Efficacy of oral trazodone slow release following intravenous administration in depressed patients: a naturalistic study

Efficacia del lento rilascio orale di trazodone dopo somministrazione endovenosa in pazienti depressi: uno studio naturalistico

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SUMMARY. Backgrounds. Up to date, no studies in literature assessed the efficacy of a treatment schedule including i.v. trazodone followed by its oral administration. In light of this lack of evidence, the aim of the present study was to evaluate the efficacy and tolerability of trazodone, administered first i.v. and then orally in a sample of Major Depressive Disorder (MDD) patients. **Methods.** Thirty four patients underwent i.v. administration of trazodone (75-100 mg in 250 mL of saline) for 1 week. During the second week, oral extended-release formulation (150-300 mg per day) was added to the i.v. administration. Finally, extended-release trazodone was orally administration at doses of 150-300 mg per day. Psychometric scales were performed at baseline (T0), after 2 weeks (T1), 6 weeks (T2), after 3 months (T3), and 6 months (T4). **Results.** The total sample included 34 subjects (14 males and 20 females). There was a statistically significant decrease in Hamilton Depression Rating Scale total scores from T0 to T1 (t=9.06; df=33), from T1 to T2 (t=4.96; df=29), from T2 to T3 (t=4.08; df=19), and from T3 to T4 (t=2.25; df=19); in Hamilton Anxiety Rating Scale total scores from T0 to T1 (t=8.79; df=33) and from T1 to T2 (t=5.61; df=29); in Montgomery-Asberg Depression Rating Scale total scores from T0 to T1 (t=9.30; df=33), from T1 to T2 (t=5.69; df=29), and from T2 to T3 (t=3.16; df=19). **Conclusions.** This finding confirms previous results on depression with concomitant anxiety symptoms: focusing on trazodone prolonged-release formulation, available data documented its efficacy in MDD.

KEY WORDS: major depressive disorder, antidepressant, trazodone, maintenance treatment.

RIASSUNTO. A oggi, nessuno studio in letteratura ha valutato l'efficacia di un programma di trattamento comprendente trazodone i.v. seguito dalla successiva somministrazione orale. Alla luce di questo, lo scopo del presente studio è stato di valutare l'efficacia e la tollerabilità del trazodone, somministrato prima i.v. e poi per via orale in un campione di pazienti affetti da episodio depressivo maggiore. **Metodi.** Trentaquattro pazienti sono stati sottoposti a somministrazione i.v. di trazodone (75-100 mg in 250 mL di soluzione salina) per 1 settimana. Durante la seconda settimana, la formulazione orale a rilascio prolungato (150-300 mg al giorno) è stata aggiunta alla somministrazione i.v. Infine, il trazodone a rilascio prolungato è stato somministrato per via orale a dosi di 150-300 mg al giorno. Le scale psicometriche sono state eseguite al basale (T0), dopo 2 settimane (T1), 6 settimane (T2), dopo 3 mesi (T3) e 6 mesi (T4). **Risultati.** Il campione totale comprendeva 34 soggetti (14 maschi e 20 femmine). C'è stata una diminuzione statisticamente significativa nei punteggi totali della Hamilton Depression Rating Scale da T0 a T1 (t=9,06; df=33), da T1 a T2 (t=4,96; df=29), da T2 a T3 (t=4,08; df=19) e da T3 a T4 (t=2,25; df=19); nella Hamilton Anxiety Rating Scale il punteggio totale è stato da T0 a T1 (t=8,79; df=33) e da T1 a T2 (t=5,61; df=29); nella Montgomery-Asberg Depression Rating Scale i punteggi totali sono stati da T0 a T1 (t=9,30; df=33), da T1 a T2 (t=5,69; df=29) e da T2 a T3 (t=3,16; df=19). **Conclusioni.** Questo risultato conferma i risultati precedenti su pazienti con sintomi depressivi e con sintomi concomitanti di ansia: concentrandosi sulla formulazione a rilascio prolungato di trazodone, i dati disponibili hanno documentato la sua efficacia negli episodi depressivi maggiori.

PAROLE CHIAVE: disturbo depressivo maggiore, antidepressivi, trazodone, terapia di mantenimneto.

INTRODUCTION

The main goals of the treatment of Major Depressive Disorder (MDD), which is considered one of the most leading causes of disability worldwide[1], are the full symptom remission and the recovery of function[2,3].

In order to achieve these goals and to prevent relapses, resulting from a longer duration of untreated illness (DUI)[4], an early and targeted treatment is necessary for MDD patients. However, although properly treated, 20%-30% of patients present only a partial response or no response to antidepressants[5,6].

The first-line approach is antidepressant monotherapy, particularly the Selective Serotonin Reuptake Inhibitors (SSRIs) and the Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs), associated or not to evidence-based psychotherapy[7,8]. Nevertheless, some limitations, such as low remission rate (<50%)[9] or delayed effectiveness[10], may impact their administration in clinical practice. Furthermore, some patients usually report side effects, such as sexual dysfunction[11], weight gain[12], insomnia or somnolence[13], and anxiety or nervousness[14], thus leading to a poor compliance.

In selected cases, adherence to treatment, onset of action, and efficacy of antidepressants can be improved using intravenous (i.v.) administration[15-17].

Among the few antidepressants for i.v. administration, trazodone is a serotonin receptor antagonist (both $5HT_{2A}$ and $5HT_{2C}$) and a serotonin transporter (SERT) inhibitor (SARI) available since the early 1970s[12,18].

Trazodone is efficacious in MDD at 75-300 mg per day, being potentially increased up to 600 mg per day in hospitalized patients[19]. Recently, a novel prolonged-release formulation named Contramid® has been developed and commercialized in USA and Europe[20]. Intravenously, trazodone can be administered at 100-200 mg in 250-500 mL of saline, according to clinicians' judgement.

The efficacy of trazodone oral formulation in depressed patients has been demonstrated in several studies, particularly due to its hypnotic and anxiolytic effects[21,22]. Orally administered trazodone has been mostly investigated in the elderly, demonstrating not only superiority vs placebo and similar efficacy vs imipramine[23], but also efficacy in patients presenting comorbidity with dementia or agitated behavior[24]. Moreover, trazodone showed a good tolerability profile and a comparable antidepressant efficacy to SSRIs[25] and venlafaxine[26,27]. In augmentation with paroxetine, trazodone was as efficacious as other compounds in treatment-resistant depression (TRD)[28].

Nevertheless, data about the efficacy of intravenously administered trazodone is limited: according to Roccatagliata et al.[29], it improved depressive symptoms in a small sample of organic depressed patients, whereas Berzewski[30] reported positive results in an open trial with high doses of i.v. trazodone.

In particular, up to date, no studies in literature assessed the efficacy of a treatment schedule including i.v. trazodone followed by its oral administration. In light of this lack of evidence, the aim of the present study was to evaluate the efficacy and tolerability of trazodone, administered first i.v. and then orally in a sample of MDD patients.

MATERIALS AND METHODS

Sample

The sample studied included 34 patients (14 males and 20 females), affected by MDD and current Major Depressive Episode (MDE), according to the Diagnostic and Statistical Manual for Mental Disorders, fourth edition, text revision (DSM-IV-TR)[31].

In order to meet inclusion criteria, patients had to have more than 18 years and an acute depressive symptomatology, as defined by Hamilton Depression Rating Scale (HAM-D)[32]; baseline total score ≥15. Treatment partial response was defined by reduction ≥25% at HAM-D total score, while treatment response was defined by a reduction ≥50% at HAM-D total score, whereas the full remission by a HAM-D score <8[33].

Exclusion criteria for study participation were ascertained hypersensitivity to trazodone, pregnancy and breastfeeding, and TRD, defined as a history of no-response to at least two antidepressants from different classes, administered for an adequate period of time and at adequate doses.

All patients were visited, treated, and followed up at the outpatient service (Day Hospital) of the Mood Disorders Clinic within the University Department of Psychiatry in Milan, after giving their written informed consent and receiving a full explanation of the study protocol, which had been previously approved by the local Ethical Committee.

Treatment schedule

After performing physical examination, electrocardiogram, and laboratory tests for all subjects to exclude potential contraindications to i.v. treatment, patients underwent i.v. administration of trazodone (75-100 mg in 250 mL of saline) for 1 week. The infusion started in the morning and lasted approximately 1-2 hours. Duration and dosages of i.v. treatment were chosen according to the data sheet of the compounds.

After the first week, extended-release trazodone was orally administrated at doses of 150-300 mg per day when partial response was achieved. Giving oral administration of trazodone may contribute to avoid relapse of depressive episode.

Of note, the extended-release formulation allowed the administration of the drug once a day, ensuring better tolerability, greater ability to maintain appropriate levels of drug concentrations, and definitely a better compliance.

Psychometric scales were performed at baseline (T0), after 2 weeks (T1), 6 weeks (T2), after 3 months (T3), and 6 months (T4).

Assessment

The Structured Clinical Interview for DSM-IV-TR criteria (SCID-I)[34] was administered to assess diagnoses. The HAM-D, the Montgomery-Asberg Depression Rating Scale (MADRS)[35], and the Hamilton Rating Scale for Anxiety (HAM-A)[36] were administered at baseline (T0), after 2 weeks (T1), 6 weeks (T2), after 3 months (T3), and after 6 months (T4) during follow-up visits. At each visit after baseline, safety and tolerability were assessed, considering spontaneously reported side effects and registering rates of discontinuation for adverse events. The raters were blinded with respect to the pharmacological treatment which had been prescribed to each patient. All the raters were trained to clinical scale administration, with good inter-rater reliability. In addition, the raters had received a specific training for the administration of the rating scales.

The main demographic and clinical variables of the sample were collected (e.g., age, sex, age at onset, DUI, number of previous depressive episodes, duration of the last depressive episode, seasonality, family history for psychiatric disorders in first-degree relatives, number of suicide attempts, number of hospitalizations, lifetime history for psychotic symptoms, presence of atypical symptoms, lifetime substance abuse, type of abuse, reported side effects, reason for discontinuation, mean doses administered, treatment response/remission, and HAM-D, MADRS, HAM-A total scores).

Statistical analysis

Demographic and clinical variables of the entire samples were collected and described.

A paired-samples t-test was conducted to evaluate the efficacy of trazodone over time in terms of reduction of the psychometric scales total scores (HAM-D, HAM-A, MADRS).

For all the analyses, the level of statistical significance was set at 0.05. All the statistical analyses were performed using SPSS, version 22.0 (SPSS Inc., Chicago, Ill).

RESULTS

The total sample included 34 subjects (14 males and 20 females). Trazodone has been administered at mean doses of 39.71 (±12.49) mg i.v. and 157.69 (±59.06) mg orally. Demographic and clinical variables of the total sample are summarized in Table 1.

There was a statistically significant decrease in HAM-D total scores from T0 to T1 (t=9.06; df=33; p<0.001), from T1 to T2 (t=4.96; df=29; p<0.001), from T2 to T3 (t=4.08; df=19; p=0.001), and from T3 to T4 (t=2.25; df=19; p=0.037) (Figure 1); in MADRS total scores from T0 to T1 (t=9.30; df=33; p<0.001), from T1 to T2 (t=5.69; df=29; p<0.001), and from T2 to T3 (t=3.16; df=19; p=0.005) (Figure 2); in HAM-A total scores from T0 to T1 (t=8.79; df=33; p<0.001) and from T1 to T2 (t=5.61; df=29; p<0.001) (Figure 3).

The decrease was not statistically significant in HAM-A total scores from T2 to T3 (t=1.71; df=19; p=0.103) and from T3 to T4 (t=0.66; df=19; p=0.519), and in MADRS total scores from T3 to T4 (t=1.44; df=19; p=0.167).

At end point, 53% of patients responded to the treatment, while the remitters were 30% of the total sample.

Sixteen patients (47% of the total sample) discontinued the treatment: among these, 2 patients for side effects, 10 patients for no-response, 1 for non-compliance, and 3 because of symptom remission or switch to hypomanic symptoms. In particular, 4 (11.8%) patients discontinued the treatment between T1 and T2 (1 for side effects, 2 for no-response and 1 for non-compliance); among the remaining 30 patients, 10 (33.3%) discontinued the treatment between T2 and T3 (1 for side effects, 7 for no-response, 2 for switch to hypomanic symptoms); finally, among the last 20 patients, 2 (10%) discontinued after T4 (1 for no-response and 1 for symptom remission).

During the treatment period, side effects were reported by 36.4% of patients, although none of them discontinued the treatment for serious adverse events. The following side effects were observed: somnolence/sedation (30.3%), rash (3.0%), and dizziness (3.0%).

DISCUSSION

The study protocol was aimed to investigate whether i.v. followed by oral extended-release trazodone administration was efficacious in improving anxiety and depressive symptoms in MDD patients with current MDE. Of note, to our knowledge this is the first study investigating the effect of i.v. and oral extended-release trazodone over time. Infact, avail-

Table 1. Socio-demographic and clinical variables of the total sample.

Variables		N=34
Gender	Male	14 (41.2%)
	Female	20 (58.8%)
Age		54.74 (±15.5)
Seasonality	None	30 (88.2%)
	Spring/autumn	4 (11.8%)
	Summer/winter	0 (0%)
Age at onset		36.90 (±18.3)
DUI		4.67 (±6.6)
Family history of psychiatric disorder	None	13 (38.3%)
	MDD	10 (29.4%)
	BD	1 (2.9%)
	Suicide	2 (5.9%)
	Schizophrenia	0 (0%)
	Other mood disorders	8 (23.5%)
Suicide attempts	Yes	4 (11.8%)
	No	30 (88.2%)
Number of previous depressive episodes		4.42 (±4.1)
Duration of the last depressive episode (days)		96.96 (±99.9)
Lifetime psychotic symptoms	Yes	0 (0%)
	No	34 (100%)
Atypical symptoms	Yes	8 (23.5%)
	No	26 (76.5%)
Number of hospitalizations		0.71(±1.3)
Substance abuse	Yes	14 (41.2%)
	No	20 (58.8%)
Kind of substance abuse	None	20 (58.8%)
	Cannabinoid	5 (14.7%)
	Cocaine	2 (5.9%)
	Alcool	7 (20.6%)
	Other (BDZ)	0 (0%)
Intravenous mean doses		39.71 (±12.5)
Oral mean doses		157.69 (±59.1)
Responders	Yes	16 (53.3%)
	No	14 (46.7%)
Remitters	Yes	9 (30.0%)
	No	21 (70.0%)
	Side effects	2 (5.9%)

(Continued)

(Continued) - Table 1.

Variables		N=34
Discontinuation rates	No-response	10 (29.4%)
	Non-compliance	1 (2.9%)
	Symptom remission	3 (8.8%)
	Somnolence/sedation	10 (30.3%)
Side effects	Rash	1 (3.0%)
	Dizziness	1 (3.0%)

Legend: MDD= major depressive disorder; BD= bipolar disorder; DUI= duration of untreated illness; BDZ= benzodiazepines. Standard Deviation for continuous variables and percentage for categorical ones are reported into brackets.

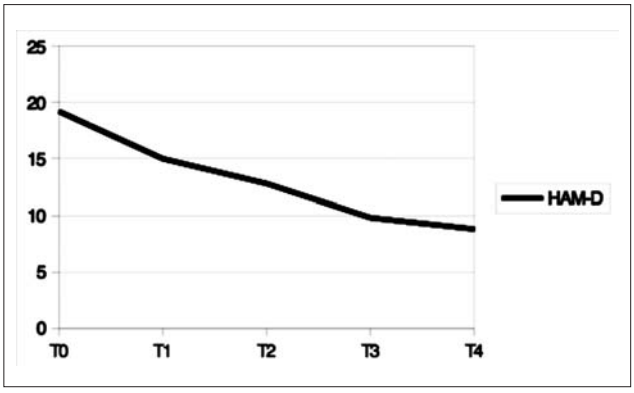

Figure 1. HAM-D mean scores at T0-T1-T2-T3 and T4 timepoints.

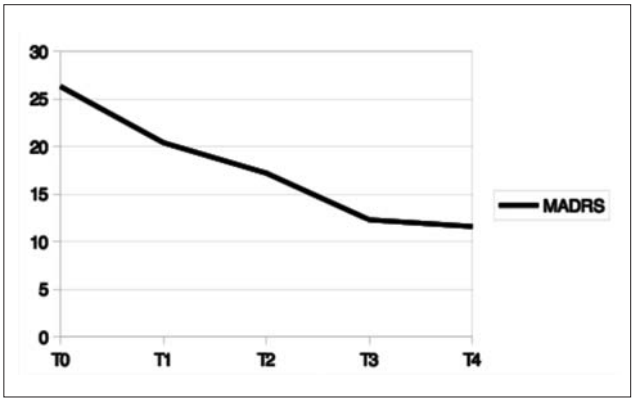

Figure 2. MADRS mean scores at T0-T1-T2-T3 and T4 timepoints.

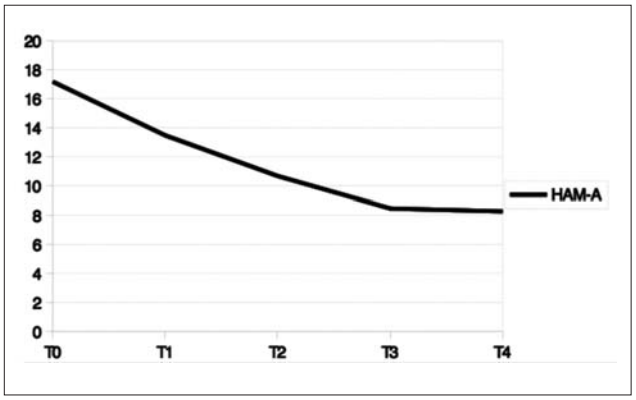

Figure 3. HAM-A mean scores at T0-T1-T2-T3 and T4 timepoints. *Legend*: HAM-D= Hamilton Depression Rating Scale; HAM-A= Hamilton Rating Scale for Anxiety; MADRS= Montgomery-Asberg Depression Rating Scale.

able data in literature mainly concern the oral formulation of the drug and agree in its efficacy[25,37,38], with only limited evidence on trazodone i.v. administration.

The main finding of the study is that anxiety symptoms improved and reached stabilization between T0 and T2 (after 4 weeks of treatment), while depressive symptoms showed permanent improvement between T0 and T3 (after 12 weeks of treatment). More specifically, this difference in reduction over time (4 weeks vs 12 weeks) was evident between HAM-A and MADRS total scores, while HAM-D total scores presented a continuous and statistically significant decrease over the six-months period (from T0 to T4). This result could be explained considering that HAM-D includes both depressive and anxiety items, while HAM-A and MADRS specifically assess anxiety and depressive symptoms respectively, thus suggesting that trazodone pharmacological action is faster in improving anxiety symptoms than depressive ones.

Moreover, in our sample, 53% of the patients responded to the treatment and 30% presented symptom remission at the end of treatment, thus supporting the efficacy of trazodone administered i.v. and then orally in improving both depressive and anxiety symptoms in MDD patients.

On one hand, this finding confirms previous results on depression with concomitant anxiety symptoms: focusing on trazodone prolonged-release formulation, available data documented its efficacy in depression[39-41], also in those patients more difficult to treat because suffering from MDD with anxiety, insomnia, dementia or (hypo)manic symptoms[42]. Furthermore, it was not significantly different when compared with sertraline and paroxetine in terms of efficacy in randomized, double-blind studies[43,44].

On the other hand, our study, providing data about i.v. trazodone followed by oral extended-release administration, is different from the previous ones: the results showed an early improvement of both anxiety and depressive symptoms which was already statistically significant in the first phase of the treatment protocol (from T0 to T1) in all the psychometric scales, suggesting that the combined treatment, which

started with the i.v. administration, may have led to a faster treatment response.

Moreover, being administered once a day, the extended-release formulation seems to improve the tolerability and the ease-of-use of the drug, thus ameliorating patients' compliance[45,46]. Our results are in line with the latter findings, showing the great tolerability of trazodone extended-release.

In terms of i.v. trazodone tolerability, its administration was related to positive results. During the infusion, lasting about 1 hour every day in the first week, no adverse events due to the administration *per se* (e.g. arm or forearm rash, paresthesia) were reported.

Taken as a whole, in our study 36.4% of subjects reported side effects, most of them without dropping-out. Only two patients (5.9% of the total sample) discontinued the treatment for side effects, none of them for serious adverse events. The most commonly described side effect in our sample was somnolence (30.3%), followed by one case of rash and one of dizziness. In literature, somnolence, headache, dizziness, gastrointestinal dysfunctions, weight gain, and dry mouth were the most frequently described side effects[21,47].

Finally, in our sample, the most common reason for discontinuation was the lack of treatment response; in particular, most of patients that discontinued for no-response suspended between T2 (6 weeks) and T3 (12 weeks); they were taking trazodone extended-release at a mean dose of 162.5 mg per day.

The present work had some strengths and limitations. First, to authors' knowledge, this is the first study investigating the efficacy of trazodone over time, when administered i.v. and then orally using Contramid® formulation. Secondly, the availability of follow-up data up to six months (T4) can be considered a strength of the study. Finally, the naturalistic design allowed to present data more adherent to the clinical practice. Among limitations, the small sample size, the high drop-out rate, the lack of double-blind conditions, and the setting (the Day Hospital Unit) potentially ensuring a higher compliance and a stronger therapeutic alliance[48] may have impacted the results. Further studies with larger samples and double-blind randomized conditions are warranted to confirm and extend our findings.

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