Randomised Controlled Trial

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Sertraline versus escitalopram in South Asians with moderate to severe major depressive disorder: (SOUTH-DEP) a double-blind, parallel, randomized controlled trial

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Objective: The study design included the double-blind, parallel, randomized controlled trial. The aim of this randomized controlled trial was to compare the efficacy and safety of sertraline and escitalopram in participants with moderate to severe major depressive disorder (MDD).

Methods: The study was conducted in South Asian participants. A total of 744 participants with moderate to severe MDD were randomly assigned to receive either sertraline or escitalopram for 8 weeks. Drug dosages and titration schedules were based on the recommendations of the prescribing information for each product and according to the judgment of the clinicians involved in the study. The primary outcome measures were changes from baseline on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the clinical global impression (CGI) scale as well as the frequency of adverse events in both groups. Baseline MADRS scores in the escitalopram and sertraline groups were 28.2 ± 0.47 (mean ± SD) and 29.70 ± 0.46 (mean ± SD) respectively, and was no variability in the baseline assessments. Changes in MADRS as well as CGI scales at the end of the study were significant only for the sertraline group whereas they remained statistically nonsignificant for the escitalopram group. Results: The results of the study showed that sertraline was more efficacious than escitalopram in reducing depression rating scales such as MADRS and CGI, and that participants subjectively felt better regarding their symptoms in the sertraline group. Sertraline displays enhanced safety or tolerability than other groups of antidepressants, which frequently cause high levels of drowsiness, dizziness, blurred vision, and other undesirable effects. Adverse events were seen in both groups, but delayed ejaculation was the most frequent adverse event seen in both groups. However, a greater number of participants reported having nausea and insomnia in the sertraline group compared to the escitalopram group.

Conclusion: Our study clearly highlights that there is a statistically significant difference in efficacy between sertraline and escitalopram at the doses used in our study. Sertraline was able to significantly lower the depression rating scales like MADRS and CGI in participants with moderate to severe MDD. Participants subjectively felt better regarding their symptoms in the sertraline group. The most frequent adverse event in both groups was delayed ejaculation. From an efficacy standpoint, sertraline was more efficacious than escitalopram. The study indicates that the prevalence of depressive disorders in South Asia is comparable to the global estimate, and Bangladesh and India has higher proportions of people with depressive disorders in South Asia. Additionally, females and older adults (75–79 years) have the highest burden of depressive disorders across all countries in the region. This study's limitation included the absence of a placebo arm. An additional limitation of the current study was the lack of an evaluation of inter-rater reliability and the research sample could not have been uniform in terms of the kind of depressive disorders and bipolarity.

Keywords: depressive disorder, escitalopram, humans, major, sertraline, South Asian people

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Introduction

Background

Major depressive disorder (MDD) is the leading psychiatric disorder that has impregnated every stratum of people and has been prejudicial to public health and productivity[1,2]. It is usually characterized by at least 2 weeks of steady depressed mood and loss of interest, accompanied by decreased appetite, fatigue, difficulty concentrating, inability to sleep, and hopelessness[3]. The disease affected roughly 2% of the population in the world (163 million people) in 2017[4] and it is more prevalent in industrialized countries than in developing countries[5]. It has been reported that MDD commonly affects youth specifically females suffer twice as males[3,5], and is the second leading cause of disability-adjusted life years after lower back pain[6]. Options to treat MDD include psychotherapy, pharmacotherapy, and electroconvulsive therapy, but the treatment mainly depends upon the individual's preference, comorbidities, and severity of the disease[7].

Escitalopram is an antidepressant that works by blocking the selective serotonin reuptake of serotonin. Escitalopram was found to be beneficial at a beginning dosage of 10 mg/day in placebo-controlled studies, with a rate of discontinuation owing to adverse events (AEs) comparable to that of the control group[7]. Six and 8 week placebo-controlled studies were used to determine the selective serotonin reuptake inhibitors (SSRI) sertraline's antidepressant effectiveness. Sertraline should be used for the first time at a dosage of 50 mg per day to treat depression. The National Institute for Health and Care Excellence (UK) inferences that SSRI such as escitalopram, paroxetine, and sertraline have 50% greater effectiveness in treating moderate to severe depression than placebo[8]. Escitalopram, an SSRI, is the most selective in this class with the highest efficacy and acceptability rate among different antidepressants. A dose of 10 mg/day was shown to be effective and not significantly different in terms of discontinuation due to AEs when compared to a placebo[9]. The dosage range of 50–200 mg/day is recommended for sertraline as it correlates with the dose and peak plasma concentration and does not have any significant side effects[10]. According to a single study, participants using sertraline and escitalopram experienced equal degrees of improvement in their depressive symptoms. Placebos do not truly treat a condition or cure a sickness, but they may assist in the relief of symptoms like pain, exhaustion, or sleeplessness brought on by stress. Sertraline dosage increases to 200 mg/day at intervals of no less than 1-week may be beneficial for patients who do not react to 50 mg/day. Sertraline is routinely prescribed by doctors for depression at dosages more than 100 mg/day, in accordance with IMS data[11].

The WHO estimates that almost one-third of people suffering from depression worldwide live in South Asia, making the region home to a large majority of the world are depressed[12]. A mental health expert at London's King's College, states that the South Asian population carries 'a bigger notion of shame' with them than other ethnic populations. South Asian religious and cultural influences often do not consider mental health a medical issue, referring to it as a 'superstitious belief'. A 2010 study by the campaign Time to Change found that South Asians rarely discuss mental health because of the risk the subject poses to their reputation and status.

HIGHLIGHTS

- Major depressive disorder is the leading psychiatric disorder that has impregnated every stratum of people and has been prejudicial to public health and productivity.
- Our study clearly highlights that there is a statistically significant difference in efficacy between sertraline and escitalopram at the doses used in our study.
- Sertraline was more efficacious than escitalopram in reducing depression rating scales such as the Montgomery-Åsberg Depression Rating Scale and clinical global impression.
- Participants subjectively felt better regarding their symptoms in the sertraline group.

The aim of our study was to determine if there was any significant difference in the efficacy and tolerability of escitalopram and sertraline in the South Asian population with moderate or severe MDD. The objectives included changes in depression scores as per the MADRS and CGI scores in South Asian patients with moderate to severe depression. This study will provide valuable information on the efficacy and tolerability of sertraline over escitalopram in the South Asian population with MDD, which is underrepresented in previous studies on this topic. By employing appropriate measures to ensure adequate allocation concealment, thereby minimizing the potential for selection bias in the assignment of participants to treatment groups, we studied if there was any significant difference in in efficacy and tolerability between oral sertraline (50–200 mg/day) and oral escitalopram (10 mg/day) given either at night or during the day in the South Asian population for the treatment of moderate to severe MDD[13,14]. No differences in efficacy were observed for fixed-dose escitalopram 10 mg/day and sertraline flexibly dosed from 50–200 mg/day. At these doses, both escitalopram and sertraline were generally well tolerated.

This is a monocentric, double-blind, parallel, randomized controlled trial conducted in Khan Research Laboratories (KRL) hospital, Islamabad, Pakistan, for a total period of 16 weeks and a short period of 8 weeks. 744 South Asian patients with moderate to severe MDD as per the MADRS scale who had consented to participate in the trial and who fulfilled the inclusion criteria were included in our study. The study was conducted at KRL hospital. KRL hospital is a 350-bedded hospital that offers versatile services and treatment of human medicine including psychiatric care. Psychiatry is a well-renowned medical field, in which psychiatrists diagnose and treat diseases plus disorders related to the mind, emotions, and human behaviors. Psychiatrists of the KRL hospital are both nationally and internationally accredited. The psychiatrists in KRL hospital treat the patients with great respect, care, and with utmost safety to ensure the best treatment results.

Methods

Inclusion and exclusion criteria

This study aimed to enroll adult outpatients, aged 20–80, of either sex from Islamabad, Pakistan, who had been diagnosed with MDD as per the DSM-V criteria[15], as determined by the mini-international neuropsychiatric interview[16]. Eligible participants

had to have a score of at least 20 on the MADRS at both screening and baseline visits. The MADRS score was chosen by the primary investigator at this value to accommodate almost all participants who had moderate or severe depression and minimize or exclude those with no or mild depression. Study participants had to have normal results on physical examination, laboratory tests, and ECG, or any abnormalities had to be clinically insignificant. Female participants of childbearing potential had to have a negative pregnancy test and be using medically approved contraception. Lactating women were not eligible to participate. Furthermore, individuals with a psychiatric disorder other than MDD, a history of any DSM-IV defined psychotic disorder, or a current diagnosis of bipolar disorder, schizophrenia, obsessive-compulsive disorder, intellectual disability, or pervasive development disorder were excluded from the study. In addition, participants with current substance abuse or dependency, suicidal risk, or personality disorders that would impede participation were also not eligible to participate. Participants were also not eligible to participate if they had used a SSRI in the past 2 weeks (past 5 weeks if they used fluoxetine). Participants with a MADRS score of less than or equal to 19 were also excluded from our study. All participants provided written informed consent and the study protocol was approved by the institutional review board of KRL hospital. The study was conducted in accordance to the principles outlined in the Declaration of Helsinki and the International Conference on Harmonization. No animals were used or studied in this study.

Data collection

Patients were randomized into two groups, one receiving escitalopram (10 mg/day) and up-titrated to a maximum dose of 20 mg/day and the other receiving sertraline (200 mg/day) using a double blinded parallel-group design and followed up till 16 weeks of duration and a short period of 8 weeks. Sertraline was initiated at 50 mg/day, and could be increased by 50 mg/day at weekly intervals based on clinical need and tolerability at the lower dose level. Sertraline was used to increase the levels of a mood-enhancing chemical called serotonin in the brain. The study design involved a progression of phases for eligible patients. Initially, a 1-week single-blind placebo lead-in period was undertaken, in which participants who met the necessary criteria were given a placebo treatment. Those who completed this phase and continued to meet entry requirements were randomly assigned to either receive 16 weeks or 8 weeks of double-blind treatment with escitalopram or sertraline. To maintain study blinding, identical capsules were provided for both treatment groups. During the first week of double-blind treatment, patients were instructed to take one capsule per day, with the option to increase the dosage at weekly intervals up to a maximum of four capsules per day, at the discretion of the investigator, based on the patient's response and the absence of AEs. For patients assigned to receive sertraline, each capsule contained 200 mg of the study drug. For those assigned escitalopram, one capsule contained 10 mg of the medication, with the remaining capsules being placebos. Participants were instructed to take the capsules as a single dose in the evening, but switching to a morning dose was allowed if preferred. Compliance with the study medication was recorded at all postbaseline visits. Participants unable to tolerate the minimum dosage of their assigned treatment were discontinued from the trial.

The study recruited a sample of 744 patients based on the sample size calculator riskcalc[17], with the aim of achieving a statistical significance level of 0.05 and a power of 0.8. This sample size was chosen in order to ensure that any observed differences in the study outcomes would be statistically meaningful and robust in the study.

During the study, visits were scheduled for the participants. These visits were conducted at the initial screening and baseline and then at the end of the study. The baseline visit took place at the conclusion of the placebo lead-in period. In the event that a participant withdrew prematurely from the study, they still received all evaluations at the end of the study. The study investigators carried out safety assessments at all visits, which included monitoring vital signs, body weight, any concomitant medication being taken, and any AEs. The patients were specifically asked about any AEs. Physical examinations and laboratory tests, including hematology, chemistry, and urinalysis, were performed for all patients at the screening and at the end of study, or upon early termination. A 12-lead ECG, urine drug screen, thyroid function test, and serum human chorionic gonadotropin pregnancy test for women of childbearing potential were only done at the screening visit. Efficacy evaluations included the MADRS and clinical global impression (CGI) scale at the baseline and the end of study.

Both drugs sertraline and escitalopram remission achieved of the study participants and significantly greater than escitalopram.

Outcomes were assessed using the CGI scale at the end of study. Tolerability was assessed by the frequency of AEs in participants of each arm in the trial. A drug that significantly improved participant CGI and MADRS scales was considered to be superior in efficacy while drug that caused least number of AEs was considered to be superior in tolerability.

Data analysis

IBM Corp. released 2015. IBM SPSS Statistics for Windows, Version 23.0.: IBM Corp software was used for data analysis. The mean MADRS and CGI scores were calculated at baseline and at the end of the study. A *t*-test was used to compare means and test for significance in the change for MADRS and CGI-I between both groups to determine the overall efficacy of both drugs.

Our study is fully compliant with STROCSS 2021 guidelines[18]. A complete STROCSS checklist has been provided as a supplementary file (Supplemental Digital Content 1, http://links.lww.com/MS9/A235). Our study is in accordance with the Declaration of Helsinki.

A consolidated standards of reporting trials (CONSORT) flow diagram has also been depicted in Figure 1 below.

Results

Baseline characteristics of MADRS and CGI

This double-blind parallel-group randomized controlled trial was conducted on a sample of 744 participants that fulfilled the inclusion criteria for the study. Participants were randomized into either the sertraline group or the escitalopram group and change in MADRS and CGI scores from baseline as well as the frequency of AEs were assessed. Participants in both groups contained an equal number of participants based on sex with half being males

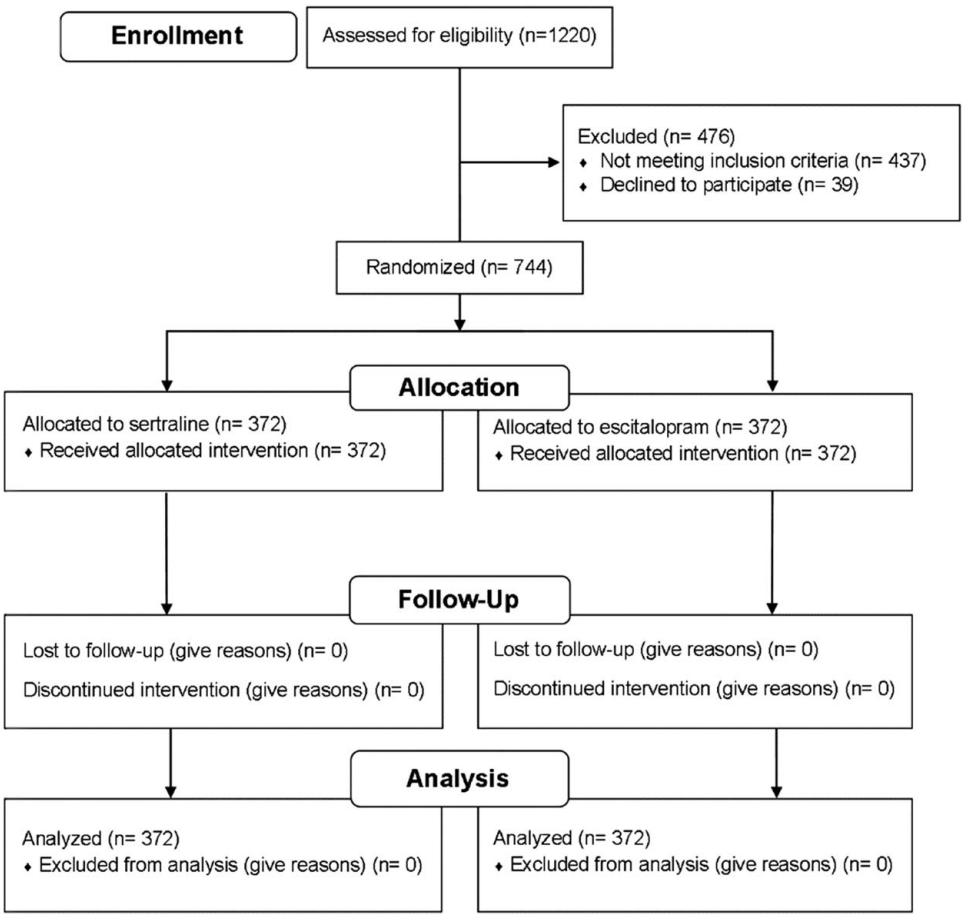

Figure 1. Consolidated standards of reporting trials (CONSORT) flowchart for methodology.

and half being females in our study. The mean age of participants randomized to the escitalopram group was 50.27 ± 14.02 (mean ± SD) and the mean age of study participants randomized to the sertraline group was 48.49 ± 12.85 (mean ± SD). Baseline MADRS scores in the escitalopram and sertraline groups were 28.2 ± 0.47 (mean ± SD) and 29.70 ± 0.46 (mean ± SD) respectively, and was no variability in the baseline assessments. Changes in MADRS as well as CGI scales at the end of the study were significant only for the sertraline group whereas they remained statistically nonsignificant for the escitalopram group.

Both drugs achieved remission in more than 50% of the study participants but sertraline was seen to achieve remission and response rates significantly greater than escitalopram. Further details on the results are tabulated in Table 1. The relative risk of remission of major depression was highest in the sertraline group with a relative risk of 1.23 (95%CI: 1.07–1.42; $P < 0.05$) as shown in Table 2. Delayed ejaculation was the most frequently reported adverse event with more than 17% (129) and 32.66%

Table 1

Table of baseline and outcome characteristics.

Characteristic	Mean ± SD	*P*	SEM
Age (in years) of study participants randomized to escitalopram group	50.27 ± 14.02	–	0.73
Age (in years) of study participants randomized to sertraline group	48.49 ± 12.85	–	0.67
MADRS - escitalopram group (baseline)	28.2 ± 0.47	0.036	0.02
Change in MADRS from baseline - escitalopram group	− 17.32 ± 4.86	0.632	0.04
MADRS - sertraline group (baseline)	29.70 ± 0.46	0.043	0.02
Change in MADRS from baseline - sertraline group	**− 23.85 ± 0.89**	**0.021**	**0.05**
CGI-I - escitalopram group	− 1.1 ± 0.47	0.778	0.02
CGI-I - sertraline group	**− 2.22 ± 0.49**	**0.002**	**0.04**
	sertraline-group *n* = 372 (%)	escitalopram-group *n* = 372 (%)	
Remission (defined as number of study participants with MADRS score of ≤ 6 at the end of study)	267 (71.78)	232 (62.37)	
Response (defined as at least 50% decrease in MADRS score from baseline)	222 (59.68)	176 (47.31)	

CGI-I, clinical global impression-improvement; MADRS, Montgomery-Asberg depression rating scale; SEM, standard error of the mean.
A *P*-value of <0.05 was considered to be significant and significant values are highlighted in bold.

Table 2

Relative-risks for remission in sertraline and escitalopram groups.

For remission (MADRS score maintained at ≤6 for more than 4 weeks)	Value	95% Confidence Interval	
		Lower	Upper
Relative risk-sertraline group	1.23	1.07	1.42
Relative risk-escitalopram group	0.80	0.68	0.95

(243) participants in escitalopram and more than 10% of all patients in the sertraline group 39.78% (296) and 10.22% (76) reporting delayed ejaculation as an adverse event as shown in Figure 2. Insomnia was reported as an adverse event in only 3% (23) and 46.9% (349) of participants in the escitalopram group and its frequency was reported to be double in the sertraline group 43.95% (327) and 6.09%,(45) also shown in Figure 2. These shows a total of 744 patients' results. Details regarding AEs such as nausea and diarrhea are visualized in detail in Figure 3. The frequency of having an upper respiratory infection as an adverse event is visualized in Figure 4. Patients were asked at the end of the study regarding their subjective feeling of disease improvement and participants from both groups reported feeling better but the number of participants that felt better were greater in the sertraline group compared to the escitalopram group, as shown in Figure 5. All participants participated in the study till the end and there was no attrition in our study.

Discussion

Double-blind studies are particularly useful for preventing bias due to demand characteristics or the placebo effect. Blinding is generally viewed as an effective method by which to mitigate bias and decreasing the risk of incorrect decision-making and wrong assumptions about the data). Blinding poses certain limitations, and there are some profound benefits of unblinding certain members of the research team including statisticians. Our study clearly highlights that there is a statistically significant difference in efficacy between sertraline and escitalopram at the doses used in our study. Participants in the sertraline group had a statistically significant difference in changes from the baseline and this was not the case for the participants in the escitalopram group. Moreover, the most frequent adverse event in both groups was delayed ejaculation. From an efficacy standpoint, sertraline was more efficacious than escitalopram. Sertraline was able to significantly lower the depression rating scales like MADRS and CGI in participants with moderate to severe MDD. There appears to be a relatively good correlation between MADRS and CGI scores. Inter-rater reliability and validity on the MADRS with different pairs of raters has been reported to be 0.89–0.97. Inter-rater reliability between raters of different disciplines (psychiatrist/nurse) has also been demonstrated to be good. Participants subjectively felt better regarding their symptoms in the sertraline group. They also felt better in the escitalopram group, but not to the extent as in the sertraline group. AEs were seen in both groups. A greater number of participants reported of having nausea and insomnia in the sertraline group versus the escitalopram group. All other AEs were greater in the escitalopram group. Delayed ejaculation was the most frequent adverse event but seen in both groups. Although participants in both groups suffered from this adverse event, there were greater number of participants in the escitalopram group compared to the sertraline group[19].

Escitalopram is a medication that is commonly used to treat certain mental health conditions. It is approved for use at dosages of 10 and 20 mg. When taken orally, it reaches its maximum concentration in the blood (T_{max}) in about 5 h, and it is 56% bound to proteins. It takes 1–2 weeks for it to reach a steady-state concentration in the blood[20–22]. Sertraline is another medication that is used to treat mental health conditions. It is approved for use at higher dosages, with a typical daily dose of 200 mg. When taken orally, it reaches T_{max} in 5–9 h, it is highly protein bound

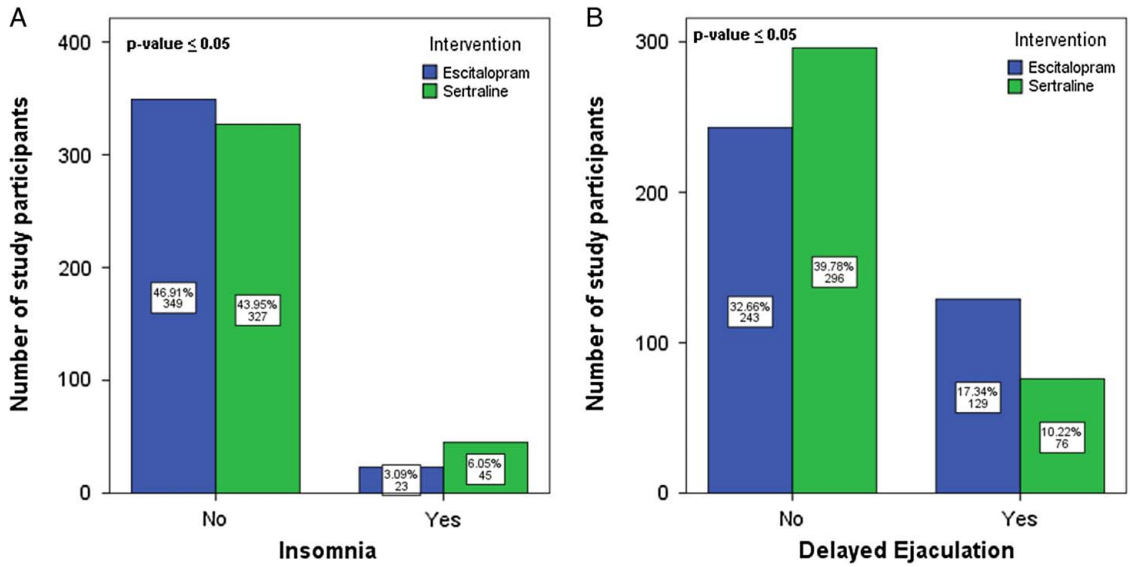

Figure 2. Figure depicting adverse events insomnia (A) and delayed ejaculation (B); numbers along with percentages in each box indicate number and percent of study participants that had these events.

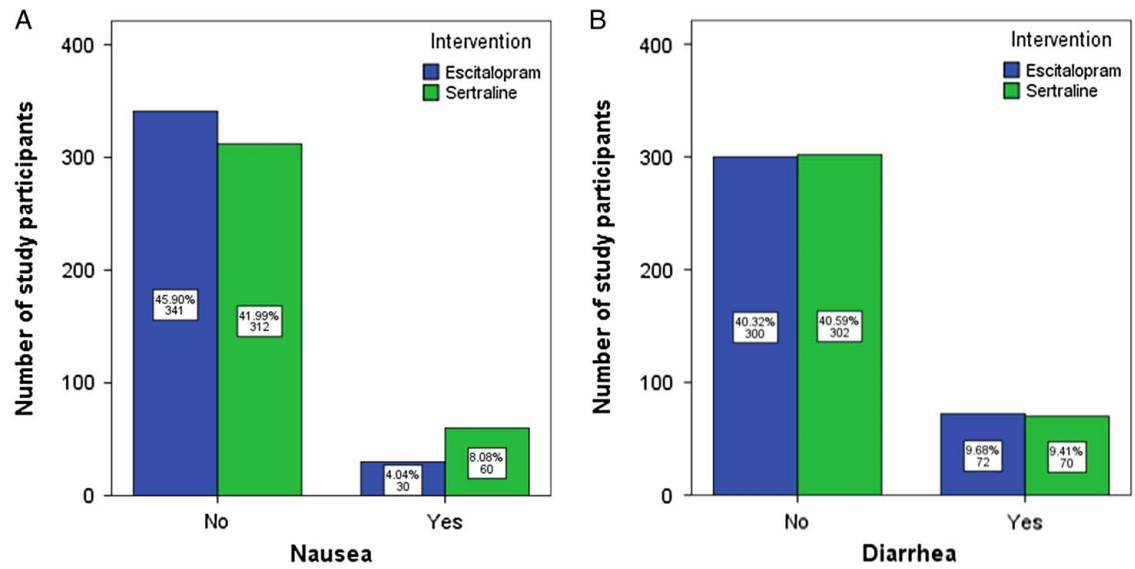

Figure 3. Figure depicting adverse events nausea (A) and diarrhea (B); numbers along with percentages in each box indicate number and percent of study participants that had these events.

(99%), and it reaches steady-state concentration in the blood within 1-week[23,24]. Studies from preclinical or clinical show mixed data with the majority showing that escitalopram is more potent and efficacious, which is in disagreement to our results.

There have been multiple clinical trials that have shown that escitalopram and sertraline are more effective in treating depression than paroxetine. In addition to this, escitalopram is considered more efficacious than other SSRIs. This has been demonstrated in head-to-head comparisons, meta-analyses, and literature reviews. The mechanism theorized behind this increased efficacy may be related to escitalopram's actions at allosteric sites of the serotonin transporter (SERT). Studies have characterized the allosteric mechanism of escitalopram[25–28] and other compounds have also been reported to have allosteric activities at the SERT, but are less well characterized[29,30].

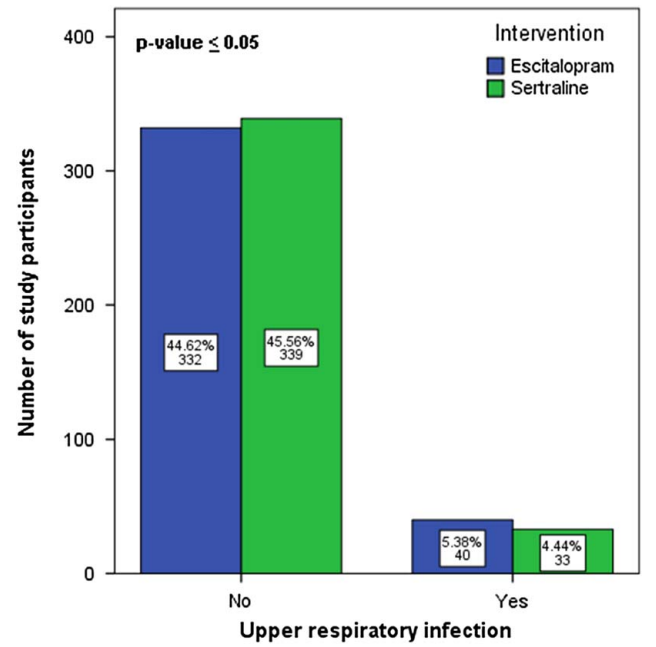

Figure 4. Figure depicting adverse event upper respiratory infection; numbers along with percentages in each box indicate number and percent of study participants that had these events.

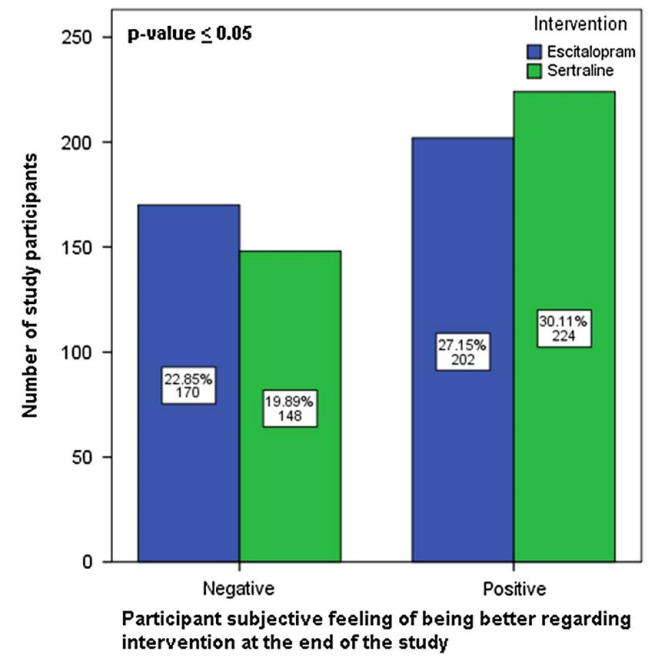

Figure 5. Figure depicting participant subjective feeling of being better regarding intervention at the end of the study; numbers along with percentages in each box indicate number and percent of study participants that expressed these feelings.

In a randomized, double-blind, placebo-controlled trial conducted in primary care centers in Canada, Europe, and the United Kingdom, patients treated with escitalopram (10 mg/day) for 8 weeks experienced a significantly greater decline in mean scores on the MADRS than did placebo treated patients. Scores for escitalopram treated patients were significantly lower from the second week of treatment forward. At week 8, 55% of patients receiving escitalopram achieved a clinical response (i.e. $\geq 50\%$ reduction from baseline in MADRS score)[31]. A total of 85% of these responders also achieved remission (i.e. a MADRS score ≤ 12). Rates of response and remission associated with escitalopram were significantly higher than those in placebo-treated patients and were particularly noteworthy in light of the moderate-to-severe levels of depression at the start of the study (mean baseline MADRS score of 29). In the pivotal clinical trials conducted for the regulatory submission to the USFDA, escitalopram was seen to be more effective than placebo as assessed by standard study endpoints (change in MADRS, HAM-D, and CGI scores) in randomized, double-blind studies in patients with major depression. Efficacy analysis showed a significantly superior therapeutic effect for escitalopram versus placebo from week 1 onwards (observed cases). By comparison, escitalopram 20 mg/day did not demonstrate a statistically significant effect compared to placebo indicating a faster onset of action of escitalopram. The difference between the active treatment groups was not statistically significant[32].

Clinical studies using PET imaging and radioligands have shown that a SERT occupancy rate of around 80% is necessary to achieve therapeutic effects from SSRI treatment. Studies using drugs such as sertraline and citalopram have found that at higher doses, a maximum of 85% occupancy is achieved. Similar results have been observed with escitalopram using a different radioligand in SPECT studies, with a maximum of 82% SERT occupancy. These findings suggest that increasing the dose of SSRIs beyond a certain point does not further improve efficacy, but rather leads to additional side effects and higher rates of discontinuation. Based on these preclinical observations, it can be inferred that the increase in extracellular 5-HT in humans taking escitalopram may be greater than for those taking paroxetine or sertraline, despite a similar plateau in SERT occupancy[33–36]. This is in stark contrast to our findings where sertraline was seen to be more efficacious and tolerable than escitalopram.

Furthermore, a recent meta-analysis verified that somatic anxiety symptoms resolve more slowly in individuals with the s/s genotype of the 5-HTTLPR. In Asian people compared to Caucasians, the frequency of the G/G genotype in the HTR2A variant and the s/s genotype in the 5-HTTLPR is greater. Comparing Asians to Caucasians, antidepressant therapy may have a different or worse effect on them[37].

The dosage of antidepressants is another problem that has to be taken into account. Setting equivalent doses is required to make it easier to evaluate the results of comparative clinical trials and subsequent meta-analyses, which depend crucially on dose equivalence. However, categorical dosage categorization was used to assess the doses of various antidepressants in earlier research that claimed escitalopram was better or that there was no difference in effectiveness amongst antidepressants[38].

In comparison to patients with severe depression, we discovered that individuals with baseline mild depression had greater response and remission rates. Additionally, moderate depression had a considerably larger fall in and MADRS scores. These results are consistent with four escitalopram studies in individuals with MDD in the Pakistani community[39] Escitalopram did; however, outperform other SSRIs in treating individuals with severe depression at baseline, according to many trials. However, this study's limitations might be attributed to the lack of a placebo or alternative treatment group for comparing of treatment efficacy.

Many AEs were not observed or reported rarely, such that there were only one or two events in the intervention arm and zero in the comparator arm. For several other AEs, data were not reported in the peer reviewed literature at all. The issue of sparse data throughout the evidence base was further complicated by the treatment phases that studies used, as most were specific to treating the acute phase of MDD (> 12 weeks), but others evaluated only the continuation (12 weeks up to 48 weeks) or maintenance (beyond 48 weeks) phases of treatment. Data beyond the acute treatment phase were very limited[40].

Future research recommendations include conducting a study in multiple centers to increase the power of the study and allow for more robust conclusions to be drawn about the efficacy and safety of sertraline and escitalopram. Additionally, conducting the study in different populations such as the elderly, children, or different ethnic groups would allow for more generalizable conclusions about the efficacy and safety of sertraline and escitalopram. A genetic analysis of South Asian participants would provide more information about the genetic factors that may influence response to sertraline and escitalopram.

Conclusion

The study found that sertraline was more efficacious than escitalopram in reducing depression rating scales such as MADRS and CGI, and that participants subjectively felt better regarding their symptoms in the sertraline group. AEs were seen in both groups, but delayed ejaculation was the most frequent adverse event seen in both groups. However, a greater number of participants reported having nausea and insomnia in the sertraline group compared to the escitalopram group. The study's findings disagree with previous studies that have shown that escitalopram is more potent and efficacious than sertraline. The study suggests that future research should investigate a possible genetic mechanism behind the increased efficacy of sertraline in treating depression in the South Asian population, and explore the potential for sertraline to be used as an alternative to escitalopram in the treatment of depression.

Limitation

This study's limitation included the absence of a placebo arm. As a result, it was difficult to determine the placebo response rate and rule out the potential that depression symptoms would have improved as the disease progressed naturally. An additional limitation of the current study was the lack of an evaluation of inter-rater reliability. A systematic diagnostic interview, which would have allowed for a more in-depth evaluation of mental comorbidities and subtypes of depression, was also not conducted. Finally, despite the fact that the research sample could not have been uniform in terms of the kind of depressive disorders and bipolarity, the problems associated with bipolarity were not addressed. The use of CGI-S also has some inherent limitations. Standardization across clinics typically does not occur; so, neither

inter-rater reliability nor a consensus of how much each rating relies on symptoms or daily function or satisfaction has been agreed. A limitation of the MADRS in bipolar clinical trials is its absence of focus on common bipolar depressive symptoms such as feelings of worthlessness, anhedonia, and motor retardation. Finally, although changes in scores on clinical scales such as the MADRS and CGI are well-established measures of clinical efficacy, antidepressants can also be assessed using validated surrogate outcomes, which may be better measures of 'real-life' efficacy, such as remission rates, quality of life, patient-reported outcomes and productivity, for example, the recent study by Demyttenaere *et al*.[41], showed that patients treated with escitalopram reported a statistically and clinically significant improvement in quality of life enjoyment and satisfaction using data from eight randomized, 8-week, clinical trials. This study did not assess efficacy in terms of these patient-centered outcomes; however, a number of Leonard and Taylor observational or naturalistic studies were included, and these can be assumed to better capture the treatment efficacy of sertraline and escitalopram in the 'real-life' clinical setting.

Ethical approval

This study involving human participants was reviewed and approved by institutional review board (IRB) of KRL hospital under approval number KRL/02/19/1 on 18th April 2022, and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines. The patients/participants provided their written informed consent to participate in this study.

Consent

The patients/participants provided their written informed consent to participate in this study. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Authors contribution

All authors qualify for authorship as per the ICMJE criteria for authorship. All authors significantly contributed to conceptualization, data curation, writing – original draft, writing – review and editing and visualization.

Conflicts of interest disclosure

The author declares they have no conflicts of interest including financial or other relationships, that may have influenced the conduct or interpretation of the study.

Research registration unique identifying number (UIN)

Researchregistry8989 identifies our trial registration and is available online from: https://www.researchregistry.com/browse-the-registry#home/registrationdetails/64551a4b8096db002780bcdc/

Guarantor

Hassan Mumtaz.

Data availability statement

Data from the randomized controlled trial will be made available upon request to qualified researchers for the purpose of reproducing and validating the study's findings. Requests for data can be sent to the corresponding author.

Provenance and peer review

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