Review of the Antidepressants Effectiveness for Reducing the Quality and Quantity Symptoms of Irritable Bowel Syndrome

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ABSTRACT

Background: IBS or irritable bowel syndrome was one of the functional gastrointestinal disorder in lower gastrointestinal system. The exact pathogenesis mechanisms were still not well studied, however there were several strong evidences that shown there were signalling problems link between ENS (enteric nervous system) and brain (brain-gut-axis). Antidepressants act in the CNS (central nervous system) and could modify function of the brain-gut-axis which theoretically could be a therapeutic option for IBS. Aim: To review the effect of antidepressants on overall symptom improvement, improvement of quality of life, and comparing both safety and side effect of each antidepressant groups**.** Methods: A systematic review of published literatures of clinical trials from various databases such as PubMed, Science Direct, and Cochrane Library with using keywords "Antidepressive, agent" and "irritable bowel syndrome" in their MeSH terms and free terms form. Results: There were 5 articles that matched the restriction criteria. The synthesis results of the all articles shows that TCAs could consistently reduce IBS symptoms and improve quality of life, whereas SSRIs have shown inconsistent results and did not give significantly beneficial result compared to placebo. However, the TCAs group had higher side effects than SSRIs group because SSRIs had high tolerability thus that the side effects were lower than TCAs. Among TCAs tianeptine has the least side effects and highest efficacy for both overall symptom reduction and quality of life improvement. Conclusion: TCAs has better efficacy in compared to SSRIs, although the side effects were higher than SSRIs. Therefore, we suggested that antidepressants should not be used as first line treatment for IBS, unless the patient has psychiatric disorder comorbid. Further research on these mechanisms and long term-effects were required.

Keywords: *antidepressants, TCAs, SSRIs, IBS symptoms, IBS Quality of Life*

1. INTRODUCTION

IBS or irritable bowel syndrome was a syndrome that affects the digestive tract in the lower intestine. This syndrome is characterized by changes in abdominal activity and chronic abdominal pain. These symptoms divided into several groups, such as predominant diarrhea symptoms (IBS-D), constipation symptoms (IBS-C), combination/alternator (IBS-M), and unsubtyped (IBS-U) [1]. In addition, other symptoms could also include abdominal pain, bloating, changes in the shape of the stool and the presence of mucus that comes out with the stool [2]. IBS is also one of the most frequently encountered diseases by doctors. IBS patients were often referred to the internal medicine department, had various medical examinations, prescribed various medicines and treatments, were absent from work and also had a poor quality of life [3]. The diagnosis of IBS was established using the Rome IV criteria which were the latest diagnostic criteria for functional gastrointestinal diseases [4]. IBS symptoms come and go over time, and often associated with non-gastrointestinal somatic pain and another functional gastrointestinal disorders [3].

The prevalence of IBS is 11% of entire population globally [5], Europe 8.1% [4], America ranges from 10-15% [6], and Asia between 6.8% to 33.3% [7]. Only 30% of people who have IBS seek medical assistance

and almost 70% of people who experience symptoms do not go to health services [5]. Approximately 80% of people with IBS have psychiatric symptoms such as anxiety and also depression [8]. During the era of COVID-19 pandemic the rate of depression increased by 3 times fold [9,28,29] which of course had an influence on increasing IBS incidence rates. In Indonesia, the prevalence of IBS is still quite difficult to determine because of the limited data available. Based on a study conducted in Palembang, data on the prevalence of IBS in adolescents was 30.2% for the age of 15.8 ± 0.97 years [10]. Globally predominance of who sufferers IBS is women [4] but equal for men and women in Asia. IBS is more common in younger age groups [7]. Until now the etiologies and pathogenesis of IBS were not well known [8] and there is no specific pathological sign consistently shown in IBS patients [11] and to establish the diagnosis of IBS itself must exclude the evidence of organic disease that may exists [12]. Due to the many mechanisms that were still not yet fully understood, there were no known specific drugs or treatment for IBS and treatment strategies were limited with managing the symptoms [13].

Antidepressants are central agents used as one of the treatments associated with IBS symptoms. Antidepressants may work as IBS therapy due to their effects on motility, pain perception, and the patient's mood. This could have an effect on brain-gut-axis dysregulation. The two classes of antidepressants that could provide efficacy in treating IBS symptoms were TCAs (tricyclic antidepressants) and SSRIs (selective serotonin reuptake inhibitors). Some data also show that SNRIs (selective norepinephrine reuptake inhibitors) could also treat IBS symptoms. The choice of antidepressant class could vary based on habitual defecation patterns, the presence of sleep disturbances, or comorbid anxiety and depression [15]. The well-known mechanism of action of antidepressants were primarily acts on serotonin and noradrenergic receptors by inhibiting the reuptake of the neurotransmitter. TCAs, especially in the secondary amine subtype, has an anticholinergic effect thus that it could increase intestinal transit time and could cause side effects in the form of constipation, although the tertiary amine subtype has a similar effect, but not as high as the secondary amine [16]. Tricyclic antidepressants with their anticholinergic effects may support their use in IBS-D [17]. However, TCAs could also cause constipation, therefore their use for IBS-C is not recommended. Patients with insomnia, anorexia, or weight loss may benefit from the use of TCAs. Meanwhile, SSRIs were better choice for use in IBS-C patients because their prokinetic effects could increase motility and for patients with IBS with significant anxiety. The initial dose is given at a low dose and increased slowly if the response is inadequate [15].

Previously, from a systematic review and meta-analysis was conducted by Ford, et al., 2019 by analyzing the effects of various types of antidepressants and psychotherapy on IBS. The results of the study concluded that tricyclic antidepressants, SSRIs, cognitive behavioural therapy, relaxation, hypnotherapy, dynamic and multicomponent psychotherapy were thought to be effective treatments for IBS [14]. In their research, the authors took secondary data from articles related to antidepressants released before 2010. However, several literature sources have shown results that were not entirely the same as the results found by Ford, et al. and even today, the FDA (United States Food and Drug Administration) has not recognized the general use of antidepressants as a treatment for IBS [18]. We also searched at the IBS therapy guidelines by the American Gastroenterological Association Institute only recommended the use of antidepressants when abdominal pain is very severe [19] and do not recommended the use of SSRIs in the treatment of IBS patients, based from the lack of improvement in general symptom improvement from a meta-analysis of 5 different RCTs [20]. However, the use of tricyclic antidepressants is still recommended by the American College of Gastroenterology as a general treatment for IBS symptoms [16]. This is what makes the authors interested and become the background in the preparation of this study because there were still differences of results from various articles regarding the benefits of using antidepressants for IBS treatment. We use more recent sources of articles released after 2010 as an update in this research. In this study, the authors will analyze the efficacy of antidepressants more specifically in reducing IBS symptoms, improvement of quality of life in IBS patient, and comparing the safety and side effect of each antidepressant groups.

2. METHOD

This study design was a systematic literature review with a narrative method based on previously published research results. This research has been carried out and received approval from the Health Research Ethics Commission (KEPK) FK UMS. This research was conducted by searching, collecting and selecting data from the results of clinical trials conducted from all ethnicities, races, and locations around the world. The time of this research was carried out from November 2020 and completed on January 2021. The data sources were secondary data from published research articles from 2010 and above for articles discussing Antidepressants through searches on several e-databases: PubMed, Cochrane Library, and Science Direct using the words "Antidepressant" and "Irritable Bowel Syndrome" keys, both in the form of the MeSH term and in the form of the free terms. Only randomized clinical trials were undertaken to explore the effect of antidepressant therapy in reducing IBS complaint. The

author used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Group (PRISMA) as a basis for the steps in conducting the systematic review. The applications used for data processing were EndNote X9 and Microsoft Excel.

2.1. Inclusion criteria

Randomized clinical trials articles that containing the keywords antidepressive, agent[MeSH Term] and irritable bowel syndrome[MeSH Term] in addition with their free terms that have synonymous or related meanings published in 2010 and above. The articles contain studies that provide data on the effectiveness of antidepressant use in IBS that could be analysed and the full text articles that could be accessed.

2.2. Exclusion criteria

Full text in languages other than English and Indonesian. IBS Diagnoses does not use the Rome criteria or using other diagnostic criteria. Age of research subjects were children less than 17 years old. Research subjects have comorbid organic disease in the lower gastrointestinal. The duration of the study was less than 2 weeks during the intervention.

The outcomes that will be sought in this study were how the efficacy of antidepressants on improving overall IBS symptoms, the antidepressant's effect on improving the IBS patient's quality of life, and analyzes the safety also advantages and disadvantages of each antidepressant groups.

3. RESULT

The search results found 429 articles on PubMed, 5 articles on the Cochrane Library, and 695 articles on Science Direct. A total of 1129 articles were found according to the year of the search. The authors will then conduct a screening to determine the articles to be synthesized using PRISMA Flow Diagrams. We obtained 5 articles with experimental research design that intervened using antidepressants. The total number of patients included in this research were 507 patients. The results of the PRISMA Flow Diagram could be seen in the figure 1.

From Ladabaum, et al. reported that 54 patients with IBS were included in their study. In the Citalopram group there were 10 IBS C, 12 IBS D, and 5 IBS M patients. For the placebo group there were 11 IBS C, 11 IBS D, and 5 IBS M patients. There were no statistically significant differences between the two groups in symptom relief adequately during the 8-week trial. On quality-of-life IBS QoL (quality of life) scores improved slightly over 8 weeks for both groups. However, there was no significant difference in scores at weeks 0 to 8 (p=0.47). There was no significant difference between the results of symptom scores and individual satisfaction at weeks 4 and 8 of therapy both in stool consistency, weekly bowel movements, urgency, abdominal pain, symptoms subsided adequately every week, satisfaction in reducing IBS symptoms, and decreasing overall IBS symptoms [21].

Table 1. Improvement of IBS symptoms by citalopram compared to placebo [21].

	Week 4 mean (SD)			Week 8 mean (SD)		
	Placebo (n=25)	Citalopram (n=22)	P value	Placebo (n=25)	Citalopram (n=20)	P value
Overall IBS symptoms	4.4 (2.4)	4.0 (2.2)	0.48	4.4 (3.0)	3.3 (2.5)	0.24
Satisfaction with IBS symptoms	4.6 (3.0)	5.4 (2.7)	0.42	5.4 (3.4)	5.9 (3.4)	0.71
Days with adequate relief per week	3.4 (2.1)	3.6 (2.1)	0.76	4.0 (2.3)	4.0 (2.3)	0.88
Abdominal pain	4.4 (2.5)	4.2 (2.6)	0.80	4.3 (3.0)	3.7 (2.6)	0.39
Urgency	3.3 (2.6)	3.7 (2.6)	0.60	3.2 (2.7)	3.6 (2.5)	0.56
Number of bowel movements per week	2.2 (3.2)	2.2 (1.1)	0.09	1.9 (1.6)	2.3 (1.4)	0.29
Stool consistency	6.0 (1.9)	6.5 (2.0)	0.37	6.1 (1.8)	6.3 (2.0)	0.79

The overall response rates to the therapeutic effect were 12 out of 27 (44%) in the citalopram group and 15 out of 27 (56%) from the placebo group (P 0.59). Responders were showed citalopram has no better response compared to placebo for any IBS subgroups (IBS-C, 5 of 10 vs 6 of 11; IBS-D, 6 of 12 vs 6 of 11; IBS-M, 1 of 5 vs 3 of 5).

From Agger, et al. reported 33 of the 63 (53%) patients given imipramine responded "better" and "much better" when compared to placebo group, only 14 of 57 (25%) patients responded "better". The results of the OR analysis of the increase in outcome with imipramine was 3.3 (p = 0.001).

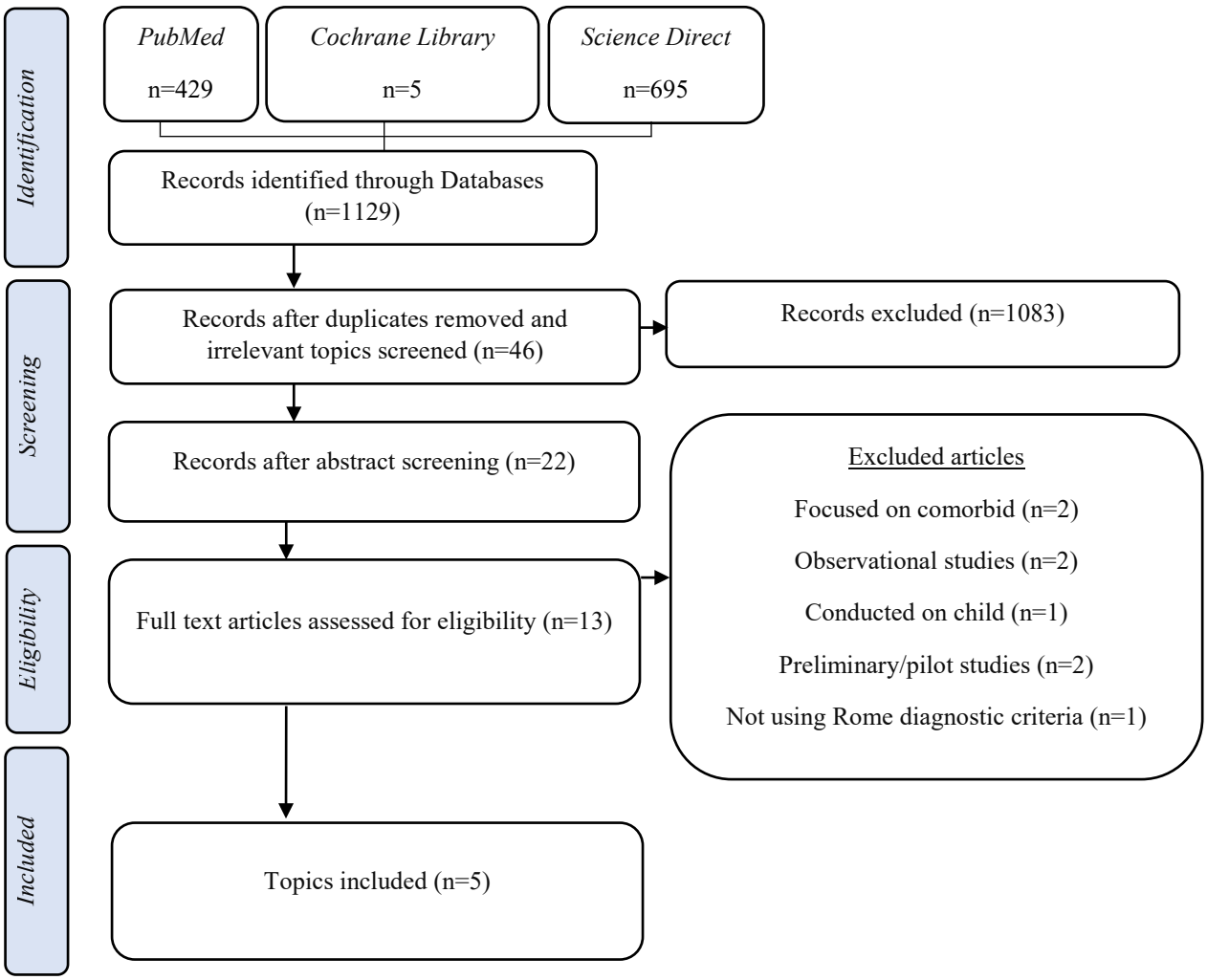

Figure 1. PRISMA flow diagram

The proportion of patients percentage who had experienced generalized reduction in IBS symptoms at week 4 was 66.0% (70/106) in the amitriptyline group and 81.1% (99/122) in the tianeptine group [22].

Table 2. Improvement of overall IBS symptoms by imipramine compared to placebo [22].

	Imipramine (n=65)	Placebo (n=60)
Much worse	1 (2%)	1 (2%)
Worse	4 (6%)	11 (18%)
Unchanged	25 (39%)	31 (52%)
Better	22 (34%)	14 (23%)
Much better	11 (17%)	0 (0%)

A total of 49% of patients receiving imipramine and 17% of patients receiving placebo experienced at least one side effect of moderate intensity. The most common side effects were dry mouth 40%, vertigo 35%, nausea 22%, sweating 17%, sleep disturbances 15%, lethargy 15%, headache 12%, constipation 11%, and other GI disorders as much as 9% [22].

From Najafabadi, et al., reported that the intervention was carried out on 33 IBS patients (IBS C 10, IBS D 12, IBS M 11). In the fluoxetine group with a baseline IBS QoL Score of 59.18 before the intervention, the score increased to 59.27 (p=0.753) at week 2 of therapy, 61.33 (p<0.001) at week 4, and 67.36 (p<0.001) at 6 weeks of therapy. The average increase in each IBS subtype was in IBS C = 6.90, in IBS D = 6.16, in IBS M = 11.54. The side effects felt by the subjects were headache 4 (12.1%), dry mouth 4 (12.1%), nausea 4 (12.1%), daytime sleepiness 4 (12.1%), constipation 3 (9%), sweating 3 (9%), and vomiting 3 (9%) [23].

Table 3. IBS QoL score improvement by fluoxetine [23]

	Mean	SD	p-value
Baseline	59.18	7.28	-
Week 2	59.27	6.21	0.753
Week 4	61.33	6.74	<0.001
Week 6	67.36	7.58	<0.001

From Sohn, et al., (2012) reported 228 IBS patients were included as subjects in this study. The proportion of patients who had experienced generalized reduction in IBS symptoms at 4th week by percentage were shown at 66.0% (70 of 106) from amitriptyline group and 81.1% (99 of 122) from tianeptine group. There was a significant change in both the amitriptyline and tianeptine groups between the baseline score and the results of week 4 therapy in reducing symptoms of abdominal pain, abdominal discomfort, frequency of defecation in a day, stool consistency, and quality of life [24].

Tianeptine has better results in reducing abdominal pain, abdominal discomfort, frequency of defecation and improving quality of life. The proportion of patient satisfaction with therapy given at the end of the study at 4th week the precentage was 52.8% (56 of 106) from amitriptyline group and 72.1% (88 of 122) from tianeptine group [24].

Table 4. Improvement of overall IBS symptoms by tianeptine and amitriptyline [24].

	Amitriptyline group (N=106)			Tianeptine group (N=122)		
	Baseline	4th week	P value	Baseline	4th week	P value
VAS scores abdominal pain	42,9 ± 25.6	21.1 ± 21.0	<0.005	42.5 ± 23. 2	17.8 ± 19.6	<0.005
VAS scores abdominal discomfort	51.1 ± 20.2	27.9 ± 20.7	<0.005	49.4 ± 20.7	22.1 ± 20.0	<0.005
Stool frequency per day	3.8 ± 3.1	2.6 ± 2.1	<0.005	3.8 ± 2.5	2.4 ± 1.7	<0.005
Stool Form (BSFS)	5.9 ± 0.8	4.8 ± 1.1	<0.005	5.8 ± 0.7	4.3 ± 1.1	<0.005
EQ-5D scores	0.76 ± 0.26	0.86 ± 0.20	<0.005	0.77 ± 0.22	0.91 ± 0.14	<0.005

There were several side effects felt by the subjects during the study such as dry mouth (tianeptine 7% and amitriptyline 20%, $p < 0.005$), constipation (tianeptine 1% and amitriptyline 6%, $p < 0.05$), dizziness (tianeptine 5% and amitriptyline). 11%, $p < 0.06$), drowsiness (tianeptine 2% and amitriptyline 7%, $p < 0.07$). In addition, in the tianeptine group, other side effects occurred in the form of 5% lethargy, 5% insomnia, 7% vertigo, 8% nausea, 8% epigastric discomfort, 6% abdominal pain, and 6% satiety. In the amitriptyline group, other side effects occurred in the form of 8% lethargy, 6% insomnia, 11% vertigo, 8% nausea, 7% epigastric discomfort, and 5% abdominal pain [24].

From Seddighnia, et al., reported 66 IBS patients were included in this study. There were 10 IBS C patients (27.8%), 17 IBS D patients (47.2%), and 9 IBS M patients (25%) in the placebo group. For the treatment group with vortioxetine there were 10 IBS C patients (27.8%), 15 IBS D patients (41.7%), 11 IBS M patients (30.6%). In the vortioxetine group at 2,4, and 6 weeks of therapy, the MD IBS QoL scores were 0.47 (p=0.161), 2.81 (p<0.001), 8.44 (p<0.001). MD IBS QoL scores in the placebo group were 0.22 (p=0.11), 1.17 (p=0.001), and 4.17 (p<0.001) [25].

The baseline IBS QoL score for vortioxetine was 58.86 to 67.31 at week 6. There was a significant effect indicating that vortioxetine had a better effect than placebo (p<0.001). Better efficacy was found in the IBS M group compared to IBS C or IBS D (p<0.001), but the response to vortioxetine therapy was significantly faster in the non-IBS M group than the IBS M group [25].

Table 5. Improvement of quality of life of IBS score by vortioxetine compared to placebo [25].

	Placebo			Vortioxetine		
	MD	SEM	MD	SEM	MD	SEM
Week 2	0.22	0.11	0.044	0.47	0.33	0.161
Week 4	1.17	0.32	0.001	2.81	0.49	<0.001
Week 6	4.17	0.80	<0.001	8.44	0.74	<0.001

No side effects were found with a significant difference between the placebo group and the vortioxetine group. There were 3 patients experienced headache (8.3%), 4 experiencing dry mouth (11.1%), 4 experienced nausea (11.1%), 2 experienced vomiting (5.6%), 2 experiencing itching (5 ,6%), 3 vertigo (8.3%), and 2 sexual dysfunction (5.6%). In the vortioxetine group, 1 patient headache (2.8%), 2 dry mouth (5.6%), 2 nausea (5.6), 4 vomiting (11.1%), 1 itching (2.8%), 1 vertigo (2.8%), and 1 sexual dysfunction (2.8%). There were no serious side effects and the number of subjects experiencing side effects was lower in the vortioxetine group.

The results of the narrative analysis that has been carried out above will then be compiled into a table by including name, year, country, number of samples, duration/dose of therapy, outcomes and instruments, post test results, and summary which could be seen in the table following:

Table 6. Narrative summary of the articles synthesis

Authors	Year and Country	Number of samples	Duration/ dose of therapy	Outcomes and Instruments	Post Test Result	Summary
U. Ladabaum, A. Sharabidze, T.R. Levin, W.K. Zhao, E. Chung, P. Bacchetti, C. Jin, B. Grimes, R.J. Pepin	2010, USA	54 patients (21 IBS C, 23 IBS D, 10 IBS M)	Citalopram 20 mg 1 capsule daily for weeks 1 to 4 and 2 capsules daily for weeks 5 to 8	Improvement of symptoms with Symptom and Satisfaction Score and Quality of Life with IBS QoL	12 out of 27 (44%) in the citalopram group and 15 out of 27 (56%) in the placebo group (P 0.59). Response rates were no better for citalopram than for placebo for any of the IBS types (IBS C, 5 out of 10 vs 6 out of 11; IBS D, 6 out of 12 vs 6 out of 11; IBS M, 1 out of 5 vs 3 out of 5) in week 8	Citalopram did not gave significantly better results than placebo in terms of both symptom improvement and the quality of life.
J.L. Agger, A. Schröder, L.K. Gormsen, J.S. Jensen, P.K. Fink	2017, Denmark	120 patients with functional somatic multiple syndrome (43 samples had IBS (36%)). Type of IBS not reported	The initial dose of 10 mg per day is increased to 25 mg per day after 1 week to a maximum of 75 mg per day for up to 13 weeks.	Symptom improvement, no specific instrument	Patients with IBS in the antidepressant group were 31% and 39% in the placebo group. 33 of 63 (53%) patients given imipramine responded better and only 14 of 57 (25%). The results of the OR analysis of the increase in outcome with imipramine was 3.3 (p = 0.001)	Imipramine gave significantly better results than placebo.
W. Sohn, Y. Lee, J.G. Kwon, K.S. Park, J.Y. Lim, T.H. Kim, S.W. Jung, J.I. Kim	2012, Korea	228 IBS patients. Type of IBS not reported	Tianeptine 12.5 mg and amitriptyline 10 mg daily for 4 weeks	Symptom improvement and quality of life, with European Quality of Life 5 Dimension	Improvement 66.0% (70 of 106) in the amitriptyline group and 81.1% (99 of 122) in the tianeptine group at week 4. EQ-5D score amitriptyline on baseline 0.75 ± 0.26 to 0.86 ± 0.20 (<0.05) on week 4 whereas for tianeptine 0.77 ± 0.22 to 0.91 ± 0.14 (<0.05).	Tianeptine gave better results than amitriptyline terms of both symptom improvement and quality of life.
B.T. Najafabadia, K. Ghamaria, T.K. Ranjabarib, A.A. Noorbalab, N.E. Daryanic, E. Vanakia, S. Akhondzadeha	2019, Iran	33 IBS patient (10 IBS-C, 12 IBS-D, 11 IBS-M)	Fluoxetine 20mg twice daily for 6 weeks.	Quality of life with IBS QoL scoring	In the fluoxetine group with a baseline IBS QoL Score of 59.18 before the intervention, the score increased to 59.27 (p=0.753) at week 2 of therapy, 61.33 (p<0.001) at week 4, and 67.36 (p<0.001) at 6 weeks of therapy.	Fluoxetine gave significantly better results on the posttest compared to the baseline.
A.Seddighnia, B.T.	2019, Iran	72 IBS patient (20 IBS-C, 32	Vortioxetine 10 mg daily	Quality of life with	In the vortioxetine group at 2,4, and 6 weeks of	Vortioxetine gave significantly better

4. DISCUSSION

After synthesized article results were obtained, there are several things that we need to discuss to determine the outcome that is the goal of our research.

4.1. Efficacy for Overall Symptoms Improvements

In general, there was a decrease in symptoms in the TCA therapy group when compared to the control group. SSRIs appeared to provide various and inconsistent results in reducing symptoms for IBS patients. Thus, in accordance to that the citalopram do not appeared to be better than placebo at reducing IBS symptoms. Inconsistent results in studies regarding the effect of SSRIs in improving IBS symptoms have been frequently found in previous studies.

The interesting thing is seen in the results of the study by Seddighnia, et al. [25], theoretically SSRIs were used for IBS C therapy because of their trait to reduce intestinal transit time [26]. However, the results obtained vortioxetine has a better efficacy in IBS M than type C IBS in reducing symptoms in general. The authors suspect this is because the use of vortioxetine which was first used in a trial as a therapy for IBS thus that there may be several factors and mechanisms that were different from drugs in other SSRI groups but of course this still needs to be proven by further research.

In the TCA group, the efficacy of using tianeptine showed better results than amitriptyline and imipramine in improving IBS symptoms. TCAs also provide better pain relief than SSRIs. This is also supported by a review of previous articles in which 3 out of 5 studies evaluating abdominal pain showed no significant benefit in using SSRIs to reduce pain [27]. Antidepressants work in reducing general symptoms of IBS through pathophysiological mechanisms of IBS due to abnormalities in the serotonergic signalling process or metabolic disorders and communication regulation between the enteric nervous system and the brain (brain-gut-axis) which is one of the possible pathophysiological mechanisms [18]. The mechanism of action of antidepressants themselves in reducing pain works both centrally and peripherally. Centrally, antidepressants act in a multifactorial manner and may include reducing central pain activation in the anterior cingulate cortex and pain processing centers. At the periphery, antidepressants have a decreasing effect on pain sensation by adjusting the colonic and visceral afferent function. This explains the pain-reducing effect of antidepressant use [26]. It is unfortunate that there were no articles discussing SNRIs given that their mechanism is similar to that of TCAs. It balanced affinities of norepinephrine and serotonin (5-HT) reuptake transporters that might modulate the affective dimension of pain, reducing pain and other physical symptoms associated with IBS [18]. Furthermore, the dilemma in the antidepressant's usage for the IBS treatment of is related to existing comorbid diseases. Previously it has been mentioned that 80%-90% of IBS patients experience mental disorders such as depression and anxiety [8], but it seems that the administration of TCA in IBS, especially at high doses (definitive therapeutic doses of affective disorders) shows a high level of side effects which is high enough that many stop their use during therapy [18]. On the other hand, SSRIs show better tolerance than the previous generation, but their efficacy shows inconsistent results.

4.2. Efficacy for Quality-of-Life Improvements

Still relevant to symptom reduction, TCA group showed significant results in improving the quality of life of IBS patients. This time, SSRIs still show inconsistent results in improving quality of life. 1 in 3 studies show insignificant results in quality-of-life improvement. There were 2 data that have the same instrument, therefore the authors decided to conduct a forest plot to assess whether there is a significant effect between the use of SSRIs on improving quality of life when compared to placebo in figure 2.

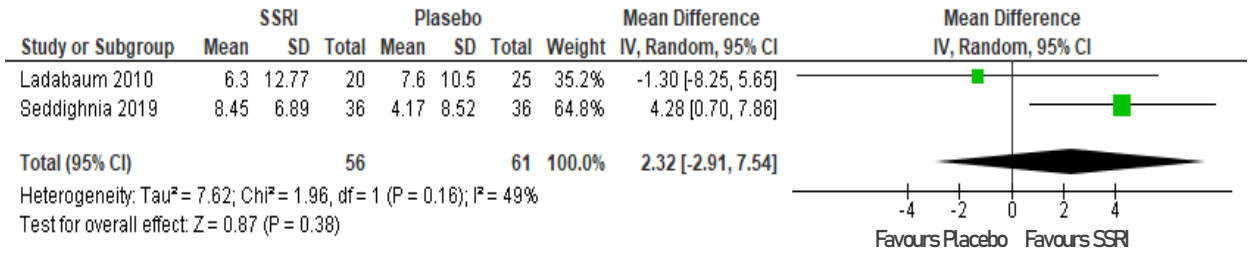

Figure 2. IBS QoL forest plot analysis of SSRIs compared to placebo

The outcome that appeared in the analysis above shows that although the use of the SSRI was still favourable, the therapeutic effect did not show a significant result on improving quality of life compared to placebo (P=0.38).

Although TCAs has shown significant results in reducing IBS symptoms and improving quality-of-life, the authors noted significantly higher incidence side effects of TCAs compared to placebo. Some of the side effects that often arise from the usage of antidepressants from the articles that we have synthesized:

Table 7. Comparison of side effects of each antidepressant

Side effect	Imipramine	Amitriptyline	Tianeptine	Vortioxetine	Fluoxetine
Dry mouth	40%	20%	7%	5.6%	12.1%
Dizziness	35%	11%	7%	2.8%	-
Nausea	22%	8%	8%	5.6%	12.1%
Sweating	17%	-	-	-	9%
Drowsiness and sleep disturbances	15%	7%	2%	-	12.1%
Tiredness	15%	-	-	-	-
Headache	12%	11%	7%	2.8%	12.1%
Constipation	11%	6%	1%	-	9%
Other GI disturbances	9%	9%	8%	11.1%	9%

4.3. Safety of each therapy groups

The side effects shown in the table above were indeed in accordance with the characteristics of each subtype of tricyclic antidepressants. Tianeptine was a tertiary amine subtype which in theory will indeed provide fewer side effects compared to Imipramine and Amitriptyline which was secondary amine groups [16]. The results shown in the use of SSRIs show the opposite results. The use of SSRIs did not show any significantly more severe side effects than placebo. Side effects that could occur with SSRIs include vomiting and sexual dysfunction.

In this study, we encountered several limitations that may affect the results obtained, including:

1. The number of samples and the presentation of data were limited by the synthesized articles, thus there was a risk of bias in the result of this review.
2. Due to the heterogeneity of the data, outcomes, and instruments in the synthesized articles make it not poassible to conduct meta-analysis.
3. The causes of IBS were multifactorial with unclear etiologies therefore that the effects and mechanisms of reducing IBS symptoms by antidepressants were still uncertain due to mental disorders that become comorbid.
4. There were no articles discuss further follow-up of the patient's condition after the post test is completed.

The authors could conclude it appears that TCAs therapy might be an effective treatment to relieve symptoms and improving quality of life of IBS patient. The SSRIs group has inconsistent results and could has an insignificant therapeutic effect compared to placebo. There is also a comparison in terms of advantages and disadvantages of TCA, which is that it has good and consistent efficacy, but the drawback was its low tolerability, which often causes side effects. Meanwhile, SSRIs have inconsistent efficacy but high tolerability thus that side effects were lower than TCAs. As our recommendation, antidepressants should not be the first choice of IBS treatment. The use of antidepressants, especially TCAs, should be used with caution based on the results that have been obtained from the data above which gives quite a lot of side effects. SSRIs could be used as IBS therapy if the patient have comorbid affective and anxiety disorders.

AUTHORS' CONTRIBUTIONS

Syahrun El Mubaraq contributed in designed the research, collecting data, performing PRISMA screening, synthesize articles, and wrote the paper. Zaid Ziyaadatulhuda Ashshiddiq contributed in performing PRISMA screening as the second reviewer. Erna Herawati contributed in providing advices and supervision in the writing of this paper.

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