Comparative Efficacy of Antidepressants for Symptoms Remission of Gastroesophageal Reflux: A Bayesian Network Meta-analysis of Randomized Controlled Trials

Xiao-Bei Si[1], Lin-Yu Huo[2], De-Ying Bi[1], Yu Lan[1], Shuo Zhang[3]

[1]Department of Gastroenterology, Beijing Jishuitan Hospital, Beijing, China
[2]Department of Neurology, Beijing Haidian Hospital, Beijing, China
[3]Department of Cardiology, Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Beijing, China

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ABSTRACT

Background: *The present study aimed to compare and evaluate the efficacy of antidepressants in remission of esophageal reflux symptoms.*
Methods: *A comprehensive literature review was performed including sources published on MEDLINE, EMBASE, the Cochrane Central Registry of Controlled Trials (Cochrane), Web of Science, China National Knowledge Infrastructure Database (CNKI), Chinese VIP Information Databases (VIP), Chinese Biology Medicine disc (CBM), and Wan-Fang databases for randomized controlled trials, published up to and including March 31, 2020. We analyzed relevant randomized, placebo-controlled trials reporting the effect of antidepressant therapy in relieving esophageal reflux symptoms. ADDIS 1.16.8 was used to perform the network meta-analysis. Furthermore, we performed a split analysis to test inconsistency, and rank probability was complemented for comparison among antidepressants.*
Results: *A total of 10 randomized controlled trials (RCTs) examining the effects of antidepressants, selective 5-HT reabsorption inhibitor (SSRI), 5-HT 1A receptor agonist (5-HT1AA), tricyclic antidepressants (TCAs), and the complex of flupentixol-melitracen (FM) were included. Flupentixol-melitracen and SSRIs exhibited a significantly higher rate of remission than placebo. However, there was no statistically significant difference among different antidepressants compared. Rank probability showed that FM exhibited the highest probability of rank 1 compared with other antidepressants and placebo.*
Conclusion: *This network meta-analysis of RCTs supported the use of FM and SSRIs as a potentially effective regimen for symptom remission of gastroesophageal reflux. Furthermore, according to our analysis, FM represents the most efficient antidepressant with highest probability of symptom remission.*
Keywords: *Antidepressants, efficacy, gastroesophageal reflux, network meta-analysis, randomized controlled trials*

INTRODUCTION

Gastroesophageal reflux (GER) is the retrograde movement of gastric contents into the esophagus through the lower esophageal sphincter, and GER symptoms are the clinical syndromes with manifestations including acid-reflux, heartburn, chest pain, throat discomfort, cough, and epigastric discomfort.[1,2] Gastroesophageal reflux disease (GERD) as well as functional heartburn (FH) and reflux hypersensitivity (RH) may be attributed to GER symptoms.[2] Earlier studies have reported the global incidence of GER symptoms to be approximately 13% with geographic variation.[3] Moreover, an increasing trend has been observed during the recent decades.[3,4]

Psychosocial disorders such as anxiety and depression may also be the co-causative factors of GER symptoms,[5] and the use of antidepressants may be effective in relieving GER symptoms.[6] In recent years, a series of randomized controlled trials have been conducted with antidepressant therapy for symptoms associated with GER.[7-15] Antidepressants including selective serotonin uptake inhibitors (SSRIs),[9,15] and tricyclic antidepressants (TCAs),[8,14] serotonin 1A receptor agonists (5-HT1AA),[12] and a fixed-dose combination (FDC) tablet of flupentixol-melitracen (FM)[10-12] were evaluated, with conclusions that these antidepressants might have a role in reducing GER symptoms. However, a meta-analysis comparing these antidepressant regimens is still lacking. Thus, there is no evidence to guide optimal treatment with an antidepressant for patients with GER. To overcome these limitations, this network meta-analysis was designed and conducted to compare and evaluate the relative efficacy of antidepressants in remission of esophageal reflux symptoms based on

Corresponding author: ***Yu Lan****, e-mail:* ***lany_2020@163.com***
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direct evidence from previous randomized controlled trials.

MATERIALS AND METHODS

Protocol

The protocols for this meta-analysis were designed and developed with protocols.io (https://www.protocols.io) under the title "Comparative Efficacy of Antidepressants for Symptoms Remission of Gastroesophageal Reflux: A Bayesian Network Meta-Analysis of Randomized Controlled Trials (protocol)." (https://dx.doi.org/10.17504/protocols.io.bb72irqe)

Search for Publications

We performed an extensive literature search of electronic databases including MEDLINE, EMBASE, the Cochrane Central Registry of Controlled Trials (Cochrane), Web of Science, China National Knowledge Infrastructure Database (CNKI), Chinese VIP Information Databases (VIP), Chinese Biology Medicine disc (CBM), and Wan-Fang databases (Wanfang), from their inception to March 31, 2020, without language restriction or limitation of study duration. We used a combination of MeSH-terms and keywords strategy (Gastroesophageal reflux* OR antidepressant* OR randomized controlled trials). The search strategies were summarized in Column 1 using a MEDLINE search strategy as an example. The study was conducted in accordance with the standards set forth by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[16]

Inclusion and Exclusion Criteria

The inclusion criteria applied for the present study were as follows: (i) the study subjects were patients who complained of GER symptoms including GERD and/or FH and/or RH, with or without specifically diagnosed psychological disorders such as anxiety and depression; (ii) study subjects in the experimental group were treated with antidepressants; (iii) the participants in the control group were treated with antidepressants (different from that of experimental group) or placebo; (iv) the primary outcome was the total remission rate of GER symptoms, calculated as the total remission rate = a number of patients with remission of at least 1 symptom/total number × 100%; and (v) the study design was a randomized controlled trial (RCT).

We excluded studies that were: (i) duplicate publications; (ii) literature reviews; (iii) non-randomized trials or trials with inaccurate randomization method; and (iv) case reports.

Data Extraction and Quality Evaluation

All retrieved studies were independently screened by 2 reviewers (Xiao-Bei Si and Lin-Yu Huo). Titles and abstracts were screened for all relevant articles. Full texts were screened for further assessments according to the inclusion and exclusion criteria. Any disagreements between the reviewers were resolved by discussion or consensus through consultation with an additional specialist.

The retrieved articles were screened and reviewed for their eligibility independently by 2 reviewers (Xiao-Bei Si and De-Ying Bi). The differences in the determination of a study's eligibility were resolved through discussion. The data extracted from the included trials included the first author's name, year of publication, geographical location, protocol registration, sample size, interventions, primary outcome, and significance of the primary outcome.

Quality Evaluation

The methodological quality of each trial was evaluated based on the Cochrane Collaboration Risk of Bias Tool.[17] Quality was also assessed on 7 different RCT domains including random sequence generation, allocation concealment, the blinding of participants and personnel, incomplete outcome data, the blinding of outcome assessments, selective outcome reporting, and other sources of bias. For each domain, the trials were assessed based on the criteria provided by the Cochrane Collaboration Tool. We assessed each study as being at "low risk of bias," "high risk of bias" or "Unclear risk of bias" for each of the "Risk of bias" items.

Statistical Analysis

All the statistical analyses were performed using ADDIS software (version 1.16.5) based on the Bayesian framework. The primary evaluation and data processing were performed using the Markov chain Monte Carlo algorithms. The consistency test was performed using the inconsistency standard deviation (ISD) and node-splitting analysis, which represents an alternative method to assess inconsistency in network meta-analysis. For the closed-loop index, both node-splitting analysis and ISD analysis were used. However, only ISD was used to test the consistency for the open-loop indicators. For ISD, if the range of 95% CI of ISD was included, then the consistency model was used; otherwise, the inconsistency

model was used.[18] For node-splitting analysis, if the *P*-value of the node-splitting analysis was more than .05, the consistency model was used to calculate the pooled effect size. Otherwise, the nonconsistency model was used. The convergence of the model was determined by the potential scale reduction factor (PSRF) of the Brooks–Gelman–Rubin method.[19] If PSRF was close to 1, it was considered to imply good convergence and might be accepted. The parameters for the ADDIS software were as follows: number of chains, 4; tuning iterations, 20 000; simulation iterations, 50 000; thinning interval, 10; inference samples, 10 000; and variance scaling factor, 2.5.

RESULTS

Literature Selection

A total of 905 relevant studies were initially retrieved using our established search strategy. Of these, 864 were excluded as duplicated records and unrelated records. We subjected 38 studies to full-text screening. A total of 24 studies were excluded due to the interventions in control groups that did not meet the inclusion criteria. Four studies were excluded due to the outcomes that did not meet the inclusion criteria. Finally, a total of 9 studies[7-15] met the eligibility criteria and were included for this meta-analysis. A schematic representation of the article searches and study selection process is illustrated in Figure 1.

Characteristics of Included Studies

A total of 9 trials were included referring to the antidepressants imipramine (TCA),[8] citalopram (SSRI),[9,15] paroxetine (SSRI),[10] tandospirone (5-HT1AA),[12] amitriptyline (TCA),[13,15] FM,[7,10-12] and nortriptyline (TCA).[14] The comparison network of included trials is represented in Figure 2. Four studies were published in English[8,9,14,15] and the other 5 were published in Chinese.[7,10-13] One study[11] enrolled patients with refractory GERD and 3 studies[7,10,13] enrolled non-erosive reflux disease (NERD) patients with anxiety and/or depression. However, the history of proton pump inhibitor (PPI) therapy, as well as therapeutic effects, was unknown in the study from Nie et al.[11] One study[8] investigated patients with a low response to previous 3-month PPI therapy, who had been diagnosed with RH and FH by upper gastrointestinal endoscopy and esophageal 24-hour pH-impedance monitoring. One study[9] investigated patients of RH with failed PPI-therapy twice daily, that is, with a complaint of more than 3 episodes of GER symptoms per week following such therapy. One study[14] investigated patients of FH based on the typical reflux symptoms of heartburn, normal endoscopy, as well as ambulatory 24-hour pH monitoring. Furthermore, a total of 4 studies[10-13] included patients with concurrent anxiety/depression. The basic characteristics of the included trials are summarized in Table 1.

Varied tools were adopted for GER symptom assessment, including the Chinese GERD Questionnaire (Chinese-GERDQ),[20] the GERD Symptoms Score designed by Allen (Allen's score),[21] the GERD-Health-Related Quality of Life (GERD-HRQOL),[22] The Digestive Health Status Instrument GERD scale (DHSI),[23] and Reflux Disease Questionnaire (RDQ).[24] Besides, 2 studies[7,13] assessed GER symptoms using self-made scales. Two studies[9,15] assessed GER symptoms according to participants' description. The results of the included studies are shown in Table 2.

Quality Assessment of Included Studies

Of all included studies, 4[8,9,11,12] reported a random sequence generation approach and 5 studies[7,8,11,13] were placebo-controlled trials. However, most except 3[8,9,11] of the included studies did not provide adequate information on quality assessment terms (Table 3).

Network Meta-analysis of the Total Remission Rate of Esophageal Reflux Symptoms

The analysis revealed that OR with 95% CI of the ISD were 1.22 (0.46, 2.73) and 1.22 (0.49, 2.69) for intention-to-treat analysis (ITT analysis) and per-protocol analysis (PP analysis) respectively. The node-splitting analysis revealed that all *P*-values were more than .05. All the PFRFs were 1.00, indicating good convergence with stable results. Thus, the network meta-analyses of both ITT and PP analysis were performed based on the concordance model. After pooled estimation, the present NMA indicated that the total remission rates of FM and SSRI, but not 5-HT1AA and TCAs, were significantly higher than those of placebo ($P < .05$) in both ITT and PP analyses. The network comparison of the antidepressants mentioned above presented no significant differences in the total remission rate (Supplementary Tables S1 and S2). After pooled estimation, the network meta-analysis revealed that FM exhibited the highest probability (Rank1 probability 0.52 for ITT analysis and 0.53 for PP analysis) to provide the most effective therapy in relieving the GER-associated symptoms (Supplementary Tables S3 and S4; Figure 3A and 3B).

DISCUSSION

In 2016, the Rome IV committee for functional gastrointestinal disorders of the digestive system[24] had

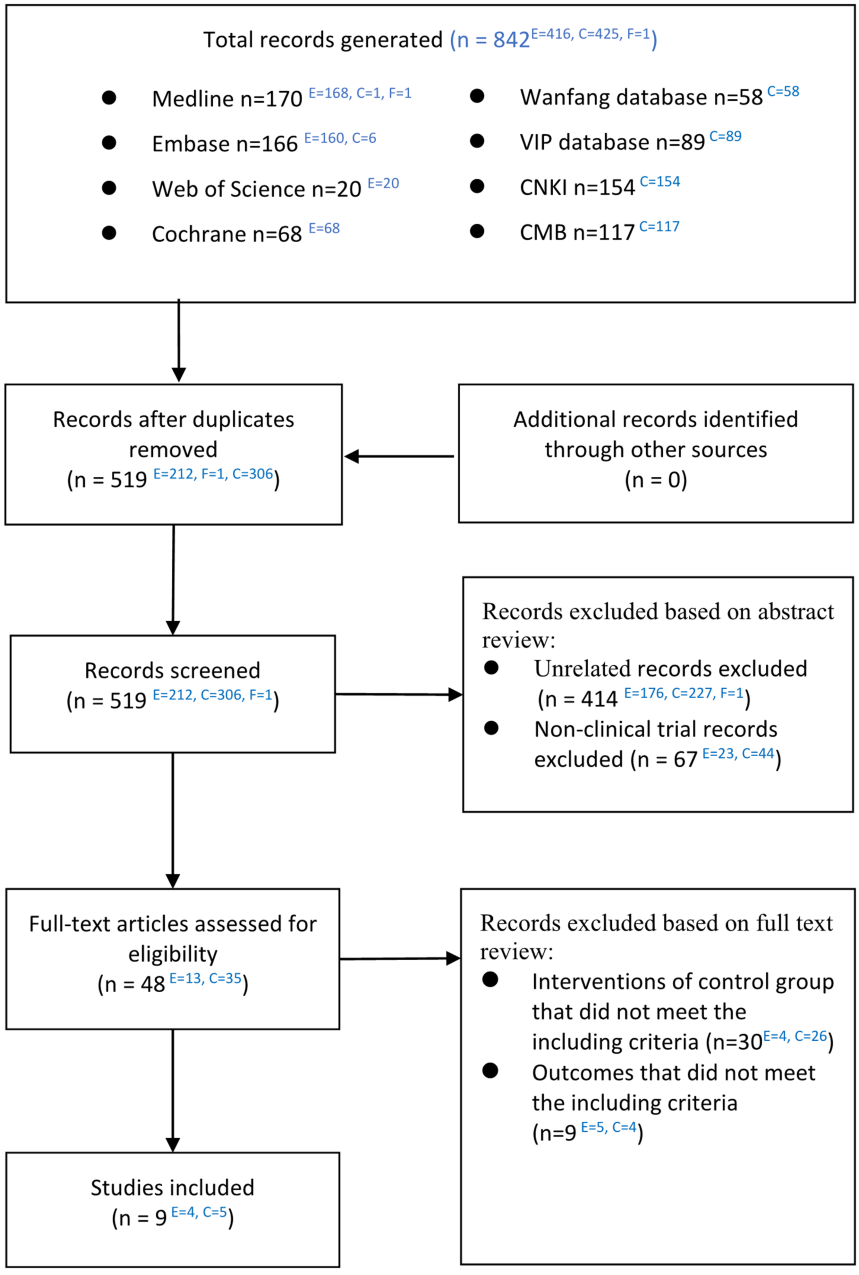

Figure 1. Flow chart of included studies. E, number of studies in English; C, number of studies in Chinese; F, number of studies in French.

introduced a major revision in the classification of functional disorders. For the first time, RH was isolated from the spectrum of GERD and viewed as a branch of functional disorders of the esophagus. Functional heartburn, RH, and GERD present similar clinical symptoms of reflux, heartburn, and regurgitation, and may overlap with each other as well, which makes it challenging to differentiate between them based on symptoms. Furthermore, psychological disorders such as anxiety and depression may manifest as the common etiology of these diseases.[2,6] This association makes it even more difficult to differentiate between these 3 conditions. Therefore, it was suggested that 24-hour esophageal pH-impedance monitoring combined with clinical symptoms should be exploited for further differentiation of the 3 diseases.[25] In this review, GERD/esophageal functional disorders presenting as symptoms of GER were discussed based on the limitations of the current knowledge about the

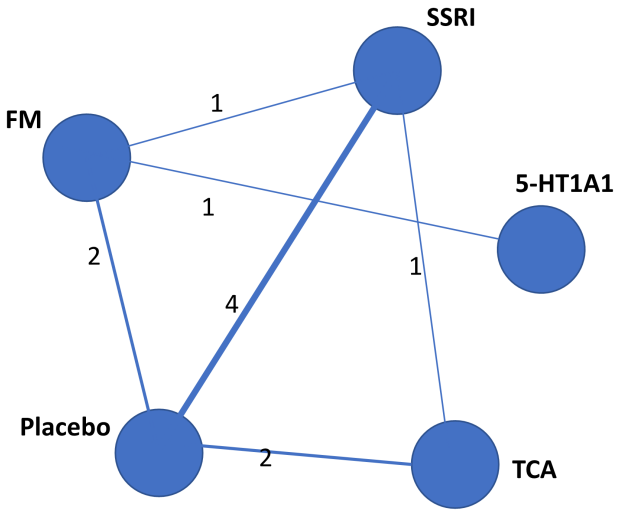

Figure 2. Comparison network of included RCTs. Each line connects 2 antidepressants or placebo from original studies. The number on the line refers to the number of studies (or subgroup studies) comparing each pair of antidepressants (or placebo), which are also represented by the width of the lines. 5-HT1AAs, Serotonin 1A receptor agonist; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; FM, flupentixol-melitracen.

etiology of these symptoms and investigation for functional disorders of the esophagus.[26] In addition, only 4 trials comprising patients with FH and/or RH[8,9,14,15] were included in this study to adequately differentiate between GERD and esophageal functional disorders by adjunctive investigations such as endoscopy and esophageal pH-impedance monitoring. The inclusion of patient diagnostic criteria in the remaining studies claims to conform to the GERD guidelines at home and abroad; however, the above-mentioned literature and corresponding "guidance" documents were published before the Rome IV criteria, and the inclusion criteria did not mention esophageal pH-impedance monitoring. Thus, it may be difficult to effectively differentiate between any of the phenotypic presentations of GERD and heartburn-associated esophageal functional disorders or overlapping esophageal functional disorders. Overall, the study included patients with GER symptoms separately and discussed that antidepressant therapy may be more appropriate.

To the best of our knowledge, the present review was the first to compare the efficacy of different agents in alleviating GERD-associated symptoms using a network meta-analysis. The results revealed that FM and SSRIs, but not TCAs and 5-HT1AA, exhibited a significantly higher rate of remission than placebo, while FM might function as the most potent and effective antidepressant in patients with GER.

Previously, accumulating studies have indicated that psychological factors may play a crucial role in the generation of GER symptoms.[5] Possibly, psychological disorders such as anxiety and depression affect brain–enteral axis, leading to increased esophageal sensitivity[27] as well as aggravated GER symptoms. As a result, there might be an increased risk of GER in patients with anxiety and depression.[28] At the same time, patients with chronic GER symptoms tend to suffer psychological disorders as well, leading to further aggravation of GER symptoms.[29] In fact, the correlation between psychological distress and severity of GER symptoms had been confirmed in clinical research studies.[30,31]

Antidepressants can potentially influence GER through multiple mechanisms. First, antidepressants, particularly SSRIs and TCAs, may play a role in modulating esophageal sensitivity in addition to treating co-existing psychosocial disorders,[26] thereby relieving GER symptoms. Second, in patients with GER associated with anxiety and depression, antidepressants may exacerbate GER symptoms due to increased intragastric pressure caused by excessive gas ingestion, and treatment of anxiolytic depression can at the same time improve GERD-related symptoms by relieving excessive gas ingestion.[32]

Flupentixol-melitracen is an FDC tablet containing melitracen 10 mg and flupentixol 0.5 mg. Flupentixol is a potent dopamine receptor antagonist. However, when used at relatively low doses, it acts on the prefrontal dopamine autoregulatory receptors to promote dopamine synthesis and release. Melitracen increases the local concentration of monoamine transmitters in the synaptic space by inhibiting the reuptake of 5-HT by the presynaptic membrane. When a low dose of flupentixol and melitracen is combined, the significant pharmacological effects of flupentixol and melitracen are produced by a combination of the 2 components, which simultaneously exert anxiolytic and antidepressive properties and effectively improve patients' anxiety and depressive disorders and their associated somatization symptoms.[33]

The safety of FM was another point for clinical use and research. Extrapyramidal symptoms, the common side effects of flupentixol, might be one of the reasons for reduced safety of FM.[34] Previously, a series of clinical trials evaluated the efficacy as well as safety of FM, with a few minor side effects reported, including lethargy,

Table 1. Characteristics of Included RCTs Investigating the Effect of Antidepressants on Gastroesophageal Reflux

				Interventions		
Study	Year	N(E/C)	Diagnosis	E	C	Duration(W)
Jia et al.[7]	2019	108/108	NERD combined with depression and/or anxiety	FM 1 tablet q.d.; Rabeprazole 10 mg b.i.d.	Placebo; Rabeprazole 10 mg b.i.d.	6
Limsrivilai et al.[8]	2016	20/13	Patients of RH and/or FH with failed 3-month PPI therapy	Promediazine 25 mg q.n.	Placebo	8
Viazis et al.[9]	2012	39/36	RH	Citalopram 20 mg q.d.	Placebo	24
Sun et al.[10]	2012	21/21	NERD combined with depression without PPI and antidepressants therapy within the past 2 weeks	FM 1 tablet q.d.	Paroxetine W1-W2, 10 mg/d; W3-W4, 20 mg/d	4
Nie et al.[11]	2014	65/58	Refractory GERD combined with depression and/or anxiety	FM 1 tablet b.i.d.; Esomeprazole 40 mg q.d.	Placebo; Esomeprazole 40 mg q.d.	4
Luo et al.[12]	2016	61/61	NERD combined with depression and/or anxiety without medication of PPI and/or antidepressants and/or prokinetics within the past 1 month	FM 1 tablet b.i.d.; Esomeprazole 40 mg q.d.	Tandospirone 10 mg t.i.d.; Esomeprazole 40 mg q.d.	4
Chen et al.[13] - subgroup 1	2008	30/30	NERD combined with mild depression	Amitriptyline 12.5 mg t.i.d.; Omeprazole 20 mg b.i.d.; Cisapride 10 mg t.i.d.	Placebo; Omeprazole 20 mg b.i.d.; Cisapride 10 mg t.i.d.	8
Chen et al.[13] - subgroup 2	2008	30/30	NERD combined with middle depression	Amitriptyline 12.5 mg t.i.d.; Omeprazole 20 mg b.i.d.; Cisapride 10 mg t.i.d.	Placebo; Omeprazole 20 mg b.i.d.; Cisapride 10 mg t.i.d.	8
Chen et al.[13] - subgroup 3	2008	30/30	NERD combined with severe depression	Amitriptyline 12.5 mg t.i.d.; Omeprazole 20 mg b.i.d.; Cisapride 10 mg t.i.d.	Placebo; Omeprazole 20 mg b.i.d.; Cisapride 10 mg t.i.d.	8
Basu et al.[14]	2014	20/20	FH	Nortriptyline 25mg q.n.; Omeprazole 20mg q.d.	Placebo; Omeprazole 20mg q.d.	12
Karamanolis et al.[15]	2016	14/14	FH	Citalopram 20mg q.d.	Amitriptyline 50mg q.d.	12

N, number of enrolled subjects; E, experimental group; C, control group; W, weeks; RH, reflux hypersensitivity; FH, functional heartburn; GERD, gastroesophageal reflux disease; NERD, non-erosive reflux disease; W, week; q.d., once per day; b.i.d., twice per day; t.i.d., three times per day; q.n., once per day in the evening; FM, flupentixol-melitracen (flupentixol: 0.5 mg/tablet; melitracen: 10 mg/tablet).

dizziness, dry mouth, insomnia, and nausea.[35] In addition to these trials, a case report by Kao et al.[36] reported a depressed patient with FM-associated tardive dyskinesia and tardive akathisia after taking FM for 25 consecutive years. To our knowledge, this might be the only report of severe side effects of FM. In the present review, 4 included studies evaluated the efficacy of FM while 2 of them[11,12] evaluated safety as well, with side effects of liver damage,[12] xerostomia,[11,12] bitter taste,[12] lethargy,[12] and constipation[11] reported. All these records were of minor side effects which disappeared later after interventions [withdrawal of drugs[12] and cathartic treatment[11]] or on their own.

Several reviews with meta-analysis hold evidence that medication with antidepressants might be beneficial in relieving the GER symptoms. In 2015, Weinberg et al.[26] performed a meta-analysis to compare

Table 2. The Results of the Included Studies

Study	GER Assessment Tools	Results of GER Assessment Tools		Results of Total Remission Rate (ITT)		*P* of Remission Rates
		E	C	E	C	
Jia et al.[7]	Self-made scale	NM	NM	94.45%	73.15%	<.05
Limsrivilai et al.[8]	Allen's score	NM	NM	37.2%	37.5%	.98
Viazis et al.[9]	Participants' description	-	-	61.5%	33.3%	.021
Sun et al.[10]	Chinese GERDQ	Reflux	Reflux	94.2%	90.5%	NM
		4.67 ± 1.79 (pretherapy)	4.91 ± 1.78 (pretherapy)			
		1.62 ± 1.07 (posttherapy)	0 (post therapy)			
		Heartburn	Heartburn			
		5.38 ± 2.01 (pretherapy)	5.19 ± 1.77 (pretherapy)			
		0.62 ± 0.80 (posttherapy)	0.81 ± 0.87 (posttherapy)			
		Chest burning pain	Chest burning pain			
		5.14 ± 1.56 (pretherapy)	4.62 ± 1.32 (pretherapy)			
		1.69 ± 0.67 (posttherapy)	1.67 ± 0.65 (posttherapy)			
Nie et al.[11]	RDQ	NM	NM	77.94%	8.82%	<.05
Luo et al.[12]	DHSI	Reflux	Reflux	84%	89%	>.05
		1.94 ± 0.81 (pretherapy)	1.99 ± 0.79 (pretherapy)			
		0.15 ± 0.08 (posttherapy)	0.16 ± 0.08 (pretherapy)			
		Heartburn	Heartburn			
		2.18 ± 0.77 (pretherapy)	2.15 ± 0.75 (pretherapy)			
		0.14 ± 0.07 (posttherapy)	0.15 ± 0.06 (posttherapy)			
		Chest burning pain	Chest burning pain			
		1.83 ± 0.91 (pretherapy)	1.86 ± 0.87 (pretherapy)			
		0.16 ± 0.05 (posttherapy)	0.15 ± 0.05 (posttherapy)			
Chen et al.[13] - subgroup 1	Self-made scale	NM	NM	93.3%	63.3%	<.01
Chen et al.[13] - subgroup 2	Self-made scale	NM	NM	93.3%	60.0%	<.01
Chen et al.[13] - subgroup 3	Self-made scale	NM	NM	93.3%	33.3%	<.01
Basu et al.[14]	GERD-HRQOL	26 (pretherapy)	25 (pretherapy)	20%	45%	<.001
		17 (posttherapy)	17 (posttherapy)			
Karamanolis et al.[15]	Participants' description	-	-	35.7%	42.8%	.033

GERD-HRQOL, GERD-Health-Related Quality of Life; DHSI, the Digestive Health Status Instrument GERD scale; Allen's score, GERD symptoms score designed by Allen CJ; NM, not mentioned; TRR, total remission rate; RDQ, Reflux Disease Questionnaire; GER, gastroesophageal reflux; E, experimental group; C, control group.

Table 3. Results of Quality Assessment

Studies	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Jia et al.[7]	Unclear	Unclear	Low risk of bias	Low risk of bias	Unclear	Unclear	Unclear
Limsrivilai et al.[8]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear
Viazis et al.[9]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear
Sun et al.[10]	Unclear	Unclear	High risk of bias	Unclear	Unclear	Unclear	Unclear
Nie et al.[11]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear	Unclear
Luo et al.[12]	Low risk of bias	Unclear	High risk of bias	Low risk of bias	Unclear	Unclear	Unclear
Chen et al.[13]	Unclear	Unclear	Low risk of bias	Unclear	Unclear	Unclear	Unclear
Basu et al.[14]	Unclear	Unclear	Low risk of bias	Low risk of bias	Unclear	Unclear	Unclear
Karamanolis et al.[15]	Unclear	Unclear	High risk of bias	High risk of bias	Unclear	Unclear	Unclear

the effects of antidepressants for esophageal dysfunction/GERD with placebo as control and found that antidepressants exhibited higher remission rate than placebo, particularly for symptoms of heartburn; besides, SSRIs might be superior to TCAs, based on subgroup analysis. Similarly, a meta-analysis by Lin et al.[37] compared the remission of GERD symptoms employing routine treatment with SSRIs (or SSRI alone) and routine treatment for GERD, and the results indicated that SSRIs exhibited higher remission rate for GERD symptoms than that of control. Furthermore, a meta-analysis conducted by Zou et al.[38] showed that FM combined with acid suppression treatment significantly improved GER symptoms compared with acid-suppression alone. Compared with these above-mentioned meta-analyses, the present review included only randomized placebo-controlled trials while the results of network meta-analysis were consistent with those.

This network meta-analysis is acknowledged to have several limitations. First, as we aimed to investigate the role of antidepressants in patients with GER symptoms, the included studies shared different inclusion criteria. Five studies enrolled patients of GERD [including refractory GERD[11] and NERD[7,10,12,13]] while another 4 enrolled patients of FH[8,14,15] and RH.[8,9] Two studies[8,11] enrolled patients all with definite history of previously failed PPI therapy, but not the another 7.[7,9,10,12,13-15] Five studies[7,10-13] enrolled patients of GER symptoms combined with depression and/or anxiety, but not another 4.[8,9,14,15] These differences obviously contributed to the heterogeneity. At the same time, interventions among included studies differed substantially. Five studies[7,11-14] adopted antidepressant/placebo in combination with PPI while others[8-10,15] did not. Moreover, varied assessment tools were adopted. All these differences contributed to bias for further meta-analysis. Second, 5 included studies (5/9, 55.56%) were published in Chinese with participants from the Chinese population, which resulted in strong Chinese domination in this network analysis. Previous surveys of epidemiology found that the prevalence of GERD in China was lower than that in Western countries.[4,39] However, compared with patients in western countries, Chinese patients with GERD shared lower frequency of reflux symptoms but higher prevalence of depression and anxiety.[40,41] Such differences should not be neglected, especially for application of the present study as clinical evidence. Third, this study compared the effects of different antidepressants in alleviating gastroesophageal symptoms using a network meta-analysis, and we only included placebo-controlled and multi-antidepressant-controlled trials. Thus, only 9 studies were included. Moreover, some of the included studies were of low quality due to shortcomings predominantly in randomization, blindness, and allocation concealment. All these factors limited the quality of evidence quality for meta-analysis. Fourth, due to limitations of the included literature studies, this study failed to further analyze and compare the efficacy of treatment for single symptoms (e.g., heartburn or retrosternal pain) and the safety of these drugs.

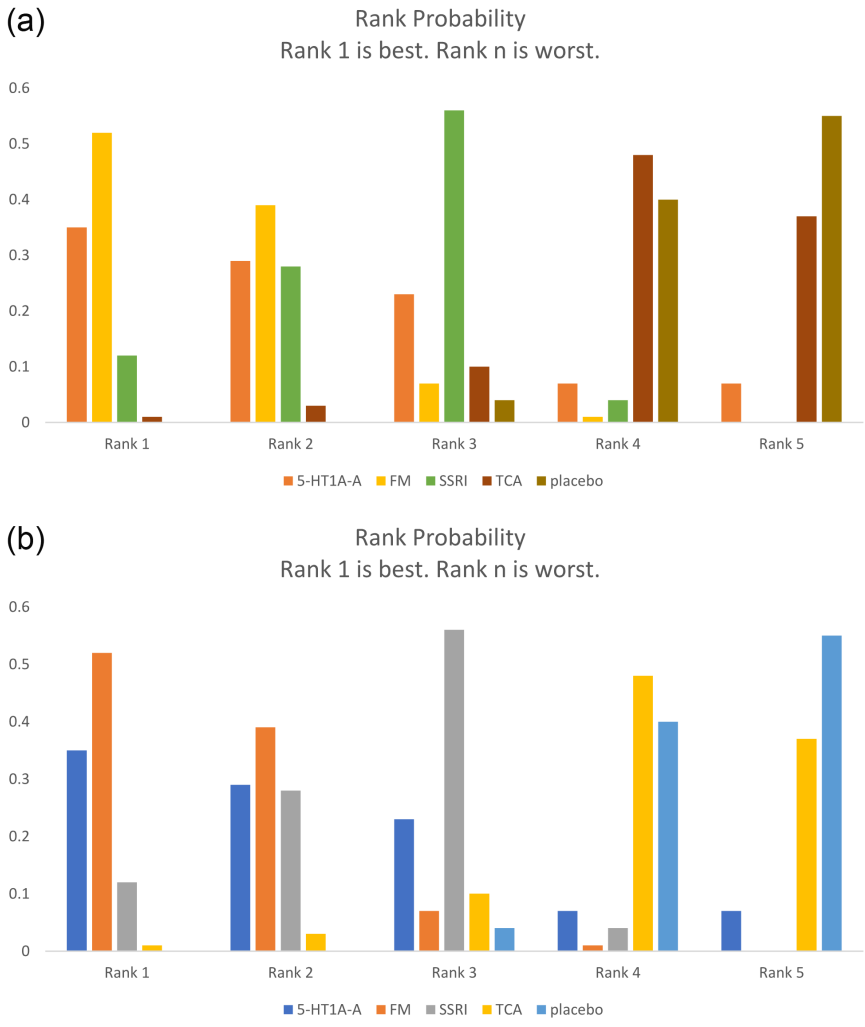

Figure 3. Rank probability for antidepressants in gastroesophageal reflux symptoms for intention to treat analysis (A) and per-protocol analysis (B) 5-HT1AAs, Serotonin 1A receptor agonist; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; FM, flupentixol-melitracen.

Therefore, a more methodological and comprehensive discussion of randomized, double-blind, controlled trials with large sample sizes is warranted for a more definitive conclusion.

In conclusion, this network meta-analysis of RCTs supported the use of FM and SSRIs as a potentially effective regimen for symptomatic remission of GER. Furthermore, FM represents the most efficient antidepressant with maximum probability based on our analysis. However, further large-scale well-designed RCTs are needed to validate these findings.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – X.S.; Design – X.S.; Supervision – Y.L.; Resource – Y.L.; Materials – X.S. and D.B.; Data Collection and/or Processing – X.S., L.H., and D.B.; Analysis and/or Interpretation – X.S., D.B. and S.Z.; Literature Search – X.S. and D.B.; Writing – X.S. and L.H.; Critical Reviews – Y.L.

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Supplementary Table S1. The Results of Network Meta-analysis for Different Antidepressants Based on a Consistency Model (Intention to-Treat Analysis)

Comparisons [Odds Ratio (95% CI)]				
5-HT1A-A	1.55 (0.07, 36.98)	0.58 (0.01, 27.73)	0.12 (0.00, 7.83)	0.10 (0.00, 3.94)
0.65 (0.03, 14.73)	FM	0.38 (0.04, 3.50)	0.08 (0.01, 1.23)	0.06 (0.01, 0.43)
1.73 (0.04, 86.68)	2.65 (0.29, 24.59)	SSRI	0.21 (0.03, 1.74)	0.16 (0.04, 0.69)
8.38 (0.13, 514.52)	12.80 (0.82, 195.74)	4.84 (0.57, 39.52)	TCA	0.81 (0.11, 5.32)
10.43 (0.25, 448.47)	16.20 (2.35, 123.93)	6.09 (1.45, 25.35)	1.24 (0.19, 8.97)	placebo

5-HT1AAs: Serotonin 1A receptor agonist; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressants; FM: flupentixol-melitracen.

Supplementary Table S2. The Results of Network Meta-analysis for Different Antidepressants Based on a Consistency Model (Per-protocol Analysis)

Comparisons [Odds Ratio (95% CI)]				
5-HT1A-A	1.53 (0.08, 33.19)	0.57 (0.01, 23.21)	0.12 (0.00, 6.88)	0.09 (0.00, 3.34)
0.65 (0.03, 13.30)	FM	0.37 (0.04, 3.17)	0.08 (0.01, 1.15)	0.06 (0.01, 0.39)
1.77 (0.04, 67.20)	2.69 (0.32, 24.15)	SSRI	0.22 (0.03, 1.77)	0.16 (0.04, 0.66)
8.02 (0.15, 417.77)	12.38 (0.87, 174.60)	4.54 (0.57, 37.76)	TCA	0.74 (0.11, 4.81)
10.90 (0.30, 397.56)	16.73 (2.53, 114.98)	6.15 (1.51, 25.89)	1.36 (0.21, 8.94)	placebo

5-HT1AAs: Serotonin 1A receptor agonist; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressants; FM: flupentixol-melitracen.

Supplementary Table S3. Rank-probability results for antidepressants (intention to-treat analysis)

	Probability values				
Antidepressants	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
5-HT1A-A	0.35	0.29	0.23	0.07	0.07
FM	0.52	0.39	0.07	0.01	0
SSRI	0.12	0.28	0.56	0.04	0
TCA	0.01	0.03	0.1	0.48	0.37
Placebo	0	0	0.04	0.4	0.55

5-HT1AAs: Serotonin 1A receptor agonist; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressants; FM: flupentixol-melitracen.

Supplementary Table S4. Rank-Probability Results for Antidepressants (Per-protocol Analysis)

	Probability Values				
Antidepressants	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
5-HT1A-A	0.34	0.31	0.22	0.07	0.07
FM	0.53	0.39	0.06	0.01	0.00
SSRI	0.11	0.27	0.57	0.04	0.00
TCA	0.01	0.03	0.12	0.51	0.33
Placebo	0.00	0.00	0.03	0.37	0.60

5-HT1AAs: Serotonin 1A receptor agonist; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressants; FM: flupentixol-melitracen.