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Do Antidepressants Improve the Quality of Life and Decrease the Severity of Symptoms in Patients with Irritable Bowel Syndrome?

Courtney E. Houde

Philadelphia College of Osteopathic Medicine, courtneyho@pcom.edu

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Do antidepressants improve the quality of life and decrease the severity of symptoms in patients with irritable bowel syndrome?

Courtney E. Houde PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not the use of antidepressants improves the quality of life and decreases the severity of symptoms in patients with IBS.


Data sources: Randomized controlled trials comparing the use of three different antidepressants to a controlled placebo were found on PubMed, OVID and the Cochrane database.

Outcome(s) Measured: Primary end point was overall bowel symptom score at the end of twelve weeks. Secondary end points include individual BSS for each irritable bowel syndrome subset, constipation, pain, or discomfort. Other secondary end points assessed adequate relief of symptoms, IBS-quality of life, and rectal sensitivity. Outcomes were measured through the use of questionnaires.

Results: Three randomized controlled trials were included in this review. The study by Abdul-Baki H. indicated that imipramine was superior to treating IBS when compared to placebo, making this the only therapy evaluated in this review to be effective. Study by Ladabaum U. indicated that citalopram was less effective than placebo. Study by Saito Y. determined that St. John’s Wort was less effective than placebo in decreasing symptoms of IBS.

Conclusions: The results of the study using imipramine concluded that the drug was effective in reducing symptoms and improving quality of life for patients with IBS. The other two studies concluded that the therapy drugs were less effective than the placebo in treating symptoms of IBS. The population studied in some of the studies was not very large and one study had a majority of females which are factors that should be changed in future studies.

Key Words: Irritable bowel syndrome, antidepressants, quality of life
Introduction

Irritable bowel syndrome (IBS) is a condition that causes abdominal pain which affects approximately 10-15% of the adult population.\textsuperscript{1} IBS is defined by the Rome II criteria and is characterized by constipation, diarrhea, or an alternation of the two. It is also defined by the presence of abdominal pain, fullness, bloating, and relief after defecation present for at least three days per month for the past three consecutive months.\textsuperscript{1} In recent years, there has been a dramatic rise of the diagnosis of IBS due to increased awareness of the condition. While it is estimated that 10-15% of the adult population is affected by IBS, only 50% of patients with symptoms search for aid.\textsuperscript{2}

The epidemiology of the condition may depend on where the patient lives or the regional culture in regards to healthcare. For example, in the United States, women are more likely to be effected or report symptoms. However, men are more likely to be effected in India and Sri Lanka.\textsuperscript{2} The pathophysiology of IBS is still unclear, which is why there is so much research being done for treatment options.\textsuperscript{1} This paper evaluates three RCTs studying the effectiveness of antidepressants in decreasing symptoms and improving quality of life for patients with IBS.

The total cost for IBS patients in the United States for health care 21.5 billion dollars a year.\textsuperscript{3} The cost in the first year of healthcare for IBS diagnosis is $4,044 and the sum of all patients lose 205 million dollars from lost work days due to either the condition itself or days spent seeking healthcare.\textsuperscript{3} There was an average of approximately 3.65 million visits a year between 1998-2000 for patients with IBS.\textsuperscript{3} There is not much that is known for certain about the condition. In recent studies, it was found that up to 80% of patients with IBS have an associated psychiatric etiology.\textsuperscript{1} There are many theories regarding what initiates IBS and how the condition produces symptoms, however, the exact physiology of the condition is unknown. Some
hypotheses believe that there may be disturbance of motility, gastrointestinal (GI) changes from infection, or altered perception of pressure in the GI tract.\(^1\)

Researchers have determined that the pathophysiology is based on the individual. In some individuals, it has been found that there is increased activity of the prefrontal lobe with colonic activity. \(^1\) Therefore, indicating that these patients may have increased sensitivity and awareness of abdominal discomfort. In other studies it was found that serotonin plays a large role in symptomatology of IBS. Serotonin is released into the gut and stimulates peristalsis. \(^1\) It has been found that patients with diarrhea symptoms do not reabsorb the serotonin from the gut properly, therefore over stimulating the intestines and producing diarrhea. \(^1\)

Treatment methods depend on the symptoms of patients. Physicians often recommend to patients beginning treatment with an alteration of diet. For example, food items such as coffee, legumes, and artificial sweeteners have been found to aggravate symptoms, particularly in patients with diarrhea symptoms. \(^1\) For patients with constipation symptoms, patients are recommended to increase fiber to 30g a day and consume probiotics. \(^1,4\) Other non-pharmacologic treatments involve stress management or hypnotherapy. \(^1\)

Pharmacologic treatment approaches IBS from different aspects of the pathophysiology behind the condition. For example, anti-diarrheal medications are the first line drugs of choice for patients with diarrhea. \(^1\) Anti-spasmodic use is still somewhat controversial. It has been found that this class of drugs may help to alleviate pain by decreasing the amount of intestinal cramps. \(^1\) This paper evaluates three randomized controlled trials (RCT) for the effectiveness of antidepressant use in decreasing symptoms and improving quality of life for patients with IBS.

**Objective**
The objective of this selective EBM review is to determine whether or not the use of antidepressants decreases symptoms and improves the quality of life in patients with IBS.

**Methods**

The criteria for selection involved a population of men and women between the ages of 18 and 75 who meet the Rome II criteria of IBS. The intervention used was three different antidepressants including imipramine, citalopram, and St. John’s Wort. The experimental group was compared to an identical placebo given to the control group. The outcomes measured were improvement of IBS symptoms, in regards to frequency and severity, and increased quality of life. The types of studies used were RCTs.

Key words used to find literature were irritable bowel syndrome, antidepressant use, and quality of life. All articles were published in the English language. All articles were published in peer review journals after the year 2009 and there were at least three articles published after the meta-analysis which was published in 2008. Research for articles was completed by me using PubMed and OVID after using the Cochrane database. Articles were selected based on relevance to the subject of interest and the outcomes measured in relationship to the patient, or a POEM. All articles chosen were randomized, controlled double blind studies. Articles were excluded in the studies if the patients were under 18 years old or if the results were not measured based on patient outcome. The statistics that were used in the articles were confidence interval(CI), p values, relative risk reduction(RRR), absolute risk reduction(ARR), numbers needed to treat (NNT), numbers needed to harm (NNH). Table 1 demonstrates the demographics included in the studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># of pts</th>
<th>Age</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>w/d</th>
<th>intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saito et al., 2010</td>
<td>RCT</td>
<td>70</td>
<td>18-70</td>
<td>Pts that meet the Rome II criteria for IBS</td>
<td>Concurrent GI diagnosis; symptoms of severe depression; MR; past or current Hx of psychotic d/o; current use of mood/pain or symptom altering meds- planned surgery during trial; allergy to St. John’s wort; any current chronic or acute diseases; ETOH abuse; professional drivers or operators of heavy equipment; major CV events in the last 6 mo; use of IBS drugs in the past 30 day</td>
<td>10</td>
<td>Double blind Randomized 450 mg BID St. John’s Wort vs. placebo.</td>
</tr>
<tr>
<td>Abdul-Bakiet et al., 2009</td>
<td>RCT</td>
<td>107</td>
<td>&gt;18 y/o</td>
<td>Pts that meet the rome II criteria for IBS and have an unsatisfactory response to 1+ prescription antispasmodics available on the Lebanese market</td>
<td>&lt; 18 y/o; allergy to imipramine; Hx of melena/hematochezia/wt loss/cardiac arrhythmias; any use drugs of drugs that could change bowel habits; lactose intolerance; use of antidepressants; clinical depression</td>
<td>51</td>
<td>Double blind randomized, 25 mg tablet of imipramine vs identical placebo</td>
</tr>
<tr>
<td>Ladabau m et al., 2010</td>
<td>RCT</td>
<td>54</td>
<td>18-75 y/o</td>
<td>Pts that meet the rome II criteria for IBS;good health; normal sigmoidoscopy/colonoscopy w/in 5 yrs; normal CBC and TFS</td>
<td>Depression or use of antidepressants; pregnancy; use of IBS medication/antispansmodics/anticholinergics; chronic pain meds using opiates; prior rectal/colon surgery; major organ disease</td>
<td>9</td>
<td>Double blind randomized, 20 mg citalopram vs identical placebo</td>
</tr>
</tbody>
</table>

*Information from Saito YA., Abdul-Baki H., and Ladabau U. was used in the above table.*
Outcomes measured

Outcomes measured were based on patient-oriented problems. In the study using St. John’s Wort (SJW), outcomes were measured using a bowel symptoms score (BSS) and IBS quality of life (IBS-QoL). The BSS was based on pain, bloating, constipation and diarrhea. The IBS-QoL has thirty-four questions assessing quality of life. The imipramine study used the IBS-QoL, as well as, a SF-36 questionnaire. The citalopram study used Beck’s Depression Inventory, daily symptom scoring on a scale from 1-10, IBS-QoL, and a barostat study to assess outcomes.

Results

The results were presented in dichotomous data for all three articles. The study using SJW randomly assigned participants to a group using 450 mg of SJW by mouth twice a day or an identical placebo for twelve weeks. Patients were asked to evaluate their symptoms on a BSS and IBS-QoL prior to the start of the study and again at twelve and twenty-four weeks after the start of the study. The study also assessed depression symptoms using center for epidemiological studies depression scale (CES-D).

In Saito et al., the mean change from the baseline BSS score decreased in both groups. However, it was found that the BSS in SJW was seventy-six compared to forty-four in the placebo group, indicating that the placebo group had a better outcome. At twelve weeks, “51% of the study drug group compared to 54% of the placebo group felt that the drug had helped decrease the symptoms”. The P value was .03 (Table 2), the relative benefit increase (RBI) was - .055, the absolute benefit increase (ABI) was -.03 and the number needed to treat (NNT) was -34. The negative NNT indicates that for every thirty-four patients who were treated with SJW, there would be one fewer patient that would have decreased symptoms or increased QoL than if they had been treated with placebo.
The study using imipramine randomly assigned participants to a group using 25 mg of the drug by mouth once a day before bedtime or identical placebo for twelve weeks.⁶ Patients were asked on week four, eight and twelve if they “had significant improvement in symptoms since the start of the study drug.”⁶ At twelve weeks patients were asked to assess the QoL based on a SF-36 questionnaire. At week 16 a follow-up questionnaire was given to evaluate overall symptoms.⁶ In Abdul-Baki et al., “80.6% of the imipramine group compared to 48.0% of the placebo group” reported relief in IBS symptoms. The p-value, per protocol, was .053(Table 2), the RBI was .68, the ABI was .33, and the NNT was 4. This indicates that for every four patients treated with imipramine one more patient had decreased symptoms or improved QoL than if they had been treated with the placebo.

In the study using citalopram, patients were randomly assigned to a group using 20 mg of the drug by mouth for the first four weeks or a group using identical placebo.⁷ After the first four weeks, patients were instructed to take two tablets for another four weeks, resulting in either 40 mg of citalopram therapy or two tablets of placebo a day.⁷ If patients experienced side effects while on two tablet therapy they were instructed to decrease dose to one tablet a day. Prior to the start of the study, participants filled out the Beck’s Depression Inventory, daily symptom scoring on a scale from 1-10, IBS-QoL, and a barostat study.⁷

Throughout the study, questionnaires were given weekly to evaluate the symptoms on a scale from 1-10 and whether or not adequate relief had been achieved. At week eight of the study, participants completed a second IBS-QoL and barostat study.⁷ Ladabaum U. et al. demonstrated that “44% in the citalopram group compared to 56% in the placebo group showed improvement.”⁷ The P value was .59(Table 2) and there was a 95% CI .61-1.04, indicating that the treatment effect is precise. The RBI was -.214, the ABI was -.12, and the NNT was -9.⁷ The
negative NNT indicates that for every nine patients who were treated with SJW, there would be one fewer patient that would have decreased symptoms or increased QoL than if they had been treated with placebo.

Table 2 Comparison of study results$^{5,6,7}$

<table>
<thead>
<tr>
<th>Study</th>
<th>Response in the study group</th>
<th>Response in the control group</th>
<th>RBI</th>
<th>ABI</th>
<th>NNT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ladabaum (2010)</td>
<td>44%</td>
<td>56%</td>
<td>-0.241</td>
<td>-0.12</td>
<td>-9</td>
<td>0.59</td>
</tr>
<tr>
<td>Saito (2010)</td>
<td>51%</td>
<td>54%</td>
<td>-0.055</td>
<td>-0.03</td>
<td>-34</td>
<td>0.03</td>
</tr>
<tr>
<td>Abdul-Baki (2009)</td>
<td>80.6%</td>
<td>48.0%</td>
<td>0.68</td>
<td>.129</td>
<td>4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Information from Saito YA., Abdul-Baki H., and Ladabaum U. was used in the above table.

In the studies using SJW and citalopram the NNT was a negative value while the study using imipramine demonstrated a positive value for NNT. Of the three studies used, imipramine was the only drug that was found to improve symptoms and IBS-QoL. There were a high percentage of dropouts in the imipramine study. In the imipramine and placebo group, 14/59 and 6/48, respectively, dropped out due to side effects. $^6$ Three of the fourteen participants that dropped out on the imipramine group due to adverse side effects reported sleep disturbance, making this the most common side effect. A higher percentage of patients taking imipramine experienced adverse effects compared to placebo, “25% and 12.5%” respectively. $^6$ This indicates that the relative risk increase is 1.03, the absolute risk increase is .129, and the number needed to harm is 8. $^6$ This indicates that for every eight people that are treated with imipramine, one person experiences an adverse effect.
Table 3 - Reason for dropout in both study groups

<table>
<thead>
<tr>
<th>Reason</th>
<th>Imipramine (n=59)</th>
<th>Placebo (n=48)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dropouts</td>
<td>28 (47.5%)</td>
<td>23 (47.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Premature withdrawal</td>
<td>8 (13.6%)</td>
<td>14 (29.2%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>3 (5.1%)</td>
<td>3 (6.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>3</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Side effects</td>
<td>14 (23.7%)</td>
<td>6 (12.5%)</td>
<td>0.094</td>
</tr>
</tbody>
</table>

This table comes directly from Abdul-Baki H. et al.

Discussion

The RCT (Saito Y. et al.) assessing the efficacy of SJW to reduce IBS symptoms, determined that SJW was less effective than the placebo. The BSS, AR, and IBS-QoL measured all indicated similar results. There are very few well designed studies evaluating the use of herbal and alternative medicine. For example, there are no studies indicating what the appropriate dose of SJW is, therefore, producing an inconsistency in the study. The population of this study may alter the results. The participants included were from a smaller area with both mild IBS symptoms and mood disorders. Patients with severe mood disorders were excluded from the study. Also, this study is limited due the evaluation of all IBS subtypes. In theory, one subset may benefit over another but that issue was not addressed. Another limitation to this study is the inclusion of a majority females compared to male participants.

In the RCT (Abdul-Baki H. et al.) assessing the efficacy of imipramine use for IBS symptoms, it was determined that the drug may provide relief. The SF 36 assessment completed after the study indicated a rise in QoL. Limitations to the study include a lack of evaluation of baseline psychiatric illness prior to the start of the study. Another issue in the study that limits the results is the possibility of “unblinding due to the presence of anticholinergic effects.” The high drop-out rate is also a limitation to the study. Additionally, there is a large chance of a non-adherence to the medication throughout the trial.
In the RCT (Ladabaum U.) assessing the efficacy of citalopram use for IBS symptoms, it was determined that the drug was less effective than the placebo. A stipulation of the study is that the drug only evaluates non-depressed patients, which may affect the results reported. One limitation to the study is the small sample size. Another limitation is the “possibility of unblinding due to side effects.”

Conclusion

Evidence regarding anti-depressant therapy for improving IBS-QoL and decreasing IBS symptoms is conflicting. Of the three RCTs used in this systematic review, only one of them concluded that the drug was effective for improving symptoms of IBS. The study using SJW stated that the therapy was less effective than the placebo. However, the study also stated that there are very few well-designed studies testing the efficacy of herbs and alternative treatments. The study using citalopram also concluded that the drug was less effective than placebo for treatment of IBS symptoms. The study using imipramine was the only therapy found to be effective. Lack of a specific antidepressant or class of antidepressants is a flaw in research for this systematic review. For further research, one would isolate the therapy that has been found to be effective and expand upon that. For example, sample size of the study can be increased to assess a larger population which would provide a better representation of a typical population. Additionally, it reasonable to design future studies using drugs with similar mechanism of action to that of imipramine, such as other tricyclic antidepressants. Further research is necessary to conclude whether or not antidepressant therapy is effective in decreasing symptoms and improving QoL in patients with IBS.
Works Cited