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Fluvoxamine in Treatment of Depression in Russian Patients: An Open-Label, Uncontrolled and Non-Randomized Multicenter Observational Study

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Abstract

Background: Fluvoxamine, a selective serotonin reuptake inhibitor is widely used in the treatment of depression, one of the most common disorders prevalent in Russia. However, studies demonstrating its efficacy and safety in routine settings in Russia are scarce. Methods: This prospective, uncontrolled, open-label study was conducted at 11 centers in Russia. Total 293 patients (aged ≥ 18 years), meeting DSM-IV criteria for depression and scoring ≥ 17 on 17-item Hamilton Rating Scale of Depression (HAMD-17) received fluvoxamine 50 - 300 mg for 6 weeks. Primary efficacy measures included change from baseline in the HAMD-17 and Clinical Global Impression (CGI) scores. Secondary efficacy measure was evaluation of sleep quality changes on HAMD-17 subscale. Safety was assessed by monitoring of adverse drug reactions (ADRs). Results: Mean age of patients was 42.7 years and the majority of them were women (72%). At the end of treatment (day 42), clinically significant reduction was observed in mean HAMD-17, CGI-severity of illness and HAMD-17 sleep sub-score from 23.1, 4.5 and 3.9 at baseline to day 42; change from baseline (Δ) was: Δ-17.3 [95% CI: −18.0; −16.7]), Δ-2.1 and Δ-3.4 [95% CI: −3.53; −3.20]), respectively. At day 42, 20.8% patients reported as normal (not at all ill) on the CGI-severity scale and 85% patients reported as "much improved" or "very much improved" on the CGI-change in severity and quality of life scores. Nausea (12.6%) and somnolence (5.1%) were the most frequently reported ADRs. No deaths or serious ADRs were reported but eight patients discontinued treatment due to ADRs. Conclusion: Treatment with fluvoxamine under routine settings showed marked improvement in Russian patients with depression as measured by HAMD-17 and CGI ratings and was thus efficacious as well as safe and well-tolerated.

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Keywords

Fluvoxamine, Depression, Hamilton Rating Scale of Depression, Routine Settings

1. Introduction

Depression is a complex mental disorder having a long-term negative impact on the health and economic well-being of both individuals and society. Globally, it affects more than 350 million people annually [1] with life time prevalence rates in general population ranging from 10% to 15% [2]. It is projected that by the year 2020 it will rank second for the Disability Adjusted Life Years calculated for all ages [3].

The scenario is similar in Russia where recent studies have indicated the prevalence of lifetime and current depressive disorders to be 30% and 20.7%, respectively [4] with high percentages in both women (44%) and men (23%) [5]. Biochemical, endocrinal, neurophysiological, psychological and social-economical factors are known to play a role in the aetiology of depression. Social circumstances in particular, have a strong influence in increasing human depressive symptoms [6]. This is particularly evident in Russia, where social upheaval over a last few decades have led to high psychological distress and increased incidence of depression and related disorders [5]. Depressive disorders in general population needs immediate attention as it reduces a person's social functioning, ability to work and have a negative impact on the physical health and quality of life [7]. Moreover, its presence as a comorbid medical illness [8] with other prevalent psychotic disorders in Russia such as schizophrenia [9] raises concern as it usually tends to emerge in the form of psychogenic disorders and worsens the course of the primary disease [10]. A high quality of care for patients with depression in primary care settings is, therefore needed in order to minimize the morbidity caused by such a prevalent condition.

Various antidepressants currently dominate the medical management of depressive disorders and amongst different classes (e.g. tricyclic antidepressants [TCA], monoamine oxidase inhibitors, etc.), selective serotonin reuptake inhibitors (SSRIs) are recommended for wider usage around the world [11] [12]. The SSRIs act by selectively inhibiting the reuptake of neurotransmitter serotonin, which improves the transmission of neural signals, thereby reducing depressive symptoms and elevating the state of mind [12]. They are equivalent to TCAs in terms of efficacy, but score better on safety and tolerability [13]. National Institute for Health and Clinical Excellence recommends the use SSRI in generic form after considering potential side effects and patient preferences [14].

Among SSRIs, fluvoxamine is approved for the treatment of depression in many countries [15]. It has suitable pharmacokinetics that supports once-daily dosing [16] and has shown greater therapeutic benefit when compared with imipramine in patients with severe depression [17] [18]. Treatment with fluvoxamine is also associated with improvement in sleep quality [19] and has a lower impact on body weight [20].

Although fluvoxamine-based treatment is widely used for the management of depressive disorders in Russia, there are limited efficacy trials that are conducted in carefully selected populations under controlled conditions [4] [21]-[23]. Information on its efficacy and safety in treating depression under routine, uncontrolled settings, which is intended to have a greater generalizability in Russian population, is scarce. As a part of post-marketing surveillance, the present uncontrolled, multicenter, observational study was conducted to evaluate the efficacy and safety of fluvoxamine-based treatment for management of patients with depression under routine settings in Russia.

2. Methods

2.1. Study Design

This was an open label, observational study conducted at 11 centers in Russia from November 2006 to May 2007. Eligible patients received fluvoxamine 50 - 300 mg once-daily for 6 weeks with study visits scheduled on day 1, 7, 14, 28 and 42 (**Figure 1**). The recommended starting dose was 50 to 100 mg once-daily and if necessary, the dose was increased by 50 mg weekly up to a maximum of 300 mg/day according to the patient's response and was divided in those receiving >150 mg/day.

The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki
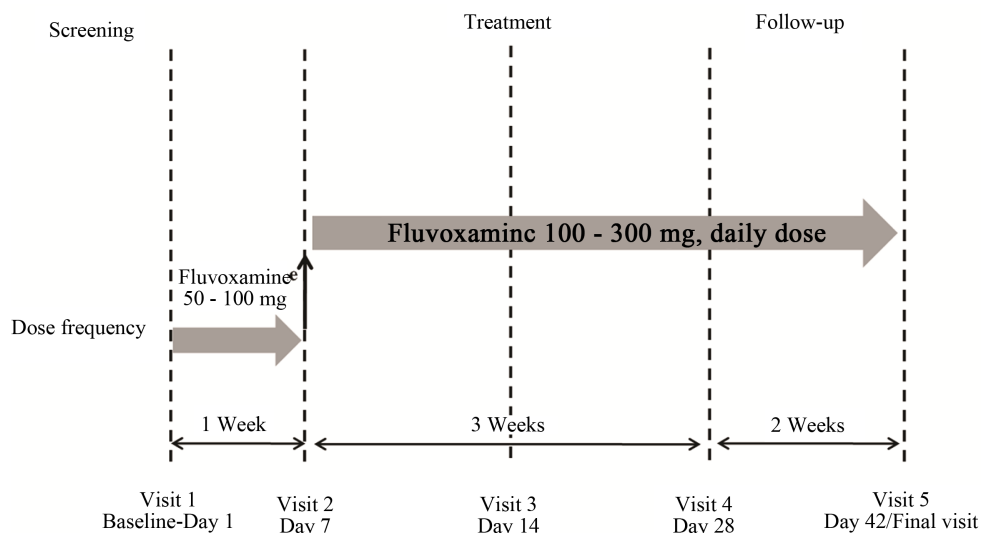
Figure 1. Study design.

and European Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the protocol.

2.2. Patients

Adult male or female outpatients of 18 years of age and above with established depression, and who fulfilled the diagnostic criteria defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and had a score ≥ 17 on the 17-item Hamilton Rating Scale of Depression (HAMD-17) were included in the study.

Patients with proven hepatic or renal insufficiency and those hypersensitive to the drug were excluded from the study. Other exclusion criteria included treatment with tizanidine or irreversible monoamine oxidase inhibitors within two weeks prior to baseline visit as well as pregnant or lactating women. Various classes of drugs that were not allowed during the surveillance period of the study included; antidepressants other than fluvoxamine, sedatives, tranquillizers, neuroleptics, antipsychotics, narcotics, anticonvulsants, anticoagulants and drugs like cisapride, propranolol, theophylline, cyclosporine, methadone, mexiletine, tacrine, metoprolol, terfenadine and astemizole. All patients were free to withdraw their participation in the study at any time.

2.3. Efficacy Assessments

The primary efficacy end points were the change from baseline in HAMD-17 total score and Clinical Global Impression (CGI). The HAMD-17 total scores were assessed at baseline and study days 7, 14, 28 and day 42 (or upon early withdrawal from the study), while CGI was recorded at baseline and day 42.

The secondary efficacy end point was the change from baseline in the sleep quality as assessed by items 4, 5 and 6 of the HAMD-17 over the six-week period.

2.4. Safety Assessments

Tolerability and safety were assessed through collection and monitoring of any spontaneously reported adverse drug reactions (ADRs), serious ADRs, and physical examination (height and weight). All concomitant medications were also reviewed and vital characteristics such as systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate were measured at baseline and day 42.

2.5. Statistical Analysis

No formal sample size calculation was done. Based on the feasibility, a total number of 300 patients were considered adequate to collect considerable exposure of fluvoxamine. Safety analysis was performed on all patients

who received at least one dose of study medication (safety population), whereas efficacy analysis was performed on all patients who were included in the safety sample and had at least one post-baseline assessment of any efficacy measurement (ITT population).

Descriptive statistics were used to summarize the demographic variables. Changes from baseline for all efficacy measures were presented by descriptive statistics, including 95% confidence intervals (CIs) and one-sample t-test. Endpoint refers to the last non-missing observation during a post-baseline visit.

Safety was assessed primarily by reporting of ADR. All reported treatment-emergent ADRs were taken into account, coded according to Medical Dictionary for Regulatory Activities (MedDRA) and presented in summary tables with the number and percentage of patients who reported that ADR.

3. Results

3.1. Patient Disposition, Baseline Demographics and Clinical Characteristics

A total of 293 patients were recruited and treated with fluvoxamine. Total 15 patients withdrew before completion of the six weeks of treatment, reasons were: ADRs (n = 8; nausea being the most frequent [n = 3]), lack of efficacy (n = 3), loss to follow-up (n = 2) and withdrawal of consent (n = 2). No clinically relevant protocol deviations were observed during the study.

The patient's baseline characteristics are listed in **Table 1**. The mean age was 42.7 years with body mass index

Table 1. Patient baseline demographics and clinical characteristics.

Parameter	Value
Age (years)	
N	293
Mean (SD)	42.7 (13.9)
Age category (years), n (%)	
17 - 29	59 (20.1)
30 - 49	138 (47.1)
50 - 64	76 (25.9)
≥65	20 (6.8)
Sex, *n* (%)	
Men	81 (27.6)
Women	212 (72.4)
Height (cm)	
n	287
Mean (SD)	168.0 (8.6)
Weight (kg)	
n	292
Mean (SD)	70.2 (13.6)
Body Mass Index (Kg/m^2)	
n	287
Mean (SD)	24.9 (4.2)
Diastolic Blood Pressure (mmHg)	
n	292
Mean (SD)	78.0 (9.1)
Systolic Blood Pressure (mmHg)	
n	292
Mean (SD)	123.0 (13.5)
HAMD-17 Total Score	
n	293
Mean (SD)	23.1 (4.6)
CGI-S	
n	293
Mean (SD)	4.5 (0.8)
HAMD-17 Sleep Sub-score	
n	293
Mean (SD)	3.9 (1.3)

CGI-S: Clinical Global Impression Severity, HAMD-17: 17-item Hamilton Rating Scale of Depression, SD: standard deviation.

(BMI) of 24.9 kg/m^2 and majority of them were women (72%). The most frequently reported pre-existing medical conditions were cardiovascular diseases (15%), cranial trauma (13.0%) and psychiatric disorders other than depression (9.9%). Drug/alcohol abuse was recorded in nine patients (3.1%).

The most frequently prescribed concomitant medications were sedatives (23.9%), cardiovascular drugs (12.6%), anti-epileptic drugs (9.6%) and antipsychotics (9.6%). Antidepressant combination therapy was prescribed for seven patients (2.4%).

3.2. Efficacy Variables

3.2.1. HAMD-17 Total Score

A visit-wise plot of mean change in HAMD-17 total score is presented in **Figure 2**. At baseline, the mean (±SD) total HAMD-17 score was 23.1 ± 4.6 and decreased steadily over time and improved to 5.8 ± 4.3 at the final visit on day 42 (change from baseline Δ [95% CI]: −17.3 [−18.0; −16.7]). Overall, a reduction of 74.89% was observed in the mean scores of HAMD-17 from baseline to the final visit on day 42.

3.2.2. HAMD-17 Sleep Sub-Score

The mean (±SD) HAMD-17 sleep sub-score decreased from 3.9 ± 1.3 at baseline to 0.6 ± 0.8 at the final visit on day 42 (change from baseline Δ [95% CI]: −3.4 [−3.53; −3.20]). At endpoint, the mean score was 0.7 ± 1.0 (**Figure 3**).
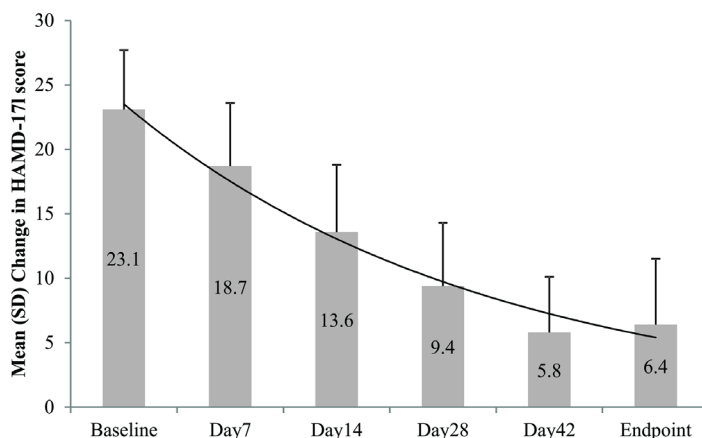

Figure 2. Change from baseline to day 42 in HAMD-17 total score (intent-to-treat analysis set) HAMD-17: 17-item Hamilton Rating Scale of Depression.
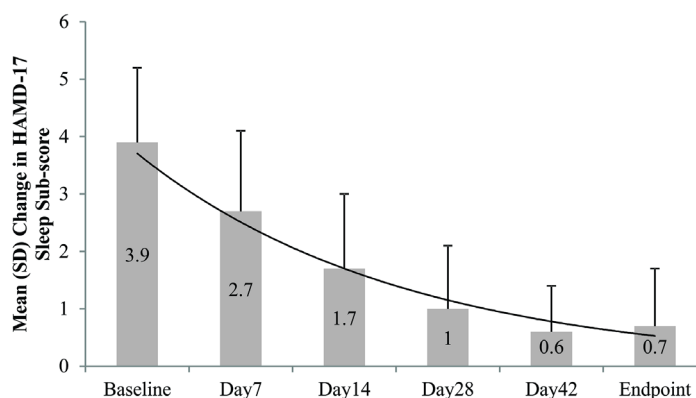

Figure 3. Changes from baseline to day 42 in the HAMD-17 sleep sub-score (intent-to-treat analysis set) HAMD-17: 17-item Hamilton Rating Scale of Depression.

3.2.3. CGI Scores

The mean CGI-severity score decreased from 4.5 (moderately to markedly ill) at baseline to 2.4 (borderline to mildly ill) on day 42. Overall, a reduction of 46.67% was recorded in the mean CGI-scores at the end of treatment (day 42). More than 85% of patients were reported as "much improved" or "very much improved" as per the CGI-change in severity and quality of life scores at day 42 (**Figure 4**).

At the end of treatment (day 42), 20.8% patients (n = 58) were reported as normal (not at all ill) on the CGI-severity scale by the investigator. There was a substantial improvement in patient's clinical condition classified as "borderline mentally ill" when compared to baseline in this category (40.9% vs 0.7%) (**Table 2**). The majority of patients and investigators rated the treatment as good (66.67%) to excellent (20% - 21%).

3.3. Safety and Tolerability

A total of 72 patients (24.6%) experienced at least one ADR during the six-week period (**Table 3**). The majority of ADRs were mild or moderate in severity. Nausea (37, 12.6%) and somnolence (15, 5.1%) were the most frequently reported ADRs. No deaths and serious ADRs were reported, but eight patients discontinued treatment
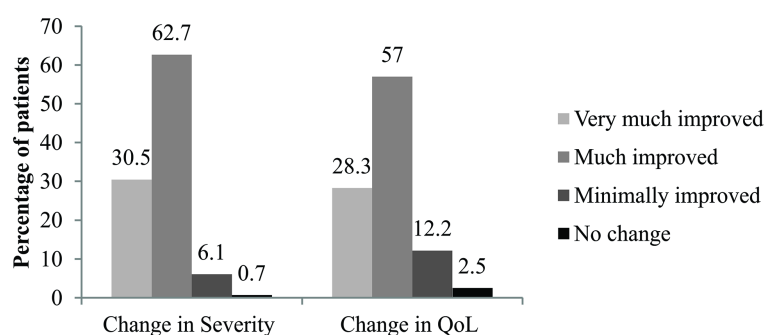

Figure 4. CGI per classifications of change in severity and change in QoL (intent-to-treat analysis set) CGI: Clinical Global Impression, QoL: Quality of Life.

Table 2. CGI-S classification at baseline and day 42 (intent-to-treat analysis set).

Severity	Baseline n (%)	Day 42 n (%)
Normal, not at all ill	0 (0.0)	58 (20.8)
Borderline mentally ill	2 (0.7)	114 (40.9)
Mildly ill	19 (6.5)	67 (24.0)
Moderately ill	140 (47.8)	30 (10.8)
Markedly ill	102 (34.8)	9 (3.2)
Severely ill	29 (9.9)	1 (0.4)
Most extremely ill	1 (0.3)	0 (0.0)

CGI-S: Clinical Global Impression Severity.

Table 3. Adverse events reported in >1% of patients (Safety analysis set) (order of frequency).

Adverse Drug Reaction (ADR)	n (%)
Patients with ≥1 ADR	72 (24.6)
Nausea	37 (12.6)
Somnolence	15 (5.1)
Headache	6 (2.0)
Vertigo	5 (1.7)
Asthenia	4 (1.4)
Constipation	4 (1.4)

due to ADRs during the study. Nausea in two patients, sleepiness and diarrhea in one patient each were the only severe ADRs. No clinically significant changes were observed in vital signs, body weight, BMI, pulse rate, DBP, and SBP.

4. Discussion

Prevalence of depression in Russian population is substantial, but studies dealing with the treatment needs in this population under routine settings are limited. Although, fluvoxamine is the preferred line of treatment for depression, studies examining its effectiveness under daily practice from Russia are scarce. This observational study established the efficacy of fluvoxamine-based treatment as evidenced by a significant improvement in HAMD-17 total scores and CGI scores. To the best of our knowledge, this is the first open-label observational study to examine the efficacy and safety of fluvoxamine-based treatment in Russian patients with depression under uncontrolled routine settings.

The high percentage of female patients with depression (72%) in this study is line with other published reports [24] [25] reporting high prevalence of depression in Russian females in comparison with the male population; similarly observed worldwide.

The efficacy results of this study are consistent with other studies using the same drug in populations from Europe and other regions [19] [26]-[28]. The observed 75% reduction in the HAMD-17 score with fluvoxamine treatment is similar to the clinically significant change of 71% recorded in another study [29].

Fluvoxamine in contrast to other anti-depressants is known to have an early onset of action, which is an important consideration as depressed patients are prone to harm themselves if not treated at an earlier stage. Early onset of action may also reduce the occurrence of treatment discontinuations, which may be due to lack of efficacy, one of the commonest factors seen in routine settings. Thus, decrease in HAMD-17 score as early as day 7 may explain why very few patients discontinued the treatment due to lack of efficacy [30]. These findings correlate with a double-blind study wherein fluvoxamine was reported to have a relatively faster onset of therapeutic action when compared with other SSRIs [19].

Similar to HAMD-17 total score, improvement was also noted in the CGI scores. A 46.67% reduction in the mean CGI-severity scores was recorded at the endpoint and a total of 20.8% patients were categorized as being "normal" and "not at all ill", as per the CGI-severity scale. Earlier studies have reported significantly more responders on the CGI-severity and a greater reduction of CGI-severity scores for fluvoxamine treatment when compared to other SSRIs at week 2, but not at week 4 or 6 [19]. As we only evaluated the CGI scores at baseline and week 6 (day 42), our study provides further evidence of a favorable response of fluvoxamine on CGI scores also at week 6.

Depression is associated with a poor quality of life [31]. This study showed improvement in quality of life of the patients over a 6-week treatment, which is in conformance with other studies [26] [32]. Improvements were also observed in quality of sleep, as measured by the HAMD-17 sleep sub-score and the results are in accordance with the previous studies [19] [33] where fluvoxamine treatment was shown to have a faster onset of action against depressive symptoms and better improvement in sleep quality as compared with other SSRIs.

Fluvoxamine treatment exhibited good safety and favorable tolerability profile in this study. Nausea and somnolence were the most commonly reported ADRs. These results are consistent with the previous studies [20] [34]-[36]. In this study, fluvoxamine treatment led to no remarkable changes in either body weight or BMI. These findings are highly encouraging in the treatment of depression as it enhances adherence and reduces non-compliance in patients requiring long-term treatment [20].

Although an open-label, uncontrolled study has its own limitations; the routine setting does provide a more realistic approximation of clinical practice when compared to a double-blind study. Limitation of the study was its short duration, which disallowed information about relapse and remission maintenance in patients with depression.

5. Conclusion

Treatment with fluvoxamine under routine settings showed marked improvement in Russian patients with depression as measured by HAMD-17 and CGI ratings and was thus efficacious as well as safe and well-tolerated. The lack of empirical evidence in the treatment of depression in primary care settings serves a major barrier in the management of depression. The routine setting of this study targets to fill this gap to some extent while vali-

dating and extending the safety and efficacy of fluvoxamine treatment for depression in the Russian population.

Acknowledgements

Conflict of Interest

Disclosure

All authors met ICMJE criteria and all those who fulfilled those criteria were listed as authors. All authors had access to the study data and made the final decision about where to present these data.

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