Post-traumatic stress disorder (PTSD)	5	Cyclobenzaprine (Flexeril, Amrix), glecaprevir/pibrentasvir (Mavyret), MDMA (3,4-methylenedioxymethamphetamine), 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), remternetug, 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, soliriamfol (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)
Brilaroxazine (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]
Brexpiprazole (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]

Brexpiprazole (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. Brexpiprazole 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, toludesvenlafaxine, 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]

Toludesvenlafaxine (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 Adminstration (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 (Wafermine)	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-resistent 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-HT2C 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]
SR58611A (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-HT1A 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-HT2C 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), toludesvenlafaxine (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]

Toludesvenlafaxine (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 implmentation 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-HT2A 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-HT2A and 5-HT2C 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 change, 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-HT2A 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-glycose 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-HT6 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 mihgt be a significant delay in the development of new treatments and their impact on the general population.

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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]

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