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REVIEW

Recent advances in psychiatric medicines: from rapid-acting antidepressants to precision psychiatry

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Psychiatric disorders represent a leading cause of global disease burden, with depression, schizophrenia, bipolar disorder, and anxiety disorders contributing substantially to disability-adjusted life years worldwide. Despite decades of pharmacological research, conventional psychiatric medicines, primarily monoaminergic antidepressants and dopamine receptor–based antipsychotics, remain limited by delayed onset of action, incomplete response rates, relapse, and significant adverse effects. Over the past decade, however, psychiatric drug development has entered a transformative phase marked by the emergence of rapid-acting antidepressants, neuroactive steroid modulators, novel receptor targets, psychedelic-assisted therapies, and precision-based approaches. This mini-review critically examines recent advances in psychiatric medicines, focusing on mechanistic innovations, clinical evidence, regulatory milestones, and translational challenges. Key developments include glutamatergic modulators such as ketamine and esketamine, GABAergic neuroactive steroids for postpartum depression, muscarinic and trace amine-associated receptor 1 (TAAR1)-based antipsychotics, the resurgence of psychedelic research, advances in long-acting injectable formulations, and the integration of pharmacogenomics and biomarker-guided therapy. Collectively, these innovations signal a paradigm shift toward faster, more targeted, and individualized psychiatric treatment strategies.

Keywords: psychiatric pharmacotherapy, rapid-acting antidepressants, neuroactive steroids, psychedelics, TAAR1 agonists, precision psychiatry

Introduction

Psychiatric illnesses affect more than one billion individuals globally and constitute a major public health challenge. Disorders such as major depressive disorder (MDD), schizophrenia, bipolar disorder, anxiety disorders, and postpartum depression (PPD) significantly impair quality of life and productivity while increasing mortality through suicide and comorbid medical conditions. Although pharmacotherapy remains a cornerstone of psychiatric treatment, progress in drug development was relatively stagnant for several decades, relying heavily on monoamine-based antidepressants and dopamine D_2 receptor antagonists (1, 2).

Selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and classical antipsychotics have undoubtedly improved outcomes for many patients; however, their limitations are increasingly recognized. Delayed therapeutic onset, treatment resistance, metabolic and neurological adverse effects, poor adherence, and lack of efficacy for negative and cognitive symptoms are persistent challenges. Approximately one-third of patients with depression fail to achieve remission with existing therapies, underscoring the need for novel approaches (3, 4).

Recent advances in neuroscience, molecular pharmacology, and translational psychiatry have revitalized the psychiatric drug pipeline. The focus has shifted from monoaminergic modulation toward glutamatergic, GABAergic, cholinergic, inflammatory, and neurosteroid pathways, as well as toward personalized medicine strategies. This review synthesizes major advancements in psychiatric medicines over the past decade and evaluates their clinical and translational significance.

Rapid-acting antidepressants and glutamatergic modulation

Ketamine and esketamine

One of the most significant breakthroughs in psychiatric pharmacotherapy has been the discovery of the rapid antidepressant effects of ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. Unlike conventional antidepressants that require weeks to exert clinical benefit, ketamine produces symptom relief within hours, even in patients with treatment-resistant depression (TRD) and acute suicidal ideation (5).

The antidepressant effects of ketamine are believed to involve glutamatergic disinhibition, enhanced α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor signaling, activation of mammalian target of rapamycin (mTOR) pathways, and synaptogenesis in the prefrontal cortex. These neuroplastic effects represent a departure from traditional monoamine-centric models of depression.

Esketamine, the S-enantiomer of ketamine, was developed as an intranasal formulation and approved for TRD under controlled administration settings. Clinical trials demonstrated its superiority over placebo when used as an adjunct to oral antidepressants. Esketamine has also shown benefit in rapidly reducing suicidal ideation, although sustained efficacy requires repeated dosing and careful monitoring (6, 7).

Despite their promise, ketamine-based therapies present challenges, including dissociative symptoms, blood pressure elevation, potential for misuse, cost, and limited long-term safety data. Nonetheless, they have reshaped antidepressant research by validating glutamate as a therapeutic target.

Neuroactive steroids and postpartum depression

Brexanolone

Postpartum depression (PPD) is a severe mood disorder affecting women following childbirth and is associated with maternal morbidity, impaired mother–infant bonding, and long-term developmental consequences for children. Conventional antidepressants are often slow to act and inadequately address the neurobiological changes associated with PPD (8, 9).

Brexanolone, an intravenous formulation of allopregnanolone, is a neuroactive steroid that positively modulates GABA_A receptors. It was the first drug specifically approved for PPD. Clinical trials demonstrated rapid and sustained reductions in depressive symptoms following a 60-hour continuous infusion (10).

However, brexanolone administration requires hospitalization and monitoring due to risks of excessive sedation and loss of consciousness, limiting accessibility.

Zuranolone

Zuranolone, an oral neuroactive steroid, represents a major advancement by offering a more practical alternative to brexanolone. Approved in 2023 for PPD, zuranolone produces rapid symptom improvement with a short treatment course. Its mechanism similarly involves enhancement of GABAergic inhibitory neurotransmission.

The success of neuroactive steroids highlights the role of hormonal and GABAergic dysregulation in mood disorders and opens avenues for treating other conditions such as major depression and anxiety disorders (11, 12).

Psychedelic-assisted therapies

Psilocybin and mood disorders

The renewed scientific interest in psychedelics marks a notable shift in psychiatric research. Psilocybin, a serotonergic psychedelic acting primarily at 5-HT_2A receptors, has demonstrated antidepressant and anxiolytic effects in controlled clinical settings. Studies suggest that psilocybin induces profound alterations in brain network connectivity, facilitating cognitive and emotional flexibility.

Randomized trials in MDD and end-of-life anxiety have shown significant symptom reductions following one or two supervised dosing sessions combined with psychotherapy. However, results have been heterogeneous, and some large trials have failed to demonstrate superiority over active comparators (13).

Challenges and ethical considerations

Psychedelic therapies are uniquely dependent on psychological context, including preparation, therapeutic support, and integration sessions. Regulatory concerns, long-term safety, risk of psychological distress, and scalability

remain unresolved. While promising, psychedelic-assisted therapies require rigorous standardization before routine clinical adoption (14, 15).

Novel antipsychotic mechanisms beyond dopamine D_2

TAAR1 agonists

Trace amine-associated receptor 1 (TAAR1) has emerged as a novel target for schizophrenia. TAAR1 modulates dopaminergic and serotonergic neurotransmission indirectly, offering the potential to treat psychosis without direct D_2 antagonism.

Ulotaront (SEP-363856), a TAAR1 agonist with additional 5-HT1A activity, demonstrated antipsychotic efficacy in early trials with minimal extrapyramidal and metabolic side effects. Although later-stage trials yielded mixed results, TAAR1 remains a promising target, particularly for addressing negative and cognitive symptoms (16–19).

Muscarinic receptor modulation

Another major breakthrough is the development of muscarinic receptor agonists for schizophrenia. Xanomeline, an M1/M4 muscarinic agonist, showed antipsychotic efficacy but caused intolerable peripheral cholinergic side effects. Its combination with trospium, a peripherally acting anticholinergic, resulted in improved tolerability (KarXT).

Late-stage clinical trials demonstrated significant improvements in positive symptoms, validating muscarinic modulation as a non-dopaminergic antipsychotic strategy (20).

Table 1 summarizes the major recent advances in psychiatric medicines, highlighting novel mechanisms of action, clinical indications, and regulatory status.

TABLE 1 | Recent advances in psychiatric medicines: mechanisms, indications, and clinical status.

Drug/class	Primary mechanism of action	Clinical indication	Key advantage over conventional therapy	Regulatory/clinical status
Ketamine (18)	N-methyl-D-aspartate (NMDA) receptor antagonism; enhanced α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) signaling; synaptogenesis	Treatment-resistant depression (TRD), acute suicidality	Rapid antidepressant effect within hours	Off-label use with strong clinical evidence
Esketamine (7)	NMDA receptor antagonism (S-enantiomer of ketamine)	TRD	Faster onset than selective serotonin reuptake inhibitors (SSRIs); effective in severe depression	Food and drug administration (FDA)-approved (restricted clinical setting)
Brexanolone (10)	Positive allosteric modulator of GABAA receptors	Postpartum depression (PPD)	First drug specifically approved for PPD; rapid symptom relief	FDA-approved (IV infusion)
Zuranolone (12)	Oral neuroactive steroid; GABAA receptor modulation	PPD	Oral administration; short treatment course	FDA-approved (2023)
Psilocybin (14)	5-HT2A receptor agonism; enhanced neural plasticity	Major depressive disorder (MDD), end-of-life distress	Sustained antidepressant effect after limited dosing	Phase II–III clinical trials
Ulotaront (TAAR1 agonist) (17, 19)	TAAR1 activation; indirect dopaminergic modulation	Schizophrenia	Antipsychotic effect without D2 blockade; fewer extrapyramidal symptoms (EPS)	Phase III trials (mixed outcomes)
Xanomeline–Trospium (KarXT) (21)	Muscarinic M_1/M_4 receptor agonism with peripheral blockade	Schizophrenia	Non-dopaminergic antipsychotic; improved tolerability	Late-stage clinical development
Lumateperone (22)	Multimodal serotonin–dopamine–glutamate modulation	Schizophrenia, bipolar depression, adjunct MDD	Favorable metabolic and neurological safety	FDA-approved
Long-Acting Injectable Antipsychotics (LAIs)	Sustained dopamine receptor modulation	Schizophrenia, bipolar disorder	Improved adherence; reduced relapse	Widely approved
Pharmacogenomic-guided therapy (23)	Genotype-based drug selection	MDD	Personalized treatment; reduced trial-and-error	Increasing clinical adoption

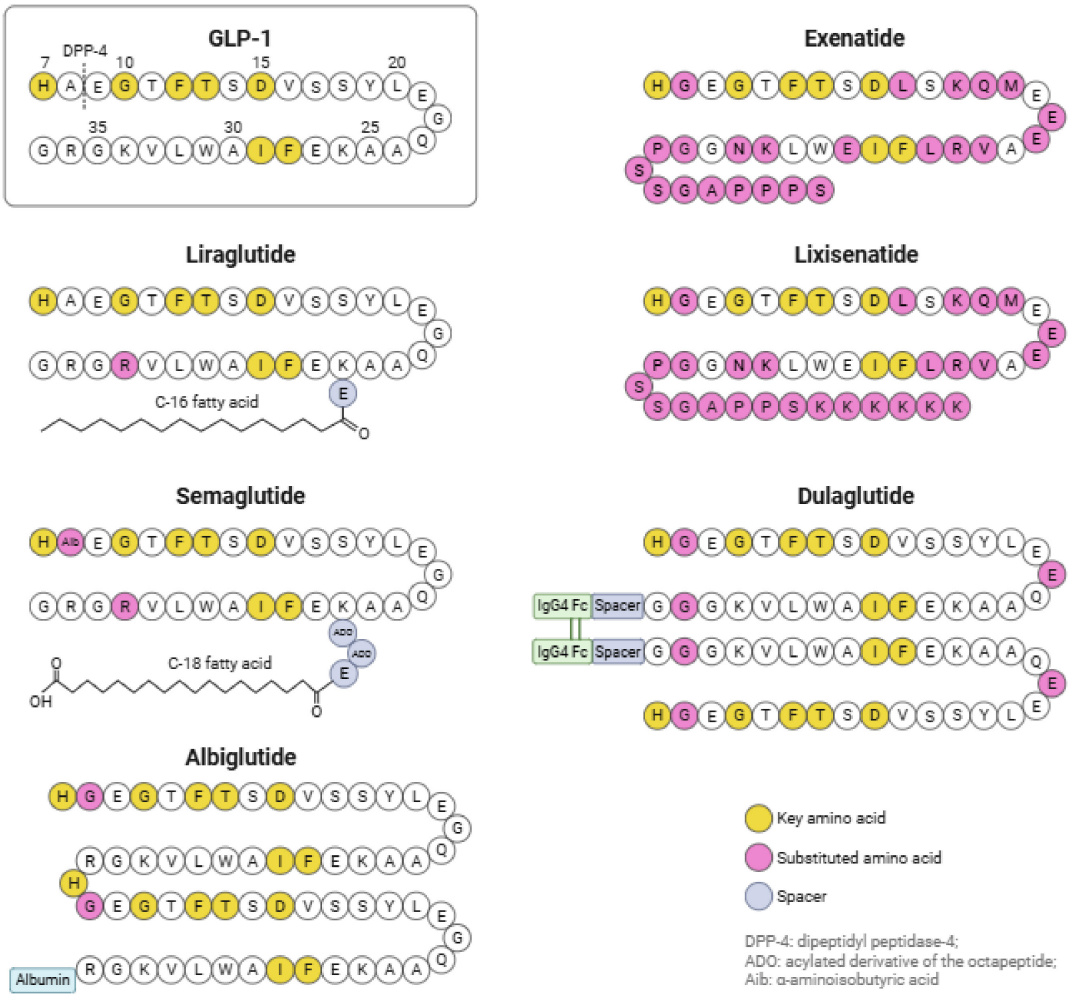

FIGURE 1 | Structural comparison of native GLP-1 and marketed GLP-1 receptor agonists highlighting amino acid substitutions, spacers, and conjugation strategies used to enhance stability and half-life.

Repurposing and multimodal agents

Lumateperone is an atypical antipsychotic with a unique pharmacological profile involving serotonin, dopamine, and glutamate modulation. Initially approved for schizophrenia, it has since gained indications for bipolar depression and adjunctive treatment of MDD (22).

Such repurposing strategies accelerate drug availability while maximizing clinical utility, particularly for disorders with overlapping pathophysiology.

Advances in drug delivery and long-acting injectables

Poor medication adherence is a major contributor to relapse in schizophrenia and bipolar disorder. Long-acting injectable (LAI) antipsychotics address this issue by ensuring sustained drug delivery over weeks to months (23).

Recent meta-analyses indicate that LAIs reduce relapse and hospitalization rates compared with oral therapy, particularly in real-world settings. Innovations in formulation technology have improved tolerability and dosing flexibility, reinforcing LAIs as a key component of modern psychiatric care.

Precision psychiatry and pharmacogenomics

Precision psychiatry aims to tailor treatment based on individual biological, genetic, and clinical characteristics. Pharmacogenomic testing has gained attention for guiding antidepressant selection, particularly genes encoding cytochrome P450 enzymes and serotonin transporters.

Meta-analyses suggest modest but significant improvements in response and remission rates when pharmacogenomic guidance is used. While not yet universally adopted, such approaches represent a step toward personalized treatment (24).

Inflammation-targeted and biomarker-guided therapies

Growing evidence implicates immune and inflammatory mechanisms in subsets of depression and psychosis. Elevated inflammatory markers such as C-reactive protein and interleukins have been associated with treatment resistance.

Anti-inflammatory agents, including cytokine inhibitors and non-steroidal anti-inflammatory drugs, show antidepressant effects primarily in patients with elevated baseline inflammation. This supports a stratified treatment model rather than a one-size-fits-all approach (25).

Structural modifications of GLP-1 and marketed GLP-1 receptor agonists

Figure 1 compares the amino acid sequence of native glucagon-like peptide-1 (GLP-1) with various clinically used GLP-1 receptor agonists and highlights the structural modifications responsible for their improved therapeutic profiles. Native GLP-1 is rapidly inactivated by dipeptidyl peptidase-4 (DPP-4), whereas analogues such as exenatide and lixisenatide contain targeted amino acid substitutions that enhance resistance to enzymatic degradation. Longer-acting agents, including liraglutide and semaglutide, are modified by fatty-acid acylation, which promotes albumin binding and prolongs circulation time. Dulaglutide and albiglutide achieve extended half-lives through conjugation to large protein carriers, such as IgG Fc fragments or albumin. These structural strategies collectively improve stability, extend duration of action, and reduce dosing frequency in clinical use.

Regulatory, safety, and access considerations

Despite scientific progress, access to novel psychiatric medicines remains limited by high costs, regulatory restrictions, infrastructure requirements, and safety concerns. Drugs such as esketamine and brexanolone require supervised administration, increasing healthcare burden.

Post-marketing surveillance and real-world evidence will be critical to defining long-term safety, cost-effectiveness, and optimal patient selection (26).

Future directions

Future psychiatric drug development will likely emphasize:

- Mechanism-based drug discovery beyond monoamines
- Biomarker-driven patient stratification
- Integration of digital and neuroimaging tools
- Combination of pharmacotherapy with psychotherapy and neuromodulation
- Improved accessibility and health-system integration

Conclusion

Recent advances in psychiatric medicines represent a paradigm shift from symptom-based, monoaminergic treatment toward mechanism-driven, rapid-acting, and personalized therapies. Innovations such as glutamatergic antidepressants, neuroactive steroids, novel antipsychotic targets, and precision psychiatry tools offer renewed hope for patients with refractory mental illness. Continued interdisciplinary research, ethical oversight, and health-policy adaptation will be essential to translate these advances into equitable clinical benefit.

Author contributions

Conceptualization, literature search, manuscript drafting, and final approval were performed by the author.

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