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Antidepressants in irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Irritable bowel syndrome (IBS) treatment relies on a low level of evidence. In this systematic review with meta-analysis of randomized, double-blind, placebo-controlled trials we assessed the efficacy of antidepressants in IBS.

Methods This study followed the PRISMA guidelines and was registered in the PROSPERO database (CRD42024502427). PubMed, EMBASE and the Cochrane Library were searched from inception to January 2024. Only randomized, double-blind, placebo-controlled trials were included. Quality of evidence was assessed using the Cochrane tool (RoB 2). A random-effects model was used. Heterogeneity was evaluated by the I^2 statistic and publication bias by funnel plots and the Egger test.

Results The search strategy identified 1340 studies, of which 20 were included in the systematic review and 16 in the meta-analysis, totaling 1428 patients. The meta-analysis unveiled the efficacy of antidepressants in patients with IBS in overall symptom improvement (odds ratio [OR] 3.02; 95% confidence interval [CI] 2.16-4.2). Subgroup analysis revealed similar results regarding the efficacy of tricyclic antidepressants (OR 3.39, 95%CI 2.24-5.12); of selective serotonin reuptake inhibitors (OR 2.39, 95%CI 1.14-5.01); in patients refractory to first-line measures (OR 2.96, 95%CI 1.67-5.25); in patients without known comorbid psychological conditions (OR 2.92, 95%CI 1.6-5.31); and in the improvement in abdominal pain (OR 3.27, 95%CI 1.63-6.53), and bloating (OR 2.4, 95%CI 1.11-5.22). Publication bias was detected, and potential sources were identified. Sub-analysis without these sources of bias revealed similar results.

Conclusions Antidepressants demonstrate efficacy in IBS. These medications can be beneficial to patients resistant to initial treatments and those lacking psychopathological symptoms.

Keywords Irritable bowel syndrome, antidepressants, tricyclic antidepressants, selective serotonin reuptake inhibitors, meta-analysis

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Introduction

Irritable bowel syndrome (IBS) is one of the most prevalent gastrointestinal conditions, impacting more than 10% of the world population and imposing a significant economic burden on healthcare systems [1,2]. The physiopathology of this condition is yet to be fully understood, being complex and multifactorial. Adverse life events, depression, illness anxiety disorder, acute and chronic stressors, visceral hypersensitivity, and abnormal gas handling and accommodation have been recognized as being implicated [3]. Mechanisms already shown to be involved are serotonergic signaling abnormalities, and increased awareness of and activation by visceral stimuli [4]. Additionally, stress can influence intestinal sensitivity, motility, secretion and permeability, potentially playing a role in the pathophysiology of IBS and triggering flares [5]. These findings led to the conclusion that IBS resulted from a dysfunction of the gut–brain axis.

European and American scientific societies have both issued recent guidelines to establish recommendations regarding the

diagnosis and treatment of this condition [6,7]. Nevertheless, the quality of evidence of the majority of the recommendations regarding therapies is low to moderate, and the therapeutic armamentarium available for these patients is very limited.

IBS can manifest across a broad spectrum, ranging from mild to severe forms. Mild cases of IBS can often be alleviated through lifestyle adjustments, such as adopting a low-FODMAP diet, or utilizing therapies with a favorable safety profile, such as probiotics, although these are not universally recommended [6,7]. Severe cases of IBS remain challenging to manage effectively. A significant proportion of patients continue to struggle to find adequate relief from symptoms. Indeed, certain symptoms such as bloating, which are commonly reported, lack widely successful therapeutic options [8]. This not only leads to a diminished quality of life for these individuals but also results in substantial healthcare expenditure and economic burden [9,10].

Antidepressants have been postulated to be gut–brain modulators, having an impact not only in the brain, as is already widely known, but also peripherally in the gastrointestinal tract [11]. The recognized mechanisms of action of neuromodulators include enhancing neurotransmission by increasing the synaptic transmission of neurotransmitters such as serotonin, norepinephrine and dopamine, which leads to the regulation or desensitization of postsynaptic receptors. Additionally, they act on receptors along the gut–brain axis, thereby influencing intestinal motility, the central regulation of visceral signals, neurogenesis, and also peripheral effects through their action on the enteric nervous system [12]. The most important effect is the modulation of pain, both centrally and peripherally. Tricyclic antidepressants (TCAs) have been widely recommended in the most recent guidelines, with a moderate level of evidence, solely as a second-line therapy [6,7]. While selective serotonin reuptake inhibitors (SSRIs) have been recommended with a low level of evidence by the British guidelines, the American College of Gastroenterology provides no recommendation for or against this class of antidepressants [6,7]. There is a gap in our knowledge regarding the efficacy of antidepressants in all patients with IBS, and whether this effectiveness is similar across all classes of these drugs.

The most recent meta-analyses addressing this issue are now dated, and several new studies, including a larger number of patients, have been performed since then [13-15]. Moreover, some studies have been performed assessing the efficacy of other classes of antidepressants in this setting [16-19]. We thus aimed to conduct a systematic review and to perform a meta-analysis of randomized, double-blind, placebo-controlled trials, to enhance the understanding of the potential efficacy of antidepressants in IBS.

Materials and methods

Protocol and registration

The current systematic review and meta-analysis was performed according to the most recent Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary Table 1) [20]. The protocol was previously registered at the International Prospective Register of Systematic Reviews (PROSPERO) platform under the identification number CRD42024502427.

Eligibility criteria

The Population, Intervention, Comparison, Outcome (PICO) framework was used to define eligibility criteria. The Population included adult patients (≥18 years old) with IBS. The criteria used by the studies to define the presence of IBS have varied over time. Either the 4 editions of the Rome criteria, the Manning criteria, or criteria defined by the authors that fulfilled the nowadays accepted criteria for the diagnosis of IBS, were considered as valid.

The Intervention was the use of antidepressants of all classes, for a minimum period of 4 weeks. The Comparison group was assigned placebo in all included trials. Multiple Outcomes regarding the efficacy of antidepressants were evaluated: overall symptom improvement, improvement in abdominal pain, in bloating, and in quality of life.

Information sources and search strategy

MEDLINE, Embase and the Cochrane Library were searched from database inception to January 2024, without any other restriction. The search used terms were "irritable bowel syndrome", "IBS", "functional gastrointestinal disorder" or "refractory irritable bowel symptoms", and "Antidepressant", "Anxiolytics", "Antipsychotics", "Hypnosedatives", "Tricyclic antidepressants", "Selective serotonin reuptake inhibitors", "Serotonin norepinephrine reuptake inhibitors", "Atypical antipsychotics", "Imipramine", "Desipramine", "Amitriptyline", "Nortriptiline", "Doxepin", "Clomipramine", "Maprotiline", "Nortriptyline", "Fluoxetine", "Paroxetine", "Sertraline", "Tianeptine", "Citalopram", "Escitalopram", "Trazodone", "Mianserin", "Mirtazapine", "Venlafaxine", "Fluvoxamine", "Duloxetine", "Nefazodone", "Bupropion", "Amineptine", "Agomelatine", "Viloxazine", "Reboxetine", "Milnacipran". An additional search was conducted manually in the references of the included studies to mitigate the risk of inadvertent exclusion. The search strategy is shown schematically in Fig. 1.

Study selection

Two reviewers (MJT and MC) independently screened all titles and abstracts of the studies generated by the search, as well as full-text reference lists, according to the eligibility criteria previously defined. Disagreement was resolved by discussion and consensus among the authors. Data collection was performed by MJT using a predefined spreadsheet. Only double-blind randomized placebo-controlled trials were included.

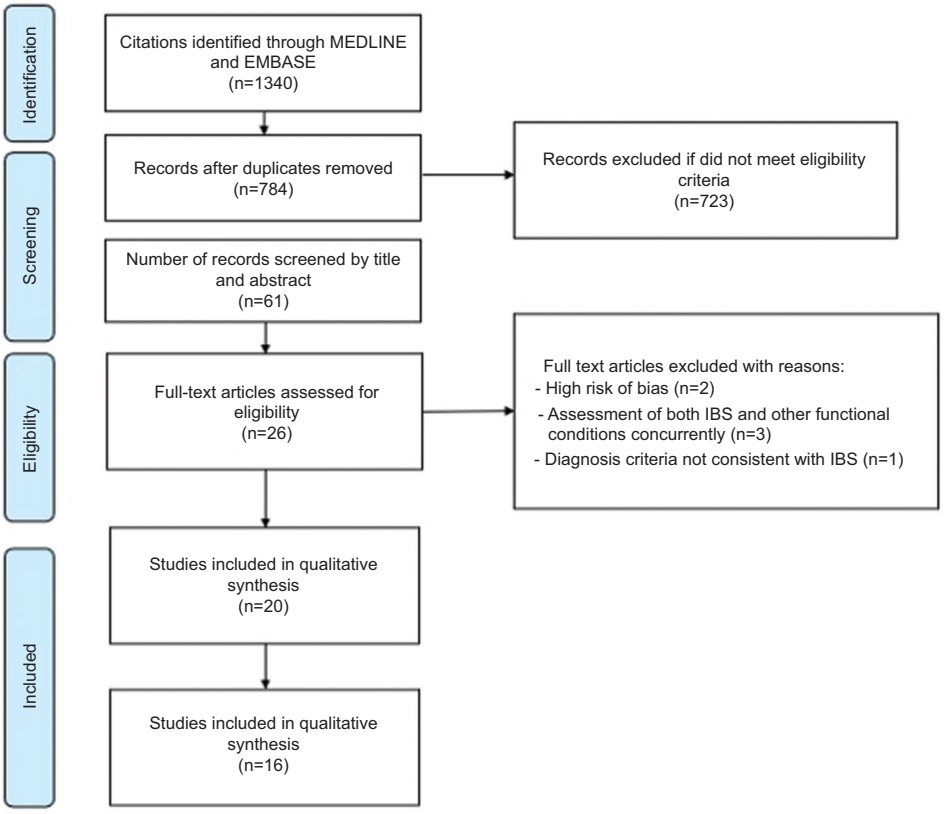

Figure 1 PRISMA diagram showing the selection of relevant studies for inclusion in the systematic review
IBS, irritable bowel syndrome

Data collection

The collected data included the criteria used for the diagnosis of IBS; the criteria used for defining response/improvement; any subpopulation specifications, such as refractoriness to first-line therapies or exclusion of individuals with known comorbid psychological conditions; the antidepressant assessed, the dosage and duration of treatment and follow up; as well as rates of improvement or mean differences of scores used to assess response.

Risk of bias assessment

The risk of bias of the included studies was appraised using the revised version of the Cochrane tool (RoB 2) independently by the 2 reviewers (MJT and MC) [21]. In case of any discrepancies, the reviewers reached a consensus after carrying out a recheck of the study under evaluation. Studies with a high risk of bias according to the authors' evaluation were excluded from the review and meta-analysis.

Statistical analysis

Statistical analysis was performed using STATA software, version 16 (Statacorp). An intention-to-treat analysis was conducted. The studies included in the quantitative analysis were those that reported results using a categorical approach, as this was the most commonly employed method across the studies. Studies that were not included presented their results as continuous variables, rather than as response or non-response, which precluded their inclusion in the analysis designed to encompass the largest possible number of studies. The heterogeneity of effect sizes across studies was assessed using I^2 statistics. The presence of statistical heterogeneity was considered as I^2>75% [22]. A random-effects analysis was used to calculate the pooled outcome (odds ratio; OR). In case of I^2=0%, a fixed effects (Mantel-Haenszel model) and sensitivity analysis were performed. A forest plot was performed to estimate individual and pooled effect sizes with associated 95% confidence interval (CI). Publication bias was assessed by funnel plot and Egger's test (a P-value <0.05 was considered as indicating the presence of publication bias). If publication bias was identified, the potential sources were investigated and a sub-analysis was performed without the culprit studies.

Table 1 Summary of the characteristics of the studies included in the meta-analysis assessing the efficacy of antidepressants in patients with irritable bowel syndrome (IBS)

Study [ref.]	Year	Definition of IBS	Sample size	Female (%)	Duration of treatment	Primary endpoint	Antidepressant and daily dose	Improvement with treatment (%)	Improvement with placebo (%)
Heefner *et al* [23]	1978	Criteria compatible with IBS	44	11.7%	2 months	Improvement in abdominal pain	Desipramine 150 mg	54.5	45.5
Nigam *et al* [30]	1984	Criteria compatible with IBS	168	45%	12 weeks	Improvement in global symptoms	Amitriptyline 12.5 mg	51.2	23.8
Greenbaum *et al* [31]	1987	Criteria compatible with IBS	28	62%	6 weeks	Improvement in global symptoms	Desipramine 50 mg 1st week, 100 mg 2nd week, 150 mg 3th to 6th	53.6	17.9
Rajagopalan *et al* [32]	1998	Rome I	40	45.5%	12 weeks	Improvement in global symptoms	Amitriptyline 25 mg 1st week, 50 mg 2nd week, 75 mg until the end	35.0	15.0
Kuiken *et al* [33]	2003	Rome I	40	55%	6 weeks	Improvement in global symptoms	Fluoxetin 20 mg	47.6	31.6
Tabas *et al* [34]	2004	Rome I	81	72.9%	12 weeks	Improvement in global well-being	Paroxetin 10 mg	50.0	23.3
Vahedi *et al* [35]	2005	Rome II	44	61.4%	12 weeks	Improvement in global symptoms	Fluoxetin 20 mg	72.7	13.6
Morgan *et al* [36]	2005	Rome II	19	100%	4 weeks	Improvement in global symptoms	Amitriptyline 25 mg 1st week, 50 mg until the end	68.4	26.3
Vahedi *et al* [37]	2008	Rome II	54	42%	2 months	Improvement in global symptoms	Amitriptyline 10 mg	63.0	25.9
Marks *et al* [24]	2008	Rome II	72	87.5%	12 weeks	Improvement in abdominal pain	Paroxetin 12.5 mg, increased biweekly, until 50 mg	52.8	38.9
Abdul-Baki *et al* [25]	2009	Rome II	107	42.1%	12 weeks	Improvement in global symptoms	Imipranine 25 mg	42.4	25.0
Masand *et al* [26]	2009	Rome II	72	87.5%	12 weeks	Improvement in abdominal pain	Paroxetin 12.5 mg, increased biweekly, until 50 mg	52.8	30.6
Ladabaum *et al* [27]	2010	Rome II	54	81.5%	8 weeks	Improvement in global symptoms	Citalopram 20 mg 1st 4 weeks, 40 mg 2nd 4 weeks	44.4	55.6
Ghadir *et al* [28]	2011	Rome III	75	45%	2 months	Improvement in global symptoms	Doxepin 10 mg	72.0*	16.0*
							Nortriptiline 10 mg	56.0*	56.0*
Khalilian *et al* [17]	2021	Rome IV	67	67.2%	8 weeks	Improvement in global symptoms	Mirtazapine 15 mg 1st week, 30 mg until the end	61.8	30.3
Ford *et al* [29]	2023	Rome IV	463	68%	6 months	Improvement in global symptoms	Amitriptyline 10 mg with dose titration until 30 mg	53.9	38.1

**% improvement was not available for global improvement, so a % improvement in abdominal pain was used as criterion*

Results

Study selection and study characteristics

The search strategy identified 1340 studies, screened by assessment of titles and abstracts. A total of 61 full articles were then screened for inclusion. Twenty studies were included in the systematic review (comprising a total of 1572 patients) and 16 studies were incorporated in the meta-analysis (1428 patients). The PRISMA flowchart of the selection of studies for the systematic review and meta-analysis is shown in Fig. 1. The characteristics of the included studies are presented in Table 1. The publication dates ranged from 1978-2023. The assessment of the risk of bias of each included study is detailed in Fig. 2.

Improvement in global symptoms

In total, 16 studies examined the effectiveness of antidepressants in improving overall symptoms [17,23-37]. Abdominal pain was considered an indicator of general improvement when data on the latter were unavailable. Of the 1473 patients included in the analysis, 753 were treated with antidepressants and 720 received placebo. Within the intervention group, 405 patients (55.3%) reported improvement, compared to only 227 patients (32.5%) in the control group.

Effect sizes were computed (pooled OR 3.02, 95%CI 2.16-4.20), indicating an improvement in IBS symptoms following antidepressant treatment. Heterogeneity was moderate (I^2=46.3%) (Fig. 3). The funnel plot displayed asymmetry (see Supplementary Fig. 1), and the Egger test yielded a significant result (P=0.03). The potential sources of publication bias were identified: 2 studies by Vahedi *et al* and Ghadir *et al* [28,35]. A sub-analysis was conducted, excluding these studies. In this sub-analysis, the efficacy remained similar (pooled OR 2.41, 95%CI 1.86-3.13), with lower heterogeneity (I^2=13.6%). The Egger test result became statistically non-significant (P=0.32).

TCAs

A sub-analysis was conducted to assess the efficacy of TCAs in these patients, encompassing 9 studies with a total of 1045 participants [23,25,28-32,36,37]. Among these, 541 received antidepressant treatment, while 504 were administered placebo. Within the intervention group, 289 patients (53.4%) described benefits, compared to 158 patients (31.3%) in the control group, resulting in a pooled OR of 3.39 (95%CI 2.24-5.12). Heterogeneity was moderate (I^2=44.7%). The funnel plot was asymmetric (Supplementary Fig. 2), and the Egger test had a statistically significant result (P=0.03). The source of publication bias was further explored, and when the study of Ghadir *et al* was excluded the Egger test became statistically non-significant (P=0.06) [28]. In a subsequent sub-analysis without this study, efficacy remained comparable (pooled OR 2.67, 95%CI 1.88-3.68), with lower heterogeneity (I^2=22.8%).

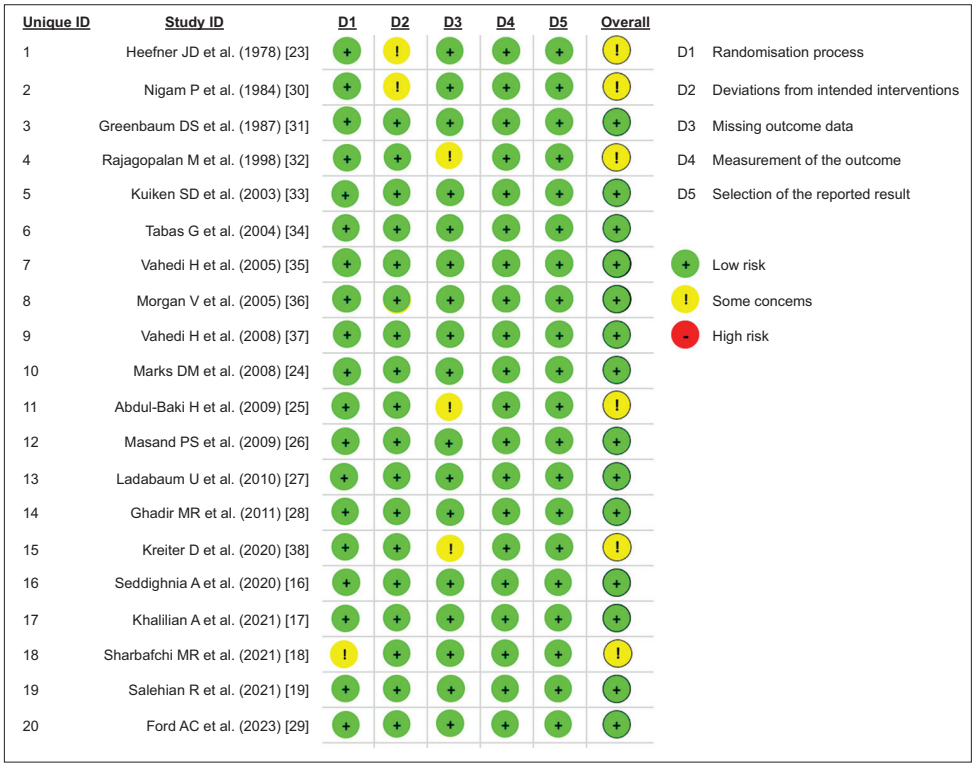

Figure 2 Risk of bias according to the revised version of the Cochrane tool (RoB 2)

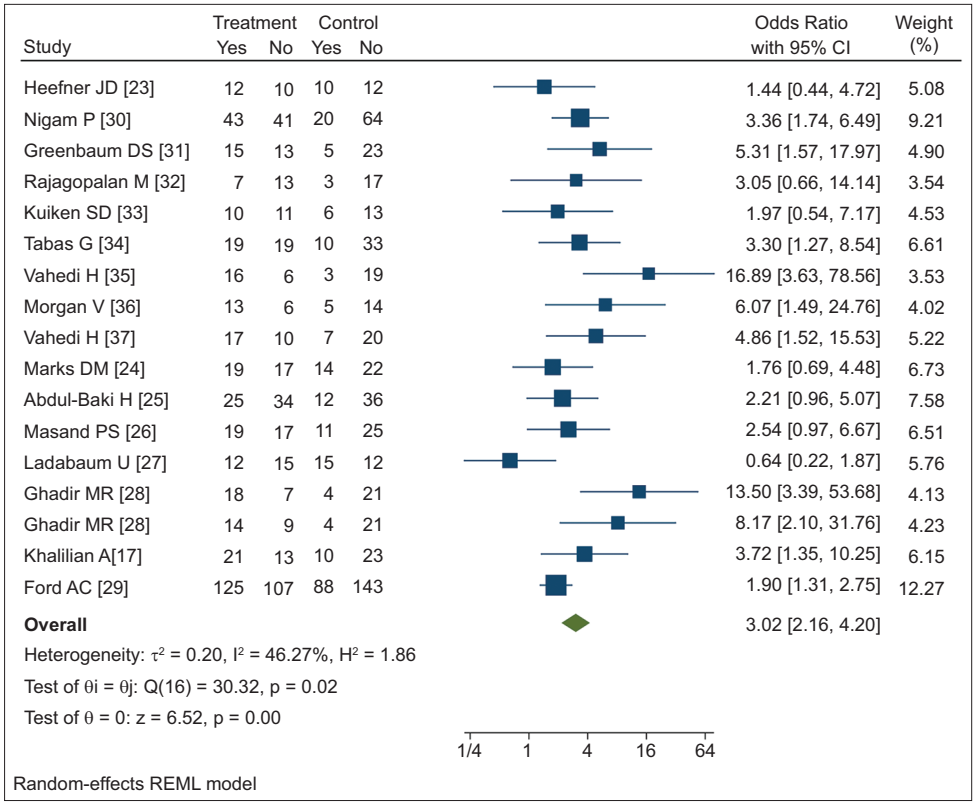

Figure 3 Forest plot of improvement in global symptoms in patients with irritable bowel syndrome undergoing treatment with antidepressants
CI, confidence interval

SSRIs

The efficacy of SSRIs was evaluated through a sub-analysis including 6 studies with a total of 363 patients [24,26,27,33-35]. Antidepressants were allocated to 180 patients and placebo to 183. SSRIs demonstrated an association with overall improvement in 95 (52.8%) patients in the intervention group and in 59 (32.2%) in the placebo group, resulting in a pooled OR of 2.39 (95%CI 1.14-5.01). Heterogeneity was I^2=63.3%. The funnel plot appeared symmetric (Supplementary Fig. 3) and the Egger test was not statistically significant (P=0.16).

A study by Kreiter *et al* met the inclusion criteria, but was excluded from the meta-analysis because its results could not be combined with those of the other studies, being presented in a different way, as previously detailed [38]. In this study, which involved 14 patients, 5 of whom were assigned to the intervention group receiving escitalopram, the medication was linked to improvements in abdominal pain and bloating among IBS patients with concomitant panic disorder.

Serotonin and norepinephrine reuptake inhibitors (SNRIs)

Two randomized, controlled trials (RCTs) meeting the inclusion criteria evaluated venlafaxine and duloxetine, both of which are antidepressants belonging to the group of serotonin and norepinephrine reuptake inhibitors (SNRIs) [18,19]. However, these studies were not included in the meta-analysis because of disparities in result presentation.

The RCT conducted by Sharbafchi *et al* involved 34 patients, with 17 assigned to receive venlafaxine and 17 to receive placebo over a 3-month period. The intervention group reported statistically significant improvements in abdominal pain, bloating, bowel movements and quality of life [18].

Similarly, the study by Salehian *et al* included 60 patients, 30 randomized to receive duloxetine 30 mg daily alongside mebeverine, and 30 to receive mebeverine plus placebo over a period of 12 weeks [19]. The intervention group exhibited statistically significant superiority in terms of overall symptom alleviation and quality of life.

Tetracyclic antidepressant

Khalilian *et al* evaluated the effectiveness of mirtazapine in treating diarrhea-predominant IBS [17]. This RCT involved 67 patients, 34 assigned to the mirtazapine group and 33 to the placebo group. The study demonstrated statistically significant superiority in the intervention group in terms of overall symptoms, abdominal pain, bowel movements and quality of life. However, this therapy did not achieve statistical significance in relieving abdominal distention.

Serotonin modulator and stimulator

The RCT conducted by Seddighnia *et al* evaluated the efficacy of vortioxetine in enhancing quality of life among IBS patients [16]. This study was not incorporated into the meta-analysis because of its outcome assessment and presentation methods. The study involved 80 patients, randomized either to vortioxetine (n=40) or to placebo (n=40). The intervention group reported statistically significant superiority in quality of life.

Patients refractory to first-line measures

The efficacy of antidepressants in improving global symptoms among patients with IBS refractory to first-line measures (mainly probiotics, loperamide or laxatives), was assessed in a sub-analysis comprising 6 studies and a total of 732 patients [25,29,32,33,35,36]. Among these, 373 were assigned to the antidepressant and 359 to placebo. In these patients, antidepressants were associated with an overall improvement in 196 (52.5%) patients in the intervention group and 117 (32.6%) in the placebo group, resulting in a pooled OR of 2.96 (95%CI 1.67-5.25). Heterogeneity was I^2=47.8%. The funnel plot appeared asymmetric and the Egger test was statistically significant (P=0.02) (Supplementary Fig. 4). Once again, when the potential source of publication bias was excluded, the Egger test lost significance (P=0.23), while efficacy remained similar (pooled OR 2.1, 95%CI 1.54-2.87), but heterogeneity became I^2=0 [35]. A fixed-effect analysis was conducted, but heterogeneity was similar (I^2=0). Given the values of τ^2=0 and I^2=0%, a sensitivity analysis was performed, and the pooled OR obtained with different values of τ^2 remained analogous, with statistical significance assessed by the values of the different CI.

Patients without known comorbid psychological conditions

A sub-analysis to evaluate the efficacy of antidepressants in improving global symptoms among patients with IBS, but without known comorbid psychological conditions, was also performed, encompassing 8 studies with a total of 471 patients [17,25,27,34-36]. Of these, 240 were randomized to the intervention group and 231 to the placebo group. In this study, antidepressants were associated with an overall improvement in 123 (51.3%) patients in the intervention group and 64 (27.7%) in the placebo group, resulting in a pooled OR of 2.92 (95%CI 1.6-5.31). Heterogeneity was I^2=53.2%. The funnel plot appeared symmetric and the Egger test did not yield statistical significance (P=0.18) (Supplementary Fig. 5).

Effect of antidepressants on abdominal pain

The efficacy of antidepressants in alleviating abdominal pain specifically was evaluated, encompassing 7 studies with a total of 456 patients [23,24,26,28,33-35,37]. Among these, 237 patients were assigned to the antidepressant group and 219 to the placebo group. Antidepressants in these patients were associated with a reduction in abdominal pain, with 133 patients (56.1%) in the intervention group reporting improvement compared to 77 patients (35.2%) in the placebo group. A pooled OR of 3.27 (95%CI 1.63-6.53) was calculated, and heterogeneity was I^2=66.1%. The funnel plot appeared asymmetric, and the Egger test was statistically significant (P<0.001) (Supplementary Fig. 6). The potential sources of publication bias were identified, and a sub-analysis excluding these studies revealed a pooled OR of 1.75 (95%CI 1.04-2.96) with lower heterogeneity (I^2=24.5%). The Egger test became statistically nonsignificant (P=0.09) [28,35].

Effect of antidepressants on bloating

A sub-analysis of the efficacy of antidepressants in alleviating bloating was also conducted, comprising 4 studies with a total of 224 patients [28,33,34,37]. Of these, 123 were assigned to the antidepressant and 101 to placebo. Antidepressants in these patients revealed an association with improvement in bloating in 57 (46.3%) patients in the intervention group and in 35 (34.7%) in the placebo group. A pooled OR of 2.4 (95%CI 1.11-5.22), was calculated, and heterogeneity was I^2=48.8%. The funnel plot appeared asymmetric, but the Egger test was not statistically significant (P=0.06) (Supplementary Fig. 7).

Effect of antidepressants on quality of life

A qualitative analysis of the efficacy of antidepressants in improving quality of life of IBS patients was also undertaken, involving 6 studies with a total of 402 patients [16-19,25,34]. Because of the diverse methods used to assess quality of life improvement, quantitative synthesis was not feasible. Nonetheless, all the studies reported statistically significant differences in quality-of-life improvement between the group of patients treated with antidepressants and those who received placebo.

Discussion

IBS is one of the most common gastrointestinal disorders, with an enormous prevalence and a rising incidence [1]. In spite of this, the treatment strategies available are far from curing or even modifying the disease course, in the majority of cases achieving only partial symptomatic relief with recurrent flares. In the past decades, efforts have been made to enhance the treatment of IBS, but therapies with strong evidence are lacking [7]. Therefore, it is crucial to identify therapies with established efficacy for IBS to effectively manage this condition.

Antidepressants are thought to be gut–brain axis modulators, addressing not only anxiety and depressive symptoms, often

present in patients with IBS, but also abdominal pain and bowel movements [7]. The results of our review reinforce the role of antidepressants in the treatment of IBS. This analysis revealed that antidepressants are effective in alleviating IBS symptoms. Firstly, regarding the global symptom improvement, although publication bias compromised the analysis with all 16 studies, the sources of this limitation were identified and a sub-analysis comprising 14 studies achieved similar results with low heterogeneity. Moreover, both TCAs and SSRIs were associated with alleviation of IBS symptoms. The analysis of SSRIs effectiveness revealed substantial, but not significant, heterogeneity, in line with previous analyses [15]. Antidepressants only recently evaluated in this setting, namely duloxetine, venlafaxine, mirtazapine and vortioxetine, proved to be advantageous in IBS patients: SNRIs and mirtazapine were valuable in the improvement of global symptoms, abdominal pain and quality of life, while vortioxetine was beneficial in improving quality of life. The only potential limitation of these new drugs was the inability of mirtazapine to demonstrate a statistically significant improvement in bloating or abdominal distension.

This meta-analysis included multiple sub-analyses in particular subgroups of patients. In patients refractory to first-line therapies, antidepressants proved to be beneficial, with very low heterogeneity. Moreover, we concluded that antidepressants are not only beneficial in IBS patients overall, but also specifically in patients with no history of comorbid psychological conditions, indicating that these therapies not only treat comorbid psychological disorders, but also act on the gut–brain axis, both centrally and peripherally.

In addition, we concluded that these therapies are not only effective in the improvement of abdominal pain, but also of bloating. These results are of the utmost importance, as the management of bloating is extremely challenging. No therapy studied to date in this setting has proven consistent efficacy [8]. These findings show that these drugs may be the path to pursue in the alleviation of this complaint in IBS patients.

Regarding IBS subtypes, it is important to consider that some patients tend to develop diarrhea, while others may experience constipation, or alternating diarrhea and constipation. Additionally, these gastrointestinal symptoms are recognized as potential adverse effects of antidepressants [39]. In fact, only a limited number of studies have analyzed the efficacy of the antidepressant under evaluation based on IBS subtypes, which hinders definitive conclusions regarding the preferential use of specific drug classes according to the predominance of diarrhea or constipation. The theoretical assumption that TCAs may be more suitable for patients with diarrhea, while SSRIs may be more beneficial for those with constipation, given their adverse event profiles, cannot be confirmed or refuted by the results of the included studies. This issue should be explored more thoroughly in future studies, as these symptoms not only significantly impact quality of life, but may also hinder therapeutic adherence.

The most recent meta-analysis addressing this matter is a study by Ford *et al* from 2019, which included 18 studies assessing the efficacy of TCAs and SSRIs in the treatment of IBS [15]. The conclusion reached was that both classes were effective, but the assessment of SSRIs' effectiveness had significant heterogeneity. This review only evaluated overall improvement of symptoms and alleviation of abdominal pain. Moreover, the inclusion of open-label trials may have induced some bias in the analysis. A systematic review by Kułak-Bejda *et al*, conducted in 2017 and including 18 RCTs, confirmed that antidepressants are effective in the management of IBS, but reported that TCAs seemed to be more efficacious than SSRIs in this setting [40]. In 2015, Xie *et al* also performed a meta-analysis assessing the efficacy and safety of antidepressants in IBS [13]. This review included 12 RCTs, comprising 799 IBS patients, and confirmed that TCAs were effective in this context, but this effectiveness did not extend to SSRIs. Chao *et al* evaluated the efficacy of amitriptyline in IBS patients [41]. This meta-analysis, published in 2013, only included 4 studies and concluded that this agent was successful in the management of IBS. However, this meta-analysis had several limitations recognized by the authors, including considerable bias.

Our study is the first to exclusively evaluate randomized double-blind placebo-controlled trials. This study design reduces multiple sources of bias, being the most appropriate for inferring causality. In fact, the conclusions of this study are strengthened by the exclusion of open-label trials, which helps prevent limitations such as the influence of patients' expectations on their perceptions of improvement, the inadvertent bias of researchers in treatment or assessment, and participants altering their behavior or reporting based on their knowledge of the treatment. The use of double-blind methodology enhances the objectivity and validity of the results. In contrast, open-label trials make it difficult to determine whether the outcomes are due to the intervention itself or to factors such as patient expectations. Furthermore, only placebo-controlled studies were included, allowing for the evaluation of the true effect of the treatment, separate from psychological effects, thereby enhancing both internal validity and generalizability. In spite of these restrictions, to the best of the authors' knowledge, our systematic review is the most comprehensive conducted to date, including 20 studies and comprising 1572 patients. Moreover, our study is the first to perform quantitative sub-analyses in patients refractory to first-line therapies, in patients with no known comorbid psychological conditions, and specifically assessing the efficacy of antidepressants in improvement of bloating. Additionally, this review is the first to incorporate RCTs investigating classes of antidepressants that have only recently been evaluated in this setting, such as duloxetine and venlafaxine, SNRIs, mirtazapine, a tetracyclic antidepressant, and vortioxetine, a serotonin modulator and stimulator [16-19]. These drugs have shown promising results; however, additional large-scale trials are needed to confirm these findings.

Nevertheless, it is important to acknowledge certain limitations. There was a significant time gap between the conduct of the included studies, which could have led to variations in IBS diagnosis criteria over time and differences in methods for assessing symptoms and treatment responses. The authors endeavored to mitigate this by imposing strict inclusion criteria and standardizing the analysis as far as possible. Unfortunately, not all studies could be included in the meta-analysis, because of heterogeneity in the way results were presented. Additionally, some analyses revealed substantial heterogeneity, prompting investigation into possible sources. Nonetheless, none of the

analyses exhibited statistically significant heterogeneity [22]. Regarding publication bias, it was identified in some analyses, and was probably due to the tendency to publish more positive findings in fields such as IBS. However, analyses excluding the studies most likely to be responsible for this bias confirmed the robustness of the results observed when those studies were included. Furthermore, no minimum sample size was specified for the selection of included studies, in order to ensure that the broadest range of available literature was considered. Although this approach may introduce a potential source of publication bias, the use of a random-effects model accounts for the influence of small sample sizes.

As regards future perspectives, the development of drugs capable of not only improving symptoms, but also modifying the course of IBS, would be invaluable. With a greater understanding of the pathophysiology of IBS and of the gut–brain axis, it is becoming clear that a shift in therapeutic management needs to emerge: from symptom-directed therapies to disease-modifying treatments.

In conclusion, antidepressants, including both TCAs and SSRIs, are undoubtedly effective in patients with IBS. This comprehensive meta-analysis, exclusively incorporating RCTs with the highest level of evidence, reinforces this conclusion. Moreover, the application of these therapies is not restricted to these classes of antidepressant, and may be extended to SNRIs, mirtazapine and vortioxetine. Antidepressants also proved to be applicable to patients resistant to first-line treatments and those lacking known comorbid psychological conditions. Finally, this is the first study to conclude that antidepressants represent one possible therapy with efficacy in alleviating bloating.

Summary Box

What is already known:

- The treatment of irritable bowel syndrome is complex, and many of the recommended therapies lack high-quality evidence
- Several neuromodulators exert localized effects on both the central and peripheral nervous systems and may offer benefits to these patients

What the new findings are:

- Atidepressants from various classes have demonstrated efficacy not only in refractory patients or those with underlying psychopathology but also in the majority of patients, regardless of subgroup classification
- Beyond their role in alleviating overall symptoms, antidepressants serve as a valuable therapeutic option for the relief of abdominal pain and bloating—the latter being a symptom for which few treatments have been conclusively proven effective

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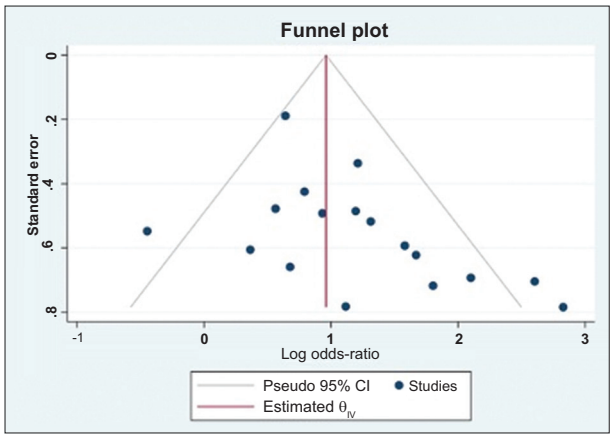
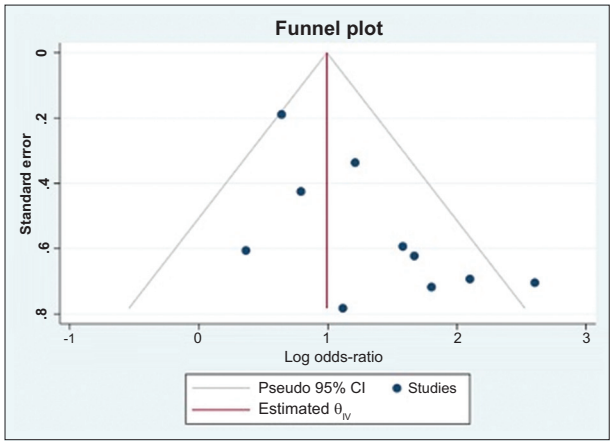
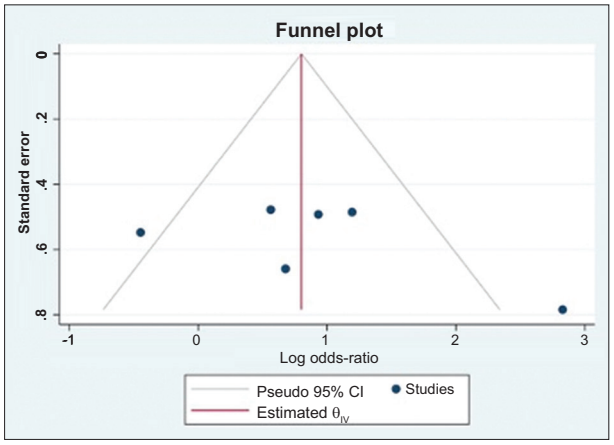
Supplementary material



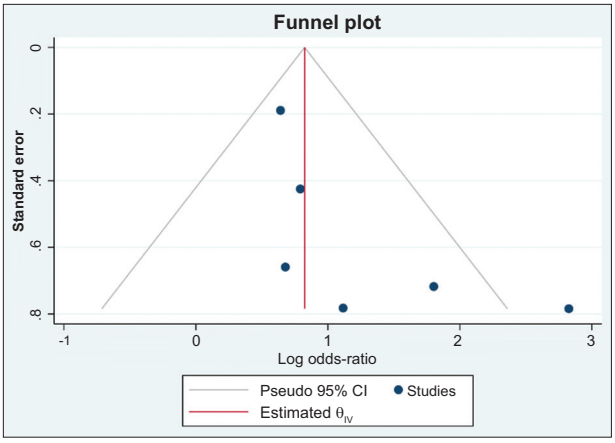
Supplementary Figure 1 Funnel plot of the studies included in the analysis assessing the improvement in global symptoms
CI, confidence interval



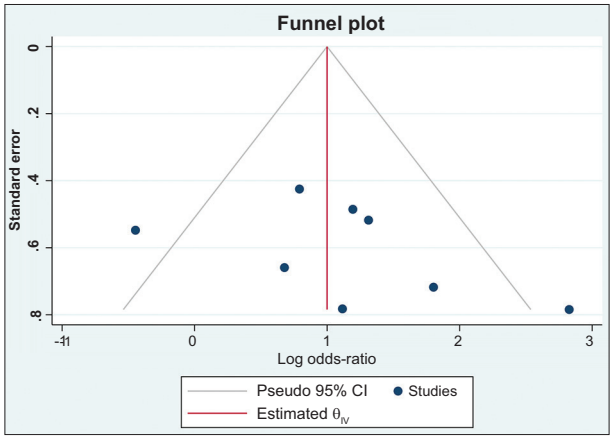
Supplementary Figure 2 Funnel plot of the studies included in the sub-analysis assessing the efficacy of tricyclic antidepressants
CI, confidence interval



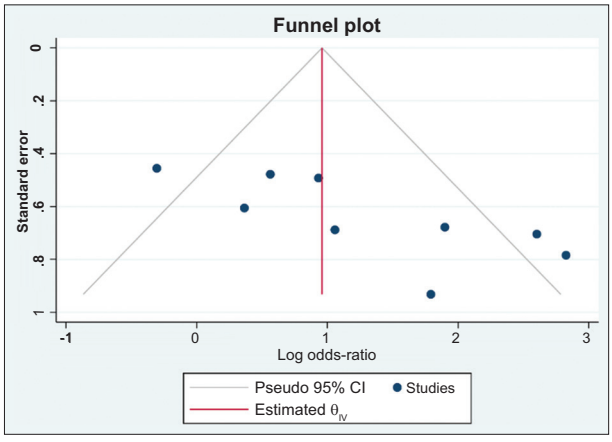
Supplementary Figure 3 Funnel plot of the studies included in the sub-analysis assessing the efficacy of selective serotonin reuptake inhibitors
CI, confidence interval



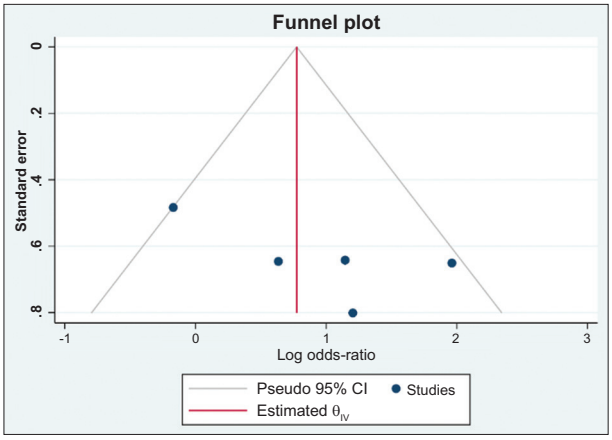
Supplementary Figure 4 Funnel plot of the studies included in the analysis assessing the efficacy of antidepressants in patients refractory to first-line measures
CI, confidence interval



Supplementary Figure 5 Funnel plot of the studies included in the sub-analysis assessing the efficacy of antidepressants in patients without known comorbid psychological conditions
CI, confidence interval



Supplementary Figure 6 Funnel plot of the studies included in the sub-analysis assessing the efficacy of antidepressants in relieving abdominal pain
CI, confidence interval



Supplementary Figure 7 Funnel plot of the studies included in the sub-analysis assessing the efficacy of antidepressants in relieving bloating
CI, confidence interval

Supplementary Table 1 PRISMA guidelines

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	√
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	√
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	√
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	√
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	√
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	√
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	√

(*Contd...*)

Supplementary Table 1 (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	√
Effect measures	12	Specify for each outcome the effect measure (s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	√
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	√
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	√
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	√
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	√
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	√
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	√
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	√
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	√
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	√
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	√
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	√
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	√
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	√
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	√
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	√
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	√
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	√

(*Contd...*)

Supplementary Table 1 (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	√
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	√
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	√
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/