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Original Research Article

Comparative Real-world Adverse Drug Reactions of Fluoxetine and Sertraline in Outpatients with Depression

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Abstract

Background: Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine and sertraline, are widely prescribed for depression due to their favorable safety profiles compared to older anti-depressants. However, these medications are associated with various adverse drug reactions (ADRs) that may affect patient adherence and treatment outcomes.
Objectives: This study evaluates the prevalence and characteristics of ADRs in outpatients treated with fluoxetine and sertraline, comparing ADR rates in real-world clinical settings.
Materials and Methods: A prospective cross-sectional study was conducted at a tertiary care psychiatric hospital from July to December 2018, involving 65 outpatients with depression who had been on fluoxetine (n = 47) or sertraline (n = 18) for at least 4 weeks. Data on ADRs were collected using a validated questionnaire, and comparisons were performed using chi-square and Fisher's exact tests.
Results: The mean age of participants was 47.55 ± 16.14 years for fluoxetine and 45.16 ± 19.47 years for sertraline, with no significant differences in gender or treatment duration. Common ADRs included sedation, insomnia, and gastrointestinal symptoms. Anorexia was significantly more frequent in the fluoxetine group (21.28%, p = .05), while nausea/vomiting was higher in the sertraline group (27.78%, p = .001). Other ADRs, including sexual dysfunction and cardiovascular effects, were similar between the groups.
Conclusion: These findings underscore the importance of recognizing distinct ADR profiles to optimize treatment decisions for outpatients with depression.

Keywords

Adverse drug reactions, fluoxetine, sertraline, depression

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Introduction

Depression is a leading cause of disability worldwide, characterized by physical symptoms such as fatigue, weight loss, and decreased appetite. A hallmark of depression is anhedonia, the inability to experience pleasure. It is often accompanied by diminished motivation, sleep disturbances, cognitive impairments, and emotional symptoms, including feelings of guilt.[1] The World Health Organization (WHO) estimates that depression contributes to 4.3% of the global disease burden and is projected to become the leading cause by 2030, driven by premature deaths and years lived with disability.[2]

Despite the availability of effective treatments, approximately 50%–70% of patients with depression remain undiagnosed,[3] and thus untreated, especially when depression coexists with other physical or psychiatric conditions that can result in increased mortality.[4] The treatment includes both pharmacological and non-pharmacological approaches. Non-pharmacological treatments involve lifestyle interventions aimed at improving physical symptoms and the use of innovative methods.[5] Anti-depressants are the cornerstone of

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managing depression, with most current guidelines recommending selective serotonin reuptake inhibitors (SSRIs) as the first-line treatment for patients with major depression.[6] Anti-depressants can be used for both acute- and maintenance-phase treatment. Continuing anti-depressant therapy in patients with depression who have responded to initial treatment reduces the risk of relapse by half in both specialized and primary care settings.[7] Comparisons between SSRIs and placebo indicate statistically significant effects on depressive symptoms; however, the clinical relevance of these effects remains debatable. Additionally, SSRIs were associated with a significantly increased risk of both serious and non-serious adverse events compared to placebo.[8]

The six main SSRIs, fluoxetine, citalopram, escitalopram, paroxetine, sertraline, and fluvoxamine, are structurally different but share a common mechanism of action. Despite this, they vary in pharmacokinetics, pharmacodynamics, side effect profiles, and efficacy, making each more suitable for specific clinical situations. Selecting the right SSRI depends on individual patient needs and whether its side effects can be leveraged as secondary therapeutic benefits. Common adverse effects across all SSRIs include sexual dysfunction, gastrointestinal distress, prolonged QT interval, and xerostomia, which also help distinguish them.[9] In a previous study,[10] 86% of patients receiving SSRIs for depression reported experiencing at least one side effect, and 55% had one or more side effects that were significant enough to impact their treatment. In another study,[11] a total of 131 patients were monitored for adverse drug reactions (ADRs) related to anti-depressant use, with 29 patients (22.1%) reporting at least one ADR during the study period. The most reported ADR was weight gain, observed in eight (18.1%) patients, followed by somnolence in four (9.1%) patients. Escitalopram was the most frequently implicated drug, associated with ADRs in 13 (29.6%) patients, while fluoxetine was linked to ADRs in six (13.6%) patients.

Fluoxetine and sertraline are two commonly prescribed SSRIs. An 8-week double-blind, multicenter study comparing their efficacy and safety in treating major depression found no statistically significant difference between the two drugs in various efficacy measures. The incidence of adverse events was similar, with 40.4% for sertraline and 39.3% for fluoxetine. However, patients generally rated the severity of adverse events as lower in the sertraline group.[12] A study of patients with depression who did not respond to initial sertraline therapy found that switching to fluoxetine could be effective. These findings suggest that fluoxetine and sertraline are not interchangeable. Patients who have difficulty tolerating or do not respond to sertraline may still benefit from treatment with fluoxetine.[13] However, recent nationwide, population-based registry data indicate that, compared to sertraline, fluoxetine, paroxetine, and escitalopram are associated with a higher risk of non-response, while citalopram shows no difference. This suggests that sertraline may have a lower likelihood of treatment failure compared to fluoxetine and certain other SSRIs.[14]

In terms of ADRs, fluoxetine exhibits the least specific binding to the serotonin transporter (SERT) and, at higher doses, can also increase synaptic norepinephrine and dopamine levels. This reduced binding specificity may contribute to fluoxetine's association with higher rates of weight loss, agitation, and anxiety compared to other SSRIs. For sertraline, the most reported ADR during the acute phase of treatment is diarrhea.[9] The differences in study design can influence the reporting of ADRs. In randomized controlled trials comparing fluoxetine and sertraline in outpatients, nausea was the most reported side effect in both groups, affecting 23% of sertraline-treated and 17% of fluoxetine-treated patients. However, the difference was not statistically significant. Treatment-related headaches or migraines were reported by 5% of sertraline patients and 7% of fluoxetine patients. Other less common side effects included trembling, gastralgia, diarrhea, somnolence, fatigue, insomnia, vomiting, dry mouth, and constipation. No significant differences were found between the two groups in the incidence of any adverse events.[15] In a cross-sectional study conducted in a naturalistic setting, the side effects of three commonly used SSRIs, sertraline, escitalopram, and fluoxetine, were assessed using a self-rating instrument. Among the patients, 53% were taking sertraline, 38% were taking escitalopram, and 8% were taking fluoxetine. The most reported side effects across all groups included flatulence, somnolence, memory impairment, decreased concentration, yawning, fatigue, dry mouth, weight gain, light-headedness, and sweating. Notably, patients on escitalopram experienced a higher incidence of headaches, pruritus, memory impairment, decreased concentration, and dizziness. Those treated with sertraline reported a significantly decreased appetite.[16]

Given the widespread use of SSRIs and their associated ADRs, this study aims to provide a comprehensive evaluation of the prevalence and characteristics of ADRs in patients treated with fluoxetine and sertraline, which will contribute valuable information to clinical practice. Unlike randomized controlled trials, this study adopts a naturalistic design, reflecting real-world treatment conditions and patient experiences. This approach allows for a more realistic assessment of ADRs as they occur in routine clinical settings, providing insights that are highly relevant to everyday clinical practice.

Materials and Methods

This study employs a prospective cross-sectional design to evaluate ADRs in patients diagnosed with depression who were treated with fluoxetine or sertraline. The study was conducted at the outpatient department of a tertiary psychiatric hospital from July 1, 2018, to December 31, 2018.

Study Population and Inclusion Criteria

The study included male and female patients aged 18 years or older who were diagnosed with depression and had been

prescribed either fluoxetine or sertraline for at least 4 weeks. Both patients who were newly diagnosed with depression and those with recurrent episodes were eligible to participate. Patients who were taking fluoxetine or sertraline in combination with other anti-depressants (except mianserin and trazodone for insomnia) could influence the treatment of depression. Patients who had poor drug compliance, described as self-reported using fluoxetine or sertraline less than 80% or were unwilling to provide consent, were excluded.

Sample Size

All patients meeting the inclusion criteria and attending the outpatient department during the study period were invited to participate. Data collection was performed through patient self-reported questionnaires designed by the researchers.

Development and Validation of the Questionnaire

A structured questionnaire was developed to assess ADRs associated with fluoxetine and sertraline use. The questionnaire was reviewed by clinical experts and pretested before implementation. It included sections on demographic data, medication history, and ADRs categorized by system organ class.

To ensure the validity of the questionnaire, the index of item objective congruence (IOC) was utilized. The questionnaire items were reviewed by three experts in the field, who rated each item as +1 (clearly congruent with the objectives), 0 (uncertain), or −1 (not congruent). The IOC values for each item were calculated, and an overall average IOC score of 0.74 was achieved, indicating acceptable content validity. Items with an IOC score below 0.50 were revised or removed as per the experts' suggestions. Additionally, the reliability of the questionnaire was assessed using Cronbach's alpha coefficient, which was calculated after a try-out with a sample of 20 patients. The overall Cronbach's alpha was 0.755, demonstrating acceptable internal consistency for the questionnaire.

Data Collection and Assessment of ADRs

The assessment of ADRs was conducted using a validated questionnaire, which was administered through interviews by trained researchers. The questionnaire consisted of structured questions regarding ADRs categorized into several systems, including the central nervous system (e.g., sedation, insomnia, agitation, headache), endocrine and reproductive system (e.g., sexual dysfunction), peripheral nervous system (e.g., dry mouth, blurred vision), cardiovascular system (e.g., palpitation, orthostatic hypotension), gastrointestinal system (e.g., increased appetite, anorexia, nausea, vomiting, constipation), and other systems (e.g., rash). ADRs were evaluated based on patient self-reports, observations, and interview responses.

Before data collection, the researchers explained the study objectives and ensured patient confidentiality. Informed consent was obtained from all participants.

Statistical Analysis

Baseline characteristics, including demographic data, treatment duration, and severity of depression, were summarized using descriptive statistics. Continuous variables were reported as Mean ± Standard Deviation (SD) or medians [min–max], depending on the distribution of data. Categorical variables were presented as frequencies and percentages.

Comparative analysis between the fluoxetine and sertraline groups was performed using chi-square tests for categorical variables, Fisher's exact tests where expected counts were less than 5, *t*-tests for normally distributed continuous variables, and Wilcoxon rank-sum tests for non-normally distributed continuous variables. A p value of $<.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 65 outpatients with depression were included in this study, with 47 patients receiving fluoxetine and 18 receiving sertraline. The baseline characteristics of the two groups are summarized in Table 1. The mean age of the patients in the fluoxetine group was 47.55 ± 16.14 years, while the mean age in the sertraline group was 45.16 ± 19.47 years ($p = .61$). There were no significant differences in gender distribution between the two groups, with females constituting 68.09% of the fluoxetine group and 77.78% of the sertraline group ($p = .55$).

The median treatment duration was 6 months (range 1–48) for fluoxetine and 8 months (range 1–36) for sertraline ($p = .44$). All patients in the fluoxetine group had moderate depression (F32.1), while 83.33% in the sertraline group were classified as moderate, with 5.56% being mild (F32.0) and 11.11% severe (F32.2, F32.3) ($p = .02$). The median doses were 20 mg (range 10–60) for fluoxetine and 50 mg (range 25–100) for sertraline, with a statistically significant difference ($p < .001$).

Concomitant use of benzodiazepines was common, with lorazepam being the most frequently used, seen in 66.67% of the fluoxetine group and 37.50% of the sertraline group ($p = .10$). Co-medications such as mianserin, trazodone, and folic acid were also observed, but without significant differences between the groups.

Comparison of ADRs

The incidence of ADRs between fluoxetine and sertraline is presented in Table 2. In the central nervous system, sedation was reported by 23.40% of fluoxetine users compared to

Table 1. Baseline Characteristics (n = 65).

Characteristics	Fluoxetine (n = 47)	Sertraline (n = 18)	p Value
Gender, n (%)			
Female	32 (68.09)	14 (77.78)	.55
Male	15 (31.91)	4 (22.22)	
Age (Mean ± SD)	47.55 ± 16.14	45.16 ± 19.47	.61
Treatment duration (months, median [min– max])	6 [1–48]	8 [1–36]	.44
Severity, n (%)			
Mild (F32.0)	0 (0.00)	1 (5.56)	.02
Moderate (F32.1)	47 (100.00)	15 (83.33)	
Severe (F32.2, F32.3)	0 (0.00)	2 (11.11)	
Dose (mg, median [min–max])	20 [10–60]	50 [25–100]	<.001
Benzodiazepines, n (%)			
Clorazepate	3 (9.09)	1 (12.50)	.10
Clonazepam	1 (3.03)	2 (25.00)	
Diazepam	7 (21.21)	2 (25.00)	
Lorazepam	22 (66.67)	3 (37.50)	
Co-medications, n (%)			
Mianserin	7 (35.00)	0 (0.00)	.14
Trazodone	8 (40.00)	1 (33.33)	
Propranolol	1 (5.00)	0 (0.00)	
Folic	1 (5.00)	2 (66.67)	
Multivitamin	3 (15.00)	0 (0.00)	

Notes: p values derived from chi-square test for categorical variables, Fisher's exact test where expected counts are less than 5, t-test and Wilcoxon rank-sum test for continuous variables. SD: Standard deviation.

11.11% of sertraline users, though the difference was not statistically significant (p = .33). Insomnia was similar in both groups (23.40% for fluoxetine, 22.22% for sertraline; p = .91). Agitation was observed only in the sertraline group (11.11%; p = .07), while headaches were more common in sertraline users (33.33%) than in those taking fluoxetine (14.89%; p = .10).

In the endocrine and reproductive systems, sexual dysfunction was reported by 11.11% of patients on sertraline, with no cases in the fluoxetine group (p = .07). For the peripheral nervous system, dry mouth was noted in 27.66% of fluoxetine users and 33.33% of sertraline users (p = .65), while blurred vision was more frequent in the fluoxetine group (27.66%) compared to sertraline (11.11%; p = .20).

In the cardiovascular system, palpitations occurred in 6.38% of fluoxetine patients and 11.11% of sertraline patients (p = .61). Orthostatic hypotension was reported by 36.17% of the fluoxetine group and 33.33% of the sertraline group (p = .83).

Regarding gastrointestinal symptoms, anorexia was significantly higher in the fluoxetine group (21.28%) compared to none in the sertraline group (p = .05), while nausea or vomiting was more prevalent in the sertraline group (27.78%) than in the fluoxetine group, with no cases reported (p = .001). Other gastrointestinal symptoms, such as increased appetite and constipation, showed no significant differences between the groups.

Other ADRs included ataxia, reported by one sertraline patient (5.56%) but none in the fluoxetine group (p = .28). Fatigue was noted in 6.38% of the fluoxetine group and 16.67% of the sertraline group (p = .34).

Discussion

This study provides insights into the prevalence and characteristics of ADRs associated with fluoxetine and sertraline, two commonly prescribed SSRIs for the treatment of depression. By adopting a naturalistic design, this study reflects real-world clinical settings, which allows for a more comprehensive understanding of ADRs as they occur during clinical practice.

The results indicate that both fluoxetine and sertraline are associated with specific ADRs, though certain patterns have emerged. Notably, patients on fluoxetine reported a higher prevalence of anorexia compared to those on sertraline (21.28% vs. 0%, p = .05). This finding aligns with previous studies suggesting that fluoxetine may initially lead to weight

Table 2. Comparison of Adverse Drug Reactions (ADR) Between Fluoxetine and Sertraline.

ADR	Fluoxetine (*n* = 47)	Sertraline (*n* = 18)	*p* Value
Central nervous system, n (%)			
Sedation	11 (23.40)	2 (11.11)	.33
Insomnia	11 (23.40)	4 (22.22)	.91
Agitation	0 (0.00)	2 (11.11)	.07
Headache	7 (14.89)	6 (33.33)	.10
Endocrine and reproductive system, n (%)			
Sexual dysfunction	0 (0.00)	2 (11.11)	.07
Peripheral nervous system, n (%)			
Dry mouth	13 (27.66)	6 (33.33)	.65
Blurred vision	13 (27.66)	2 (11.11)	.20
Cardiovascular system, n (%)			
Palpitation	3 (6.38)	2 (11.11)	.61
Orthostatic hypotension	17 (36.17)	6 (33.33)	.83
Gastrointestinal system, n (%)			
Increase appetite	2 (4.26)	1 (5.56)	1.00
Anorexia	10 (21.28)	0 (0.00)	.05
Nausea or vomiting	0 (0.00)	5 (27.78)	.001
Constipation	2 (4.26)	1 (5.56)	1.00
Other, n (%)			
Ataxia	0 (0.00)	1 (5.56)	.28
Fatigue	3 (6.38)	3 (16.67)	.34

Note: *p* values derived from chi-square test for categorical variables, Fisher's exact test where expected counts are less than 5.

loss by −2.7 kg and body mass index by −1.1 kg/m^2, likely due to its appetite-suppressing effects.[17] On the other hand, nausea or vomiting was significantly more common among sertraline users (27.78%) compared to those on fluoxetine, where no such cases were observed ($p = .001$). A recent meta-analysis[18] also found that sertraline is more likely to cause gastrointestinal side effects, such as nausea and diarrhea, due to its strong inhibition of serotonin reuptake and its effects on dopamine transporters. This can lead to increased extracellular serotonin and altered dopamine levels in the gut, resulting in inflammation and digestive issues. In contrast, fluoxetine has a lower risk of such side effects, highlighting differences in their gastrointestinal side effect profiles.

The incidence of sexual dysfunction, sedation, and cardiovascular effects showed no statistically significant differences between the two groups. However, these ADRs remain clinically relevant, as they may affect patient adherence. Sexual dysfunction was reported more frequently in the sertraline group (11.11%) than in the fluoxetine group (0%), although the difference was not statistically significant. This aligns with evidence that SSRIs can impair sexual function, likely due to increased serotonin levels affecting other hormones and neurotransmitters, such as testosterone and dopamine. Comparatively, paroxetine has been found to cause more sexual dysfunction than fluvoxamine, sertraline, and fluoxetine, respectively.[19] The lack of differences in sedation and insomnia between fluoxetine and sertraline aligns with findings from a double-blind study on depression, where 284 patients showed similar improvements in depression and insomnia across fluoxetine, sertraline, and paroxetine, with no significant differences in adverse events related to activation or sedation, regardless of baseline insomnia levels.[20] The study of side effects on medication adherence found that somnolence and headache, along with other unspecified ADRs, have been associated with higher dropout rates for SSRIs.[21] To address this, our study allowed the combined use of benzodiazepines or sedating antidepressants, such as low doses of mianserin or trazodone, which may have influenced the observed effects related to sedation and insomnia.

The absence of significant differences in cardiovascular ADRs, such as palpitations and orthostatic hypotension, is encouraging, suggesting a favorable safety profile for cardiovascular disease. SSRIs generally have a more acceptable safety margin and a lower risk of toxicity compared to other anti-depressant classes, with cardiovascular events being mild and uncommon at therapeutic doses. However, orthostatic hypotension, mild bradycardia, and conduction abnormalities, including QT interval prolongation, have been reported with SSRI use.[22]

One of the strengths of this study is its naturalistic design, which reflects real-world patient experiences and medication use patterns, providing practical insights for clinicians. Additionally, the use of a validated questionnaire ensured comprehensive data collection regarding ADRs, contributing to the reliability of the findings.

However, several limitations should be considered. The relatively small sample size, particularly in the sertraline group, may have limited the statistical power to detect differences in less common ADRs. Furthermore, the reliance on patient self-reports could lead to underreporting or recall bias,[23] especially for symptoms that patients may not immediately associate with medication use. Additionally, our study could not account for pharmacogenetic variations, particularly concerning CYP2D6. Fluoxetine and its metabolites are primarily metabolized via CYP2D6, and fluoxetine is also a potent inhibitor of this enzyme. This can lead to an "iatrogenic poor phenotype" or "phenocopy" when combined with other drugs metabolized by CYP2D6, such as venlafaxine, potentially increasing the risk of toxicity due to elevated plasma drug levels. Patients with poor CYP2D6 function may have reduced metabolism of fluoxetine and paroxetine, resulting in higher plasma concentrations and a greater likelihood of experiencing side effects.[24] Future studies with larger sample sizes and more objective measures of ADRs (e.g., blood pressure measurement for orthostatic hypotension) are recommended to confirm these findings.

The findings of this study emphasize the importance of monitoring for specific ADRs when prescribing fluoxetine and sertraline to outpatients with depression. While both medications are generally well-tolerated, clinicians should be aware of the potential for anorexia with fluoxetine and gastrointestinal issues, such as nausea, with sertraline. Providing patients with information on possible side effects can help improve medication adherence and overall treatment outcomes.

Conclusion

In conclusion, this study highlights the distinct ADR profiles of fluoxetine and sertraline, with anorexia being more common in fluoxetine users and nausea being more prevalent among those on sertraline. While both medications have specific side-effect patterns, they remain effective options for the management of depression. Clinicians should consider these findings when selecting anti-depressant therapy and counseling patients accordingly to ensure better treatment adherence and outcomes.

Abbreviations

ADRs: Adverse drug reactions; **CNS:** Central nervous system; **COA:** Certificate of approval; **CYP2D6:** Cytochrome P450 2D6; **doi:** Digital object identifier; **F32.0:** Mild depression (ICD-10 code); **F32.1:** Moderate depression (ICD-10 code); **F32.2:** Severe depression without psychotic symptoms (ICD-10 code); **F32.3:** Severe depression with psychotic symptoms (ICD-10 code); **IOC:** Index of item objective congruence; **kg:** Kilograms; kg/m^2: Kilograms per square meter; **mg:** Milligrams; **PMID:** PubMed identifier; **SD:** Standard deviation; **SERT:** Serotonin transporter; **SSRIs:** Selective serotonin reuptake inhibitors; **WHO:** World Health Organization.

Authors Contribution

CW: Research question, writing—reviewing & editing, conceptualization; TB: Research question, data analysis, writing—original draft, writing—reviewing & editing; PH, JS: Methodology, data extraction, data management, data synthesis, writing—reviewing & editing.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Ethical approval was granted by the Prasrimahabhodi Psychiatric Hospital Research Ethics Committee (COA No. 006/2561) and the study conforms to the Declaration of Helsinki.

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Informed Consent

Complete written informed consent was obtained from the patient for the publication of this study.

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