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TED (Trazodone Effectiveness in Depression): effectiveness of trazodone extended-release in subjects with unsatisfactory response to SSRIs

Marcin Siwek[1], Adrian Chrobak[2], Anna Julia Krupa[1], Aleksandra Gorostowicz[2], Adrian Gerlich[3], Andrzej Juryk[1], Dominika Dudek[2]

[1] Department of Affective Disorders, Department of Psychiatry, Jagiellonian University Medical College

[2] Department of Adult Psychiatry, Jagiellonian University Medical College

[3] Department of Adult, Child and Adolescent Psychiatry, University Hospital in Cracow

Summary

Aim. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used drugs to treat major depressive disorder (MDD). However, about 50% of MDD patients do not achieve treatment response to SSRIs and there is little evidence on which drugs are effective as second-line treatment in those who do not respond to SSRIs.

Method. In this work, the data of 79 patients with MDD were analyzed to evaluate the effectiveness of trazodone XR in the group of individuals treated de novo and those switched to trazodone XR after failed treatment attempt with SSRIs. The assessments were performed at baseline and weeks 2, 4, 8 and 12 using tools to evaluate the degree of: depression (Montgomery-Åsberg Depression Rating Scale, clinician- and patient-rated Quick Inventory of Depressive Symptomatology – the primary endpoints of the study), therapeutic effectiveness (Clinical Global Impression Scale), anhedonia (Snaith-Hamilton Pleasure Scale), anxiety (Hamilton Anxiety Rating Scale), insomnia (Athens Insomnia Scale), psychosocial functioning (Sheehan Disability Scale) and sexual functioning (Female Sexual Function Inventory in women/International Index of Erectile Function in men).

Results. The rates of treatment response and remission were largely similar in both studied groups.

Conclusions. The results showed that effectiveness of trazodone XR in the treatment of patients with MDD who did not respond to SSRIs administered as first-line treatment of a particular depressive episode was comparable to that noted in patients treated de novo. Furthermore, trazodone XR effectively improved depression, anxiety, insomnia, anhedonia and psychosocial functioning in both studied groups. Additionally, trazodone XR as second-line treatment improved sexual functions in male subjects previously treated with SSRIs.

Key words: major depression, SSRI, trazodone

Introduction

Despite decades of drug development and the ever expanding range of available antidepressants in recent years, the issue of insufficient effectiveness of antidepressant drugs in the treatment of major depressive disorder (MDD) remains. At present, the majority of clinicians use selective serotonin reuptake inhibitors (SSRIs) as the first choice for MDD treatment and the majority of current MDD treatment guidelines encourage SSRIs as first-line therapy [1–3]. Understandably so, as SSRIs are largely effective in reducing the severity of depressive symptoms. However, similarly as in the case of other antidepressants used as first-line treatment, about one half of depressed individuals achieve no or only partial treatment response to SSRIs and only one third of them achieve remission [4, 5]. Yet the evidence and guidelines on the treatment of MDD in the case of lack of/inadequate response to SSRIs is scant. The available clinical recommendations on the second-line pharmacotherapy of MDD do not distinguish between particular antidepressants or antidepressant classes which failed but rather suggest a switch to an antidepressant with a different mechanism of action [5]. Several second-line monotherapies have shown efficacy in MDD patients with no/inadequate response to SSRIs, that is: switch to sertraline, venlafaxine [4], vortioxetine or agomelatine [6–8], reboxetine [9], and bupropion [10].

It is vital that more evidence is gathered which could inform clinical practice on the choice of antidepressant after failed SSRI treatment because as it was shown, the rates of treatment response and remission drop with each subsequent treatment attempt [4]. Furthermore, several issues are related to SSRI treatment. Firstly, SSRIs have limited efficacy in improving hedonic tone and might induce emotional blunting. This might thwart the achievement of recovery as it was shown that anhedonia and emotional blunting mediate the improvement of depression as well as general functioning and quality of life [11]. Secondly, while sexual dysfunctions affect around 50% of individuals with MDD, they might be aggravated by SSRIs, thereby negatively impacting the quality of patients' life and posing a risk of nonadherence [12]. Thirdly, in genetically predisposed subsets of MDD patients, SSRIs are ineffective in alleviating insomnia related to MDD and might exacerbate it [13]. Therefore, a search for therapeutic alternatives for patients who do not achieve satisfactory treatment results with SSRIs in warranted.

Trazodone is a versatile drug which presents various pharmacodynamic actions depending on the administered dose and is available in several formulations: immediate-release (IR), controlled-release (CR), and extended-release (XR), [which is also referred to as Contramid®/once-daily (OAD)]. The XR formulation seems most suitable for MDD treatment as the dosing regimen (once vs. thrice a day in the case of IR) and higher tolerance (due to lower peak plasma concentration which translates to

lower likelihood of adverse effects) are likely to promote adherence. It is classified as a serotonin receptor antagonist and reuptake inhibitor (SARI). A clinically significant occupation of the serotonin transporter (SERT) which exerts antidepressant effects is noted with doses of 150-600 mg/d. Trazodone is also an antagonist of 5HT2 A/C which prevents the restriction of noradrenergic and dopaminergic transmission in the prefrontal cortex due to increased serotonin stimulation, which is thought to be the mechanism explaining the emotional blunting and limited efficacy of SSRIs in alleviating anhedonia. Moreover, the blockade of 5HT2 A/C may prevent or limit the severity and risk of sexual dysfunction induced by serotonin reuptake blockade and together with H1 and α1 adrenoreceptor antagonism facilitates the sleep promoting and anxiolytic activity of trazodone [14–16]. As shown in a pilot analysis of this study, trazodone XR has shown good antidepressant effectiveness in MDD, not only in the reduction of depression symptom severity but also improvement of anhedonia, sexual functions, sleep and general functioning [17].

The aim of this work was to assess the effectiveness of trazodone XR in multiple symptomatic dimensions in patients with MDD receiving it as a first-line treatment in comparison to subjects switched to trazodone XR after failing to achieve satisfactory response to first-line treatment with SSRIs.

Method

This analysis included data from 1) patients treated with trazodone XR de novo ($n = 42$) in the first phase of the TED – Trazodone Effectiveness in Depression study, a 12-week naturalistic observation of trazodone XR vs. SSRI effectiveness in MDD (precise methodology described in [17], and 2) patients with unsatisfactory response to SSRI treatment in the first phase of the TED study, who were switched to trazodone XR in the second 12-week naturalistic observation phase of the TED study ($n = 37$). Patients treated with SSRIs received: sertraline (dose of 50–200 mg/d), citalopram (dose of 20–40 mg/d), escitalopram (dose of 10–20 mg/d), and paroxetine (dose of 20–60 mg/d) in monotherapy for 12 weeks; the SSRI doses were adjusted by the attending physician in accordance to the patient's needs.

In the second phase of the TED study, patients with unsatisfactory response to SSRIs were switched to trazodone XR. Subjects were assessed in 5 time points: upon entrance to the study and after 2, 4, 8 and 12 weeks. Similarly to the first phase of the study, evaluations included:

- scales to measure depression severity: Montgomery–Åsberg Depression Rating Scale (MADRS); Quick Inventory of Depressive Symptomatology (QIDS)—clinician-rated (CR) and self-rated (SR),
- scale to assess anxiety: Hamilton Anxiety Rating Scale (HAM-A),
- tool to evaluate the level of anhedonia: Snaith–Hamilton Pleasure Scale (SHAPS),

- questionnaire to assess psychosocial functioning: Sheehan Disability Scale (SDS),
- scale to measure the severity of insomnia: Athens Insomnia Scale (AIS),
- inventories to asses sexual functioning: Female Sexual Function Inventory (FSFI) for women and International Index of Erectile Function (IIEF) for men,
- tool to evaluate the severity of symptoms and the treatment response: Clinical Global Impression Scale (CGI).

Description of the questionnaires:

- MADRS is a clinician-rated tool which was developed to assess the severity of depression in MDD patients and detect change resulting from antidepressant treatment. MADRS measures: apparent and reported sadness, inner tension, reduced sleep and appetite, concentration difficulties, lassitude, inability to feel, pessimistic and suicidal thoughts. Each of the 10 items is scored 0-6 (total score 0-60) with higher results indicating higher severity of the symptoms [18].
- QIDS is available in clinician- and patient-rated versions. QIDS was constructed to measure the symptoms of MDD focusing on the frequency more so than on the severity of symptoms. QIDS items assess: sad mood, poor concentration, self-criticism, suicidal ideation, anhedonia, energy/fatigue, sleep disturbance, decrease/increase in appetite/weight, and psychomotor agitation/retardation and are sensitive to change due to antidepressant treatment. All 9 items are scored 0-3 (total score 0-27) with higher results signifying higher severity of depression [19].
- HAM-A is a clinician-rated scale which was created to measure anxiety and is widely used in clinical trials. HAM-A assesses: anxious mood, tension, fears, insomnia, cognitive problems, depressed mood, general somatic: muscular, sensory, cardiovascular, gastro-intestinal, respiratory, genito-urinary and autonomic symptoms, behavior at interview. Each of the 14 items is scored 0-4 (total score 0-56), higher scores indicate higher levels of anxiety [20].
- SHAPS is a self-rated tool developed to evaluate hedonic tone. Each of the 14 items is scored 0-1 (total score 0-14), higher scores translate to higher anhedonia [21].
- SDS is a self-report measure of the impairment of functioning in the domains of work/school, social life/leisure activities, and family life/home responsibilities. Each domain is scored 0-10 (total score 0-30), with higher scores indicating higher levels of disability [22].
- AIS is an auto-questionnaire assessing: sleep induction, awakenings during the night, final awakening, total sleep duration, sleep quality; well-being, functioning capacity, and sleepiness during the day. Each of the 8 items is scored 0-3 (total 0-24), higher scores suggest more severe insomnia [23].
- FSFI is a self-assessment inventory to evaluate female sexual function. It consists of 19 items in 6 domains: desire, arousal, lubrication, orgasm, satisfac-

tion and pain. Items in the domains of arousal, lubrication, orgasm, and pain are scored 0-5 and in the domains of desire and satisfaction 1-5 (total score 4-95), with higher scores signifying higher levels of sexual functioning [24].

– IIEF is a self-report tool to evaluate male sexual function. It consists of 15 items in 5 domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. Each item is scored 0/1-5 (total score 5-75), higher scores indicate higher levels of sexual functioning [25].
– CGI is a clinician-rated scale constructed to briefly evaluate patients' global functioning prior and after the initiation of treatment. It consists of subscales assessing illness severity (CGI-S), improvement and treatment response (CGI-I) [26].

The primary endpoints were the changes in the severity of depression (QIDS, QIDS-SR, MADRS). Treatment response was defined as a reduction of the severity of depression of ≥50% on the QIDS-CR, QIDS-SR, or MADRS scales or a CGI-I score of 1 or 2 ("Very Much Improved" or "Much Improved") after 12 weeks of treatment with trazodone XR. Remission was defined as score of <6 on the QIDS-CR or QIDS-SR or <10 on the MADRS after 12 weeks of treatment.

Statistical analysis

Data of 79 participants were included in the analyses. Baseline group characteristics and clinical measures were compared using the *t*-test for quantitative variables and $\chi 2$ for qualitative variables between the groups receiving trazodone XR as first- or second-line treatment. The Shapiro-Wilk test was used to assess the distribution of quantitative variables. Qualitative variables were presented as proportions and quantitative as means and standard deviations.

To measure the changes in the total scores of primary and secondary endpoints of the study assessed with symptom severity and functioning scales a Linear Mixed-Effects Model (MMRM – mixed model for repeated measures) was constructed. The analysis was carried out via lmer function from lme4 package in R (version R 4.2.1 [27]). The model consisted of time points of measurement (0, 2, 4, 8 and 12 weeks) and treatment group (trazodone XR or SSRIs) as fixed effects and participants as a random effect (with Restricted Maximum Likelihood [REML] applied). Effects of time, treatment and time x treatment (interaction) on the dependent variable (symptom severity and functioning scores) were evaluated. Effect size was calculated as partial-eta squared for interaction. Between-group comparisons (trazodone XR as first- or second-line treatment) were calculated for the estimated marginal means at each timepoint. Secondary analysis was performed with the same method for all the outcomes with the duration of the previous psychiatric treatment and age included as covariates in the model.

Internal consistency reliability was previously evaluated and described in the pilot of this study [17].

Proportions of treatment response and remission as evaluated with QIDS-CR, QIDS-SR, and MADRS were compared between trazodone XR as first- or second-line treatment using $\chi 2$ test. The level of statistical significance was defined as a two-sided *p*-value of <0.05.

Results

Baseline group characteristics

Comparisons of baseline group characteristics are presented in Table 1. The groups did not significantly differ regarding sex and BMI. Patients receiving trazodone XR as second-line treatment were significantly older than those receiving trazodone XR as first-line treatment (37.5 vs. 31.3 years, $p < 0.028$). The duration of previous psychiatric treatment was longer in the subjects receiving trazodone XR as second- vs. first-line treatment (65.6 vs. 2.21 months, $p < 0.001$). The severity of depression, anhedonia, anxiety, insomnia and levels of psychosocial as well as sexual functioning were comparable between trazodone XR as first- vs. second-line treatment (Table 1).

Table 1. **Baseline group characteristics**

	Trazodone XR first-line treatment (n = 42)	Trazodone XR second-line treatment (n = 37)	p
Sex (% female)	51.22%	47.22%	0.903[a]
Age (in years): mean (SD)	31.3 (9.65)	37.5 (13.2)	0.028[b]
BMI (in kilograms/m$^{2)}$ mean (SD)	23.8 (2.98)	24.2 (3.91)	0. 258[b]
Duration of previous psychiatric treatment (in months)	2.21 (13.5)	65.6 (79.50)	<0.001[b]
MADRS: mean (SD)	27.5 (7.10)	30.1 (7.12)	0.209[b]
QIDS-CR: mean (SD)	13.6 (3.58)	14.9 (5.00)	0.216[b]
QIDS-SR: mean (SD)	14.8 (4.58)	16.8 (4.95)	0.246[b]
CIG-S: mean (SD)	4.97 (0.99)	4.44 (0.95)	0.068[b]
SHAPS: mean (SD)	7.14 (4.05)	6.23 (4.45)	0.394[b]
HAMA: mean (SD)	20.7 (7.60)	22.2 (7.06)	0.413[b]
AIS: mean (SD)	13.9 (5.55)	13.5 (5.44)	0.722[b]
SDS: mean (SD)	19.0 (6.92)	20.2 (7.08)	0.494[b]
FSFI: mean (SD)	13.3 (9.38)	17.6 (9.43)	0.608[b]
IIEF: mean (SD)	46.3 (17.7)	33.1 (21.00)	0.072[b]

AIS – Athens Insomnia Scale, CGI-S – Clinical Global Impression Scale-severity, FSFI – Female Sexual Function Inventory, IIEF – International Index of Erectile Function, HAM-A – Hamilton Anxiety Rating Scale, MADRS – Montgomery-Åsberg Depression Rating Scale, QIDS-CR – Quick Inventory of Depressive Symptomatology – clinician-rated, QIDS-SR – Quick Inventory of Depressive

Symptomatology – self-rated, SD – standard deviation, SDS – Sheehan Disability Scale, SHAPS – Snaith-Hamilton Pleasure Scale, XR – extended-release formulation.

[a]Chi-square test, [b]Independent sample t-test

Treatment outcomes

The results of the MMRM models for each outcome measure are presented in Table 2. The effect of interaction between time and treatment type was statistically significant for the severity of symptoms measured by CGI-S [$F(4, 258.3) = 2.834$, $p < 0.025$]. No other statistically significant for both primary and secondary outcomes were found for the effect of interaction between time and treatment type (Table 2).

Table 2. **Results of mixed-effect model – significance levels and effect sizes (partial-eta squared) for all outcomes**

	Time effect, p	Treatment effect, p	Time x treatment effect, p	Partial-eta squared for interaction (with 95% CI)
MADRS	<0.001	0.073	0.343	0.009 (0.00-0.03)
QIDS-CR	<0.001	0.078	0.642	0.02 (0.00-0.05)
QIDS-SR	<0.001	0.299	<0.124	0.03 (0.00-0.07)
CGI-S	<0.001	0.479	0.025	0.04 (0.00-0.09)
SHAPS	<0.001	0.609	0.389	0.02 (0.00-0.04)
HAM-A	<0.001	0.305	<0.757	0.007 (0.00-0.02)
AIS	<0.001	0.554	<0.286	0.02 (0.00-0.05)
SDS	<0.001	0.962	0.534	0.1 (0.00-0.04)
FSFI	0.206	0.915	0.880	0.1 (0.00-0.04)
IIEF	0.002	0.496	0.109	0.07 (0.00-0.16)

AIS – Athens Insomnia Scale, CGI-S – Clinical Global Impression Scale-severity, FSFI – Female Sexual Function Inventory, IIEF – International Index of Erectile Function, HAM-A – Hamilton Anxiety Rating Scale, MADRS – Montgomery-Åsberg Depression Rating Scale, QIDS-CR – Quick Inventory of Depressive Symptomatology – clinician-rated, QIDS-SR – Quick Inventory of Depressive Symptomatology – self-rated, SDS – Sheehan Disability Scale, SHAPS – Snaith-Hamilton Pleasure Scale.

Table 3 presents the estimated marginal means for each outcome measure, at each timepoint (baseline, 2, 4, 8 and 12 weeks) with p values for comparisons between trazodone XR as first- vs. second-line treatment. Statistically significant differences between trazodone XR as first- vs. second-line treatment in favor of trazodone as first-line therapy were noted in: MADRS at 2 weeks (17.54 vs. 23.3, $p = 0.007$); the scores of QIDS-CR at 2 weeks neared statistical significance (9.07 vs. 11.3, $p = 0.05$). No other significant differences in assessed outcomes were noted between the studied groups (Table 3).

Table 3. **Between-group comparisons for each timepoint**

	Baseline emmean (95% CI)			2 weeks emmean (95% CI)			4 weeks emmean (95% CI)			8 weeks emmean (95% CI)			12 weeks emmean (95% CI)		
	T-XR 1st	T-XR 2nd	p	T-XR 1st	T-XR 2nd	p	T-XR 1st	T-XR 2nd	p	T-XR 1st	T-XR 2nd	p	T-XR 1st	T-XR 2nd	p
MADRS	27.53 (24.7–30.36)	30.14 (27.19–33.1)	0.21	17.54 (14.77–20.32)	23.3 (20.15–26.44)	0.007	12.3 (9.44–15.16)	14.79 (11.64–17.93)	0.25	7.24 (4.30–10.17)	9.04 (5.85–12.23)	0.41	5.74 (2.69–8.78)	6.42 (3.24–9.61)	0.76
QIDS-CR	13.54 (11.95–15.12)	15.00 (13.3–16.69)	0.21	9.07 (7.49–10.64)	11.37 (9.64–13.11)	0.05	4.95 (3.36–6.53)	7.21 (5.47–8.95)	0.06	3.41 (1.77–5.05)	4.27 (2.49–6.06)	0.48	2.96 (1.26–4.66)	3.55 (1.75–5.36)	0.64
QIDS – SR	14.87 (13.04–16.71)	16.48 (14.47–18.49)	0.25	11.14 (9.41–12.88)	13.36 (11.47–15.26)	0.09	7.24 (5.48–9.00)	9.09 (7.15–11.03)	0.17	6.78 (5.00–8.56)	5.53 (3.54–7.52)	0.36	4.71 (2.86–6.57)	5.40 (3.45–7.36)	0.62
CGI-S	3.97 (3.58–4.35)	3.44 (3.03–3.85)	0.07	2.4 (2.03–2.78)	2.93 (2.5–3.35)	0.07	1.79 (1.4–2.17)	2.14 (1.71–2.58)	0.23	0.98 (0.58–1.38)	1.16 (0.71–1.60)	0.57	0.73 (0.31–1.14)	0.9 (0.45–1.35)	0.58
SHAPS	7.06 (5.73–8.39)	6.23 (4.85–7.61)	0.39	5.19 (3.93–6.45)	6.26 (4.84–7.68)	0.27	3.52 (2.19–4.85)	3.26 (1.77–4.76)	0.80	3.08 (1.69–4.48)	2.25 (0.77–3.73)	0.42	2.96 (1.54–4.37)	2.1 (0.6–3.59)	0.41
HAM-A	20.66 (18.29–23.04)	22.08 (19.65–24.50)	0.41	11.95 (9.69–14.22)	14.60 (12.12–17.08)	0.12	7.08 (4.83–9.33)	8.27 (5.73–10.80)	0.49	3.63 (1.30–5.97)	4.97 (2.44–7.51)	0.44	3.63 (1.23–6.04)	3.84 (1.27–6.40)	0.91
AIS	13.93 (12.37–15.48)	13.52 (11.87–15.16)	0.72	8.07 (6.57–9.58)	10.00 (8.31–11.69)	0.09	5.15 (3.54–6.76)	6.48 (4.74–8.22)	0.29	4.77 (3.12–6.42)	3.98 (2.19–5.77)	0.52	3.80 (2.10–5.50)	3.98 (2.19–5.77)	0.89
SDS	19.32 (16.82–21.81)	20.59 (17.9–23.29)	0.49	17.56 (15.16–19.95)	18.44 (15.66–21.21)	0.64	11.44 (8.92–13.97)	12.49 (9.71–15.26)	0.58	10.05 (7.41–12.69)	8.36 (5.51–11.21)	0.39	8.05 (5.41–10.69)	6.86 (3.97–9.75)	0.55
FSFI	14.3 (9.28–19.3)	16.2 (10.64–21.9)	0.61	15.0 (10.01–19.9)	16.2 (10.68–21.6)	0.75	16.8 (11.41–22.3)	17.1 (11.61–22.6)	0.95	17.6 (12.29–23.0)	17.1 (11.39–22.8)	0.89	19.2 (13.85–24.6)	18.1 (12.31–23.9)	0.79
IIEF	44.8 (34.5–55.1)	31.4 (21.1–41.8)	0.07	46.7 (37.6–57.5)	37.7 (27.1–48.4)	0.18	46.2 (36.1–56.3)	44.0 (33.4–54.7)	0.77	46.7 (36.4–57.1)	48.9 (38.3–59.5)	0.77	52.0 (40.9–63.1)	55.0 (43.9–66.1)	0.70

Values are presented as estimated marginal means with 95% Confidence Intervals. Emmean – estimated marginal mean.

AIS – Athens Insomnia Scale, CGI-S – Clinical Global Impression Scale-severity, FSFI – Female Sexual Function Inventory, IIEF – International Index of Erectile Function, HAM-A – Hamilton Anxiety Rating Scale, MADRS – Montgomery-Åsberg Depression Rating Scale, QIDS-CR – Quick Inventory of Depressive Symptomatology – clinician-rated, QIDS-SR – Quick Inventory of Depressive Symptomatology – self-rated, SDS – Sheehan Disability Scale, SHAPS – Snaith-Hamilton Pleasure Scale, T-XR 1st – subjects receiving trazodone XR as first-line treatment, T-XR 2nd – subjects receiving trazodone XR as second-line treatment

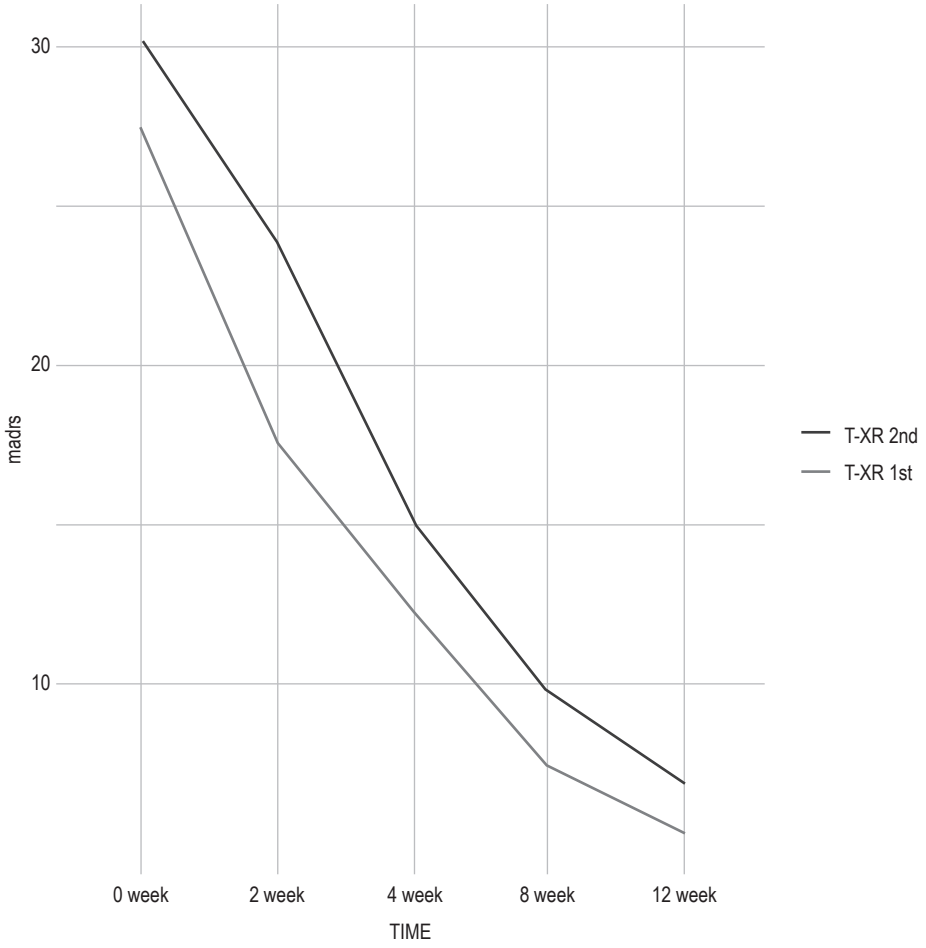
Table 4 presents the results of the MMRM models for each measured outcome, with the duration of previous psychiatric treatment and age included as covariates. There was a statistically significant effect of the interaction between time and treatment type for the scores in the CGI-S [$F(4, 234.2) = 3.27$, $p = 0.012$], the effect size for this interaction was small ($\eta 2 = 0.05$). Furthermore, there was a statistically significant effect of the interaction between time and treatment type for the scores in the IIEF [$F(4, 92.4 = 2.65)$, $p = 0.038$], the effect size for this interaction was moderate ($\eta 2 = 0.1$). No statistically significant effects of time-treatment interactions were observed for other outcomes (Table 4). The improvement of MADRS scores across subsequent time points is depicted in Figure 1.

Table 4. **Results of the mixed-effect model, with the duration of previous psychiatric treatment and age as covariates, showing the significance levels and effect sizes (partial eta squared) for all outcomes**

	Treatment effect, p	Time effect, p	Age effect, p	Duration of treatment effect, p	Time x treatment effect, p	Partial-eta squared for interaction (with 95% CI)
MADRS	0.305	<0.001	0.135	0.685	0.509	0.003 (0.00-1.00)
QIDS-CR	0.370	<0.001	0.419	0.923	0.917	0.004 (0.00-1.00)
QIDS-SR	0.445	<0.001	0.043	0.439	0.179	0.03 (0.00-1.00)
CGI-S	0.455	<0.001	0.078	0.176	0.012	0.05 (0.00-1.00)
SHAPS	0.992	<0.001	0.974	0.421	0.404	0.02 (0.00-1.00)
HAM-A	0.441	<0.001	0.313	0.652	0.809	0.007 (0.00-1.00)
AIS	0.833	<0.001	0.729	0.264	0.174	0.03 (0.00-1.00)
SDS	0.699	<0.001	0.140	0.335	0.653	0.01 (0.00-1.00)
FSFI	0.826	0.073	0.797	0.826	0.533	0.04 (0.00-1.00)
IIEF	0.586	0.005	0.049	0.760	0.038	0.1 (0.00-1.00)

AIS – Athens Insomnia Scale, CGI-S – Clinical Global Impression Scale-severity, FSFI – Female Sexual Function Inventory, IIEF – International Index of Erectile Function, HAM-A – Hamilton Anxiety Rating Scale, MADRS – Montgomery-Åsberg Depression Rating Scale, QIDS-CR – Quick Inventory of Depressive Symptomatology – clinician-rated, QIDS-SR – Quick Inventory of Depressive Symptomatology – self-rated, SDS – Sheehan Disability Scale, SHAPS – Snaith-Hamilton Pleasure Scale.

Table 5 shows the results of repeated measures ANOVA controlled for the duration of psychiatric treatment and age across time, for comparisons of CGI-S scores between baseline and each subsequent time point, separately for trazodone XR as first – vs. second-line treatment. The association between changes in CGI-S and age and duration of psychiatric treatment are depicted in Figure 2a and 2b. Significant reduction of the severity of illness was noted on each subsequent assessment from the 2nd to 12th week of the trial in the group treated with trazodone XR de novo and



T-XR 1st – subjects receiving trazodone XR as first-line treatment, T-XR 2nd – subjects receiving trazodone XR as second-line treatment

Figure 1. **Improvement in MADRS scores across subsequent time points in studied groups**

from 4th to 12th week of the trial in the group receiving trazodone XR as a second-line treatment (Table 5; Figure 3).

Table 5. **Changes in the severity of illness assessed with CGI-S across time in studied groups**

Weeks	TR-X 1st			TR-X 2nd		
	estimate	SE	p	estimate	SE	p
baseline vs. 2	1.646	0.243	<0.001	0.522	0.241	0.198
baseline vs. 4	2.173	0.245	<0.001	1.308	0.246	<0.001

table continued on the next page

baseline vs. 8	3.099	0.250	<0.001	2.296	0.249	<0.001
baseline vs. 12	3.555	0.257	<0.001	2.556	0.255	<0.001

SE – standard error of estimate, T-XR 1st – subjects receiving trazodone as XR first-line treatment, T-XR 2nd – subjects receiving trazodone XR as second-line treatment

Table 6 shows the results of repeated measures ANOVA controlled for the duration of psychiatric treatment and age across time, for comparisons of IIEF scores between baseline and each subsequent time point, separately for trazodone XR as first- vs. second-line treatment. The association between changes in IIEF and age and duration of psychiatric treatment are depicted in Figure 4a and 4b. While no changes were noted in the group treated with trazodone XR as first-line treatment, subjects receiving trazodone XR as second-line treatment reported significant improvement of sexual functions on the 8th and 12th week compared to baseline (Table 6; Figure 5).

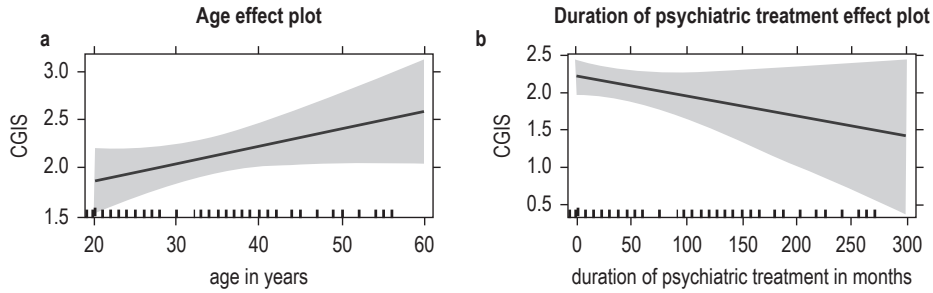


Figure 2. **Association between changes in CGI-S and: a) age and b) duration of psychiatric illness**

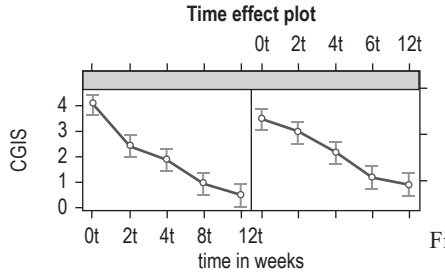


Figure 3. **Changes in the severity of illness assessed with CGI-S across time in studied groups**

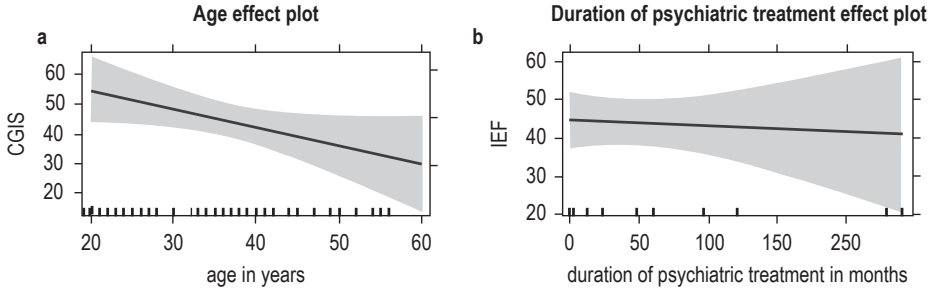


Figure 4. **Association between changes in IIEF and: a) age and b) duration of psychiatric treatment**

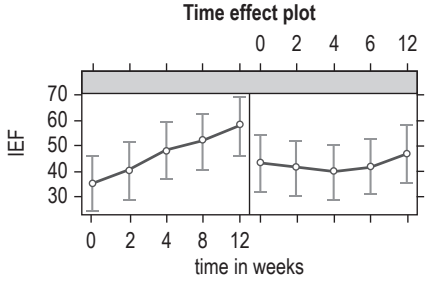


Figure 5. **Changes in sexual functioning in male subjects evaluated with IIEF across time in studied groups**

Table 6. **Changes in sexual functioning in male subjects evaluated with IIEF across time in studied groups**

Weeks	TR-X 1st			TR-X 2nd		
	estimate	SE	p	estimate	SE	p
baseline vs. 2	1.584	4.74	0.997	-4.976	4.87	0.844
baseline vs. 4	3.154	4.90	0.968	-12.745	4.87	0.075
baseline vs. 8	1.119	4.84	0.999	-16.425	4.94	0.011
baseline vs. 12	-3.844	5.27	0.949	-22.708	5.22	<0.001

SE – standard error of estimate, T-XR 1st – subjects receiving trazodone XR as first-line treatment, T-XR 2nd – subjects receiving trazodone XR as second-line treatment

Table 7 shows the comparison of proportions of patients achieving treatment response and remission in trazodone XR as first- vs. second-line treatment groups as assessed after 12 weeks. As measured by QIDS-CR, the proportion of participants achieving treatment response was higher in the trazodone XR used as first- vs. second-line treatment group. No other statistically significant differences in proportions of patients achieving treatment response, remission or clinical improvement were detected (Table 7).

Table 7. **Comparison of proportions of therapeutic response, remission and clinical improvement in patients treated with trazodone XR as first- vs. second-line treatment after 12 weeks**

	T-XR 1st	T-XR 2nd	p
Treatment response (≥ 50 % reduction of MADRS score after 12 weeks), % of patients	79.31%	86.20%	0.728
Treatment response (≥ 50 % reduction of QIDS-CR score after 12 weeks), % of patients	67.74%	35.71%	0.028
Treatment response (≥ 50 % reduction of QIDS-SR score after 12 weeks), % of patients	70.83%	61.90%	0.751
CGI-I score 1 or 2 after 12 weeks of treatment, % of patients	83.33%	82.14%	>0.99
Remission (<10 points in MADRS) after 12 weeks, % of patients	80.64%	75.86%	0.892
Remission (<6 points in QIDS-CR) after 12 weeks, % of patients	81.25%	75.86%	0.841
Remission (<6 points in QIDS-SR) after 12 weeks, % of patients	70%	60.71%	0.641

CGI-I – Clinical Global Impression Scale – Improvement, MADRS – Montgomery-Åsberg Depression Rating Scale, QIDS-CR – Quick Inventory of Depressive Symptomatology – clinician-rated, QIDS-SR – Quick Inventory of Depressive Symptomatology – self-rated, T-XR 1st – subjects receiving trazodone XR as first-line treatment, T-XR 2nd – subjects receiving trazodone XR as second-line treatment

Discussion

The results indicate that trazodone XR is effective in the treatment of patients with MDD who did not respond to SSRIs administered as first-line treatment of the current depressive episode. What is more, our analysis shows that the effectiveness of trazodone XR used as second-line treatment in patients with MDD who did not respond to SSRIs is comparable to its effectiveness as first-line MDD treatment. Additionally, we noted that the reduction of the severity of illness (as measured with CGI-S but not with other tools) was greater in subjects receiving trazodone as second- vs. first-line treatment but occurred later (from the 4th vs. 2nd week on). On top of that, male patients receiving trazodone as second-line treatment reported significant improvement of sexual functions, which manifested from the 8th week on, while no such improvement was observed in male participants treated with trazodone XR de novo.

The baseline group characteristics were similar in terms of sex and BMI. Interestingly, subjects treated with trazodone XR as second-line treatment were characterized by older age (37.5 vs. 31.3 years, $p < 0.028$) and longer duration of illness (65.6 vs. 2.21 months, $p < 0.001$). Both these characteristics could influence the results of this study, potentially favoring the effectiveness of trazodone XR as first- vs. second-line

treatment. Firstly, because as it was shown in the mega-analysis by Strawn et al. [28], the antidepressant response varies between group ages as it is higher in subjects aged 22-35 vs. 36-54 years old. Secondly, because longer duration of depression treatment might hamper the efficacy of antidepressant drugs [29]. However, the majority of tools used to measure the severity of depression in this study (MADRS, QIDS-SR, CGI-I) indicated that the levels of treatment response and remission were comparable between both groups, while only one tool (QIDS-CR) suggested that the rates of treatment response were higher in those who were treated with trazodone XR as first-line treatment. These results do not corroborate those observed in the STAR*D study which showed that the proportions of patients achieving treatment response and remission drop with each following treatment attempt, as they show that treatment with trazodone XR is comparably effective as first- and second-line treatment in subjects ineffectively treated with SSRIs [4]. However, it should be noted that in STAR*D patients were switched to drugs with different mechanisms of action (sertraline, venlafaxine, bupropion) than trazodone XR. Also, unlike STAR*D our trial did not include patients with substance abuse disorders or serious somatic comorbidities which are known to limit the efficacy of antidepressant drugs. The rates of treatment response noted in our sample were similar or somewhat higher than those observed by Fava et al. [10] in patients switched from fluoxetine, paroxetine or sertraline to bupropion (~60%), Fava et al. [9] in patients switched from fluoxetine to reboxetine (73.4%), and Montgomery et al. [7] in patients switched from SSRIs or selective serotonin and noradrenaline reuptake inhibitors to vortioxetine (69.8%) or agomelatine (56%). This might be due to the differences in methodology of our study which was a 12-week open-label naturalistic observation in both its phases vs. the other trials which were either randomized controlled trials [7] or were shorter in duration [9, 10, 30].

Furthermore, the innovation of this study consists in the thorough assessment of various symptomatic dimensions with the use of dedicated tools. Ours is the first trial to thoroughly assess the effectiveness of trazodone XR not only in reducing depression, but also in improving anxiety, anhedonia, insomnia, psychosocial and sexual functioning. The knowledge on the unique pharmacodynamic and pharmacokinetic properties of trazodone XR and clinical experience allows one to assume that trazodone XR will be effective in all these symptomatic dimensions. Yet, aside from Buoli et al. [31] who showed that trazodone XR effectively reduced anxiety as assessed with HAM-A, no previous study has confirmed these assumptions. The pilot analysis indicated that trazodone XR is effective in the reduction of depression severity as well as anxiety, insomnia, anhedonia and in improving psychosocial functioning [17]. The current results corroborate those noted in the pilot analysis and additionally confirm that 1) the reduction of severity of illness was greater in individuals receiving trazodone XR as second- vs. first-line treatment, and 2) trazodone XR as second-line treatment improves sexual functioning in male MDD patients who were treated with SSRIs as

first-line treatment. These results remained significant even after controlling for the duration of treatment and age as covariates.

This work should be seen in the context of its limitations. The naturalistic observation methodology of this study and a lack of randomization could have added to the differences in baseline characteristics noted between the groups. In an attempt to avoid potential bias additional analyses were performed, which controlled the results for the duration of psychiatric treatment and age which are dissimilar in the studied groups. Nevertheless, the differences in the studied groups did not hinder the ability of this work in confirming 1) the effectiveness of trazodone XR in treatment of MDD patients who did not respond to SSRIs, given that the group receiving trazodone as second-line treatment was characterized by older age and longer duration of treatment which both could limit the effectiveness of the drug, and 2) the effectiveness of trazodone XR as both first- and second-line MDD treatment in improving depression, anxiety, insomnia, anhedonia, psychosocial functioning and sexual functions in male patients. Other, possibly confounding factors, were: the single-center design, dissimilar antidepressant doses and inclusion of different SSRIs in the group which received trazodone XR as second-line treatment.

Conclusions

In essence, the results indicate that trazodone XR is effective in MDD both as a first-line treatment and as a second-line treatment in individuals who did not achieve response to SSRIs. Moreover, these data show that trazodone XR is effective in reducing the severity of depression, as well as anxiety, insomnia, anhedonia and improving psychosocial functioning both as a first- and second-line treatment. They also indicate that trazodone XR is a valuable second-line treatment choice for male patients with impaired sexual functions who received SSRIs as first-line treatment.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of the Jagiellonian University in Krakow (approval no. 1072.6120.113.2021).

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Address: Marcin Siwek
Department of Affective Disorders
Department of Psychiatry JUMC
31-501 Kraków, M. Kopernika Street 21 A
e-mail: marcin.siwek@uj.edu.pl