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ORIGINAL ARTICLE

Clinical effectiveness of parenteral trazodone for the management of psychomotor activation in patients with bipolar disorder

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Abstract

OBJECTIVES: Trazodone is a multifunctional triazolopyridine drug with antidepressant, anxiolytic, sedative, and hypnotic properties. The current retrospective study was designed to investigate the effectiveness of trazodone for reducing acute psychomotor activation (PA) in patients with bipolar disorder (BD). We specifically reasoned that a parenteral route of administration could offer potential advantages in this clinical setting.

METHODS: We assessed the effectiveness and safety of parenteral trazodone in a retrospective study conducted in 64 inpatients with BD and acute PA. The effectiveness assessment was the Clinical Global Impression Scale – Severity Of Illness (CGI-S) rated before the administration of parenteral trazodone (baseline) and at the end of treatment. A post-treatment reduction in CGI-S score ≥ 20% compared with baseline was considered as the primary outcome measure.

RESULTS: Administration of parenteral trazodone was associated with significant improvements in CGI-S scores from baseline (5.4 ± 0.9) to the end of the study (4.2 ± 1.0; $p < 0.001$, Wilcoxon matched-pairs signed-ranks test). A total of 34 patients (53.1%) showed a post-treatment reduction in CGI-S score ≥ 20% compared to baseline. Multivariable binary logistic regression analysis using a forward selection procedure identified treatment duration (in days) as the only independent predictor of post-treatment reduction in CGI-S score ≥ 20% (odds ratio: 1.28; 95% confidence interval: 1.02–1.60, $p < 0.05$). Adverse effects occurred in 13 (20.3%) patients.

CONCLUSIONS: Parenteral trazodone is well-tolerated and effective in 53.1% of patients with BP and acute PA. Treatment duration was identified as an independent predictor of response in our sample.

INTRODUCTION

Psychomotor activation (PA) – defined as acceleration, distractibility, hyperactivity, and restlessness – is common in patients with bipolar disorder (BD) and frequently accompanies noneuphoric hypomanic symptoms (Scott *et al.* 2017; Akiskal & Benazzi, 2005). Notably, a large multicenter study conducted in 1158 patients has previously shown that PA is the most potent discriminator between unipolar and bipolar disorders (Cassano *et al.* 2012). From a clinical standpoint, PA is characterized by increased motor activity and painful inner tension that frequently represent a staggering challenge (Swann 2013).

PA is an important therapeutic target in the acute and/or emergency setting, as well as for longer-term care of patients with BD (Scott *et al.* 2017). When inadequately managed, PA can result in an increased number and duration of inpatient hospital stays, a reduced likelihood of discharge to community and use of coercive measures and/or escalation to patient violence, presenting a substantial economic burden to the healthcare system (Scott *et al.* 2017; Akiskal & Benazzi, 2005). Oral antipsychotic agents given alone or in combination with benzodiazepines have been the preferred treatment of PA in patients with BD (Vieta 2008). However, while a preferred route of delivery in terms of maintaining a non-traumatic experience for the patient, orally dosed agents may not invariably be optimal in terms of delivering a sufficiently rapid onset of therapeutic effect (Buoli *et al.* 2017; Pallanti *et al.* 2002). In addition, the selection of a specific agent (or combination of agents) should be guided by etiologic considerations, efficacy of the drug(s), side effects, potential drug interactions, and drug formulation.

Trazodone is a multifunctional triazolopyridine derivative characterized by a number of distinct pharmacological actions (i.e., antidepressant, anxiolytic, sedative, and hypnotic) (Stahl 2009; Bossini *et al.* 2015). Trazodone may exert sedative actions by behaving as an antagonist of the serotonin 2A (5-HT2A) and 2C (5-HT2C) receptors, an antagonist of the alpha1 (α1) adrenergic receptors, and as an inhibitor of the H1 histamine receptors (Stahl 2009; Bossini *et al.* 2015). In addition, it acts as a partial agonist of the the serotonin 1A (5-HT1A) receptors, resulting in sedative and antidepressant effects (Odagaki *et al.* 2005). The latter action is nonetheless chiefly driven by the blockade of the serotonin transporter (SERT) (Stahl 2009; Fagiolini *et al.* 2012). Several studies have focused on the effectiveness of trazodone in various patient populations (Bossini *et al.* 2012; Khouzam 2017; Mittur 2014); however, no data are currently available on its clinical utility for the treatment of acute PA in patients with BD. We therefore designed the current retrospective study to investigate the effectiveness of trazodone for reducing acute PA in patients with BD. We specifically reasoned that a parenteral route of administration could offer potential advantages (i.e., immediate achievement of an unsustained peak level in the bloodstream, complete bioavailability, and ensured compliance) in this clinical setting.

METHODS

Study sample and design

We assessed the effectiveness and safety of parenteral trazodone in a retrospective study conducted in 64 inpatients with BD and acute PA (47 females and 17 males, mean age: 52.2 ± 15.9 years). The subjects were recruited from the Division of Psychiatry, University of Siena, from December 2013 to March 2018 on the basis of specific inclusion and exclusion criteria. Patients who fulfilled the DSM-5 criteria (APA 2013) for BD were deemed eligible in presence of signs and symptoms of acute PA (acceleration, distractibility, hyperactivity, and restlessness) (Cassano *et al.* 2012). Patients were excluded when at least one of the following conditions was met: 1) organic brain syndrome, 2) schizophrenia, schizoaffective disorder, epilepsy, or any other neurological disorder; 3) imminent risk of causing injury to themselves or others; 4) suicidal risk as judged clinically; 5) serious or unstable medical illnesses; 6) history of severe drug allergy or hyper-sensitivity to trazodone; and 7) pregnancy or breastfeeding. Each case was recorded in detail on a specially designed proforma, which included the consent form and demographic data. The study medication is available as a parenteral preparation of 5 mL/vial containing 50 mg trazodone (Angelini, Rome, Italy). Parenteral trazodone was given either intravenously or intramuscularly with a flexible schedule, as permissible. Because no definite recommendations currently exist on the optimal route of administration for parental trazodone, intravenous or intramuscular injections were used at the physician's discretion. The investigator also had the option to adjust the daily dose depending on individual patient's response and/or presence of adverse effects. Concomitant medications and adverse effects were recorded. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Study outcomes

The effectiveness assessment was the Clinical Global Impression Scale – Severity Of Illness (CGI-S) rated 1) before the administration of parenteral trazodone (baseline) and 2) at the end of parenteral treatment. The CGI-S is a clinician-rated effectiveness measure of psychopathology severity based on an 1 to 7 scale, as follows: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients (Busner & Targum 2007). All patients had a CGI-S score ≥4 at baseline. A post-treatment reduction in CGI-S score ≥ 20% compared with baseline was considered

as the primary outcome measure. The achievement of a post-treatment CGI-S score ≤ 3 served as a secondary outcome.

Data analysis

Continuous data are given as mean ± standard deviation, whereas categorical data are expressed as counts (percentages). A Wilcoxon matched-pairs signed-ranks test was performed to compare baseline and post-treatment CGI-S values. Multivariable binary logistic regression analysis with a forward selection procedure was used to identify the independent predictors of a post-treatment reduction in CGI-S score ≥ 20% compared with baseline. The following covariates were entered into the multivariable model: age, sex, mean dosage of parenteral trazodone, route of patenteral administration (intravenous versus intramuscular), and duration of parenteral treatment (expressed in days). All calculations were performed using the SPSS software package, version 20.0 (IBM, Armonk, NY, USA). Two-tailed p values <0.05 were considered statistically significant.

RESULTS

The mean dosage of parenteral trazodone administered to the 64 study patients was 77.64 ± 38.69 mg/day (range: 25–250 mg/day) for an average of 3.89 ± 3.18 days (range: 1–19 days). Trazodone was administered intravenously and intramuscularly in 39 (60.9%) and 25 (39.1%) patients, respectively. Concomitant mood stabilizers, antipsychotic agents, benzodiazepines, gabapentin/pregabalin, and antidepressants were given to 55 (85.9%), 52 (81.3%), 49 (76.6%), 22 (34.4%), and 17 (26.6%) patients, respectively. Administration of parenteral trazodone was associated with significant improvements in CGI-S scores from baseline (5.4 ± 0.9) to the end of the study (4.2 ± 1.0; $p < 0.001$, Wilcoxon matched-pairs signed-ranks test; Figure 1). A total of 34 patients (53.1%) showed a post-treatment reduction in CGI-S score ≥ 20% compared to baseline in response to parental trazodone. Eighteen patients (28.1%) showed a CGI-S score ≤ 3 in response to parental trazodone. Multivariable binary logistic regression analysis using a forward selection procedure identified treatment duration (in days) as the only independent predictor of a post-treatment reduction in CGI-S score ≥ 20% (odds ratio: 1.28; 95% confidence interval: 1.02–1.60, p <0.05). Adverse effects occurred in 13 (20.3%) patients, with the most frequent being sedation (n = 7, 10.9%), followed by orthostatic hypotension (n = 2 patients), dizziness (n = 2; 3.9%), nausea (n = 1; 1.5%), and oral paresthesia (n = 1; 1.5%). No patient discontinued parenteral treatment because of adverse effects.

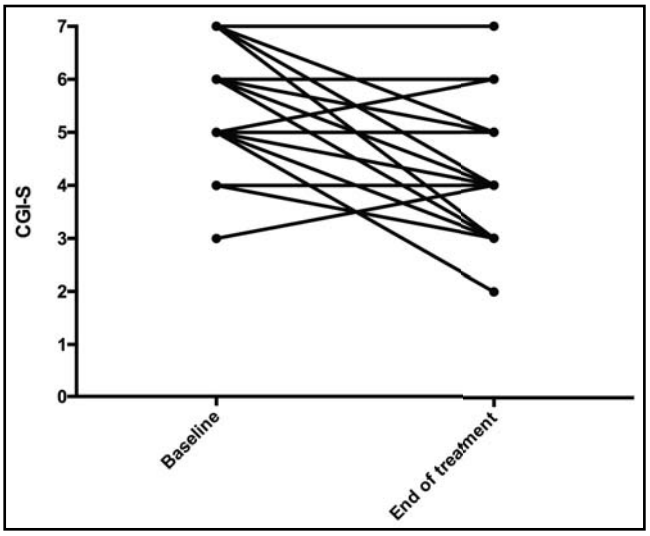

Fig. 1. Observed changes in CGI-S scores from baseline to the end of the study in the 64 study patients.

DISCUSSION

Serotonergic, adrenergic, and histaminergic neurotrasmitter systems have been implicated in the pathogenesis of acute PA and may serve as therapeutic targets in the clinical management of this condition (Lindenmayer 2000; Munari *et al.* 2015). Trazodone is a multifunctional drug that offers unique therapeutic flexibility for a large number of comorbidities associated with mood disorders (Bossini *et al.* 2012; Mittur 2011). As far as acute PA is concerned, trazodone may have therapeutic potential owing to its ability to inhibit H1 receptors along with simultaneous 5-HT2A and α1-adrenergic receptor antagonism (Stahl 2009). It was therefore reasonable to expect that trazodone might have a role in the treatment of PA in BP, with a lower burden of adverse drug events traditionally associated with oral antipsychotic agents (given alone or in combination with benzodiazepines). Herein, we demonstrated that 1) parenteral trazodone is well-tolerated and effective in 53.1% of patients with BP and acute PA and 2) treatment duration (in days) as the only independent predictor of a post-treatment reduction in CGI-S score ≥ 20%.

The primary rationale for parenteral (*versus* oral) administration of trazodone is the immediate achievement of an unsustained peak level in the bloodstream (Stahl 2009; Nilsen & Dale 1992). This specific pharmacokinetic profile is expected to induce a clinically significant hypnotic action not apparently accompanied by tolerance over time (Stahl 2009). Parenterally administered trazodone may also be instrumental in avoiding the hepatic first-pass effect, resulting in a complete bioavailability and ensuring patient compliance (owing to the supervised drug administration) (Buoli *et al.* 2017; Berzewski 1988). Another interesting finding from our study is that the duration of treatment was identified as an independent predictor of the primary efficacy measure (the longer being the treatment duration, the higher the likelihood of CGI-S reduction). Albeit speculative, this phenomenon could be explained by

the 5-HT1A partial agonist action of trazodone (Odagaki *et al.* 2005). Specifically, 5-HT1A agonist effects are believed to occur as a result of adaptive neuronal and receptor events occuring over time – and not by the acute engagement of the receptor *per se* (Odagaki *et al.* 2005; Settimo & Taylor 2018; Stahl 2013). Consequently, the observed clinical effects of trazodone toward PA may on one side rely upon its immediate inhibition of H1 receptors along with simultaneous 5-HT2A and α1-adrenergic receptor antagonism and – on the other side – upon longer-term modulation of 5-HT1A receptor function. Our current observations may prompt further studies aimed at specifically investigating the optimal duration of parenteral trazodone in the clinical management of acute PA.

Our preliminary results need to be interpreted cautiously given the small sample size, the retrospective nature of the study, the use of concomitant medications, the lack of blinded outcome ratings, and the absence of a placebo control group. These limitations notwithstanding, our real-world data indicate that parenteral trazodone is well-tolerated and reasonably effective in the treatment of PA in BP. The current findings should be considered as exploratory and hypothesis-generating, warranting independent confirmation in well-designed, adequately controlled ad hoc clinical trials.

DISCLOSURE

Andrea Fagiolini is/has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Generici DOC, Lundbeck, Italfarmaco, Janssen, Otsuka, Pfizer, Recordati, Roche, and Sanofi Aventis. All other authors have no conflicts of interest to disclose.

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