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ORIGINAL ARTICLE

Efficacy and tolerability of trazodone retard monotherapy: results of the Serbian non-interventional study

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ABSTRACT

Objective: Trazodone is an effective antidepressant. The present study was designed as a non-interventional open-label, multi-centre, post-marketing study. The aim of the study was to evaluate the therapeutic effectiveness and tolerability of trazodone retard formulation (Trittico® retard) in everyday clinical practice.

Methods: Two hundred and forty-two patients with depressive disorder from 19 different centres were included in the study. The antidepressant and anxyolitic effects were assessed using Hamilton anxiety rating scale 14 items version, Hamilton depression rating scale 14 items version and Clinical Global Impression Severity scale.

Results: After only two weeks of therapy, a statistically significant improvement in the HAM-D score, was observed. This observation was maintained over the whole study period, up to the day 56.

Conclusions: Our study points toward clinical effectiveness of the prolonged-release formulation of trazodone in the treatment of unselected depressed patients in real-world practice.

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Introduction

Depression is a serious, debilitating illness that affects persons of all ages, races and socioeconomic backgrounds. Depression and stress-related mood disorders impact approximately 17% of the population in Europe and the USA during their lifetime. A recent consensus document by the European Brain Council estimated the annual cost of mood disorders at 106 billion EUR, with a prevalence of 21 million people across 28 European countries. The neurobiology underlying depression has not yet been fully identified. Currently available antidepressants, although widely prescribed for depression and other mood and anxiety-related illnesses, have significant limitations, including a long time lag for a therapeutic response and troublesome side effects.

Almost all known antidepressants block the reuptake of the monoamines 5-hydroxytryptamine (5-HT or serotonin) and norepinephrine. Trazodone is an effective antidepressant structurally unrelated to the TCAs, SSRIs or MAOs antidepressants (Andrews & Nemeroff 1994). It was the first antidepressant available that was not lethal in overdose, unless the patient also consumed considerable quantities of alcohol.

Trazodone was introduced into clinical practice almost 40 years ago as the first triazolopyridine derivative to be developed as an antidepressant. Its development was the result of a disease-oriented research approach, first described as the so-called 'mental pain hypothesis of depression' by Silvestrini (1986). Clinical trials in the 1980s made trazodone the most widely prescribed antidepressant in the USA (Burke & Preskorn 1995), which was mainly due to its good tolerability and safety profile over short- and long-term treatment, especially in the elderly (Gershon 1984), along with its hypnotic properties (Mouret et al. 1988). However, surprisingly few studies with trazodone controlled released formulation (trazodone retard) were published (Saletu-Zyhlarz et al. 2003).

Trazodone is a good example of a dose dependent multifunctional drug in psychopharmacology. Low doses act only via its most potent binding properties, but higher doses acquire additional pharmacologic actions and become 'multifunctional' with a mixture of pharmacologic functions, depending on a given dose. Trazodone's most potent binding property is 5-HT2A antagonism. Moreover, it has significant serotonin reuptake transporter protein (SERT) blocking ability. Since both of these actions are considered necessary for antidepressant efficacy, trazodone's multifunctional actions are categorised as 'serotonin antagonist-reuptake inhibition' (SARI).

Trazodone is safe in overdose and has a mild side effect profile, with sedation as the most common side effect. Sleep electroencephalogram and clinical studies have shown trazodone to be effective in improving sleep in normal subjects, insomniac patients and patients with major depression. Tolerance and rapid eye movement rebound on discontinuation do not occur. The most common dosage regime for trazodone is 150 mg daily, increased if needed up to 200–300 mg for full antidepressant efficacy (Fabre 1990). The drug is given predominantly at bedtime.

Patients and methods

Study design

The present study was designed as a non-interventional, open-label, multi-centre, post-marketing surveillance. Our aim was to evaluate the therapeutic effectiveness, tolerability and safety of standard therapeutic doses of trazodone retard formulation (Trittico® retard) in patients with major depression in daily routine practice. We investigated drug's effects as a monotherapy in subjects with depressive symptoms. This model was chosen since it best resembles the way this drug is used in everyday clinical

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practice. While randomised, controlled clinical trials are the regulatory standard these studies often are designed with numerous controls that may limit the ability to answer questions related to the everyday, real-world situations. Moreover, non-interventional studies give the opportunity to evaluate the effects and especially the tolerability of drugs in a large population without selection under daily practice conditions, including patients with co-morbidities and combination therapies. Finally, studying the use of a drug in a real-world setting can yield insights into costs, optimum co-therapies and medical best practices that are not available through clinical trials. So, unlike most previous trials (i.e., double blind, parallel group, randomised trials), our trial was conducted under real-world conditions.

Patient selection

This non-interventional trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Local ethics committees as well as the Serbian authorities approved the study design and eligible patients gave their written informed consent before participating.

This prospective eight-week observational, non-interventional, open-label study was carried out in 19 psychiatric in and outpatient departments between March 2009 and January 2010 in Serbia. The study included 242 adult patients with the diagnosis of major depression with first manifestation or recurrent episode. Depressive episode had to be without psychotic features. Furthermore, subjects had to have a primary diagnosis of depression according to ICD-10. Depressive symptoms had to be present for at least one month before starting the treatment with Trittico® retard. Although we are aware that both diagnostic systems (ICD and DSM) accept duration of depression for two weeks in order to make diagnosis of depression, we wanted to include patients with depression as clear as it would be possible (i.e., exclusion of borderline depressive patients with duration of depression of two weeks). Moreover, having in mind that in real-world settings most of depressive patients came to treatment after several weeks of illness we wanted to include these patients. Additionally, minimum Hamilton Psychiatric Rating Scale (HAM-D 17) score had to be 16 (maximal value is 52) in order to include the particular patient in the study. Minimum screening and baseline scores on the Clinical Global Impressions-Severity scale (CGI-S) of 4 or 5 for outpatient subjects and 4, 5 or 6 for hospitalised subjects, were also required. The recommended dosage of trazodone, according to the product, information was 50 mg initially. The dose of the study medication was gradually increased to maximum dose of 150 mg daily.

Patients were excluded if they had any current psychiatric disorder other than depressive disorder as defined in the ICD-10, or a current or past history of a manic or hypomanic episode, schizophrenia or any other psychotic disorder, mental retardation, organic mental disorders or mental disorders due to a general medical condition, any current diagnosis of substance abuse or dependence, the presence or history of a clinically significant neurological disorder, or any neurodegenerative disorder that might compromise their participation in the study. Patients at serious risk of suicide, on the basis of the investigator's clinical judgment, were excluded, as were those receiving psychotherapy, those with current depressive symptoms considered by the investigator to have been resistant to two adequate antidepressant treatments of at least six-week duration.

Patients were also excluded if they had a clinically significant unstable illness, history of cancer in remission for less than five years, clinically significant abnormal vital signs as determined by the investigator.

Excluded from the study were all female subjects who were either pregnant or breast feeding and patients who had known hypersensitivity to any substance contained in Trittico® retard tablets. Also, use of any antidepressant within one week prior to starting the treatment with Trittico® retard, or prior treatment with the study medicine, was considered to be an exclusion criterion. No concomitant psychiatric medications were allowed during the study. In fact the only concomitant medications that were allowed were medications for concomitant somatic disorders which had to be at stable dosing regimen for more than one month prior study. The previous psychiatric medications had to be stopped one or two weeks before study. Moreover, psychoactive herbal remedies, any drug used for augmentation of antidepressant action or any other antidepressant drugs, oral antipsychotic and antimanic drugs, or dopamine antagonists, any anxiolytics (including benzodiazepines) and any anticonvulsant drug, serotonergic agonists, narcotic analgesics or cough agents were prohibited for one or two weeks before study (depending on their halflife) and during the study. Occasional use of zolpidem for severe insomnia was allowed for a maximum of 2 days/week, but not the night before a study visit.

Study procedures

The observation period for each patient was eight weeks. Over the study period, data collection was performed at four visits, i.e., on days 0, 14, 28 and 56.

All relevant data, including precise assessment of psychiatric disorder and demographic characteristics of each subject were recorded at the screening visit. This included age, sex, height, weight, medical history of depression (first occurrence of symptoms, number of depressive episodes in the past, duration of disease, previous and/or current antidepressant or other treatment, hospitalisations due to depression, suicidal attempts), neuropsychiatric or somatic comorbidities, psychotropic or other co-medications.

During the study period of eight weeks, participants were required to come to the clinic four times for symptoms assessments. This included rating scales for depression and anxiety, sleep disturbances, adverse events and global clinical impression. During this period Trittico® retard was administered as a monotherapy, once daily, in the evening, after the meal, according to the following scheme:

Day 1 to 3 = 50 mg in the evening;

Day 4 to 6 = 100 mg in the evening and

Day 7 to 14 = 150 mg in the evening.

However, the investigator had the option of increasing the dose after day 14 of the study. If by day 14 of the study the HAM-D score had decreased as compared to the baseline value, the study medication dose remained unchanged, i.e., 150 mg daily. However, if by the 14th day of the study the HAM-D score had increased or remained unchanged vs. baseline, then the Trittico® retard dose could be increased to 300 mg/day.

For assessment of the evolution of depressive symptoms HAM-D 17 (Hamilton depression rating scale 17 items version) and the Clinical Global Impression of Improvement Scale (CGI-I) were used at V2, V3 and V4. Furthermore, the CGI-S was applied to check the severity of depression at all visits. Anxiety was assessed using HAM-A 14 scales (Hamilton anxiety rating scale 14 items version).

The CGI scale was also employed to evaluate several additional parameters such as patient's assessment of the therapeutic effect (five-point scale) and severity and frequency of adverse events (four-point scale). All unused study medication was returned at

each visit, and compliance to the study medication was assessed from unused containers and blisters.

Safety and tolerability of trazodone were assessed by means of standardised documentation of adverse drug reactions (i.e., at each visit, all adverse events, both spontaneously reported by patients and those following active questioning, were recorded), reasons for premature discontinuation and by global assessment of tolerability by the physician.

Statistical analysis

Statistical tests were interpreted at a 5% significance level (two-tailed). Efficacy analysis was performed on the Intention-To-Treat population (ITT). The ITT population was defined as all included patients who had the baseline assessment, at least one dose of the study medication and at least one post-baseline efficacy assessment. Missing values were replaced by the Last Observation Carried Forward (LOCF) value. Mean changes from the baseline in HAM-D and HAM-A were compared over the study period using Student's *t*-test, while other nonparametric methods (Mann–Whitney's and Cochran's) were used in the evaluation of changes in CGI parameters.

Results

Demographic data

Over the study period, patients were treated in 19 different centres. Altogether 242 patients were included in the study, consisting of 76 (31.40%) men and 166 (68.60%) women. On average, the men weighed significantly more than the women (considering BMI; $p < 0.001$) and had significantly lower HAM-A score values ($p = 0.040$). In accordance with this is also the fact that the women had relatively more hospitalisations (not statistically significant) than the men and more often than the men were hospitalised rather than treated in ambulatory care (statistically significant at $p = 0.05$). Two hundred and thirty-nine patients completed the eight-week trial. In only three patients trazodone was discontinued. Reasons for discontinuation were different (i.e., one patient felt interpretative, another had severe nausea and one had severe sedation).

The mean age of the participants was 48.62 years and more than one quarter of patients (25.62%) were 50–54 years old, with high percentages also in the groups from 55 to 59 years of age (16.53%), 45 to 49 (13.64%) and 40 to 44 years of age (11.57%).

Most of the patients were treated ambulatory (71.78%) and had their diagnosis already previously established (61.41%). The mean illness duration among the patients in the study was approximately 4 years and nine months.

According to the ICD-10, most of the patients included in the study (92.49%) had either a depressive episode (F32; 47.07%) or recurrent depressive disorder (F33, 45.42%), with only a small proportion having other diagnoses such as F38 (other mood disorder) and F41.2 (mixed anxiety and depressive disorder). Finally according to actual DSM-5 criteria 170 patients had melancholic specifier, 34 anxious and 20 atypical specifiers. None of patients had neither mixed nor psychotic features.

HAM-D score

Results presented in Tables 1 and 2 show a steady decrease in HAM-D score, in points (Table 1) and as % decrease (Table 2) over the study period. Confidence intervals for each assessment point are suggestive of a remarkable coherence of the effects observed. The study population was coherent at the baseline and remained so over the whole study period. *p* Values in the table show the tendency to be of high statistical significance. All *p* values are results of *t*-test comparison of one assessment point with the previous one.

After only two weeks of therapy, the result is the statistically significant improvement in the key study parameter, the HAM-D score. Also, this tendency is maintained over the whole study period, up to the day 56. The cumulative improvement in the HAM-D score over the study period was 63.48%.

HAM-A score

Concurrent to the HAM-D score decrease, the decline in HAM-A scores over the study period was steady. Again, the narrow confidence intervals and median values close to mean scores, show a study population which was coherent at baseline and remained over the whole study period (Table 3). In addition, all three *p* values shown are considerably below the 0.05 threshold, marking changes in HAM-A score as statistically significant.

Comparable to the reduction of the HAM-D scores at the end of the study period, the cumulative improvement of the HAM-A score (Table 4) is remarkably similar to the overall improvement percentage for HAM-D score (63.89% vs. 63.48%, respectively).

Clinical global impression parameters

Since the variables that make up the CGI were assessed on a verbal rating scale, percentages of patients in each category were calculated and displayed for each study visit, rather than calculating mean values. A reduction of the Severity of Disease parameter was observed relatively early and continued during the study period (Table 5).

Table 1. HAM-D score changes over the study period.

Day	Mean	−95% CI	+95% CI	p^a
0	23.74	23.15	24.33	–
14	17.32	16.59	18.06	<0.001
28	12.40	11.68	13.12	<0.001
56	8.67	8.02	9.32	<0.001

[a]Compared to the previous assessment.

Table 2. HAM-D score improvement in %, over the study period.

Day	Mean	−95% CI	+95% CI
0–14	27.52	25.34	29.69
14–28	28.67	25.82	31.53
28–56	28.13	24.77	31.49
Over the Study Period	63.48	60.89	66.07

Table 3. HAM-A score changes over the study period.

Day	Mean	−95% CI	+95% CI	p^a
0	24.18	23.39	24.97	–
14	17.93	17.11	18.76	<0.001
28	12.75	11.91	13.59	<0.001
56	8.58	7.86	9.30	<0.001

[a]Compared to the previous assessment.

Table 4. HAM-A score improvement in %, over the study period.

Day	Mean	−95% CI	+95% CI
0–14	26.22	23.91	28.53
14–28	29.83	26.72	32.94
28–56	31.03	27.65	34.41
Over the study period	63.89	61.04	66.75

Consistent with the data in Table 5, a high percentage of patients (87.33%) achieved respectable improvement levels already on day 14 of the study. This percentage slowly, but steadily raised to a level of 94.31% at the end of week 8 (Table 6).

When another two CGI parameters are analysed, i.e., therapeutic effect according to both investigators and patients, a similar trend is seen. Percentages of patients with a therapeutic effect score of 4 (moderate improvement), or 5 (exceptional improvement), are shown in Table 7. According to the investigators, approximately half of the patients (47.16%) had this status on day 14, which increased to 80.09% on day 28 and 91% on day 56. Patients had somewhat lower estimations of this effect, nonetheless more than two-fifths of participants belonged to this group at day 14, with as much as 84.06% at day 56.

Responders

According to the study protocol, subjects achieving $\geq$50% reduction in HAM-D and/or HAM-A score at the end of 8 weeks of treatment (as compared to the baseline), were to be considered *responders*. Hence, subjects with unchanged or increased HAM-D or HAM-A score or improvement in these scores below 50% of the baseline value at the end of eight week treatment, were considered *non responders*.

As mentioned above, the study protocol defined that a responder was a patient who achieved at least 50% improvement in either HAM-D or HAM-A score at the end of the study. However, due to the favourable response of patients to the study medication it was possible to calculate the responder to non-responder ratio as early as day 14 of the study. Patients showed exactly the same percentage of responders according to both scales (11.80%) on day 14, after which time point percentage of responders according to HAM-D scale is slightly higher than the one according to HAM-A scale. Percentage of responders according to HAM-D and HAM-A scales are shown in Tables 8 and 9.

Different dosage regimens

The results discussed so far are the results obtained for the whole study population (ITT, intention to treat dataset). However, there is an additional interesting patient subgroup in this study. If on day 14 (first post-baseline assessment) HAM-D score increased or remained unchanged compared to the baseline, the dose could be increased to 300 mg daily. The higher dose was given to 54 patients, while 185 patients remained on the 150 mg daily dose. Therefore, two groups of patients can be compared; 54 patients with an increased drug dosage after day 14 of the study and 185 patients with no dosage change.

After the first 14 days of the study, while all patients were still receiving the same dose of trazodone, the above-mentioned subgroup of 54 patients clearly showed a statistically significant ($p< 0.001$) lower response to therapy. This lower response can be seen on both HAM-D and HAM-A scores (Table 10, row 'Day 0 to Day 14'). At this time point, the patients with lower response rates started to receive a higher dose of the study drug. However after the next 14-day period, the difference between the two groups is still statistically significant, but with some new elements worth considering. First, the improvement in the patient group treated with initial dose of 150 mg remained very similar over the second 14-day period. However, in patients who were not responding adequately to the initial 150 mg dose and started with the higher dose on day 14, improvements for HAM-D score rose from 18.01% over the first 14 days to 23.09% over the next 14 days. Same is true for increase in HAM-A score, which rose from 15.35% to 23.03%. Also, p values comparing the two treatment groups start to rise and become closer to the non-significant threshold of 0.05.

After the additional 28-day time period, the patients treated with 300 mg started to show similar improvement percentages as the patients who were responding well from the start of the therapy. p values show that at this time point (between day 28 and day 56), there is no statistically significant difference between the two treatment schedules ($p= 0.919$ and $p= 0.482$ for HAM-D and HAM-A improvement, respectively). The difference over the whole study period remains significant, because of the high contribution of the first two 14-day periods to the overall result.

Safety – number of adverse events

In total, 52 patients included in this study (21.49% of all participants) experienced adverse events over the study period. The highest number of simultaneous adverse events was observed on day 14 of the study, with 42 patients experiencing adverse event at this assessment point. On day 28 of the study, only 16 patients reported an adverse event. This number decreased further, on day 56 of the study, only seven patients reported adverse events (Figure 1).

Both proportions, i.e., 52 patients or 21.49% of study population experiencing AEs at any given time over the study period, and maximum of 42 patients experiencing adverse events simultaneously, are consistent with the number of adverse events observed

Table 5. Severity of disease percentage of patients with severity of disease 3 (mild) or less.

Day	*N*	%
0	4	1.65
14	61	26.63
28	145	67.13
56	180	85.31

Table 6. Overall improvement percentage of patients with overall improvement 3 (slight) or more.

Day	*N*	%
14	200	87.33
28	206	95.37
56	199	94.31

Table 7. Therapeutic effect percentage of patients with therapeutic effect 4 (moderately improved) or more.

	Investigator's assessment		Patient's assessment	
Day	*N*	%	*N*	%
14	108	47.16	91	40.44
28	173	80.09	153	72.17
56	192	91.00	174	84.06

Table 8. Responders according to HAM-D scale.

Time point	% Responders	% Non-responders
Day 14	11.80	88.20
Day 28	50.46	49.54
Day 56	84.36	15.64

Table 9. Responders according to HAM-A scale.

Time point	% Responders	% Non-responders
Day 14	11.80	88.20
Day 28	48.61	51.39
Day 56	81.04	18.96

Table 10. HAMD and HAMA score improvement in % by study drug dose, after day 14.

	Study period	Mean improvement in % dose <300 mg	Mean improvement in % dose =300 mg	*p*
HAM-D improvement	0–14	30.45	18.01	<0.001
	14–28	30.49	23.09	0.027
	28–56	28.23	27.82	0.919
	Over the study period	66.59	53.72	<0.001
HAM-A improvement	0–14	29.57	15.35	<0.001
	14–28	32.04	23.03	0.014
	28–56	31.71	28.90	0.482
	Over the study period	67.38	52.94	<0.001

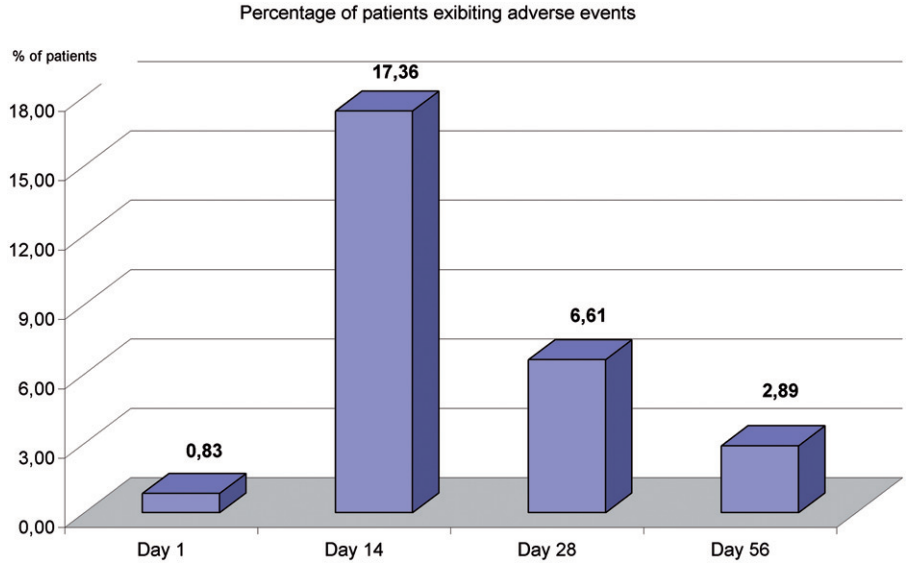

Figure 1. Percentage of patients exhibiting adverse events.

in other clinical trials (Fink et al. 2003). For example, in a study with similar design, Saletu-Zyhlarz et al. (Saletu-Zyhlarz et al. 2003) side effects were reported by 16.9% of patients after two weeks and only by 7.6% of the patients after six weeks of treatment with trazodone retard. Of note in this study 66% of 519 patients remained on 150 mg dose. In our study, the majority of patients (77.4%) remained on 150 mg dose. Having in mind that lower dose is associated with lower incidence of adverse events this could explain low incidence of side effects in our study. Some patients had more than one adverse event so that complete number of adverse events reported in the study was 73. Mean duration of an 'average' adverse event in this study was 11.25 days.

In detail, after two weeks of therapy sedation was reported by twelve, nausea by seven, headache by six, morning tiredness by six, vertigo by four patients and dry mouth and lowered blood pressure by two patients each. Other side effects were reported by thirteen patients. After eight weeks of treatment, headache was reported by three patients, nausea by two, and dry mouth, insomnia and heavy legs by one patient each. According to investigators, 62.12% of all adverse events were rated as mild, 28.9% were rated as moderate and 4.5% were rated either as severe (vertigo and nausea) or other (i.e., moderate/severe – agitation and headache) (Figure 2).

The most frequent side effects were headache (15 cases – 6.2% of patients), sedation with sleepiness (15 – 6.2% of patients) and nausea (10 – 4.13% of patients). All adverse events were spontaneously and completely recovered.

Discussion and conclusions

There are many studies with trazodone. We found a wide range of papers covering almost all aspects of safety and efficacy of this medication. The first controlled clinical study is from the year 1970 (De Gregorio & Dionisio 1971), while more recent studies cover different aspects of trazodone's possible or established effects. In the past 10 years, different effects of trazodone have been investigated. This included studies in disorders such as tinnitus (Dib et al. 2007), frontotemporal dementia (Kessler et al. 2007), Alzheimer's disease (Lopez-Pousa et al. 2008), migraine (Damen et al. 2006), chronic pain (Miller & Rabe-Jabłońska 2005) (including also the burning mouth pain (Tammiala-Salonen & Forssell 1999), agitation (Martinon-Torres et al. 2004), PTSD (Asnis et al. 2004), bulimia nervosa (Bacaltchuk & Hay 2003), alcohol (Le Bon et al. 2003) and benzodiazepine post-withdrawal syndromes (Rickels et al. 1999), generalised anxiety disorder (Kapczinski et al. 2003), analgesia (Lynch 2001), erectile dysfunction (Enzlin et al. 2000) combination of late-life chronic schizophrenia and tardive dyskinesia (Hayashi 1997).

However, depression and insomnia continue to be the two main diseases for which this drug is used. The last two randomised, double-blind comparative studies comparing trazodone to either paroxetine or sertraline (Kasper et al. 2005; Munizza et al. 2006) confirmed fully the efficacy of trazodone in the main indication. Authors concluded that after six weeks, trazodone, paroxetine and sertraline were not different in reducing symptoms of depression and in obtaining disease remission. Also, according to the same authors, trazodone is a valid therapeutic option in the treatment of patients with major depression, especially if they also show prevalent sleep disturbances.

Similar conclusions were drawn in a recent meta-analysis of clinical trials comparing trazodone to a whole range of SSRIs (Papakostas & Fava 2007), as well as in a study comparing it to venlafaxine (Florkowski et al. 2005).

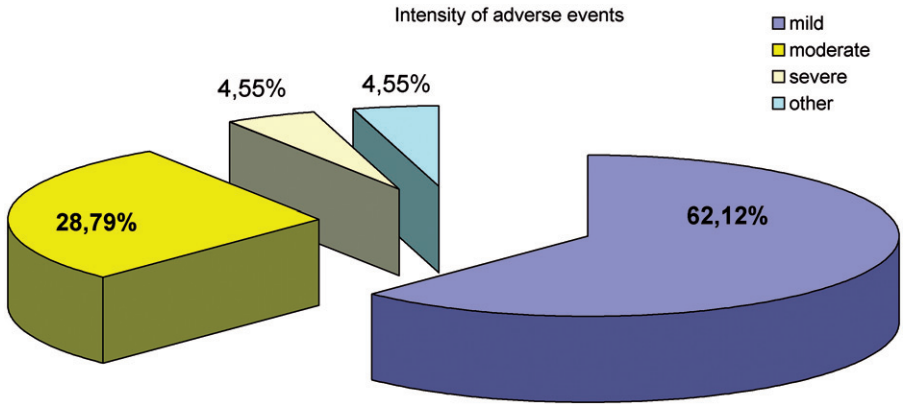

Figure 2. Intensity of adverse events.

Currently there is no reason to conduct another comparative or confirmatory study with trazodone hydrochloride. Rather, the aim of this study was to assess, as precisely as possible, the effectiveness and tolerability of the prolonged-release formulation of this drug as monotherapy in everyday clinical practice. Therefore, the study was designed as an open-label, multi-centre, post-marketing surveillance, examining a total number of 242 patients in order to assess effectiveness and tolerability of Trittico® retard (trazodone hydrochloride) treatment. Patients with diagnosis of MDD (Major depressive disorder), based on the ICD-10 criteria were included. The inclusion criteria stated that depressive symptoms had to be present for a minimum of one month prior to the study inclusion. Additionally, patients had to have minimum screening/baseline total score of 16 on the Hamilton Psychiatric Rating Scale for depression (HAM-D 17).

The study medication was administered as monotherapy at increasing doses, defined by the protocol. The initial dose was 50 mg daily over the first three days of the study, followed by 100 mg daily over the next 3 days and 150 mg daily from day 7 to day 14 of the study. After this period, the investigators had the choice of leaving each patient on the previous dose of 150 mg. However, if their HAM-D score remained the same or increased over the first two weeks of the study, the dose could be raised to 300 mg daily. This left us with possibility of comparing two dosage groups: higher and lower after day 14 of the study.

Due to the study design, our results i.e., significant reduction of HAM-D and HAM-A scores, may be interpreted as a sign of the effectiveness of both trazodone and psychiatric care in the real-world situation. This means that without control group it is not possible to attribute beneficial effects solely to trazodone. In this regard, our study resembles more to so-called effectiveness studies in wider clinical practice. However, while the use of a placebo-controlled, randomised controlled trials remains the most important method for establishing treatment efficacy of antidepressants, the final conclusion regarding the value of treatment can only be drawn from its use in routine clinical practice (Baghai et al. 2011). Moreover, there seems to be a generally promising trend of 'real-world' studies showing better results than randomised controlled trials (Kasper et al. 2014). However, this should not be confused with causality unless tested.

Finally, similar to our results, in two recently published studies (Kasper et al. 2005; Munizza et al. 2006) a proportion of patients benefited from the increase of the daily dose of trazodone up to 450 mg. In our opinion, a dose titration related to the early outcome of the HAM-D and HAM-A scores change, should be seriously considered prior to therapy augmentation or decision to change therapy.

Study weakness

Generally speaking, studies without placebo arm have several problems. First one can argue that reduction of symptoms simply can be explained by the reduction to the mean. However, having in mind magnitude of symptom reduction, it is hard to support this explanation. Similarly, absence of placebo arm, makes the results of positive effect of dosage increase, in subgroup of patients with low response, highly vulnerable, for the same explanation (regression to mean), since subjects who do not respond initially are more likely to show a relatively larger response during follow up. Finally concerning adverse events reader should keep in mind relative small amount of included patients (242 patients). Simply the lower the true probability of an event the, less exact the estimated incidence will be, given the limited sample size. Clearly, large numbers are needed to obtain stable estimates of these probabilities that are needed to inform clinical practice.

Key points

- The aim of the study was to evaluate the effectiveness and tolerability of monotherapy of standard therapeutic doses of trazodone hydrochloride retard formulation (Trittico® retard).
- Our study included 242 patients with depressive disorder.
- The results show that statistically significant improvement in HAM-D and HAM-A score as early as second week of treatment. This observation was maintained over the whole study period, up to the day 56.
- Our results points toward the effectiveness and tolerability of trazodone hydrochloride retard formulation (Trittico® retard) in treating depression in real-world clinical practice settings.

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Disclosure statement

None to declare.

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