A Meta-analysis of the Therapeutic Effects of Amitriptyline for Treating Irritable Bowel Syndrome

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Abstract

Objective We aimed to evaluate the efficacy of amitriptyline as a therapeutic option for irritable bowel syndrome (IBS) through a meta-analysis of randomized controlled trials.

Methods For the years from 1966 until May 2012, PubMed, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials were searched for double-blind, placebo-controlled trials investigating the efficacy of amitriptyline in the management of IBS.

Results Four randomized, placebo-controlled clinical trials met our criteria and were included in the meta-analysis. The pooled relative risk for clinical improvement with amitriptyline therapy was 4.18 (95% CI: 2.00 to 8.77, p=0.0001).

Conclusion It was thus concluded that amitriptyline exhibits a clinically and statistically significant control of IBS symptoms.

Key words: irritable bowel syndrome, amitriptyline, meta-analysis

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Introduction

Irritable bowel syndrome (IBS) is the most common reason patients seek medical advice from primary care doctors and gastroenterologists. It generates a considerable workload and constitutes 36% of all visits to gastroenterologists (1). The costs associated with IBS are significant, with an estimated $30 billion spent per year in direct and indirect costs in the United States alone (2, 3). The diagnosis of IBS is based on clinical symptoms and can be made using various criteria. However, its etiology remains unknown. The most popular pathogenetic theory involves a combination of dysregulated gastrointestinal (GI) motility and heightened visceral sensitivity in the context of chronic life stresses and other psychological factors (4).

Nowadays, the mainstays of pharmacotherapy include bulking agents, antidiarrheal agents, laxatives, antispasmodics, antidepressants, serotonergic agonists or antagonists, antibiotics and probiotics (5-8). However, in spite of numerous studies evaluating the treatment of IBS (9, 10), there is still no universally accepted satisfactory treatment for this condition. It is well recognized that approximately 20-30% of IBS patients have heightened levels of anxiety and a similar population reports having depression (11). Therefore, antidepressants are extensively used to treat IBS, especially in patients with prolonged severe symptoms, daily functional disorders, depression and panic attacks (4).

Amitriptyline is an effective drug for treating patients with IBS. However, some studies evaluating the efficacy of this drug have been inconclusive due to the lack of control groups. In some cases, amitriptyline has been used in combination with other drugs, and in most studies, the number of subjects was small. In a meta-analysis performed in 2009 (12), the efficacy of tricyclic antidepressants in patients with IBS was reported. In the present paper, the efficacy of single amitriptyline in IBS patients was reviewed in a meta-analysis of all randomized controlled trials.

Materials and Methods

We searched PubMed, Scopus, Web of Science and the...
Cochrane Central Register of Controlled Trials for studies investigating the efficacy of amitriptyline in patients with IBS. Data were collected for the years 1966 to 2012 (up to May). The search terms were: “amitriptyline” and “irritable bowel,” “functional bowel diseases” or “irritable colon.” The search was restricted to the English literature. We searched the references of reviewed articles for additional articles missed by the computerized database search. All primary and review articles, as well as their references, were reviewed independently in duplicate.

All controlled trials investigating the efficacy of amitriptyline in patients with IBS were considered. The studies were screened for inclusion through a review of the published article based on the following criteria: randomization, placebo control and measurable outcomes reported. Each article was reviewed in duplicate for inclusion, with substantial inter-rater agreement. Trials were disqualified if they were not placebo-controlled or their outcomes did not consider efficacy. The reviewers independently extracted data on patient characteristics, therapeutic regimens, dosages, trial duration and outcome measures.

We used Jadad scores to assess the quality of each article. The Jadad score, which evaluates studies based on their description of randomization, blinding and dropouts (withdrawals), was used to assess the methodological quality of each trial (13). The quality scale ranges from 0 to 5 points, with a low quality report scoring 2 points or less and a high quality report scoring at least 3 points.

All analyses were performed using the STATA 10.0 and Revman 5.0 software programs. Data from selected studies were extracted into 2x2 tables. All included studies were weighted and pooled. Relative risk (OR) and 95% confidence intervals (95% CI) were calculated, and the effect size (weighted mean difference) meta-analysis was performed using the Revman 5.0 software program. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using an L’Abbe plot as an aid to explore the heterogeneity of the effect estimates. In cases of homogeneity, a fixed-effect model was used for the meta-analysis; otherwise, a random-effect model was applied. In addition to Kendall’s t-test (14), funnel plots were used as an indicator of publication bias (15).

### Results

#### Article selection

The literature search identified 42 citations involving amitriptyline and irritable bowel syndrome, four of which met the inclusion criteria (16-19). Of the 38 excluded articles, 10 were review articles, three were observational studies that compared amitriptyline with other medicines, seven were experiments, five were conducted in children and adolescents, two were meta-analysis of other medicines, four were letters, one was a movie and four studied other conditions besides IBS (Fig. 1).

#### Jadad score assessment

The quality of each of the four articles was assessed using Jadad scores (Table 1). The score of each article was 3. Therefore, all four articles were of high quality.

The patient characteristics, IBS subtypes, dosages and duration of treatment/follow-up in each study are reported in Table 2. All subtypes of IBS (diarrhea-predominant, constipation-predominant and alternating) were incorporated in the included studies. This meta-analysis included 130 IBS patients randomized to receive amitriptyline or a placebo. The definition of clinical response used in each study is reported in Table 3.

#### Heterogeneity test

We performed the heterogeneity test using the $\chi^2$ test. $\chi^2 = 0.40, \ p=0.94$ (Fig. 2). It was found that this study did not cause heterogeneity in our meta-analysis. Therefore, a fixed-
Table 1. Jadad Quality Scores of the Randomized Controlled Trials Included in the Meta-analysis

<table>
<thead>
<tr>
<th>studies</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Withdrawals and dropouts</th>
<th>Total Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mertzet et al[16], 1998</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Morgan et al[17], 2005</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Rajagopalan et al[18], 1998</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Vahedi et al[19], 2008</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of the Papers Included in the Meta-analysis

<table>
<thead>
<tr>
<th>studies</th>
<th>Mean age</th>
<th>IBS subtype</th>
<th>Daily dosage</th>
<th>duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mertzet et al[16], 1998</td>
<td>44</td>
<td>ND</td>
<td>50mg</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Morgan et al[17], 2005</td>
<td>39</td>
<td>D-IBS, C-IBS, ALT-IBS</td>
<td>First 25mg, then 50mg</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Rajagopalan et al[18], 1998</td>
<td>34.8</td>
<td>ND</td>
<td>First week: 25 mg; 2nd week: 50 mg; Thereafter to the end: 75 mg</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Vahedi et al[19], 2008</td>
<td>36</td>
<td>D-IBS</td>
<td>10mg</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

Table 3. Response to Treatment

<table>
<thead>
<tr>
<th>studies</th>
<th>Definition of response</th>
<th>response</th>
<th>Amitriptyline</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mertzet et al[16], 1998</td>
<td>improvement of IBS symptoms determined by patients</td>
<td>5/7</td>
<td>2/7</td>
<td></td>
</tr>
<tr>
<td>Morgan et al[17], 2005</td>
<td>improvement of IBS symptoms determined by patients</td>
<td>13/22</td>
<td>5/22</td>
<td></td>
</tr>
<tr>
<td>Rajagopalan et al[18], 1998</td>
<td>improvement of IBS symptoms determined by patients</td>
<td>7/11</td>
<td>3/11</td>
<td></td>
</tr>
<tr>
<td>Vahedi et al[19], 2008</td>
<td>Complete loss of symptoms at the end of the study or at least two scores with a decrease in the number of symptoms</td>
<td>17/25</td>
<td>10/25</td>
<td></td>
</tr>
</tbody>
</table>

effect model was used for the meta-analysis.

Bias assessment

The reason for bias was based on the fact that positive result research can be published easily, while negative result research cannot be published easily. Bias may have also resulted because the researchers gave up due to obtaining a negative result, which would lead to the article not being published, so as to have an affect on the results of the meta-analysis. A funnel plot is a useful tool to assess bias in a systematic review. From the funnel plot (Fig. 3), we found that the four samples were distributed symmetrically; therefore, we do not believe that there was a significant publication bias or, at least, that any potential bias would not have a substantial influence on the final conclusions. Therefore, we were able to conduct the meta-analysis.

Merging and meta-analysis

Based on the meta-analysis, the heterogeneity among the four studies was not statistically significant (p=0.94); therefore, we used the fixed-effects model for the meta-analysis. From the forest map, we determined that the diamond was on the right side of the vertical line and did not intersect with the line. Based on Fig. 2, we determined the following values: OR=4.18, 95%CI=2.00-8.77, Z=3.79, p=0.0001 (Fig. 2). This meant that the value of OR was statistically significant. It also meant that amitriptyline had effect on irritable bowel syndrome. However, because the number of included articles was limited, more studies should be conducted and further analyses should be performed in the future.

Discussion

Irritable bowel syndrome is a chronic functional GI disorder characterized by episodes of abdominal pain and/or discomfort and altered bowel habits. The diagnosis of IBS, a highly prevalent functional gastrointestinal disorder (FGID),
is currently made based on the presence of a characteristic symptom profile (abdominal pain/discomfort, bloating/distension, alterations in defecatory function) in the absence of a demonstrable organic disease of the GI tract (20). IBS is an important health problem throughout the world (21, 22). Despite many years of research, the disorder continues to have an uncertain etiology and is often associated with non-colonic symptoms (23, 24). The burden of IBS is significant enough to contribute to considerable impairment of quality of life. Patients with IBS exhibit higher healthcare resource utilization than non-IBS patients in terms of more frequent physician visits, more tests, a greater frequency of medication use and increased rates of unnecessary surgery (25).

Recently, several pharmacological treatments have been proposed for the treatment of IBS. The treatment of IBS is notoriously unsatisfactory (26). However, although many drugs are currently used to treat IBS, these drugs are essentially administered in an attempt to reduce the severity of symptoms, and more than one drug is often prescribed for the same patient (27). The efficacy of therapeutics for IBS is undoubtedly impacted by the heterogeneous pathogenesis of IBS, and there is no currently recognized reference treatment for this pathology.

Visceral hypersensitivity and dysregulation of central pain perception in the brain-gut axis is considered to play a pivotal role in the pathophysiology of IBS. IBS patients have a lower sensory threshold to colonic and rectal balloon distention and electrical stimulation (28). Therefore, the beneficial effects of antidepressants can be explained by partial increments in the central pain threshold. Other mechanisms by which antidepressants might express their effects include anticholinergic effects, regulation of GI transit and peripheral anti-neuropathic effects (29). Some articles have reported that tricyclic antidepressants can be used to treat patients with IBS, especially those with refractory symptoms, and several studies have shown the efficacy of low-dose tricyclic antidepressant (TCA) in IBS patients (30).

Amitriptyline is a TCA. It has been shown to be significantly more effective than a placebo in adults with IBS in producing global improvements, increased feelings of well-being, reduced abdominal pain and increased satisfaction with bowel movements (18). The effects of amitriptyline in pediatric patients with IBS have yet to be reported. Bahar et al. (31) reported the findings of a double-blind placebo-controlled trial evaluating the effects of amitriptyline in the treatment of IBS in adolescents. Based on the improvements in overall quality of life observed in the study, the authors concluded that amitriptyline should be considered for adolescents with IBS. However, we did not include pediatric IBS patients in our analysis; we only considered adults in this study.

Our meta-analysis of four published, randomized controlled trials suggests that amitriptyline may reduce the symptoms of IBS. These results were consistent whether assessing continuous or dichotomous measures of outcome, and all published results indicated that treatment was effective. Thoua et al. (32) reported that amitriptyline appears to decrease stress-induced electrical hypersensitivity, independent of autonomic tone. The gut response to acute stress deserves further study as a model for evaluating drug efficacy in IBS. Forootan et al. (33) compared the effects of nortriptyline, amitriptyline and fluoxetine. The results demonstrated improvements in abdominal pain, flatulence and general performance in all subgroups. Amitriptyline and nortriptyline improved the frequency of defecation in both diarrhea and constipation-predominant IBS patients, while fluoxetine improved GI transit in patients with constipation-predominant IBS.

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**Figure 2.** Meta-analysis of amitriptyline for treating IBS.

**Figure 3.** Bias assessment plot.
In our analysis, we included four articles, and there were 130 samples all together. However, the results of the meta-analysis are limited. First, the number of samples in each study was not adequate. Second, because the duration of treatment was different in each study and there are only four articles included, we could not analyze how long amitriptyline produces benefits for treating IBS. Third, because the assessment of improvements in each study was different and not detailed, it was difficult to accurately assess the effects of amitriptyline. Fourth, because the side effects of amitriptyline were not recorded in each study, we could not assess the side effects that occur when using amitriptyline to treat IBS. Fifth, many negative results were not reported; thus, our meta-analysis had some bias. Therefore, although we found that amitriptyline has benefits for IBS patients, further studies including more samples should be conducted so as to obtain accurate results.

Conclusion

This meta-analysis showed that amitriptyline is beneficial for IBS adult patients. However, this review is associated with some limitations. This requires researchers to conduct further studies of amitriptyline in IBS patients so that more accurate results can be obtained.

The authors state that they have no Conflict of Interest (COI).

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References
