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REVIEW ARTICLE

Literature Review: Personalised Medicine Tools for Antidepressant Management

Mikhail A Parshenkov,[1] Anna N Dyakonova,[2] Polina P Skovorodko,[1] Galina M Rodionova[2]

1. Laboratory of Histology and Immunohistochemistry, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia.
2. Department of Pharmaceutical and Toxicological Chemistry named after A.P. Arzamastsev, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia.

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Corresponding author:
MIKHAIL PARSHENKOV
E: misjakj@gmail.com;
T: +7(919) 7201-069

Abstract

Antidepressants are widely used in clinical practice, including for conditions beyond major depression (MD) disorders. However, clinicians still lack reliable tools to match patients with the right drug. Many individuals either fail to respond to the first prescribed agent or discontinue treatment due to side effects. This review focuses on two promising solutions: therapeutic drug monitoring (TDM) and pharmacogenetic testing. TDM measures the actual drug concentration in blood, rather than the prescribed dose. It's important to keep in mind that some individuals exhibit rapid or slow drug metabolism, leading to side effects or no effect at all. For example, for antidepressants like escitalopram, venlafaxine and paroxetine, blood levels often explain treatment response better than dose alone. Pharmacogenetics adds another layer, showing how genetic differences, especially in CYP2C19 and CYP2D6 – can change how drugs are processed. Other gene variants, like those in ABCB1 or SLC6A4, affect how well the drug gets into the brain or how patients tolerate it. Taken together, TDM and pharmacogenetics shift antidepressant prescribing from guesswork to evidence-based decision-making. By measuring drug levels and accounting for genetic variability, clinicians can better match each patient with the right treatment: earlier and with greater confidence. This approach improves efficacy, minimises adverse effects and reduces unnecessary switching or prolonged suffering. As prescribing expands, often beyond psychiatric indications and into long-term use without follow-up – the need for precision grows. What was once an aspirational model of care is becoming a clinical streamline in modern pharmacology.

Key words: Drug monitoring; Pharmacogenetics; Antidepressive agents; Depressive disorder, major; Monoamine hypothesis; Precision medicine.

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Introduction

Antidepressants act on monoaminergic systems to modulate synaptic transmission and reduce depressive symptoms.[1] Initially developed for major depressive disorder (MDD), they are now widely prescribed for conditions like anxiety, chronic pain, sleep disturbances and other non-psychiatric conditions.[2, 3]

Prescribing rates rose in the early 2000s, when newer agents (selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs)) replaced tricyclic antidepressants (TCAs), offering improved tolerability and broader applicability in day-to-day practice.[4, 5] Lower perceived risk, combined with unclear stopping strategies, has led to long-term use, often maintained without diagnosis or structured follow-up. Current estimates suggest that

up to 70 % of users do not meet criteria for any psychiatric disorder.[6, 7] As prescribing outpaces diagnostic precision, the rationale for indefinite pharmacological treatment becomes increasingly difficult to defend.

Antidepressant treatment outcomes remain largely unpredictable, even after decades of research and the availability of multiple pharmacological classes. Around half of patients do not respond to the first prescribed drug and switching strategies are often driven by habit or availability rather than mechanistic rationale.[8–10] This pattern, widely known as the "trial-and-error" model,[11] reflects a critical gap in psychiatric care: the absence of reliable tools to match patients with the most effective therapy from the outset.

To move beyond the "trial-and-error" model, many point to therapeutic drug monitoring (TDM) and pharmacogenetic testing (PGT) as promising tools for guiding treatment choice. Among them, TDM and PGT offer a way to tailor treatment based on individual pharmacokinetics and genetic profiles.[12, 13] These tools have improved treatment precision in oncology and cardiology, where they are now part of routine care.[14–16] In psychiatry, however, their adoption remains limited. Clinical guidelines provide few actionable recommendations and the supporting evidence is fragmented, with inconsistent findings across drug classes, study designs and patient populations. As a result, these methods remain underutilised despite their potential to inform more rational prescribing.

This literature review critically examines current strategies for individualising antidepressant therapy, with a focus on therapeutic drug monitoring and pharmacogenetics. It outlines a practical and clinically grounded framework to support more targeted, biologically informed prescribing in routine psychiatric care.

Methods

A structured literature search was performed in *PubMed, Scopus* and *Web of Science* to identify studies on TDM and PGT in antidepressant therapy. The search combined controlled vocabulary and free-text terms with Boolean operators, including "therapeutic drug monitoring", "TDM", "pharmacogenetics", "pharmacogenomics", "antidepressant", "depression", "personalised medicine" and "precision psychiatry".

The primary focus was on publications from January 2021 to June 2025, reflecting the most recent evidence, while seminal earlier studies were also considered when they provided foundational insights. Only peer-reviewed original studies, clinical trials, reviews and clinical guidelines in English that directly addressed the application of TDM and PGT in antidepressant therapy were included. Non-peer-reviewed works and articles without direct relevance to personalised antidepressant management were excluded. Data were extracted by three independent researchers. Titles and abstracts were screened first, followed by full-text review and key data from eligible studies were extracted and synthesised thematically to provide a critical overview of current knowledge and clinical perspectives.

The clinical landscape

MDD is a systemic disorder, shaped by the dynamic interplay between the brain, endocrine system, immune response and environment (Figure 1).[17, 18] Although its precise pathogenesis remains unresolved, researchers have proposed multiple hypotheses to explain its onset and progression. In their recent comprehensive review, Cui and colleagues synthesised a range of hypotheses underlying MDD pathogenesis: genetic vulnerability, chronic psychosocial stress, neuroinflammation, monoaminergic and glutamatergic dysregulation, impaired neurotrophic signalling and endocrine imbalance (with involving the hypothalamic-pituitary-adrenal (HPA) axis).[5]

Over the past two decades, the leading hypotheses of MDD pathogenesis have shifted from the narrow focus on neurotransmitter imbalance to a broader, systems-level understanding of brain function. This expanded view emphasises the complex interplay among multiple physiological systems: stress reactivity, synaptic remodelling and neuroimmune crosstalk, while highlighting astrocytic signalling as an emerging convergent pathway of particular interest.[19–21] As recent studies suggest, acknowledging these mechanisms may ultimately shift how MDD is approached.

Off-label conditions. MDD is the most common indication for "mood-directed" pharmacotherapy,

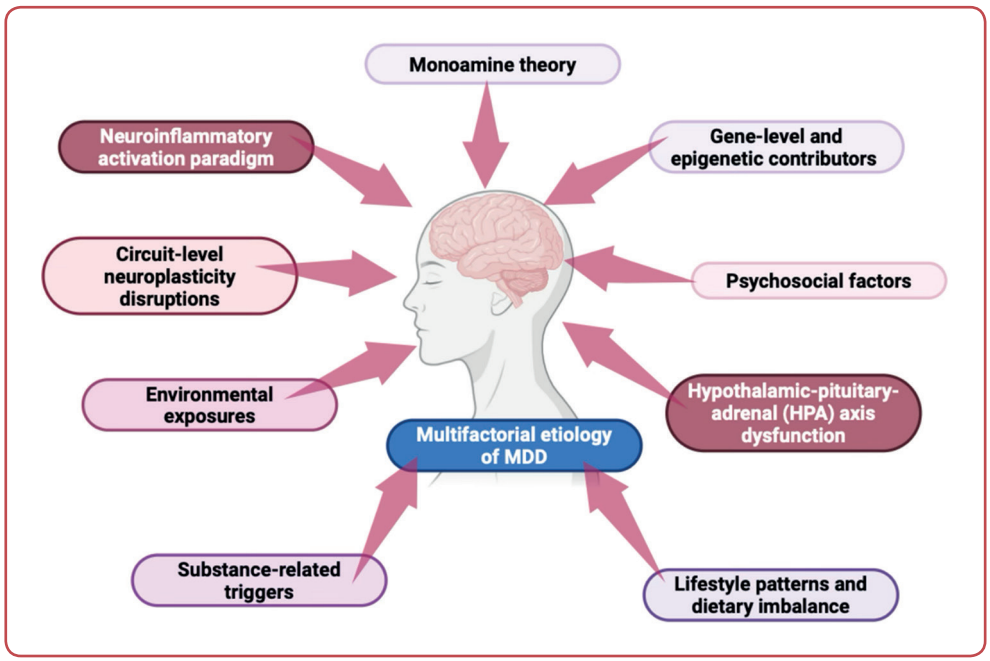

Figure 1: Schematic summary of the multifactorial origins of major depressive disorder (MDD)

but clinical practice has increasingly extended its use to a broader range of conditions. A growing body of evidence supports the application of these treatments in disorders not traditionally classified as affective. For example, there are chronic pain syndromes, eating disorders, sleep disturbances, nicotine dependence, menopausal symptoms and a variety of other somatic and behavioural conditions.[22–25]

Many of these conditions share neurobiological or psychosomatic features with depression (dysregulated neurotransmission, heightened stress reactivity, or impaired affective processing). In clinical practice, such overlaps have broadened therapeutic targets, leading to the use of psychotropic medications beyond their traditional psychiatric indications.

Notably, large-scale prescription data from North America and Europe suggest that off-label use of drugs conventionally associated with depression now constitutes a significant proportion of real-world practice.[26] These trends raise important questions about diagnostic fluidity, neurochemical commonalities across disorders and the adaptability of existing treatments across divergent clinical presentations.

Monoamine hypothesis

In the mid-20th century, two pharmacologically unrelated drugs: iproniazid (N'-(propan-2-yl) pyridine-4-carbohydrazide; Figure 2A) – used to treat tuberculosis and imipramine (3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-N,N-dimethyl-1-propanamine hydrochloride (1:1); Figure 2B) – tested for allergic conditions, were observed to improve mood in patients.[27] These unexpected clinical effects became the foundation for the monoamine hypothesis, which proposed that depression results from depleted levels of serotonin, norepinephrine, or dopamine in the synaptic cleft.[28, 29]

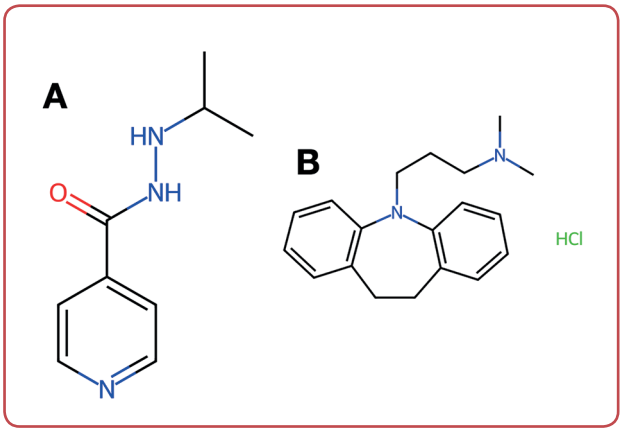

Figure 2 : Molecular structures of key early antidepressants: (A) Iproniazid (N'-(propan-2-yl)pyridine-4-carbohydrazide); (B) Imipramine (3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-N,N-dimethyl-1-propanamine hydrochloride (1:1))

This idea was further supported by findings with reserpine, an antihypertensive drug that induced depressive symptoms by depleting monoamines through inhibition of their vesicular storage.[30, 31] Together, these observations linked monoaminergic modulation to mood regulation and laid the groundwork for decades of antidepressant development, including monoamine oxidase inhibitors (MAOIs), TCAs and eventually SSRIs.

Pharmacology of antidepressants

Antidepressants are conventionally grouped by their mechanism of action, with primary classes: TCAs, SSRIs, SNRIs and atypical agents – noradrenergic and specific serotonergic antidepressants (NaSSAs) or serotonin antagonist and reuptake inhibitors (SARIs) (Figure 3).[32, 33] Each of these drug classes targets the monoaminergic system but does so through distinct pharmacodynamic profiles.

Mechanisms of actions

The development of antidepressant medications has been largely guided by the monoamine hypothesis – the idea that mood disorders arise from functional deficits in key neurotransmitters like serotonin (5-HT), norepinephrine (NE) and dopamine (DA) (Figure 4).[34] Most first-line pharmacological treatments, like SSRIs and SNRIs, aim to increase synaptic levels of these neurotransmitters by blocking their reabsorption at presynaptic terminals.[35] For instance, SSRIs (eg, fluoxetine or escitalopram) selectively inhibit the serotonin transporter (SERT), thereby enhancing serotonergic transmission.[36] SNRIs (like venlafaxine or duloxetine) act on both SERT and the norepinephrine transporter (NET), with compounds as milnacipran showing greater selectivity toward NE.[37]

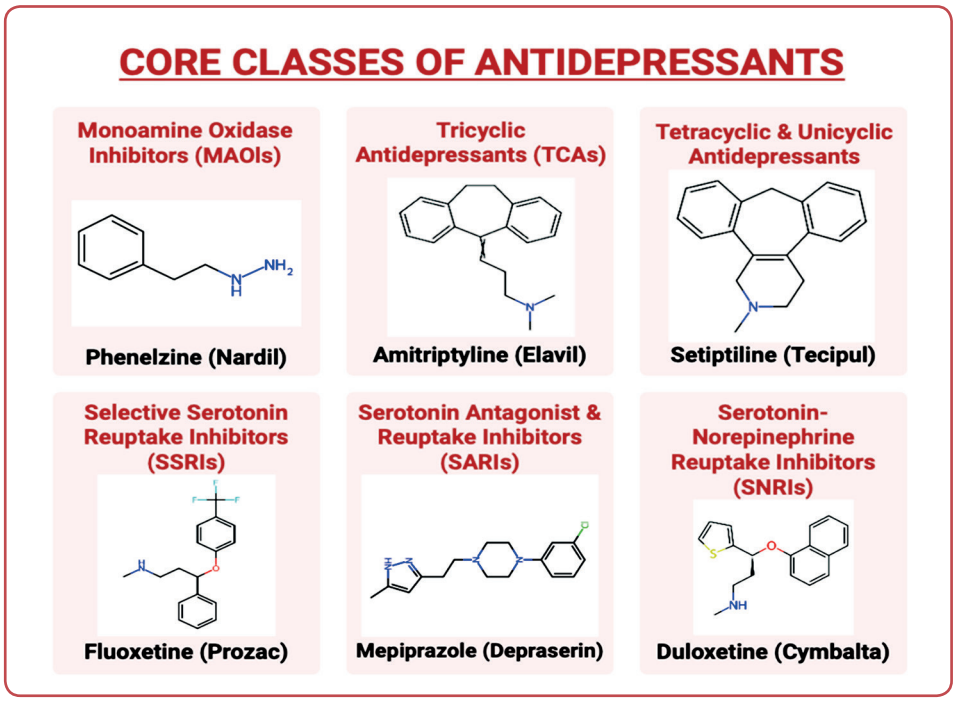

Figure 3: Representative antidepressants from core pharmacological classes. This figure illustrates the conventional grouping of antidepressants based on their primary mechanisms of action, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and atypical agents (eg noradrenergic and specific serotonergic antidepressants (NaSSAs) or serotonin antagonist and reuptake inhibitors (SARIs)). Boundaries between these classes are not absolute, reflecting the complex and often overlapping pharmacodynamic profiles.

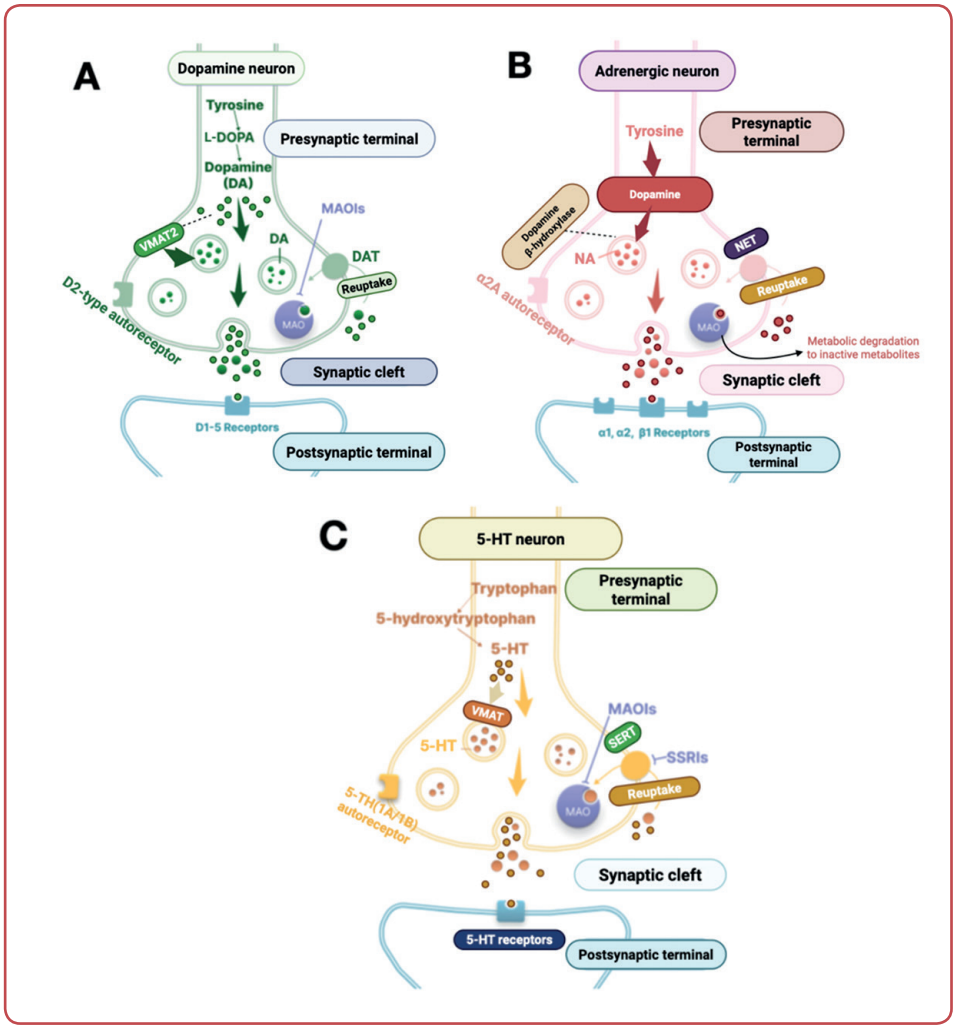

Figure 4: Monoaminergic synapses and antidepressant targets: (A) – dopamine neuron; (B) – adrenergic neuron; (C) – 5-HT-neuron

DA – dopamine; NA – norepinephrine; 5-HT – serotonin; VMAT – vesicular monoamine transporter; DAT – dopamine transporter; NET – norepinephrine transporter; SERT – serotonin transporter; MAO – monoamine oxidase; SSRIs – selective serotonin reuptake inhibitors; MAOIs – monoamine oxidase inhibitors; L-DOFA – L-3,4-dihydroxyphenylalanine.

However, antidepressant efficacy cannot be explained solely by acute increases in monoamine levels. Clinical improvement typically occurs after several weeks (suggest of involvement of downstream mechanisms). Chronic antidepressant use has been shown to activate intracellular signalling pathways (eg, cAMP/PKA, MAPK, mTOR), promote expression of brain-derived neurotrophic factor (BDNF) and stimulate neurogenesis – particularly in the hippocampus.[38, 39] This shift from monoamines to neuroplasticity mechanisms has led to a broader understanding of antidepressant pharmacology.

Pharmacokinetics and clinical considerations

Pharmacokinetic profiles of antidepressants vary substantially across and within classes, influencing onset of action, half-life and metabolism. For instance, fluoxetine has a long half-life (4 – 6 days) and produces active metabolites (a property that can benefit patients with poor adherence).[40, 41] In contrast, paroxetine has a shorter half-life and higher risk of withdrawal.[42] Drug-drug interaction profiles also vary: fluvoxamine is a potent CYP1A2 and CYP2C19 inhibitor, whereas sertraline, with weaker effects on these enzymes, poses a lower interaction risk.[43]

Side effects reflect receptor binding profiles beyond primary monoaminergic targets. TCAs, for example, antagonise muscarinic, histaminergic and α_1-adrenergic receptors.[44] For TCAs, the main (most common) side effects are anticholinergic effects, sedation and orthostatic hypotension.[45] SSRIs are better tolerated but commonly cause gastrointestinal symptoms, sexual dysfunction

and sleep disturbances.[4] Atypical antidepressants like bupropion, which primarily inhibits dopamine and norepinephrine reuptake – have distinct profiles, often associated with insomnia but minimal sexual side effects.[46]

The monoamine model, while foundational, has clear limitations. A significant proportion of patients fail to respond to monoaminergic agents and no biomarker robustly predicts treatment response. This has spurred research into alternative targets, such as the glutamatergic system. Esketamine, an NMDA receptor antagonist, exemplifies this shift and demonstrates rapid antidepressant effects in treatment-resistant cases by modulating synaptic plasticity via BDNF and mTOR pathways.[47, 48] Similar interest surrounds novel agents like dextromethorphan-bupropion and brexanolone, which engage GABA-ergic or neurosteroid mechanisms.[49]

This pharmacological diversity underscores the need for a precision approach. Multiple comparative studies (eg Cipriani et al[50]) demonstrate that efficacy and tolerability vary not only between classes of antidepressants but also within them, with outcomes often influenced by individual pharmacogenetics, comorbidities and symptom profiles.

The role of drug monitoring and pharmacogenetics

Therapeutic drug monitoring

TDM refers to the measurement of drug concentrations in biological fluids (typically plasma), aimed at maintaining levels within a defined therapeutic window – that is, high enough to ensure efficacy, but low enough to avoid toxicity (Figure 5).[51] In clinical settings marked by polypharmacy, metabolic variability and organ dysfunction, prescribed doses often fail to predict actual drug exposure. TDM addresses this gap.[52]

This principle is especially critical for medications with narrow therapeutic profile: lithium,[53] tricyclic antidepressants,[54] digoxin,[55] or methotrexate,[56] where small deviations in concentration can result in loss of effect or serious harm. By providing real-time, individualised pharmacokinetic data, TDM allows clinicians to quantify systemic drug levels, detect nonadherence and optimise therapy with greater precision.

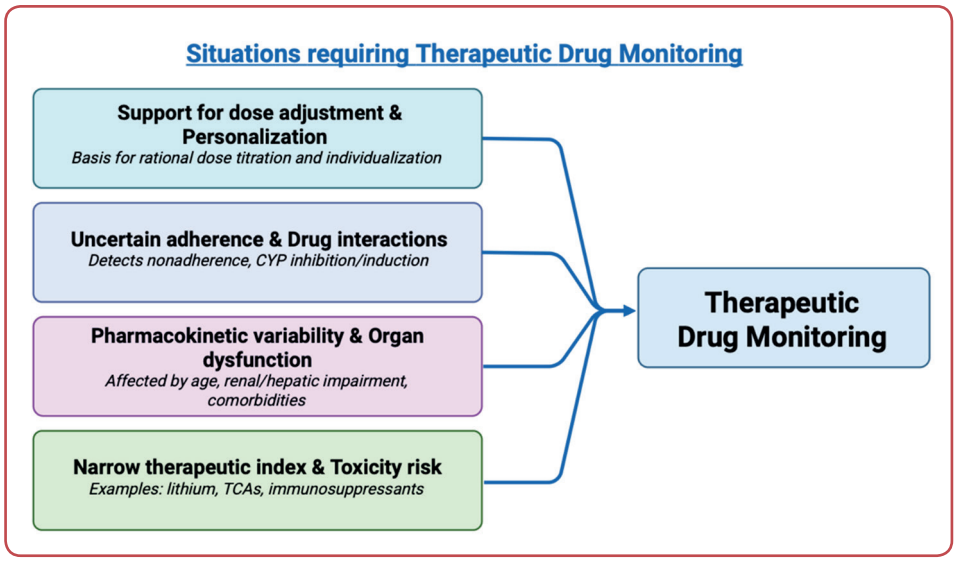

Figure 5: Clinical contexts supporting therapeutic drug monitoring (TDM). This schematic illustrates various clinical scenarios where TDM is beneficial – all of which can lead to unpredictable drug exposure despite consistent prescribed doses. TDM helps in maintaining drug levels within the therapeutic window, optimising efficacy and minimising toxicity.

The antidepressant therapy

Therapeutic drug monitoring is rapidly becoming an indispensable component of antidepressant pharmacotherapy (the name "personalised targeted medicine" can often be found in the medical literature).[57] By enabling direct quantification of systemic drug exposure, TDM offers clinicians a real-time compass to optimise efficacy while minimising adverse effects, especially when dose-response relationships are steep or nonlinear.

Recent studies demonstrate practical clinical relevance. For example, imaging works using PET ligands (eg, DASB) have demonstrated that plasma levels of SSRIs correlate more precisely with serotonin transporter occupancy than with prescribed dose, with high SERT occupancy (80 %) typically required for clinical response. As previously discussed, serotonin transporter occupancy is a key mechanism of action for SSRIs. The correlation between plasma levels and SERT occupancy highlights the importance of TDM in achieving optimal therapeutic effects.[58, 59] Moreover, agents like venlafaxine and citalopram show concentration-dependent clinical outcomes: plasma levels below defined thresholds (< 195 ng/mL for venlafaxine + its active metabolite O-desmethylvenlafaxine (ODV); < 50 ng/mL for citalopram) have been consistently associated with poor response and prolonged hospitalisation.[60]

Recent clinical findings challenge the long-standing belief that newer antidepressants lack meaningful plasma response relationships. Thus, in the study by Ostad Haji and colleagues, paroxetine was shown to exhibit a steep "plasma-efficacy curve" that closely mirrored serotonin transporter.[61] Building on this, Eichentopf et al identified a therapeutic range (for escitalopram) of 20 – 40 ng/mL, with levels above 15 – 20 ng/mL generally sufficient for clinically relevant transporter binding.[62] Another work, Jukic et al demonstrated that ultrarapid metabolisers had markedly lower serum concentrations and were three times more likely to discontinue or switch therapy[63], which emphasises the importance of understanding each patient's genotypic characteristics. Therapeutic drug monitoring becomes not only a guide for efficacy but also a safeguard against toxicity.

Pharmacogenetic

Pharmacogenetic, in context of pharmacology – explores how genetic differences shape individual responses to different drugs. By identifying key variants in drug metabolism and target receptors, it helps personalise treatment decisions within both treatment efficacy and adverse drug reactions.[64, 65]

Cytochrome P450 enzymes play a key role in how our genes influence antidepressant metabolism and clinical response. For example, Wong et al demonstrated that CYP2C19 ultrarapid metabolisers are significantly more likely to switch antidepressants within one year of initiation (in this study, escitalopram was used to demonstrate how metabolic phenotypes influence treatment continuity and tolerability).[66] Similarly, the study by Alchakee et al revealed that CYP2D6 poor metabolisers receiving venlafaxine (it belongs to the class of SNRIs) exhibited elevated plasma levels and a higher incidence of cardiovascular and CNS-related side effects.[67]

Beyond cytochrome P450 enzymes, transporter proteins also shape antidepressant efficacy by regulating drug bioavailability and central nervous system (CNS) penetration. In a study by Wyska et al, polymorphisms in ABCB1 (the gene encoding P-glycoprotein) were shown to alter the efflux of SSRIs across the blood-brain barrier.[68] Similarly, Brunoni and Krout demonstrated that variations in the SLC6A4 gene, particularly the 5-HTTLPR polymorphism, are associated with differential SSRI efficacy and tolerability.[69, 70] Although some subsequent studies have failed to replicate these associations, recent findings by Altar et al and Rothschild et al suggest that combinatorial pharmacogenomic testing – which integrates multiple gene variants, may provide more clinically actionable insights than single-gene approaches.[71, 72]

Moreover, integrating pharmacogenetics with therapeutic drug monitoring substantially enhances precision dosing, particularly for agents with narrow therapeutic indices. For instance, the same SSRI dose may result in subtherapeutic exposure in a CYP2C19 ultrarapid metaboliser but lead to toxicity in a poor metaboliser (PM) – a discrepancy that cannot be resolved by symptom tracking alone.[73, 74]

Today, more and more studies on genetic features of metabolism of different pharmacologic classes of drugs are appearing in the literature. Taken together, these findings confirm that pharmacogenetics is not a theoretical tool but a central

component of data-driven antidepressant selection. When combined with TDM and structured symptom assessment, it enables the construction of rational, biologically-informed treatment algorithms: capable of minimising risk, enhancing efficacy and replacing the conventional "trial-and-error" model.

Conclusion

Antidepressants have become a ubiquitous element of modern medical practice, prescribed far beyond psychiatric indications and often maintained without diagnosis, monitoring, or mechanistic rationale. This literature review underscores a pressing need to move beyond the "trial-and-error" paradigm that continues to dominate antidepressant therapy. By integrating therapeutic drug monitoring and pharmacogenetic profiling, clinicians can tailor treatment based on each patient's unique metabolic and receptor landscape (ie enhancing efficacy, minimising adverse effects and restoring logic to prescribing decisions). Personalised antidepressant therapy is no longer aspirational – it is a clinical imperative. As antidepressant use expands globally, especially in contexts with limited regulatory oversight, adopting data-driven strategies will be essential to ensure rational, safe and effective care for every patient.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Mikhail Alekseevich Parshenkov (MAP):
0009-0004-7170-8783
Anna Nikolaevna Dyakonova (AND):
0009-0004-4520-192X
Polina Petrovna Skovorodko (PPS):
0009-0000-5624-4731
Galina Mikhailovna Rodionova (GMR):
0000-0002-0536-9590

Author contributions

Conceptualisation: MAP, AND, PPS, GMR
Methodology: MAP, AND, PPS, DAP
Validation: AND, PPS
Formal analysis: MAP, PPS
Investigation: AND, PPS
Data curation: AND, PPS
Writing – original draft: MAP, AND, PPS, GMR
Writing – review and editing: MAP, PPS, GMR
Visualisation: MAP, PPS
Supervision: MAP, GMR
Project administration: MAP.

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