

Psychiatric Pharmacotherapy and the Problem of Mechanistic Validation: A Critical Review

Waqar Husain

Department of Humanities, COMSATS University Islamabad, Islamabad Campus, Park Road, Islamabad 45550, Pakistan

Abstract

Psychiatric pharmacotherapy is among the most widely practiced and epistemically contested domains of contemporary medicine. Antidepressant consumption has risen significantly across OECD countries over the past decade, yet the neurobiological hypotheses used to justify these prescriptions remain unvalidated. This critical review examines the principal psychiatric drug classes, including antidepressants, antipsychotics, mood stabilizers, benzodiazepines and related anxiolytics, and psychostimulants. For each, the pharmacological composition, proposed mechanism, clinical goals, and evidence of effectiveness are reviewed. The central argument is that virtually none of these agents treats a confirmed biological cause of the disorder for which it is prescribed. The serotonin hypothesis of depression lacks consistent evidentiary support, the dopamine hypothesis of schizophrenia remains mechanistically inconclusive, and the catecholamine hypothesis underlying stimulant use in attention-deficit/hyperactivity disorder has not established a causal deficit. The serendipitous discovery of foundational psychiatric drugs, the substantial placebo response in antidepressant trials, publication bias, weak diagnostic validity, the physical health burden of long-term antipsychotic use, and benzodiazepine dependence are examined as compounding weaknesses in the field's scientific foundations. Emerging treatments, including ketamine and psilocybin, show early promise alongside unresolved mechanistic questions. The review concludes with a call for epistemic transparency: symptomatic improvement, while clinically valuable, should not be presented to patients as mechanistic cure, and the gap between pharmacological effect and biological understanding should be openly acknowledged.

Keywords:

psychiatric pharmacotherapy; antidepressants; antipsychotics; serotonin hypothesis; dopamine hypothesis; mechanistic validation; placebo effect; DSM diagnostic validity

I. Introduction

Modern medicine derives its authority from the principle that treatment should follow from mechanistic understanding of disease [1,2]. Cardiology treats hypertension through well-characterized renin-angiotensin-aldosterone pathways [3]. Endocrinology prescribes insulin because the pathophysiology of beta-cell failure and peripheral insulin resistance is understood in molecular detail [3]. Infectious diseases employ antibiotics because specific bacterial pathogens can be identified and their biological machinery precisely targeted [4]. In each of these cases, there is a coherent directional explanatory chain: a known cause produces a known pathophysiology, which is addressed by a mechanism-specific intervention. The result, at least ideally, is not merely the suppression of symptoms but the correction of an identified biological lesion.

* Corresponding Author:

Waqar Husain, Department of Humanities, COMSATS University Islamabad, Islamabad Campus, Park Road, Islamabad 45550, Pakistan, drsukoon@gmail.com (<https://orcid.org/0000-0003-3047-1834>)



© 2026 Copyright by the Author.

Licensed as an open access article using a CC BY 4.0 license.

This contrast requires an important qualification. Even in cardiology, the analogy to a fully solved mechanistic chain is imperfect: essential hypertension, which accounts for approximately 90 to 95 percent of all hypertension cases, has no single identifiable cause, and antihypertensive drugs are themselves prescribed symptomatically, to lower blood pressure, rather than to correct a confirmed underlying lesion [5,6]. The distinction being drawn here is therefore one of degree rather than kind: psychiatry's diagnostic categories are defined entirely by symptom clusters with no biological marker at all, whereas essential hypertension is at least defined by a directly measurable physiological quantity (blood pressure) [6] even where its ultimate cause is unknown.

Psychiatry operates under a fundamentally different epistemological arrangement, and one that the specialty has been reluctant to acknowledge openly. Its diagnostic categories are defined entirely by symptom clusters rather than by validated biological markers, confirmed etiological agents, or identifiable pathological processes [7,8]. Its pharmacological treatments were, in most cases, discovered not through rational mechanistic design but through chance observations made while drugs developed for entirely different purposes were being administered [9,10]. Its theoretical frameworks, including the serotonin hypothesis of depression, the dopamine hypothesis of schizophrenia, and the catecholamine hypothesis of attention-deficit/hyperactivity disorder (ADHD), were constructed retrospectively as post-hoc explanations for observed drug effects rather than as a priori scientific prediction that led to drug discovery [9]. For antipsychotics, for example, the dopamine-receptor basis of drug action was characterized in the decades after chlorpromazine entered clinical use [11]. When these hypotheses have been rigorously tested, they have consistently failed to establish the causal relationship they purport to describe [12,13].

The scale of psychiatric prescribing makes this epistemological problem a matter of significant public health consequence. Antidepressant consumption across 30 OECD countries rose from a mean defined daily dose of 52.42 per 1000 inhabitants in 2010 to 69.5 in 2020, reflecting a statistically significant linear increase in the majority of included nations [14]. A cross-sectional time-series analysis spanning 64 countries documented globally rising use of antidepressants, atypical antipsychotics, and benzodiazepines from 2014 to 2019, with high-income countries showing the highest consumption rates [15]. Consumption has continued to rise: across 91 countries, total psychotropic consumption increased from 34.12 to 36.15 defined daily doses per 1000 inhabitants per day between 2020 and 2022, with the largest relative annual increase for antidepressants [16]. These figures indicate large-scale population exposure to medications whose mechanistic justification remains scientifically unresolved, against a global burden of an estimated 970 million people living with mental disorders [17].

This does not mean that psychiatric medications are without clinical value. For many patients, these drugs provide meaningful symptomatic relief, reduce hospitalization rates, enable functional recovery, and in some cases contribute to life-saving interventions [18]. These are not trivial accomplishments and must not be dismissed. However, the clinical utility of a drug and the scientific validity of the theory used to explain that drug's mechanism are entirely separate matters [19]. Limited progress has been made in developing new and better psychiatric medications, and a legacy endures that new drugs should align with outdated and overinclusive diagnostic categories [20]. Psychiatry has for decades conflated them in ways that may have misled patients [21,22], distorted the research agenda, slowed genuinely mechanistic treatment development [22], and created what one former director of the National Institute of Mental Health (NIMH), Steven Hyman, called an "epistemic prison" in which diagnostic categories lacking biological validity are treated as though they refer to discrete disease entities [7].

It is worth situating this problem within a wider limitation of contemporary neuroscience. Unlike hypertension or diabetes, where the physiological quantities of interest (blood pressure, blood glucose) are directly measurable, the core phenomena of psychiatry, mood, thought, and emotion, are subjective states without an agreed physical correlate. Even for emotion, researchers disagree about the neural correlates of subjective feeling [23], large-scale imaging studies have struggled to replicate associations between brain measures and mental health phenotypes [24], and this gap extends to diagnostic biomarkers [8]. Modern neuroscience has not yet produced a validated, consensus biological account of consciousness: a 2022 review by Seth and Bayne in *Nature Reviews Neuroscience* surveying the leading theoretical frameworks (higher-order theories, global workspace theory, integrated information theory, and predictive-processing accounts) concluded that it remains unclear how these theories relate to one another or whether they can be empirically distinguished [25]. The neural basis of memory storage is similarly unsettled at the mechanistic level: Josselyn and Tonegawa's 2020 review on memory engrams notes that, despite substantial recent progress in identifying and manipulating engram cells in rodents, the field has not yet established how these enduring synaptic and cellular changes give rise to a specific, retrievable memory, and major questions about how memories are updated, generalized, and transformed into knowledge remain open [26]. The neurobiology of subjective emotional experience is subject to comparable debate [27]. This is not unique to psychiatry; it reflects an unsolved problem across neurosciences. It does, however, mean that psychiatry inherited an especially difficult starting position, and the field's premature claims of mechanistic certainty should be read against this backdrop rather than treated as a failure specific to psychiatric researchers.

Before proceeding, it is useful to separate five distinct questions that are easily conflated in discussions of psychiatric pharmacotherapy: (1) whether the disorder in question has a confirmed biological etiology; (2) whether the drug used to treat it has a well-characterized pharmacological mechanism of action; (3) whether that mechanism is known to correct the etiological process identified in (1); (4) whether the drug is clinically effective, regardless of mechanism; and (5) whether the drug is safe and acceptable to patients over the timeframes it is typically used. A drug can score well on (2), (4), and (5) while (1) and (3) remain unresolved, and this combination, not an absence of evidence for benefit, is the pattern this review documents across most psychiatric drug classes.

2. Method

This critical review is written from the perspective of a clinical psychologist. Consistent with the definition of a critical review, it aims not only to describe the literature but to critically evaluate its quality and to advance an analytical argument [28]. It does not aim to advocate for or against psychiatric practice; its purpose is to appraise the evidence for the mechanistic explanations offered for psychiatric drugs. The importance of this review lies in the scale of psychiatric prescribing described in the Introduction: antidepressant and antipsychotic use has risen substantially in many countries over the past decade [14,15], and benzodiazepines remain widely prescribed [29], meaning that the mechanistic assumptions examined here bear on the care of very large numbers of patients worldwide.

The goal of this review is to synthesize and critically evaluate the literature judged most relevant and informative on the topic, drawing on the author's expertise to identify key studies, landmark papers, and areas of scientific controversy. Literature for this review was identified primarily through targeted searches of PubMed and Google Scholar, using each drug class name (and its principal agents) combined with terms such as 'mechanism of action,' 'serotonin hypothesis,' 'dopamine hypothesis,' 'placebo,' and 'discontinuation syndrome,' (for example: ("selective serotonin reuptake inhibitor" OR SSRI) AND ("mechanism of action" OR "serotonin hypothesis" OR placebo OR "discontinuation syndrome")). Equivalent strings were used for antipsychotics, mood stabilizers, benzodiazepines and related hypnotics, buspirone, stimulants, and emerging treatments (ketamine, esketamine, and psilocybin), with hypothesis terms adapted to each class. Historical and landmark sources were included regardless of publication date, with the search concluding in August 2026. Priority was given to systematic reviews, meta-analyses, and large randomized controlled trials over single small studies, and to publications in indexed peer-reviewed journals. Reference lists of key papers were also hand-searched for additional relevant sources. This paper compiles a wide-ranging comprehensive critical account of psychiatry's major drug classes: what they contain, what they claim to do, what the evidence shows about their effectiveness, and above all, what remains scientifically unproven about the mechanisms invoked to justify their use. The review begins with the historical foundations of the field, then proceeds through each drug class, followed by cross-cutting critical analysis covering the placebo problem, publication bias, diagnostic invalidity, and the physical health burden of long-term psychotropic use. Where applicable, each drug-class section concludes with pharmacy practice considerations (counselling, monitoring, and deprescribing).

Sources were eligible if they were peer-reviewed publications in English that addressed a drug class's origin, proposed mechanism of action, the evidence for the underlying disease biology, clinical effectiveness, or safety and discontinuation. Regulatory documents and standard reference works (for example, FDA safety communications and the DSM-5-TR) were also included. Sources were excluded if they were not peer reviewed (other than the documents just listed), were not in English, or did not bear on the mechanism, effectiveness, or safety of the drug classes examined.

The author screened titles, abstracts, and, where needed, full texts. No second reviewer or formal flow diagram was used, because this is not a systematic review. Within the eligible literature, selection followed an explicit evidence hierarchy (umbrella reviews and meta-analyses, then large randomized trials, then smaller studies). For each drug class, sources were chosen to represent its origin, its proposed mechanism and tests of that mechanism, the evidence on effectiveness, and its safety and discontinuation profile. Counterevidence and published critiques were sought deliberately, so that opposing positions are represented.

A methodological note is warranted regarding the concentration of citations to a specific set of authors, particularly Moncrieff, Hengartner, Kirsch, and Read [12,13,30,31], in the sections addressing the serotonin and dopamine hypotheses and the placebo response. This concentration reflects the fact that these authors have produced the largest-scale, most methodologically rigorous studies directly testing the causal claims examined in this review, rather than an unexplained preference for one school of thought. Where methodological critiques of this body of work exist, most notably Jauhar et al. [32] in response to Moncrieff et al. [12], and Fountoulakis and Möller [33] in response to Kirsch et al. [30], they are cited and discussed directly in the relevant sections rather than omitted, and the manuscript's conclusions are qualified accordingly where these critiques raise legitimate concerns.

In terms of scientific reasoning, this review consistently distinguishes between different levels and types of evidence: it prioritizes large-scale umbrella reviews, meta-analyses, and randomized controlled trials over single studies or case reports, and it explicitly flags where a claim rests on a single study, a hypothesis rather than an established finding, or an author's own interpretation rather than a direct empirical result. Landmark or unusually large studies (e.g., genetic association studies involving over 100,000 participants) are identified as such to help readers weigh their evidentiary strength. Key comparative findings across drug classes, including proposed mechanism, strength of etiological evidence, and major safety concerns, are summarized in Table 1.

Findings were synthesized narratively and organized by drug class around five questions: whether the disorder has a confirmed biological etiology; whether the drug has a well-characterized mechanism of action; whether that mechanism is known to correct the etiological process; whether the drug is clinically effective regardless of mechanism; and whether it is safe and acceptable over the timeframes it is typically used. No quantitative synthesis was attempted.

Critical reviews such as this one carry recognized limitations relative to systematic reviews. Because literature selection is guided by the author's judgment rather than a pre-registered, exhaustive search protocol, the review is subject to the possibility of selective citation, in which studies supporting the author's argument may be more readily identified or emphasized than those that complicate it. No formal quality-appraisal instrument was applied to the individual studies discussed, and no quantitative synthesis (such as meta-analysis) was performed; conclusions are therefore based on the author's qualitative reading of the literature rather than a pooled statistical estimate. The author's disciplinary background as a clinical psychologist, rather than a psychiatrist, pharmacologist, or clinical pharmacist, likely shapes which aspects of the literature are foregrounded, particularly the emphasis placed on diagnostic validity and the ethics of patient communication, and readers should weigh the arguments presented here alongside reviews written from other clinical vantage points.

These limitations should be weighed against what a critical review format offers that a systematic review cannot. The central argument of this paper, that mechanistic explanation in psychiatric pharmacology has often been constructed retrospectively to rationalize an observed clinical effect rather than derived prospectively from confirmed disease biology, is a conceptual and historical argument that spans multiple drug classes, decades of scientific practice, and several distinct bodies of evidence (pharmacology, genetics, clinical trials, and diagnostic classification). A systematic review, by design, narrows its scope to a single well-defined question answerable by a specific, replicable search strategy, and would not have been well suited to tracing this cross-cutting pattern across the entire field. Critical review is the appropriate tool for synthesizing a broad and heterogeneous literature into a coherent argument, situating individual findings within their historical and conceptual context, and raising questions that a narrower, more mechanically executed search might not surface. The author has attempted to offset the format's inherent risk of selective emphasis by prioritizing systematic reviews, meta-analyses, and large randomized controlled trials wherever available, and by explicitly acknowledging counterevidence and disciplinary limitations throughout the text.

3. Historical Context: Serendipity as the Foundation of a Specialty

The psychopharmacological revolution of the twentieth century is routinely presented as a triumph of biomedical science. In terms of the number of patients treated and the scale of institutional change it produced, closing asylums and inaugurating community psychiatry, it was certainly transformative. In terms of scientific methodology, however, it was almost entirely a product of chance. Several of the foundational drugs of modern psychiatry were not designed to correct known neurochemical deficits; they were discovered through unexpected clinical observations while researchers were looking for something else [10,34], and their theoretical explanations were formulated afterward [9,11].

The role of serendipity in drug discovery has been documented across pharmacology generally [35], but its centrality in psychiatry is pronounced. A comprehensive review by Ban, published in *Dialogues in Clinical Neuroscience* [9], examined twelve serendipitous drug discoveries, including prototype psychotropic drugs that led to modern pharmacological treatment in psychiatry and other drugs that influenced its development. Ban defined serendipity as finding one thing while looking for something else, and he classified the twelve discoveries into groups. Because Ban's sample consists of discoveries selected as serendipitous, these counts do not estimate the proportion of psychiatric drugs discovered in this way. This is not a minor historical footnote. It is an important epistemological feature of the origins of the field.

Chlorpromazine, the molecule that inaugurated modern antipsychotic therapy and triggered what was called the "psychopharmacological revolution," was synthesized by the French pharmaceutical company Rhone-Poulenc originally as an antihistamine [36]. It was administered to surgical patients in 1951 by the anesthesiologist Henri

Laborit, who was exploring its potential for potentiating anesthesia and reducing autonomic reactions during surgery [36]. Laborit observed that patients receiving the drug exhibited a striking state of calm indifference that he believed might have applications in psychiatry [36]. When psychiatrists Jean Delay and Pierre Deniker administered it to psychotic patients at the Sainte-Anne Hospital in Paris in 1952, they found it suppressed hallucinations and agitation [36]. No one had designed it to do this, no one understood why it worked, and the dopamine hypothesis of schizophrenia, the post-hoc theoretical explanation constructed to account for chlorpromazine's observed effects, was not proposed until the 1960s [9,37].

Imipramine, the first tricyclic antidepressant, followed an almost identical trajectory. Originally synthesized as a structural analogue of chlorpromazine in the hope that it might be a superior antipsychotic, imipramine was found by Roland Kuhn in 1957 to be ineffective against psychosis but to produce marked improvement in depressed patients [9]. Once again, a psychiatric drug had been discovered through opportunistic clinical observation rather than mechanistic design. The monoamine hypothesis of depression was constructed afterward to explain why a drug that blocked neurotransmitter reuptake happened to improve depressed mood [38].

Lithium's story is perhaps the most remarkable of all. John Cade, an Australian psychiatrist, was investigating the hypothesis that uric acid toxicity might play a role in mania in 1949 when he used the highly soluble salt lithium urate to test his hypothesis in guinea pigs. He noticed that the animals became unexpectedly calm following lithium administration and proceeded to administer lithium carbonate to manic patients, finding it dramatically effective [9]. His hypothesis about uric acid was entirely wrong. His empirical findings were genuinely important. The mechanistic explanation for why lithium stabilizes mood in bipolar disorder remains, as of the time of this writing, incompletely understood despite more than 75 years of clinical use [39].

Iproniazid, the first monoamine oxidase inhibitor and one of the first antidepressants to enter clinical use, was developed as a treatment for tuberculosis [9]. Clinicians administering it to tubercular patients at Sea View Hospital in New York in the early 1950s noticed that patients seemed inexplicably energized and cheerful, sometimes dancing in the corridors despite their serious physical illness [9]. This observation led to its repurposing as a psychiatric agent. Once again, a psychiatric drug was discovered not because scientists understood the biology of depression and designed a molecule to correct it, but because a drug developed for an entirely different purpose happened to produce mood-altering effects that were subsequently exploited [9].

This pattern of serendipitous discovery followed by retrospective theoretical rationalization is not merely a historical curiosity from an era before modern pharmacology. It established a structural problem that has never been corrected: psychiatric pharmacology has been doing its scientific reasoning backwards, inferring mechanism from observed drug effect rather than deriving drug design from confirmed disease mechanism [9]. The result is that decades of research and clinical practice have been organized around theoretical frameworks that were never adequately validated and that, when subjected to rigorous examination, have not held up [12].

4. The Diagnostic Foundation Problem: Treating Categories Without Confirmed Biology

Before examining individual drug classes, it is essential to understand the epistemological problem at the base of psychiatric pharmacology, which is the diagnostic system itself. Psychiatric medications are prescribed for DSM-defined diagnoses [40], and the validity of those diagnoses as biological entities has been seriously and repeatedly questioned by researchers working within psychiatry itself [7,41,42].

The Diagnostic and Statistical Manual of Mental Disorders (DSM) was radically reorganized with its third edition in 1980, in a deliberate effort to achieve interrater reliability by providing operationalized symptom-based criteria for each disorder [7]. This effort was largely successful: clinicians using DSM criteria do achieve reasonable agreement on diagnosis [43]. However, as Steven Hyman, former director of NIMH and a neuroscientist at Harvard Medical School, argued in a landmark 2010 paper in the *Annual Review of Clinical Psychology*, the focus on reliability came at a time when the scientific understanding of mental disorders was embryonic and could not yield valid disease definitions [7]. The result, in Hyman's words, was that DSM categories became reified, meaning that despite their lack of biological validity, they were increasingly treated as though they referred to distinct disease entities that exist independently of the observer's conceptualization [7]. Hyman argued that the modern DSM system, intended to create a shared clinical language, also created "epistemic blinders that impede progress toward valid diagnoses" [7].

This diagnostic validity problem directly undermines psychiatric pharmacology in the following way: if the categories for which drugs are prescribed do not correspond to biologically distinct entities, then the neurobiological theories invoked to explain drug mechanisms in those categories cannot be meaningfully tested or validated. A drug

cannot be said to correct a serotonin deficiency in “major depressive disorder” if “major depressive disorder” is itself a heterogeneous category without a unified biological substrate [7,43].

The NIMH acknowledged this problem explicitly when it announced in 2013 that it would reorient its research funding away from DSM diagnostic categories toward the Research Domain Criteria (RDoC) framework, which attempts to map mental disorders onto dimensional biological and psychological constructs rather than symptom-cluster categories [44]. This was an institutional acknowledgment that DSM categories, the very categories for which billions of psychiatric prescriptions are written annually, do not reliably map onto biology in a way that can support mechanistic research [44].

5. Antidepressants

5.1. Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs constitute the most widely prescribed class of psychiatric medications globally [15]. The class includes fluoxetine (Prozac), sertraline (Zoloft), escitalopram (Lexapro), paroxetine (Paxil), citalopram (Celexa), and fluvoxamine (Luvox). Each of these agents shares a common pharmacological core mechanism: the blockade of the serotonin transporter protein (SERT), which under normal physiological conditions removes serotonin from the synaptic cleft back into the presynaptic neuron through a reuptake process. By binding to and inhibiting SERT, SSRIs reduce this reuptake, increasing the concentration of serotonin in the synaptic space [45].

The theoretical rationale for this mechanism was derived from the serotonin hypothesis of depression, first formally proposed by Alec Coppen in his 1967 paper in the *British Journal of Psychiatry* [38]. Coppen observed that drugs which appeared to have antidepressant effects also appeared to potentiate serotonergic activity, and proposed that depression might result from deficient serotonin neurotransmission [38]. This hypothesis was not based on direct measurement of serotonin levels in depressed brains, because the technology to do so reliably did not exist in 1967. It was an inference from pharmacological observation, constructed by reasoning backward from drug effect to disease mechanism [38]. Over subsequent decades, and particularly following the commercial launch of fluoxetine in 1987, the serotonin hypothesis was extensively promoted to the public under the phrase “chemical imbalance,” a marketing framing that significantly outran the supporting evidence [12].

The most comprehensive scientific evaluation of the serotonin hypothesis to date was published in 2022 by Moncrieff and colleagues in *Molecular Psychiatry*, as a systematic umbrella review covering all major areas of serotonin research in relation to depression [12]. The authors searched PubMed, EMBASE, and PsycINFO for systematic reviews, meta-analyses, and large dataset analyses across six research domains: serotonin and its metabolite 5-HIAA in body fluids, serotonin 5-HT_{1A} receptor binding, serotonin transporter (SERT) levels measured by imaging or post-mortem examination, tryptophan depletion studies, SERT gene associations, and SERT gene-by-environment interactions [12]. The findings across all six domains were consistent in their failure to support the serotonin deficiency model of depression. The authors concluded that the main areas of serotonin research provide no consistent evidence of an association between serotonin and depression, and no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations [12].

Particularly striking were the findings from the genetic domain. The two largest and highest quality studies of the serotonin transporter gene included in the review, one genetic association study involving 115,257 participants and one collaborative meta-analysis involving 43,165 participants, both found no evidence of any association between SERT gene variants and depression, nor any gene-by-stress interaction producing depression [12].

These are not small, underpowered studies. They represent some of the largest psychiatric genetics investigations ever conducted, and they found no signal. Moncrieff’s review attracted both significant public attention and methodological criticism from within the field. Jauhar et al. (2023) argued that an umbrella review documenting mixed or null findings across individual serotonin markers does not, on its own, establish that serotonin plays no role in depression; they noted that some evidence, such as tryptophan depletion effects concentrated in individuals with a family history of depression, may indicate a role for serotonergic vulnerability in specific subpopulations that a pooled analysis across all research domains could understate. However, the core empirical finding, that direct evidence linking serotonin to the causation of depression is absent across the six domains examined, was not refuted by this critique [32].

Furthermore, the umbrella review noted that some evidence was consistent with the possibility that long-term antidepressant use may itself reduce serotonin concentrations, which raises the troubling possibility that SSRIs, far from correcting a pre-existing serotonin deficit, may actually create one over time [12]. This is a hypothesis rather than an established finding, but its plausibility within the pharmacological literature warrants serious attention.

It is important to acknowledge that SSRIs produce observable pharmacological effects and that many patients report subjective improvement during SSRI treatment. These observations are not disputed. What is disputed is whether the improvement is attributable to correction of the theorized serotonergic deficit, or whether it arises through other mechanisms including non-specific psychobiological effects, expectation-driven placebo response, emotional blunting, reduction of autonomic arousal, or neuroplastic downstream effects unrelated to the original serotonin hypothesis [12,46]. These alternatives have not been adequately investigated because the field has for decades treated the serotonin hypothesis as settled when it was not.

SSRIs are also associated with a clinically significant discontinuation syndrome upon cessation of treatment. A systematic review documented that incidence rates of symptoms associated with SSRI cessation ranged from 27% to 86% across studies, with nearly half of affected patients rating their symptoms at the highest level of severity on the rating scale used, and symptom durations ranging from days to years in some cases [31]. A more recent meta-analysis that accounted for symptoms after stopping placebo estimated that one in six to seven patients experience symptoms directly caused by stopping medication, and about one in 35 experience severe symptoms [47]. Serotonin and noradrenaline reuptake inhibitors and paroxetine are associated with higher withdrawal risks than other antidepressants, and longer duration of use and higher doses are also associated with greater risk [48]. Symptoms include dizziness, nausea, sensory disturbances described as “brain zaps,” insomnia, anxiety, irritability, and emotional lability [31]. This discontinuation syndrome was for years euphemistically distinguished from “withdrawal” in official communications, partly to avoid the implication that antidepressants could produce dependence [49]. However, structurally the discontinuation syndrome shares the defining features of drug withdrawal: it is caused by drug cessation, it is reversed by drug reinstatement, and it can be mitigated by gradual tapering [31]. The DSM-5-TR itself now lists antidepressant discontinuation syndrome as a recognized condition [49]. The existence of a significant discontinuation syndrome in a drug class prescribed as a non-addictive alternative to benzodiazepines is a clinically and ethically important fact that patients frequently are not informed of at the point of prescription.

Pharmacists can counsel patients at initiation that abrupt cessation may cause discontinuation symptoms, that symptoms appearing after a dose change may reflect discontinuation rather than relapse, and that dose reductions should be gradual and agreed with the prescriber. Because the risk appears higher with longer use, higher doses, and some agents such as paroxetine, medication reviews are a natural point to identify patients who may need a supervised taper. Counselling can also explain honestly that the drug is believed to alter serotonin signaling, without asserting that a specific deficit is being corrected.

5.2. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs extend the pharmacological profile of SSRIs by adding concurrent blockade of the norepinephrine transporter (NET) alongside SERT inhibition. The principal agents in this class are venlafaxine (Effexor), duloxetine (Cymbalta), desvenlafaxine (Pristiq), and levomilnacipran (Fetzima). At lower doses, venlafaxine acts predominantly as an SSRI; meaningful NET inhibition emerges at higher dose ranges, giving it a functionally dose-dependent dual mechanism [50].

The rationale for dual mechanism antidepressants arose from the broader monoamine hypothesis of depression, which implicates both serotonin and norepinephrine in the pathophysiology of depressive illness [38]. If serotonin deficiency alone did not fully account for depression, the reasoning went, perhaps a combined serotonergic and noradrenergic intervention would be more effective. In practice, however, the evidence base does not consistently support the superiority of SNRIs over SSRIs [51]. A network meta-analysis of antidepressant efficacy and acceptability in acute-phase major depression, one of the most comprehensive comparative analyses of antidepressants ever conducted, found as its primary result that all 21 antidepressants studied were significantly more effective than placebo [52]. Beyond this headline finding, differences between individual antidepressants in efficacy were generally modest, with SNRIs such as venlafaxine showing statistically significant but clinically modest advantages over some SSRIs in certain comparisons [52]. The overall message of this analysis was not the superiority of dual-mechanism agents as a class but the broad pharmacological equivalence of most antidepressants despite their varied mechanisms [52]. This is itself a finding that challenges any single-mechanism hypothesis of depression: if drugs with entirely different pharmacological targets all produce similar antidepressant effects, the specificity of any one mechanistic explanation is undermined.

SNRIs carry an extended side effect profile relative to SSRIs. The addition of norepinephrine reuptake inhibition produces more pronounced cardiovascular effects, including dose-dependent increases in blood pressure and heart rate, which necessitate monitoring in patients with pre-existing cardiovascular conditions [50]. The discontinuation syndrome with venlafaxine is among the most pronounced of any antidepressant, given its short half-life, and has been

described in the clinical literature as one of the more difficult aspects of venlafaxine management [31,49]. Duloxetine additionally holds regulatory approval for fibromyalgia, diabetic peripheral neuropathic pain, and chronic musculoskeletal pain, applications that are pharmacologically unrelated to any theory of depression but that nonetheless rely on the same norepinephrine reuptake mechanism, suggesting that the drug's analgesic properties may be at least as clinically significant as its antidepressant ones [50].

Given the dose-dependent rises in blood pressure and heart rate described above, pharmacists can check these measurements at review in patients with cardiovascular conditions, and can counsel about the short half-life of venlafaxine, which makes missed doses and abrupt stopping more likely to provoke discontinuation symptoms.

5.3. Tricyclic Antidepressants (TCAs)

Before SSRIs displaced them, tricyclic antidepressants were the dominant pharmacological treatment for depression for approximately three decades. The class includes imipramine, amitriptyline, nortriptyline, clomipramine, desipramine, doxepin, and trimipramine. Their discovery was entirely serendipitous: imipramine was designed as an antipsychotic, found to be ineffective for that indication, and discovered to have antidepressant properties through opportunistic clinical observation by Roland Kuhn [9].

Pharmacologically, TCAs are far less selective than SSRIs [53,54]. In addition to inhibiting SERT and NET, they antagonize muscarinic acetylcholine receptors (M1), histamine H1 receptors, and alpha-1 adrenergic receptors [55]. This pharmacological promiscuity is directly responsible for the extensive adverse effect profile that has limited their contemporary use. Muscarinic receptor blockade produces the classical anticholinergic effects of dry mouth, urinary retention, constipation, blurred vision, and impaired memory [55]. H1 antagonism produces sedation and weight gain, while alpha-1 blockade contributes to orthostatic hypotension and dizziness [55]. Most consequentially, TCAs block cardiac sodium and potassium channels, producing QRS widening (QRS complex: a component of the electrocardiogram representing ventricular depolarization) and QTc (Corrected QT interval) prolongation that render overdose potentially fatal from ventricular arrhythmia [55]. This cardiac toxicity profile makes TCAs among the most dangerous medications in clinical use in terms of therapeutic index, and a significant contributor to intentional overdose mortality among depressed patients [55].

Despite these liabilities, TCAs remain in clinical use for specific indications. Amitriptyline is widely used at low doses for neuropathic pain [56], although the certainty of evidence is low, and as a sleep aid, exploiting its antihistaminergic sedation [57] rather than its monoaminergic antidepressant properties. Guidelines endorse sedating antidepressants for insomnia only for short-term use [57]. Clomipramine retains a first-line role for obsessive-compulsive disorder, where it has demonstrated robust efficacy in controlled trials, though its superior efficacy over SSRIs for OCD is attributed to its more potent SERT inhibition rather than to any unique mechanistic action specific to OCD [58]. Nortriptyline and desipramine are sometimes used as second- or third-line antidepressants when SSRIs have failed, owing to their somewhat more favorable side effect profiles relative to other TCAs [55].

The fact that TCAs, with their broad and relatively nonspecific pharmacological footprint, produce antidepressant effects comparable to the more selective SSRIs in head-to-head comparisons is itself epistemologically significant [52]. If depression were caused by a specific serotonin deficiency, one would predict that more selective serotonin reuptake inhibitors would be superior to agents that also block acetylcholine, histamine, and norepinephrine receptors. The absence of such a pattern suggests that neither selectivity for serotonergic targets nor selectivity for any other specific neurotransmitter system is the essential driver of antidepressant response [52].

Because of their cardiac toxicity in overdose, pharmacists can review the quantity supplied for patients at risk of self-harm, screen for interacting drugs, and counsel on anticholinergic effects and orthostatic hypotension, particularly in older adults.

5.4. Monoamine Oxidase Inhibitors (MAOIs)

MAOIs represent the oldest class of antidepressants still in clinical use [10]. They include the irreversible agents phenelzine, tranylcypromine, and isocarboxazid [59], and the reversible inhibitor of monoamine oxidase A (RIMA) moclobemide [60]. Their mechanism of action involves inhibition of the monoamine oxidase enzymes (MAO-A and MAO-B), which are responsible for the intracellular metabolic degradation of the biogenic amines serotonin, norepinephrine, and dopamine [61]. By inhibiting these enzymes, MAOIs increase the cytoplasmic concentration of all three monoamines simultaneously, representing the broadest monoaminergic intervention among the antidepressant classes [61].

The discovery of MAOIs as antidepressants was, again, serendipitous. Iproniazid was developed and marketed as a tuberculosis treatment in the early 1950s. Clinicians at Sea View Hospital in Staten Island, New York, observed that patients receiving iproniazid for tuberculosis appeared unusually and inappropriately cheerful given the severity of their illness, sometimes described in contemporary reports as dancing in the corridors [9]. This observation prompted the psychiatrist Nathan Kline to conduct clinical trials of iproniazid in depressed patients in 1957, finding it effective [9]. The monoamine oxidase enzyme was identified as the relevant pharmacological target afterward, and the theoretical framework of MAO-mediated monoamine deficiency in depression was constructed to rationalize this already-observed clinical effect [9].

Irreversible MAOIs require patients to avoid tyramine-rich foods including aged cheeses, cured and fermented meats, certain wines, and broad bean pods, due to the risk of a potentially fatal hypertensive crisis caused by the inability to metabolize dietary tyramine in the gut and liver [61]. Under normal conditions, MAO-A in the gastrointestinal tract degrades tyramine before it enters systemic circulation. When MAO-A is irreversibly inhibited, dietary tyramine reaches systemic circulation and triggers a massive, potentially life-threatening surge of catecholamine release [61]. This dietary restriction, combined with extensive drug-drug interactions, including dangerous interactions with other antidepressants, opioids, and sympathomimetic agents, has relegated irreversible MAOIs to a third-line role in contemporary practice despite their potentially superior efficacy in treatment-resistant depression and atypical depression [61].

The reversible MAOI moclobemide carries a significantly reduced risk of the tyramine reaction due to its competitive and reversible mechanism, and is more widely prescribed internationally, though it remains unlicensed in the United States [61]. Selegiline, available as a transdermal patch, is licensed in the United States at lower doses for depression, exploiting the observation that at low doses it preferentially inhibits MAO-B without requiring dietary restriction, though higher doses that inhibit MAO-A do require it [61].

Pharmacists are well placed to counsel on dietary tyramine and to screen prescriptions for interacting drugs, including other antidepressants, opioids, and sympathomimetics, using current specialist guidance.

5.5. Atypical and Novel Antidepressants

The category of atypical antidepressants encompasses agents that do not fit cleanly into the preceding classes, unified by their shared clinical indication rather than by a common pharmacological mechanism.

Bupropion (Wellbutrin, Zyban) is a norepinephrine-dopamine reuptake inhibitor (NDRI) with no clinically significant serotonergic activity [62]. Its antidepressant mechanism is thus entirely outside the serotonin framework, yet it demonstrates efficacy comparable to SSRIs in controlled trials [52]. This observation is pharmacologically inconvenient for any hypothesis that positions serotonin as the essential mediating pathway for antidepressant response. Bupropion has a lower incidence of sexual dysfunction and weight gain than SSRIs, which may reflect its absence of serotonergic activity [62]. It also holds regulatory approval for smoking cessation under the brand name Zyban, and its use is associated with a dose-dependent reduction in seizure threshold, which is an important contraindication in patients at risk for seizures [62].

Mirtazapine (Remeron) works through a mechanism that is architecturally different from either reuptake inhibition or enzyme inhibition. It acts as a presynaptic alpha-2 adrenergic autoreceptor antagonist, which disinhibits the release of norepinephrine and serotonin, and it additionally blocks postsynaptic serotonin 5-HT₂ and 5-HT₃ receptors and histamine H₁ receptors [63]. The H₁ antagonism produces pronounced sedation and significant appetite stimulation leading to weight gain, effects that can be clinically exploited in depressed patients with insomnia and anorexia but that are problematic in others [63]. Mirtazapine's pharmacological profile is so different from SSRIs or SNRIs that its comparable antidepressant efficacy further undercuts the specificity of any single-target mechanistic account of depression [52].

Trazodone is a serotonin antagonist and reuptake inhibitor (SARI) with complex pharmacology including 5-HT_{2A} antagonism, weak SERT inhibition, and H₁ and alpha-1 adrenergic blockade [64]. Its antidepressant efficacy at higher doses is modest, and in contemporary practice it is most commonly prescribed at low doses as a sedative-hypnotic, exploiting its antihistaminergic and alpha-1 blocking properties to promote sleep without the dependence risk of benzodiazepines [64].

Agomelatine represents perhaps the most pharmacologically distinct antidepressant available, combining melatonin MT₁ (Melatonin receptor type 1) and MT₂ (Melatonin receptor type 2) receptor agonism with serotonin 5-HT_{2C} antagonism [65]. It has no direct effect on monoamine reuptake or monoamine oxidase. Its clinical trials have demonstrated antidepressant efficacy comparable to SSRIs in some studies, though concerns about hepatotoxicity and a requirement for liver function monitoring have limited its uptake [65]. From a mechanistic perspective,

agomelatine's antidepressant efficacy achieved entirely outside the serotonin reuptake framework constitutes strong evidence that antidepressant response can be produced through pathways that have nothing to do with the serotonin hypothesis [65].

The collective pharmacological diversity of the antidepressant class is, in itself, a notable finding, though it should not be over-interpreted. When drugs as mechanistically distinct as serotonin reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, alpha-2 receptor antagonists, monoamine oxidase inhibitors, and melatonin receptor agonists all produce comparable antidepressant efficacy in clinical trials [52], one interpretation is that no single neurochemical target constitutes the mechanism of antidepressant action. However, an equally parsimonious alternative is that these diverse upstream mechanisms converge on a common downstream pathway. The most developed version of this alternative is the neurotrophic hypothesis, which proposes that chronic stress reduces brain-derived neurotrophic factor (BDNF) expression in limbic structures such as the hippocampus and prefrontal cortex, and that effective antidepressants of multiple mechanistic classes share the downstream effect of restoring BDNF signaling and synaptic plasticity in these regions [66]. If correct, this would mean the diversity of receptor-level mechanisms is fully compatible with, rather than evidence against, a unifying causal account of antidepressant action. The neurotrophic hypothesis, however, faces the same evidentiary limitation documented throughout this review for other psychiatric mechanistic hypotheses: it has not been established that reduced BDNF or synaptic plasticity is a primary cause of depression rather than a general correlate of chronic stress, a consequence of the depressive state itself, or a downstream marker of treatment response measured only in already-treated patients. The mechanistic diversity of effective antidepressants therefore does not, on its own, establish either that no unifying mechanism exists or that one does; it establishes only that the causal story for antidepressant action remains open at both the receptor level and the proposed convergent downstream level [12,38,66]. For bupropion, pharmacists can screen for seizure risk factors before dispensing, given its dose-dependent reduction in seizure threshold.

6. The Placebo Problem: What Are Antidepressants Really Doing?

No critical examination of antidepressant pharmacotherapy can be complete without direct engagement with the placebo literature, which represents one of the most consequential and uncomfortable bodies of evidence in all psychiatric research [67,68].

In 2008, Irving Kirsch and colleagues published a landmark meta-analysis of FDA-submitted clinical trial data for four widely prescribed antidepressants: fluoxetine, venlafaxine, nefazodone, and paroxetine [30]. Crucially, the authors obtained their data through Freedom of Information Act requests to the FDA rather than from the published literature, allowing them to include both published and unpublished trials. This methodological decision was essential because the psychiatric trial literature is severely affected by publication bias, the systematic tendency for positive trials to be published and negative trials to be suppressed or filed away [69].

Turner and colleagues had documented this bias in a parallel 2008 analysis in the *New England Journal of Medicine*, also using FDA data. Among 74 FDA-registered antidepressant studies, 31% involving 3449 study participants were not published, and the effect sizes extracted from published journal articles were inflated by 32% overall compared to the effect sizes calculated from the complete FDA dataset that included both published and unpublished trials [69]. For individual drugs, the inflation of apparent efficacy ranged from 11% to 69% [69]. This means that the scientific literature available to prescribers systematically overstates the efficacy of antidepressants relative to what the complete data show.

Returning to Kirsch's analysis, the drug-placebo difference across all trials for all four antidepressants was found to be 1.8 points on the 17-item Hamilton Depression Rating Scale (HAM-D-17) [30]. The threshold for clinical significance established by the UK National Institute for Health and Care Excellence (NICE) at the time was a difference of 3 points on the HAM-D-17 [30]. The mean antidepressant-placebo difference, which is to say the pharmacological effect of the drug above and beyond the placebo response, did not reach the established criterion for clinical significance [30]. Only in patients with very severe depression did the drug-placebo difference approach clinical significance, and this appeared to reflect a decrease in placebo response rather than an increase in drug response in this subgroup [30]. Both the drug and placebo groups improved substantially: approximately 8.3 points on the HAM-D-17 for patients receiving placebo and 10.1 points for patients receiving active medication [46]. The fact that placebo patients improved by more than 80% of the amount that medicated patients improved is a finding of substantial clinical importance [46].

It must be acknowledged that Kirsch's conclusions attracted methodological criticism, and several re-analyses were conducted by researchers who disputed his interpretation of the data [33]. These critiques raised legitimate concerns about the NICE threshold for clinical significance and about the statistical approaches used. However, even

critics who recalculated the drug-placebo difference arrived at figures (2.18 to 2.68 HAMD-17 points) that remained below or at the margins of clinically meaningful effect [33]. A more recent and considerably larger re-examination of this question came from Stone et al. [70], who conducted an individual-participant-data analysis of 232 FDA-submitted trials comprising 73,388 patients, the largest patient-level dataset assembled on this question to date. Rather than a single average drug-placebo difference, the authors modeled a trimodal distribution of patient responses and found that a meaningful subgroup, approximately 15% of patients, experienced a large, substantially drug-specific improvement, while the majority showed either a non-specific or minimal response similar across drug and placebo arms. This finding complicates any simple claim that antidepressant response is uniformly non-specific: it suggests that a genuine drug effect exists for an identifiable subgroup of patients, even as it confirms that most of the aggregate improvement seen in trials reflects non-drug-specific factors. The fundamental empirical finding from this literature, that the average drug-placebo difference is small and that response is highly heterogeneous across patients, has not been successfully refuted, but the heterogeneity itself is a finding of practical importance that a focus on average effects can obscure [46,69].

What explains this large placebo response in depression trials? Multiple mechanisms have been proposed, including the natural remitting course of many depressive episodes, regression to the mean following assessment at symptom peak, the therapeutic effects of clinical attention and monitoring, and expectation-driven physiological and psychological changes [46]. These non-pharmacological mechanisms of improvement are real, clinically significant, and entirely consistent with a model in which psychiatric medications are producing some of their observable benefit through channels other than the correction of a specific neurochemical deficit [46].

The publication bias problem identified by Turner and colleagues [69] has additional implications beyond its effect on apparent efficacy. It means that prescribers, policymakers, and patients have been making decisions about antidepressant therapy based on a systematically distorted evidence base, one that portrays these drugs as more effective than the complete evidence shows them to be [69]. This is an ethical problem as much as a scientific one.

7. Antipsychotics

7.1. First-Generation (Typical) Antipsychotics

First-generation antipsychotics (FGAs), also termed typical antipsychotics or neuroleptics, include chlorpromazine, haloperidol, fluphenazine, perphenazine, thioridazine, trifluoperazine, and flupentixol [71]. Their primary mechanism of action is dopamine D2 receptor blockade, particularly in the mesolimbic pathway, which represents the pharmacological basis of the dopamine hypothesis of schizophrenia [37].

The dopamine hypothesis of schizophrenia proposes that psychosis results from excess dopaminergic activity in mesolimbic circuits, producing the positive symptoms of hallucinations, delusions, and thought disorder [37]. In its more refined versions, the hypothesis additionally posits prefrontal hypodopaminergia as the mechanism of negative symptoms (social withdrawal, flat affect, avolition) and cognitive impairment [37]. Like the serotonin hypothesis of depression, the dopamine hypothesis was not derived from direct measurement of dopaminergic abnormality in psychotic patients and then used to design a therapeutic intervention. Rather, it was constructed retrospectively after chlorpromazine was found to suppress psychotic symptoms, and the observation that antipsychotic potency correlated with D2 receptor binding affinity was taken as pharmacological evidence for the hypothesis [37].

The dopamine hypothesis has been subjected to rigorous critical examination. Howes and Kapur (2009) published a comprehensive version of the hypothesis, designated “Version III: the Final Common Pathway,” reviewing over 6700 articles on dopamine and schizophrenia and proposing a framework in which multiple environmental and genetic risk factors converge on striatal presynaptic dopaminergic dysfunction [37]. While acknowledging that this model was a substantial advance, the authors noted that much of the evidence supporting earlier versions of the hypothesis relied on inferences from animal studies or other clinical conditions, that there was no direct evidence for low dopamine levels in the frontal cortex, and that direct evidence for elevated striatal dopaminergic function was limited [37].

Hengartner and Moncrieff published a detailed methodological critique in *Frontiers in Psychiatry* in 2018, arguing that the evidence supporting the dopamine hypothesis is fundamentally compromised by the confounding effects of prior antipsychotic use, by methodological limitations in neuroimaging studies, and by the failure to account for environmental adversity as a primary driver of dopaminergic changes [13]. Their central observation was methodologically decisive: most studies demonstrating dopaminergic abnormalities in people with schizophrenia have been conducted in patients who are already taking antipsychotic medications, making it impossible to determine whether the observed neurochemical changes reflect the underlying illness or the pharmacological effect of the drugs

themselves [13]. They further noted that a comprehensive meta-analysis of randomized trials had demonstrated that antipsychotic medication does not prevent the development of schizophrenia in persons at ultra-high risk of psychosis [13]. If schizophrenia were truly caused by dopaminergic dysregulation that antipsychotics correct, one would expect prophylactic antipsychotic treatment in at-risk individuals to prevent illness onset. The consistent failure of this prediction is a significant challenge to the causal version of the dopamine hypothesis [13].

FGAs are demonstrably effective at suppressing the positive symptoms of psychosis. Their clinical utility in reducing hallucinations, delusions, and agitation is supported by substantial evidence and is not disputed by this review. What is disputed is the claim that this efficacy reflects the correction of a known dopaminergic disease mechanism. The available evidence is more consistent with the interpretation that D2 blockade produces a general reduction in dopaminergic signal transmission that nonspecifically suppresses psychotic symptomatology, without addressing an identified etiological cause [13].

The side effect profile of FGAs is severe and warrants detailed attention. Extrapyramidal side effects (EPS) arise directly from D2 receptor blockade in the nigrostriatal pathway and include acute dystonia (painful involuntary muscle contractions), drug-induced parkinsonism (tremor, rigidity, bradykinesia), and akathisia, a state of profound inner motor restlessness that patients consistently describe as one of the most unbearable aspects of antipsychotic treatment [72]. Long-term use of FGAs carries a substantial risk of tardive dyskinesia (TD), a potentially irreversible hyperkinetic movement disorder characterized by involuntary, repetitive movements predominantly affecting the orofacial region but capable of involving any body part [72]. A review published in *CNS Drugs* found an estimated TD prevalence of approximately 20% in patients receiving atypical antipsychotics and higher rates with typical antipsychotics, noting that the pathophysiology of TD is currently unknown and that no general management guidelines can be established [72]. A review reported a mean prevalence of tardive dyskinesia of approximately 20% to 25% among antipsychotic-treated individuals, with reported ranges spanning 15% to 50% in various settings [73]. The development of TD after prolonged antipsychotic use can persist or worsen even after drug discontinuation, representing an irreversible neurological consequence of a treatment prescribed for a condition whose biological mechanism remains unknown [72,73].

7.2. Second-Generation (Atypical) Antipsychotics

Second-generation antipsychotics (SGAs) were introduced in the 1990s with the claim that their pharmacological differentiation from FGAs, primarily the addition of 5-HT_{2A} receptor antagonism alongside D2 blockade, would produce superior efficacy, particularly for negative symptoms and cognitive function, with a more favorable side effect profile [74]. This class includes clozapine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, asenapine, lurasidone, and paliperidone. Aripiprazole is pharmacologically distinct from other SGAs in that it acts as a partial agonist at D2 receptors rather than a pure antagonist, and also as a partial agonist at 5-HT_{1A} receptors [75].

The clinical promise of SGAs was subjected to rigorous real-world evaluation in the landmark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a large-scale double-blind effectiveness trial funded by NIMH, published in the *New England Journal of Medicine* in 2005 [74]. The study enrolled 1493 patients with chronic schizophrenia at 57 sites across the United States and randomly assigned them to olanzapine, quetiapine, risperidone, ziprasidone, or the first-generation agent perphenazine, followed for up to 18 months. The primary outcome was time to all-cause treatment discontinuation, reflecting the real-world composite of efficacy, tolerability, and patient preference [74].

The CATIE findings significantly revised the optimistic claims that had driven the widespread adoption of SGAs. Olanzapine demonstrated modest superiority over other agents in time to discontinuation for any cause, but this advantage was substantially offset by metabolic side effects: olanzapine was associated with the greatest weight gain, most pronounced increases in hemoglobin A1c, and most significant lipid abnormalities compared to other study drugs [74]. Critically, perphenazine, a first-generation antipsychotic included to provide a comparator from the older class, did not differ significantly from most SGAs in time to discontinuation, directly challenging the marketed superiority of the newer generation [74]. The conclusion that the superiority of SGAs over FGAs was far less clear in real-world effectiveness than in industry-sponsored efficacy trials was a finding of considerable importance for prescribing practice and for the commercial narrative that had driven the SGA market [74]. A network meta-analysis of 127 trials found no clear differences between antipsychotics for relapse prevention, and concluded that the choice for maintenance treatment should be guided mainly by tolerability [76].

Clozapine occupies a unique position within the SGA class by virtue of its demonstrated superior efficacy in treatment-resistant schizophrenia, defined as psychosis that fails to respond to at least two adequate trials of other

antipsychotics [77]. What is pharmacologically paradoxical about clozapine is that it has a relatively weak D2 receptor affinity compared to many other antipsychotics, yet it is the most clinically effective agent in the most refractory cases [37]. This observation presents a direct challenge to the D2-centric dopamine hypothesis: if D2 blockade were the essential mechanism of antipsychotic action, the drug with the weakest D2 affinity should not be the most effective agent in difficult-to-treat cases [37]. Clozapine's pharmacological profile includes antagonism at multiple dopamine receptor subtypes (D4 more than D2), serotonin 5-HT_{2A}, muscarinic, histaminergic, and alpha-adrenergic receptors, suggesting that its therapeutic superiority may arise from a complex polysynaptic mechanism that existing theory cannot fully account for [77].

A separate and more recent line of research has examined oxidative stress and inflammation as contributors to schizophrenia pathophysiology, offering another candidate mechanism alongside the dopamine hypothesis. A narrative review of 76 studies found that individuals with schizophrenia show increased oxidative damage to lipids and reduced non-enzymatic antioxidant capacity, with antioxidant deficits detectable even before psychosis onset in at-risk individuals [78]. A meta-analysis found that antioxidant status was more impaired in unmedicated than medicated patients, with markers such as catalase and glutathione lower only in the unmedicated group, suggesting that antipsychotic treatment may be associated with partial improvement in antioxidant defenses [79]. As with the dopamine and serotonin hypotheses, however, it remains unclear whether oxidative stress is a cause of psychiatric illness, a consequence of it, or an artifact of prior antipsychotic exposure in the patients studied, since disentangling illness effects from medication effects requires comparison with drug-naïve cohorts that are difficult to assemble at scale. This line of research illustrates that the mechanistic picture in psychiatry continues to evolve, but also that new candidate mechanisms face confounding and directionality problems similar to those already documented for dopamine and serotonin.

Clozapine carries a risk of agranulocytosis in approximately 1% to 2% of patients, a potentially fatal reduction in white blood cells requiring mandatory hematological monitoring, typically weekly for the first 18 weeks and monthly thereafter [77]. The burden of this monitoring program is significant for patients and health systems, and the risk-benefit calculation must be carefully individualized.

The metabolic consequences of SGAs, particularly olanzapine and clozapine, constitute a major and underappreciated public health problem. A systematic review confirmed that the life expectancy of people with schizophrenia is reduced by approximately 20%, with 60% of excess mortality attributable to physical illness rather than suicide or accidents [80]. A meta-analysis of 135 studies found all-cause mortality was increased in people with schizophrenia compared with non-schizophrenia controls (RR 2.52, 95% CI 2.38 to 2.68) [81]. Antipsychotic-induced metabolic syndrome, comprising weight gain, dyslipidemia, glucose intolerance, and hypertension, is a major contributor to this physical health burden and premature mortality [80]. A network meta-analysis published in *World Psychiatry* in 2023 documented the mid- to long-term metabolic effects of antipsychotics across randomized controlled trials, confirming that metabolic side effects are a significant and clinically consequential feature of long-term antipsychotic use, with substantial variation across agents [82]. Individuals with schizophrenia are approximately twice as likely to die from cardiovascular disease compared to the general population, and the documented average reduction in life expectancy of over 20 years is substantially attributable to cardiometabolic consequences of the very medications prescribed to treat their psychiatric condition [80].

This is perhaps the starkest illustration of the core problem this review seeks to document. Patients who are prescribed antipsychotics for a condition whose biological mechanism is unknown receive drugs that suppress their symptoms but simultaneously increase their cardiovascular risk, metabolic burden, and risk of irreversible neurological injury from tardive dyskinesia. These medications manage symptoms effectively for many patients; what they do not do, based on the evidence reviewed here, is correct a confirmed underlying biological cause, and the resulting cardiometabolic and neurological costs of long-term treatment warrant the same clinical attention as the psychiatric benefit itself.

Given the reduced life expectancy and cardiometabolic burden in schizophrenia, pharmacists can help coordinate baseline and follow-up monitoring of weight, blood pressure, glucose, and lipids for patients on second-generation antipsychotics, ask about involuntary movements and akathisia at review, and, for clozapine, confirm that hematological monitoring is current before supply where the health system allows. Where a patient and prescriber consider dose reduction, pharmacists can support adherence to the agreed plan, while noting that the trial discussed above found gradual dose reduction was associated with a higher risk of severe relapse than maintenance treatment.

8. Mood Stabilizers

8.1. Lithium

Lithium remains the gold-standard pharmacological treatment for long-term prophylaxis of bipolar disorder [83,84] despite being one of the oldest psychotropic agents in contemporary use, first introduced into psychiatry in 1949 through the serendipitous animal experiments of John Cade [9,10], although the degree to which the discovery was purely serendipitous has been debated [85]. It is the only element on the periodic table prescribed as a psychiatric medication.

Lithium's mechanism of action is complex, pleiotropic, and incompletely understood despite more than seven decades of research [39]. The most extensively studied target is glycogen synthase kinase 3 beta (GSK-3 beta), a serine-threonine kinase that regulates multiple intracellular signaling pathways involved in synaptic plasticity, apoptosis, circadian rhythm regulation, and inflammatory response [39]. Lithium inhibits GSK-3 beta directly by competing with magnesium at the active site, and indirectly by promoting inhibitory phosphorylation of the enzyme through Akt kinase pathways [39]. Additional documented mechanisms include inhibition of inositol monophosphatase (IMPase), which depletes cellular inositol and disrupts phosphatidylinositol signaling cascades, modulation of brain-derived neurotrophic factor (BDNF) expression, effects on circadian clock gene expression including CLOCK and BMAL1, and attenuation of oxidative stress through multiple pathways [39,86].

Despite this mechanistic richness, a critical limitation persists. The specific processes through which lithium's therapeutic effects occur and are maintained in bipolar disorder remain unclear [39]. Even GSK-3 beta inhibition, the most compelling mechanistic candidate, cannot be confirmed as the mechanism responsible for mood stabilization, as lithium also inhibits inositol monophosphatase, several structurally related phosphomonoesterases, phosphoglucomutase, and the scaffolding function of beta-arrestin-2, and it is not known which of these targets is responsible for the behavioral or therapeutic effects of lithium in vivo [87]. This is an extraordinary admission for a drug that has been in continuous clinical use for more than 75 years. We can describe what lithium does biochemically at multiple molecular targets; we cannot identify which of those biochemical effects produces mood stabilization, and we therefore cannot claim with scientific accuracy that lithium corrects a known pathophysiological process in bipolar disorder.

The clinical utility of lithium is nonetheless real and, in certain respects, among the most robustly supported in all of psychiatry. Meta-analyses confirm its efficacy in reducing the frequency and severity of both manic and depressive episodes in bipolar disorder, and its anti-suicidal properties, which appear to extend beyond its mood-stabilizing effects, are among the most replicated findings in psychopharmacology [88]. These clinical strengths do not require the mechanism to be fully understood; they require only that the empirical evidence of benefit be honest. The distinction the author wishes to maintain is between acknowledging lithium's clinical value and accepting the false premise that we understand precisely why it works.

Lithium has a narrow therapeutic index, requiring regular serum level monitoring given the small margin between therapeutic (0.6 to 1.2 mmol/L) and toxic concentrations [88]. Acute toxicity produces neurological symptoms including tremor, ataxia, dysarthria, and confusion, which can progress to seizures, renal failure, and death [88]. Long-term use is associated with thyroid dysfunction, occurring in approximately 20% to 40% of patients, and chronic kidney disease, with a small but significant proportion of long-term lithium users developing progressive renal impairment requiring eventual dialysis [88].

Pharmacists can reinforce regular serum level, renal, and thyroid monitoring, counsel patients on signs of toxicity, and screen for drugs that alter lithium clearance, since pharmacokinetic and pharmacodynamic interactions can affect the success of long-term treatment.

8.2. Anticonvulsant Mood Stabilizers

Valproate (valproic acid, sodium valproate, divalproex sodium) and lamotrigine are the most widely used anticonvulsant mood stabilizers. Both were originally developed as antiepileptic agents, and their mood-stabilizing properties were discovered through clinical observation in patients with epilepsy who also had mood symptoms [89].

Valproate's pharmacological mechanisms include enhancement of GABAergic inhibition through increased GABA synthesis and reduced GABA catabolism, inhibition of voltage-gated sodium channels, and inhibition of histone deacetylases (HDACs), which produce epigenetic modifications affecting gene expression in ways relevant to neuroplasticity and neuroprotection [89]. Which of these mechanisms is responsible for mood stabilization in bipolar disorder is not established. Valproate is effective for acute mania and for the prevention of manic episodes, but is less effective for the depressive phase of bipolar disorder [88,89].

The most serious safety concern with valproate is its teratogenic profile. Valproate is associated with the highest rate of major congenital malformations among commonly used mood stabilizers, with an estimated 6.2% to 16% rate of major congenital malformations in exposed pregnancies [90]. The risk of neural tube defects with valproate

exposure is approximately 1% to 5%, compared with approximately 0.5% to 1% for carbamazepine and background rates of 0.1% to 0.2% in the general population [90]. Furthermore, children exposed to valproate in utero show significantly reduced cognitive outcomes, with reduced IQ scores, behavioral problems, and an increased risk of autism spectrum disorder documented in longitudinal follow-up studies [91]. The FDA issued a safety warning regarding fetal IQ reduction in 2013 and reclassified valproate from pregnancy category D to category X for migraine prophylaxis in pregnancy [92]. Despite this, valproate continues to be prescribed to women of childbearing age in many settings, a practice that several national guidelines have moved to restrict but which remains widespread [90,91].

Lamotrigine acts primarily through voltage-gated sodium channel inhibition, reducing neuronal excitability and inhibiting the presynaptic release of glutamate [89]. It is particularly effective for the depressive phase of bipolar disorder, making it pharmacologically complementary to valproate in a bipolar treatment regimen [88]. The most significant adverse effect of lamotrigine is a potentially life-threatening skin reaction, Stevens-Johnson syndrome and toxic epidermal necrolysis, which occurs in approximately 0.1% of adult patients and more frequently in pediatric patients, necessitating slow titration protocols designed to minimize this risk [89].

The fact that agents as pharmacologically diverse as lithium (a monovalent cation), valproate (a branched-chain fatty acid), lamotrigine (a phenyltriazine), carbamazepine (an iminostilbene), and quetiapine (an atypical antipsychotic) all carry evidence for mood stabilization in bipolar disorder further illustrates that bipolar disorder's biological substrate cannot be attributed to any single, identifiable neurochemical system. The convergence of mechanistically diverse agents on a common clinical outcome suggests either that bipolar disorder involves multiple simultaneously dysregulated systems, or that "mood stabilization" is a non-specific pharmacological phenomenon that can be produced through diverse biochemical perturbations whose final common clinical pathway is not yet understood [88].

Pharmacists can ensure that women of childbearing age understand the teratogenic risk, that valproate should not be taken by non-pregnant women of childbearing age unless essential and that effective contraception should be used, and that women who are pregnant and taking it should not stop suddenly but should speak to their prescriber promptly. For lamotrigine, pharmacists can reinforce slow titration and counsel patients to report a rash immediately.

9. Anxiolytics and Sedative-Hypnotics

9.1. Benzodiazepines

Benzodiazepines are among the most widely prescribed psychotropic medications in the world [16,29], although sales data suggest that their use has been stable or declining in some regions [15]. These are used for the acute management of anxiety disorders, panic disorder, insomnia, alcohol withdrawal, seizure disorders, and procedural sedation [15]. The class includes diazepam (Valium), lorazepam (Ativan), alprazolam (Xanax), clonazepam (Klonopin), temazepam (Restoril), nitrazepam, oxazepam, and many others. Their primary mechanism of action is positive allosteric modulation of the GABA-A receptor, the principal inhibitory ligand-gated ion channel in the mammalian central nervous system [93,94].

Under normal physiological conditions, the inhibitory neurotransmitter GABA binds to GABA-A receptors and opens chloride ion channels, producing membrane hyperpolarization and neuronal inhibition. Benzodiazepines bind to an allosteric site at the interface of alpha and gamma subunits on the GABA-A receptor, distinct from the GABA binding site, where they enhance the receptor's sensitivity to GABA by increasing the frequency of chloride channel opening [93,94]. The molecular pharmacology of this interaction is among the best characterized in psychopharmacology: the binding site has been crystallographically mapped, the subunit selectivity of different benzodiazepines has been determined, and the downstream electrophysiological consequences have been thoroughly documented [93,94].

This molecular clarity does not, however, translate into validation of any specific etiological hypothesis about anxiety disorders. The fact that GABAergic enhancement reliably reduces anxiety does not establish that anxiety disorders are caused by a primary deficiency of GABA or by constitutive underactivity of GABA-A receptors in anxious individuals. GABAergic dysfunction is implicated in anxiety disorders, but the nature and directionality of this relationship remain uncertain, and there is no confirmed etiological model of any anxiety disorder based on a specific GABAergic lesion [93,94].

The clinical limitations of benzodiazepines are well established and represent a significant iatrogenic problem [95]. A comprehensive review on benzodiazepine tolerance published in *Advances in Pharmacological Sciences* documented that tolerance to the sedative and anticonvulsant effects develops relatively quickly with repeated use, while the situation for anxiolytic and amnesic tolerance is more complex and variable [93]. Physical dependence

occurs with regular use, manifesting as a characteristic withdrawal syndrome upon discontinuation that includes rebound anxiety more severe than the original presenting complaint, insomnia, tremor, diaphoresis, autonomic instability, perceptual disturbances, and, in severe cases, generalized tonic-clonic seizures that can be life-threatening [93]. A review published in *Molecular Psychiatry* in 2026 synthesized current knowledge on benzodiazepine tolerance, concluding that prolonged benzodiazepine administration frequently results in the development of tolerance arising from complex neuroadaptive processes that induce long-lasting reorganization of neural circuits regulating stress responsiveness, arousal, and reward processing [96].

A review in *Frontiers in Psychiatry* on GABA-A receptor subtypes and benzodiazepine misuse documented that alpha-1 containing GABA-A receptors play an integral role in benzodiazepine-induced plasticity in reward-related brain areas and may be involved in the development of tolerance and dependence [94]. These neuroadaptive changes mean that benzodiazepines prescribed to control anxiety may ultimately worsen anxiety through chronic neuroadaptation, creating a pharmacologically self-defeating dynamic in many patients: the drug that was prescribed to treat anxiety creates a neurological state in which cessation of the drug generates more anxiety, often more severe, than the patient experienced before starting it [93,94,96]. This is not a cure for anxiety; it is the superimposition of a drug-dependent neurological condition on top of the original disorder.

Because physical dependence can develop within days to weeks even at prescribed doses, pharmacists can counsel on expected duration of use and withdrawal risks at the point of supply and identify long-term users for review. Deprescribing was more successful when supported by non-pharmacological methods (rate ratio 3.26) but the evidence was of very low to low quality, and low-certainty evidence suggests that patient education and a pharmacist-led educational intervention may increase discontinuation. Tapering should be gradual, individualized, and coordinated with the prescriber.

9.2. Non-Benzodiazepine Hypnotics

The Z-drugs (zolpidem, zaleplon, eszopiclone) were developed with the hypothesis that by targeting specific GABA-A receptor subtypes, particularly the alpha-1 subunit-containing receptors that mediate sedation, it might be possible to achieve hypnotic efficacy with reduced dependence potential relative to non-selective benzodiazepines [94]. This hypothesis was partially borne out: Z-drugs do carry a somewhat reduced dependence profile compared to classical benzodiazepines in most patients. However, they are not dependence-free, and long-term use is associated with tolerance, withdrawal phenomena, rebound insomnia upon discontinuation, and, in the case of zolpidem, complex sleep behaviors including sleep-walking, sleep-driving, and sleep-eating that carry significant safety risks [94]. The theoretical rationale for their development, subunit-selective GABA-A modulation, was scientifically reasonable; the clinical reality has been a more modest improvement over classical benzodiazepines than was hoped.

For Z-drugs, pharmacists can counsel about complex sleep behaviors such as sleep-walking and sleep-driving, and about short-term use (up to four weeks for sedating hypnotics in current guidance). For buspirone, they can explain that benefit takes one to two weeks of consistent use, so that patients do not stop early or take extra doses.

9.3. Buspirone

Buspirone is a non-benzodiazepine anxiolytic that acts primarily as a partial agonist at serotonin 5-HT_{1A} receptors, with additional D₂ receptor activity [97]. Its anxiolytic mechanism is presumed to involve modulation of serotonergic tone in the raphe-limbic circuit, a hypothesis consistent with serotonin's involvement in anxiety regulation, though the causal relationship between 5-HT_{1A} activity and anxiety reduction remains inferential rather than proven [97]. Buspirone does not produce the sedation, psychomotor impairment, or physical dependence characteristic of benzodiazepines, but it requires one to two weeks of consistent administration before anxiolytic effects emerge, limiting its utility in acute anxiety states [97]. Its comparable efficacy to benzodiazepines in generalized anxiety disorder in controlled trials, despite an entirely different pharmacological mechanism, again illustrates the non-specificity of pharmacological approaches to anxiety disorders [97].

10. Stimulants and ADHD Medications

10.1. Methylphenidate

Methylphenidate (Ritalin, Concerta, Methylin) is the most widely prescribed psychostimulant for attention-deficit/hyperactivity disorder (ADHD) globally. Its primary mechanism involves concurrent blockade of the dopamine

transporter (DAT) and norepinephrine transporter (NET), thereby inhibiting the reuptake of dopamine and norepinephrine from the synaptic cleft back into presynaptic neurons and increasing extracellular concentrations of both neurotransmitters in key brain regions including the prefrontal cortex and striatum [98]. Unlike amphetamines, methylphenidate does not promote vesicular release of dopamine; its mechanism is limited to transporter inhibition [98].

Recent cryo-electron microscopy studies have provided high-resolution structural characterization of how methylphenidate binds to the orthosteric site of the human dopamine transporter, stabilizing it in an outward-facing conformation that physically prevents dopamine reuptake [98]. This is among the more molecularly precise mechanistic characterizations in psychopharmacology, and it confirms that the drug does what its pharmacological classification claims: it blocks dopamine and norepinephrine reuptake.

However, the existence of a well-characterized molecular target does not validate the broader etiological hypothesis. The use of methylphenidate in ADHD is rationalized by the catecholamine hypothesis of ADHD, which proposes that ADHD results from dopaminergic and noradrenergic dysfunction, particularly in prefrontal circuits mediating executive function and attention regulation [98]. This hypothesis is supported by neuroimaging studies showing structural and functional differences in prefrontal and striatal circuits in ADHD, and by genetic studies implicating DAT and dopamine receptor genes in ADHD susceptibility [99]. The evidence is more substantial than for the serotonin hypothesis of depression, but it shares the same fundamental limitation: we know there are neurobiological correlates of ADHD, but we have not established that any specific catecholaminergic deficit is the primary cause of ADHD rather than a correlated biological feature, a consequence of the condition, or an artifact of the heterogeneous ADHD diagnostic category itself [7,100].

A critical Cochrane review on stimulant medications for ADHD in children and adolescents rated the certainty of evidence supporting the efficacy of methylphenidate and other stimulants as low, primarily due to limitations in study quality, inconsistency of results, and imprecision in outcome measurement [101]. This is not a fringe assessment. It reflects the consensus of the Cochrane Collaboration, widely regarded as the most rigorous systematic review body in clinical medicine. The conclusion that the certainty of evidence is low does not mean methylphenidate is ineffective; it means that the strength of the evidence base is insufficient to make high-confidence claims about long-term outcomes, given the quality of available research [101].

Methylphenidate's cardiovascular profile warrants attention in prescribing practice. It produces dose-dependent increases in heart rate and blood pressure, and concerns have been raised about cardiovascular events in patients with pre-existing cardiac conditions [98]. In terms of abuse potential, methylphenidate's mechanism of increasing extracellular dopamine in the striatum, the neural substrate of reinforcement and reward, is pharmacologically analogous to the mechanism of cocaine, though methylphenidate's slower pharmacokinetic profile reduces but does not eliminate its reinforcing properties and potential for misuse [98].

10.2. Amphetamine-Based Agents

Amphetamines, including mixed amphetamine salts (Adderall), lisdexamfetamine (Vyvanse), and dextroamphetamine (Dexedrine), share a broader mechanism than methylphenidate. In addition to DAT and NET inhibition, amphetamines actively promote the vesicular release of dopamine and norepinephrine through reversal of transporter direction, and inhibit vesicular monoamine transporter 2 (VMAT-2), leading to greater and more sustained increases in synaptic monoamine concentrations than methylphenidate alone [100]. This broader mechanism of monoamine displacement, rather than simple reuptake inhibition, is associated with greater reinforcing properties and higher dependence potential than methylphenidate [100].

The clinical pharmacology of amphetamines in ADHD follows the same catecholaminergic rationale as methylphenidate, and the same mechanistic limitations apply. Lisdexamfetamine is a prodrug that requires enzymatic cleavage in the bloodstream to release active d-amphetamine, a pharmacological design intended to reduce abuse potential by providing a slower-onset, longer-duration drug effect and by making intravenous or intranasal abuse pharmacologically unproductive [100].

10.3. Non-Stimulant ADHD Medications

Atomoxetine (Strattera) is a selective NET inhibitor approved for ADHD that does not carry the scheduled controlled substance classification of stimulants. Its anxiolytic and blood pressure effects are consistent with noradrenergic pharmacology, and its lack of significant DAT activity reduces but does not eliminate cardiovascular concerns [100]. Guanfacine (Intuniv) and clonidine (Kapvay) are alpha-2A adrenergic receptor agonists that reduce

norepinephrine release through presynaptic autoreceptor stimulation, producing prefrontal enhancement through a mechanism distinct from both stimulants and atomoxetine [99]. The efficacy of these mechanistically diverse non-stimulant agents in ADHD, while generally inferior to stimulants, further illustrates that ADHD symptom reduction can be achieved through multiple pharmacological routes, consistent with the heterogeneous neurobiological landscape of the disorder.

Pharmacists can monitor heart rate and blood pressure trends, screen for cardiac conditions, and counsel about misuse, diversion, and safe storage of these controlled medicines.

II. Emerging Treatments

II.1. Ketamine and Esketamine

Ketamine is a dissociative anesthetic that has attracted substantial interest as a rapid-acting antidepressant following observations of dramatic and rapid mood improvements in treatment-resistant depressed patients receiving subanesthetic intravenous infusions [102]. Esketamine (Spravato), the S-enantiomer of ketamine, received FDA approval in 2019 as an intranasal formulation for treatment-resistant depression and major depressive disorder with acute suicidal ideation, administered under clinical supervision [102]. In a randomized trial, esketamine nasal spray plus an SSRI or SNRI was superior to extended-release quetiapine plus an SSRI or SNRI for remission at week 8 (27.1% vs. 17.6%) [103].

Ketamine's primary pharmacological mechanism is open-channel blockade of N-methyl-D-aspartate (NMDA) glutamate receptors [102]. NMDA receptor antagonism reduces the tonic inhibitory influence that GABA interneurons exert on glutamatergic pyramidal neurons, producing a transient surge of glutamate release in key cortical and limbic circuits [102]. This glutamate surge activates AMPA receptors, triggering downstream cascades including activation of the mammalian target of rapamycin (mTOR) pathway and increased synthesis and release of brain-derived neurotrophic factor (BDNF), leading to rapid synaptogenesis and restoration of synaptic density in prefrontal and hippocampal circuits that may be diminished in severe depression [102].

A comprehensive narrative review published in the *International Journal of Molecular Sciences* in 2024 synthesized the literature on ketamine's molecular actions, confirming that while the drug primarily works through NMDA receptor antagonism, its precise mechanisms remain unclear and multifaceted [104]. The review documented multiple additional ketamine targets including opioid receptor activity, effects on AMPA and metabotropic glutamate receptors, modulation of astrocytic glutamate transporter expression, and interactions with the sigma-1 receptor [104]. A parallel review in *Neuropsychopharmacology* in 2024 by Krystal, Kavalali, and Monteggia noted that two partially distinct downstream pathways have been identified, one involving eukaryotic elongation factor 2 kinase (eEF2K) suppression leading to BDNF translation de-suppression, and another involving mTOR activation through AMPA receptor-driven glutamate surges, and that the relative contributions of these pathways to ketamine's rapid and sustained antidepressant effects remain to be determined [102].

Ketamine does not cure depression. Its antidepressant effects are rapid in onset, typically within hours to days, but time-limited, typically lasting one to two weeks following a single infusion, necessitating repeated administration to maintain benefit [102]. Questions about optimal dosing schedules, long-term safety including risks of bladder toxicity, cognitive effects, and potential for dissociative addiction, and the extent to which ketamine's antidepressant effects can be separated from its dissociative and psychotomimetic side effects, remain unresolved [102,104]. Ketamine's emergence as a treatment for depression represents an important clinical advance for a population with treatment-resistant illness, but it also introduces a new set of mechanistic and safety questions that the field has not yet answered.

Because esketamine is administered under clinical supervision, pharmacists in relevant settings can support protocols for supervised administration and counsel on expected dissociative effects and the need for repeated treatment.

II.2. Psilocybin and Psychedelic-Assisted Therapy

Psilocybin, the active psychedelic compound in certain species of mushroom, has experienced a significant resurgence of clinical research interest since the mid-2010s, following decades of research prohibition. Phase 2 clinical trials have demonstrated promising antidepressant effects in both treatment-resistant depression and major depressive disorder [105]. In a trial of 233 adults with treatment-resistant depression, a single 25 mg dose reduced depression

scores more than a 1 mg dose at 3 weeks, but adverse effects were more common and the response was not sustained at 12 weeks [106].

A systematic review and meta-analysis published in *Frontiers in Psychiatry* in 2024, covering 10 studies including 524 adult patients, found a large effect size in favor of psilocybin for depression relief (Hedges' $g = -0.89$, 95% CI -1.25 to -0.53) [107]. A separate systematic review in the same journal, covering randomized controlled trials specifically in major depressive disorder, also documented significant symptom reduction compared to placebo or active comparison conditions, though the authors noted important limitations in blinding given the undeniable subjective effects of the drug [105].

Psilocybin is a prodrug rapidly dephosphorylated in vivo to psilocin, which acts primarily as a serotonin 5-HT_{2A} receptor agonist, producing its characteristic perceptual, emotional, and cognitive effects through this mechanism [107]. Neuroimaging studies have documented psilocybin-induced alterations in default mode network (DMN) activity and connectivity, and it has been proposed that psilocybin exerts its antidepressant effects partly through disruption of rigid, ruminative patterns of thought associated with excessive DMN self-referential processing in depression [107]. Carhart-Harris and colleagues published a randomized controlled trial comparing psilocybin with escitalopram for depression in the *New England Journal of Medicine* in 2021, finding that psilocybin was not inferior to escitalopram on the primary outcome and showed advantages on several secondary measures, including response rate and measures of emotional connectedness, though the trial was not powered to demonstrate superiority [108].

Despite these encouraging findings, important cautions apply. The field faces a fundamental methodological challenge in that adequate blinding is impossible in psychedelic trials given the unmistakable subjective effects of the drug [105]. Placebo response in depression trials is known to be substantial [30,46], and the enthusiastic therapeutic context, specialized clinical settings, and high therapeutic alliance that characterize psilocybin trials may amplify non-pharmacological therapeutic factors beyond what would occur in routine clinical practice [105]. The precise mechanism by which psilocybin produces antidepressant effects, if it does so independently of the therapeutic context, is not yet established [107]. Phase 3 trials are underway, and their results will provide important information, though the blinding problem will remain methodologically challenging regardless of trial design [105].

12. Cross-Cutting Analysis: The Patterns in Mechanistic Interpretation

12.1. The Pattern of Mechanism Construction

Across every drug class reviewed in this paper, a consistent pattern emerges: clinical effect precedes mechanistic explanation, and mechanistic explanation is constructed to rationalize observed clinical effect rather than to guide drug development [9,30]. This backwards epistemological sequence has produced a pharmacology that is empirically derived but mechanistically unvalidated, which is a charitable description. A less charitable but equally accurate description is that psychiatric pharmacology has spent decades claiming to correct neurochemical imbalances while lacking the evidence to identify what those imbalances are [12].

This pattern matters beyond academic interest. When a theory is constructed to explain an observation that preceded it, that theory is not independently validated by the observation it was designed to explain. The serotonin hypothesis was constructed to explain why SSRIs, discovered accidentally, improved depression. The hypothesis then cannot derive its validation from the observation that SSRIs improve depression, because the hypothesis was designed precisely to explain that observation [12,38]. Independent validation requires showing, through methods other than the drug effect itself, that serotonin deficiency characterizes depressed individuals prior to treatment. Moncrieff and colleagues' umbrella review was an attempt to provide precisely such independent validation, and it failed to find support [12].

12.2. The Diagnostic Validity Problem as an Amplifier

The diagnostic validity crisis amplifies all other problems reviewed in this paper [7]. If psychiatric diagnostic categories do not correspond to biologically distinct entities, then the following cascade of problems becomes inescapable. The neurobiological hypotheses proposed for each diagnostic category cannot be properly tested, because the category itself does not select for a biologically homogeneous population [7]. Clinical trials testing drug efficacy in DSM-defined populations include participants with heterogeneous underlying neurobiologies, obscuring mechanistic signals and producing average effects that may not reflect any individual's biology [43]. Treatment response becomes inherently unpredictable, and the current clinical reality in which prescribers cycle through multiple medications empirically until one appears to help reflects exactly this problem [52]. Patients who respond to drug A

may have a different neurobiological substrate from patients who respond to drug B despite sharing the same DSM diagnosis, but without biomarkers to identify those substrates, rational matching of patient to treatment is impossible [7].

12.3. Long-Term Outcomes and the Chronification of Treatment

A question that receives insufficient attention in the psychiatric pharmacology literature is the long-term course of mental disorders in individuals who receive sustained pharmacological treatment compared to those who do not, or who recover and discontinue [88]. The prevailing clinical model in psychiatry for conditions such as major depression, bipolar disorder, schizophrenia, and generalized anxiety disorder has increasingly moved toward long-term or lifelong maintenance pharmacotherapy to prevent relapse [88]. This model is supported by evidence from maintenance trials showing that discontinuation of pharmacotherapy is associated with higher relapse rates [88]. In a randomized trial in primary care, relapse by 52 weeks occurred in 39% of patients who maintained their antidepressant and 56% of those who discontinued, and the discontinuation group also had more withdrawal symptoms [109].

However, the interpretation of these relapse findings is complicated by the discontinuation syndrome problem. When a patient who has been taking an SSRI for two years discontinues it and experiences a return of depressive symptoms within weeks, it is clinically and scientifically ambiguous whether this represents a relapse of the underlying depressive disorder or a manifestation of antidepressant discontinuation syndrome [31]. Distinguishing between the two requires careful clinical characterization that is not routinely performed, and maintenance trial designs have been criticized for not adequately controlling for discontinuation effects [31]. If a significant portion of apparent relapse following antidepressant discontinuation is actually SSRI withdrawal, then the evidence base for long-term antidepressant maintenance would be substantially overstated [31].

Similar concerns apply to antipsychotic discontinuation. Evidence from longer-term observational studies, notably work by Harrow and colleagues following patients with schizophrenia spectrum disorders over 20 years, found that patients who discontinued antipsychotics had better long-term outcomes in several domains than those who remained on them continuously, though this finding must be interpreted cautiously given the possibility of selection effects favoring discontinuation in patients with milder illness trajectories [110]. In a randomized trial, gradual antipsychotic dose reduction did not improve social functioning and was associated with a higher risk of severe relapse than maintenance treatment [111].

12.4. Informed Consent and the Ethics of Prescribing Without Proof

The considerations documented throughout this review raise a set of ethical questions about the conditions under which it is justifiable to prescribe pharmacological agents whose mechanisms are not understood, whose diagnostic targets are not biologically validated, whose apparent efficacy is substantially inflated by publication bias, and whose long-term effects on brain structure and function are incompletely characterized.

This is not an argument against prescribing. Many patients benefit meaningfully from psychiatric medications, and the ethical calculus for an individual in acute psychiatric crisis is clear: available treatments with evidence of symptomatic relief are preferable to no treatment [18]. The ethical problem, rather, is one of informed consent and epistemic honesty. Patients are routinely told that their depression is caused by a serotonin imbalance that SSRIs will correct [12]. This is not an accurate representation of the scientific evidence [12]. Patients are told that antipsychotics correct an excess of dopamine in their brain [13]. This is not an established fact [13]. Patients are told that ADHD stimulants correct a dopamine deficiency in their attention circuits [98]. This is at best an oversimplification and at worst an inference that has not been causally established [7,98].

Honest informed consent would require clinicians to explain that these medications produce real pharmacological effects that help many people, that the precise mechanisms are not fully understood, that there is no confirmed biological test for the condition being treated, and that the drugs manage symptoms rather than curing underlying causes. Such conversations are more difficult than “you have a chemical imbalance,” but they are more truthful, and they respect the epistemic autonomy of patients in a way that simplified neurobiological narratives do not.

Table 1. Comparative summary of major psychiatric drug classes: proposed mechanism, etiological evidence, established clinical role, and major safety concerns.

Drug Class	Proposed Mechanism	Strength of Etiological Evidence	Established Clinical Role	Major Safety Concerns	References *
SSRIs	Blockade of the serotonin transporter (SERT), increasing synaptic serotonin	Weak. An umbrella review across six research domains found no consistent evidence linking serotonin to depression (critics note a role in subgroups is not excluded)	Most widely prescribed class of psychiatric medications globally; all 21 antidepressants in a network meta-analysis outperformed placebo	Discontinuation symptoms (27% to 86% in one systematic review; about 1 in 6 to 7 in a placebo-adjusted meta-analysis), with higher risk for paroxetine, longer use, and higher doses; higher incidence of sexual dysfunction and weight gain than bupropion	[12,15,31,32,45,47,48,52,62]
SNRIs	Blockade of SERT and the norepinephrine transporter (NET); venlafaxine acts mainly as an SSRI at lower doses	Weak. Efficacy comparable to SSRIs despite the added mechanism (small, clinically modest advantages in some comparisons) undermines single-target specificity	Effective versus placebo; duloxetine also approved for fibromyalgia, diabetic neuropathic pain, and chronic musculoskeletal pain	Dose-dependent rises in blood pressure and heart rate; pronounced discontinuation syndrome, especially venlafaxine	[31,49–52]
TCAs	SERT and NET inhibition plus muscarinic, histamine H1, and alpha-1 adrenergic antagonism	Weak. Broad, nonselective pharmacology with efficacy comparable to selective agents challenges serotonin specificity	Low-dose amitriptyline for neuropathic pain (low certainty of evidence) and sleep (short-term use only); clomipramine retains a first-line role in OCD; nortriptyline and desipramine as second- or third-line antidepressants	Anticholinergic effects, sedation, weight gain, orthostatic hypotension; cardiac sodium and potassium channel blockade, potentially fatal in overdose	[52–58]
MAOIs	Inhibition of MAO-A and MAO-B, raising serotonin, norepinephrine, and dopamine	Weak. Theoretical framework built after an accidental clinical observation (iproniazid in tuberculosis patients)	Third-line in current practice, though possibly more effective in treatment-resistant and atypical depression; reversible moclobemide carries lower tyramine risk	Tyramine-induced hypertensive crisis with irreversible agents (dietary restriction); dangerous interactions with other antidepressants, opioids, and sympathomimetics	[9,61]
Atypical antidepressants (bupropion, mirtazapine, trazodone, agomelatine)	Diverse: norepinephrine-dopamine reuptake inhibition (bupropion); alpha-2 antagonism with 5-HT2 and H1 blockade (mirtazapine); 5-HT2A antagonism (trazodone); melatonin agonism with 5-HT2C antagonism (agomelatine)	Weak. Mechanistically unrelated agents with comparable efficacy undermine any single-neurotransmitter hypothesis; a convergent BDNF pathway is	Comparable antidepressant efficacy in some studies (agomelatine); mirtazapine useful with insomnia and poor appetite; low-dose trazodone used for sleep; bupropion also used for smoking cessation	Seizure risk (bupropion); sedation and weight gain (mirtazapine); hepatotoxicity requiring liver monitoring (agomelatine)	[52,62–66]

		proposed but unestablished		
First-generation antipsychotics (FGAs)	Dopamine D2 receptor blockade, particularly in the mesolimbic pathway	Weak to moderate. Potency correlates with D2 affinity, but the dopamine hypothesis was built retrospectively after chlorpromazine and is confounded by prior drug exposure	Chlorpromazine suppressed hallucinations and agitation when first given to psychotic patients; D2 blockade suppresses psychotic symptoms without addressing an identified cause	Extrapyramidal symptoms (dystonia, parkinsonism, akathisia); tardive dyskinesia (about 20% to 25%; reported range 15% to 50%) [13,36,37,72,73]
Second-generation antipsychotics (SGAs)	D2 blockade plus 5-HT2A antagonism; aripiprazole is a D2 partial agonist	Weak. Clozapine's superior efficacy despite weak D2 affinity challenges a D2-centered account	Clozapine superior in treatment-resistant schizophrenia; in CATIE, perphenazine did not differ significantly from most SGAs in time to discontinuation, so superiority was not shown; no clear differences between antipsychotics for relapse prevention in a network meta-analysis	Metabolic syndrome (weight gain, dyslipidemia, glucose intolerance; greatest weight gain, hemoglobin A1c, and lipid changes with olanzapine in CATIE); agranulocytosis with clozapine (about 1% to 2%; mandatory blood monitoring) [37,74–80,82]
Lithium	Multiple targets; GSK-3 beta inhibition most studied; mechanism responsible for mood stabilization unconfirmed	Weak on mechanism, strong on outcome. Unresolved after more than seven decades	Gold-standard long-term prophylaxis in bipolar disorder; reduces manic and depressive episodes; anti-suicidal effect among the most replicated findings in psychopharmacology	Narrow therapeutic index (0.6 to 1.2 mmol/L) requiring serum monitoring; toxicity; thyroid dysfunction (about 20% to 40%); chronic kidney disease [39,83,84,87,88]
Anticonvulsant mood stabilizers (valproate, lamotrigine)	Valproate: GABAergic enhancement, sodium channel inhibition, HDAC inhibition. Lamotrigine: sodium channel inhibition, reduced glutamate release	Weak. Which mechanism underlies mood stabilization is not established; diverse agents converge on similar outcomes	Valproate effective for acute mania and prevention of manic episodes; lamotrigine effective for the depressive phase	Valproate: major congenital malformations (estimated 6.2% to 16% of exposed pregnancies), neural tube defects, reduced offspring IQ. Lamotrigine: Stevens-Johnson syndrome (about 0.1% of adults; slow titration) [88–92]
Benzodiazepines	Positive allosteric modulation of the GABA-A receptor	Mechanism molecularly well characterized, but no confirmed GABAergic etiology for any anxiety disorder	Among the most widely prescribed psychotropic medications; used for acute anxiety, panic disorder, insomnia, alcohol withdrawal, seizures, and procedural sedation	Tolerance, physical dependence, and withdrawal (rebound anxiety, seizures that can be life-threatening); neuroadaptation that may ultimately worsen anxiety [15,16,29,93–96]
Non-benzodiazepine hypnotics (Z-drugs)	Subunit-selective (alpha-1) GABA-A modulation	Same as benzodiazepines; selectivity only	Hypnotics with somewhat lower dependence than	Tolerance, withdrawal, rebound insomnia; complex [94]

		partially reduces dependence risk	classical benzodiazepines in most patients; improvement more modest than hoped	sleep behaviors with zolpidem (sleep-walking, sleep-driving, sleep-eating)
Bupirone	Partial agonism at serotonin 5-HT1A receptors (with some D2 activity)	Weak. Causal link between 5-HT1A activity and anxiety reduction remains inferential	Efficacy comparable to benzodiazepines in generalized anxiety disorder in controlled trials; no sedation, psychomotor impairment, or physical dependence	Delayed onset (1 to 2 weeks), limiting use [97] in acute anxiety
Methylphenidate	Dopamine transporter (DAT) and NET reuptake blockade	Moderate. Neuroimaging and genetic correlates exist, but a causal catecholamine deficit is not established	A Cochrane review rated certainty of evidence for efficacy as low, which does not mean it is ineffective	Dose-dependent rises in heart rate and blood pressure; abuse and misuse potential (mechanism pharmacologically similar to cocaine, with slower onset) [7,98–101]
Amphetamines	DAT/NET blockade plus vesicular release and VMAT-2 inhibition	Moderate. Same catecholamine hypothesis as methylphenidate, with a broader mechanism	Same clinical rationale as methylphenidate; lisdexamfetamine is a prodrug designed to reduce abuse potential	Greater reinforcing properties and higher dependence potential [100] than methylphenidate
Non-stimulant ADHD medications (atomoxetine, guanfacine, clonidine)	Selective NET inhibition (atomoxetine); alpha-2A adrenergic agonism (guanfacine, clonidine)	Moderate. Mechanistically diverse agents work through multiple routes, consistent with heterogeneous ADHD biology	Non-stimulant options for ADHD acting through mechanisms distinct from stimulants	Cardiovascular concerns reduced but not eliminated compared with stimulants [99,100]
Ketamine/esketamine	NMDA receptor antagonism, triggering AMPA/mTOR/BDNF signaling	Emerging. Mechanism unclear and multifaceted	Rapid antidepressant effect in treatment-resistant depression; esketamine FDA-approved in 2019 (given under supervision); superior to quetiapine for remission in a randomized trial	Dissociative and psychotomimetic effects; bladder toxicity; potential for dissociative addiction; benefit time-limited (1 to 2 weeks after a single infusion) [102–104]
Psilocybin	Serotonin 5-HT2A receptor agonism; altered default mode network activity	Emerging. Mechanism independent of therapeutic context not established; adequate blinding is difficult given subjective effects	Investigational; promising effects in Phase 2 trials and a large effect size in a meta-analysis; a single 25 mg dose outperformed 1 mg at 3 weeks, but the response was not sustained at 12 weeks; not inferior to escitalopram in one trial; Phase 3 trials underway	Adverse effects more common with the 25 mg dose than the 1 mg dose [105–108]

Notes: * Reference numbers refer to the numbers in the Reference list of this paper. Ratings of etiological evidence reflect the author's qualitative appraisal (see Method) and concern whether a drug's proposed mechanism corrects a confirmed disease

process, not whether the drug works. Abbreviations: 5-HT, serotonin (5-HT1A, 5-HT2, 5-HT2A, 5-HT2C: serotonin receptor subtypes); ADHD, attention-deficit/hyperactivity disorder; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; D2, dopamine receptor subtype 2; DAT, dopamine transporter; FDA, Food and Drug Administration; FGA, first-generation antipsychotic; GABA, gamma-aminobutyric acid; GABA-A, gamma-aminobutyric acid receptor type A; GSK-3 beta, glycogen synthase kinase 3 beta; H1, histamine receptor subtype 1; HDAC, histone deacetylase; MAO, monoamine oxidase; MAOI, monoamine oxidase inhibitor; mTOR, mammalian target of rapamycin; NET, norepinephrine transporter; NMDA, N-methyl-D-aspartate; OCD, obsessive-compulsive disorder; SERT, serotonin transporter; SGA, second-generation antipsychotic; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VMAT-2, vesicular monoamine transporter 2.

13. Conclusions

This critical review has documented, with extensive citation to the peer-reviewed literature, that psychiatric pharmacotherapy rests on a set of mechanistic assumptions that have not been scientifically established. The serotonin hypothesis of depression lacks consistent evidentiary support across multiple research domains. The dopamine hypothesis of schizophrenia remains a plausible but unvalidated framework in which much of the supporting evidence is confounded by prior drug exposure and methodological limitations. The catecholamine hypothesis of ADHD, though more biologically grounded than its counterparts, does not establish a confirmed causal neurobiological deficit that stimulant medications correct. The mood stabilizer lithium, in clinical use for more than 75 years, still lacks a fully characterized mechanism of mood stabilization. Benzodiazepines, the best mechanistically understood of all psychiatric drugs, produce pharmacological dependence that may worsen the very condition they were prescribed to treat. And the placebo response accounts for a clinically and statistically substantial proportion of apparent antidepressant efficacy in controlled trials.

The serendipitous origins of virtually all foundational psychiatric drugs are not merely a historical anecdote. They reveal a structural problem: that a specialty built its entire pharmacological practice on post-hoc explanatory frameworks designed to rationalize discovered effects rather than on a priori mechanistic knowledge of disease. This backward epistemology has been perpetuated by a clinical trial literature inflated by publication bias, by a diagnostic system that lacks biological validity, and by a culture of confident mechanistic explanation that the underlying science does not support.

None of this means that psychiatric medications are valueless. Millions of patients receive genuine symptomatic benefit from these agents, and for conditions as disabling and dangerous as treatment-resistant schizophrenia, severe bipolar disorder, and suicidal depression, symptomatic relief is a legitimate and important medical goal. The argument of this review is not that these medications should not be prescribed, but that they should be prescribed with honesty: honesty about what the evidence supports, honesty about what it does not, honesty about the risks of long-term use, and honesty about the distinction between managing symptoms and curing a disease.

The emerging treatments, ketamine and psilocybin, offer genuine therapeutic promise and introduce novel mechanistic ideas involving glutamatergic plasticity and serotonin receptor-mediated network reconfiguration. But they too have been received with a degree of premature mechanistic confidence that the evidence does not yet justify. The lesson of the preceding seven decades should be that premature theoretical certainty in psychiatric pharmacology has consistently generated more harm than good: it has misled patients, obscured the placebo response, delayed genuine mechanistic progress, and immunized practitioners against the evidence of failure.

What psychiatry needs, and what patients deserve, is not a new set of confident hypotheses to replace the old ones, but an honest accounting of what is known and what is not, a willingness to say that these drugs produce real effects whose mechanisms remain incompletely understood, that psychiatric disorders are real sources of suffering whose biology is not yet resolved, and that symptomatic management, while valuable, is not the same as cure. A clinical psychologist, working alongside prescribing psychiatrists, can observe daily the consequences when this distinction is blurred: patients who feel dependent on medications they were told they needed to correct an imbalance, patients who struggle to discontinue drugs whose discontinuation syndromes were never disclosed, and patients whose physical health has been compromised by metabolic and neurological side effects of agents prescribed for conditions whose biological basis could not be confirmed.

The call of this review is not for nihilism about psychiatric pharmacotherapy, but for epistemic honesty in its practice. These medications produce measurable pharmacological effects and provide real symptomatic relief for many patients, and those facts are not contested here. What is contested, and what the evidence reviewed in this paper consistently fails to support, is the claim that these drugs correct confirmed biological causes of the disorders for

which they are prescribed. Symptomatic management is a legitimate medical goal. It is not, however, equivalent to cure, and presenting it as such to patients is a scientific misrepresentation that psychiatry can no longer afford.

Several concrete steps could operationalize this call for epistemic honesty. Patient medication information leaflets could replace language describing drugs as correcting a “chemical imbalance” with plainer statements that the medication is believed to work by altering neurotransmitter activity and that this reduces symptoms in many patients, without asserting that a specific deficit has been corrected. Pharmacology and psychiatry textbooks could distinguish more clearly between a drug’s established receptor pharmacology and the unproven disease hypotheses historically used to explain it. Clinical guidelines could explicitly flag where recommended treatments lack confirmed mechanistic validation, alongside their evidence grade for efficacy. Science journalism and public communication about psychiatric drugs would benefit from routinely distinguishing statements about clinical efficacy (well supported for many agents) from statements about disease mechanism (frequently unproven), a distinction this review has argued is too often collapsed into a single narrative.

Clinical pharmacy practice offers a direct route for translating this distinction into everyday patient care. At the counter, pharmacists who explain that a medication is believed to work by altering neurotransmitter signaling, while being honest that the underlying disease mechanism remains unconfirmed, give patients a more accurate basis for shared decision-making than a flat assertion that the drug corrects a chemical imbalance. Pharmacist-led medication review and deprescribing services are well placed to identify patients on long-term psychiatric medication who may be candidates for a supervised dose reduction or discontinuation trial in collaboration with the prescriber. Benzodiazepine stewardship is a particularly clear opportunity for pharmacist involvement, given the dependence and withdrawal risks discussed earlier in this review, through structured medication review, patient education on long-term risks, and closely monitored, individualized tapering protocols. Pharmacists are also well positioned to lead or coordinate metabolic monitoring for patients on second-generation antipsychotics, tracking weight, blood pressure, glucose, and lipid profile at baseline and follow-up, directly mitigating one of the most serious physical health costs documented in this review. Finally, because pharmacists are often the first healthcare professional a patient consults when new symptoms emerge after a dose change, they are well placed to distinguish an antidepressant or benzodiazepine discontinuation syndrome from relapse of the underlying condition, counsel on gradual tapering, and escalate to the prescriber when appropriate. Together, these roles turn the epistemic concerns raised in this review, particularly the risk of patients being given an inaccurate account of what their medication is doing and why, into concrete, achievable improvements in everyday pharmacy practice.

List of Abbreviations

5-HT1A	Serotonin receptor subtype 1A
5-HT2A	Serotonin receptor subtype 2A
5-HT2C	Serotonin receptor subtype 2C
5-HT3	Serotonin receptor subtype 3
5-HIAA	5-Hydroxyindoleacetic acid
ADHD	Attention-deficit/hyperactivity disorder
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	Brain-derived neurotrophic factor
BMAL1	Brain and muscle ARNT-like protein 1
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CLOCK	Circadian locomotor output cycles kaput
CNS	Central nervous system
D2	Dopamine receptor subtype 2
D4	Dopamine receptor subtype 4
DAT	Dopamine transporter
DMN	Default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
eEF2K	Eukaryotic elongation factor 2 kinase
EPS	Extrapyramidal side effects
FDA	Food and Drug Administration
FGA	First-generation antipsychotic
GABA	Gamma-aminobutyric acid
GABA-A	Gamma-aminobutyric acid receptor type A
GSK-3 beta	Glycogen synthase kinase 3 beta
H1	Histamine receptor subtype 1
HAMD-17	Hamilton Depression Rating Scale (17-item)

HDAC	Histone deacetylase
IMPase	Inositol monophosphatase
M1	Muscarinic acetylcholine receptor subtype 1
MAO-A	Monoamine oxidase A
MAO-B	Monoamine oxidase B
MAOI	Monoamine oxidase inhibitor
MT1	Melatonin receptor type 1
MT2	Melatonin receptor type 2
mTOR	Mammalian target of rapamycin
NDRI	Norepinephrine-dopamine reuptake inhibitor
NET	Norepinephrine transporter
NICE	National Institute for Health and Care Excellence
NIMH	National Institute of Mental Health
NMDA	N-methyl-D-aspartate
OCD	Obsessive-compulsive disorder
OECD	Organisation for Economic Co-operation and Development
QRS	QRS complex (a component of the electrocardiogram representing ventricular depolarization)
QTc	Corrected QT interval
RDoC	Research Domain Criteria
RIMA	Reversible inhibitor of monoamine oxidase A
SARI	Serotonin antagonist and reuptake inhibitor
SERT	Serotonin transporter
SGA	Second-generation antipsychotic
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TD	Tardive dyskinesia
VMAT-2	Vesicular monoamine transporter 2

Author Contributions

Conceptualization, methodology, software, validation, investigation, resources, writing—original draft preparation, writing—review and editing, visualization, supervision, project administration: W.H. The sole author has read and agreed to the published version of the manuscript.

Availability of Data and Materials

No datasets were generated or analyzed during the current study.

Consent for Publication

Not applicable.

Conflicts of Interest

The author declares that there are no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

AI Declaration

The author declares that Claude Sonnet 5 Medium (Anthropic; <https://claude.ai>) was utilized in the preparation of this manuscript for the following purposes: enhancing clarity of expression, refining grammar and syntax, and improving overall academic writing quality. The AI tool was used iteratively during the revision process to ensure consistency

and readability. All substantive contributions to this work remain the exclusive responsibility of the author. The author reviewed and verified all AI-generated suggestions and accepts full accountability for the final manuscript content. No AI-generated text was used without author review and approval. The graphical abstract accompanying this manuscript along with Figure 1 are original to this paper and were generated with the assistance of ChatGPT 5.6 Luna Model (OpenAI) based solely on the text based on the current paper. The AI system was used exclusively as a visual design tool to translate the authors' content into an infographic format. The graphical abstract and Figure 1 do not constitute an independent source of evidence and should be interpreted in conjunction with the full manuscript.

References

- [1] Aronson, J.K.; La Caze, A.; Kelly, M.P.; Parkkinen, V.P.; Williamson, J. The Use of Mechanistic Evidence in Drug Approval. *J. Eval. Clin. Pract.* **2018**, *24*(5), 1166–1176. <https://doi.org/10.1111/jep.12960>.
- [2] Wilde, M. The EBM+ Movement. *Int. J. Biostat.* **2023**, *19*(2), 283–293. <https://doi.org/10.1515/ijb-2022-0126>.
- [3] Ritter, J.M.; Flower, R.J.; Henderson, G.; Loke, Y.K.; MacEwan, D.; Rang, H.P. *Rang & Dale's Pharmacology*; Elsevier: Amsterdam, The Netherlands, 2020.
- [4] Munita, J.M.; Arias, C.A. Mechanisms of Antibiotic Resistance. *Virulence Mech. Bact. Pathog.* **2016**, *4*(2), 481–511. <https://doi.org/10.1128/9781555819286.ch17>.
- [5] Carretero, O.A.; Oparil, S. Essential Hypertension. Part I: Definition and Etiology. *Circulation* **2000**, *101*(3), 329–335. <https://doi.org/10.1161/01.CIR.101.3.329>.
- [6] Carey, R.M.; Moran, A.E.; Whelton, P.K. Treatment of Hypertension: A Review. *JAMA* **2022**, *328*(18), 1849–1861. <https://doi.org/10.1001/jama.2022.19590>.
- [7] Hyman, S.E. The Diagnosis of Mental Disorders: The Problem of Reification. *Annu. Rev. Clin. Psychol.* **2010**, *6*, 155–179. <https://doi.org/10.1146/annurev.clinpsy.3.022806.091532>.
- [8] Abi-Dargham, A.; Moeller, S.J.; Ali, F.; DeLorenzo, C.; Domschke, K.; Horga, G.; Jutla, A.; Kotov, R.; Paulus, M.P.; Rubio, J.M.; Sanacora, G.; Veenstra-VanderWeele, J.; Krystal, J.H. Candidate Biomarkers in Psychiatric Disorders: State of the Field. *World Psychiatry* **2023**, *22*(2), 236–262. <https://doi.org/10.1002/wps.21078>.
- [9] Ban, T.A. The Role of Serendipity in Drug Discovery. *Dialogues Clin. Neurosci.* **2006**, *8*(3), 335–344. <https://doi.org/10.31887/dens.2006.8.3/tban>.
- [10] Lyndon, S.; John, V.P. Serendipity in Psychiatric Discoveries: Historical Lessons and Future Imperatives for Clinical Observation. *BJPsych Bull.* **2026**, 1–9. <https://doi.org/10.1192/bjb.2025.10209>.
- [11] Seeman, M.V. History of the Dopamine Hypothesis of Antipsychotic Action. *World J. Psychiatry* **2021**, *11*(7), 355–364. <https://doi.org/10.5498/wjp.v11.i7.355>.
- [12] Moncrieff, J.; Cooper, R.E.; Stockmann, T.; Amendola, S.; Hengartner, M.P.; Horowitz, M.A. The Serotonin Theory of Depression: A Systematic Umbrella Review of the Evidence. *Mol. Psychiatry* **2023**, *28*(8), 3243–3256. <https://doi.org/10.1038/s41380-022-01661-0>.
- [13] Hengartner, M.P.; Moncrieff, J. Inconclusive Evidence in Support of the Dopamine Hypothesis of Psychosis: Why Neurobiological Research Must Consider Medication Use, Adjust for Important Confounders, Choose Stringent Comparators, and Use Larger Samples. *Front. Psychiatry* **2018**, *9*, 00174. <https://doi.org/10.3389/fpsy.2018.00174>.
- [14] Peano, A.; Calabrese, F.; Pechlivanidis, K.; Mimmo, R.; Politano, G.; Martella, M.; Gianino, M.M. International Trends in Antidepressant Consumption: A 10-Year Comparative Analysis (2010–2020). *Psychiatr. Q.* **2025**, *96*(2), 241–255. <https://doi.org/10.1007/s11126-025-10122-0>.
- [15] Alabaku, O.; Yang, A.; Tharmarajah, S.; Suda, K.; Vigod, S.; Tadrous, M. Global Trends in Antidepressant, Atypical Antipsychotic, and Benzodiazepine Use: A Cross-Sectional Analysis of 64 Countries. *PLoS ONE* **2023**, *18*, e0284389. <https://doi.org/10.1371/journal.pone.0284389>.
- [16] Huang, C.; Yang, Y.; Wei, Y.; Yan, V.K.C.; Lee, K.J.; Leung, S.M.; Lai, F.T.T.; Chai, Y.; Brauer, R.; Castle, D.J.; Wei, L.; Hayes, J.F.; Luo, H.; Siskind, D.; Yan, E.W.C.; Chan, E.W.Y. Psychotropic Medication Consumption before and after Onset

- of COVID-19 Pandemic in 91 Countries and Regions: A Time-Series Analysis. *Lancet Reg. Health-West. Pacific* **2025**, *64*, 101711. <https://doi.org/10.1016/j.lanwpc.2025.101711>.
- [17] Collaborators, G. 2019 M. D. Global, Regional, and National Burden of 12 Mental Disorders in 204 Countries and Territories, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* **2022**, *9*(2), 137–150. [https://doi.org/10.1016/S2215-0366\(21\)00395-3](https://doi.org/10.1016/S2215-0366(21)00395-3).
- [18] Moncrieff, J. The Myth of the Chemical Cure. In *The myth of the Chemical Cure: A Critique of Psychiatric Drug Treatment*; Moncrieff, J., Ed.; Springer: London, UK, 2008; pp. 217–224.
- [19] Kendler, K.S. A Working Scientist’s View on Causality in Psychiatry. In *Causal Concepts in Psychopathology*; Kendler, K.S., Parnas, J., Zachar, P., Ed.; Cambridge University Press: Cambridge, UK, 2026; pp. 112–127. <https://doi.org/10.1017/9781009390620.018>.
- [20] Miller, A.H.; Raison, C.L. Burning down the House: Reinventing Drug Discovery in Psychiatry for the Development of Targeted Therapies. *Mol. Psychiatry* **2023**, *28*(1), 68–75. <https://doi.org/10.1038/s41380-022-01887-y>.
- [21] Ang, B.; Horowitz, M.; Moncrieff, J. Is the Chemical Imbalance an ‘Urban Legend’? An Exploration of the Status of the Serotonin Theory of Depression in the Scientific Literature. *SSM-Ment. Health* **2022**, *2*, 100098. <https://doi.org/10.1016/j.ssmmh.2022.100098>.
- [22] Schroder, H.S.; Tovey, J.; Forer, R.; Schultz, W.; Kneeland, E.T.; Moser, J.S. Where Do “Chemical Imbalance” Beliefs Come from? Evaluating the Impact of Different Sources. *Front. Psychol.* **2024**, *15*, 1469913. <https://doi.org/10.3389/fpsyg.2024.1469913>.
- [23] Engelen, T.; Mennella, R. Piecing Together the Puzzle of Emotional Consciousness. *Neurosci. Conscious.* **2023**, *2023*(1), niad005. <https://doi.org/10.1093/nc/niad005>.
- [24] Marek, S.; Tervo-Clemmens, B.; Calabro, F.J.; Montez, D.F.; Kay, B.P.; Hatoum, A.S.; Donohue, M.R.; Foran, W.; Miller, R.L.; Hendrickson, T.J.; et al. Reproducible Brain-Wide Association Studies Require Thousands of Individuals. *Nature* **2022**, *603*(7902), 654–660. <https://doi.org/10.1038/s41586-022-04492-9>.
- [25] Seth, A.K.; Bayne, T. Theories of Consciousness. *Nat. Rev. Neurosci.* **2022**, *23*, 439–452. <https://doi.org/10.1038/s41583-022-00587-4>.
- [26] Josselyn, S.A.; Tonegawa, S. Memory Engrams: Recalling the Past and Imagining the Future. *Science* **2020**, *367*(6473), eaaw4325. <https://doi.org/10.1126/science.aaw4325>.
- [27] Ledoux, J.E.; Brown, R. A Higher-Order Theory of Emotional Consciousness. *Proc. Natl. Acad. Sci. USA* **2017**, *114*(10), E2016–E2025. <https://doi.org/10.1073/pnas.1619316114>.
- [28] Grant, M.J.; Booth, A. A Typology of Reviews: An Analysis of 14 Review Types and Associated Methodologies. *Health Inf. Libr. J.* **2009**, *26*(2), 91–108. <https://doi.org/10.1111/j.1471-1842.2009.00848.x>.
- [29] Brauer, R.; Alfageh, B.; Blais, J.E.; Chan, E.W.; Chui, C.S.L.; Hayes, J.F.; Man, K.K.C.; Lau, W.C.Y.; Yan, V.K.C.; Beykloo, M.Y.; et al. Psychotropic Medicine Consumption in 65 Countries and Regions, 2008–2019: A Longitudinal Study. *Lancet Psychiatry* **2021**, *8*(12), 1071–1082. [https://doi.org/10.1016/S2215-0366\(21\)00292-3](https://doi.org/10.1016/S2215-0366(21)00292-3).
- [30] Kirsch, I.; Deacon, B.J.; Huedo-Medina, T.B.; Scoboria, A.; Moore, T.J.; Johnson, B.T. Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration. *PLoS Med.* **2008**, *5*(2), 0260–0268. <https://doi.org/10.1371/journal.pmed.0050045>.
- [31] Davies, J.; Read, J. A Systematic Review into the Incidence, Severity and Duration of Antidepressant Withdrawal Effects: Are Guidelines Evidence-Based? *Addict. Behav.* **2019**, *97*, 111–121. <https://doi.org/10.1016/j.addbeh.2018.08.027>.
- [32] Jauhar, S.; Arnone, D.; Baldwin, D.S.; Bloomfield, M.; Browning, M.; Cleare, A.J.; Corlett, P.; Deakin, J.F.W.; Erritzoe, D.; Fu, C.; et al. A Leaky Umbrella Has Little Value: Evidence Clearly Indicates the Serotonin System Is Implicated in Depression. *Mol. Psychiatry* **2023**, *28*(8), 3149–3152. <https://doi.org/10.1038/s41380-023-02095-y>.
- [33] Fountoulakis, K.N.; Möller, H.J. Efficacy of Antidepressants: A Re-Analysis and Re-Interpretation of the Kirsch Data. *Int. J. Neuropsychopharmacol.* **2011**, *14*(3), 405–412. <https://doi.org/10.1017/S1461145710000957>.

- [34] López-Muñoz, F.; D'Ocón, P.; Romero, A.; Guerra, J.A.; Álamo, C. Role of Serendipity in the Discovery of Classical Antidepressant Drugs: Applying Operational Criteria and Patterns of Discovery. *World J. Psychiatry* **2022**, *12*(4), 588. <https://doi.org/10.5498/wjpv12.i4.588>.
- [35] Hargrave-Thomas, E. Serendipity in Anticancer Drug Discovery. *World J. Clin. Oncol.* **2012**, *3*(1), 1. <https://doi.org/10.5306/wjco.v3.i1.1>.
- [36] López-Muñoz, F.; Alamo, C.; Cuenca, E.; Shen, W.W.; Clervoy, P.; Rubio, G. History of the Discovery and Clinical Introduction of Chlorpromazine. *Ann. Clin. Psychiatry* **2005**, *17*(3), 113–135. <https://doi.org/10.1080/10401230591002002>.
- [37] Howes, O.D.; Kapur, S. The Dopamine Hypothesis of Schizophrenia: Version III—The Final Common Pathway. *Schizophr. Bull.* **2009**, *35*(3), 549–562. <https://doi.org/10.1093/schbul/sbp006>.
- [38] Coppen, A. The Biochemistry of Affective Disorders. *Br. J. Psychiatry* **1967**, *113*(504), 1237–1264. <https://doi.org/10.1192/bjp.113.504.1237>.
- [39] Malhi, G.S.; Tanious, M.; Das, P.; Coulston, C.M.; Berk, M. Potential Mechanisms of Action of Lithium in Bipolar Disorder: Current Understanding. *CNS Drugs* **2013**, *27*(2), 135–153. <https://doi.org/10.1007/s40263-013-0039-0>.
- [40] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. In *Diagnostic and Statistical Manual of Mental Disorders: DSM-5™*; American Psychiatric Publishing, Inc.: Washington, DC, USA, 2022. <https://doi.org/10.1176/appi.books.9780890425787>.
- [41] Cuthbert, B.N. Research Domain Criteria (RDoC): Progress and Potential. *Curr. Dir. Psychol. Sci.* **2022**, *31*(2), 107–114. <https://doi.org/10.1177/09637214211051363>.
- [42] Kotov, R.; Krueger, R.F.; Watson, D.; Cicero, D.C.; Conway, C.C.; Deyoung, C.G.; Eaton, N.R.; Forbes, M.K.; Hallquist, M.N.; Latzman, R.D.; et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): A Quantitative Nosology Based on Consensus of Evidence. *Annu. Rev. Clin. Psychol.* **2021**, *17*, 83–108. <https://doi.org/10.1146/annurev-clinpsy-081219-093304>.
- [43] Regier, D.A.; Narrow, W.E.; Clarke, D.E.; Kraemer, H.C.; Kuramoto, S.J.; Kuhl, E.A.; Kupfer, D.J. DSM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses. *Am. J. Psychiatry* **2013**, *170*(1), 59–70. <https://doi.org/10.1176/appi.ajp.2012.12070999>.
- [44] Insel, T.; Cuthbert, B.; Garvey, M.; Heinssen, R.; Pine, D.S.; Quinn, K.; Sanislow, C.; Wang, P. Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *Am. J. Psychiatry* **2010**, *167*(7), 748–751. <https://doi.org/10.1176/appi.ajp.2010.09091379>.
- [45] Stahl, S.M. Mechanism of Action of Serotonin Selective Reuptake Inhibitors. Serotonin Receptors and Pathways Mediate Therapeutic Effects and Side Effects. *J. Affect. Disord.* **1998**, *51*(3), 215–235. [https://doi.org/10.1016/S0165-0327\(98\)00221-3](https://doi.org/10.1016/S0165-0327(98)00221-3).
- [46] Kirsch, I. Antidepressants and the Placebo Effect. *Zeitschrift für Psychol./J. Psychol.* **2014**, *222*(3), 128–134. <https://doi.org/10.1027/2151-2604/a000176>.
- [47] Henssler, J.; Schmidt, Y.; Schmidt, U.; Schwarzer, G.; Bschor, T.; Baethge, C. Incidence of Antidepressant Discontinuation Symptoms: A Systematic Review and Meta-Analysis. *Lancet Psychiatry* **2024**, *11*(7), 526–535. [https://doi.org/10.1016/S2215-0366\(24\)00133-0](https://doi.org/10.1016/S2215-0366(24)00133-0).
- [48] Horowitz, M.A.; Framer, A.; Hengartner, M.P.; Sorensen, A.; Taylor, D. Estimating Risk of Antidepressant Withdrawal from a Review of Published Data. *CNS Drugs* **2023**, *37*(2), 143–157. <https://doi.org/10.1007/s40263-022-00960-y>.
- [49] Fava, G.A.; Benasi, G.; Lucente, M.; Offidani, E.; Cosci, F.; Guidi, J. Withdrawal Symptoms after Serotonin-Noradrenaline Reuptake Inhibitor Discontinuation: Systematic Review. *Psychother. Psychosom.* **2018**, *87*(4), 195–203. <https://doi.org/10.1159/000491524>.
- [50] Stahl, S.M.; Grady, M.M.; Moret, C.; Briley, M. SNRIs: The Pharmacology, Clinical Efficacy, and Tolerability in Comparison with Other Classes of Antidepressants. *CNS Spectr.* **2005**, *10*(9), 732–747. <https://doi.org/10.1017/S1092852900019726>.
- [51] Kishi, T.; Ikuta, T.; Sakuma, K.; Okuya, M.; Hatano, M.; Matsuda, Y.; Iwata, N. Antidepressants for the Treatment of Adults with Major Depressive Disorder in the Maintenance Phase: A Systematic Review and Network Meta-Analysis. *Mol. Psychiatry* **2023**, *28*(1), 402–409. <https://doi.org/10.1038/s41380-022-01824-z>.

- [52] Cipriani, A.; Furukawa, T.A.; Salanti, G.; Chaimani, A.; Atkinson, L.Z.; Ogawa, Y.; Leucht, S.; Ruhe, H.G.; Turner, E.H.; Higgins, J.P.T.; Egger, M.; Takeshima, N.; Hayasaka, Y.; Imai, H.; Shinohara, K.; Tajika, A.; Ioannidis, J.P.A.; Geddes, J.R. Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults with Major Depressive Disorder: A Systematic Review and Network Meta-Analysis. *Lancet* **2018**, *391*(10128), 1357–1366. [https://doi.org/10.1016/S0140-6736\(17\)32802-7](https://doi.org/10.1016/S0140-6736(17)32802-7).
- [53] Stahl, S.M. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*; Cambridge University Press: Cambridge, UK, 2021. <https://doi.org/10.1017/9781108975292>.
- [54] Gillman, P.K. Tricyclic Antidepressant Pharmacology and Therapeutic Drug Interactions Updated. *Br. J. Pharmacol.* **2007**, *151*(6), 737–748. <https://doi.org/10.1038/sj.bjp.0707253>.
- [55] Labbate, L.A.; Fava, M.; Rosenbaum, J.F.; Arana, G.W. *Handbook of Psychiatric Drug Therapy*; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2012; Volume 6.
- [56] Ferreira, G.E.; Abdel-Shaheed, C.; Underwood, M.; Finnerup, N.B.; Day, R.O.; McLachlan, A.; Eldabe, S.; Zadro, J.R.; Maher, C.G. Efficacy, Safety, and Tolerability of Antidepressants for Pain in Adults: Overview of Systematic Reviews. *BMJ* **2023**, *380*, e072415. <https://doi.org/10.1136/bmj-2022-072415>.
- [57] Riemann, D.; Espie, C.A.; Altena, E.; Arnardottir, E.S.; Baglioni, C.; Bassetti, C.L.A.; Bastien, C.; Berzina, N.; Bjorvatn, B.; Dikeos, D.; et al. The European Insomnia Guideline: An Update on the Diagnosis and Treatment of Insomnia 2023. *J. Sleep Res.* **2023**, *32*(6), e14035. <https://doi.org/10.1111/jsr.14035>.
- [58] Fineberg, N.A.; Brown, A.; Reghunandanan, S.; Pampaloni, I. Evidence-Based Pharmacotherapy of Obsessive-Compulsive Disorder. *Int. J. Neuropsychopharmacol.* **2012**, *15*(8), 1173–1191. <https://doi.org/10.1017/S1461145711001829>.
- [59] Van den Eynde, V.; Abdelmoemin, W.R.; Abraham, M.M.; Amsterdam, J.D.; Anderson, I.M.; Andrade, C.; Baker, G.B.; Beekman, A.T.F.; Berk, M.; Birkenhäger, T.K.; et al. The Prescriber's Guide to Classic MAO Inhibitors (Phenelzine, Tranylcypromine, Isocarboxazid) for Treatment-Resistant Depression. *CNS Spectr.* **2023**, *28*(4), 427–440. <https://doi.org/10.1017/S1092852922000906>.
- [60] Giménez-Palomo, A.; Chamdal, A.K.; Gottlieb, N.; Lotfaliany, M.; Jokinen, T.; Bastawy, E.M.; Adlington, K.; Benachar, N.; Dodd, S.; Pacchiarotti, I.; et al. Efficacy and Tolerability of Monoamine Oxidase Inhibitors for the Treatment of Depressive Episodes in Mood Disorders: A Systematic Review and Network Meta-Analysis. *Acta Psychiatr. Scand.* **2024**, *150*(6), 500–515. <https://doi.org/https://doi.org/10.1111/acps.13728>.
- [61] Shulman, K.I.; Herrmann, N.; Walker, S.E. Current Place of Monoamine Oxidase Inhibitors in the Treatment of Depression. *CNS Drugs* **2013**, *27*(10), 789–797. <https://doi.org/10.1007/s40263-013-0097-3>.
- [62] Jefferson, J.W.; Pradko, J.F.; Muir, K.T. Bupropion for Major Depressive Disorder: Pharmacokinetic and Formulation Considerations. *Clin. Ther.* **2005**, *27*(11), 1685–1695. <https://doi.org/10.1016/j.clinthera.2005.11.011>.
- [63] Anttila, S.A.K.; Leinonen, E.V.J. A Review of the Pharmacological and Clinical Profile of Mirtazapine. *CNS Drug Rev.* **2001**, *7*(3), 249–264. <https://doi.org/10.1111/j.1527-3458.2001.tb00198.x>.
- [64] Fagioli, A.; Comandini, A.; Dell'Osso, M.C.; Kasper, S. Rediscovering Trazodone for the Treatment of Major Depressive Disorder. *CNS Drugs* **2012**, *26*(12), 1033–1049. <https://doi.org/10.1007/s40263-012-0010-5>.
- [65] Kasper, S.; Hajak, G.; Wulff, K.; Hoogendijk, W.J.G.; Montejo, A.L.; Smeraldi, E.; Rybakowski, J.K.; Quera-Salva, M.A.; Wirz-Justice, A.M.; Picarel-Blanchot, F.; et al. Efficacy of the Novel Antidepressant Agomelatine on the Circadian Rest-Activity Cycle and Depressive and Anxiety Symptoms in Patients with Major Depressive Disorder: A Randomized, Double-Blind Comparison with Sertraline. *J. Clin. Psychiatry* **2010**, *71*(2), 109–120. <https://doi.org/10.4088/JCP.09m05347blu>.
- [66] Duman, R.S.; Monteggia, L.M. A Neurotrophic Model for Stress-Related Mood Disorders. *Biol. Psychiatry* **2006**, *59*(12), 1116–1127. <https://doi.org/10.1016/j.biopsych.2006.02.013>.
- [67] Huneke, N.T.M.; Amin, J.; Baldwin, D.S.; Bellato, A.; Brandt, V.; Chamberlain, S.R.; Correll, C.U.; Eudave, L.; Garner, M.; Gosling, C.J.; et al. Placebo Effects in Randomized Trials of Pharmacological and Neurostimulation Interventions for Mental Disorders: An Umbrella Review. *Mol. Psychiatry* **2024**, *29*(12), 3915–3925. <https://doi.org/10.1038/s41380-024-02638-x>.
- [68] Jones, B.D.M.; Razza, L.B.; Weissman, C.R.; Karbi, J.; Vine, T.; Mulsant, L.S.; Brunoni, A.R.; Husain, M.I.; Mulsant, B.H.; Blumberger, D.M.; et al. Magnitude of the Placebo Response Across Treatment Modalities Used for Treatment-Resistant

- Depression in Adults: A Systematic Review and Meta-Analysis. *JAMA Netw. Open* **2021**, 4(9), e2125531. <https://doi.org/10.1001/jamanetworkopen.2021.25531>.
- [69] Turner, E.H.; Matthews, A.M.; Linardatos, E.; Tell, R.A.; Rosenthal, R. Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. *N. Engl. J. Med.* **2008**, 358(3), 252–260. <https://doi.org/10.1056/nejmsa065779>.
- [70] Stone, M.B.; Yaseen, Z.S.; Miller, B.J.; Richardville, K.; Kalaria, S.N.; Kirsch, I. Response to Acute Monotherapy for Major Depressive Disorder in Randomized, Placebo Controlled Trials Submitted to the US Food and Drug Administration: Individual Participant Data Analysis. *BMJ* **2022**, 378, e067606. <https://doi.org/10.1136/bmj-2021-067606>.
- [71] Leucht, S.; Huhn, M.; Davis, J.M. Should ‘Typical’, First-Generation Antipsychotics No Longer Be Generally Used in the Treatment of Schizophrenia? *Eur. Arch. Psychiatry Clin. Neurosci.* **2021**, 271(8), 1411–1413. <https://doi.org/10.1007/s00406-021-01335-y>.
- [72] Stegmayer, K.; Walther, S.; van Harten, P. Tardive Dyskinesia Associated with Atypical Antipsychotics: Prevalence, Mechanisms and Management Strategies. *CNS Drugs* **2018**, 32(2), 135–147. <https://doi.org/10.1007/s40263-018-0494-8>.
- [73] Bhidayasiri, R.; Jitkriksadakul, O.; Friedman, J.H.; Fahn, S. Updating the Recommendations for Treatment of Tardive Syndromes: A Systematic Review of New Evidence and Practical Treatment Algorithm. *J. Neurol. Sci.* **2018**, 389, 67–75. <https://doi.org/10.1016/j.jns.2018.02.010>.
- [74] Lieberman, J.A.; Stroup, T.S.; McEvoy, J.P.; Swartz, M.S.; Rosenheck, R.A.; Perkins, D.O.; Keefe, R.S.E.; Davis, S.M.; Davis, C.E.; Lebowitz, B.D.; Severe, J.; Hsiao, J.K. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. *N. Engl. J. Med.* **2005**, 353(12), 1209–1223. <https://doi.org/10.1056/nejmoa051688>.
- [75] Kikuchi, T.; Maeda, K.; Suzuki, M.; Hirose, T.; Futamura, T.; McQuade, R.D. Discovery Research and Development History of the Dopamine D2 Receptor Partial Agonists, Aripiprazole and Brexpiprazole. *Neuropsychopharmacol. Rep.* **2021**, 41(2), 134–143. <https://doi.org/10.1002/npr2.12180>.
- [76] Schneider-Thoma, J.; Chalkou, K.; Dörries, C.; Bighelli, I.; Ceraso, A.; Huhn, M.; Sifakis, S.; Davis, J.M.; Cipriani, A.; Furukawa, T.A.; et al. Comparative Efficacy and Tolerability of 32 Oral and Long-Acting Injectable Antipsychotics for the Maintenance Treatment of Adults with Schizophrenia: A Systematic Review and Network Meta-Analysis. *Lancet* **2022**, 399(10327), 824–836. [https://doi.org/10.1016/S0140-6736\(21\)01997-8](https://doi.org/10.1016/S0140-6736(21)01997-8).
- [77] Siskind, D.; McCartney, L.; Goldschlager, R.; Kisely, S. Clozapine v. First- and Second-Generation Antipsychotics in Treatment-Refractory Schizophrenia: Systematic Review and Meta-Analysis. *Br. J. Psychiatry* **2016**, 209(5), 385–392. <https://doi.org/10.1192/bjp.bp.115.177261>.
- [78] Rambaud, V.; Marzo, A.; Chaumette, B. Oxidative Stress and Emergence of Psychosis. *Antioxidants* **2022**, 11(10), 1870. <https://doi.org/10.3390/antiox11101870>.
- [79] Goh, X.X.; Tang, P.Y.; Tee, S.F. Effects of Antipsychotics on Antioxidant Defence System in Patients with Schizophrenia: A Meta-Analysis. *Psychiatry Res.* **2022**, 309, 114429. <https://doi.org/10.1016/j.psychres.2022.114429>.
- [80] Molina, J.D.; Avila, S.; Rubio, G.; López-Muñoz, F. Metabolomic Connections between Schizophrenia, Antipsychotic Drugs and Metabolic Syndrome: A Variety of Players. *Curr. Pharm. Des.* **2021**, 27(39), 4049–4061. <https://doi.org/10.2174/1381612827666210804110139>.
- [81] Correll, C.U.; Solmi, M.; Croatto, G.; Schneider, L.K.; Rohani-Montez, S.C.; Fairley, L.; Smith, N.; Bitter, I.; Gorwood, P.; Taipale, H.; Tiihonen, J. Mortality in People with Schizophrenia: A Systematic Review and Meta-Analysis of Relative Risk and Aggravating or Attenuating Factors. *World Psychiatry* **2022**, 21(2), 248–271. <https://doi.org/10.1002/wps.20994>.
- [82] Burschinski, A.; Schneider-Thoma, J.; Chiocchia, V.; Schestag, K.; Wang, D.; Sifakis, S.; Bighelli, I.; Wu, H.; Hansen, W.P.; Priller, J.; Davis, J.M.; Salanti, G.; Leucht, S. Metabolic Side Effects in Persons with Schizophrenia during Mid- to Long-Term Treatment with Antipsychotics: A Network Meta-Analysis of Randomized Controlled Trials. *World Psychiatry* **2023**, 22(1), 116–128. <https://doi.org/10.1002/wps.21036>.
- [83] Ferencsajtajn-Rochowiak, E.; Rybakowski, J.K. Long-Term Lithium Therapy: Side Effects and Interactions. *Pharmaceuticals* **2023**, 16(1), 74. <https://doi.org/10.3390/ph16010074>.

- [84] Ferensztajn-Rochowiak, E.; Lewitzka, U.; Chłopocka-Woźniak, M.; Rybakowski, J.K. Effectiveness of Ultra-Long-Term Lithium Treatment: Relevant Factors and Case Series. *Int. J. Bipolar Disord.* **2024**, *12*(1), 7. <https://doi.org/10.1186/s40345-024-00328-9>.
- [85] López-Muñoz, F.; D'Ocón, P.; Romero, A.; Guerra, J.A.; De Berardis, D.; Álamo, C. Discovery Patterns of Drugs Approved for Treating Bipolar Disorder by Applying Operational Criteria of Serendipity: A Historical Analysis. *Ment. Illn.* **2024**, *2024*(1), 8848525. <https://doi.org/https://doi.org/10.1155/2024/8848525>.
- [86] Thangavel, M.; Sterlin Raj, T.; Chinnappan, S.; Anbalagan, M.; Arunagirinathan, N.; Kuvin, E.; Sasikumar, P.; Paranjothy, C.; Mani, R.R. Lithium-Induced Neuroprotection in Bipolar Disorder: Translational Insights into Cytoskeletal and Proteomic Mechanisms. *IBRO Neurosci. Rep.* **2025**, *19*, 725–736. <https://doi.org/10.1016/j.ibneur.2025.10.003>.
- [87] O'Brien, W.T.; Klein, P.S. Validating GSK3 as an in Vivo Target of Lithium Action. *Biochem. Soc. Trans.* **2009**, *37*(5), 1133–1138. <https://doi.org/10.1042/BST0371133>.
- [88] Yatham, L.N.; Kennedy, S.H.; Parikh, S.V.; Schaffer, A.; Bond, D.J.; Frey, B.N.; Sharma, V.; Goldstein, B.I.; Rej, S.; Beaulieu, S.; et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 Guidelines for the Management of Patients with Bipolar Disorder. *Bipolar Disord.* **2018**, *20*(2), 97–170. <https://doi.org/10.1111/bdi.12609>.
- [89] Rogawski, M.A.; Löscher, W. The Neurobiology of Antiepileptic Drugs for the Treatment of Nonepileptic Conditions. *Nat. Med.* **2004**, *10*(7), 685–692. <https://doi.org/10.1038/nm1074>.
- [90] Gentile, S. Risks of Neurobehavioral Teratogenicity Associated with Prenatal Exposure to Valproate Monotherapy: A Systematic Review with Regulatory Repercussions. *CNS Spectr.* **2014**, *19*(4), 305–315. <https://doi.org/10.1017/S1092852913000990>.
- [91] Koren, G.; Nava-Ocampo, A.A.; Moretti, M.E.; Sussman, R.; Nulman, I. Major Malformations with Valproic Acid. *Can. Fam. Physician* **2006**, *52*(4), 441–447.
- [92] FDA Drug Safety Communication: Valproate anti-Seizure Products Contraindicated for migraine Prevention in Pregnant Women due to Decreased IQ Scores in Exposed. Available online: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-valproate-anti-seizure-products-contraindicated-migraine-prevention> (accessed on).
- [93] Vinkers, C.H.; Olivier, B. Mechanisms Underlying Tolerance after Long-Term Benzodiazepine Use: A Future for Subtype-Selective GABAA Receptor Modulators? *Adv. Pharmacol. Sci.* **2012**, *2012*, 416864. <https://doi.org/10.1155/2012/416864>.
- [94] Engin, E. GABAA Receptor Subtypes and Benzodiazepine Use, Misuse, and Abuse. *Front. Psychiatry* **2023**, *13*, 1060949. <https://doi.org/10.3389/fpsy.2022.1060949>.
- [95] Edinoff, A.N.; Nix, C.A.; Hollier, J.; Sagrera, C.E.; Delacroix, B.M.; Abubakar, T.; Cornett, E.M.; Kaye, A.M.; Kaye, A.D. Benzodiazepines: Uses, Dangers, and Clinical Considerations. *Neurol. Int.* **2021**, *13*(4), 594–607. <https://doi.org/10.3390/neurolint13040059>.
- [96] Piot, A.; Jovanovic, J.N. Synaptic Correlates of Benzodiazepine Tolerance. *Mol. Psychiatry* **2026**, *31*, 3775–3785. <https://doi.org/10.1038/s41380-026-03512-8>.
- [97] Loane, C.; Politis, M. Buspirone: What Is It All About? *Brain Res.* **2012**, *1461*, 111–118. <https://doi.org/10.1016/j.brainres.2012.04.032>.
- [98] Silczuk, A.; Lewandowska, A.; Filip, M.; Atroszko, P.A.; Podolec, J.; Gałęcka, M.; Madejek, R.; Czyżewski, Ł. Current Insights into the Safety and Adverse Effects of Methylphenidate in Children, Adolescents, and Adults—Narrative Review. *Pharmacol. Rep.* **2025**, *77*(5), 1247–1259. <https://doi.org/10.1007/s43440-025-00763-0>.
- [99] Newcorn, J.H.; Krone, B.; Dittmann, R.W. Nonstimulant Treatments for ADHD. *Child Adolesc. Psychiatr. Clin. N. Am.* **2022**, *31*(3), 417–435. <https://doi.org/10.1016/j.chc.2022.03.005>.
- [100] Heal, D.J.; Smith, S.L.; Gosden, J.; Nutt, D.J. Amphetamine, Past and Present—A Pharmacological and Clinical Perspective. *J. Psychopharmacol.* **2013**, *27*(6), 479–496. <https://doi.org/10.1177/0269881113482532>.

- [101] Storebø, O.J.; Ramstad, E.; Krogh, H.B.; Nilausen, T.D.; Skoog, M.; Holmskov, M.; Rosendal, S.; Groth, C.; Magnusson, F.L.; Moreira-Maia, C.R.; et al. Methylphenidate for Children and Adolescents with Attention Deficit Hyperactivity Disorder (ADHD). *Cochrane Database Syst. Rev.* **2015**, 2015(11), CD009885. <https://doi.org/10.1002/14651858.CD009885.pub2>.
- [102] Krystal, J.H.; Kavalali, E.T.; Monteggia, L.M. Ketamine and Rapid Antidepressant Action: New Treatments and Novel Synaptic Signaling Mechanisms. *Neuropsychopharmacology* **2024**, 49(1), 41–50. <https://doi.org/10.1038/s41386-023-01629-w>.
- [103] Reif, A.; Bitter, I.; Buyze, J.; Cebulla, K.; Frey, R.; Fu, D.-J.; Ito, T.; Kambarov, Y.; Llorca, P.-M.; Oliveira-Maia, A.J.; et al. Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression. *N. Engl. J. Med.* **2023**, 389(14), 1298–1309. <https://doi.org/10.1056/nejmoa2304145>.
- [104] Antos, Z.; Żukow, X.; Bursztynowicz, L.; Jakubów, P. Beyond NMDA Receptors: A Narrative Review of Ketamine's Rapid and Multifaceted Mechanisms in Depression Treatment. *Int. J. Mol. Sci.* **2024**, 25(24), 13658. <https://doi.org/10.3390/ijms252413658>.
- [105] Li, L.J.; Mo, Y.; Shi, Z.M.; Huang, X.B.; Ning, Y.P.; Wu, H.W.; Yang, X.H.; Zheng, W. Psilocybin for Major Depressive Disorder: A Systematic Review of Randomized Controlled Studies. *Front. Psychiatry* **2024**, 15, 1416420. <https://doi.org/10.3389/fpsyt.2024.1416420>.
- [106] Goodwin, G.M.; Aaronson, S.T.; Alvarez, O.; Arden, P.C.; Baker, A.; Bennett, J.C.; Bird, C.; Blom, R.E.; Brennan, C.; Brusch, D.; et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. *N. Engl. J. Med.* **2022**, 387(18), 1637–1648. <https://doi.org/10.1056/nejmoa2206443>.
- [107] Fang, S.; Yang, X.; Zhang, W. Efficacy and Acceptability of Psilocybin for Primary or Secondary Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Front. Psychiatry* **2024**, 15, 1359088. <https://doi.org/10.3389/fpsyt.2024.1359088>.
- [108] Carhart-Harris, R.; Giribaldi, B.; Watts, R.; Baker-Jones, M.; Murphy-Beiner, A.; Murphy, R.; Martell, J.; Blemings, A.; Erritzoe, D.; Nutt, D.J. Trial of Psilocybin versus Escitalopram for Depression. *N. Engl. J. Med.* **2021**, 384(15), 1402–1411. <https://doi.org/10.1056/nejmoa2032994>.
- [109] Lewis, G.; Marston, L.; Duffy, L.; Freemantle, N.; Gilbody, S.; Hunter, R.; Kendrick, T.; Kessler, D.; Mangin, D.; King, M.; et al. Maintenance or Discontinuation of Antidepressants in Primary Care. *N. Engl. J. Med.* **2021**, 385(14), 1257–1267. <https://doi.org/10.1056/nejmoa2106356>.
- [110] Harrow, M.; Jobe, T.H.; Faull, R.N. Does Treatment of Schizophrenia with Antipsychotic Medications Eliminate or Reduce Psychosis? A 20-Year Multi-Follow-Up Study. *Psychol. Med.* **2014**, 44(14), 3007–3016. <https://doi.org/10.1017/S0033291714000610>.
- [111] Moncrieff, J.; Crellin, N.; Stansfeld, J.; Cooper, R.; Marston, L.; Freemantle, N.; Lewis, G.; Hunter, R.; Johnson, S.; Barnes, T.; et al. Antipsychotic Dose Reduction and Discontinuation versus Maintenance Treatment in People with Schizophrenia and Other Recurrent Psychotic Disorders in England (the RADAR Trial): An Open, Parallel-Group, Randomised Controlled Trial. *Lancet Psychiatry* **2023**, 10(11), 848–859. [https://doi.org/10.1016/S2215-0366\(23\)00258-4](https://doi.org/10.1016/S2215-0366(23)00258-4).

Disclaimer/Publisher's Note: The views expressed in this article are those of the author(s) and do not necessarily reflect the views of the publisher or editors. The publisher and editors assume no responsibility for any injury or damage resulting from the use of information contained herein.