

Risks of Digestive System Side-Effects of Selective Serotonin Reuptake Inhibitors in Patients with Depression: A Network Meta-Analysis

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Purpose: Selective serotonin reuptake inhibitors (SSRIs) are the preferred treatments for depression. The most common adverse drug reactions are symptoms involving the digestive system, leading to low compliance in patients with depression. Therefore, it is important to assess the safety of SSRIs with respect to the digestive system. Several meta-analyses have compared the risks of digestive side effects of SSRIs and other antidepressants. We aimed to compare the risks of various SSRIs (fluoxetine, escitalopram, citalopram, paroxetine, and sertraline) for adverse reactions of the digestive system.

Methods: Systematic searches returned 30 randomized controlled trials ($n = 5004$) of five antidepressants and placebos.

Results: Fluoxetine had the lowest probability of digestive side effects, ranking fifth at 0.548. Sertraline had the highest probability of digestive side effects, with a probability of 0.611. For gastrointestinal tolerability, escitalopram was better than paroxetine (odds ratio [OR] = 0.62, 95% confidence interval [CI] 0.43–0.87) and sertraline (OR = 0.56, 95% CI 0.32–0.99).

Conclusion: Fluoxetine exhibited distinct advantages compared to other SSRIs, while sertraline had the greatest likelihood of digestive system side effects. These findings will help doctors understand the relative advantages of various antidepressants.

Keywords: depression, selective serotonin reuptake inhibitors, digestive system side effects, network meta-analysis

Introduction

Depression is the most common psychiatric disorder, and SSRIs are first-line drugs for its treatment.^{1,2} Among SSRIs, fluoxetine, escitalopram, citalopram, paroxetine, and sertraline are the most prescribed drugs.³ SSRIs act by inhibiting the 5-hydroxytryptamine (5-HT) transporter (5-HTT) on the axonal terminals of serotonergic neurons in the raphe nuclei, which terminates serotonin signaling through rapid presynaptic reuptake.⁴ Under the action of SSRIs, 5-HT reuptake is inhibited; therefore, the levels of 5-HT in the neurosynaptic junction are increased, leading to the relief of depression symptoms.⁵ SSRIs are usually taken orally,⁶ but orally administered drugs often cause gastrointestinal side effects, which may lead to poor patient compliance. Some adverse drug reactions can occur during SSRI treatment, the most common of which are symptoms concerning the digestive system and abdomen, such as nausea and diarrhea, possibly owing to the increase in the usability of 5-HT in the gastrointestinal system. Digestive side effects appear early in the treatment process, which is extremely common during the critical first few weeks of treatment and poses a risk of patient noncompliance.^{7,8}

Some studies have shown that fluoxetine can cause diarrhea and nausea.^{9,10} However, studies have also shown that fluoxetine can be used to treat constipation.¹¹ Nausea occurred in 42.5% of the escitalopram-treated patients.¹² Acute treatment with citalopram also temporarily reduced gastric basal tone and gastric regulation, leading to nausea.^{13,14} In

addition to causing nausea, paroxetine causes constipation by delaying upper gastrointestinal transit.^{15,16} However, sertraline was related to a significantly lower frequency of constipation and a higher frequency of nausea and diarrhea.^{13,17} Diarrhea and nausea were the most common adverse associated with vilazodone and venlafaxine.^{18–20} Although several meta-analyses have compared the risk of digestive side effects between SSRIs and other antidepressants,^{21–23} there has been no comparative analysis of the risk of digestive side effects of various SSRIs.

Therefore, this study aimed to conduct a network meta-analysis to comparatively analyze the most widely used SSRIs antidepressants (fluoxetine, escitalopram, citalopram, paroxetine, and sertraline) with respect to their incidence of digestive side effects among patients with depression to rank the incidence of SSRI-induced digestive side effects and provide clear evidence for clinicians making the best choices for patients with depression.

Methods

Inclusion Criteria

Participants

We included patients aged more than 18 years, of either sex, and with a preliminary diagnosis of depression according to international diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III, (DSM)-IV, International Classification of Diseases (ICD)-10, and Chinese Classification and the Diagnosis Criteria of Mental Disorders (CCMD)-3.

We excluded patients with secondary affective disorders, postpartum depression, postmenopausal depression, atypical depression, dysthymia, and studies involving older patients. We also excluded participants diagnosed with other psychiatric disorders or concomitant medical disorders.

Interventions

The following antidepressants were included: fluoxetine, escitalopram, citalopram, paroxetine, and sertraline. We only included studies in which patients were randomly assigned drugs within the permitted dose range.

Outcomes

The main outcome of this review was the digestive side effects caused by SSRIs in patients with depression. Side effects were assessed by encouraging patients to express both negative and positive effects of the drug. In this study, the digestive side effects included dyspepsia, stomach discomfort, burning sensation, nausea, vomiting, abdominal pain, diarrhea and constipation. We excluded studies in which patients were diagnosed with peptic ulcers, gastropathy, or other relevant comorbidities, as these factors would interfere with the results.

Types of Studies

We included double-blind, randomized controlled trials (RCT) comparing one SSRI with another or placebo as monotherapy in the acute-phase treatment of depression. Although there is no direct relationship between understanding the digestive side effects of placebo and clinical practice, many trials compare SSRIs to placebo, and including them in the network provides important indirect evidence for a more precise evaluation of clinically relevant drugs. Studies on relapses, switching to other drugs, or combination therapy were excluded.

Length of Trial

We considered the number of participants with adverse events in each treatment group at 8 weeks. If the information at 8 weeks was not available, we used the data from 6 to 12 weeks (the time point closest to 8 weeks was preferred).

Comparability of Dosages

We included only study groups in which patients were randomized to drugs within the approved dose. Both fixed-dose and flexible-dose designs were permitted.

Search Strategy

The entire EMBASE, PubMed, CNKI, ProQuest, ScienceDirect, Cochrane Central, Web of Science, Clinicalkey databases were searched from 1980 to January 1, 2020, to identify studies on the acceptability of five drugs for

depression treatment. We used the search terms “depression” or “RCT” combined with a list of all included antidepressants without language restrictions.

The article screening process included: (1) conducting preliminary screening based on subjects and abstracts to select RCTs and reviews that may be related to the subject; (2) using the references of articles screened out by preliminary screening to identify articles missed in the computer database search. Two researchers independently searched for and screened the articles. Any differences were resolved through discussions with a third member of the review team.

Data Extraction

The following basic information was extracted from the included studies: first author, publication year and country, diagnostic criteria, primary outcomes, length of RCT, intervention drug, control drug, and sample size of the intervention and control groups.

Quality Assessment

We assessed the risk of bias in the included studies using the tool described in the Cochrane Collaboration Handbook as a reference guide. Graphic representations of potential biases within and between studies were generated using RevMan V.5.3. Two researchers independently assessed the risk of bias in the included studies. Any disagreements were resolved through discussions with a third member of the review panel.

Statistical Analysis

We plotted a network diagram to present the available evidence graphically. The width of the lines was proportional to the number of trials that compared each pair of treatments. The size of each circle is proportional to the number of randomly assigned participants. We used R software for the network meta-analysis. The model calculations based on Bayesian theory adopt Markov chain Monte Carlo, with $n_{\text{adapt}} = 10000$ and $n_{\text{iter}} = 50000$. Convergence was checked by running multiple chains and monitoring their mixing using the Brooks-Gelman-Rubin diagnostic. We also used the model to draw forest plots and ordination maps and to perform tests for consistency and heterogeneity. We used a random-effects meta-analysis model to synthesize data for each pairwise comparison in the dataset to obtain ORs with 95% confidence intervals. Consistency in network meta-analysis refers to the similarity between the direct and indirect comparison results. The node-splitting method was used to evaluate the consistency assumption. We calculated the p-value, which measures consistency, by calculating the probability of observing the outcomes from the data sample, assuming that the null hypothesis is true. The smaller the p-value, the greater the inconsistency. $p < 0.05$ indicated that the direct and indirect evidence in the network are significantly inconsistent. Heterogeneity was evaluated using Cochran's Q-statistic and quantified using the I^2 statistic. Cochran's I^2 value above 50% indicated very high heterogeneity. Publication bias was assessed using comparison-adjusted funnel plots. The horizontal axis of the graph represents the difference between the effect of one paired comparison in a study and the comprehensive effect of multiple similar comparisons, whereas the vertical axis usually represents the standard error of the effect size. If there were no small-sample effects, the funnel plots adjusted for comparison were symmetrical about the zero line.

Results

Study Selection

We searched the databases according to the search strategy and initially obtained 43533 potentially eligible trials. After screening titles and abstracts, 42625 studies were excluded. Among the remaining 304 full-text studies, 274 were excluded because of a lack of valuable results. In total, 30 articles were eventually included in this study to evaluate the digestive system safety of SSRIs.^{24–53} A flowchart of the study selection process is shown in [Figure 1](#).

Study Characteristics and Risk of Bias Within Studies

A total of 30 studies were included in this review ([Table 1](#) shows basic information in the literature). A total of 5004 patients with depression were randomly assigned to receive one of five effective drugs or a placebo. Of these, 1782

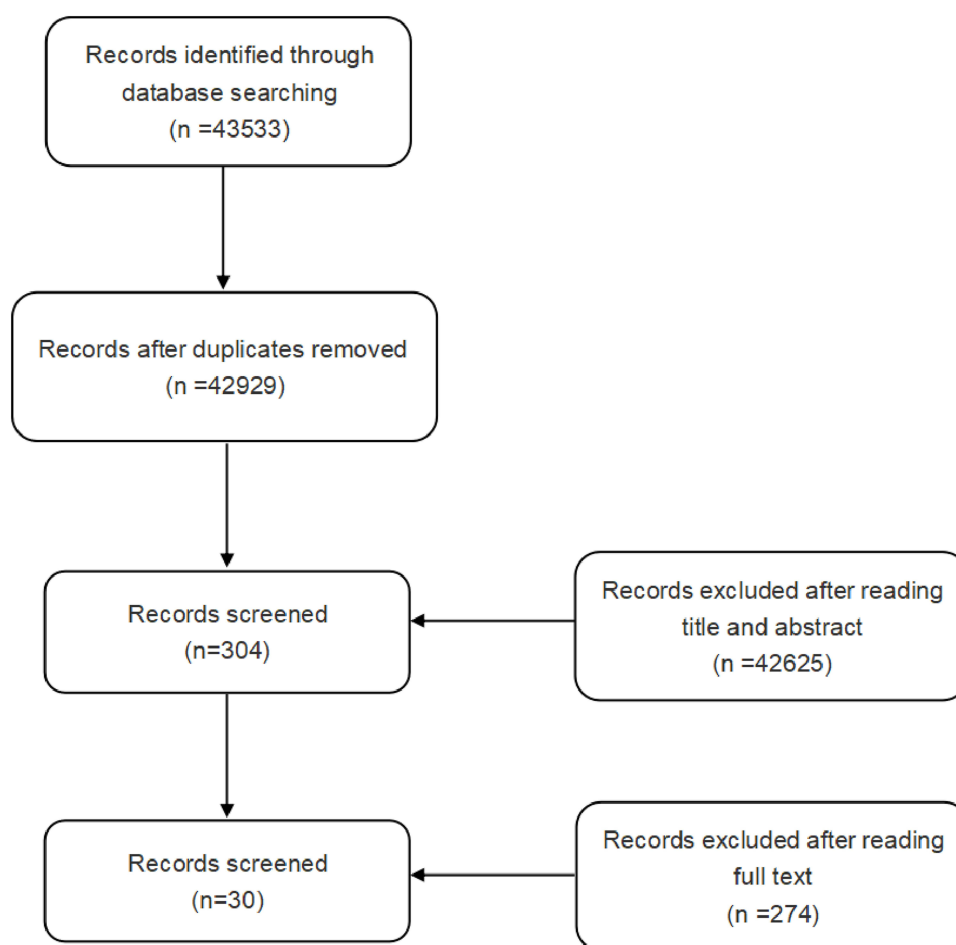


Figure 1 Flow diagram of search.

received escitalopram, 854 received citalopram, 189 received fluoxetine, 651 received paroxetine, 218 received sertraline, and 56.7% of the patients were from China. The mean study sample size was 167 patients. The risk of bias plots and summaries are shown in [Figure 2](#). [Figure 3](#) shows all available evidence for the meta-analysis of the digestive side effects of SSRIs.

Network Meta-Analysis

As shown in [Table 2](#), the incidence of digestive side effects was significantly higher for the five drugs than for the placebo. Escitalopram (OR 2.5, 95% CI 1.8–3.5); citalopram (OR 2.9, 95% CI 1.9–4.5); sertraline (OR 4.4, 95% CI 2.6–7.3); fluoxetine (OR 2.3, 95% CI 1.1–4.6); paroxetine (OR 4.0, 95% CI 2.9–5.7). Escitalopram had a significantly lower incidence of digestive side effects than paroxetine (OR=0.62, 95% CI 0.43–0.87). Escitalopram also had a significantly lower incidence of digestive side effects than sertraline (OR=0.56, 95% CI 0.32–0.99). The other comparisons were not statistically significant. A forest plot of the network results is shown in [Figure 4](#).

We ranked the probabilities of digestive side effects caused by the five drugs, in [Table 3](#) and [Figure 5](#). The drugs were ranked according to the number of digestive side effects from highest to lowest; the smaller the number, the higher the drug's safety. The probability of digestive side effects with fluoxetine was the lowest (0.547), ranking fifth. Escitalopram had a probability of 0.548, ranking fourth. Sertraline and paroxetine are most likely to cause digestive side effects. Sertraline ranked first, with a probability of 0.611, and paroxetine ranked second, with a probability of 0.566.

Table I Characteristic of Included Studies

Study	Year	Length of RCT	Age	Diagnostic criteria	Recruitment	Intervention	Sample Size	Response
Yevtushenko VY ²⁴	2007	6	25–45	DSM-IV	Russia	Esc/Cia	108/108	2/8
Wade A ²⁵	2002	8	18–65	DSM-IV	NA	Esc/Pla	191/189	17/7
Moore N ²⁶	2005	8	18–65	DSM-IV	France	Esc/Cia	142/152	6/11
Valle-Cabrera R ²⁷	2018	10	18–65	DSM-IV	Cuban	Ser/Pla	39/38	27/12
Mao PX ²⁸	2008	8	18–65	DSM-IV	China	Esc/Flu	123/117	15/16
Dunbar GC ²⁹	1993	6	18–65	DSM-III	US	Par/Pla	167/169	93/35
Wang YJ ³⁹	2016	6	20–65	CCMD-3	China	Esc/Cia	48/48	3/3
Zhu YH ⁴¹	2015	8	19–64	ICD-10	China	Par/Esc	23/23	4/1
Liu R ⁴²	2013	6	18–60	CCMD-3	China	Esc/Cia	40/40	3/6
Xu Y ⁴³	2011	6	18–60	CCMD-3	China	Esc/Cia	35/35	9/7
Wang XF ⁴⁴	2010	6	18–55	CCMD-3	China	Esc/Flu	36/34	5/5
Zhang XX ⁴⁵	2010	6	18–62	CCMD-3	China	Esc/Ser	35/35	9/9
Hu MR ⁴⁶	2010	6	18–60	CCMD-3	China	Esc/Cia	25/23	3/5
Xun GL ⁴⁷	2009	6	18–65	CCMD-3	China	Esc/Cia	115/117	26/26
Liu XB ⁴⁸	2009	6	18–65	CCMD-3	China	Esc/Par	37/36	10/16
Xu FL ⁵²	2009	6	18–60	CCMD-3	China	Esc/Flu	39/38	12/8
Yang R ⁴⁹	2008	6	24–61	CCMD-3	China	Par/Cia	27/29	4/1
Hsu JW ³⁰	2011	6	20–65	DSM-IV	China	Ser/Cia	26/25	7/5
Ou JJ ³¹	2011	6	18–65	DSM-IV	China	Esc/Cia	115/117	22/25
Woo YS ³²	2017	6	18–65	DSM-IV	Korean	Par/Esc	150/148	44/40
Detke MJ ³³	2004	8	≥18	DSM-IV	USA	Par/Pla	86/93	16/6
Perahia DG ³⁴	2006	8	≥18	DSM-IV	NA	Par/Pla	97/99	10/6
Jin XS ⁵⁰	2015	12	≥18	CCMD-3	China	Par/Esc	34/37	8/12
Croft H ³⁵	1999	8	≥18	DSM-IV	US	Ser/Pla	118/119	68/25
Rickels K ³⁶	1989	6	≥18	DSM-III	NA	Par/Pla	55/56	29/8
Goldstein DJ ³⁷	2004	8	≥18	DSM-IV	US	Par/Pla	87/89	26/5
Lepola UM ³⁸	2003	8	18–65	DSM-IV	Denmark	Esc/Cia/Pla	155/160/154	37/35/19
Zhou ZX ⁴⁰	2018	12	≥18	CCMD-3	China	Par/Esc	28/28	8/3
Cen LP ⁵³	2009	6	18–62	CCMD-3	China	Par/Esc	28/28	9/7
Nierenberg AA ⁵¹	2007	8	≥18	DSM-IV	NA	Esc/Pla	274/137	88/32

Abbreviations: CCMD, Chinese Classification and the Diagnose Criterion of Mental Disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; RCT, random controlled trial; Esc, escitalopram; Cia, citalopram; Flu, fluoxetine; Par, paroxetine; Pla, placebo; Ser, sertraline; US, the United States; NA, not available.

Heterogeneity, Consistency, and Publication Bias

Heterogeneity was assessed using the I^2 test, with an $I^2 > 50\%$ indicating the presence of heterogeneity (Figure 6); there was no significant heterogeneity among the included studies. The consistency of direct and indirect evidence was assessed using the node-splitting method. A forest plot is shown in Figure 7. No significant differences were observed in this study. We used a comparison-adjusted funnel plot to assess publication bias and small-sample effects. The horizontal axis of the graph represents the difference between the effect of one paired comparison in a study and the combined effect of many similar comparisons, whereas the vertical axis usually represents the standard error of the effect size. If there is no small-sample effect or publication bias, the funnel plot adjusted by comparison will be symmetrical around the zero line. A funnel plot is shown in Figure 8. It can be seen from the figure that the funnel chart is roughly symmetrical. There was no significant publication bias, and a small-sample effect was found.

Discussion

This study found that fluoxetine had a lower risk of digestive side effects than other SSRIs. Patients treated with sertraline are at a high risk of digestive side effects such as nausea and diarrhea. These results may help inform patients, doctors, and policymakers about the relative advantages of different SSRIs for depression.

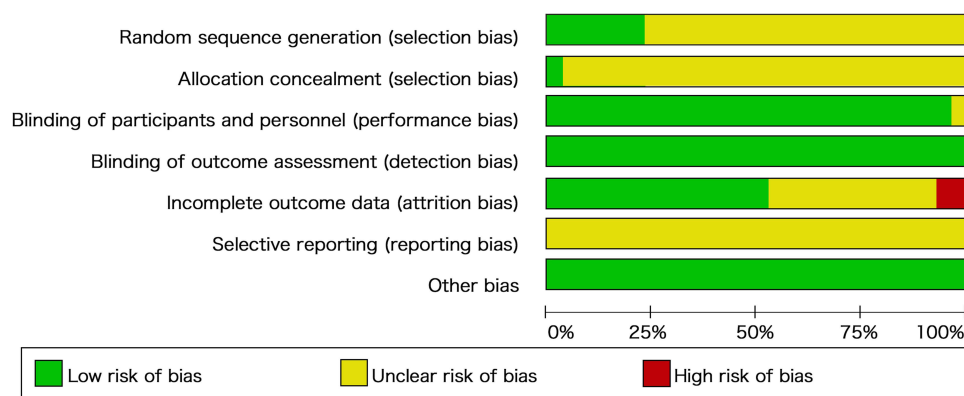


Figure 2 Risk of bias.

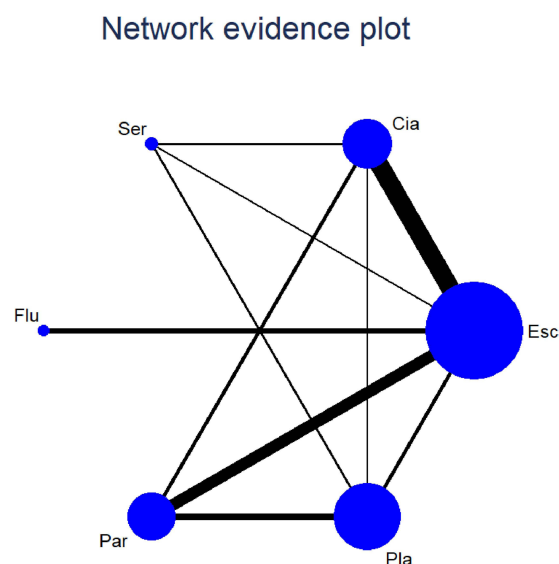


Figure 3 Network of evidence.

Notes: Width of the lines was proportional to the number of trials comparing every pair of treatments. Size of every circle was proportional to the number of randomly assigned participants.

Abbreviations: Cia, citalopram; Esc, escitalopram; Flu, fluoxetine; Ser, sertraline; Par, paroxetine; Pla, placebo.

Fluoxetine is a classical antidepressant that inhibits brain-derived neurotrophic factor (BDNF) precursor protein (proBDNF)/pan neurotrophin receptor 75 (p75NTR) signaling in monocytes/macrophages in the intestine.⁵⁴ ProBDNF is an intermediate in the synthesis of mature BDNF, which is involved in the development of depression.^{54,55} Studies have shown that direct intracerebral injection of pro-BDNF can induce depression-like behavior in rodents. Notably, depressive symptoms were relieved by injecting antibodies against pro-BDNF into the brain or periphery.⁵⁶ ProBDNF combines with p75NTR to regulate the inflammatory response, affects the function of smooth muscle and nerves, and leads to gastrointestinal dysfunction, such as constipation.⁵⁴ A study showed that upregulation of proBDNF/p75NTR in peripheral blood mononuclear cells of patients with depression was positively correlated with gastrointestinal diseases.⁵⁴

The most obvious digestive side effects of sertraline are nausea and diarrhea.^{27,35} Sertraline is the most potent antidepressant against dopamine transporter (DAT). DAT regulates the concentration of dopamine (DA) in the synaptic cleft by rapidly clearing the neurotransmitters released from the extracellular space. Evidence suggests that DAT exists in the endocrine cells of the gut that produce DA.⁵⁷ DA promotes diarrhea by triggering inflammatory responses via DA receptors on immune cells in the colon. In vitro studies have demonstrated that sertraline is 2 to 10 times stronger than other antidepressants in inhibiting serotonin reuptake. Sertraline inhibits the 5-HTT.⁵⁸ 5-HTT absorbs 5-HT through the dissipation of the Na⁺ gradient established by the electrogenic pump Na/K ATPase.⁵⁹ Sertraline inhibits various Na⁺

Table 2 Results of SSRIs for the Incidence of Induced-Digestive System Side-Effects from Network Meta-Analysis

Esc					
0.86 (0.61, 1.19)	Cia				
0.56 (0.32, 0.99)	0.66 (0.36, 1.21)	Ser			
1.07 (0.58, 2.04)	1.24 (0.63, 2.61)	1.9 (0.82, 4.47)	Flu		
0.62 (0.43, 0.87)	0.72 (0.45, 1.14)	1.1 (0.61, 1.97)	0.58 (0.28, 1.15)	Par	
2.47 (1.75, 3.51)	2.87 (1.85, 4.5)	4.39 (2.64, 7.31)	2.31 (1.12, 4.61)	3.97 (2.85, 5.68)	Pla

Note: Bold values indicate $P < 0.05$, data presented as OR (95% CI).

Abbreviations: Esc, escitalopram; Cia, citalopram; Flu, fluoxetine; Ser, sertraline; Par, paroxetine; Pla, placebo.

channels.⁶⁰ A study showed that sertraline has a concentration-dependent inhibitory effect on intracellular Na^+ channels in mice.⁶¹ Sertraline may inhibit 5-HTT by inhibiting Na^+ channels, increasing the extracellular 5-HT levels. Elevated 5-HT levels and decreased 5-HTT levels in the gut are considered the basis of gastrointestinal disturbances such as

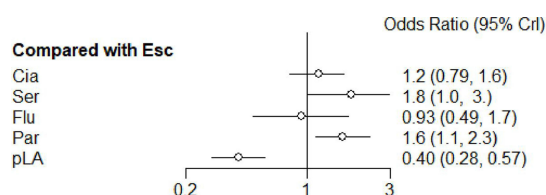
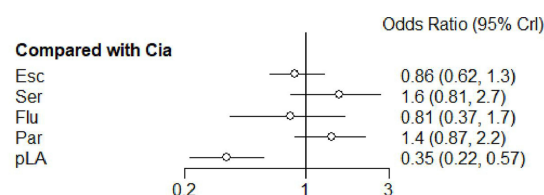
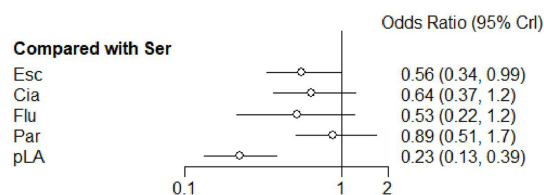
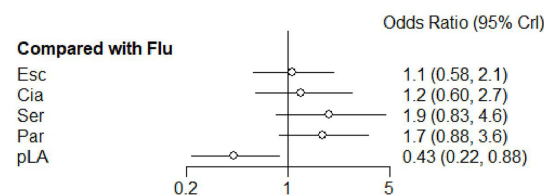
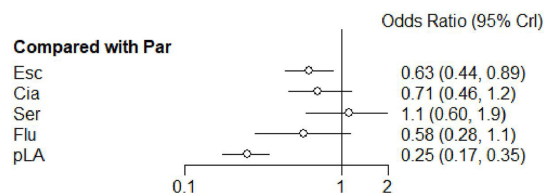
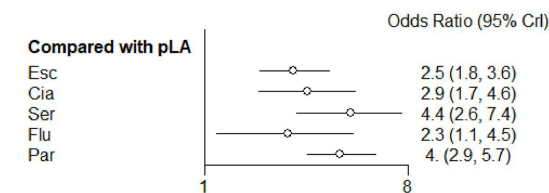
**A****B****C****D****E****F**

Figure 4 Forest plots of network meta-analysis of all trials for acceptability. **(A)** Forest plots for the outcomes compared with Escitalopram. **(B)** Forest plots for the outcomes compared with Citalopram. **(C)** Forest plots for the outcomes compared with Sertraline. **(D)** Forest plots for the outcomes compared with Fluoxetine. **(E)** Forest plots for the outcomes compared with Paroxetine. **(F)** Forest plots for the outcomes compared with Placebo.

Abbreviations: Cia, citalopram; CrI, confidence intervals; Esc, escitalopram; Flu, fluoxetine; Ser, sertraline; Par, paroxetine; Pla, placebo.

Table 3 Rank Probability of Caused Digestive System Side Effects Among SSRIs

	1	2	3	4	5	6
Esc	0.0005	0.00375	0.1189	0.54815	0.32915	0
Cia	0.0209	0.0962	0.54315	0.24135	0.0984	0
Ser	0.61095	0.282	0.07395	0.0219	0.0112	0
Flu	0.02965	0.05195	0.18205	0.17665	0.54715	0.01255
Par	0.33845	0.5661	0.08195	0.0119	0.0016	0
Pla	0	0	0	0.0005	0.0125	0.98745

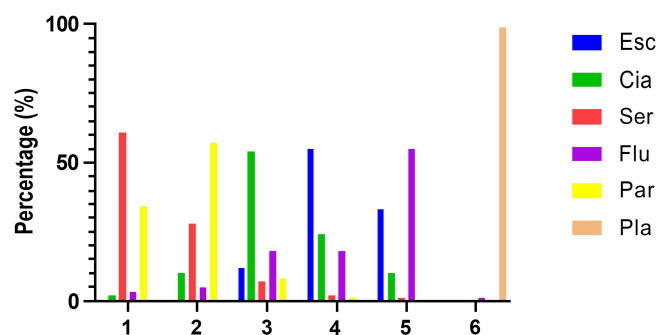
Abbreviations: Esc, escitalopram; Cia, citalopram; Flu, fluoxetine; Ser, sertraline; Par, paroxetine; Pla, placebo; Rank probability, preferred direction=1.

diarrhea and inflammation. For example, the deletion of 5-HTT in mice results in increased fecal water content (suggesting a diarrheal phenotype).⁶² In addition, 5-HT can induce nausea by stimulating 5-HT₃ receptors on vagal afferent nerves. Activation of the 5-HT₃ receptor induces rapid excitatory postsynaptic potentials and rapid depolarization of serotonergic neurons, leading to an increase in the intracellular Ca²⁺ concentration that causes the release of different emetic neurotransmitters.⁶³ This results in a high risk of digestive side effects of sertraline.

In this study, we also found that citalopram was more likely to cause digestive side effects than escitalopram. Escitalopram significantly increased serum levels of the anti-inflammatory cytokine interleukin-10 (IL-10).⁶⁴ IL-10 is one of the most important anti-inflammatory cytokines affecting intestinal mucosal immune response.⁶⁵ Administration of IL-10 can prevent the worsening of inflammation and, therefore, disease development.⁶⁵ However, citalopram did not affect changes in serum levels of IL-10, and the anti-inflammatory effect of citalopram was inferior to that of escitalopram.⁶⁴ Citalopram showed weaker blocks of the norepinephrine transporter than paroxetine in vitro.⁶⁶ High norepinephrine levels may lead to gastric motility disorders.⁶⁷ This might explain why paroxetine is more likely to cause gastrointestinal side effects than citalopram.

Inclusion criteria were strictly limited in this study to ensure transferability between comparisons. Consistency was the primary method for determining the accuracy and reliability of the network meta-analysis. In network meta-analysis, consistency refers to the similarity between the results of direct and indirect comparisons. This study did not find that the results of direct and indirect comparisons were inconsistent. In general, this network meta-analysis has good consistency and reliable results.

Our study had some limitations. The first major limitation is that more than 50% of the included studies were from China, and the number of included trials was relatively small. Second, fluvoxamine was not included in this study because we did not find any articles on the digestive side effects of fluvoxamine compared with other SSRI drugs during the literature search. Third, in accordance with our protocol, we excluded participants with depression and anxiety. This exclusion is intended to maintain network transmissibility. However, it might have limited the universality of the results of this study, as such patients account for a significant proportion of patients in real clinical settings. Finally, we did not perform a specific classification of digestive side

**Figure 5** Rank probability of caused digestive system side effects among SSRIs.

Abbreviations: Cia, citalopram; Esc, escitalopram; Flu, fluoxetine; Ser, sertraline; Par, paroxetine; Pla, placebo.

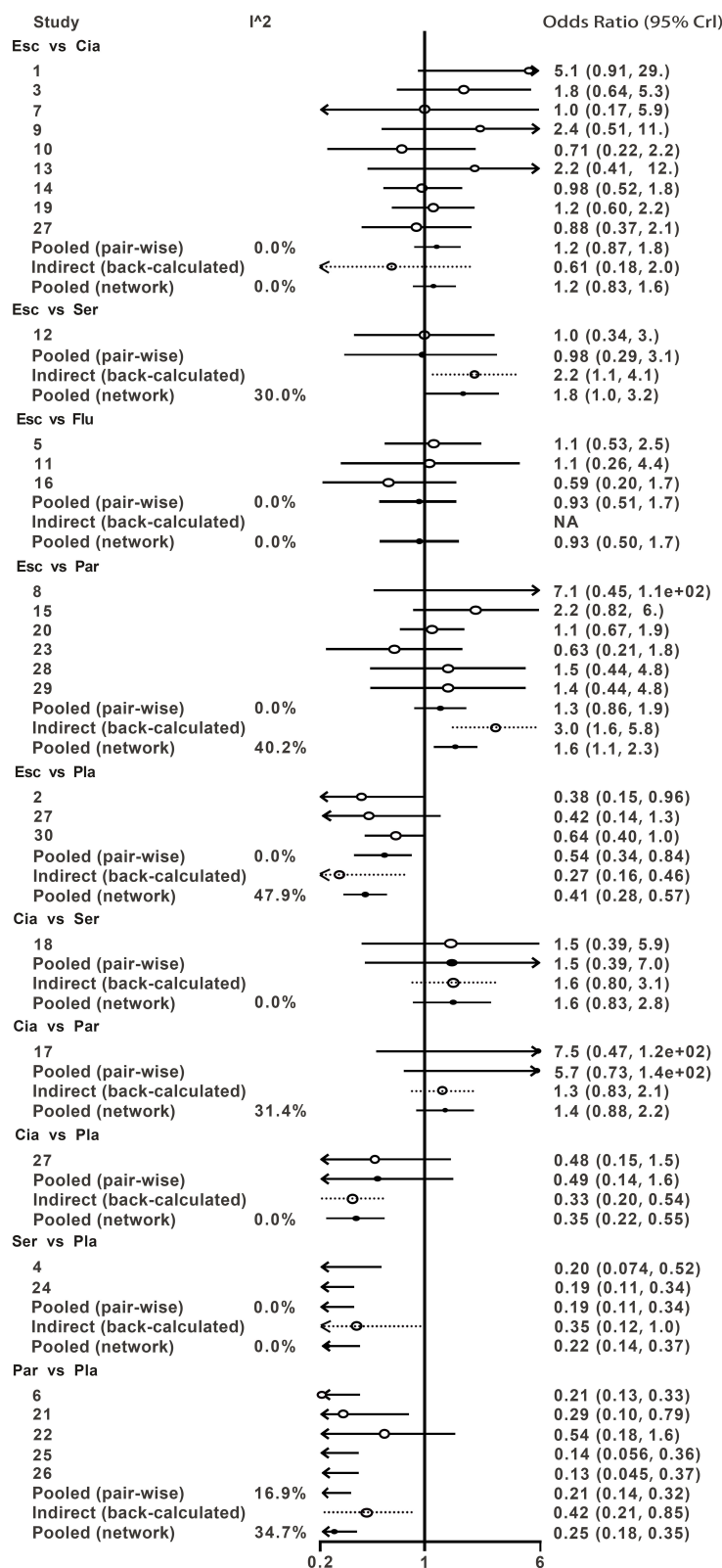


Figure 6 The heterogeneity of the included studies.

Abbreviations: Cia, citalopram; Esc, escitalopram; Flu, fluoxetine; Ser, sertraline; Par, paroxetine; Pla, placebo.

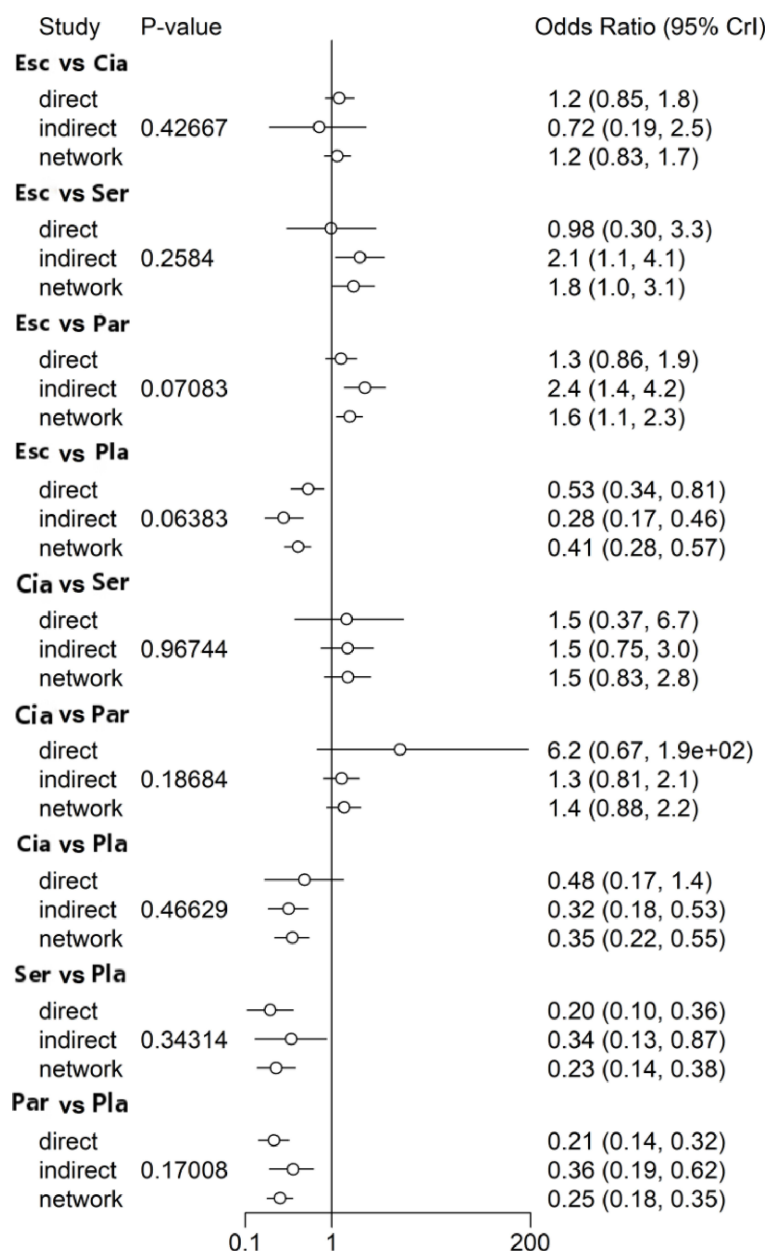


Figure 7 Summarized results of direct and indirect comparisons between different SSRI.

Abbreviations: Cia, citalopram; Esc, escitalopram; Flu, fluoxetine; Ser, sertraline; Par, paroxetine; Pla, placebo.

effects such as nausea and vomiting. Although specific digestive symptoms were mentioned in the included RCTs, the number of subjects with specific digestive symptoms included in the studies meeting the inclusion criteria was too small to constitute a network meta-analysis of specific digestive symptoms; studies with a small number of subjects can cause publication bias and generate a relatively large side effect. Therefore, we suggest that more subjects be included in future studies, and the incidence of specific digestive side effects caused by SSRIs should be ranked to provide better clinical treatment suggestions and guidance for patients with depression.

Conclusion

In summary, regarding digestive system safety, fluoxetine exhibited the least probability of inducing digestive side effects when used in patients with depression, whereas sertraline exhibited the highest probability of inducing digestive side effects among patients with depression. Therefore, clinicians must choose the best drug according to the specific situation

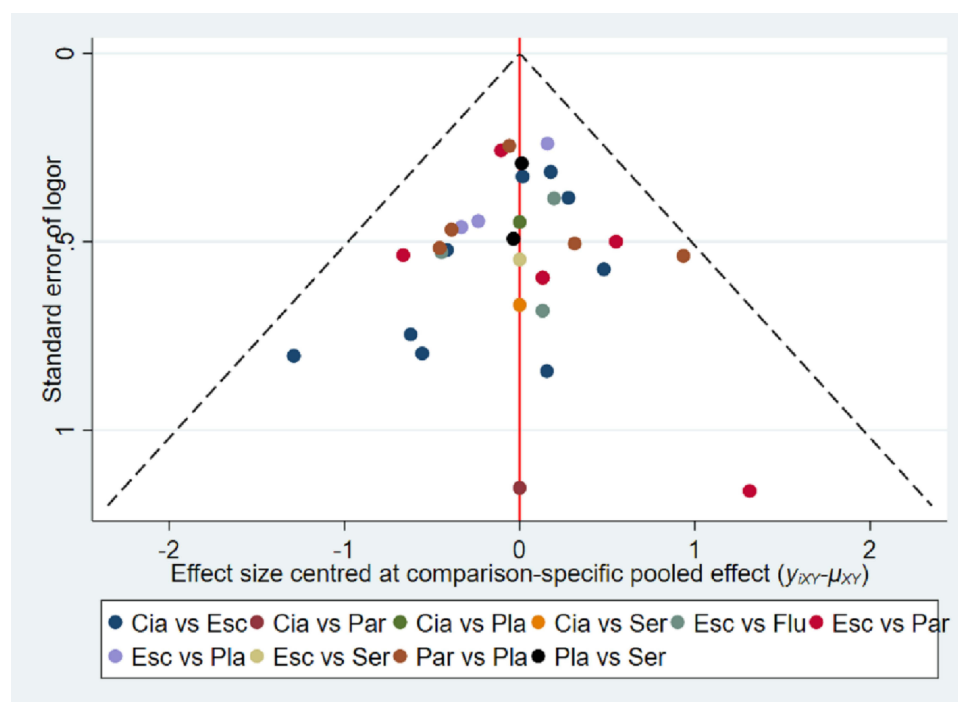


Figure 8 Comparison-adjusted funnel plots.

Notes: The red line suggests the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. Different colors represent different comparisons.

of the patient. Our findings may provide a useful perspective for making these decisions. Future studies should include more studies and include participants with depression accompanied by anxiety to confirm these conclusions.

Abbreviations

SSRIs, Selective serotonin reuptake inhibitors; OR, odds ratio; CI, confidence interval; 5-HT, 5-hydroxytryptamine; 5-HTT, 5-hydroxytryptamine transporter; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; CCMD, Chinese Classification and the Diagnosis Criteria of Mental Disorders; RCT, randomized controlled trials; BDNF, brain-derived neurotrophic factor; proBDNF, brain-derived neurotrophic factor precursor protein; p75NTR, pan neurotrophin receptor 75; DAT, dopamine transporter; DA, dopamine; IL-10, interleukin-10.

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Disclosure

The authors report no conflicts of interest for this work.

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