

## Review

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# Early response to trazodone once-a-day in major depressive disorder: review of the clinical data and putative mechanism for faster onset of action

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**Abstract**

**Background.** Most antidepressants have a delayed onset of action and must be administered for several weeks to generate therapeutic effects. Trazodone is a serotonin antagonist and reuptake inhibitor approved for the treatment of major depressive disorder. The once-a-day (OAD) formulation of trazodone has an improved tolerability profile compared to its conventional formulations. In this study, we systematically reviewed the evidence available for the antidepressant efficacy and early improvement in depressive symptoms with trazodone OAD treatment.

**Method.** We conducted a PubMed database search for randomized controlled trials published from 2005 to 2020.

**Results.** Two studies, a placebo-controlled and an active-comparator (venlafaxine extended-release or XR) study were found. Both the studies demonstrated that trazodone exhibits antidepressant activity at a starting dose of 150 mg/day and results in statistically significant greater reduction in Hamilton Depression Rating Scale (HAM-D17) scores within 1 week of starting treatment compared to placebo or venlafaxine XR ( $P < .05$ ). Trazodone also resulted in significant early improvement in the HAM-D17 sleep disturbance factor compared to placebo or venlafaxine XR at day 7 ( $P < .05$ ). This clinical effect is supported by in vitro proprietary data for the affinity of trazodone for different target receptors. Activity at these receptors may underlie trazodone's fast antidepressant action.

**Conclusions.** Trazodone, if properly dosed, can be an effective antidepressant with early onset of action and good tolerability. Future studies designed to specifically evaluate onset and timing of improvement of depressive symptoms remain necessary to confirm and extend these results.

**Introduction**

Major depressive disorder (MDD) is a serious psychiatric condition and one of the leading causes of illness-induced disability worldwide.<sup>1–3</sup> According to the World Health Organization (WHO), over 300 million people suffer from depression worldwide.<sup>4</sup> The WHO has ranked MDD as the third leading cause of burden of disease worldwide and projected that the disease will rank first in contributing to the global disease burden by 2030.<sup>5</sup>

While antidepressant therapy is the mainstay of pharmacological treatment for MDD, the effectiveness of standard antidepressants remains suboptimal.<sup>6–8</sup> Naturalistic studies such as the STAR\*D have shown that only one-third of patients with MDD achieve remission after a single course of antidepressant treatment, and even after a year of 4 sequenced treatments with different antidepressants, only about two-thirds of the patients with depression achieved remission.<sup>7,8</sup>

Another major limitation associated with antidepressant use is their delayed onset of action. It usually takes 4 to 6 weeks for the full therapeutic effect to manifest.<sup>9–12</sup> This lag in antidepressant action may have negative consequences, such as increased risk of suicide attempts (presumably due to a mismatch in patients' improvement of symptoms; their lack of energy may be resolved while they are still depressed with negative thoughts), psychosocial dysfunction, and poor quality of life.<sup>13,14</sup>

Ineffective early treatment may also lead to treatment noncompliance, thus resulting in poor outcomes or treatment failure.<sup>15–17</sup> In addition to lack of efficacy, approximately 23% to 36% of patients with MDD being treated with antidepressant therapy discontinue treatment due to adverse effects.<sup>16,18</sup> About 15% of patients show early worsening of anxiety and 64% experience

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insomnia within the first 2 weeks of selective serotonin reuptake inhibitor (SSRI) treatment.<sup>18,19</sup> Such adverse events that appear early during the treatment course, or late adverse effects such as sexual dysfunction and weight gain, may further contribute to treatment noncompliance and discontinuation.<sup>18-22</sup>

Therefore, faster-onset antidepressants with improved tolerability that are devoid of initial activating/anxiety-inducing effects are greatly needed to improve the treatment of MDD.

Interest in early onset of action has been heightened by the studies of treatment resistant patients with second line agents such as ketamine, esketamine, other N-methyl-D-aspartate (NMDA) antagonists, and neuroactive steroids,<sup>12,14,15</sup> so it seems timely to clarify whether the once-a-day (OAD) formulation of a conventional antidepressant—trazodone may also have an early onset of action for first line treatment of MDD.

Trazodone belongs to the class of serotonin antagonist and reuptake inhibitors that has been available since the early 1970s for the treatment of MDD.<sup>23-25</sup> It is a multifunctional and multimodal drug with dose-dependent pharmacological actions.<sup>23-26</sup> Trazodone has the strongest binding affinity for the 5-HT<sub>2A</sub> receptors, and it functionally acts as an antagonist. It binds with moderate affinity to serotonin transporters (SERT). It also acts as a partial agonist at 5-HT<sub>1A</sub> receptors and an antagonist at 5-HT<sub>2C</sub> receptors. Other clinically relevant pharmacological actions of trazodone include blockade of histamine H<sub>1</sub> receptors and  $\alpha$ 1 adrenergic receptors with affinity higher than that of SERT.<sup>25,26</sup> It is well known among clinicians that trazodone exerts sedative/hypnotic effects by blocking 5-HT<sub>2A</sub> receptors,  $\alpha$ 1 adrenergic receptors, and H<sub>1</sub> receptors.<sup>26</sup> At proper doses, starting from 100 to 150 mg/day, trazodone can significantly block SERT like SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs), thus exploiting its potential as an antidepressant.<sup>23,25,26</sup> In fact, several comparative studies have demonstrated that the efficacy of trazodone is comparable to that of other antidepressants, including tricyclic antidepressants, SSRIs, and SNRIs, but these studies did not compare early onset of action.<sup>27-32</sup>

The antidepressant efficacy of trazodone has been shown to be significantly correlated to its steady-state plasma levels.<sup>33</sup> Therefore, the formulations of trazodone with different release rates can show a variable course of effectiveness in the medium- and long-term treatment of a depressive episode. This means that for trazodone, the specific pharmacokinetic profile of the formulation used is crucial to address individual patients' needs.

Trazodone is available in 3 different formulations: immediate-release (IR), prolonged-release (PR), and OAD tablets.<sup>23,34,35</sup> The IR formulation has a rapid onset and short duration of action. Therefore, the need for multiple daily dosing, and the presence of daytime sedation associated with high trazodone peak plasma levels, limits the use of the IR formulation as an antidepressant.<sup>24-26</sup> The PR formulation is characterized by an absorption boost as soon as it is administered and reaches the  $C_{max}$  after around 2.75 hours<sup>36</sup>; this necessitates a second administration during the day to maintain a proper plasma level for antidepressant efficacy with an increased risk of daytime sedation. The OAD formulation provides a controlled release of trazodone over 24 hours without the early high peak plasma concentration seen with the IR and PR formulations (Supplementary Figure S1), thus generating an antidepressant effect with improved tolerability.<sup>23,25,26,37</sup> Moreover, the once-daily dose of the controlled-release formulation also simplifies the dosing regimen for patients and may improve treatment compliance.<sup>38,39</sup>

In this study, we systematically reviewed results from different randomized clinical trials of trazodone OAD formulation vs active

comparator or placebo to determine whether trazodone OAD shows an early antidepressant effect after 7 days of initiating treatment. We also show some recent *in vitro* proprietary receptor-binding data for trazodone, which largely corroborates the preexisting literature, and discuss putative mechanisms for the faster onset of antidepressant action of trazodone OAD.

## Methods

### Search strategy

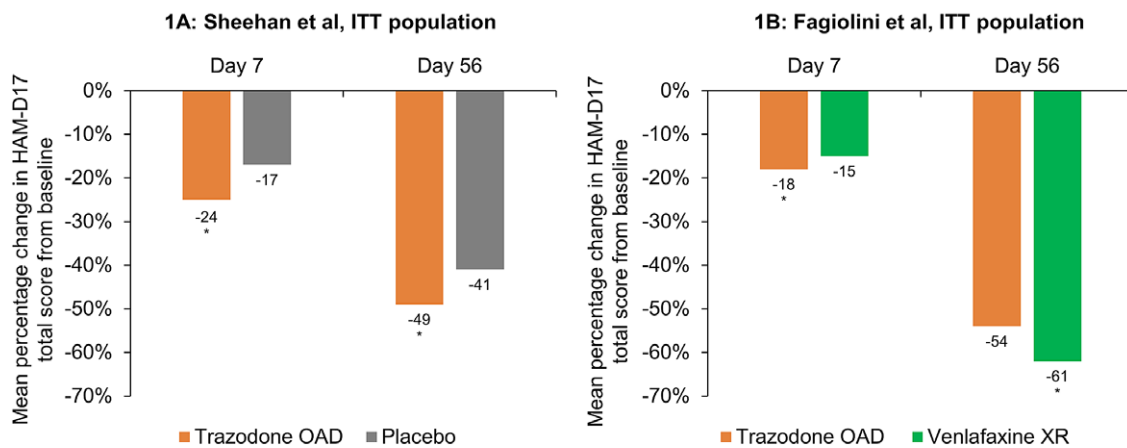
A comprehensive search of PubMed was carried out to conduct a systematic review of studies reporting early antidepressant response in patients treated with trazodone OAD formulation within 1 week of initiating treatment. The search was limited to (1) randomized clinical trials that evaluated the use of only one formulation of trazodone for the treatment of depressive symptoms in patients with MDD and (2) studies published in the last 15 years from 2005 to 2020. The year 2005 was chosen as the lower limit because it was the year that the provisional U.S. patent application for trazodone OAD was filed.<sup>40</sup> The medication was first approved for use by the Food and Drug Administration in 2010 and in Europe in 2014.<sup>41,42</sup> The articles included in this review were identified using the following search terms: ((trazodone [Title/Abstract] AND (once a day [Title/Abstract])) OR ((trazodone [Title/Abstract] AND (once daily [Title/Abstract])) OR ((trazodone [Title/Abstract] AND (once-a-day [Title/Abstract])). The studies of trazodone IR and PR formulations were excluded from this review because their pharmacokinetic profiles are distinct from that of the OAD formulation, and the doses needed to generate an antidepressant response may be associated with adverse effects, such as sedation, that may limit their use as antidepressants.<sup>26,43</sup>

### Data extraction

The data in the included studies were extracted into a standardized Microsoft Excel spreadsheet. The following data were extracted: mean scores on the factor composition of HAM-D17 at all study visits including baseline, sample size at each study visit for the HAM-D17 factor analysis, incidence of adverse events reported by  $\geq 5\%$  of the patients, and discontinuation rates.

### Data analysis

The mean score change from baseline in the HAM-D17 total score and HAM-D17 factors (anxiety/somatization, cognitive disturbance, retardation, and sleep disturbance) was analyzed at each postbaseline visit using an analysis of covariance (ANCOVA) model where baseline served as a covariate and treatment and pooled centers were sources of variation.<sup>44,45</sup> Analysis of variance (ANOVA) was used in cases where the statistical assumptions of ANCOVA were not met.<sup>44</sup> Two-sided 95% confidence intervals (CIs) were calculated for the differences in mean score change from baseline for trazodone OAD vs placebo, as well as trazodone OAD vs venlafaxine XR, for the same HAM-D17 outcomes analyzed by ANCOVA or ANOVA.<sup>44</sup> For trazodone OAD vs venlafaxine XR, the noninferiority was accepted if the upper limit of the 95% CIs for the difference between treatments did not surpass the threshold of 3, which represented the maximum difference associated with no clinical relevance.<sup>44</sup> Trazodone vs placebo was analyzed similarly, except it was treated as a superiority study.



**Figure 1.** Data are shown as mean percentage change in the Hamilton Depression Rating Scale (HAM-D17) total score from baseline in the intent-to-treat (ITT) population. (A) Sheehan et al: mean HAM-D17 total scores at baseline were 23.2 points and 22.4 points for trazodone once-a-day (OAD) and placebo, respectively. 95% confidence intervals [CIs] for differences in mean score change from baseline between trazodone OAD vs placebo at Day 7 were  $[-2.4; -0.4]$  and at Day 56 were  $[95\% \text{ CI}, -3.4; -0.4]$ . (B) Fagiolini et al: mean HAM-D17 total scores at baseline were 23.7 points and 23.8 points for trazodone OAD and venlafaxine XR, respectively. 95% CIs differences in mean score change from baseline between trazodone OAD vs venlafaxine XR at Day 7 were  $[-1.5; -0.2]$  and at Day 56 were  $[95\% \text{ CI}, 0.4; 2.9]$ . \* $P < .05$ ; \*\* $P < .01$ , mean score change from baseline between trazodone OAD vs placebo or venlafaxine XR.

## Results

### Search results

Our search term criteria yielded articles that only studied the effects of trazodone OAD formulation. Of the 18 articles studying trazodone OAD formulation, only 2 studies were randomized controlled trials (RCTs) that evaluated the antidepressant efficacy of only 1 formulation of trazodone in patients with MDD and reported results at Day 7 after treatment initiation. The results from the 2 RCTs studying trazodone OAD formulation are therefore reviewed here. Both the studies were randomized, double-blind trials in patients with MDD, which showed that trazodone OAD is an effective antidepressant (at a starting dose of 150 mg/day). One of the studies compared trazodone OAD vs placebo and the other compared it to an active comparator, venlafaxine XR.<sup>44,45</sup> In both studies, enrollees were instructed to undergo a washout period according to a taper schedule that encompassed 5 elimination half-lives of their specific medication.<sup>44,45</sup> Here, we present an in-depth review of both the studies and discuss the results as they relate to trazodone OAD's early effects on depression.

### Early improvement of depressive symptoms with trazodone OAD formulation

In a study of 412 patients with MDD, Sheehan et al found that patients treated with trazodone OAD (dose range during the first week: 150–225 mg/day) showed significantly greater reduction in the mean HAM-D17 total score compared to placebo within 1 week of treatment (intent-to-treat [ITT] population: trazodone OAD  $-5.6$  points vs placebo  $-3.9$  points  $[95\% \text{ CI}, -2.4; -0.4]$ ; Per protocol (PP) population: trazodone OAD  $-6.0$  points vs placebo  $-4.2$  points  $[95\% \text{ CI}, -2.6; -0.4]$ ). The difference between the treatment groups in both the ITT and PP populations was statistically significant ( $P < .05$ ). The corresponding percentage reduction at Day 7 in the mean HAM-D17 total score in the trazodone OAD group was 24% compared to 17% in the placebo group for the ITT population (Percentage reduction in the HAM-D17 total score in the PP population: trazodone OAD 26% vs placebo group 19%). This significantly higher improvement in the depressive symptoms

was sustained in the patients treated with trazodone OAD until the study endpoint (Day 56) compared to patients receiving placebo (Figure 1A and Supplementary Figure S2A).<sup>45,46</sup>

Similarly, Fagiolini et al<sup>44</sup> showed that trazodone OAD (dose during the first week: 150 mg/day) showed faster onset of antidepressant action compared to an SNRI, venlafaxine XR (dose during the first week: 75 mg/day) in 324 patients with MDD. A significantly greater reduction in the mean HAM-D17 total score was observed in the trazodone OAD group compared to venlafaxine XR within 7 days of treatment (ITT population: trazodone OAD  $-4.3$  points vs venlafaxine XR  $-3.5$  points  $[95\% \text{ CI}, -1.5; -0.2]$ ; PP population: trazodone OAD  $-4.4$  points vs venlafaxine XR  $-3.5$  points  $[95\% \text{ CI}, -1.6; -0.2]$ ;  $P < .05$ ). This improvement in the depressive symptoms corresponded to an 18% reduction in the HAM-D17 total score in the trazodone OAD group vs 15% in the venlafaxine group for the ITT population (percentage reduction in the HAM-D17 total score in the PP population: trazodone OAD 19% vs venlafaxine group 15%). After the first week, the dose for the trazodone OAD group was increased to 300 mg/day. In contrast to Day 7, at the study endpoint (Day 56), both trazodone (median dose of 300 mg/day) and venlafaxine XR (median dose of 75 mg/day) showed similar overall antidepressant efficacy. (Figure 1B and Supplementary Figure S2B).<sup>44,46</sup>

This early antidepressant efficacy observed with trazodone OAD is consistent with the evidence from studies of other trazodone formulations for the treatment of MDD. Results from double-blind, randomized clinical trials of trazodone IR and PR formulations demonstrating its faster onset of antidepressant action are summarized in Table 1.<sup>27,30,46,47</sup>

### Efficacy of the trazodone OAD formulation for improvement in the HAM-D17 factors

Depression is a multifaceted disorder, which is characterized by depressed mood along with several significant psychological, cognitive, and behavioral components. Different antidepressants, based on their pharmacological profile, may initiate improvement in various clinical components at different rates.<sup>48,49</sup> Therefore, we also reviewed the efficacy of trazodone OAD in improving

**Table 1.** Summary of Randomized, Controlled Trials of Trazodone (IR and PR Formulations) in Patients with MDD Demonstrating Its Early Onset of Action

Study	Study Duration	Patients (N)	Study Population	Treatment	HAM-D Score at Baseline	HAM-D Score at Day 7	HAM-D Percentage Reduction at Day 7	P Value
<b>Active comparator studies</b>								
Weisler et al <sup>30a</sup>	6 wk	DSM-III-defined moderate to severe MDD (124)	ITT (LOCF <sup>b</sup> —Center 1)	Trazodone IR	24.8	19.6	–21%	<.01
				Bupropion	25.4	23.1	–9%	
Beasley et al <sup>27a</sup>	6 wk	DSM-III-defined MDD (126)	–	Trazodone IR	24.3	16.3	–33%	.01
				Fluoxetine	23.4	17.6	–25%	
<b>Placebo-controlled study</b>								
Zhang et al <sup>47c</sup>	6 wk	DSM-IV-TR-defined MDD (363)	ITT	Trazodone PR	21.6	17.7	–18%	<.05

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; MDD, major depressive disorder; IR, immediate-release; ITT, intent-to-treat; PR, prolonged-release.

<sup>a</sup>HAM-D21.

<sup>b</sup>Last observation carried forward.

<sup>c</sup>Graphical extrapolation.

individual depression dimensions as assessed by the scores on 4 HAM-D17 factors: anxiety/somatization, cognitive disturbance, retardation, and sleep disturbance. The scores on the 4 HAM-D17 factors are comprised of the following items: anxiety/somatization—anxiety (both psychic and somatic), somatic symptoms (both general and gastrointestinal), hypochondriasis, and insight; cognitive disturbance—feelings of guilt, suicide, and agitation; retardation—depressed mood, work and activities, retardation, and genital symptoms; sleep disturbance—insomnia early, insomnia middle, and insomnia late.

In the placebo-controlled study, conducted by Sheehan et al,<sup>45</sup> trazodone OAD showed a trend for early improvement at Day 7 in the HAM-D anxiety/somatization factor compared to placebo; however, this difference was statistically significant only at Day 21 for both the ITT [95% CI, –1.0; –0.1] and the PP [95% CI, –1.3; –0.2] populations ( $P < .05$ ) (Figure 2A and Supplementary Figure S3A). In the active-comparator study by Fagiolini et al,<sup>44</sup> both trazodone OAD and venlafaxine showed similar improvements in the anxiety/somatization factor at Day 7, and the difference between the groups was statistically significant in the favor of venlafaxine XR at Days 35 [95% CI, 0.1; 1.0] and 56 [95% CI, 0.3; 1.3] for the ITT population and only at Day 56 [95% CI, 0.0; 1.0] for the PP population ( $P < .05$ ) (Figure 2B and Supplementary Figure S3B).

For the HAM-D cognitive disturbance factor, trazodone OAD showed statistically significant ( $P < .05$ ) early improvement compared to placebo at Day 7 for the ITT [95% CI, –0.7; –0.2] and the PP [95% CI, –0.6; 0.0] groups, which was sustained until the end of the study for both populations in the study by Sheehan et al<sup>45</sup> (Figure 2A and Supplementary Figure S3A). In the study by Fagiolini et al,<sup>44</sup> both trazodone OAD and venlafaxine XR showed similar reduction in the cognitive disturbance scores for both the ITT and PP populations (Figure 2B and Supplementary Figure S3B).

In the Sheehan et al<sup>45</sup> study, trazodone OAD showed a trend for early improvement in the HAM-D retardation factor at Day 7, but the difference between trazodone and placebo was only statistically significant at Day 21 [95% CI, –1.4; –0.5] for the ITT population ( $P < .05$ ). However, for the PP population, treatment with trazodone resulted in significantly greater reduction in the retardation factor within 1 week of treatment compared to placebo [95% CI, –0.9; 0.0], which was maintained at all study visits until the analyzed endpoint. ( $P < .05$ ) (Figure 2A and Supplementary Figure S3A). In the Fagiolini et al<sup>44</sup> study, both trazodone OAD

and venlafaxine XR showed similar reduction in the retardation factor scores at Day 7 for the ITT [95% CI –0.2; 0.4] as well as PP [95% CI, –0.3; 0.3] populations. However, the difference between treatment groups was statistically significant ( $P < .05$ ) in the favor of venlafaxine at Days 21 [95% CI, 0.1; 0.8], 35 [95% CI, 0.4; 1.3], and 56 [95% CI, 0.4; 1.4] for the ITT population and at Days 35 [95% CI, 0.2; 1.1] and 56 [95% CI, 0.2; 1.1] for the PP population (Figure 2B and Supplementary Figure S3B).

In the Sheehan et al<sup>45</sup> trial, trazodone OAD showed statistically significant ( $P < 0.05$ ) early improvement in the HAM-D sleep disturbance factor at Day 7 compared to placebo for both the ITT [95% CI, –1.0; –0.3] and PP [95% CI, –1.0; –0.1] populations. Trazodone OAD also showed a greater reduction ( $P < 0.05$ ) in this measurement at Day 7 as compared to venlafaxine XR for both the ITT [95% CI, –1.1; –0.4] and PP [95% CI, –1.1; –0.3] populations.<sup>44</sup> This greater improvement in the sleep disturbance factor observed with trazodone was sustained at all the post-baseline visits until the study endpoint, except for Day 56 in the ITT population in the Fagiolini et al study, where trazodone treatment showed a trend for improvement in sleep disturbance; however, the difference between treatment groups did not achieve statistical significance (Figure 2A,B and Supplementary Figures S3A,B).<sup>44,45</sup>

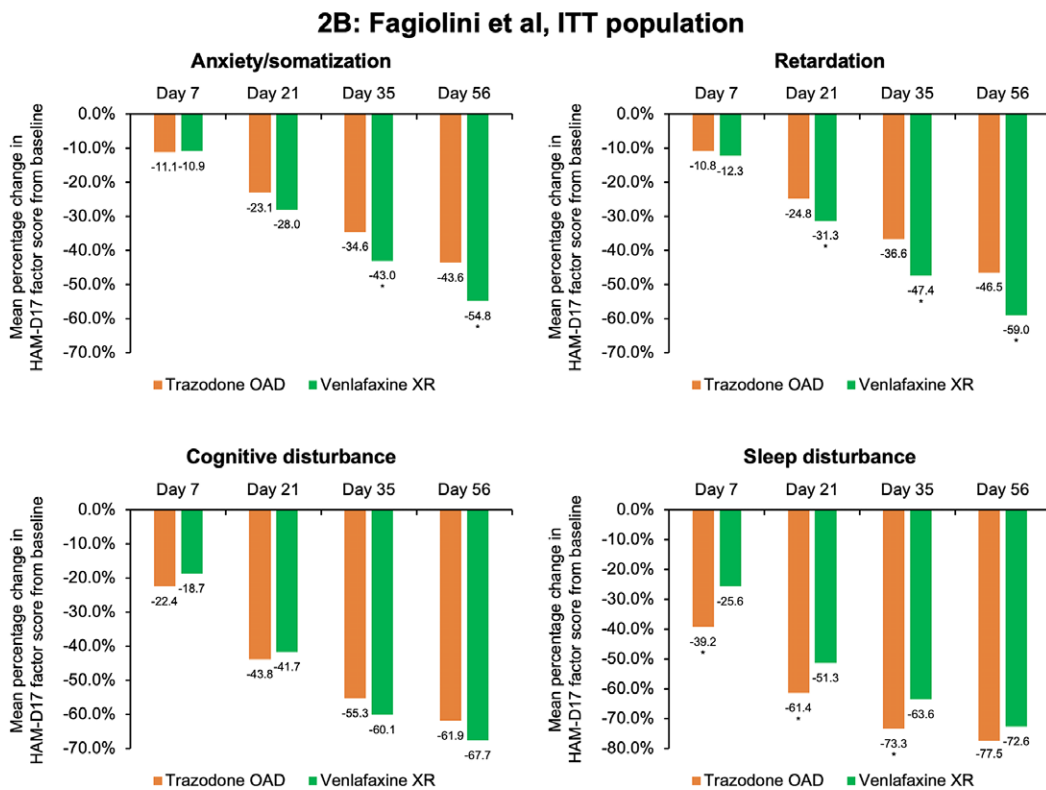
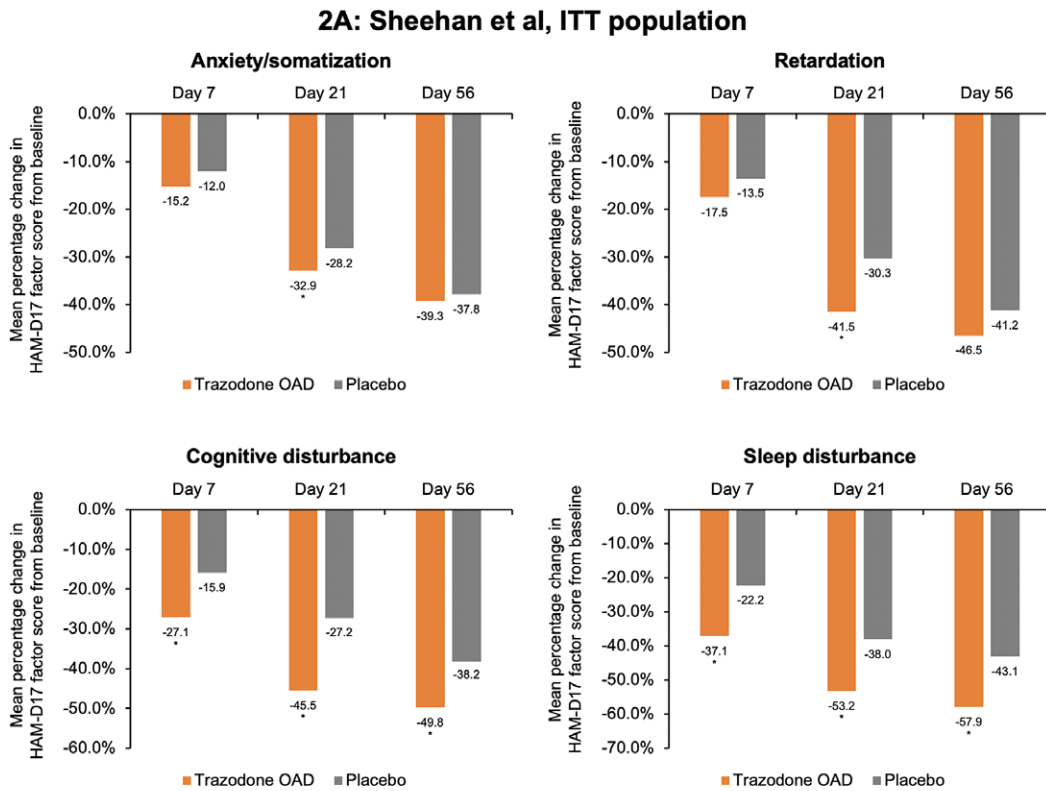
### Safety and tolerability of the trazodone OAD formulation

Trazodone OAD formulation is well tolerated for the treatment of MDD. The severity of adverse events in both the studies was mild to moderate. The most common adverse events ( $\geq 5\%$  in any treatment group) in both the studies were headache, somnolence, dizziness, dry mouth, and nausea (Table 2). Additionally, the incidence of serious adverse events was low (Fagiolini et al: 3/165; Sheehan et al: 3/202). More patients in the trazodone OAD discontinued treatment due to adverse events in both studies. The most common adverse events that led to treatment discontinuation in the trazodone OAD group were dizziness, sedation, somnolence, and electrocardiogram (ECG) abnormality/ECG QT prolongation.<sup>36,44,45</sup>

### Discussion

Early onset of antidepressant action is a desirable therapeutic outcome, and the emphasis on this action by novel antidepressants

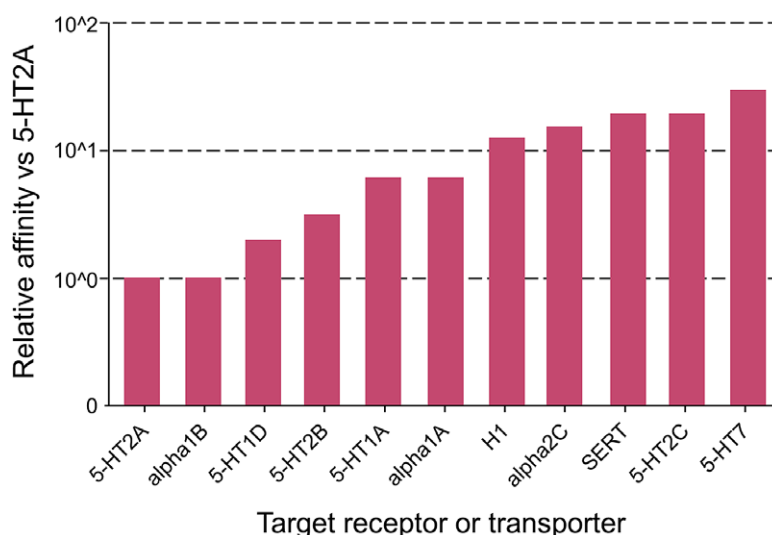




**Figure 2.** Mean percentage change from baseline in the factor composition of Hamilton Depression Rating Scale (HAM-D17) for the intent-to-treat (ITT) population. (A) Sheehan et al study. Ninety-five percent confidence intervals (CIs) were calculated for mean score change from baseline in trazodone once-a-day (OAD) vs placebo-treated patients for anxiety/somatization at Day 7 [-0.5; 0.3], Day 21 [-1.0; -0.1], and Day 56 [-1.0; 0.2]; for retardation at Day 7 [-0.6; 0.1], Day 21 [-1.4; -0.5], and Day 56 [-1.1; 0.0]; for cognitive disturbance for Day 7 [-0.7; -0.2], Day 21 [-0.8; -0.2], and Day 56 [-0.8; -0.2]; and for sleep disturbance for Day 7 [-1.0; -0.3], Day 21 [-1.1; -0.3], and Day 56 [-1.1; -0.3]. (B) Fagiolini et al study. 95% CIs were calculated for mean score change from baseline in patients treated with trazodone OAD vs venlafaxine XR for anxiety/somatization at Day 7 [-0.3; 0.3], Day 21 [0.0; 0.8], Day 35 [0.1; 1.0], and Day 56 [0.3; 1.3]; for retardation at Day 7 [-0.2; 0.4], Day 21 [0.1; 0.8], Day 35 [0.4; 1.3], and Day 56 [0.4; 1.4]; for cognitive disturbance for Day 7 [-0.3; 0.0], Day 21 [-0.2; 0.3], Day 35 [-0.1; 0.3], and Day 56 [0.0; 0.4]; and for sleep disturbance for Day 7 [-1.1; -0.4], Day 21 [-0.9; -0.2], Day 35 [-0.8; -0.2], and Day 56 [-0.5; -0.1]. \*P < .05, mean score change from baseline between trazodone OAD vs placebo or venlafaxine XR.

**Table 2.** Summary of Adverse Events Observed with Trazodone once-a-day (OAD) in the Placebo- and Active-Comparator Studies

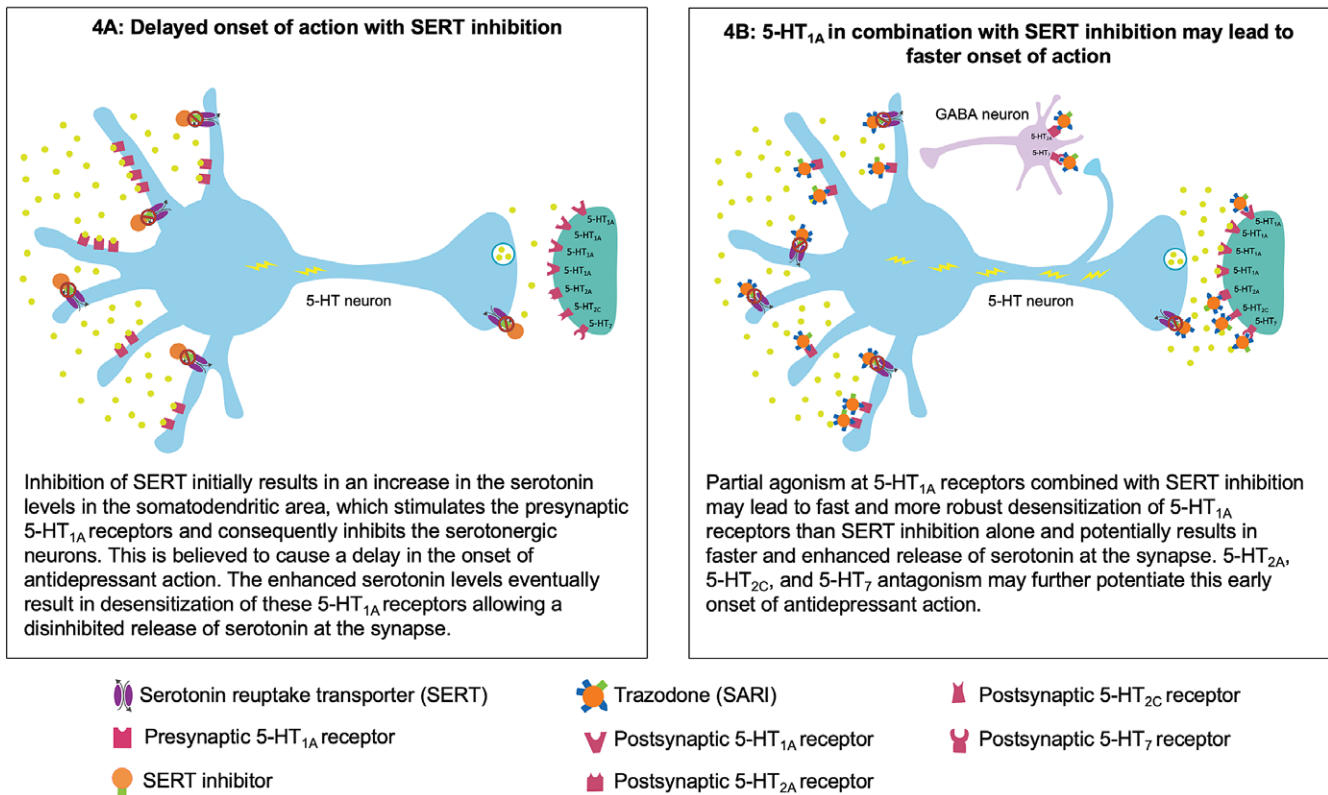
Most Frequent Adverse Events ( $\geq 5\%$ in Any Group)	Sheehan et al <sup>45</sup>		Fagiolini et al <sup>44</sup>	
	Trazodone OAD (n = 202)	Placebo (n = 204)	Trazodone OAD (n = 165)	Venlafaxine XR (n = 156)
Headache	33.2%	27%	6.83%	11.80%
Somnolence	31.2%	15.7%	8.70%	–
Dry mouth	25.2%	12.7%	6.83%	1.86%
Dizziness	24.8%	12.3%	11.18%	3.73%
Electrocardiogram QT	–	–	5.59%	3.73%
Nausea	20.8%	12.7%	6.21%	14.29%
Palpitations	–	–	2.48%	5.59%
Sedation	16.8%	3.4%	–	–
Fatigue	14.9%	8.3%	–	–
Diarrhea	9.4%	11.3%	–	–
Constipation	7.9%	2%	–	–
Back pain	5.4%	3.4%	–	–
Vision blurred	5.4%	–	–	–

**Figure 3.** Relative binding affinities of trazodone for neurotransmitter receptors and transporters. 5-HT, 5-hydroxytryptamine (serotonin) receptors (different subtypes); alpha, alpha adrenergic receptors (different subtypes); H, histamine receptor (subtype); SERT, serotonin reuptake transporter.

with NMDA antagonist and neuroactive steroid mechanisms for second-line treatment of resistant depressed patients highlights the need as well for early onset of action for first line treatment of MDD. This systematic review of 2 randomized, double-blind clinical trials evaluating the efficacy and safety of trazodone OAD formulation in patients with MDD suggests that trazodone OAD can result in an early antidepressant effect within 7 days of initiating treatment. However, the limited number of studies in this review warrant future clinical studies assessing the onset and time course of improvement with trazodone OAD treatment to confirm our findings. Trazodone OAD treatment resulted in statistically significant reduction in the total HAM-D score within 7 days of starting treatment compared to placebo or an active comparator (venlafaxine XR).<sup>44-46</sup> At the study endpoint (Day 56), this improvement in depressive symptoms was sustained in the placebo-controlled study with the trazodone OAD treatment. However, in the active-comparator study at Day 56,

venlafaxine XR showed greater antidepressant efficacy compared to trazodone OAD in the ITT population and no significant difference was observed in the PP population (the study population with a higher-level treatment compliance); in fact, the severity of depression in both trazodone OAD as well venlafaxine XR groups decreased from moderate to mild in the both the ITT and PP population.<sup>44</sup> Interestingly, other studies have also shown that while venlafaxine may be a comparable or even more effective antidepressant at the study endpoint, treatment with trazodone may result in an early onset of antidepressant effect.<sup>29,31,32</sup>

In fact, this early antidepressant efficacy of trazodone OAD was also observed in studies of other trazodone formulations (including the IR and PR formulations).<sup>27,30,47</sup> Overall, the percentage reduction of the HAM-D score after 7 days of treatment with trazodone (all formulations) ranged from 18% to 33%.<sup>27,30,44,45,47</sup> While the pharmacokinetic profiles of the IR and PR formulations may limit



**Figure 4.** Putative mechanism for the fast onset of antidepressant action of trazodone. (A) Delayed onset of action with serotonin reuptake transporter (SERT) inhibition. (B) Partial agonism at 5-HT<sub>1A</sub> in combination with SERT inhibition may contribute to faster onset of action.

the treatment tolerability and compliance in patients due to the need for multiple dosing during the day, the early antidepressant response observed with trazodone regardless of the formulation further lends supporting evidence for early response in depression with trazodone treatment. This early antidepressant efficacy of trazodone OAD has also been observed in routine clinical practice. In an observational study conducted by Češková *et al.*<sup>41</sup> in 8 psychiatric centers treating patients with moderate to severe depression, trazodone OAD formulation demonstrated statistically significant decreases in the overall Montgomery-Åsberg Depression Rating Scale score of patients at Week 1 after initiating the treatment. Most patients reported improvement in the overall severity of their illness as assessed by the Clinical Global Impression-Severity scale after 6 days of treatment, thus demonstrating that the early improvement observed with trazodone was clinically meaningful.<sup>41,50</sup> This suggests that early onset of antidepressant action is a specific characteristic of trazodone.

Early improvement with antidepressants has important clinical implications. Several pooled analyses of RCTs and prospective naturalistic studies have demonstrated that early improvement in depressive symptoms is a clinically useful predictor of sustained response and lack of early improvement can predict nonresponse.<sup>51–55</sup> In fact, in the study by Sheehan *et al.*,<sup>45</sup> early improvement with trazodone OAD formulation was further characterized by a greater number of HAM-D responders compared to placebo. The ability to know as early as possible that a patient will or will not respond to an antidepressant allows the clinicians to encourage the ultimate responders to keep taking the medication and adjust the treatment plan for the ultimate non-responders to minimize their time spent on ineffective treatment.

In addition to trazodone OAD's fast onset of action in improving the overall core symptoms, we also reviewed early improvements in specific depressive symptoms. The sleep disturbance factor showed the greatest improvement at Day 7 across the ITT and PP populations in both the placebo-controlled and active-controlled studies of trazodone OAD formulation.<sup>44,45</sup> This early improvement observed with trazodone OAD compared to placebo sustained until the end of the study duration. Trazodone's efficacy for improvement in insomnia in patients with MDD, particularly early in the therapy, has also been previously reported in other randomized, double-blind studies comparing trazodone to placebo or other standard antidepressants.<sup>23,29,30,56,57</sup> A post-hoc analysis of the placebo-controlled study by Sheehan *et al.*<sup>58</sup> further showed that the antidepressant efficacy of trazodone OAD was independent of the early improvements observed in the sleep disturbance factor. Thus, this suggests that treatment with trazodone OAD can provide early depressive symptom relief including the early and sustained benefit on insomnia.

Insomnia is reported in more than 90% of the patients with MDD.<sup>24</sup> It is one of the most frequent residual symptoms that persists after treatment with standard antidepressants, resulting in relapse and recurrence.<sup>24,38,59</sup> Therefore, an antidepressant such as trazodone OAD, with the ability to reduce sleep disturbance, may improve overall outcomes in patients with MDD.

The sedative/hypnotic property of trazodone suggests that trazodone may also confer anxiolytic benefits.<sup>58</sup> Our review of the placebo-controlled study of trazodone OAD showed a trend of early improvement in the anxiety/somatization factor, but the change in the HAM-D factor score from baseline to Day 7 was not statistically significant.<sup>45</sup> While systematic studies demonstrating the efficacy of

trazodone for treating anxiety are limited, several studies comparing the efficacy of trazodone and other antidepressants have shown that trazodone can alleviate symptoms of anxiety with the first week of treatment.<sup>23,56,60</sup> A randomized double-blind study comparing the trazodone PR formulation to sertraline for treatment of MDD demonstrated early onset of anxiolytic activity for patients taking trazodone, compared to those taking sertraline, within 1 week of treatment as assessed by the reduction in the Hamilton Anxiety Rating Scale (HAM-A).<sup>56</sup>

Many data for binding affinity of trazodone with different neurotransmitter targets (receptor and transporters) are already available in literature.<sup>25,26,61</sup> In Figure 3, we show some recent *in vitro* proprietary data for binding affinity of trazodone for its targets.<sup>62</sup> Trazodone shows high to medium affinity (pKi 6-8) on a series of receptors subtypes. Trazodone has the highest binding affinity for 5-HT<sub>2A</sub> receptors. Most affinities are comparable to other reported in literature, but interestingly, a higher affinity for 5-HT<sub>7</sub> with respect to previously published data were found (not substantially different from SERT), supporting the hypothesis that a pharmacological activity on this receptor could be exerted at therapeutic concentrations for antidepressant activity.<sup>62</sup>

Trazodone's early onset of antidepressant action may be attributable to its multifunctional and multimodal pharmacological properties. At a starting dose of 100 to 150 mg/day, trazodone exerts antidepressant action by blocking SERTs.<sup>23-26</sup> At these doses, trazodone also acts at other receptors in the range of SERT or for which it has a higher affinity. In fact, according to a published pharmacokinetic simulation study, the binding affinity of trazodone for selected receptors at a dose of 150 mg/day could be sufficient to fully occupy these receptors in steady state conditions. It is possible that trazodone's activity at these receptors, along with SERT inhibition, has a synergistic effect that accelerates the onset of antidepressant action.<sup>11</sup>

Trazodone's partial agonist actions at the 5-HT<sub>1A</sub> receptors in combination with SERT inhibition may contribute to its faster onset of antidepressant action.<sup>63,64</sup> In general, the antidepressant effect of serotonin reuptake inhibition is potentially mediated via presynaptic and postsynaptic 5-HT<sub>1A</sub> receptors. Following SERT inhibition, the increased serotonin levels inhibit the serotonergic neurons in the raphe nuclei via the stimulation of the presynaptic somatodendritic 5-HT<sub>1A</sub> receptors, which are believed to cause a delay in the onset of antidepressant effect. Eventually, this increase in the serotonin levels leads to desensitization of these presynaptic 5-HT<sub>1A</sub> receptors, resulting in enhanced serotonin release at the synapse with subsequent antidepressant actions mediated via the postsynaptic 5-HT<sub>1A</sub> receptors.<sup>12,26</sup> Preclinical studies suggest that 5-HT<sub>1A</sub> partial agonism along with SERT inhibition leads to much faster action at these 5-HT<sub>1A</sub> receptors, thus resulting in more immediate and robust increase in the serotonin release.<sup>64-67</sup> It has recently been shown that trazodone partial agonism of 5-HT<sub>1A</sub> receptors, combined with adrenergic blockade, could help regulate firing of raphe neurons and consequently contribute to serotonin modulation in an early stage of administration.<sup>63</sup>

Trazodone's most potent binding property, leading to 5-HT<sub>2A</sub> antagonism, could further complement this rapid onset of antidepressant action.<sup>25,26,68</sup> Luparini et al<sup>68</sup> demonstrated that trazodone increases serotonin levels through a dual mechanism: at low concentrations by reducing the inhibitory GABAergic tone through the antagonism of 5-HT<sub>2A</sub> receptors and at high concentrations through SERT inhibition. Therefore, 5-HT<sub>2A</sub> antagonism along with SERT inhibition may exert an additive effect in terms of serotonin release, which may result in antidepressant activity,

possibly through 5-HT<sub>1A</sub> downregulation.<sup>69-71</sup> In addition to an antidepressant effect, antagonism of 5-HT<sub>2A</sub> and partial agonism of 5-HT<sub>1A</sub> receptors in combination with histamine H<sub>1</sub> receptors and  $\alpha$ 1 adrenergic receptors potentially contribute to trazodone's sedative/hypnotic and anxiolytic effects.<sup>23-26</sup>

Trazodone also antagonizes 5-HT<sub>2C</sub> and 5-HT<sub>7</sub> receptors, which may further contribute to its fast antidepressant action.<sup>25,26,72,73</sup> Trazodone's affinity for 5-HT<sub>2C</sub> and 5-HT<sub>7</sub> receptors is in the range of SERT.<sup>25,26,62</sup> In preclinical *in vivo* depression models, 5-HT<sub>2C</sub> antagonists have been shown to induce fast-onset antidepressant action within 5 days of treatment initiation compared to SSRIs.<sup>72</sup> Evidence from literature suggests that this 5-HT<sub>2C</sub> antagonism induces rapid onset, possibly through an increase in the mesocortical dopaminergic signaling.<sup>26,72,74,75</sup> Antagonism of 5-HT<sub>2C</sub> receptors may also contribute to trazodone's beneficial effect in alleviating symptoms of anxiety. It has been shown that serotonin release from the dorsal raphe nucleus enhances fear and anxiety through activation of 5-HT<sub>2C</sub> receptors on a subpopulation of corticotropin-releasing factor neurons.<sup>76,77</sup> Therefore, antagonism at 5-HT<sub>2C</sub> receptors along with trazodone's action at other serotonergic receptors may potentiate its anxiolytic effects.

Pharmacological blockade of 5-HT<sub>7</sub> receptors in preclinical studies has also been shown to induce fast antidepressant response within a week of initiating treatment.<sup>73</sup> The firing of raphe serotonergic neurons is under negative 5-HT<sub>7</sub> receptor control, possibly through GABAergic neurons.<sup>24,73</sup> Therefore, blocking 5-HT<sub>7</sub> receptors increases the release of serotonin, probably by preventing the inhibition of raphe serotonergic neurons by GABA.<sup>24,73,76,78</sup> In addition to brainstem raphe nuclei, the 5-HT<sub>7</sub> receptors are also localized in the hippocampus, cortex, and thalamus, possibly on GABA interneurons or glutamate terminals. Many preclinical studies suggest that agents with 5-HT<sub>7</sub> receptor antagonist property improve cognition, probably through their actions in these brain regions. Therefore, the improvement in the cognitive disturbance HAM-D factor observed in the Sheehan et al study may be attributable to trazodone's 5-HT<sub>7</sub> receptor antagonist activity.<sup>24,79</sup>

Future research to understand the multifunctional properties of trazodone at different doses and treatment times, and a better knowledge of human brain receptor occupancy at different doses, could provide further insight into the mechanism for trazodone's fast onset of antidepressant action.

The pharmacological profile of trazodone also contributes to its favorable safety profile.<sup>24,26</sup> The overall severity of the adverse events associated with the treatment of trazodone OAD in both Sheehan et al<sup>45</sup> and Fagiolini et al<sup>44</sup> studies was mild to moderate. Simultaneous inhibition of SERT and antagonism of 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> with trazodone can lead to an antidepressant effect while avoiding the side effects associated with use of conventional antidepressants (including SSRIs and SNRIs) due to 5-HT<sub>2A/2C</sub> stimulation, such as sexual dysfunction, anxiety, and insomnia.<sup>26</sup> In fact, in the placebo-controlled study of trazodone OAD, only 1 patient reported anxiety in the trazodone group compared to 5 patients in the placebo group. Moreover, the incidence of sexual dysfunction was also low (trazodone OAD 4.9% vs placebo 2.5%).<sup>45</sup> Additionally, the OAD formulation has a better tolerability profile compared to the IR and PR formulations.<sup>23,24</sup> The antidepressant efficacy, combined with improved tolerability and improvements in sleep disturbance observed with trazodone OAD, may have important clinical implications, like enhanced compliance and decreased use of concomitant medications. In fact, the observational study conducted by Češková et al<sup>41</sup> showed that adherence



with trazodone OAD formulation was high (>70%) after 21 weeks of treatment. The study also reported a significant reduction in the need for concomitant medications, such as anxiolytics, hypnotics, and other psychotropic medications.

One of the main limitations of this systematic review on early response to trazodone OAD in depression is that it is based on results from only 2 RCTs that were designed to evaluate efficacy at the study endpoint and not specifically to examine onset and time course of improvement. Therefore, the evidence supporting our findings about the early onset of antidepressant action with trazodone OAD treatment is limited. Second, infrequent assessments in a typical RCT study design (such as weekly intervals) may have low sensitivity to detect early improvements in depressive symptoms. However, consistent evidence from multiple RCTs for different formulations of trazodone, including the IR and PR formulations suggests that the trazodone may exhibit a fast onset of antidepressant action. However, future clinical studies to evaluate the timing of onset of depressive symptom improvement with trazodone OAD treatment are needed to confirm our analysis. An additional potential limitation is that the mean baseline HAM-D-17 total scores measured between both RCTs ranged from 22.4 to 24.1, which although considered severe or very severe, may be below the threshold for detecting moderate effects sizes of treatments relative to placebo.<sup>44,45,80</sup> The efficacy of a treatment over placebo may be more readily detectable in cases of even greater severity where HAM-D-17 total scores meet or exceed 25.<sup>80</sup> Therefore, it is possible that more robust early treatment effects may have been observed if baseline HAM-D-17 total scores had been higher.

## Conclusion

Trazodone is a once-a-day antidepressant with rapid onset and efficacy in treating the symptoms of anxiety and insomnia, while possibly avoiding weight gain, sexual dysfunction, and activating side effects.

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