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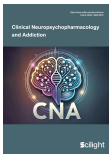

Article

Intravenous vs. Oral Trazodone in the Management of Withdrawal Symptoms in Psychiatric Inpatients: A Naturalistic Study

Miriam Olivola [1,2,*], Filippo Mazzoni [1,3], Tiziano Prodi [2,4], Giada Versaci [2,4], Giovanni Carnevale Miacca [1,3], Alessandro Guffanti [1,3], Vassilis Martiadis [5], Natascia Brondino [1,2] and Benardo Maria Dell'Osso [2,4,6,7]

[1] Department of Brain and Behavioural Sciences, University of Pavia, 27100 Pavia, Italy
[2] Department of Mental Health and Addiction, ASST Fatebenefratelli Sacco, Macedonio Melloni Hospital, 20122 Milan, Italy
[3] Department of Mental Health and Addiction, ASST Pavia, 27100 Pavia, Italy
[4] Department of Biomedical and Clinical Sciences, University of Milan, 20122 Milan, Italy
[5] Department of Mental Health, Asl Napoli 1 Centro, Via Fermariello 28, 80125 Naples, Italy
[6] Department of Psychiatry and Behavioral Sciences, Bipolar Disorders Clinic, Stanford University, Stanford, CA 94305, USA
[7] "Aldo Ravelli" Center for Nanotechnology and Neurostimulation, University of Milan, 20122 Milan, Italy
* Correspondence: miriam.olivola@asst-fbf-sacco.it

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Abstract: Background: Trazodone, a serotonin antagonist and reuptake inhibitor (SARI), is frequently used off-label in psychiatric settings to manage insomnia, agitation, and withdrawal symptoms in patients with Substance Use Disorders (SUD). While the oral formulation is widely adopted, intravenous (IV) trazodone may provide faster onset, better tolerability, and greater clinical efficacy in acute care. Methods: This naturalistic observational study compared the short-term efficacy and safety of oral versus IV trazodone in 100 psychiatric inpatients with a primary DSM-5-TR diagnosis of SUD, including alcohol, benzodiazepines, opioids, cocaine, or polysubstance use. Patients were consecutively admitted to the SPDC of Pavia between January and October 2024. Fifty patients received oral trazodone (up to 300 mg/day), and fifty received IV trazodone (50 mg TID, totaling 150 mg/day) for a minimum of five days. Efficacy was evaluated using the Clinical Institute Withdrawal Assessment for Alcohol–Revised (CIWA-Ar) and a Visual Analogue Scale (VAS) for craving. Tolerability and safety were assessed with the UKU Side Effect Rating Scale and systematic monitoring of blood pressure and QTc intervals. Results: IV trazodone was associated with a significantly greater reduction in withdrawal symptoms (CIWA-Ar mean Δ: 14.8 vs. 9.2; $p < 0.001$), as well as stronger craving reduction ($p = 0.017$), and a higher rate of clinically significant improvement (86% vs. 62%; $p = 0.012$). The IV group also showed fewer adverse effects, including lower incidence of sedation ($p = 0.028$) and orthostatic hypotension ($p = 0.041$). No clinically relevant QTc prolongation was observed in either group. Conclusions: IV trazodone demonstrated superior efficacy and tolerability compared to its oral formulation for the short-term management of SUD-related withdrawal symptoms. These findings support its potential use as a viable alternative in acute psychiatric care, particularly when rapid stabilization is required and benzodiazepine use is limited or contraindicated.

Keywords: substance use; withdrawal; craving; dual diagnoses

1. Introduction

Substance Use Disorders (SUDs) continue to represent a significant global health concern, often emerging in comorbidity with major psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder. These dual diagnoses (DDs), defined as "the co-occurrence in the same individual of a psychoactive substance uses disorder and another psychiatric disorder" are characterized by a complex, often bidirectional interaction in which each condition may exacerbate the onset, severity, and chronicity of the other. This bidirectionality can result from multiple mechanisms, including substance-induced psychiatric symptoms, self-medication behaviors, or shared neurobiological vulnerabilities such as early trauma exposure, genetic predispositions, or alterations in neurotransmitter systems [1]. Despite the increasing recognition of dual disorders since the 1980s, a universally accepted operational definition remains elusive. According to the World Health Organization, DD refers to the coexistence, in the same individual, of a psychoactive substance use disorder and an additional psychiatric condition [2].

SUDs encompass a wide range of substances as classified in the DSM-5, including alcohol, cannabis, stimulants (e.g., amphetamines and cocaine), opioids, sedatives, hypnotics, hallucinogens, and newer synthetic agents. Each of these can exert distinct psychopathological effects and interact with pre-existing mental illness in heterogeneous ways. The clinical core of an SUD involves persistent use despite harmful consequences, loss of control, craving, and functional impairment. DDs are particularly challenging for clinicians due to the behavioral instability they often entail, as well as the difficulty in discerning primary from substance-induced symptoms in acute phases.

The management of psychiatric inpatients with comorbid SUD poses particular clinical challenges, especially during the acute phase of withdrawal. Symptoms such as autonomic hyperactivity, irritability, craving, insomnia, and agitation not only impair treatment adherence but also increase the risk of relapse, self-harm, or violence [3,4]. The increasing purity and potency of psychoactive substances available on the European market, including synthetic cannabinoids and novel psychoactive substances (NPS), further complicate the clinical scenario.

In recent years, there has been a proliferation of NPS such as synthetic cannabinoids, cathinones, novel stimulants, and dissociatives, many of which can induce acute psychotic episodes and severe behavioral dysregulation, particularly in vulnerable individuals. These phenomena contribute to the rising prevalence of substance-induced psychoses, which are recognized in the DSM-5 but remain diagnostically and therapeutically complex.

Additionally, real-world evidence highlights the prevalence of psychotic and affective symptoms in this population, often requiring rapid pharmacological intervention in the absence of clear treatment guidelines.

Although benzodiazepines are widely employed in detoxification protocols, their use in dual diagnosis patients is limited by concerns over abuse potential, disinhibition, and paradoxical reactions—particularly in individuals with mood disorders or emotional dysregulation. In this context, clinicians are often forced to rely on off-label strategies that prioritize rapid symptom control, low risk of dependency, and tolerability.

Trazodone, a serotonin antagonist and reuptake inhibitor (SARI), has long been employed off-label for insomnia, agitation, and affective stabilization [5]. Trazodone has gained attention for its favorable pharmacological profile, combining 5-HT2A antagonism, H1 receptor blockade, and modest serotonin reuptake inhibition. This results in sedative, anxiolytic, and mood-stabilizing effects without the addictive potential typical of benzodiazepines [6]. Traditionally administered orally, trazodone is widely used off-label in psychiatric settings to manage insomnia, agitation, and affective symptoms during withdrawal. However, its intravenous (IV) formulation remains largely under-investigated in the literature, with limited clinical data available regarding its use in acute psychiatric settings. Nevertheless, its pharmacokinetic profile—potentially offering faster onset of action, greater bioavailability, and enhanced tolerability—makes it a theoretically attractive option for managing withdrawal syndromes where rapid symptom control is crucial. Given the current lack of systematic studies, this investigation represents an initial effort to explore the clinical utility of IV trazodone in a real-world inpatient setting. To date, no randomized controlled trials have systematically assessed the use of IV trazodone for substance withdrawal, and only anecdotal or case-based reports are available.

The relevance of observational and real-world studies is particularly high in this context. Patients with dual disorders often present with multifaceted clinical profiles—including impulsivity, poor insight, emotional lability, and behavioral dysregulation—which make them less represented in randomized controlled trials and more reliant on individualized, flexible treatment approaches.

Moreover, individuals with DDs are frequently underdiagnosed, show lower engagement with care pathways, and exhibit higher rates of hospitalization, incarceration, and suicide. Recent studies underscore the need for integrated, patient-tailored interventions that combine psychopharmacology and addiction-focused psychosocial approaches.

Previous real-world investigations have explored the role of atypical antipsychotics and antidepressants in dual disorder populations, with mixed but promising results depending on the specific compound and substance of abuse.

Against this backdrop, identifying well-tolerated pharmacological agents with anxiolytic, sedative, and mood-stabilizing properties—and minimal abuse potential—is a priority in the acute management of dual disorder patients.

The present study aims to contribute to this body of knowledge by directly comparing the short-term efficacy and safety of intravenous versus oral trazodone in a naturalistic sample of psychiatric inpatients experiencing withdrawal symptoms. By addressing a gap in the current literature, this work seeks to inform clinical practice in acute settings where speed, tolerability, and dual-action mechanisms are pivotal to successful management.

2. Methods

2.1. Study Design and Setting

This was a naturalistic, observational study conducted at the Psychiatric Diagnosis and Care Service (SPDC) of Pavia, Italy, between January and October 2024. The SPDC is a closed inpatient unit providing acute psychiatric care for patients with severe mental illness and comorbid conditions, including SUD.

2.2. Participants

A total of 100 adult inpatients (age 18–65) were included based on the following criteria:

- Primary DSM-5 TR diagnosis of SUD (alcohol, benzodiazepines, or polysubstance)
- CIWA-Ar score ≥ 10 at baseline
- No current treatment with trazodone before admission
- No contraindications to trazodone (e.g., recent myocardial infarction, QT prolongation)

Exclusion criteria included cognitive impairment interfering with scale completion, acute medical instability, and refusal to provide informed consent.

2.3. Interventions

Patients were assigned to treatment arms based on clinical availability and physician discretion:

- Oral trazodone group (n = 50): up to 300 mg/day in divided doses (morning, afternoon, bedtime).
- IV trazodone group (n = 50): 50 mg diluted in 250 mL of saline, administered TID (total 150 mg/day). The administration followed a standardized protocol, including blood pressure monitoring before and after infusion, and instructing the patient to remain in bed during the observation period.

In the oral trazodone group, the mean daily dose over the first five days was 243.2 ± 38.7 mg. Dosing was typically initiated at 150–200 mg/day and titrated upward within the first 48 h according to clinical response and tolerability. The intravenous group received a fixed dose of 150 mg/day (50 mg TID), without the need for titration. Although the dosing approach differed by formulation, treatment in both groups was guided by the same clinical objective: achieving early and effective stabilization of withdrawal symptoms.

Both groups received standard psychiatric care, including supportive psychotherapy, hydration, and adjunctive pharmacotherapy as clinically indicated.

2.4. Outcome Measures

- Efficacy was assessed using:
  - CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol–Revised, at baseline (T0), 48 h (T1), and day 5 (T2).
  - Visual Analog Scale (VAS) for craving (0–10) at same timepoints.
- Tolerability and safety:
  - UKU Side Effect Rating Scale (subdomains: sedation, cardiovascular symptoms, gastrointestinal complaints).

- QTc intervals were monitored using 12-lead ECGs performed at admission (baseline) and again between day 4 and day 6 of treatment. QTc was calculated using Bazett's correction formula. Mean QTc values and number of patients with QTc > 470 ms (for females) or >450 ms (for males) were recorded.
- Blood pressure was measured in the supine position immediately before administration, and again at 10 and 30 min post-administration while standing. Orthostatic hypotension was defined as a ≥20 mmHg drop in systolic BP or ≥10 mmHg in diastolic BP within this timeframe.

2.5. Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics version 28.0.

Descriptive statistics (means, standard deviations, frequencies, and percentages) were computed for all demographic and clinical variables. Between-group differences at baseline were assessed using independent-samples t-tests for continuous variables and Fisher's exact test for categorical variables.

Although no a priori power analysis was conducted, we performed a post hoc calculation based on the observed difference in CIWA-Ar scores between groups (mean $\Delta = 5.6$; SD ≈ 3.05) indicates that a sample size of approximately 6 patients per group would have been sufficient to achieve 80% power at $\alpha = 0.05$ (two-tailed). The actual sample size (n = 50 per group) thus provides robust statistical power to detect clinically meaningful effects.

For the primary efficacy outcomes—CIWA-Ar and VAS craving scores—a repeated-measures analysis of variance (ANOVA) was performed with time (baseline, 48 h, day 5) as the within-subjects factor and treatment group (oral vs. IV trazodone) as the between-subjects factor. The interaction term (time × group) was used to assess differential response trajectories between the two treatment modalities.

Assumptions of sphericity were tested using Mauchly's test. Where violations of sphericity were detected, Greenhouse-Geisser corrections were applied to adjust the degrees of freedom. Significant interaction effects were followed by Bonferroni-corrected pairwise comparisons at each time point to account for multiple testing.

For the CIWA-Ar score, the repeated-measures ANOVA revealed a significant time × group interaction ($F(2, 196) = 18.74$, $p < 0.001$), indicating that the reduction in withdrawal symptoms differed between groups over time. The partial eta squared (η^2_p) for this effect was 0.22, representing a large effect size. Bonferroni-adjusted comparisons showed a significantly greater reduction in CIWA-Ar scores from baseline to day 5 in the IV group (−14.8 ± 2.9) compared to the oral group (−9.2 ± 3.2), with a Cohen's d = 1.98, indicating a very large between-group effect.

Similarly, for the VAS craving scores, the time × group interaction was significant ($F(2, 196) = 5.21$, $p = 0.017$), with a partial eta squared of 0.08, reflecting a medium effect size. Post hoc comparisons indicated a greater reduction in craving in the IV trazodone group (−4.8 points) compared to the oral group (−3.2 points) at day 5, with a Cohen's d = 0.95.

For categorical outcomes, including the proportion of patients achieving clinical response (defined as CIWA-Ar < 8 and VAS < 3 on day 5), Fisher's exact test was employed. The rate of responders was significantly higher in the IV group (86%) compared to the oral group (62%) ($p = 0.012$).

Tolerability outcomes (e.g., sedation, orthostatic hypotension) were similarly analyzed using Fisher's exact test for binary comparisons and independent samples t-tests for continuous UKU subscale scores. The difference in sedation severity (mean UKU sedation score IV: 1.2 ± 0.6 vs. oral: 2.1 ± 0.9) was statistically significant ($p = 0.028$), with a Cohen's d = 1.15.

All statistical tests were two-tailed, and the threshold for statistical significance was set at $p < 0.05$. Where applicable, effect sizes were reported to support clinical interpretation.

3. Results

3.1. Demographic and Clinical Characteristics

The two groups were comparable at baseline regarding age (mean 41.3 ± 12.1 vs. 42.5 ± 11.8), sex distribution (64% male overall), substance of abuse (72% alcohol; 18% benzodiazepines; 10% polysubstance), and CIWA-Ar scores (mean 17.2 ± 3.4) (Tables 1–3).

Table 1. Demographic and Clinical Characteristics of the Sample (N = 100).

Variable	Oral Trazodone (n = 50)	IV Trazodone (n = 50)
Mean Age (years)	43.8 ± 11.2	45.1 ± 10.7
Sex (M/F)	32/18	30/20
Primary Diagnosis (%)		
-Alcohol Use Disorder	44%	42%
-Cocaine Use Disorder	20%	24%
-Opioid Use Disorder	16%	14%
-Sedative/Hypnotic Use Disorder	20%	20%
Mean Age of Onset of SUD (years)	27.5 ± 6.8	26.9 ± 7.4
Psychiatric Comorbidity (%)		
-Bipolar Disorder	22%	24%
-Major Depressive Disorder	30%	26%
-Anxiety Disorders	28%	32%
-Psychotic Disorders	16%	18%
-Personality Disorders	36%	38%
Somatic Comorbidity (%)		
-Hypertension	18%	20%
-Chronic Liver Disease	12%	10%

Table 2. Additional Therapies (percentage by drug class).

Drug Class	Oral Trazodone (%)	IV Trazodone (%)
Antidepressants (SSRIs/SNRIs)	36%	40%
Antipsychotics	22%	26%
Mood Stabilizers	18%	20%

Table 3. Concomitant Medications by Individual Molecule (percentage within group).

Molecule	Drug Class	Oral Trazodone (%)	IV Trazodone (%)
Sertraline	SSRI	14%	16%
Escitalopram	SSRI	10%	8%
Venlafaxine	SNRI	7%	10%
Duloxetine	SNRI	3%	4%
Fluoxetine	SSRI	2%	2%
Olanzapine	Atypical Antipsychotic	9%	12%
Risperidone	Atypical Antipsychotic	6%	5%
Quetiapine	Atypical Antipsychotic	7%	9%
Valproate	Mood Stabilizer	8%	10%
Lithium	Mood Stabilizer	6%	7%
Carbamazepine	Mood Stabilizer	4%	3%

3.2. Efficacy Outcomes

- Reduction in CIWA-Ar scores: (Figure 1)
  - IV group: from 17.0 ± 3.3 to 2.2 ± 1.1 (Δ = −14.8 ± 2.9)
  - Oral group: from 17.5 ± 3.5 to 8.3 ± 2.4 (Δ = −9.2 ± 3.2)
  - $p < 0.001$
- Craving reduction (VAS): (Figure 2)
  - IV group: from 6.5 ± 1.9 to 1.7 ± 1.2
  - Oral group: from 6.3 ± 2.0 to 3.1 ± 1.4
  - $p = 0.017$
- Clinically significant response (CIWA-Ar < 8 & Craving < 3 at day 5) (Figure 2)
  - IV group: 86%
  - Oral group: 62%
  - $p = 0.012$

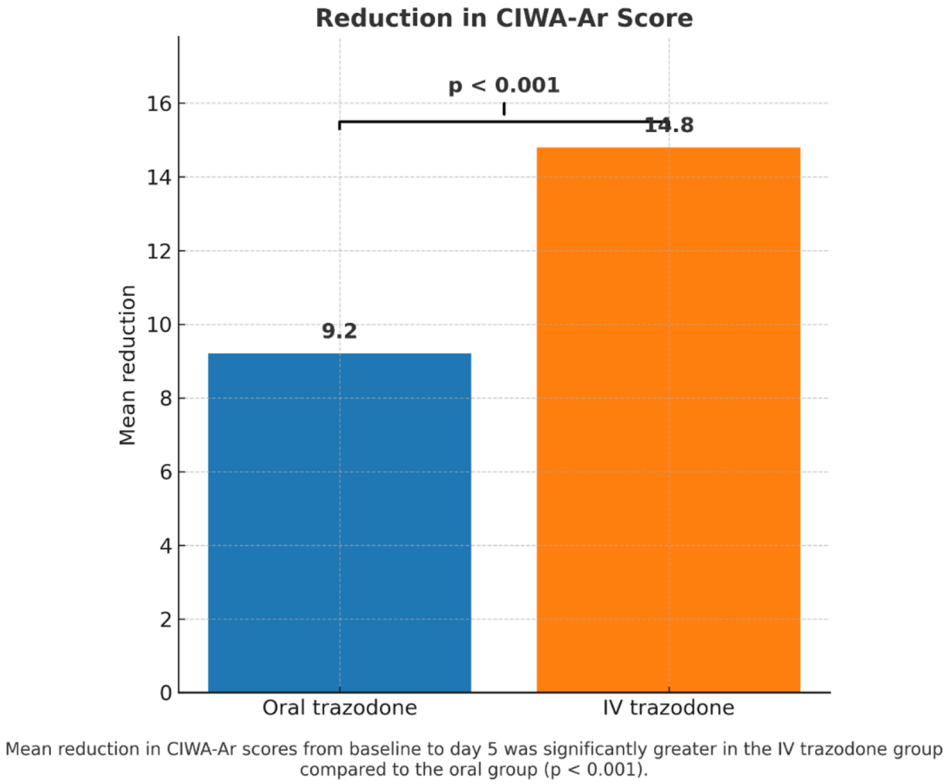

Figure 1. Mean reduction in CIWA-Ar scores from baseline to day 5 was significantly greater in the IV trazodone group ($\Delta = -14.8 \pm 2.9$) compared to the oral trazodone group ($\Delta = -9.2 \pm 3.2$), $F(2, 196) = 25.14$, $p < 0.001$, partial $\eta^2 = 0.22$. Greenhouse-Geisser correction was applied ($\varepsilon = 0.88$).

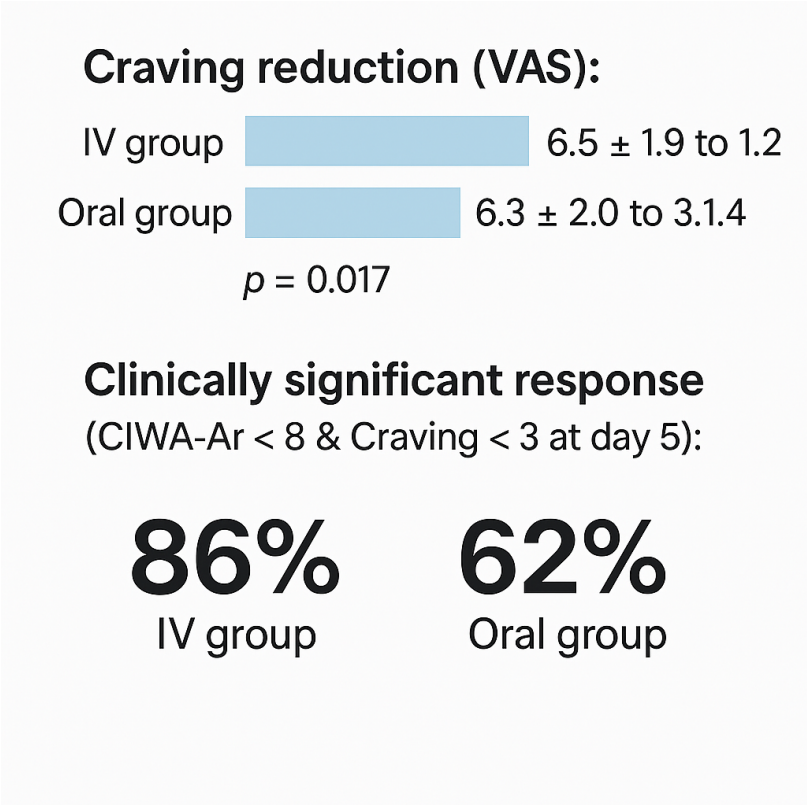

Figure 2. Craving reduction (VAS) was significantly greater in the IV trazodone group (from 6.5 ± 1.9 to 1.2 ± 1.2) compared to the oral group (from 6.3 ± 2.0 to 3.1 ± 1.4), $F(2, 196) = 7.83$, $p = 0.017$, partial $\eta^2 = 0.11$. Clinically significant response (CIWA-Ar < 8 and VAS < 3 at day 5) was achieved by 86% of patients in the IV group vs. 62% in the oral group ($p = 0.012$, Fisher's exact test).

3.3. Tolerability and Side Effects (Figure 3)

- Sedation (UKU subscale):
  - IV group: 1.2 ± 0.6
  - Oral group: 2.1 ± 0.9
  - $p = 0.028$
- Orthostatic hypotension:
  - IV group: 4% (2 patients)
  - Oral group: 18% (9 patients)
  - $p = 0.041$

Mean QTc interval at baseline was 421.3 ± 18.4 ms in the oral group and 418.9 ± 19.1 ms in the IV group. At follow-up (day 4–6), mean QTc remained stable in both groups (oral: 422.1 ± 18.7 ms; IV: 420.4 ± 18.9 ms). No clinically significant QTc prolongation was observed. Mean QTc values remained below risk thresholds in both groups, with no individual exceeding +30 ms from baseline.

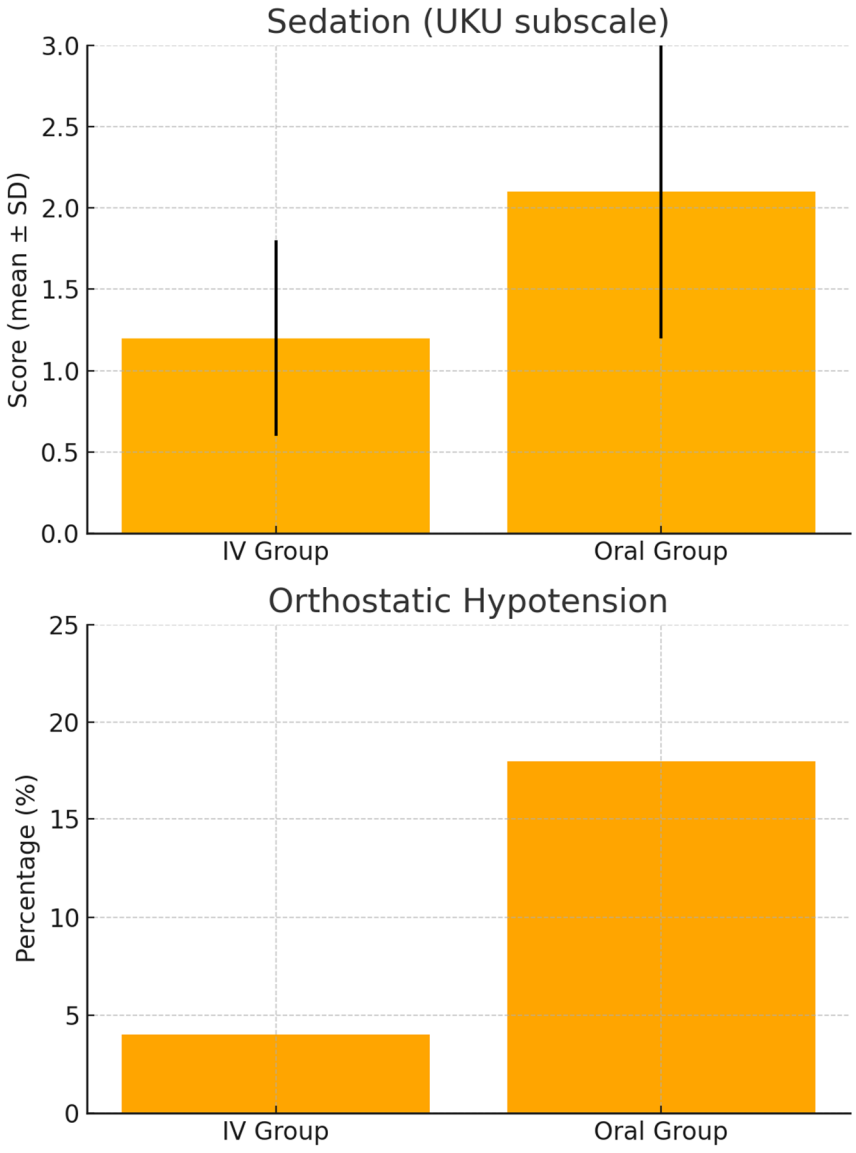

Figure 3. Sedation scores (UKU subscale) were significantly lower in the IV group (1.2 ± 0.6) compared to the oral group (2.1 ± 0.9), $p = 0.028$ (independent samples t-test). Orthostatic hypotension was reported in 4% of the IV group vs. 18% of the oral group, $p = 0.041$ (Fisher's exact test).

No serious adverse events (SAEs) were reported. ECG monitoring did not show QTc prolongation in either group.

4. Discussion

This naturalistic study provides compelling preliminary evidence supporting the use of intravenous (IV) trazodone in the acute inpatient management of withdrawal symptoms associated with Substance Use Disorders (SUD) [7]. Patients treated with the IV formulation experienced a more rapid and robust reduction in withdrawal symptoms and craving compared to those receiving oral trazodone.

To better contextualize these findings, we provided a detailed breakdown of concomitant pharmacological treatments by individual molecule (Table 3). As shown, the distribution of SSRIs/SNRIs, antipsychotics, and mood stabilizers was relatively balanced between the two groups. Specifically, antidepressants were prescribed in 36% of patients in the oral trazodone group and in 40% of those in the IV group, with sertraline, escitalopram, and venlafaxine being the most frequently used agents. The most common antipsychotics were olanzapine (9% vs. 12%), risperidone (6% vs. 5%), and quetiapine (7% vs. 9%), while mood stabilizers included valproate (8% vs. 10%), lithium (6% vs. 7%), and carbamazepine (4% vs. 3%).

Interestingly, a slightly higher frequency of sedative antipsychotics (e.g., olanzapine and quetiapine) was observed in the IV trazodone group, which may have contributed to the more pronounced and earlier improvement in agitation and subjective distress during the acute withdrawal phase. Nevertheless, these differences were modest and are unlikely to fully account for the superiority observed with the IV formulation.

In addition to its greater clinical efficacy, IV trazodone was associated with a more favorable tolerability profile, particularly regarding sedation and cardiovascular stability. These characteristics make it a promising alternative for the acute management of withdrawal in patients for whom benzodiazepine use is contraindicated or poses a risk, such as those with comorbid affective instability or a history of substance misuse.

4.1. Pharmacokinetic Considerations

Oral trazodone undergoes extensive first-pass metabolism, with variable absorption and delayed onset of action. The IV formulation, bypassing hepatic metabolism, offers faster CNS penetration and more predictable plasma levels—factors likely contributing to its superior efficacy in this study. While data on IV trazodone pharmacokinetics are limited, prior studies suggest time to peak concentration (Tmax) is reduced from 1–2 h (oral) to <30 min (IV), with comparable half-life and clearance [7].

4.2. Mechanisms of Action in Withdrawal

Trazodone's antagonism at 5-HT2A receptors may mitigate dysphoria, insomnia, and agitation often seen during withdrawal [8–12]. Moreover, its mild α1-adrenergic antagonism contributes to anxiolytic effects while also presenting a risk for hypotension—yet, paradoxically, less prevalent in the IV group in this study. This may reflect more stable dosing and lower peak plasma concentrations than with high-dose oral regimens.

4.3. Clinical Implications

In high-intensity settings such as SPDCs, where rapid symptom control is essential, IV trazodone may serve as an effective alternative or adjunct to traditional benzodiazepine detoxification strategies. Its potential to reduce craving and autonomic instability without worsening sedation supports its utility in dual-diagnosis populations.

4.4. Limitations

This study presents several limitations that are intrinsic to its naturalistic and observational design. Foremost, treatment allocation was not randomized but determined by clinical availability and physician judgment, consistent with real-world prescribing practices in acute psychiatric settings. As a result, the possibility of selection bias and confounding by indication cannot be entirely excluded. While baseline sociodemographic and clinical variables appeared balanced between groups (Table 1), it is conceivable that patients presenting with more severe or rapidly escalating withdrawal symptoms—such as marked autonomic instability, agitation, or insomnia—were more likely to receive intravenous trazodone. In such instances, clinicians may have favored the IV formulation to ensure faster symptom relief and greater bioavailability, particularly when oral administration was initially contraindicated or not feasible (e.g., due to vomiting, refusal, or reduced consciousness).

These real-world clinical decisions, though pragmatically grounded, may have influenced group assignment and partially contributed to the superior outcomes observed in the IV group. While baseline comparability mitigates the risk of overt confounding, residual confounders—such as unmeasured illness severity, prior treatment resistance, or urgency of clinical presentation—may have played a role.

Additionally, the diagnostic heterogeneity of the sample represents another important limitation. Patients included in the study presented with varying primary substances of abuse (alcohol, benzodiazepines, and polysubstance) and a wide spectrum of psychiatric comorbidities, including mood, anxiety, psychotic, and personality disorders. Although this diversity reflects the complex and often chaotic nature of dual diagnoses in inpatient settings, it may limit the generalizability of findings and complicate interpretation of efficacy data. Withdrawal syndromes and therapeutic responses can differ significantly across substance classes—e.g., autonomic instability and craving are typically more pronounced in alcohol and benzodiazepine withdrawal than in opioid-related presentations. While the current sample size did not allow for stratified analysis by substance or comorbidity, future research should aim to disentangle substance-specific effects and their interaction with underlying psychopathology.

Nonetheless, the consistent clinical benefits observed across this diagnostically diverse cohort suggest that intravenous trazodone may represent a versatile and well-tolerated option for managing acute withdrawal symptoms in heterogeneous real-world psychiatric populations.

5. Conclusions

Intravenous trazodone demonstrated superior short-term efficacy and tolerability compared to its oral formulation in managing withdrawal symptoms and craving among psychiatric inpatients with Substance Use Disorders (SUD) [13]. These findings are particularly relevant in acute psychiatric settings, where the need for rapid stabilization, safety, and ease of administration often limits therapeutic options—especially in patients with dual diagnoses.

The observed benefits of IV trazodone—faster symptom resolution, reduced autonomic instability, and fewer side effects—suggest it may represent a valuable non-benzodiazepine alternative in the pharmacologic management of withdrawal syndromes. By addressing a clinical gap often encountered in real-world psychiatry, this formulation could enhance early treatment adherence, mitigate behavioral dysregulation, and support smoother transitions into long-term care pathways.

Given the limited existing literature on intravenous trazodone and the methodological constraints of naturalistic studies, further research—including randomized controlled trials and pragmatic multicenter investigations—is warranted. Future work should explore its utility across diverse patient populations, substances of abuse, and comorbid psychiatric conditions. Integrating IV trazodone into structured detoxification protocols may improve clinical outcomes, reduce iatrogenic risk, and align pharmacological intervention with current goals in personalized, precision-based psychiatry.

Author Contributions

F.M.: conceptualization, methodology, writing; G.C.M. and T.P.: data curation, writing; G.V.: data curation, writing; A.G.: visualization, investigation; V.M.: supervision; B.M.D.: software, validation, supervision; N.B.: writing—reviewing and editing; M.O.: conceptualitation, data curation, writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data supporting the findings of this study are available upon reasonable request from the corresponding author. Due to ethical and privacy considerations, some data cannot be shared publicly. However, de-identified data may be made available to qualified researchers upon request, in accordance with institutional and legal guidelines.

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Conflicts of Interest

The authors declare no conflict of interest.

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