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Once-a-Day Trazodone in the Treatment of Depression in Routine Clinical Practice

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Keywords
Trazodone · Depression · Clinical practice · Treatment-resistant depression · Individualized treatment · Multimodal antidepressant

Abstract
Objective: The aim of the study was to evaluate the efficacy, tolerability, and safety of once-a day trazodone tablets (Trittico Prolong® 300 mg) in patients with moderate to severe depression in routine clinical practice. ***Methods:*** Men and women ≥18 years old with Montgomery-Åsberg Depression Rating Scale (MADRS) scores >21 and Clinical Global Impression – Severity (CGI/S) ≥4 were included in this post-authorization, non-interventional, observational prospective safety study, conducted in 8 psychiatric centers in the Czech Republic. The acute treatment phase lasted 5 weeks: 1 week of titration and 4 weeks of full-dose treatment. Patients had follow-up visits 9 and 21 weeks after commencing treatment. ***Results:*** Overall, 85 patients were enrolled in the study, of which 80 completed the acute treatment of 5 weeks. There were significant decreases in the overall MADRS score from the baseline mean value of 27.4–21.2 at week 1 ($p < 0.001$), and a further decrease to 7.9 at week 5 ($p < 0.001$). The severity of depression according to CGI/S gradually declined. Most patients reported improvement after 6 days of trazodone treatment. The most frequent adverse drug reactions (ADRs) reported were somnolence and fatigue. ***Conclusions:*** Trazodone, in the new extended-release formulation, had very good effects in clinical practice, both in previously untreated depressive episodes and in episodes not responsive to previous antidepressive therapy.

Objective

Trazodone was synthesized in the 1960s in the laboratories of the Angelini Company. This was the first triazolopyridine derivative developed as an antidepressant (AD). Trazodone was first launched in Italy under the brand Trittico. In 1982, it was introduced in the US, branded as Desyrel. The trazodone modified-release tablet (Trittico AC®) was launched in the market worldwide in 1990; in 2014, the drug was launched in Europe in a new extended-release formulation for once-daily dosing (Trazodone Contramid® OAD).

In the Czech Republic, trazodone has been available in the modified-release formulation (Trittico AC®) since 2002. Since 2015, it has also been available in once-daily

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formulation as Trittico Prolong®. The Czech Republic was one of the first countries where the new formulation became available. The production uses a special technology (Contramid®) to ensure extended release of the active substance without concentration peaks and to maintain the therapeutic concentration for 24 h to minimize adverse drug reactions (ADRs) and to improve adherence with the same efficacy [1].

Trazodone is the first agent of the serotonin antagonists and reuptake inhibitors class. Its AD effect is attributed to 2 fundamental mechanisms: a significant antagonism on serotonin 5-$HT2_{A/C}$ receptors and a less significant serotonin reuptake blockade, which is a new concept putting trazodone among the multimodal ADs [2, 3]. Trazodone is also defined as "multifunctional" AD because it exerts different pharmacologic functions depending on the dose. In fact, at low doses, trazodone acts – as $5HT_{2A}$ antagonist, as a weak antagonist of presynaptic $alpha_2$ adrenergic receptors, a relatively potent postsynaptic $alpha_1$ antagonist, 5-$HT1_A$ agonist, and H_1 antagonist. These activities are responsible for its sedative hypnotic and anxiolytic effect, while at higher doses, the serotonin transporter blockade provides an AD effect [4].

Two randomized, double-blind, controlled trials were performed using the new formulation of trazodone for once-daily use. The first trial, using a placebo as a comparator was conducted at 38 sites in the US and Canada [5]. The second, as-yet unpublished trial, compared trazodone to Venlafaxin XR® at 31 sites in Europe, including the Czech Republic [6].

This first observational, non-interventional, multicenter clinical study with the new drug formulation (Trittico Prolong®) was conducted in the Czech Republic. Prospective observational studies are now considered complementary to controlled clinical trials that have rigorous inclusion and exclusion criteria for the selection of eligible patients and do not always reflect the wide diversity and variability of patients in routine clinical practice, for example, in the "real world." The aim of our study was to evaluate the efficacy, tolerability, and safety of trazodone OAD tablets (Trittico Prolong® 300 mg) in patients with moderate to severe depression in routine clinical practice.

Methods

Study Design

This was a post-authorization, non-interventional, multicenter, observational prospective safety study, conducted in 8 psychiatric centers in the Czech Republic between July 2015 and November 2016. The acute treatment phase lasted 5 weeks: 1 week of titration and 4 weeks of full dose treatment. Treated patients had follow-up visits after 1 month (week 9) and again after 3 months (week 21). The study was conducted in accordance with legal and ethical requirements (Czech State Institute for Drug Control [SUKL] identification number 1505070002).

Study Treatment

The titration phase started on days 1–3 with a 150 mg dose of Trittico Prolong® taken in the evening. A 225 mg per day dose was taken on days 4–6. Starting on day 7, a 300 mg per day dose was taken, with subsequent treatment with this target dose. The tablets of Trittico Prolong® are available in 150 and 300 mg dose strengths and are easily split.

The following patients were included in the study:

1. Patients with moderate to severe depression of different etiology, according to the Summary of product characteristics; Montgomery-Åsberg Depression Rating Scale (MADRS) score >21 [7] and Clinical Global Impression – Severity (CGI/S) ≥4 [8].
2. Male and female subjects ≥18 years old who were expected to benefit from this therapy. The inclusion was entirely at the discretion and clinical judgment of the investigator.

Efficacy Assessment

Treatment efficacy was assessed by changes in the MADRS scores at weeks 1 and 5, by changes in the CGI/S scores at weeks 1 and 5, by clinical improvement as expressed in the CGI – Improvement (CGI/I) scores at week 5, and by changes in the concomitant treatment with anxiolytics/hypnotics and other psychotropic drugs at week 5 versus baseline. The onset of drug action was also monitored. To assess the rate of onset, a standard question was asked to the patients at the end of the titration period (week 1): "After how many days did you observe an improvement?"

Tolerability and Safety Assessment

Safety and tolerability were assessed at weeks 1 and 5 according to incidence and intensity of ADR, in weeks 1 and 5 according to the frequency of discontinuation of medication for ADR, and in week 5 according to the investigator and patient assessment (no ADR, mild ADR, moderate ADR, severe ADR).

The list of monitored ADRs was based on the summary of product characteristics. The intensity was evaluated in the 1–3 range: low intensity (no action required), medium intensity (requiring measures to manage the subject's status but requiring no adjustment to the trazodone treatment regimen), and severe intensity (requiring dose reduction or discontinuation of treatment with trazodone).

A serious ADR was defined according to Good Pharmacovigilance Practice.

Follow-Up Assessment

In the subsequent 1-month (week 9) and 3-month (week 21) follow-up assessments, mental status and tolerability were assessed based on investigator statements (patient depression since the last assessment was either unchanged, improved, or worsened; tolerability was either excellent, good, or bad). The need for additional treatment was monitored as in week 5.

Statistical Analysis

Data were summarized by standard descriptive statistics. The MADRS total score at weeks 1 and 5, CGI/S score at weeks 1 and 5, and MADRS individual item scores at week 5 were compared to

the baseline using the Wilcoxon test. McNemar's test was used for a comparison of the use of anxiolytics/hypnotics and other psychotropic medications at weeks 5, 9, and 21 versus baseline, as well as for a comparison of the number of patients with ADRs at week 5 vs. 1. Only patients with both measurements available were included in each analysis. No adjustments were made for multiple testing.

Results

Sample Characteristics

Altogether, 85 patients were enrolled in the study, of which 80 completed the acute treatment of 5 weeks. One patient discontinued the treatment after 1 week due to ADR, 4 other patients were "lost to follow-up" at week 5. Sample characteristics are given in Table 1.

Of the enrolled patients, 64.7% (55 out of 85) underwent prior AD treatment, most notably with mirtazapine, sertraline, escitalopram, or citalopram. At baseline, 50.6% (43 out of 85) of the patients were treated with anxiolytics and hypnotics, and 23.5% (20 out of 85) of the patients were treated with other psychotropic drugs (other AD and antipsychotics). The target dose of 300 mg per day of Trittico Prolong® was achieved by 91.8% (78 out of 85) of the patients; the 225 mg dose was maintained by 2.4% (2 out of 85); and the 150 mg dose was maintained by 5.9% (5 out of 85) of the patients.

Efficacy

Montgomery-Åsberg Depression Rating Scale

After 1 week of treatment (end of titration), a significant decrease in the overall MADRS score was reported; see Table 2 and Figure 1. The MADRS score reduction was statistically significant in all items; sleep disorders and sadness/anxiety were relatively the most affected; see Figure 2.

Clinical Global Impression

The severity of depression, as measured by CGI/S, gradually declined: at the end of acute treatment, 88.0% (71 out of 80) of the treated patients had no or very mild to moderate depression (CGI/S ≤3); see Table 2.

According to CGI/I, 93.8% (75 out of 80) of the patients showed very significant, significant, or slight improvement (CGI/I 1–3) at week 5 compared to baseline.

Onset of Action

More than one third of the patients (37.6%; 32 out of 85) reported improved status after 6 days of treatment with trazodone.

Table 1. Patient demographic and baseline characteristics

	Patients (n = 85)
Age, years	
Mean (SD)	41.3 (13.6)
Median (range)	40 (18–68)
Therapy initiation, n (%)	
Hospitalization	47 (55.3)
Outpatient care	38 (44.7)
Gender, n (%)	
Men	30 (35.3)
Women	55 (64.7)
MADRS, n (%)	
<21	1 (1.2)*
22–25	46 (54.1)
>25	38 (44.7)
Previous treatment by AD	55 (64.7)
Current treatment, n (%)	
Anxiolytics and hypnotics	43 (50.6)
Other psychotropic drugs	20 (23.5)

* One patient had the total MADRS score less than 21; however, after consultation with his psychiatrist he was included into the study and analysis (see inclusion criteria).

Table 2. Changes in MADRS and CGI/S scores during the acute treatment

	Baseline (n = 85)	Week 1 (n = 83)	Week 5 (n = 80)
MADRS			
Mean (SD)	27.4 (5.50)	21.2 (6.22)	7.9 (7.93)
Median (range)	25 (20–42)	21 (1–34)	5 (0–34)
p value		<0.001	<0.001
CGI/S			
0			1 (1.2)
1		3 (3.6)	37 (46.3)
2		2 (2.4)	21 (26.3)
3		14 (16.9)	12 (15.0)
4	44 (51.8)	49 (59.0)	4 (5.0)
5	27 (31.8)	11 (13.3)	3 (3.8)
6	14 (16.5)	4 (4.8)	2 (2.5)
p value		<0.001	<0.001

n, number of patients with available data.

p values are obtained from the comparison to the baseline score using the Wilcoxon test.

Tolerability and Safety

ADRs occurred more frequently after the first week of treatment, when reported in 50.6% (43 out of 85) of patients; after a further 4 weeks of treatment, the overall incidence was 38% lower (10 out of 80, $p < 0.001$); see Figure 3.

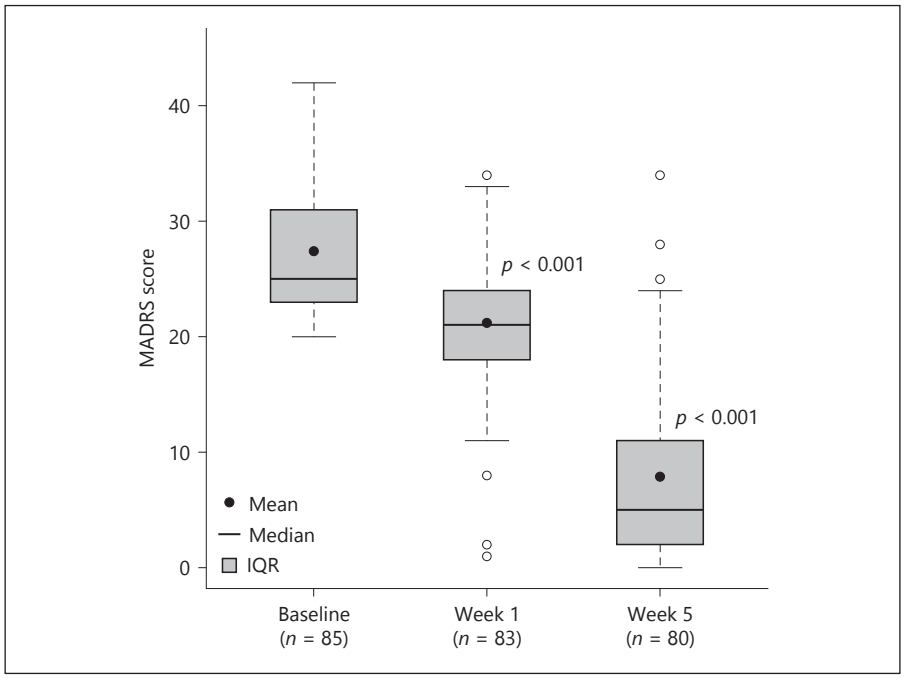

Fig. 1. MADRS scores at baseline, week 1, and week 5. The box plots display mean, median, interquartile range (IQR), extreme data points within 1.5 × IQR, and outliers. *p* values are obtained from the comparison to the baseline score using the Wilcoxon test.

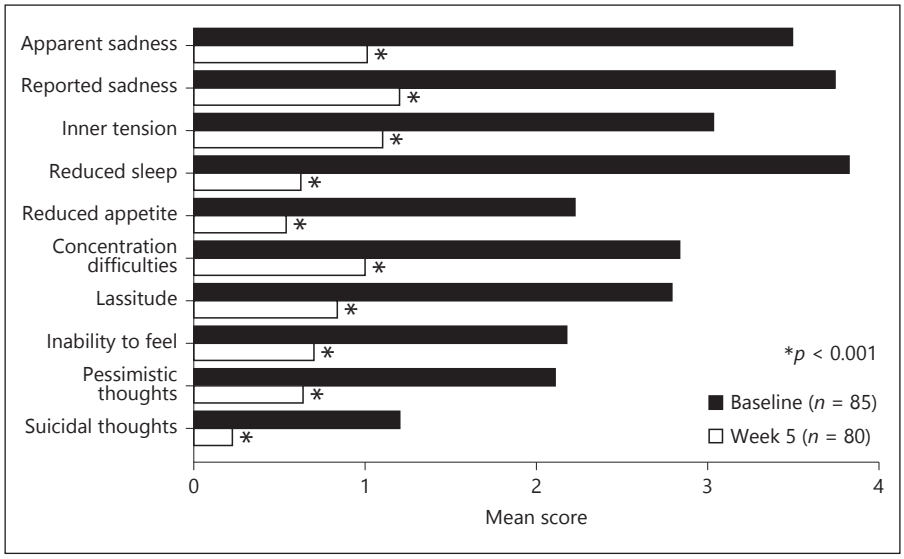

Fig. 2. MADRS individual item scores at baseline and week 5. *p* values are obtained from the comparison to the baseline score using the Wilcoxon test.

The incidence of individual ADRs at the end of titration (week 1) and at the end of acute treatment (week 5) is shown in Figure 3. After titration, fatigue (27.1%; 23 out of 85) and somnolence (22.4%, 19 out of 85) were reported most frequently. At the end of acute treatment, fatigue in 7.5% (6 out of 80) of patients and somnolence in 5.0% (4 out of 80) of patients were again the most frequently reported. Some patients experienced more than one ADR.

The intensity of the majority of the ADRs was rated by patients as low (Grade 1). Only headache and fatigue/somnolence were severe (Grade 3) in the patient assessments.

One patient discontinued the treatment after the titration phase for serious ADR (headache), and 3 patients discontinued after a further 4 weeks of treatment (2 patients due to a lack of efficacy and one for an unspecified reason).

In subjective verbal patient assessments after 5 weeks of treatment, the absence of ADRs was reported by 75%

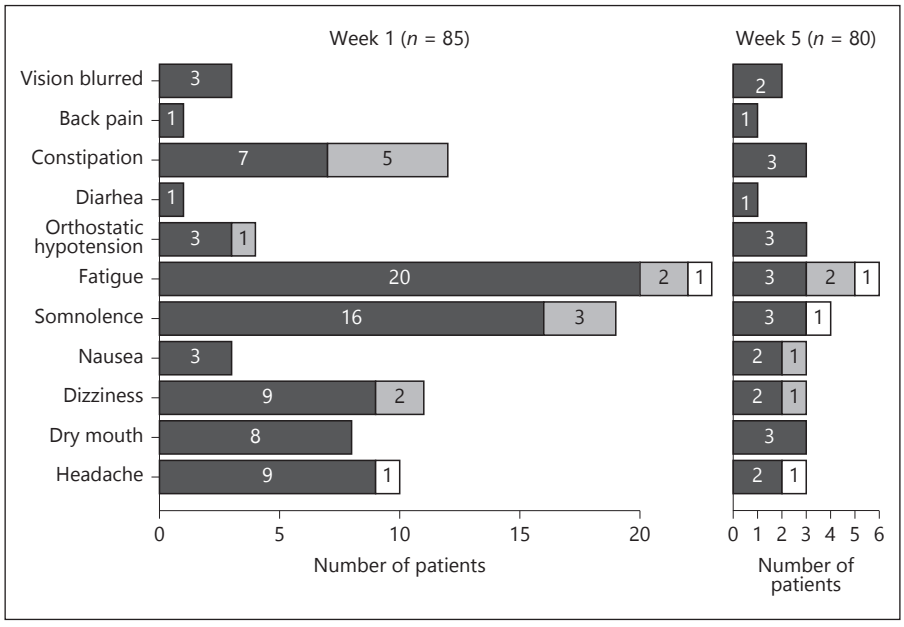

Fig. 3. Adverse drug reactions at weeks 1 and 5.

(60 out of 80) of patients; mild ADRs by 16.3% (13 out of 80), moderate ADRs by 6.3% (5 out of 80); and severe ADRs by 1.3% (1 out of 80). Investigator assessments reported 78.8% (63 out of 80), 17.5% (14 out of 80), 1.3% (1 out of 80), and 1.3% (1 out of 80), respectively.

Serious ADR, according to Good Pharmacovigilance Practice criteria, occurred only in one patient (headache) in the first week of treatment; after 4 weeks of treatment with the same dose, no other serious ADRs were reported.

Follow-Up Assessment and Concomitant Medication

Of the 80 patients, 78.8% (63) went for follow-up visits and were still taking trazodone after 1 month (week 9); 71.3% (57 out of 80 patients) after 3 more months (week 21). At week 9, the mental status was assessed by investigators as unchanged in 71.4% (45 out of 63) of patients. The remaining 28.6% (18 out of 63) of patients were further improved. At the follow-up visit after 3 more months (week 21), the mental status was assessed by investigators in 80.7% (46 out of 57) of patients as unchanged, and the remaining 19.3% (11 out of 57) of patients were further improved. No patient was rated as worsened.

The tolerability of treatment was assessed by investigators at week 9 as excellent in 88.9% (56 out of 63) and good in 11.1% (7 out of 63) of patients, and at week 21 as excellent in 94.7% (54 out of 57) and good in 5.3% (3 out of 57) of patients. No cases of bad tolerability were recorded at the follow-up visits in either of these weeks.

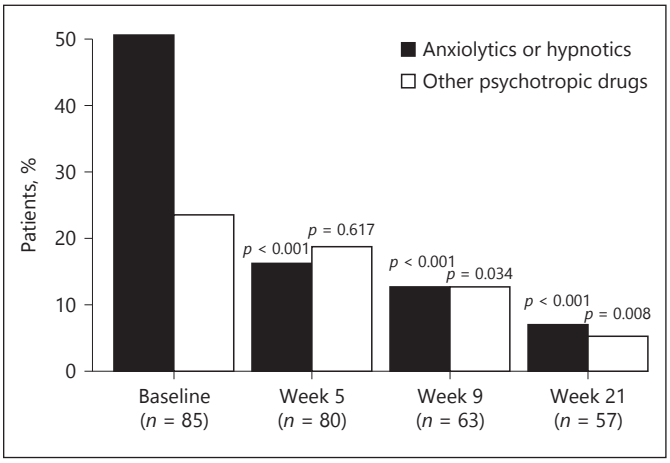

Fig. 4. Use of additional psychotropic drugs at baseline, week 5, and follow-up visits. *p* values are obtained from the comparison to the baseline score using McNemar's test.

There was a continuous reduction in the need for concomitant treatment. A significant discontinuation of anxiolytics, hypnotics, and other concomitant treatment relative to baseline was noted; see Figure 4.

Discussion

The study sample represents a classic clientele in psychiatric care, more often women older than 40 years of age. Two-thirds of the patients had been previously treated;

one-quarter of them was treated with other psychotropic drugs (another AD or antipsychotic drug) besides basic AD therapy. Their treatment was not clinically that successful; thus, the psychiatrist recommended a change to treatment with the new formulation of trazodone OAD. Half of the patients were also taking anxiolytics or hypnotics.

There are many studies with trazodone covering almost all aspects of safety and efficacy of this medication, including the recently published Chinese randomized placebo-controlled flexible-dose trial with prolonged-release trazodone [9] and Serbian non-interventional, open label post-marketing study with the same product [10]. However, there is only one controlled study published with the new one-daily formulation of trazodone [5]. Our study is the first open, observational study with this new formulation trazodone. This new formulation could be expected to have several advantages. At first, a rapid onset of action due the fact that minimal dose with antidepressive efficacy (150 mg in one dose) is administered from the beginning of the treatment, further a good tolerability due to the special pharmacokinetics (flat, sufficient high plasma levels without peaks responsible for side-effects) and finally, better adherence to treatment. The pharmacokinetics of the new drug formulation of trazodone (Trittico Prolong®) is more favorable than that of the older formulation (Trittico AC®), allowing an effective dose to be administered in one tablet once daily and thus potentially contributing to better patient compliance [11].

In this first observational real-world study, very positive effects were seen by the end of the titration period, that is, after the first week of trazodone treatment, when there was a significant decrease in the overall MADRS score. This is consistent with the randomized controlled trial in which a significantly greater decrease in the overall HAMD-17 score compared to placebo was reported within the first 7 days [5]. When analyzing the impact on individual depression symptoms using MADRS individual item scores, a significant reduction in all symptoms was observed during the acute treatment at week 5, among them sleep and anxiety were the most evident. In addition to the AD effect of trazodone, Sheehan et al. [5] emphasize its positive effect on sleep. Trittico Prolong® was well tolerated; most of the ADRs reported were mild or moderate in intensity and they quickly receded. By the end of acute treatment, the incidence of ADRs had decreased significantly. This is again in line with the above-mentioned trial, indicating a predominantly mild intensity of ADRs and their transient nature in most of the patients.

Unlike specific serotonin reuptake inhibitors (SSRIs), trazodone increases the noradrenergic transmission and does not affect the dopaminergic transmission [12]. Due to this indirect effect, it does not cause the flattened emotions described with SSRIs. The different ADR profiles (e.g., lower potential of sexual dysfunction) and anxiolytic and hypnotic effects may be more beneficial for a number of patients. Compared to other multimodal/multi-functional ADs (agomelatine, vortioxetine, and vilazodone), trazodone differs in its distinguished pharmacological profile and in the different spectra of ADRs. Its prescription is available for the first contact physician, which is an advantage over similar ADs available in the Czech Republic (e.g., agomelatine and vortioxetine). The cost surcharge covered by a patient in the Czech Republic is minimal; most of the cost is covered by health insurance. This is balanced by the fact that additional medication with hypnotics and anxiolytics, which is paid by the patient in outpatient care, is mostly unnecessary.

We are aware of the limitations of this study with regards to its sample size and design. On the contrary, in line with the current trend, this is the first observational, non-interventional study with trazodone in its new drug formulation that brings new real-world data that complement the data reported in randomized clinical trials.

As reported by this observational study, trazodone in its new once daily formulation was observed to have a very good effect in early (not yet treated) episodes in real clinical practice; hence, there is a possibility of first-line treatment. However, a good effect was also reported in depressive episodes not adequately responsive to previous AD therapy. This indicates the possibility of its use even in pharmacoresistant depressions [13]. Study in this respect is needed. Due to its pharmacodynamic profile, which is different from that of SSRI, SNRI, and NaSSA AD s, trazodone in the new drug formulation represents another possible individual approach to the pharmacotherapy of depressive patients. However, no studies comparing OAD with the older extended-release formulation have been performed.

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Disclosure Statement

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