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Clinical experience with parenteral trazodone in mood disorders: A literature review

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Summary

Trazodone is a serotonin antagonist/reuptake inhibitor, approved for treating major depressive disorder (MDD). Oral formulations are widely studied and marketed in several countries worldwide while there is little evidence to support use of parenteral formulation. Our narrative review summarizes pharmacological properties and clinical data concerning use of parenteral trazodone in mood disorders. PubMed and Web of Science were used to identify the most relevant literature. The main evidence concerns four studies evaluating efficacy in major depressive disorder and indicates that trazodone was well tolerated and effective. Off-label use in agitation associated with bipolar disorder is also reported in three studies, although prescription of concomitant treatment, as a confounding factor, may have influenced outcome measures. The limited available evidence supports parenteral trazodone use in major depressive disorder and suggests that trazodone is a suitable option in patients at high risk of treatment-emergent mania (TEM).

Key words: trazodone, parenteral, mood disorders

Introduction

Trazodone is a triazolopyridine derivative, multimodal and multifunctional drug, synthesized in the 1960s by Angelini Industries. Trazodone (as nefazodone) belongs to the class of drugs known as dual serotonin antagonist/reuptake inhibitors (SARI) and it acts with different pharmacological mechanisms of action [1, 2]. It is available in different formulations including immediate/controlled/extended-release tablets, and in a few countries as oral drops and solution for injection. Due to its complex pharmacodynamic and pharmacokinetic profile, which evolves depending on the choice

of specific dose and formulation of trazodone, similarly to vortioxetine, is among the few currently available multimodal antidepressants [3]. Efficacy and tolerability of oral formulations in major depressive disorder (MDD) are widely proven (Table 1) [4-22], while few studies have evaluated its clinical use in parenteral formulation. The injectable formulation is available in Italy under the commercial name Trittico for intramuscular/intravenous (IM/IV) use and given by 50 mg/5 ml, 100-200 mg (2-4 vials, 50 mg/vial) in 250-500 ml saline solution once or twice daily, with the following indications: intensive depression therapy, complementary pain therapy, anesthesia, and preanesthesia [23]. A new trazodone hydrochloride injectable small-volume formulation (50 mg/ml) has also been developed [24]. The purpose of this review is to summarize the current knowledge on clinical psychopharmacology of parenteral trazodone in mood disorders.

Table 1. **Summary of research on the clinical effectiveness of oral administration of trazodone in adults with major depressive disorder**

Source	Study design	Sample	Duration	Daily average dose (mg)	Change in assessment score
Blacker et al. 1988 [4]	RCT comparing efficacy of TRZ vs. AMI, MIA, DOT to treat patients with MDD	n = TRZ (112) n = AMI (44) n = MIA (36) n = DOT (35)	6 weeks	TRZ = 150 AMI = 100 MIA = 60 DOT = 150	All treatments resulted in significant, comparable improvements in HAM-D
Debus et al. 1988 [5]	RCT comparing efficacy of TRZ vs. FLU to treat patients with MDD	n = TRZ (17) n = FLU (18)	6 weeks	TRZ = 50-400 FLU = 20-60	Both treatments resulted in significant, comparable improvements in HAM-D. TRZ was superior to FLU for HAM-D at weeks 1 and 2
Moon and Davey 1988 [6]	RCT comparing efficacy of TRZ vs. MIA to treat patients with MDD	n = TRZ (19) n = MIA (20)	6 weeks	TRZ = 150 MIA = 30-60	Both treatments resulted in significant, comparable improvements in HAM-D, CFFTT, DSST
Botros et al. 1989 [7]	RCT comparing efficacy of TRZ vs. AMI to treat patients with MDD	n = TRZ (10) n = MIA (10)	3 weeks	TRZ = 50–400 AMI = 25–200	Treatments resulted in significant, comparable improvements in MADRS, SAD, NDS, overall Severity of Illness scale

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Beasley et al. 1991 [8]	RCT comparing efficacy of TRZ vs. FLU to treat patients with MDD	n = TRZ (61) n = FLU (65)	6 weeks	TRZ = 250 FLU = 20	Treatments resulted in significant, comparable improvements in HAM-D21
Cunningham et al. 1994 [9]	RCT comparing efficacy of TRZ vs. VEN vs. PLC to treat patients with MDD	n = TRZ (77) n = VEN (72) n = PLC (76)	6 weeks; responders continued RCT study for 1 year	TRZ = 50–300 VEN = 25–150	TRZ and VEN were superior to PLC for the HAM-D and MADRS. Only VEN was superior to PLC at week 6 for CGI-S
Weisler et al. 1994 [10]	RCT comparing efficacy of TRZ vs. BUP to treat patients with MDD	n = TRZ (61) n = BUP (63)	6 weeks	TRZ = 150-400 BUP = 200-450	Treatments resulted in significant, comparable improvements beyond day 7 in HAM-D, HAM-A, CGI-S
van Moffaert et al. 1995 [11]	RCT comparing efficacy of TRZ vs. MIR to treat patients with MDD	n = TRZ (100) n = MIR (100)	6 weeks	TRZ = 150–450 MIR = 24-72	MIR was superior to TRZ for HAM-D, BPRS, BDI, GAS
Kasper et al. 2005 [12]	RCT comparing effectiveness of prolonged-release TRZ vs. PAR to treat patients with MDD	n = TRZ (55) n = PAR (53)	6 weeks	TRZ = 305 PAR = 22	There was no statistical significance for HAM-D, MADRS, CGI-S, CGI-I
Munizza et al. 2006 [13]	RCT comparing effectiveness of prolonged-release TRZ vs. SER to treat patients with MDD	n = TRZ (62) n = PAR (60)	6 weeks	TRZ = 297 SER = 59	There was no statistical significance for HAM-D, HAM-A, MADRS,CGI-S, CGI-I
Sheehan et al. 2009 [14]	RCT on once-daily TRZ Contramid® vs. PLC to treat patients with MDD	n = TRZ (206) n = PLC (206)	6 weeks	TRZ = 310	TRZ was superior to PLC for HAMD-17 HAM-D, MADRS, CGI-I
Fang et al. 2011 [15]	RCT comparing effectiveness of PAR 20 mg/d augmented with RIS, VPA, BUS, TRZ, or THY to treat patients with MDD	n = TRZ (47) n = RIS (45) n = VPA (39) n = BUS (46) n = THY (48)	8 weeks	TRZ = 100 RIS = 2 VPA = 600 BUS = 30 THY = 80	There was no statistical significance among the five groups for HAMD-17

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Zhang et al. 2014 [16]	RCT on prolonged-release TRZ vs. PLC to treat patients with MDD	n = TRZ (192) n = PLC (190)	6 weeks	TRZ = 273 mg (mean maximum trazodone dosage)	TRZ was superior to PLC for the HAMD-17
Miljevic et al. 2016 [17]	Open-label observational study on prolonged-release TRZ to treat patients with MDD	n = 242	8 weeks	up to 300	TRZ was associated with significant improvements in HAM-D and HAM-A score
Češková et al. 2018 [18]	Open-label observational study on once-daily TRZ Contramid® to treat patients with MDD	n = 85	5 weeks; follow-up visits at week 9 and 21	300	TRZ was associated with significant improvements in MADRS and CGI-S score
Fagiolini et al. 2020 [19]	RCT on once-daily TRZ Contramid® vs. VEN to treat patients with MDD	n = TRZ (166) n = VEN (158)	8 weeks	TRZ = 300 VEN = 75–225	Both treatments were effective in reducing the HAMD-17 total score at week 8 compared to baseline while efficacy was significantly higher in the VEN group
Shrashimirova et al. 2023 [20]	Open-label observational study on once-daily TRZ Contramid® to treat patients with MDD	n = TRZ (200)	24 weeks	TRZ = 150-300	86.5% reported overall improvement measured with CGI-I 68.4% reported improvement of sleep significant improvement in quality of life and overall functioning measured with EQ-5D-5L and SDS

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Siwek et al. 2023 [21]	Open-label, non-inferiority study on extended-release TRZ vs. SSRIs to treat patients with MDD	n = TRZ (42) n = SSRI (34)	12 weeks	TRZ = 209.4 SSRI = mean dose 21.7 fluoxetine equivalent	No differences between the groups in the frequencies of therapeutic response and remission measured by QIDS, QIDS-SR, and MADRS scores Reduction of depression severity after 12 weeks measured by QIDS CR and SR TRZ > SSR
Dudek et al. 2023 [22]	Open-label, non-inferiority study on extended-release TRZ vs. SSRIs to treat patients with MDD	n = TRZ (92) n = SSRI (94)	12 weeks	TRZ = 150–300 SER = 50–200 CIT = 20–40 ESC = 10–20 PAR = 20–60	TRZ was more effective than SSRIs in reducing the levels of depression measured by MADRS, QIDS-SR, QIDS-CR; anxiety assessed by HAM-A; and insomnia evaluated by AIS

AIS – Athens Insomnia Scale; AMI – amitriptyline; BDI – Beck Depression Inventory; BPRS; the Brief Psychiatric Rating Scale; BUP – bupropion; BUS – buspirone; CGI-S/I – Clinical Global Impression – Severity/Impression; CFFTT – Critical Flicker Fusion Threshold Test; CIT – citalopram; CR – clinician-rated; CRT – choice reaction task; GAS – the General Psychiatric Impression Global Assessment Scale; DOT – dothiepin; ESC – escitalopram; EQ-5D-5L – 5-item scale to assess quality of life; FLU – fluoxetine; DSST – digit symbol substitution test; HAM-D – Hamilton Depression Rating Scale; IDS-C – Inventory for Depressive Symptomatology – Clinician Version; MADRS – Montgomery–Åsberg Depression Rating Scale; MDD – major depressive disorder; MIA – mianserin; MIR – mirtazapine; NDS – the Newcastle Diagnostic Scale; PAR – paroxetine; PLC – placebo; QIDS-CR/SR – Quick Inventory of Depressive Symptomatology clinician-rated/self-rated; RCT – Randomized controlled double-blind study; RIS – risperidone; SAD – the States of Anxiety and Depression Scales; SDS – Sheehan Disability Scale; SER – sertraline; SR – self-rated; SSRI – Selective serotonin reuptake inhibitor; THY – thyroid hormone; TRZ – trazodone; VEN – venlafaxine; VPA – valproic acid.

Methods

A narrative review of the literature available until March 2023 was conducted. PubMed and Web of Science were searched using the search string (trazodone and (parenteral or infusion or injectable or injection or intravenous or intramuscular)) to identify the most relevant literature. All papers evaluating clinical efficacy, tolerability/safety of parenteral trazodone in mood disorders were included. Main studies regarding pharmacokinetics and pharmacodynamics were also discussed.

Results

Pharmacokinetics of trazodone after oral and infusion administration

Human data

After oral non-fasting and fasting administration of 100 mg of trazodone, the maximum serum concentrations (Cmax) were consequently 1.88 ± 0.42 μg/mL and 1.47 ± 0.16 μg/mL and were lower than after an intravenous infusion of 90 mg of trazodone at a constant infusion rate of 1.7 ml/min [25].

Metabolism: m-CPP

About 20% of the trazodone is converted to the major active metabolite meta-chlorophenylpiperazine (m-CPP), by presystemic elimination (first-pass effect) operated by the liver and the intestinal walls [26]. It is produced by hydroxylation and oxidation of trazodone, mediated by cytochrome P450 (CYP) 3A4 and can be further converted to p-hydroxy-m-CPP by CYP2D6. It is also a metabolite of etoperidone, mepiprazole, and nefazodone [27]. After oral administration of trazodone, plasma concentration of m-CPP is 10-30% of the parental compound, half-life is 2.6 – 6.1 h [28].

Pharmacodynamic properties

The order of affinity for central nervous system (CNS) receptor types is: α 1 > 5HT2a > H1 > 5HT1a > α 2c > 5HT2c > SERT > D4 > α 2a > sigma 2 > sigma 1 > D2 > DAT > NET/M [29-31]. The receptor binding affinity of m-CPP follows this order: 5HT1a > 5HT2c > α 1> 5HT2a > α 2c > α 2a > SERT > H1 > NET > sigma 2 > D2 [29-32]. The multi-target profile of trazodone provides specific clinical effects (Table 2).

Table 2. **Binding affinity (Ki [nM])**

Receptor transporter	K_i (nM) trazodone	K_i (nM) m-CPP
5-HT2a	20	110
H1	29	449
5HT1a	96	16
α 1	12	97
α 2c	155	123
5-HT2c	402	59
SERT	690	432
D_4	703	ND

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α 2a	728	145
Sigma 2	933	8350
Sigma 1	1174	ND
D_2	3500	>10000
DAT	>7400	ND
NET	>10000	4360
M	>10000	ND
5HT – 5-hydroxytryptamine receptor; H – histamine receptor; α – alpha adrenergic receptor; SERT – serotonin transporter; D – dopamine receptor; DAT – dopamine transporter; NET noradrenaline transporter; M – muscarinic receptor; ND – no data available.		

5-HT2A / 5-HT2C receptors

Trazodone acts as a potent antagonist of 5-HT2A receptors [29]. Several studies show that 5-HT2A receptor antagonism has sleep-promoting [33], antipsychotic [34], antidepressant [35], anxiolytic [36], anti-akathisia [37], and antiparkinsonian properties [38]. Trazodone was previously considered a 5-HT2C receptor antagonist [31, 39]. In preclinical animal models, 5-HT2C agonists showed anorexigenic and antipsychotic action [40]. The role of 5-HT2C receptors in mood regulation is not yet fully defined [41, 42], while there is more consistent data on anxiolytic effects of 5-HT2C antagonists [43, 44]. The blockade of 5-HT2A/C is what differentiates trazodone from selective serotonin reuptake inhibitors (SSRI). This mechanism reduces the risk of sexual dysfunctions, which arise due to the blockade of the serotonin transporter (SERT) [21, 22, 45]. The inhibition of SERT also increases the serotonergic transmission in the prefrontal cortex thereby stimulating 5HT2 receptors, which in turn increases the release of GABA effectively limiting the dopaminergic and noradrenergic transmission. Owing to 5HT2 antagonism trazodone, unlike SSRI, is unlikely to induce emotional blunting and might be more effective in the treatment of anhedonia [21, 22, 45, 46]. Hence, low doses of trazodone might be useful as an add-on to SSRI in ameliorating some of their adverse effects resulting from 5HT2 stimulation, i.e., sleep disruption, sexual dysfunction.

5-HT1A receptors

Trazodone is an agonist for the human 5-HT1A receptors [29] that promote the tonic activation of postsynaptic 5-HT1A receptors by desensitizing the somatodendritic 5-HT1A autoreceptors and by activating the postsynaptic 5-HT1A receptors in the hippocampus [47]. These actions in the corticolimbic system have shown antidepres-

sant and anxiolytic action [48]. Moreover, 5-HT1A antagonism was shown to have procognitive effects [49].

α1 receptors

Trazodone is an alpha1 antagonist [29] which might cause orthostatic hypotension, one of the most common cardiovascular complications of this drug [50].

H1 receptors

The antagonism of histamine H1 receptors by trazodone [29] is involved in sleep-promoting effects [51].

α 2A/α 2C receptors

Trazodone thanks to α 2 receptor antagonism [29], presynaptic inhibitory receptors regulating neurotransmitter release, may contribute to its antidepressant activity [52]. Furthermore, it was shown that α 2 antagonism promotes noradrenergic and serotonergic transmission which translates to antidepressant action [53].

SERT

Trazodone is a weak inhibitor of SERT, 100-fold lower than at 5-HT2A receptors, and a stable trazodone serum level higher than 0.65 mg/L is required for an antidepressant action [1]. Clinically, it means that in order to saturate 90% of SERT, a minimal daily dose of 150 mg of trazodone is needed [45].

Sigma receptors

Trazodone is an agonist of the sigma 1 and 2 receptors with a Ki value of 1174 nM and 933 nM, respectively [30]. The sigma 1 receptors seem to be involved in the pathophysiology of mood disturbances, anxiety, schizophrenia, learning, memory, nociception and in substance abuse effects, such as cocaine, alcohol and methamphetamine. The sigma 2 receptors are involved in metabolic regulatory functions [54-56]. It is unclear if these actions are of importance to the clinical effects of trazodone.

Ion channels

Trazodone inhibits cardiac human Ether-à-go-go-Related Gene (hERG) potassium channels [57], potassium voltage-gated channel subfamily D member 3 (Kv4.3 channels) [58] and recombinant T-type calcium channels [59]. The inhibitory effect of trazodone on the Kv4.3 channels and recombinant T-type calcium channels located

in the brain may be associated with the modulation of sleep [58], while inhibition of hERG channels is associated with increased risk of prolonged QTc [60].

Clinical efficacy in mood disorders

Seven studies were selected: three trials evaluated the efficacy of parenteral trazodone in patients with bipolar disorder, four studies evaluated efficacy of parenteral trazodone in patients with MDD (Table 3).

Agitation associated with bipolar disorder

A retrospective study on 22 subjects with bipolar disorder evaluated the effectiveness of IV/IM trazodone in the management of psychomotor agitation (PMA) in patients with depressive, hypo/manic episodes with mixed features. Concomitant medications were also present. Trazodone was administered at a mean dose of 98.50 ± 43.27 mg/d. The severity of PMA was assessed by the Hamilton Anxiety Rating Scale (HAM-A), Positive and Negative Syndrome Scale – Excited Component (PANSS-EC), Clinical Global Impression for Aggression (CGI-A), and Young Mania Rating Scale (Y-MRS) scored before treatment (T0), as well as after the first (T1) and second (T2) trazodone administration. Trazodone was associated with significant improvement over time in all scales. No patient discontinued the treatment and sedation was the most common adverse effect (AE) [61].

In another retrospective analysis of 64 patients with bipolar disorder, IV/IM trazodone was evaluated to treat PMA. Concomitant medications were also administered. The severity of PMA was assessed by the Clinical Global Impression Scale − Severity of Illness (CGI-S) scored before and at the end of medication administration. Trazodone was associated with significant improvements in CGI-S scores from baseline. No patients discontinued the study because of AE; 20.3% of patients reported AE, the most common were sedation, orthostatic hypotension, dizziness, nausea and oral paresthesia [62].

In another observational study with a sample of 72 patients IV/IM trazodone efficacy was evaluated for the treatment of PMA. Patients were receiving concomitant medications and were diagnosed with bipolar disorder (n = 64), psychotic disorder (n = 5), dementia (n = 2), alcohol use disorder (n = 1). Trazodone was administered at a mean dose of 75.22 mg/d (25-400 mg/d) for an average of 3.86 days. The severity of PMA was assessed by means of the CGI, rated before (t0) and at the end of the parenteral treatment (t1). Trazodone was associated with significant improvements in CGI-S scores from baseline No patients discontinued the study because of AE; 20.8% of patients reported AE, the most common were sedation, orthostatic hypotension and dizziness [63].

Major depressive disorder

In an open label study of ten patients with MDD, five patients were treated with IV trazodone 12.5 – 100 mg/d, the other five patients were treated with IV trazodone 25 – 200 mg/d for a period of ten days. Trazodone was administered as monotherapy. The severity of depression was assessed through subsequent administrations of the depression scale of von Zehrssen. Trazodone showed antidepressant effect and good tolerability with quicker and larger effect on the decrease of depression in the sample receiving higher doses. Mild and transient drowsiness was the only AE reported [64].

In a naturalistic study, 34 patients with MDD were included and treated with IV trazodone 75-100 mg/d monotherapy for 1 week. During the second week, oral formulation 150-300 mg daily was added to the IV one. In third week IV formulation was stopped and followed by oral administration of trazodone 150-300 mg/d. The Montgomery-Asberg Depression Rating Scale (MADRS), HAM-A, Hamilton Depression Rating Scale (HAM-D) were performed at baseline (T0), after 2 weeks (T1), 6 weeks (T2), after 3 months (T3), and 6 months (T4). There was a statistically significant decrease in MADRS, HAM-A, HAM-D total scores from T0 to T1. No patients discontinued the study because of AE; 36.4% of patients reported AE, the most common were somnolence/sedation, rash and dizziness [65].

In a single blind study, 42 patients with a diagnosis of MDD were selected and treated with IV trazodone monotherapy (n = 26) or IV clomipramine monotherapy (n = 17) according to clinical judgment, followed after 1 week by oral administration. MADRS and HAM-D and HAM-A were administered at baseline, after 1, 2, 6 weeks and raters were blinded to the type of medication. The mean doses of IV trazodone and clomipramine were 44.23 mg/d and 29.69 mg/d, respectively. No differences on total scores of rating scales were found between the two treatment groups after the first week of intravenous treatment. No patients discontinued the study because of AE; 15.4% of patients in the trazodone group and 56.3% of the clomipramine group reported AE. The most common AE in the trazodone group were sedation, rash and dizziness while in the clomipramine group were xerostomia, sedation, headache and dizziness [66].

In a case series study 16 patients with depressive disorder due to another medical condition were treated with IV trazodone 100 mg/d for 15 days and 100 mg/d of phenobarbital and 5 mg of diazepam as a hypnotic in the evening. The severity of depression was assessed by the Clinical Global Impression and HAM-D administered before and at the end of medication administration. Trazodone was shown to have a marked antidepressant and anxiolytic action. No AE were noted [67].

Table 3. **Descriptive comparison between included studies**

Source	Study design	Sample	Duration	Daily average dose (mg)	Change in assessment score
Amendola et al. 2019 [61]	Retrospective study on parenteral TRZ to treat acute PMA in BD with mixed features	n = 22	no data	98.50 ± 43.27	TRZ was associated with significant improvement over time in all scales: HAM-A, PANSS-EC, CGI-A, Y-MRS
Ballerio et al. 2018 [62]	Retrospective study on parenteral TRZ to treat patients with BD and PMA	n = 64	1−19 days	77.64 ± 38.69	TRZ was associated with significant improvements in CGI-S scores
Crapanzano et al. 2019 [63]	Observational study on parenteral TRZ to treat patients affected by BD and other conditions and PMA	n = 72	3.86 days	75.22	TRZ was associated with significant improvements in CGI-S scores
Berzewski 1988 [64]	Open label study on parenteral TRZ to treat patients with MDD	TRZ low dose (n = 5) TRZ high dose (n = 5)	10 days	low dose 12.5 – 100 high dose 25 – 200	TRZ was associated with significant improvement in depression scale of von Zehrssen; TRZ high dose was superior to TRZ low dose
Fiorentini et al. 2018 [65]	Naturalistic study on parenteral TRZ to treat patients with MDD	n = 34	2 weeks	75-100	TRZ was associated with significant improvements in MADRS, HAM-A, HAM-D
Buoli et al. 2019 [66]	Single-blind study on parenteral TRZ vs. parenteral CLO to treat patients with MDD	n = TRZ (27) n = CLO (17)	6 weeks	44.23 (TRZ) 29.69 (CLO)	TRZ comparable to CLO in terms of improvement in MADRS and HAM-D and HAM-A

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Roccatagliata et al. 1977 [67]	Case series study on parenteral TRZ to treat patients with MDD due to another medical condition	n = 16	15 days	100	TRZ was associated with significant improvements in CGI and HAM-D

BD – bipolar disorder; CGI – Clinical Global Impression Scale; CGI-A – Clinical Global Impression for Aggression; CGI-S – Clinical Global Impression Scale − Severity of Illness; CLO – clomipramine; HAM-A – Hamilton Anxiety Rating Scale; HAM-D – Hamilton Depression Rating Scale; MADRS – Montgomery-Asberg Depression Rating Scale; MDD – major depressive disorder; PANSS-EC – Positive and Negative Syndrome Scale – Excited Component; PMA – psychomotor agitation; TRZ – trazodone; Y-MRS – Young Mania Rating Scale

Discussion

Three studies with a total sample of 152 patients evaluated parenteral trazodone in PMA associated with bipolar disorder and showed that parenteral trazodone was well tolerated and effectively reduced agitation symptoms [61-63]. However, conclusions should be cautiously drawn from studies enrolling patients receiving concomitant medications. In sum, four studies with a total sample of 86 patients evaluated parental trazodone on MDD and showed that infusion trazodone therapy may be effective in reducing depression and anxiety in MDD as well as agitation and anxiety in BD and is well tolerated [64-67]. Parenteral antidepressant therapy has several advantages: assurance of compliance, rapid onset of action, direct effect on the central nervous system, bypassing the first-pass effect, smaller dosages compared to oral therapy, avoidance of direct pharmacological effects on the gastrointestinal tract [63, 64]. Injection administration of trazodone produces a greater plasma peak than the oral administration [25, 26, 64] and a rapid saturation of 5HT2A, H1, alpha 1 receptors that may underlie its sedative properties [51, 62, 63]. This formulation avoids the first liver passage and limits the formation of m-CPP [26]. This active metabolite produces potential adverse effects mediated by high affinity for multiple serotonin receptors: headache, panic, anxiety, excitement, dysphoria, psychosis, sleep disruption, anorexia, increase in ACTH/cortisol, prolactin and temperature [68], because it acts as an agonist, in contrast to the parental compound.

Parenteral trazodone was not related to activation symptoms or treatment-emergent mania (TEM). What is more, a review of case reports published up to 2015 describing the switch to mania during sleep-promoting antidepressants reported only 17 cases of switch to hypo/mania which were associated with oral trazodone [69]. While available data are inconclusive regarding antidepressant monotherapy for patients with bipolar II depression, efficacy in mixed depression of any type as well bipolar I depression remains uncertain, given their potential to induce cycle acceleration. In this case antidepressants should be discontinued or given in combination with atypical antipsychotics or mood stabilizers [70, 71]. Some differences may occur among antidepressants, i.e., tricyclic

antidepressants and serotonin–norepinephrine reuptake inhibitors show a higher risk of TEM than selective serotonin reuptake inhibitors [71-73]. Currently studies comparing the risk of manic switch between trazodone and other antidepressants are lacking.

With regard to other antidepressants in the treatment of bipolar depression as an add-on to a mood stabilizer, the levels of TEM were 11.7% for vortioxetine, 15% for escitalopram, 10% for citalopram, 20.9-48.4% for venlafaxine, 16.7-29.2% for bupropion [74]. In a study assessing TEM risk in bipolar depression in a sample achieving SSRIs and nefazodone (an analog of trazodone sharing a similar receptor profile) the hypo/mania switch was noted in 30.1% and 18.8%, respectively [72]. It is worth noting that the data concerning risk of TEM in bipolar depression treated with antidepressant augmentation of normothymic drugs need to be assessed with caution as it was shown that the rates of TEM are highly dependent on the methodology of the study [75]. Nonetheless, because of its unique pharmacokinetics parenteral trazodone [25, 26, 63, 64] may hypothetically have an even lower risk of switching to mania than the oral formulation making it a suitable antidepressant option to treat depressive episodes in patients at high risk of TEM, such as those with bipolar I, rapid cycling course, substance use disorder, baseline hypo/manic symptoms, multiple previous depressive episodes, previous suicide attempts and antidepressant TEM [73].

Conclusion

Parenteral trazodone appears as an effective and well tolerated MDD treatment option and a reasonable antidepressant choice if clinical and psychopathological features associated with TEM are present. However, studies assessing the effect and safety of parenteral trazodone were largely based on retrospective analyses and included relatively small samples. Studies with more robust methodology and larger sample sizes comparing parenteral trazodone to its oral formulations are needed to further assess parenteral trazodone in the treatment of affective disorders. Evidence to support its use in psychomotor agitation associated with bipolar disorder is still scarce.

Conflicts of interest
None declared.

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