

# A randomized, double-blind study comparing the efficacy and safety of trazodone once-a-day and venlafaxine extended-release for the treatment of patients with major depressive disorder

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This double-blind, randomized study evaluated the efficacy and safety of trazodone OAD (once-a-day) in comparison with venlafaxine XR (extended-release) in 324 patients (166 trazodone and 158 venlafaxine) with major depressive disorder (MDD). The primary efficacy endpoint was the mean change from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D) at week 8. Both treatments were effective in reducing the HAM-D-17 total score at week 8 vs. baseline (intent-to-treat: trazodone  $-12.9$ , venlafaxine  $-14.7$ ; per protocol: trazodone  $-15.4$ , venlafaxine  $-16.4$ ). Patients in the venlafaxine group achieved better results after 8 weeks, whereas the trazodone group achieved a statistically significant reduction in HAM-D-17 following only 7 days of treatment. The most frequent adverse events (AEs) were dizziness and somnolence in the trazodone group, and nausea and headache in the venlafaxine group. Most AEs were mild-to-moderate in severity. This study confirmed

that both venlafaxine XR and trazodone OAD may represent a valid treatment option for patients with MDD. *Int Clin Psychopharmacol* XXX: 000–000 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

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## Introduction

Major depressive disorder (MDD) is a common psychiatric condition characterized by depressed mood combined with psychological and vegetative changes, such as sleep and/or appetite disturbances, fatigue, loss of motivation, feelings of guilt and despair, difficulties in maintaining mental focus, and suicidal thinking and behavior (Kelliny *et al.*, 2015). The WHO estimates that major depression affects approximately 350 million people worldwide and is one of the leading causes of global disability (Marcus *et al.*, 2012). According to recent projections, MDD will rise to be among the top three disabling conditions in the

world by 2030, together with HIV/AIDS and ischemic heart disease (Mathers and Loncar, 2006).

According to the current guidelines, a successful treatment for MDD includes the achievement of symptomatic remission and functional recovery (Davidson, 2010). Nevertheless, evidence from trials and clinical practice has shown that the efficacy of antidepressants is suboptimal. Indeed, approximately 30–40% of patients achieve full remission after a single course of treatment, and 30%, although achieving a clinically significant response, show residual symptoms with increased risk of relapse and affecting the social functioning (Katona and Katona, 2014).

However, antidepressants still play a crucial role in the treatment of MDD, provided that adherence to medications is guaranteed. Indeed, low adherence is widely recognized as one of the main reasons for treatment failure and is associated with an increased risk of relapse and recurrence (Ho *et al.*, 2016). Evidence from clinical studies

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show that adherence rates are generally low in patients with MDD, in some cases as low as 50% (Melartin *et al.*, 2005; Cantrell *et al.*, 2006; Akincigil *et al.*, 2007; Alekhya *et al.*, 2015a; Alekhya *et al.*, 2015b). This is mainly because mood disorders impairing cognitive focus, energy, and motivation might affect the willingness and ability of patients to maintain the treatment (DiMatteo *et al.*, 2000). The occurrence of treatment-related side effects, such as weight gain, sexual dysfunction, nausea, headache, and sleep disturbances, is also common and may influence treatment adherence.

In this context, a simplified daily regimen represents a clinical advantage, and it may be practical to increase treatment success rates in depression (Yildiz *et al.*, 2004). In fact, it is a rule that the fewer the daily doses, the better the compliance (Claxton *et al.*, 2001). The American Psychiatric Association practice guidelines for the treatment of patients with MDD report that most clinicians prefer products with once-daily dosing, which may be less often associated with withdrawal symptoms (Gelenberg *et al.*, 2010). Premature discontinuation of medication is usually associated with a poorer outcome in the treatment of mood disorders. It has been observed in clinical practice that adherence, simplicity, and efficacy usually go together (De las Cuevas *et al.*, 2014).

Trazodone hydrochloride, a triazolopyridine derivative antidepressant drug acting through 5-HT receptors and inhibiting the 5-HT transporter, is the first member of the serotonin antagonist and reuptake inhibitor (SARI) class (Stahl, 2009). Trazodone is a multimodal antidepressant (Bortolotto *et al.*, 2017); it binds with high affinity to serotonin 5-HT<sub>2A</sub> receptors, where it acts as an antagonist, and has moderate affinity for the 5-HT transporter (Stahl, 2009). It also shows activity at 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors, acting as a weak agonist and an antagonist, respectively (Stahl, 2009; Ghanbari *et al.*, 2010). Due to its dose-dependent pharmacological actions, trazodone has been also defined as ‘multifunctional’, exerting hypnotic actions by blocking 5HT<sub>2A</sub> and  $\alpha$ 1 adrenergic receptors at low doses. Its antidepressant actions are instead achieved by acting at 5-HT receptors with high affinity and by blocking serotonin transporter (SERT) at higher doses (Stahl, 2009).

Trazodone was compared to several other antidepressants, including tricyclics, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors. Overall, it was shown to be an effective and well-tolerated antidepressant (Fagiolini *et al.*, 2012).

A new controlled release formulation of trazodone, allowing a once-a-day administration due to the use of the Contramid technology, was developed with the aim of enhancing treatment compliance and of reducing both the plasma peak concentration and dosing frequency. The pharmacokinetic profile of trazodone OAD (once-a-day)

is characterized by a slow increase of plasma level with a single low and delayed peak followed by a slow decline in plasma concentration. This is an advantage of the new formulation, since high trazodone peak plasma levels may be associated with the occurrence of adverse effects, such as somnolence or hypotension, especially during the first weeks of treatment. These adverse effects might limit the treatment tolerability and compliance in patients with depression (Fagiolini *et al.*, 2012).

After a 6-week treatment period, a mean daily dose of trazodone OAD 310 mg was significantly more effective than placebo in a randomized, double-blind study performed in 412 patients with MDD (Sheehan *et al.*, 2009b). Compared to placebo, the antidepressant effect of trazodone OAD was significant as measured by the Hamilton Depression Rating Scale (HAM-D-17) starting from the first week of treatment and was maintained throughout all study visits (Sheehan *et al.*, 2009b).

The aim of the present study is to compare the efficacy and safety of trazodone OAD with that of venlafaxine XR (extended-release).

## Materials and methods

### Study design

This was a randomized, active-controlled, double-blind, parallel-group study (ClinicalTrials.gov Identifier: NCT02086929) (Supplementary Fig. 1, Supplemental digital content 1, <http://links.lww.com/ICP/A70>).

The study was performed between December 2012 and April 2014. Patients were enrolled in 31 study centers across Europe (two in Austria, nine in the Czech Republic, six in Italy, seven in Romania, six in Slovakia, and one in Spain). The study was conducted in compliance with the International Conference on Harmonization Guidelines on General Considerations for Clinical Trials and the Declaration of Helsinki as adopted by the 18th World Medical Association (WMA) General Assembly in 1964 and with subsequent revisions. All patients provided written informed consent. Written approval from all relevant Review Boards/Ethics Committees was obtained before the commencement of the study, and the study sponsor was compliant with the National Drug Agency requirements of each country involved in the study. The trial was performed in compliance with the Good Clinical Practice guidelines.

A total of 10 visits were scheduled: one in the Pretreatment Phase and nine in the double-blind Treatment Phase. Efficacy and safety evaluations occurred at Visit 2 (baseline), Visit 3 (7 days post-randomization; D7), Visit 4 (D21), Visit 6 (D35), and Visit 9 (D56). Patients receiving increased dosages at the scheduled visits (Visit 4 and Visit 6) were strictly monitored for safety with further visits at Day 28, 42, 49 (Visits 5, 7, 8, respectively).

During the pretreatment phase, patients signed the informed consent form and underwent initial screening. Potential candidates were instructed to discontinue antidepressants or prohibited medications for a wash-out period specific to allow a taper schedule based on five elimination half-lives of the medication used. On the last day of the pretreatment phase, patients were evaluated for the final eligibility, and those qualified were randomly allocated to trazodone OAD 300 mg/day (1 week of tapering with trazodone OAD 150 mg/day) or to venlafaxine XR 75 mg/day once daily, and treated for 8 weeks.

After 3 and 5 weeks of treatment, the dose was increased (in increments of 75 mg/day) up to 225 mg/day for venlafaxine XR and 450 mg/day for trazodone OAD in nonresponding patients. If symptoms or adverse events (AEs) became intolerable for the patient, dose adjustments were attempted after one week of dose increase.

Patients defined as responders at the final visit could continue treatment with the respective formulations currently available on the market. Patients not responding to treatment at the final visit tapered the study medication over 1–3 weeks according to the maximum dose reached during the study. These patients were monitored for safety throughout the tapering period (Visit 10).

If a patient discontinued early, he/she was asked to return to the clinic for the treatment early termination visit (TETV) as soon as possible, but no later than 1 week after discontinuation. All efficacy and safety evaluations were performed at the TETV.

If the treatment was judged unsuccessful and/or the tolerability unsatisfactory after dose adjustments, patients were discontinued from the study by the investigator and were started on an appropriate antidepressant therapy.

#### **Inclusion and exclusion criteria**

Male and female outpatients (18–75 years) who met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM)-IV criteria for MDD on the basis of the Mini International Neuropsychiatric Interview and 17-item HAM-D score  $\geq 18$  at both screening and baseline visits, together with a decrease not  $>20\%$  between screening and baseline were eligible for inclusion. Patients had symptoms of depression for  $\geq 1$  month before screening (Visit 1) and were legally capable of giving written informed consent to participate in the study. Women of childbearing potential had to agree not to start a pregnancy from the time of signing the informed consent up to 30 days after the last administration of the investigational product.

Exclusion criteria included the following: any experimental psychotropic or central nervous system (CNS) treatment within the past 60 days; known hypersensitivity to venlafaxine or trazodone or their excipients; use of

venlafaxine or trazodone within the previous 6 months; acute, or chronic, or recurrent medical conditions that might affect/jeopardize the study results; significant liver or renal disease; myocardial infarction within 6 months of the start of double-blind treatment; history of risk factors for Torsade de Pointes; clinically relevant laboratory values of electrolytes outside of the normal range; concomitant treatment with drugs known for QT prolongation, or with drugs producing hypokalaemia, or diuretics; QTcF interval  $>450$  ms at the screening ECG. Patients with a history of major depression resistant to medical treatments, at acute risk of suicide (HAM-D, criterion 3 with a value  $\geq 3$ ), with a history of seizure events, alcohol or psychoactive substance abuse or addiction during the last year, or a positive urine drug screen for CNS-active drugs at screening (Visit 1) were also excluded. The presence of any primary psychiatric disorder other than major depression, history or presence of bipolar disorder, any psychotic disorder, or a mental disorder due to general medical conditions, use of antipsychotic drugs within 2 months before the baseline visit (Visit 2), use of any anxiolytic or sedative-hypnotic drug within 7 days before the baseline visit and during the study (except stable low doses of benzodiazepines for insomnia), use of any psychotropic drug or CNS-active substance within 7 days before the baseline visit, or the use of any nonpsychotropic drug with psychotropic effects within 7 days before the baseline visit (unless a stable dose of the drug had been maintained for at least 1 month; 3 months for thyroid or hormonal medications) were not allowed. Pregnancy, lactation; electroconvulsive therapy within 30 days before the screening visit, concomitant treatment with cytochrome P450 3A4 (CYP3A4) inhibitors, hyperthyroidism, start or discontinuation of psychotherapy within 6 weeks before screening; clinically significant abnormalities on physical examination, vital signs, ECG, laboratory tests at the screening visit, treated or untreated supine systolic blood pressure  $> 160$  mmHg or supine diastolic blood pressure  $> 90$  mmHg at screening or baseline, inability to comply with the treatment program, or a relevant relationship to the investigator or his/her deputies were additional exclusion criteria. (for full inclusion/exclusion criteria, see Supplementary Appendix 1, Supplemental digital content 2, <http://links.lww.com/ICP/A71>).

#### **Randomization and blinding**

Patients were automatically assigned an identification number by an Interactive Web Response System (IWRS) at the screening assessment (Visit 1). At the end of the pretreatment phase, patients meeting the eligibility criteria were randomized to trazodone OAD or venlafaxine XR by the IWRS system. Neither the investigators nor the patients were aware of the treatment assigned. To maintain the blinding conditions of the study, trazodone OAD tablets and venlafaxine XR capsules were inserted into capsules having an identical appearance.

### Efficacy and safety measures

The primary study endpoint for clinical efficacy was the mean change from baseline in HAM-D score at the final visit. Secondary study endpoints were as follows: (i) mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) score at the final visit; (ii) Clinical Global Impression-Severity of Illness (CGI-S) and Clinical Global Impression-Global improvement (CGI-G) at Visit 9 (D56); (iii) rate of responders (defined as patients with a 50% decrease with respect to baseline on the HAM-D score at the final visit), (iv) rate of remitters (defined as patients with HAM-D score  $\leq 7$  at the final visit); (v) comparative safety and tolerability of trazodone OAD vs. venlafaxine XR.

### Statistical analysis

Three study populations were defined for statistical analysis: the intention-to-treat (ITT) population defined as all randomized patients who took at least one dose of study medication, and having a baseline and at least one post-baseline HAM-D-17 total score assessment; the per-protocol (PP) population defined as all randomized patients who had no major protocol violations, completed the study period (from V1 to V9) and had a 17-items HAM-D rating at the end of the study period (V9) and the Safety Population, defined as all patients who took at least one dose of the study medication.

The safety population was used for the analysis of safety parameters. The ITT and PP populations were used for the analysis of efficacy parameters as, in a noninferiority trial, the ITT and PP sets have equal importance (Committee for Proprietary Medicinal Products, 1998, 2000).

Significance tests (two-sided) were performed at an alpha level of 5%. Secondary and other analyses were supportive in nature. Therefore, no adjustment for multiplicity was planned. Efficacy parameters were analyzed on the ITT population using the last observation carried forward imputation scheme for missing data.

The primary efficacy end-point of the study, the demonstration of the noninferiority of trazodone OAD vs. venlafaxine XR evaluated as change from baseline at Visit 9 on the 17-items HAM-D total score, was analyzed by an analysis of covariance (ANCOVA) model with baseline as covariate and treatment and pooled centers as sources of variation. The noninferiority was fulfilled if the upper limit of the two-sided 95% confidence interval (CI) for the difference between treatments did not exceed the threshold of 3, representing the maximum difference of no clinical relevance (Sauer *et al.*, 2003). The change from baseline at each postbaseline visit of the HAM-D total score, of the HAM-D factors (anxiety/somatization, cognitive disturbance, retardation, sleep disturbance) and of the MADRS total score were analyzed by the same ANCOVA model [or analysis of variance (ANOVA) if

the statistical assumptions underlying the ANCOVA were not satisfied]. CGI-S and CGI-G were compared between groups using the Cochran-Mantel-Haenszel test stratified by pooled sites. Treatment groups were also evaluated treating the responses as continuous, and applying the ANCOVA or ANOVA model. Responders and remitters were compared between treatment groups by a Cochran-Mantel-Haenszel test at each visit.

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary ver. 15.1. AEs were classified as AEs started on or after the first study medication administration date, and AEs started before the first study medication administration date. Summaries of AEs started on or after the first study medication administration were presented as counts and percentages based on the number of patients exposed and compared by a Chi-square test or Fisher's exact test. Listing of pretreatment and during treatment AEs were provided by treatment group displaying the description reported by the Investigator, the preferred term and the system organ class. Serious AEs (SAEs), other significant AEs, and deaths were listed and discussed with patient narratives. Separate listings were provided for pretreatment SAEs and SAEs that emerged during the administration of study medication.

Each laboratory test was presented by descriptive statistics per treatment group, available visits, and change from screening. Shift tables were calculated on the basis of Investigators' assessment (normal, altered but not clinically significant, altered and clinically significant). Pregnancy tests were listed. Descriptive statistics were presented by treatment group for vital signs and body weight at each visit and on the change from baseline; 95% CIs were also provided. The number and percentage of patients with QTcF values higher than 450 ms or showing prolongation higher than 60 ms at any visit were provided and compared by a Chi-Square test or Fisher's exact test. The number and percentage of patients with an abnormal ECG assessed as clinically significant by the investigator were provided for each treatment group at each visit.

The number and percentage of patients showing changes in the ECG evaluations with respect to the screening (from normal to abnormal) were provided for each treatment group at each visit.

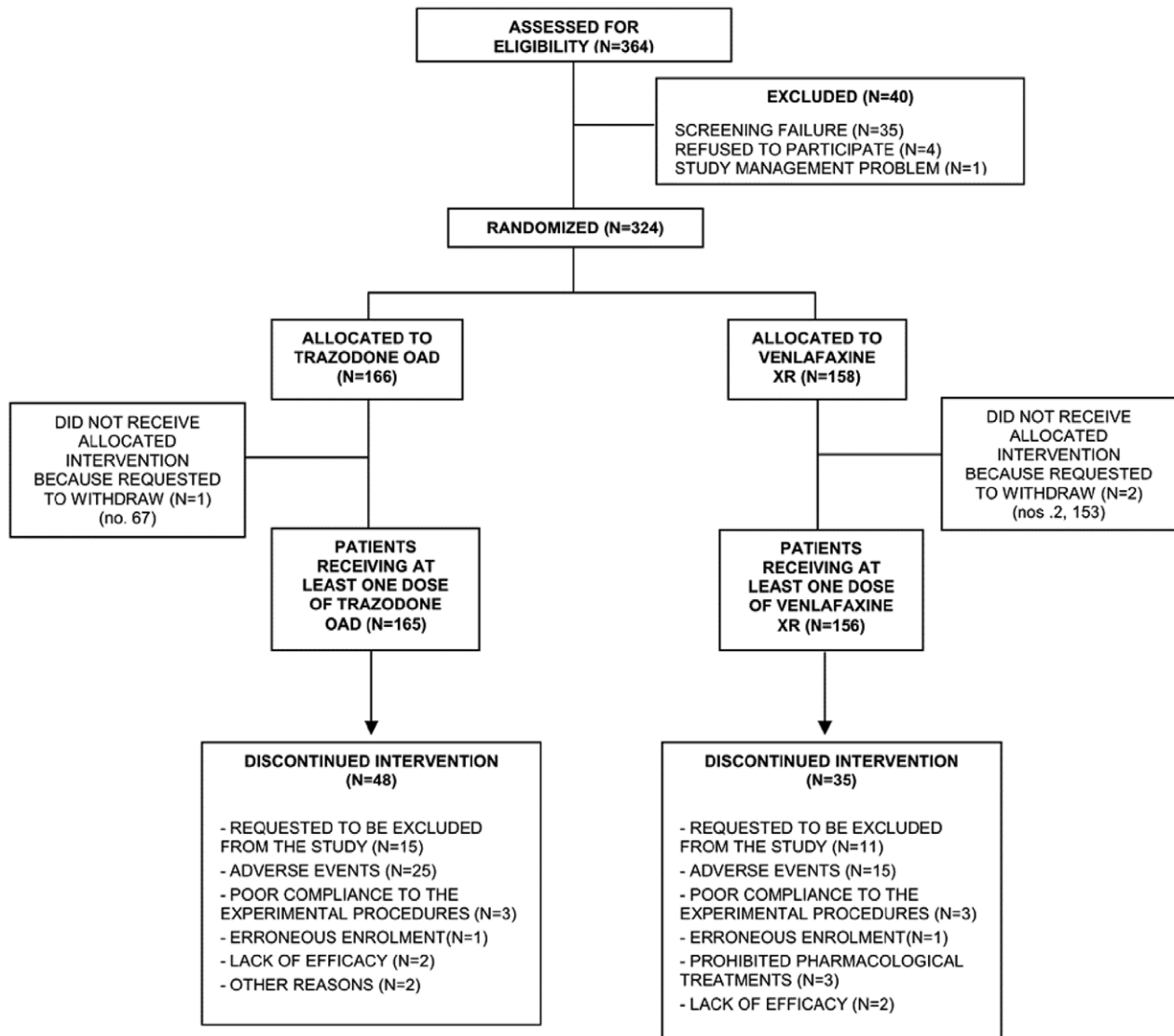
Descriptive statistics on HR, RR, PR, QRS, QT, QTcB, and QTcF were provided by treatment group at each available visit and on the changes from screening. Treatment group comparisons were performed by an ANOVA model at each visit. Changes from screening in the physical examination were reported.

### Results

Figure 1 shows the disposition of patients throughout the course of the study.



Fig. 1



Patient disposition throughout the study.

### Baseline characteristics

Patients enrolled in this study were significantly ill (moderate-to-severe depression), as measured by validated clinical inventories. There were no clinically relevant or statistically significant differences between the treatment groups in patient demographics or clinical characteristics at baseline in all populations analyzed. Among the patients of the Safety population, 99.1% were White, the majority of patients (67.5%) had not had previous episodes of depression necessitating hospitalization, and most patients (97.5%) had no other previous symptoms of other psychiatric illnesses. Baseline demographic and clinical characteristics of the Safety population are presented in Table 1.

The mean baseline severity of illness measured with HAM-D-17 total score was at least moderate for both ITT and PP populations (ITT: trazodone OAD  $23.7 \pm 3.42$ , venlafaxine XR  $23.8 \pm 3.93$ ; PP: trazodone OAD  $23.9 \pm 3.41$ , venlafaxine XR  $24.1 \pm 4.02$ ). The baseline mean MADRS score was consistent with the HAM-D-17 total score. Approximately, half (52.2%) of patients were assessed by CGI-S as at least moderately mentally ill.

### Study medication

A total of 324 patients (166 in the trazodone OAD group and 158 in the venlafaxine XR group) were randomized, and 321 received at least one dose of the allocated treatment (165 trazodone and 156 venlafaxine). At the end of the treatment period, 77.6% of patients in the trazodone

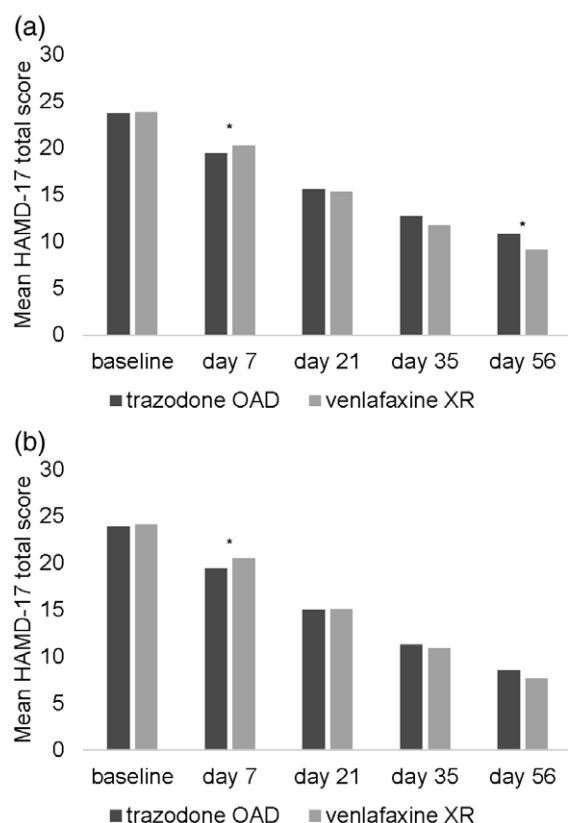
**Table 1** Baseline characteristics of patients

Characteristics	Trazodone OAD (n = 165)	Venlafaxine XR (n = 156)	Overall (n = 321)
Age [mean (SD)], (years)	47.8 (11.38)	47.9 (11.41)	47.8 (11.37)
Female [n (%)]	120 (72.7)	121 (77.6)	241 (75.1)
Weight [mean (SD)], (kg)	72.7 (15.44)	73.5 (15.45)	73.1 (15.43)
Height [mean (SD)], (cm)	167.4 (8.55)	167.3 (8.16)	167.3 (8.35)
MDD history			
Previous symptoms [n (%)]	152 (92.1)	140 (89.7)	292 (91.0)
Age at first appearance [mean (SD)], (years)	41.5 (12.02)	42.1 (12.48)	41.8 (12.22)
Duration of current episode [mean (SD)], (months)	2.9 (3.01)	2.9 (2.76)	2.9 (2.88)
Previous CNS medications [n (%)], (patients)	55 (33.3)	53 (34.0)	108 (33.6)
HAM-D-17 total score* [mean (SD)]			
ITT population	23.7 (3.42)	23.8 (3.93)	23.7 (3.67)
PP population	23.9 (3.41)	24.1 (4.02)	24.0 (3.73)
MADRS total score* [mean (SD)]			
ITT population	27.1 (4.46)	27.1 (4.56)	27.1 (4.50)
PP population	26.7 (4.03)	27.2 (4.53)	27.0 (4.29)

With the exception of HAM-D and MADRS scores, data are for the safety population.

ITT, intention-to-treat; HAM-D-17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; OAD, once-a-day; PP, per-protocol; XR, extended-release.

\*n = 165, n = 152 and n = 314 (ITT) and n = 162, n = 152 and n = 314 (PP) for Trazodone OAD, Venlafaxine XR and overall patient population, respectively.

**Fig. 2**

Mean total score over time in the ITT/LOCF population (a) and the PP population (b). HAM-D-17, 17-item Hamilton Depression Rating Scale; ITT, intention-to-treat; LOCF, last observation carried forward; PP, per-protocol; \* $P < 0.05$ .

OAD group received a dosage of 300mg, while in the venlafaxine XR group 90.4% of the patients received a dosage of 75 mg. The mean  $\pm$  SD daily dose administered during the study was 311.4 (48.72) mg for trazodone and 84.1 (29.93) mg for venlafaxine XR.

The ITT population consisted of 314 patients (162 trazodone and 152 venlafaxine) who took at least one dose of the study medication and had a baseline and at least one post-baseline 17-items HAM-D total score assessment. The PP population consisted of 249 patients (122 trazodone and 127 venlafaxine) who completed the study period and had the 17-items HAM-D rating at the final visit without major protocol violations.

## Efficacy

### Primary efficacy endpoint

Both treatments showed good efficacy in terms of reduction of mean  $\pm$  SD HAM-D-17 total score at the final visit compared to baseline (Fig. 2) (ITT: trazodone  $-12.9 \pm 6.82$ , venlafaxine  $-14.7 \pm 6.56$ ; PP: trazodone  $-15.4 \pm 5.32$ , venlafaxine  $-16.4 \pm 5.39$ ). The difference between treatments was on average 1.6 with the 95% CI ranging from 0.4 to 2.9 in the ITT population ( $P = 0.010$ ) and 1.1 with the 95% CI ranging from  $-0.0$  to 2.2 in the PP population ( $P = 0.056$ ). A statistically significant difference in favor of venlafaxine XR was detected in the ITT population after 8 weeks, whereas no difference was detected in the PP population, which represents the study population with a higher level of compliance with the study procedure.

The severity of depression in both groups decreased from moderate to mild, based on the mean HAM-D-17 total score at the final visit (ITT: trazodone  $10.8 \pm 6.49$ , venlafaxine  $9.1 \pm 6.00$ ; PP: trazodone  $8.5 \pm 4.97$ , venlafaxine  $7.7 \pm 5.07$ ). Once again, the PP population showed, in both groups, the best performance in terms of efficacy outcomes.

### Secondary efficacy endpoints

Trazodone OAD showed an early onset of action compared to venlafaxine XR. Indeed, a significantly higher reduction in the mean HAM-D-17 score was observed in the trazodone OAD group after only 7 days of treatment. This difference was statistically significant in both the

ITT and PP population ( $P < 0.05$ ) (Supplementary Fig. 2, Supplemental digital content 3, <http://links.lww.com/ICP/A72>). A summary of primary and secondary efficacy outcomes in the ITT and PP populations is presented in Table 2.

The severity of disease decreased in both arms from moderate to mild, based on the mean MADRS total score at the final visit (ITT: trazodone  $12.7 \pm 8.58$ , venlafaxine  $10.2 \pm 7.02$ ;  $P = 0.003$ ; PP: trazodone  $9.7 \pm 6.37$ , venlafaxine  $8.6 \pm 5.40$ ). A statistically significant difference in favor of venlafaxine XR was detected in both the ITT and PP population ( $P < 0.05$ ). As already observed with the HAM-D-17, the PP population showed the best performance in terms of efficacy outcomes in both groups.

The change in the mean CGI-S score from baseline showed a statistically significant difference in favor of venlafaxine at the final visit in the ITT but not in the PP population. The mean CGI-G score at the final visit showed a statistically significant difference in favor of venlafaxine both in the ITT and PP population.

The rates of responders with trazodone and venlafaxine were 65.4% and 76.3%, respectively, in the ITT population ( $P = 0.0396$ ), and 82.8% and 87.4%, respectively, in the PP population ( $P = 0.2097$ ). The difference in favor of venlafaxine was statistically significant in the ITT ( $P = 0.0396$ ) but not in the PP population ( $P = 0.2097$ ).

In the ITT population, clinical remission occurred in 37.7% and 52.0% of trazodone- and venlafaxine-treated patients, respectively ( $P = 0.0068$ ), while in the PP population remission occurred in 48.4% and 60.6% of patients, respectively ( $P = 0.0130$ ). The difference in favor of venlafaxine was statistically significant in both the ITT ( $P = 0.0068$ ) and the PP population ( $P = 0.0130$ ).

Trazodone demonstrated a statistically significant difference in HAM-D-17 sleep disturbance scores from baseline in all visits in the PP population (see Supplementary Table 1, Supplemental digital content 4, <http://links.lww.com/ICP/A73>).

### Safety and tolerability

Three hundred and twenty-one patients (165 in the trazodone OAD group and 156 in the venlafaxine XR group) who took at least one dose of the study medication were included in the safety population.

**Table 3 Summary of adverse events in the safety population**

Characteristics	Trazodone OAD (n = 165)	Venlafaxine XR (n = 156)
<b>TEAEs</b>		
Events [n (%)]	161/322 (50.0)	161/322 (50.0)
Patients [n (%)]	86 (52.1)	73 (46.8)
<b>Related AEs</b>		
Events [n (%)]	121 (75.2)	133 (82.6)
Patients [n (%)]	67 (40.6)	63 (40.4)
<b>Most frequent TEAEs [n (%)]</b>		
Nausea	10 (6.21)	23 (14.29)
Headache	11 (6.83)	19 (11.80)
Dizziness	18 (11.18)	6 (3.73)
Somnolence	14 (8.70)	—
<b>Severe AEs</b>		
Events [n (%)]	2 (1.2)	7 (4.3)
Patients [n (%)]	2 (1.2)	4 (2.6)
<b>SAEs</b>		
Events [n (%)]	4 (2.5)	1 (0.6)
Patients [n (%)]	3* (1.8)	1** (0.6)

AE, adverse event; HAM-D-17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; SAE, serious adverse event; OAD, once-a-day; TEAE, treatment-emergent adverse event; XR, extended-release.

\*One patient had mental impairment and dizziness considered to be related to treatment (i.e. certain, probable/likely, possible). All other SAEs were considered unrelated to treatment (i.e., unlikely, conditional/unclassified, unassessable/unclassifiable); \*\*Death.

**Table 2 Primary and secondary efficacy outcomes**

Outcome at day 56	Trazodone OAD	Venlafaxine XR	Mean difference (95% CI)	P value	Trazodone OAD	Venlafaxine XR	Mean difference (95% CI)	P value
	ITT population				PP Population			
<b>Primary efficacy endpoint</b>								
HAM-D-17 total score* (n)	(n = 162)	(n = 152)			(n = 122)	(n = 127)		
Change from baseline [mean (SD)]	-12.9 (6.82)	-14.7 (6.56)	1.6 (0.4–2.9)	0.010	-15.4 (5.32)	-16.4 (5.39)	1.1 (-0.0 to 2.2)	0.056
<b>Secondary efficacy endpoints</b>								
MADRS total score (n)	(n = 162)	(n = 151)			(n = 122)	(n = 127)		
Change from baseline [mean (SD)]	-14.4 (7.65)	-16.9 (7.65)	2.4 (0.8–4.0)	0.003	-17.1 (6.01)	-18.6 (6.58)	1.7 (0.3–3.2)	0.018
CGI-S Total score	(n = 162)	(n = 152)			(n = 122)	(n = 127)		
Change from baseline [mean (SD)]	-1.8 (1.16)	-2.1 (1.17)		0.032	-2.1 (1.06)	-2.3 (1.02)		0.056
CGI-G total score	(n = 162)	(n = 152)			(n = 122)	(n = 127)		
Score at day 56 [mean (SD)]	2.0 (1.12)	1.7 (0.99)		0.0088	1.7 (0.82)	1.5 (0.72)		0.0383
HAM-D-17 Response	(n = 162)	(n = 152)			(n = 122)	(n = 127)		
Responders (50% decrease in HAM-D-17 score) [n (%)]	106 (65.4)	116 (76.3)		0.0396	101 (82.8)	111 (87.4)		0.2097
Remitters (HAM-D-17 total score $\leq 7$ ) [n (%)]	61 (37.7)	79 (52.0)		0.0068	59 (48.4)	77 (60.6)		0.0130

\*Primary efficacy endpoint. Between-group differences were analyzed using ANCOVA, ANOVA or Cochran-Mantel-Haenszel, as appropriate.

CI, confidence interval; CGI-G, Clinical Global Impression of Global Improvement; CGI-S, Clinical Global Impression of Severity; HAM-D-17, 17-item Hamilton Depression Rating Scale; ITT, intention-to-treat; LOCF, last observation carried forward; MADRS, Montgomery-Asberg Depression Rating Scale; OAD, once-a-day; PP, per-protocol; XR, extended-release.

Three hundred and twenty-two AEs occurred in 159 patients: 161 AEs in 86 patients receiving trazodone OAD and 161 in 73 patients receiving venlafaxine XR. An overall summary of AEs is presented in Table 3. The most frequent AEs were dizziness (11.18%) and somnolence (8.70%) in the trazodone group, and nausea (14.29%) and headache (11.80%) in the venlafaxine group. Overall, the severity of AEs experienced with both treatments was mild-to-moderate in the majority of the cases. Two severe AEs occurred in two trazodone-treated patients, and seven severe AEs occurred in four patients of the venlafaxine group.

Two hundred and fifty-four AEs were judged by the investigators as related to the investigational medications (i.e. certain, probable/likely, possible): 121 AEs in 67 patients treated with trazodone and 133 AEs in 63 patients treated with venlafaxine. Five SAEs, including one death in the venlafaxine group, occurred during the study. They occurred in three patients of the trazodone group and one patient of the venlafaxine group (Table 3).

Statistically significant differences between the two treatment groups were found in the changes of ECG parameters from the screening at postrandomization visits. At the final visit, both groups were significantly different in the changes from screening in the following parameters: QTcF, QT, RR, and QRS. Eleven patients in the trazodone OAD group and six patients in the venlafaxine XR group showed QTcF values higher than 450 ms during the study or prolongation higher than 60 ms at any visit with respect to the screening value. This difference between the two treatment groups was not statistically significant.

## Discussion

The aim of the study was to confirm that trazodone OAD is a valid therapeutic option in patients suffering from MDD. The efficacy and safety of trazodone were previously tested vs. venlafaxine in two double-blind studies, showing comparable efficacy and safety outcomes in patients with depressive disorders (Cunningham *et al.*, 1994; Florkowski *et al.*, 2005).

Patients enrolled, who had moderate-to-severe depression, showed a significant reduction of depressive symptoms in the HAM-D-17 and MADRS total scores at the final visit, in both treatment groups.

As required by the EMA guidelines on depression (EMA/CHMP/185423/2010 Rev. 2, 2013), besides statistically significant results, the incorporation of responder/remitter analyses permits the adequate assessment of the clinical relevance of results. In this study, both treatments showed high response and remission rates, allowing the study results to be defined as robust and clinically meaningful, in accordance with the European guidance.

The venlafaxine group showed greater efficacy in terms of the primary and secondary endpoints after 8 weeks, in particular considering the responders and remitters' rates.

As expected, for both drugs, better efficacy outcomes were observed in the PP population, which represents the study population with the higher level of compliance with the study procedure and medication.

Both antidepressants showed good performance compared to the literature data, since the response rate in the trazodone and venlafaxine arms were higher than that observed with citalopram (47%) after 14 weeks of treatment in the largest 'real-world' study on the treatment of nonpsychotic depression, the STAR\*D trial (Trivedi *et al.*, 2006).

From a clinical perspective, both trazodone and venlafaxine showed a HAM-D-17 total score at the final visit comprising between 7 and 17, indicating a reduction of the symptoms of depression to within the mild depression range (Cusin *et al.*, 2010).

The results of this trial confirmed the early onset of action of trazodone that was effective after only 7 days of treatment. The early onset of action is a specific characteristic of trazodone, previously observed in a placebo-controlled study (Sheehan *et al.*, 2009b) and in an observational study (Češková *et al.*, 2018). It can be assumed that the fast response to trazodone is achieved thanks to the combination of SERT inhibition with 5-HT<sub>1A</sub> receptor partial agonism (Montalbano *et al.*, 2019). In a post-hoc analysis of the placebo-controlled study that analyzed whether the antidepressant response to trazodone OAD was associated with an early improvement in insomnia, it was confirmed that the antidepressant effect of trazodone was robust and largely independent of the known effects of trazodone on insomnia (Sheehan *et al.*, 2009a).

Since compliance and treatment adherence are crucial aspects of the outcome of MDD treatment, an early onset of antidepressant action is clinically important. Indeed, antidepressants that lead to a rapid improvement of depressive symptoms within a few days, and whose effects are sustained in time, would have an important impact on public health and on the life of MDD patients (Machado-Vieira *et al.*, 2008). A delayed onset of action could mean prolonged disability and could lead to an increased risk of suicide (Tylee and Walters, 2007). In a recent study, it was found that the effect of medication compliance directly affected the recurrence rate of depression (Cheng *et al.*, 2016).

Compared to venlafaxine, trazodone demonstrated a statistically significant difference in HAM-D-17 sleep disturbance scores in almost all visits in both the ITT and PP populations, suggesting its greater efficacy in the treatment of MDD patients experiencing secondary insomnia. This is another specific characteristic of trazodone, previously reported in double-blind placebo-controlled and



active-controlled studies (Kasper *et al.*, 2005; Munizza *et al.*, 2006). It has been observed that sleep-related disturbances, such as difficulty in initiating or maintaining sleep, are often not resolved or even worsened by antidepressant treatments. An antidepressant able to reduce sleep disturbance in depression may improve the quality of life of patients, targeting a symptom that can strongly affect depression relapse and recurrence (Nutt *et al.*, 2008).

In general, reported AEs were as expected and mild-to-moderate in severity, and more than 90% of the AEs were recovered/resolved at the final visit. The most frequent AEs were dizziness and somnolence in the trazodone group, and nausea and headache in the venlafaxine group. This finding reflects the different pharmacological characteristics of trazodone and venlafaxine. As expected, both treatments influenced ECG parameters. However, no patients experienced ECG alteration judged as 'abnormal and clinically significant' across the study.

The main limitation of this study is the lack of a placebo arm and the wide margin set for defining the noninferiority analysis. However, the results observed in this trial confirmed the evidence from comprehensive review of the literature that venlafaxine can be considered among the most effective antidepressants (Cipriani *et al.*, 2018) and reproduced the well-known efficacy and safety profile of trazodone, in particular the early onset of action and the positive effect on sleep disturbances, which are specific characteristics of the drug.

In conclusion, both trazodone OAD and venlafaxine XR proved to be effective antidepressants in patients with moderate to severe MDD. Trazodone OAD was shown to achieve an early response and good efficacy on sleep parameters, although venlafaxine XR was more effective than trazodone OAD in terms of per responder and remitter rates, confirming data from the literature showing that it may be superior to conventional antidepressants in severe depression.

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## Conflicts of interest

Umberto Albert is/has been a consultant and/or a speaker from Angelini, FB-Health, Janssen, Lundbeck, Otsuka, Recordati. Andrea Fagiolini is/has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Aspen, Boehringer Ingelheim, Doc Generici, FB-Health, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer, Recordati, Sanofi Aventis, Sunovion, Vifor. Siegfried Kasper received grants/research support, consulting fees and/or honoraria within the last three years from Angelini, AOP Orphan Pharmaceuticals AG, Celgene GmbH, Eli Lilly, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Mundipharma, Neuraxpharm, Pfizer, Sage, Sanofi, Schwabe, Servier, Shire, Sumitomo Dainippon Pharma Co. Ltd., Sun Pharmaceutical Industries Ltd. and Takeda.

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## References

- Akincigil A, Bowblis JR, Levin C, Walkup JT, Jan S, Crystal S (2007). Adherence to antidepressant treatment among privately insured patients diagnosed with depression. *Med Care* 45:363–369.

- Alekhyia P, Sriharsha M, Priya Darsini T, Reddy S, Venkata Ramudu R, Shivanandh B (2015a). Treatment and disease related factors affecting non-adherence among patients on long term therapy of antidepressants. *J Depress Anxiety* 4:2167–1044.1000175.
- Alekhyia P, Sriharsha M, Ramudu RV, Shivanandh B, Darsini TP, Siva K, *et al.* (2015b). Adherence to antidepressant therapy: sociodemographic factor wise distribution. *Int J Pharm Clin Res* 7:180–184.
- Bortolotto V, Mancini F, Mangano G, Salem R, Xia E, Del Grosso E, *et al.* (2017). Proneurogenic effects of trazodone in murine and human neural progenitor cells. *ACS Chem Neurosci* 8:2027–2038.
- Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC (2006). Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. *Med Care* 44:300–303.
- Češková E, Šedová M, Kellnerová R, Starobová O (2018). Once-a-day trazodone in the treatment of depression in routine clinical practice. *Pharmacology* 102:206–212.
- Cheng Y, Zheng L, Sun N, Jing X (2016). Analysis of influencing factors of medication compliance in discharged depressive patients and recurrence situation. *J Psychiatry Brain Sci* 1:1.
- Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, *et al.* (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 391:1357–1366.
- Claxton AJ, Cramer J, Pierce C (2001). A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 23:1296–1310.
- Committee for Proprietary Medicinal Products (1998). *Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)*. London: European Medicines Agency.
- Committee for Proprietary Medicinal Products (2000). Points to consider on switching between superiority and non-inferiority. *Br J Clin Pharmacol* 52:223–228.
- Cunningham LA, Borison RL, Carman JS, Chouinard G, Crowder JE, Diamond BI, *et al.* (1994). A comparison of venlafaxine, trazodone, and placebo in major depression. *J Clin Psychopharmacol* 14:99–106.
- Cusin C, Yang H, Yeung A, Fava M (2010). Rating scales for depression. In: Baer L, Blais MA (Editors). *Handbook of Clinical Rating Scales and Assessment in Psychiatry and Mental Health*. Springer; 52–57.
- Davidson JR (2010). Major depressive disorder treatment guidelines in america and europe. *J Clin Psychiatry* 71 Suppl E1:e04.
- De las Cuevas C, Peñate W, Sanz EJ (2014). Risk factors for non-adherence to antidepressant treatment in patients with mood disorders. *Eur J Clin Pharmacol* 70:89–98.
- DiMatteo MR, Lepper HS, Croghan TW (2000). Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 160:2101–2107.
- Fagiolini A, Comandini A, Catena Dell'Ossio M, Kasper S (2012). Rediscovering trazodone for the treatment of major depressive disorder. *CNS Drugs* 26:1033–1049.
- Florkowski A, Gruszczyński W, Galecki P, Zboralski K, Kołodziejaska I, Mikołajczyk I (2005). [Trazodone and venlafaxine in treatment of depressive disorders]. *Pol Merkur Lekarski* 18:556–559.
- Gelenberg AJ, Freeman MP, Markowitz JC, Rosenbaum JF, Thase ME, Trivedi MH, *et al.* (2010). Practice guideline for the treatment of patients with major depressive disorder: third edition. *Am J Psychiatry* 167:1.
- Ghanbari R, El Mansari M, Blier P (2010). Sustained administration of trazodone enhances serotonergic neurotransmission: *in vivo* electrophysiological study in the rat brain. *J Pharmacol Exp Ther* 335:197–206.
- Ho SC, Chong HY, Chaiyakunapruk N, Tangiisuran B, Jacob SA (2016). Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: a systematic review. *J Affect Disord* 193:1–10.
- Kasper S, Olivieri L, Di Loreto G, Dionisio P (2005). A comparative, randomised, double-blind study of trazodone prolonged-release and paroxetine in the treatment of patients with major depressive disorder. *Curr Med Res Opin* 21:1139–1146.
- Katona CL, Katona CP (2014). New generation multi-modal antidepressants: focus on vortioxetine for major depressive disorder. *Neuropsychiatr Dis Treat* 10:349–354.
- Kelliny M, Croarkin PE, Moore KM, Bobo WV (2015). Profile of vortioxetine in the treatment of major depressive disorder: an overview of the primary and secondary literature. *Ther Clin Risk Manag* 11:1193–1212.
- Machado-Vieira R, Salvatore G, Luckenbaugh DA, Manji HK, Zarate CA Jr (2008). Rapid onset of antidepressant action: a new paradigm in the research and treatment of major depressive disorder. *J Clin Psychiatry* 69: 946–958.
- Marcus M, Yasamy T, Van Ommeren M, Chisholm D, Saxena S. Depression: A global public health concern. Available from [http://www.who.int/mental\\_health/en](http://www.who.int/mental_health/en). World Health Organization Department of Mental Health and Substance Abuse; 2012.
- Mathers CD, Loncar D (2006). Projections of global mortality and burden of disease from 2002 to 2030. *Plos Med* 3:e442.
- Melartin TK, Ryttsälä HJ, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET (2005). Continuity is the main challenge in treating major depressive disorder in psychiatric care. *J Clin Psychiatry* 66:220–227.
- Montalbano A, Mlinar B, Bonfiglio F, Polenzani L, Magnani M, Corradetti R (2019). Dual inhibitory action of trazodone on dorsal raphe serotonergic neurons through 5-HT<sub>1A</sub> receptor partial agonism and  $\alpha$ 1-adrenoceptor antagonism. *PLoS One* 14:e022855.
- Munizza C, Olivieri L, Di Loreto G, Dionisio P (2006). A comparative, randomized, double-blind study of trazodone prolonged-release and sertraline in the treatment of major depressive disorder. *Curr Med Res Opin* 22:1703–1713.
- Nutt D, Wilson S, Paterson L (2008). Sleep disorders as core symptoms of depression. *Dialogues Clin Neurosci* 10:329–336.
- Sauer H, Huppertz-Helmhold S, Dierkes W (2003). Efficacy and safety of venlafaxine ER vs. Amitriptyline ER in patients with major depression of moderate severity. *Pharmacopsychiatry* 36:169–175.
- Sheehan DV, Rozova A, Gossen ER, Gibertini M (2009a). The efficacy and tolerability of once-daily controlled-release trazodone for depressed mood, anxiety, insomnia, and suicidality in major depressive disorder. *Psychopharmacol Bull* 42:5–22.
- Sheehan DV, Croft HA, Gossen ER, Levitt RJ, Brüllé C, Bouchard S, Rozova A (2009b). Extended-release trazodone in major depressive disorder: A randomized, double-blind, placebo-controlled study. *Psychiatry (Edgmont)* 6:20–33.
- Stahl SM (2009). Mechanism of action of trazodone: a multifunctional drug. *CNS Spectr* 14:536–546.
- Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, *et al*; STAR\*D Study Team. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR\*D: implications for clinical practice. *Am J Psychiatry* 163:28–40.
- Tylee A, Walters P (2007). Onset of action of antidepressants. *BMJ* 334:911–912.
- Yildiz A, Pauler DK, Sachs GS (2004). Rates of study completion with single vs. split daily dosing of antidepressants: a meta-analysis. *J Affect Disord* 78: 157–162.