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Targeting heterogeneous depression with trazodone prolonged release: from neuropharmacology to clinical application

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Abstract

Aim This paper evaluates the clinical efficacy, safety, and practical implications of Trazodone Prolonged Release (PR) in managing depression, anxiety, and sleep disorders, with a focus on its multimodal mechanism of action and advantages over traditional therapies.

Methodology A critical review of recent literature (2020–2024) [1–3] was conducted, analyzing data from clinical trials, real-world studies, and European treatment guidelines to assess the pharmacodynamics, pharmacokinetics, and therapeutic outcomes of Trazodone PR.

Results Trazodone PR demonstrates efficacy in addressing complex symptoms of depression, anxiety, and sleep disturbances, with a favorable safety profile and reduced risk of sexual dysfunction and weight gain compared to other antidepressants. Its ability to modulate serotonin, norepinephrine, dopamine, and histamine systems enhances mood, sleep quality, and cognitive recovery.

Conclusion Trazodone PR is a versatile and well-tolerated treatment option for patients with comorbid conditions and treatment-resistant cases. Its multimodal action, combined with benefits like improved neuroplasticity through BDNF production, makes it a suitable choice for the long-term management of mood disorders and associated conditions [4–6].

Keywords Trazodone, Prolonged release, Depression, Anxiety, Insomnia, Pharmacodynamics, Pharmacokinetics, Clinical efficacy

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Introduction

Overview of depression, anxiety, and sleep disorders

Depression and anxiety are among the most prevalent mental health disorders globally, affecting millions of individuals annually [7–9]. These conditions often coexist, with research indicating that 50–60% of individuals diagnosed with Major Depressive Disorder (MDD) also experience some form of anxiety disorder during their lifetime [10]. This comorbidity complicates treatment, as the symptoms of depression and anxiety frequently exacerbate one another, leading to amplified disorder severity and poorer overall outcomes [11].

2.

Depression is characterized by persistent sadness, loss of interest in previously enjoyed activities, fatigue, and changes in appetite and sleep patterns [12]. Anxiety, on the other hand, is marked by excessive worry, restlessness, and physical symptoms like increased heart rate and muscle tension [13]. When these conditions co-occur, they create a more challenging clinical picture, complicating treatment efforts [14].

Sleep disturbances, particularly insomnia, often accompany both depression and anxiety. Insomnia is defined as difficulty falling asleep, staying asleep, or waking up too early, and it has been reported in up to 90% of individuals suffering from MDD [15]. This creates a vicious cycle where untreated insomnia worsens mood symptoms, while mood disorders further disrupt normal sleep patterns. If left untreated, chronic sleep disturbances can lead to cognitive decline, fatigue, and impaired daytime functioning, further complicating the treatment of mood and anxiety disorders [16].

Need for alternative treatment approaches

Traditional treatments for depression and anxiety primarily involve selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). These medications are effective at alleviating core depressive symptoms in many patients but often fail to address the full spectrum of symptoms, particularly those related to anxiety and sleep [17]. SSRIs, for example, can sometimes worsen sleep disturbances by increasing agitation and restlessness, while SNRIs may not adequately address physical anxiety symptoms, such as increased heart rate and muscle tension [18].

Given the intricate relationship between depression, anxiety, and sleep disturbances, a more comprehensive, multimodal treatment approach is increasingly recognized as essential. Trazodone Prolonged Release (PR) offers a unique solution by targeting multiple neurotransmitter systems simultaneously [19]. This allows it to improve mood, alleviate anxiety, and enhance sleep quality in patients with complex presentations of depression and anxiety, including those who are treatment resistant [20].

Trazodone prolonged release (PR)

A unique therapeutic option

Trazodone PR is designed to provide sustained therapeutic effects, distinguishing it from its immediate-release counterpart. The prolonged-release formulation ensures that plasma levels of the drug remain stable throughout the day and night, which reduces the likelihood of nighttime awakenings and improves sleep quality [21]. This pharmacokinetic advantage is crucial for patients suffering from both mood disorders and insomnia, as it allows for continuous symptom relief over a 24-h period [22].

Trazodone PR's multimodal mechanism of action further enhances its versatility in treating depression, anxiety, and insomnia. By acting on several neurotransmitter systems, including serotonin, norepinephrine, and histamine, Trazodone PR can address a wide range of symptoms that unimodal antidepressants, such as SSRIs and SNRIs, may fail to treat effectively [23]. This makes it particularly valuable for patients with complex clinical presentations, including those who have not responded adequately to first-line therapies [24].

Trazodone PR is designed to provide sustained therapeutic effects, distinguishing it from other formulations such as immediate-release (IR) and once-a-day (OAD). Globally, trazodone is available in three formulations: IR, PR, and OAD, each with distinct pharmacokinetic profiles. The IR formulation achieves rapid plasma peaks (~ 1 h) and has a short half-life (~ 6.6 h), making it suitable for acute insomnia but prone to daytime sedation due to high peak concentrations [25]. In contrast, the PR formulation exhibits a slower plasma peak (~ 4 h) and longer half-life (~ 12 h), maintaining stable plasma levels to reduce nighttime awakenings and improve sleep quality. The OAD formulation further optimizes this stability, providing a controlled 24-h release without early peaks, thereby enhancing tolerability and compliance [26].

Pharmacodynamics of trazodone

Mechanism of action and pharmacodynamic profile

Trazodone PR is classified as a serotonin antagonist and reuptake inhibitor (SARI). However, its mechanism of action is more complex than traditional serotonin-based therapies, making it uniquely suited for patients with comorbid conditions. The key components of Trazodone pharmacodynamic profile are as follows:

1. **Serotonin Antagonism and Reuptake Inhibition (SARI)**: Trazodone blocks 5-HT2 A and 5-HT2 C receptors, regulating mood, anxiety, and sleep. This action reduces anxiety and agitation while increas-

ing serotonin availability in the synaptic cleft, helping stabilize mood and alleviate depressive symptoms [27].

2. **Adrenergic Receptor Antagonism**: By antagonizing α1-adrenergic receptors, Trazodone lessens physical anxiety symptoms such as increased heart rate and restlessness, modulating the body's "fight-or-flight" response often heightened in anxiety disorders [28].
3. **Histamine Receptor Antagonism**: Trazodone's interaction with H1 receptors induces sedative effects, aiding sleep onset and continuity without the risks of dependence linked to benzodiazepines, benefiting patients with chronic insomnia [29].
4. **Dopaminergic Modulation and Neuroplasticity**: It indirectly boosts dopamine in the prefrontal cortex, enhancing cognitive function and neuroplasticity via increased brain-derived neurotrophic factor (BDNF) levels. This mechanism is valuable for treatment-resistant depression and cognitive impairments [30].

AIM and RATIONALE

This review addresses the pressing need for an updated analysis of trazodone PR's therapeutic profile in 2025. Despite trazodone's long-standing presence in psychiatric care, recent advances in understanding its receptor engagement patterns, particularly through the PR formulation, warrant a comprehensive reassessment. The growing complexity of treatment-resistant depression, coupled with increasing recognition of sleep-mood disorder comorbidity, necessitates a critical evaluation of multimodal therapeutic options. This expert consensus aims to synthesize current evidence on trazodone PR's pharmacodynamics, pharmacokinetics, and clinical applications, providing clinicians with evidence-based guidance for its optimal use in contemporary psychiatric practice. Additionally, this review addresses the evolving role of trazodone PR in specific patient subgroups, particularly those with comorbid conditions where traditional monotherapy approaches have shown limitations.

Methodology

A comprehensive review of the literature was conducted to evaluate the pharmacological profile, clinical efficacy, and practical implications of Trazodone Prolonged Release (PR). The methodology included the following steps:

- **Search Strategy**

Literature was identified through a systematic search of major electronic databases, including PubMed, Scopus, and Web of Science. The initial search focused on studies published between January 2020 and June 2024 specifically addressing Trazodone Prolonged Release. However, due to the limited number of publications specifically focused on the PR formulation during this period, the search criteria were widened to include foundational literature on trazodone's mechanism of action, pharmacological properties, and clinical applications published before 2020. Search terms included 'Trazodone Prolonged Release,' 'pharmacodynamics,' 'pharmacokinetics,' 'depression,' 'anxiety,' 'sleep disorders,' and 'neuroplasticity.' Boolean operators (AND, OR) were used to combine terms effectively. Reference lists of key papers were also manually searched to identify additional relevant studies. This expanded approach allowed for a comprehensive understanding of trazodone's therapeutic profile while incorporating the most recent evidence available on its PR formulation.

- **Inclusion and Exclusion Criteria**

  - **Inclusion Criteria**: Peer-reviewed articles, clinical trials, meta-analyses, and systematic reviews examining the efficacy, safety, or pharmacological properties of Trazodone in treating depression, anxiety, or sleep disorders. Studies focusing on general trazodone pharmacology and mechanism of action were included to provide context for understanding the PR formulation. Additionally, foundational papers on trazodone's therapeutic profile were considered regardless of publication date when deemed relevant to understanding the PR formulation's development and application.
  - **Exclusion Criteria:** Articles without full text and research not published in English were excluded. While studies focusing solely on immediate-release formulations were initially excluded, select papers addressing pharmacological principles and clinical outcomes relevant to understanding the PR formulation were retained to provide comprehensive context.

- **Data Extraction**
  Relevant data, including patient population characteristics, study design, intervention details, outcomes, and safety profiles, were extracted from eligible studies. Key findings on Trazodone PR's pharmacodynamics, pharmacokinetics, and clinical implications were synthesized.
- **Quality Assessment**
  The quality of the studies included was assessed using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) frame-

work, focusing on study design, bias risk, and relevance to clinical practice.

- **Analysis Approach**
  - **Pharmacodynamics and Pharmacokinetics**: Data on receptor interactions, neuroplasticity effects, and absorption characteristics were analyzed to outline Trazodone PR's mechanisms of action.
  - **Clinical Efficacy and Safety**: Findings from clinical trials and real-world studies were pooled to evaluate Trazodone PR's effectiveness and tolerability in managing mood and sleep disorders.
  - **Comparative Insights**: Trazodone PR was compared to other antidepressants, including SSRIs, SNRIs, and tricyclic antidepressants, to identify unique therapeutic advantages.

Results

Insights from preclinical animal studies

As identified through the systematic literature review, preclinical trials in animal models demonstrated that Trazodone increases brain-derived neurotrophic factor (BDNF) levels, promoting synaptic plasticity and neurogenesis. These findings underline its potential in reversing cognitive deficits linked to chronic stress and depression, supporting its multimodal efficacy in treating mood disorders [31]. Additionally, studies, including a recent JAMA Network Open article (2024;7(3):1527), highlighted Trazodone's role in alleviating akathisia through modulation of neurochemical pathways, suggesting expanded use in complex psychiatric and neurological disorders.

Pharmacokinetics of trazodone PR

Data extracted from the review revealed that Trazodone PR's prolonged-release formulation ensures steady absorption, maintaining stable plasma concentrations over 24 h. This pharmacokinetic profile reduces nighttime awakenings and early-morning symptom relapses, improving overall sleep quality [32]. Trazodone PR has moderate bioavailability and a half-life of 10–12 h, enabling convenient once-daily dosing, typically in the evening, which enhances adherence [33].

The comparative analysis indicates that the prolonged-release formulation offers significant advantages in tolerability and convenience over the immediate-release form (Table 1).

Dose Optimization Across Clinical Indications A critical consideration in trazodone therapy is the dose-dependent receptor engagement profile observed across formulations and indications. For insomnia, low-dose regimens (50–100 mg/day) achieve therapeutic effects primarily through high occupancy (> 90%) of 5-HT2 A and α1-adrenergic receptors, which regulate sleep–wake cycles and sedation (68). At these doses, trazodone's occupancy of histaminergic H1 receptors remains subtherapeutic (43% at 30 mg IR), suggesting alternative mechanisms like 5-HT1 A partial agonism (68% occupancy) contribute to sleep initiation1. In contrast, antidepressant efficacy requires higher doses (150–300 mg/day) to achieve sufficient serotonergic modulation via SERT blockade (67.5% occupancy at 300 mg OAD) and broader 5-HT receptor antagonism (5-HT2 C: 65.5%, 5-HT7: 58.9%) (68). The non-linear pharmacokinetics of prolonged-release formulations create α1-adrenergic receptor occupancy thresholds—85.6% at 300 mg versus 59–64% at 30 mg—explaining the dose-dependent risk of orthostatic hypotension (68). While specific clinical trials comparing 225 mg to 300 mg doses are lacking, receptor saturation kinetics demonstrate diminishing 5-HT2 C occupancy gains beyond 300 mg (65% vs. 63% at 307 nM Ki), supporting upper dose limitations (68). Current guidelines derive titration strategies from these pharmacodynamic profiles: initiating at 50–100 mg for sleep disorders versus 150 mg for depression, aligning with the TED study's observation that 72% of depression patients require ≥200 mg/day (68). Weekly 50 mg adjustments balance target engagement against adverse effects mediated by α1/H1 receptors.

Table 1 Comparative pharmacokinetics of trazodone PR versus immediate release

Parameter	Trazodone PR	Immediate release
Absorption	Steady, prolonged release	Rapid
Plasma concentration	Stable	Peaks and troughs
Half-life	10–12 h	4–6 h
Dosing	Once daily	Multiple daily doses
Side effects	Reduced sedation risks	Higher sedation risks

Expert consensus table

Key outcomes from the most recent clinical trials and expert consensus were summarized as follows (Table 2).

Expert consensus

The expert consensus, derived from the reviewed studies and clinical trials, emphasizes Trazodone PR's broad receptor activity as a versatile treatment option for complex cases of depression, anxiety, and insomnia (32). Key findings reveal that Trazodone PR's ability to modulate serotonin, norepinephrine, dopamine, and histamine systems contributes to its therapeutic efficacy. Additionally, its role in promoting neuroplasticity through BDNF

Table 2 Comparative data on recent clinical trials (2020–2024) for trazodone PR and other antidepressants

Parameter	Trazodone PR	SSRIs	SNRIs	References
Depression Response	MADRS reduction: – 8.4 versus baseline (12 weeks)	MADRS reduction: – 5.9	Not reported	Siwek et al. [19]
Remission rate	58.3% (MADRS ≤ 10)	41.2%	Not reported	Siwek et al. [19]
Sleep quality	TST increase: + 39.88 min (P = 0.002)	Sleep disruption in 25% of cases	Sleep onset insomnia: 30%	Winkelman and Bertisch [65]
Anxiety Response	HAM-A reduction: – 6.2 versus placebo (P < 0.001)	HAM-A reduction: – 4.8	HAM-A reduction: –5.1	Fagiolini et al. [35, 63]
Sexual Dysfunction	4.2%	18.9%	16.4%	TED Study, 2023
Weight Change	+ 0.3 kg/m2 at 12 weeks	+ 1.1 kg/m^2	+ 0.9 kg/m^2	TED Study, 2023
Cognitive Function	SDS improvement: 34%	SDS improvement: 22%	SDS improvement: 25%	Jacobs et al. [52]

production supports cognitive recovery in patients with long-term depression.

Discussion

Depression and its comorbidities: the use of trazodone PR

The findings from this study underscore the significant clinical utility of Trazodone Prolonged Release (PR) in addressing depression, anxiety, and sleep disorders. By leveraging its multimodal mechanism of action, Trazodone PR effectively targets complex symptom profiles, providing a versatile solution for patients with comorbid conditions and treatment-resistant cases (33). This discussion integrates the insights from preclinical studies, pharmacokinetic analyses, and clinical trials to contextualize the efficacy, safety, and practical applications of Trazodone PR.

Efficacy in major depressive disorder (MDD)

As demonstrated in the **Results**, Trazodone PR has shown significant efficacy in treating Major Depressive Disorder (MDD), particularly in patients who have not responded adequately to first-line treatments like SSRIs and SNRIs. MDD presents a complex interplay of emotional, cognitive, and somatic symptoms. Unlike unimodal antidepressants, Trazodone PR's ability to target both mood symptoms and physical manifestations, such as restlessness, irritability, and sleep disturbances, makes it particularly effective for complex cases [34, 35].

Clinical trials reviewed in this study revealed that Trazodone PR not only alleviates depressive symptoms but also improves sleep quality and reduces anxiety, both of which are integral to reducing the overall burden of depression [36]. Its favorable side effect profile, particularly regarding reduced risks of sexual dysfunction and weight gain compared to SSRIs and SNRIs, makes it an attractive option for long-term treatment [37–39], as reflected in the Table 2.

Trazodone PR demonstrates robust efficacy in Major Depressive Disorder (MDD), particularly in patients with inadequate response to first-line SSRIs/SNRIs or those with comorbid insomnia and anxiety [34, 35]. In the TED study (n = 76), trazodone PR achieved superior reductions in MADRS scores versus SSRIs at 12 weeks ($\Delta = -8.4$ vs. -5.9, $P < 0.01$), with 58.3% of trazodone-treated patients achieving remission (MADRS ≤10) compared to 41.2% in the SSRI group [19]. This aligns with findings from Sheehan et al., where trazodone OAD (150–300 mg/day) reduced HAM-D17 scores by 24% at Day 7 versus 17% for placebo ($P < 0.05$), with sustained improvements through Week 8 [26, 40].

The PR formulation's pharmacokinetic profile—steady plasma concentrations over 24 h and α1-adrenergic receptor occupancy < 70% at 150 mg/day—enables simultaneous targeting of mood and somatic symptoms. In MDD patients with insomnia, trazodone PR improved sleep efficiency by 22% ($P < 0.001$) while reducing HAM-D17 scores by 6.2 points vs. placebo ($P < 0.001$) [41]. Its rapid onset (significant symptom reduction within 7 days) outperforms venlafaxine XR (Δ HAM-D17 = – 4.3 vs. – 3.5 at Day 7, $P < 0.05$) in active-comparator trials, attributed to early 5-HT2 A antagonism (85% occupancy) and partial 5-HT1 A agonism [26, 42].

Efficacy in anxiety disorders

The analysis also highlights Trazodone PR's efficacy in managing anxiety disorders, including Generalized Anxiety Disorder (GAD) and panic disorder. These conditions, characterized by persistent worry, tension, and hyperarousal, often co-occur with depressive disorders. Trazodone PR's serotonergic, adrenergic, and histaminergic modulation offers comprehensive relief from both the mental and physical symptoms of anxiety [43, 44].

Clinical studies showed significant reductions in anxiety symptoms and improvements in sleep and daytime functioning, supporting its dual role as an anxiolytic and

sedative [45]. This dual-action mechanism is particularly beneficial for patients with co-occurring anxiety and sleep disturbances, providing symptom relief without the risks associated with benzodiazepines [46, 47].

Trazodone PR demonstrates clinically meaningful anxiolytic effects, with significant reductions in HAM-A scores (mean difference [MD] = − 6.2 vs. placebo, $P<$ 0.001) and psychic anxiety symptoms within 1–2 weeks [26, 41]. This rapid relief stems from its dual modulation of 5-HT2 A receptors (85% occupancy at 150 mg) and α1-adrenergic blockade (72% occupancy) [26, 48]. However, the American Psychiatric Association (APA) guidelines prioritize SSRIs/SNRIs as first-line GAD treatments due to trazodone's limited long-term anxiety-specific evidence.

Notably, trazodone PR's pharmacokinetic profile—intermediate plasma peak (~ 4 h) and sustained receptor engagement—makes it particularly effective for comorbid anxiety and insomnia [26, 48]. In MDD patients with anxious distress, trazodone PR (150 mg/day) reduced HAM-A scores by 42% at 8 weeks versus 28% for sertraline ($P=$ 0.01), while improving sleep efficiency (+ 22%, $P<$ 0.001) [41, 49]. Guidelines endorse trazodone PR as a second-line option for GAD with comorbid insomnia or SSRI intolerance, particularly in elderly patients [41].

Efficacy in sleep disorders

One of the most compelling findings from this review is Trazodone PR's efficacy in treating sleep disorders, particularly insomnia associated with mood and anxiety disorders. As highlighted in the **Results**, Trazodone PR improves sleep architecture by increasing non-REM sleep, reducing sleep latency, and enhancing overall sleep quality [50–52, 76].

Unlike traditional sedative-hypnotics, such as benzodiazepines, Trazodone PR avoids risks of tolerance and dependence, making it a safer long-term option for managing chronic insomnia. Its sedative effects, mediated through histaminergic activity, further enhance its utility for patients experiencing both insomnia and mood disturbances [53–55].

Trazodone's widespread off-label use for insomnia management, particularly in patients with comorbid mood or anxiety disorders, presents a complex risk–benefit profile. While clinical studies demonstrate trazodone's capacity to improve sleep architecture—increasing total sleep time (MD = 39.88 min, $P=$ 0.002) and non-REM stage 3 sleep (SMD = 1.61, $P=$ 0.0006) while reducing sleep latency (MD = − 19.30 min, $P=$ 0.04) and nighttime awakenings (SMD = − 0.67, $P<$ 0.00001) [33]—these benefits must be weighed against guideline recommendations. The American Academy of Sleep Medicine (AASM) and U.S. Department of Veterans Affairs explicitly advise against trazodone for chronic insomnia due to low-quality evidence of sustained efficacy and documented risks of daytime drowsiness (OR = 2.53, $P=$ 0.02) and anticholinergic effects. This caution is reinforced by a Cochrane review of 23 trials ($n=$ 2,806), which found only moderate short-term sleep improvements versus placebo and no long-term benefits [56].

Notably, trazodone's utility may be greater in specific subpopulations. In patients with cerebral small1vessel disease (CSVD) and comorbid insomnia, low-dose trazodone (50 mg/day) improved sleep efficiency (+ 14.3%, $P<$ 0.01), reduced wakefulness after sleep onset (− 32 min, $P=$ 0.04), and enhanced cognitive measures like concentration ($r=$ 0.61 vs. placebo) through improved sleep continuity [49]. Similarly, in major depressive disorder (MDD) with insomnia, trazodone's dual 5-HT2 A/α1-adrenergic receptor blockade at 50–100 mg/day shows superior sleep quality improvements versus SSRIs (PSQI reduction: − 6.4 vs. − 4.5, $P<$ 0.001), though these effects diminish above 150 mg/day due to disproportionate α1 occupancy (85.6% at 300 mg vs. 59% at 30 mg) [33].

While trazodone avoids the tolerance risks of benzodiazepines, its unapproved status for insomnia and guideline contradictions necessitate careful patient selection. Current evidence supports restricted use in comorbid conditions where sleep disruption exacerbates primary pathology (e.g., CSVD-related cognitive decline), but not as first-line monotherapy for primary insomnia per AASM guidance [56].

The PR formulation demonstrates distinct advantages over IR and OAD formulations in terms of pharmacokinetics and clinical utility. With an intermediate plasma peak (~ 4 h) and half-life (~ 12 h), PR provides balanced receptor engagement that effectively manages both sleep and mood symptoms. While IR's rapid peak (~ 1 h) can cause more side effects, and OAD's 24-h plateau may be excessive for some patients, PR offers a middle ground that optimizes therapeutic benefits while minimizing adverse effects. This pharmacokinetic profile makes PR particularly suitable for patients requiring both sedative and antidepressant effects without the need for multiple daily dosing or concerns about excessive plasma concentrations [53, 55].

Cognitive benefits

Another key finding is Trazodone PR's role in enhancing cognitive function. Cognitive impairment is a common feature of depression and anxiety, often manifesting as difficulties in concentration, decision-making, and memory [75]. Preclinical studies reviewed here demonstrated that Trazodone PR increases brain-derived neurotrophic

factor (BDNF) levels, promoting neuroplasticity and synaptic repair [57, 58].

This unique property of Trazodone PR makes it particularly valuable for patients with long-term depression and cognitive deficits, offering not only mood stabilization but also cognitive recovery [59–62].

Trazodone PR demonstrates significant pro-cognitive effects through multimodal neuroplasticity enhancement, particularly relevant for depression-associated cognitive impairment. Chronic trazodone administration (150–300 mg/day) increases BDNF levels by 45% in the prefrontal cortex (PFCx) and 38% in the hippocampus compared to placebo ($P < 0.01$), as demonstrated in controlled rodent models [63]. This BDNF surge correlates with a 34% improvement in psychosocial functioning scores ($P < 0.001$) in MDD patients, mediated through TrkB receptor upregulation and CREB phosphorylation [63].

Mechanistically, trazodone PR reverses depression-induced synaptic protein depletion, restoring 82% of dysregulated hippocampal proteins involved in long-term potentiation (LTP) and mitochondrial bioenergetics within 2 weeks of treatment [64]. In prion-disease models mimicking neurodegeneration, trazodone rescues 78% of lost synaptic proteins (PSD-95, synaptophysin) and increases dendritic spine density by 41% ($P < 0.001$) through mTOR pathway activation [64]. These effects contrast with citalopram's region-specific BDNF modulation, which primarily targets the nucleus accumbens (+ 28%) rather than cortical regions [63].

Practical considerations for clinical use

Patient selection

Trazodone PR is ideal for patients with comorbid conditions, including depression, anxiety, and insomnia, particularly those who have not responded adequately to first-line treatments. Its multimodal mechanism allows it to address multiple symptom domains, making it a versatile choice for complex clinical presentations [65].

Dosing strategies

The recommended starting dose of Trazodone PR is 150 mg once daily, preferably in the evening. This dose can be adjusted based on the patient's response and tolerability, with lower starting doses recommended for elderly patients or those with hepatic or renal impairment [66].

Monitoring and follow-up

Regular monitoring using sleep diaries, anxiety scales, and depression rating scales is essential to optimize therapeutic outcomes. Clinicians should also monitor for potential side effects, such as daytime drowsiness or dizziness, especially in older patients and those with comorbid conditions [67].

Safety and tolerability of trazodone PR

As shown in the **Results**, Trazodone PR has a favorable side effect profile compared to other antidepressants. Reduced risks of sexual dysfunction, weight gain, and agitation make it particularly suitable for long-term use (52). Unlike SSRIs and SNRIs, which are frequently associated with sexual side effects, Trazodone PR offers a more patient-friendly profile, enhancing adherence to treatment [68].

Additionally, the drug's lower incidence of weight gain compared to tricyclic antidepressants (TCAs) and some SNRIs further supports its use in patients at risk of metabolic disorders [45, 69, 70].

Conclusion

Trazodone Prolonged Release (PR) remains a highly valuable treatment option in 2024, offering a multimodal mechanism of action that effectively addresses the interplay between mood disorders, anxiety, and sleep disturbances. By modulating multiple neurotransmitter systems—serotonin, norepinephrine, dopamine, and histamine—Trazodone PR provides comprehensive symptom relief, making it particularly effective for patients with comorbid conditions such as treatment-resistant depression and chronic insomnia [71].

The drug's favorable safety profile, including a lower risk of sexual dysfunction, weight gain, and agitation, distinguishes it from many traditional antidepressants, such as SSRIs and SNRIs. This makes Trazodone PR a preferred option for long-term management, particularly in patients with co-occurring mood and sleep disorders where sustained symptom improvement is essential for overall quality of life [72].

Furthermore, Trazodone PR's ability to enhance neuroplasticity and support cognitive recovery through increased BDNF production adds significant value for patients experiencing cognitive impairments linked to chronic depression. Its efficacy across multiple domains—mood stabilization, anxiety reduction, and sleep improvement— positions Trazodone PR as a versatile and effective choice for complex clinical presentations, addressing gaps left by unimodal therapies [36, 51, 52, 59–62, 73, 74].

Abbreviations

PR	Prolonged Release
MDD	Major Depressive Disorder
SSRIs	Selective Serotonin Reuptake Inhibitors
SNRIs	Serotonin-Norepinephrine Reuptake Inhibitors
H1	Histamine 1 receptor
BDNF	Brain-Derived Neurotrophic Factor
GAD	Generalized Anxiety Disorder

TCAs	Tricyclic Antidepressants
MAOIs	Monoamine Oxidase Inhibitors
5-HT2 A	Serotonin 2A receptor
5-HT2 C	Serotonin 2C receptor
SARI	Serotonin Antagonist and Reuptake Inhibitor
REM	Rapid Eye Movement
CBT	Cognitive Behavioral Therapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Author contributions
A.F., L.D.G., M.S., A.S., M.L., Č.D.M., and A.C. contributed to the conception and design of the study. A.F., M.S., and A.C. conducted the literature search and data acquisition. L.D.G., A.S., and M.L. performed data analysis. Č.D.M. and A.C. interpreted the results. A.F. and M.S. drafted the introduction and methodology sections. L.D.G. and A.S. wrote the results section. M.L. and Č.D.M. prepared the discussion section. A.C. wrote the conclusion and assembled the manuscript. All authors critically revised the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
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