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REVIEW

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A narrative review on trazodone as a multimodal and multifunctional antidepressant: clinical relevance of formulations, dosing, and pharmacokinetic/pharmacodynamic targets

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Abstract

Background Trazodone, an antidepressant, has only been approved for use in major depressive disorder (MDD), but has demonstrated potent therapeutic potential in various conditions, such as insomnia and anxiety. It targets multiple serotonergic, adrenergic, and histaminergic receptors. Given this multimodal and multifunctional profile, we aimed to provide a comprehensive overview of the pharmacodynamic and pharmacokinetic properties of trazodone and its clinical applications across various conditions.

Main text Trazodone demonstrates sedative and anxiolytic effects even at a low dose (25–75 mg) and a full antidepressant effect at higher doses (150–300 mg). The availability of trazodone in immediate-release, extended-release, intravenous, and intramuscular formulations enables flexible and personalized treatment based on the patient's symptoms, medical history, tolerability, and clinical settings. Clinical evidence also demonstrates that trazodone is effective and well-tolerated across various conditions, including MDD, treatment-resistant depression, insomnia (off-label), neurological disorders, dementia, and delirium, highlighting its versatility. Additionally, the low risk of sexual dysfunction, limited withdrawal symptoms, and weight-neutral effects make it suitable for use in patients with comorbid conditions.

Conclusion Trazodone is a multimodal and multifunctional antidepressant that exhibits a broad range of therapeutic effects in MDD and other comorbid conditions. Further research on the pharmacokinetic and pharmacodynamic relationship of trazodone, its parenteral use in acute settings, and the development of prescribing algorithms for predicting treatment responses may enhance its therapeutic outcomes in patients with MDD.

Keywords Trazodone, Multimodal antidepressant, Pharmacodynamics, Pharmacokinetics, Extended-release formulation, Insomnia, Anxiety, Major depressive disorder, Receptor occupancy

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Introduction

Major depressive disorder (MDD) is a complex, multifactorial illness often requiring treatment strategies beyond simple monoaminergic modulation [1, 2]. To effectively manage the heterogeneous symptoms of MDD, it is useful to consider multimodal/multifunctional antidepressants. Multimodal antidepressants have more than one mode of action that help produce a downstream effect on interconnected neurotransmitter systems, while multifunctional antidepressants have multiple actions at the same mode [3]. Trazodone is a well-established antidepressant developed in the 1960 s and approved for clinical use by the United States Food and Drug Administration (USFDA) in 1981 as a serotonin antagonist and reuptake inhibitor (SARI) with a unique pharmacological profile [4–6]. Although trazodone has been approved for MDD only, it has demonstrated efficacy in other conditions, including anxiety disorders, insomnia, and behavioral disturbances associated with dementia, underscoring its multifunctional clinical potential [4]. Given its multifaceted nature, trazodone stands out as a multimodal as well as multifunctional antidepressant, with clinical applications that are profoundly influenced by its formulation, dosing regimen, and pharmacokinetic/pharmacodynamic characteristics. In this review, we critically examined the pharmacodynamics, formulations, and dose-response characteristics of Trazodone and explored its practical implications in contemporary psychiatric treatment. We conducted a comprehensive literature search in PubMed/Medline databases from database inception to November 2025 for this narrative review. Our search strategy included the medical subject headings (MeSH) terms "trazodone," "major depressive disorder," "multimodal antidepressants," "multifunctional antidepressants," "depression," "pharmacokinetics," and "pharmacodynamics", in various combinations using appropriate Boolean operators ("AND" or "OR"). Additional studies were identified through manual screening of the reference lists of key publications. Eligible sources included clinical trials, systematic reviews, meta-analyses, and case reports that focused on trazodone's formulations, pharmacodynamic and pharmacokinetic characteristics, dose-response characteristics, safety profile, or its practical implications in contemporary psychiatric treatment. Additionally, regulatory and clinical resources, including the USFDA drug prescribing information, were consulted to support and contextualize the available evidence. Non-English publications and sources that lacked data relevant to the focus of this review were excluded. The selected publications were reviewed and synthesized qualitatively to provide an integrated overview of the pharmacodynamic and pharmacokinetic properties of trazodone and its clinical applications across various conditions.

Pharmacokinetic profile

Trazodone is well absorbed in the gastrointestinal tract following oral administration. The peak plasma levels are typically reached in about 1 h when trazodone is taken on an empty stomach, or in around 2 h if taken with food [7]. The bioavailability of trazodone ranges between approximately 63% and 91% [8]. After absorption, plasma concentration of trazodone declines in a biphasic manner, with the initial half-life ranging from about 3 to 6 h, and the terminal elimination half-life spanning roughly 5 to 9 h [7, 9]. Trazodone is highly protein-bound (~ 89–95%), meaning that only a small fraction remains free and pharmacologically active [5, 6, 9]. Similar to oral preparations, the pharmacokinetic parameters of a single dose of trazodone parenteral preparation include an estimated volume of distribution of about 0.84 L/kg, total body clearance of about 5.3 L/h, and a terminal half-life of 7.3 ± 0.8 h [10].

Trazodone undergoes extensive hepatic metabolism, primarily via the cytochrome P450 (CYP) 3A4 pathway, with minor involvement of CYP2D6 [9]. One major metabolite is m-chlorophenylpiperazine (mCPP), a pharmacologically active compound, which may contribute to some side effects of trazodone, such as headache in a minority of patients [9, 11]. CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) can raise trazodone levels, while CYP3A4 inducers (e.g., carbamazepine, rifampicin) can lower trazodone levels [12].

Less than 1% of an oral dose of trazodone is excreted unchanged in the urine, indicating that it is almost entirely metabolized [5, 6, 9, 10]. Renal impairment has a minimal effect on trazodone pharmacokinetics; however, careful dosing and proper monitoring are needed, especially in cases of severe renal impairment, due to its hepatic and renal metabolism [9, 12].

Extended-release (XR) formulations avoid peaks and troughs in drug concentration and provide a combination of efficacy and improved tolerability than other antidepressants. While trazodone immediate-release (IR) often requires multiple doses to maintain round-the-clock levels, trazodone XR supports once-daily dosing at night, maintaining stable plasma levels and reducing the risk of sedation or orthostatic hypotension [13–15].

Pharmacodynamic profile

Trazodone exhibits a dual mechanism of action. At the molecular level, it selectively inhibits the serotonin transporter (SERT) (with a moderate binding affinity $K_i \approx 367$ nM) while antagonizing multiple serotonin receptor subtypes, notably 5-HT_2A ($K_i \approx 36$ nM at low doses), 5-HT_2B ($K_i \approx 78$ nM), and 5-HT_2C ($K_i \approx 224$ nM). It also acts as a partial 5-HT_1A receptor agonist ($K_i \approx 118$ nM) and as an antagonist at α_1- and α_2-adrenergic receptors ($K_i \approx 153$–155 nM) and H_1-histamine receptors ($K_i \approx 220$ nM), with minimal anticholinergic activity ($K_i > 10{,}000$

nM) [5, 6, 16]. Unlike SSRIs, trazodone is an allosteric ligand that inhibits uptake and transport-associated currents through SERT in a mixed-competitive manner. Recent research has demonstrated that trazodone and its analogue, nefazodone, act as pharmacochaperones, which can potentially correct the folding defects caused by SERT mutations (SERT-N217S and SERT-A500T) in treatment-resistant depression [17].

Beyond its serotonergic actions, trazodone's blockade of adrenergic and histaminergic receptors is key to its anxiolytic and sedative properties. In particular, α_1-adrenergic antagonism reduces physical anxiety symptoms through modulation of sympathetic response. H_1-histamine receptor antagonism contributes substantially to trazodone's sedative profile, promoting sleep and calming agitation [18, 19].

Dose–occupancy studies confirm that low-dose trazodone (25–100 mg) produces near-complete blockade of 5-HT_2A receptors and significant H_1 and α_1 receptor occupancy, even while SERT occupancy is relatively low, yielding primarily sedative–anxiolytic effects without robust antidepressant activity [14, 16, 20]. Higher daily doses, especially when delivered via XR formulations, more robustly engage its antidepressant mechanisms through sustained SERT inhibition and 5-HT_2A/5-HT_7 receptor antagonism. Additionally, trazodone exhibits multimodal neuroplasticity enhancement and can confer pro-cognitive benefits [19] with recent evidence suggesting that 5-HT_7 antagonism can improve memory and cognitive function in preclinical models [21].

Dose- and formulation-dependent effects

The receptor occupancy and clinical effects of trazodone vary with dosage and formulation. Figure 1 provides the pharmacodynamic targets and clinical effects of trazodone based on the available oral doses.

Trazodone is available as IR tablets/drops, XR tablets, intramuscular (IM), and intravenous (IV) preparations (available in some regions). IR formulations have rapid absorption and a high peak plasma level shortly after dosing, whereas XR formulations slowly release trazodone over 24 h. However, trazodone IR often needs to be taken 2–3 times/day for full antidepressant dosing, and its sharper peak–trough fluctuations can increase the risk of side effects. Trazodone XR provides a steady plasma concentration, minimizing peak-related side effects, supports once-daily dosing, improves adherence, and maintains more consistent therapeutic levels throughout the day and night. Notably, trazodone XR avoids the high peak levels associated with IR dosing, thereby reducing next-morning grogginess and allowing patients to start at therapeutically effective doses for depression without

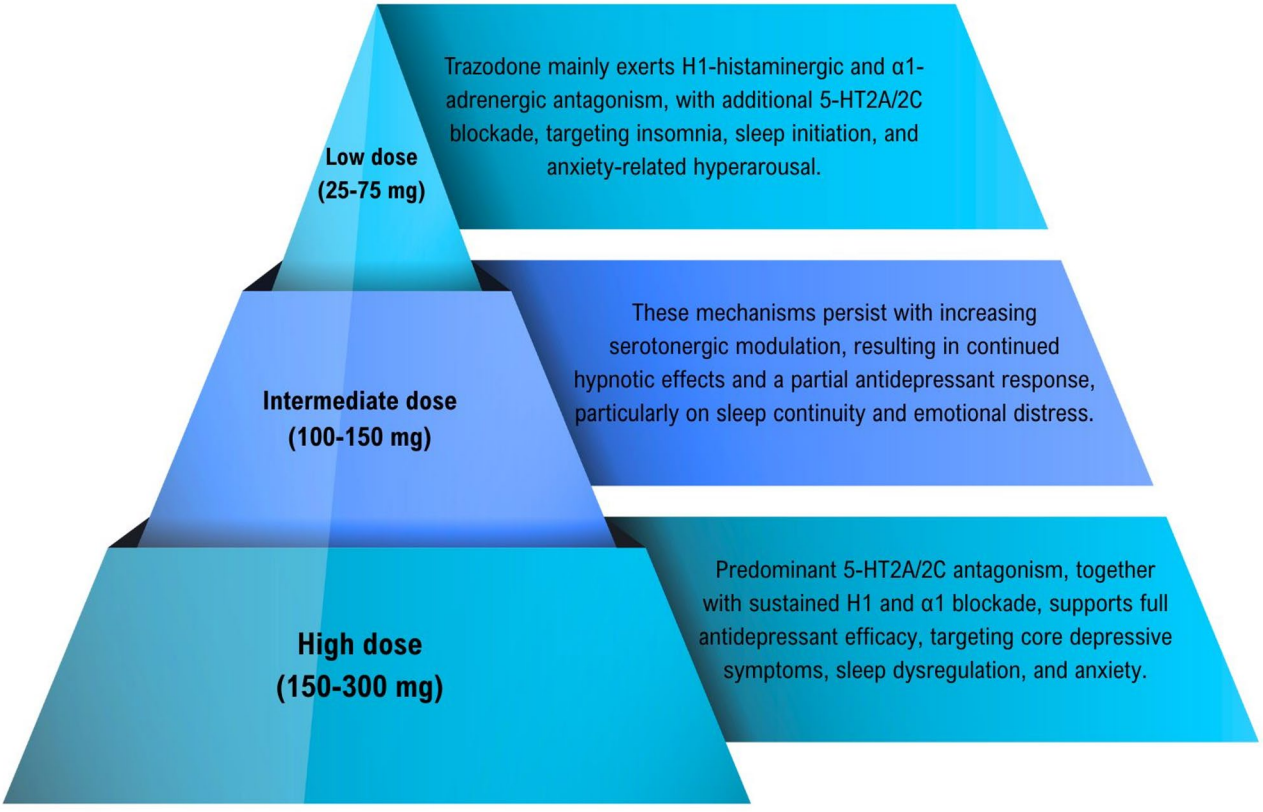

Fig. 1 Dose-dependent pharmacodynamic targets and clinical effects [14, 16, 19, 20]

titrating up from very low doses [14, 19]. Liquid trazodone drops (IR) have a relatively short half-life and reduce the risk of morning drowsiness [17]. Meanwhile, IV trazodone has a rapid onset of action and quickly engages central α_1 and 5-HT_2A receptors, making it useful for urgent tranquilization in emergency settings, such as acute agitation. IM trazodone is an alternative to IV that offers a slightly delayed but effective onset of action similar to IV trazodone and rapid symptom relief [22]. An observational study reported that parenteral administration of trazodone resulted in improvement of symptoms of psychomotor agitation [23]. However, it is important to note that this finding was observed in a small sample population, thereby limiting its generalizability and warranting cautious interpretation. Table 1 enlists the pharmacokinetic/pharmacodynamic properties of different formulations of trazodone.

Clinical applications and therapeutic versatility

The clinical applications of trazodone in MDD and other conditions are described in Table 2.

Switching and discontinuation strategies

Effective use of trazodone requires attention to initiation, maintenance, medication switching, or discontinuation. Though formal protocols are limited, emerging evidence provides guidance, especially for patients with depression and comorbid anxiety or insomnia transitioning between treatments. According to Watson et al. [48], a slow taper method/cross-taper is recommended for switching from or to trazodone. However, switching to or from a monoamine oxidase inhibitor is only possible after a washout period of at least 14 days. Although trazodone is not associated with severe withdrawal syndrome, abrupt discontinuation after prolonged use could lead to transient agitation, sleep disturbance, nightmares, vivid dreams, or anxiety in some individuals. Hence, deprescribing requires a gradual tapering of the dose to minimize rebound symptoms [5, 6, 48]. Interestingly, some observational data suggest that trazodone can be a useful substitute when discontinuing other psychotropics. Harris et al. (2024) reported that in nursing home residents, trazodone was often initiated as a replacement when antipsychotics were discontinued [49]. While this practice should be individualized, it reflects trazodone's role as a "bridge" medication to manage symptoms during the deprescribing of more harmful drugs.

Safety, tolerability, and practical considerations

Compared to other antidepressants, trazodone causes fewer instances of anxiety, insomnia, or sexual dysfunction [27]. This favorable safety profile is linked to its combined pharmacological actions, addressing complex symptoms of depression, sleep disturbances, and anxiety with reduced risk of weight gain and sexual dysfunction [28]. It is sometimes added to SSRI therapy to counter SSRI-induced insomnia or sexual dysfunction [50]. Common adverse effects of trazodone are drowsiness, headache, dizziness, and xerostomia [9, 15]. Figure 2 demonstrates the common effects of trazodone and its management.

In controlled trials and clinical use, somnolence is the primary side effect, with patients reporting increased daytime sleepiness/fatigue, especially during the first or second week of therapy or after a dose increase [9, 12]. To minimize daytime impact, clinicians recommend taking trazodone at bedtime for depression, and a larger evening dose if multiple doses are needed [15]. Patients should exercise caution while driving/operating machinery until they know how trazodone affects their alertness [5, 6]. Headache and mild nausea can occur but are usually transient [51]. Xerostomia, due to mild anticholinergic effects [52], causes discomfort, interferes with chewing/swallowing, and increases the risk of dental caries or oral

Table 1 Comparative pharmacokinetic/pharmacodynamic summary of the formulations [13, 18, 19, 22]

Characteristic	Trazodone IR	Trazodone XR	IM Trazodone	IV Trazodone
Mechanism of action	Serotonin reuptake inhibition, 5-HT_2A receptor antagonism, α−1 adrenergic receptor antagonism			
T_{max}	0.50 h	9.0 h	Immediate	Immediate
Volume of distribution	0.84–1.5 L/kg			
Absorption	Rapid	Slow and Steady	Immediate or rapid onset; 100% bioavailability	Immediate or rapid onset; 100% bioavailability
Plasma concentrations	Peaks and troughs; high fluctuation	Stable; minimal fluctuation	Rapid high peak; stable levels with slow infusion; less fluctuation than oral	Rapid high peak; stable levels with infusion; less fluctuation than oral
Half-life ($t_{1/2}$)	4–6 h	≈11.8 h	6–8 h	6–8 h
Dosing	Multiple doses a day	Once daily	100–200 mg twice daily	200 mg twice daily diluted in 250–500 mL of physiological solution
Adverse effects	Higher risk of sedation, dizziness, orthostatic hypotension	Reduced sedation	Mild sedation, dizziness, orthostatic hypotension, sedation incidence slightly lower than oral	Mild sedation, dizziness, orthostatic hypotension, sedation incidence lower than oral

IM: Intramuscular; IR: Immediate-release; IV: Intravenous; XR: Extended-release

Table 2 Clinical Applications and Therapeutic Versatility

Clinical condition	Key therapeutic insights	Brief summary
MDD	• Saturates SERT at 150–600 mg/day [24] • Blocks 5-HT_2 receptors [25] • Efficacy comparable to SSRIs/SNRIs [12] • Addresses sleep disturbances better than first-line antidepressants [15] • Early improvement in sleep latency and continuity [24] • Higher remission rates and better reduction of anxiety and insomnia symptoms with trazodone XR [26] • Less sexual dysfunction and emotional blunting [27] • Can be used as monotherapy or as an augmenting agent [15]	Strong evidence supports that trazadone is effective and well-tolerated in MDD. It can have a beneficial effect on sleep and lower sexual side effects
TRD and cognitive symptoms	• Useful in TRD and cognitive impairment [19] • Trazodone PR reduces nighttime awakenings and improves neuroplasticity through BDNF production in patients with TRD [19] • Suitable for stress-induced depression [28] • Benefits neurodegenerative comorbidities • Improves mood in depression with insomnia and cognitive function [29, 30] • Cognitive gains may result from improved sleep disturbances and mood [31]	Evidence, although from smaller or specialized studies, indicates the trazodone is beneficial for TRD and cognitive symptoms
Insomnia (Off-label use)	• Trazodone 25–150 mg gives potent hypnotic [15] • Widely prescribed despite modest evidence [24] • Well tolerated in the short term [32] • Improves slow-wave sleep [33] • Used when insomnia coexists with depression/anxiety [28] • Caution: residual morning drowsiness and orthostatic hypotension, especially in older adults upon waking [34] • Evidence supports its efficacy and safety in real-world settings [35]	Off-label use for insomnia with evidence of improvement in sleep is modest. Generally well-tolerated, but caution should be exercised as drowsiness and hypotension are possible
Neurological disorders	• Treats depression in patients with Parkinson's disease, MS, and post-stroke depression • Improves sleep quality in Parkinson's disease and is well-tolerated [36] • Preclinical evidence hints at neuroprotective properties [37] • Antidepressants are supported for the management of depression in patients with MS [38] • Improves depressive mood and functional recovery post-stroke [39] • Lower bleeding risk than SSRIs [40]. • Liquid formulation benefits patients with dysphagia or other swallowing difficulties post-stroke	Potential benefits for depression and sleep quality in neurological conditions are observed in preliminary and specialized evidence. Liquid formulation of trazodone can be beneficial in certain cases
Dementia and Delirium	• Alleviates depression, anxiety, insomnia, agitation, and apathy [41] • Well-tolerated adjuvant treatment in patients with dementia-related comorbidities [31] • Improves sleep efficiency and continuity without inducing nighttime awakening, daytime sleepiness, or self-reports of trouble sleeping [31] • Reduces agitation, aggression, and behavioral disturbances [42, 43] • First-line drug for delirium, especially at low doses, due to its minimal effects on cardiac conduction [43] • Caution is warranted regarding orthostatic hypotension and falls	Limited but promising evidence indicate that trazodone is promising for improving mood, sleep, and behavioral disturbances, mainly as adjuvant therapy. Caution should be exercised in older adults to reduce the risk of falls
Agitation in depression and acute behavioral disturbances	• IV trazodone produces a prompt sedative and anxiolytic effect without tolerance development [15] • Most symptomatic improvement noted within 2–3 days [44] • Reduces psychomotor agitation and acute anxiety [44] • Suitable for short-term crisis management [22] • Rapid calming and acute symptom relief [22] • Benefits plateau with longer therapy [45] • Mild side effects only reported [45] • Alternative to antipsychotics or benzodiazepines, particularly in mixed depression	Evidence suggests that trazodone may provide rapid symptom relief in the short term, but the benefits plateau with long-term use
Special population: Elderly patients	• Underdiagnosed depression in the elderly often presents as physical or cognitive complaints [46] • Minimal anticholinergic activity and low cardiotoxicity make trazodone safer than other antidepressants [15, 34] • Low-dose trazodone assists with sleep initiation and maintenance without altering sleep architecture [47] • α_1-blocking effect can cause orthostatic hypotension, and increase fall risk if not monitored [34] • Start at very low doses and titrate slowly while monitoring blood pressure [34]	Evidence supports the safety and efficacy of trazodone in elderly patients at low doses. Constant monitoring is essential to avoid any risks

CNS: Central nervous system; IM: Intramuscular; IV: Intravenous; IR: Immediate-release; MDD: Major depressive disorder; MS; Multiple sclerosis; SSRI: Selective serotonin reuptake inhibitors; SNRI: Selective norepinephrine reuptake inhibitors; TRD: Treatment-resistant depression; XR: Extended-release

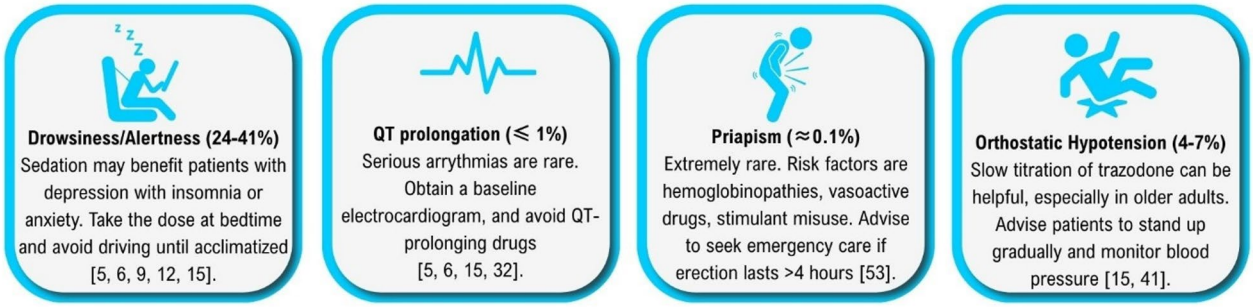

Fig. 2 Safety and Optimization-Common Effects and Management

infections, if severe. Patients should be advised to maintain good oral hygiene, stay hydrated, consider saliva substitutes if needed, and report if dry mouth is interfering with eating or medication intake [15]. Often, this side effect can be managed by dose reduction or simply encouraging sugar-free lozenges and water [51]. Importantly, because xerostomia can negatively impact adherence and quality of life, addressing it proactively is part of good trazodone management [15].

Trazodone can cause modest, dose-related QT interval prolongation, although its propensity for serious arrhythmias is low [15, 32]. Hence, it should be avoided in patients using other QT-prolonging drugs or in those with known QT prolongation [5, 6]. Orthostatic hypotension from α_1-adrenergic blockade is more common, particularly in older adults and those with cardiovascular diseases [15]. To mitigate this, trazodone can be slowly titrated [41].

A rare side effect is priapism, causing penile vasodilation and trapping of blood due to α_1 antagonism. Men starting trazodone should be informed about the possibility of permanent damage and instructed to seek emergency care if an erection lasts > 4 h [53]. Risk factors include sickle cell anemia, leukemia, multiple myeloma, autonomic nervous system dysfunction, and anatomical deformation of the penis. Fortunately, most cases of trazodone-related priapism can be resolved with early, guideline-based conservative management, but discontinuation of the medication is recommended [41, 54].

Trazodone is generally weight-neutral or may cause mild weight loss in some individuals [55]. It does not have the appetite-stimulating effect that mirtazapine or some antipsychotics do, and long-term studies show minimal impact on weight or glucose metabolism [15].

Trazodone is classified as FDA Pregnancy Category C, indicating potential risk to the fetus due to limited studies in pregnant women. However, a recent multicenter cohort study within the European Network of Teratology Information Services (ENTIS) reported that trazodone use in the first trimester was not associated with any significant increase in the risk of major congenital anomalies, pregnancy loss, or preterm birth compared to those taking SSRIs or other antidepressants. The rate of major birth defects in trazodone-exposed pregnancies was 0.6% versus 2.6% in the SSRI group, with no significant differences in miscarriage or pregnancy termination. While these findings suggest that trazodone is not a major teratogen, the sample size remains small [15, 56].

If trazodone is needed for maternal mental health, educating the patients on the limitations of the existing pregnancy safety and the lowest effective dose of trazodone that can be used is essential [57]. For breastfeeding mothers, trazodone appears in breast milk in negligible amounts [< 1% of the maternal dose (~ 0.6% on average, weight-adjusted)]. These low levels are unlikely to affect nursing infants, with no adverse outcomes reported in exposed infants [58]. However, monitoring infants for symptoms, such as sedation or poor feeding, is recommended [59].

Clinical vignettes: tailoring trazodone to the patient

We present a series of brief clinical vignettes illustrating how different formulations or dosing strategies of trazodone can be tailored to individual patient needs.

Vignette 1: Low-dose oral drops for sleep and anxiety in an elderly patient with depression: A 79-year-old woman was referred by her general practitioner for psychiatric consultation due to anxious-depressive symptoms that had emerged approximately three months earlier following her husband's death. Over the past month, her condition had worsened, with increasing anxiety, near-total insomnia, and irritability. She had no history of depressive or manic episodes and had never been prescribed psychotropic medication. She was on ramipril 5 mg and nebivolol 5 mg each morning for hypertension. Given the clinical picture at the initial visit (characterized by late-life adjustment depression with prominent anxiety and insomnia), we initiated trazodone IR oral [10 drops (~ 25 mg)] in the evening. Within days, this markedly improved her sleep onset and initial insomnia; however, she continued to experience middle-of-the-night awakenings (maintenance insomnia). Hence, the

dose was increased to 15 (~37.5 mg) drops. Trazodone has no clinically significant pharmacokinetic interactions with ACE inhibitors or beta-blockers, so no adjustments were required to her other medications; however, she was asked to monitor her blood pressure at home for the first two weeks, which remained stable. Trazodone was well tolerated without morning grogginess or orthostasis. As her insomnia resolved within the first 1–2 weeks, there was a notable reduction in her daytime restlessness and anxiety, with a concomitant improvement in mood and overall daily functioning. In this case, trazodone IR oral drops proved effective for treating insomnia and anxiety in an elderly patient with multiple co-medications. The flexible drop formulation allowed careful dose titration without pill burden, and the low dose successfully targeted her key symptoms while avoiding adverse effects or drug–drug interactions.

Vignette 2: Trazodone XR for MDD with diurnal variation: A 45-year-old man with recurrent MDD presented for an outpatient follow-up. He experienced his first depressive episode 3 years back, which responded well to sertraline 50 mg daily (continued for about one year), although he reported troublesome sexual side effects. After remaining off antidepressants for two years, he presented with symptoms of relapse of MDD, particularly restlessness, insomnia, daytime agitation, and very fragmented, unrefreshing sleep. Notably, his first episode had been characterized mainly by low mood and excessive fatigue, including clinophilia. Without consulting a psychiatrist, he self-initiated sertraline 50 mg for about three weeks but had no improvement, noting that his inner restlessness worsened and sleep remained poor. Upon evaluation, we decided to discontinue sertraline (given the lack of benefit and the prior sexual side effects) and initiate trazodone XR (Contramid®) once a day (OAD). Treatment began with 150 mg trazodone XR at night. He was instructed to take half a tablet (75 mg) for the first two nights, then a full tablet (150 mg) thereafter, at around 8 PM. This brief titration was to ensure tolerability. Over the next two weeks, he experienced a normalized sleep pattern (he fell asleep more easily and stayed asleep through the night) and reduced daytime anxiety and agitation. At the one-month follow-up, his insomnia, depressive mood, and irritability improved. Furthermore, the patient did not report the sexual side effects that he had experienced with sertraline. Trazodone XR provided steady anxiolytic and antidepressant coverage without the jitteriness (seen with activating SSRIs) and good tolerability in terms of sexual function. We later increased his dose to 225 mg at night (150 mg + 75 mg), resulting in full remission by three months. This vignette highlights how trazodone XR OAD can be a beneficial option for MDD with restlessness and insomnia, particularly in patients with prior SSRI-related issues.

Vignette 3: High-dose trazodone IR for agitated depression: A 35-year-old woman with a history of generalized anxiety disorder and recurrent MDD (no history of mania or psychosis) was being treated through community mental health services. She had undergone multiple trials of SSRIs, mood stabilizers, and antipsychotics. Over the last two months, she developed a severe depressive episode characterized by irritability, psychomotor agitation, and near-total insomnia. She was sleeping only 1–2 h/night and experienced relentless inner tension that worsened in the evenings. Initially, she was prescribed citalopram 20 mg (half tablet for one week, then full tablet) in the morning. However, after two weeks, it appeared that citalopram was not helping her insomnia or agitation, and that she felt it might be aggravating her nighttime restlessness. Given this clinical picture, citalopram was tapered off. We initiated trazodone IR in a split high-dose regimen [100 mg at late afternoon (around 6 PM) and 100 mg at bedtime] to target her agitation and insomnia at the times they were most intense. We intentionally avoided the XR formulation in her case to achieve a quick onset of effect in the evenings (XR might not peak until later in the night). The patient responded remarkably within one week. The split dosing of trazodone IR provided rapid anxiolytic and hypnotic effects, allowing her to get ~6 h of continuous sleep by the end of the first week. Her evening restlessness diminished significantly, and by two weeks, her psychomotor agitation reduced substantially. During this period, we observed no adverse effects except for mild morning grogginess, which improved after advising her to take the second dose earlier (around 9 PM instead of bedtime). This case demonstrates that a dual administration strategy of trazodone IR (even at a relatively high total dose of 200 mg) can effectively control both restlessness and insomnia in agitated depression, essentially leveraging trazodone's sedative effects to achieve a rapid calming outcome. Once the patient's acute symptoms were controlled, we maintained her on a single nighttime dose of 150 mg for several months, and she continued to do well.

Vignette 4: IM trazodone for acute psychomotor agitation in MDD: A 28-year-old man was brought to the emergency department (ED) by his family due to an episode of severe psychomotor agitation. His history included major depressive episodes with mixed features (significant irritability and agitation), but no manic episodes or psychosis. He had multiple past ED visits for similar agitation. In the current episode, he had been verbally aggressive toward family members for days, extremely anxious, pacing incessantly, and unable to sit still. On examination, he was partially cooperative and reluctant to discuss his feelings, but it was clear he was internally tense, hyperaroused, and in a state of extreme restlessness. He denied hallucinations and showed no

delusions. After ruling out medical causes of agitation, we proposed rapid tranquilization. Rather than using a benzodiazepine or antipsychotic (given his depressive background and young age), we opted for trazodone IM, which he consented to. A single IM injection of 50 mg trazodone was administered, and within an hour, the patient showed a good response. His anxiety and distress subsided substantially, and he could lie still and converse more calmly. The psychomotor agitation resolved to the point that he no longer posed a danger to himself or others. We recommended hospital admission for further stabilization and treatment of his underlying depression, which he agreed to. During inpatient care, instructions were given that if severe agitation re-emerged, a dose of IM trazodone could be repeated (though in this case it was not needed). He was started on oral trazodone for the long term. This vignette highlights parenteral trazodone as a rapid intervention for acute agitation in a depressive context, providing a calming effect without exposing him to antipsychotics (which we wanted to avoid due to their side effect profile in young men) or benzodiazepines (which carry dependency risks). The case also underlines that while IM trazodone can swiftly reduce agitation and anxiety, it should ideally be followed by appropriate ongoing treatment (here, admission and initiation of maintenance antidepressant therapy) for the patient's safety and recovery.

Vignette 5:Trazodone augmentation with antidepressants in anxious depression and insomnia: A 24-year-old man presented with symptoms of generalized anxiety, more intense in the evening, accompanied by ruminative thoughts and initial insomnia. His mood appeared depressed, and the patient complained of persistent fatigue. From the medication history, it was noted that he had been using low-dose alprazolam inappropriately (0.25–0.5 mg, taken 2–4 times a week without medical supervision) and occasionally consuming alcohol in the evenings for self-medication. A diagnosis of GAD with co-occurring depression and insomnia was made. Pharmacological therapy was initiated with sertraline at 25 mg/day, then gradually increased to 100 mg/day, in combination with trazodone IR (50 mg at bedtime, later increased to 75 mg and then to 100 mg). Subsequently, to improve tolerability, we switched to trazodone XR (150 mg at night). The therapeutic goals included normalizing sleep, reducing anxiety and ruminative thinking, discontinuing benzodiazepine use, and improving treatment adherence. After 8 weeks, the patient achieved remission of anxiety symptoms and insomnia, successfully discontinued alprazolam completely, and reported good tolerability and adherence to treatment. From a safety perspective, the patient was educated about possible side effects of trazodone, particularly orthostatic hypotension and sedation, and was advised to avoid alcohol consumption during treatment to prevent drug interactions. Additionally, special attention was given to monitoring for the potential onset of rare adverse events such as priapism, an occurrence that did not manifest during the course of treatment.

Conclusion

Trazodone emerges as an excellent example of multimodal and multifunctional antidepressants with clinical versatility extending well beyond monoaminergic frameworks. Its distinctive pharmacodynamic profile provides a robust mechanistic basis for addressing the heterogeneous symptomatology of MDD and comorbid conditions, while its formulation-specific pharmacokinetics enables an individualized approach. IR formulations facilitate rapid onset of hypnotic and anxiolytic effects and flexible dosing, while XR formulations maintain steady serotonergic modulation over 24 h with improved tolerability and adherence. The availability of parenteral preparations broadens trazodone's utility in acute psychiatric settings, especially when oral administration is not feasible. Taken together, these characteristics highlight the importance of an individualized approach that carefully matches the dose, formulation, and pharmacodynamic targets of trazodone to specific clinical presentations. Although evidence for trazodone in MDD is robust, evidence for off-label uses of trazodone (insomnia) and certain neurological conditions remains less well-established, mainly due to the study design (e.g., observational studies) and duration (e.g., short-term studies). Similarly, there are gaps in the understanding of long-term safety of trazodone and the comparative efficacy of parenteral formulations of trazodone, especially in acute settings. Future research on formulation-specific pharmacokinetic/pharmacodynamic relationships, the role of IM and IV trazodone in acute care, and the development of precision-guided prescribing algorithms to predict treatment response may be beneficial to enhance therapeutic outcomes in patients with MDD.

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Author contributions

All authors contributed substantially and equally to the conception, drafting, and critical revision of all sections of the manuscript. Alessandro Cuomo: conception, first draft, revision integration, submission; Andrea Fagiolini: supervision, clinical interpretation, critical revision; Filippo Caraci: pharmacological interpretation, revision of neuropharmacological sections; Edoardo Spina, Antonio Vita, Maurizio Pompili: critical review and literature synthesis. All authors approved the final version and agree to be accountable for the content.

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Declarations

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Consent for publication
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Maurizio Pompili serves as Editor-in-Chief of Annals of General Psychiatry. To ensure an independent and transparent process, the manuscript will be handled by an independent editor not involved in the peer review or editorial decision. All other authors (Alessandro Cuomo, Andrea Fagiolini, Filippo Caraci, Edoardo Spina, and Antonio Vita) declare no competing interests relevant to this work.

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