



A Review of the Role of Melatonin in Irritable Bowel Syndrome

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ABSTRACT

Irritable bowel syndrome (IBS) is a troubling disease experienced worldwide. The presentation of symptoms varies from patient to patient, and current prescription treatments can be inadequate in resolving symptoms. This article explores the available scientific literature supporting the use of melatonin in alleviating IBS symptoms.

Keywords: Irritable Bowel Syndrome, Current Treatments, Melatonin, Current Research

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INTRODUCTION

Irritable bowel syndrome can present in up to 15% of the global population, and is one of the most common gastrointestinal disorders worldwide affecting twice as many women as men, and is associated with poor economic status and healthcare costs in the billions of dollars every year^{1,2}. Patients afflicted with IBS will present predominantly with one of two major subsets: IBS-C which is constipation predominant, or IBS-D which is diarrhea predominant. Regardless of the subset diagnosis, IBS is associated with several potential life disrupting symptoms including abdominal pain and/or discomfort, altered bowel movements, bowel distension and flatulence. In addition, external manifestations such as fibromyalgia, chronic pelvic pain and chronic fatigue syndrome are seen in this patient population.¹ A frustrating aspect for IBS patients is the diagnosis process. While the Rome III criteria² is set to diagnose IBS it is not typically used clinically and IBS remains to be a diagnosis of exclusion. Patients are often subjected to multiple invasive and non-invasive gastrointestinal tests searching for occult blood and parasites or bacteria such as *C. difficile*, only to have inconclusive results.¹ The Rome III is the most widely used and the most clinically relevant diagnostic criteria in clinical trials assessing IBS. These criteria² are provided in the following section.

The Rome III Criteria for Diagnosing Irritable Bowel Syndrome²

IBS is a chronic disorder characterized by abdominal pain or discomfort associated with disordered defecation. Symptoms should have developed at least 6 months before the diagnosis can be made.

Diagnostic criteria must include *both* of the following:

1. Abdominal discomfort or pain should be present at least 3 days per month for 3 months and should be associated with 2 or more of the following at least 25% of the time:
 - a) Improvement with defecation
 - b) Onset associated with a change in frequency of stool
 - c) Onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the patient's symptoms

Pathophysiology of IBS

The pathophysiology of IBS is complex and involves many potential unknown mechanisms³. These mechanisms may consist of: food sensitivities (impaired carbohydrate absorption, gluten sensitivity and food allergies), visceral hypersensitivity caused by bloating or distension (which

send messages to the brain via afferent neural pathways indicating a feeling of pain), altered gut flora (leading to irregularity and pain), disordered intestinal motility, and psychological stressors (causing dysregulation in the gut-brain axis). Neurotransmitters in the CNS and gastrointestinal tract, including serotonin and melatonin (a close derivative of serotonin), influence motility, sensation and the psychological aspect of the gut-brain axis.⁴⁻⁶

Traditional Management Strategies

Since the etiology of IBS is not fully understood and it is highly patient variable, treatment goals are usually based on symptom management. Traditional strategies include dietary manipulation, fiber intake, probiotics, antispasmodics, antidiarrheals, antidepressants, and serotonergic agents.¹

Dietary manipulation.

Dietary manipulation is usually the first recommendation. Patients often report certain foods they can and cannot eat, and are encouraged to avoid the foods they might cause upset. Gluten-free and low FODMAP (fermentable, oligosaccharides, disaccharides, monosaccharides and polyols) diets show promise,⁷⁻⁹ but are patient specific and difficult to manage.

Fiber

Though increased dietary fiber intake seems like a logical treatment, insoluble fiber has shown to lead to greater discomfort and soluble fibers such as psyllium, do not alleviate symptoms in every patient.¹⁰ However fiber has a role in alleviating symptoms in IBS-C.

Probiotics

Probiotics have been suggested and studied extensively in IBS, but results have been inconclusive and inconsistent.¹¹⁻⁴⁷ No particular strain can be recommended.

Antispasmodics

Antispasmodics, such as hyoscyamine⁴⁸⁻⁵⁰ and dicyclomine,⁵¹ can provide temporary relief to patients with IBS-D, but not without anticholinergic side effects such as dry mouth, dizziness and blurred vision.

Antidiarrheals

Although loperamide may seem a logical choice in IBS-D, in clinical studies it has not been shown any more effective than placebo in relieving global symptoms of IBS.⁵²⁻⁵³

Antidepressants

Depression and anxiety (psychological factors) have been observed as being quite frequent comorbidities in IBS, therefore antidepressants have been shown to have benefits in this disease. Both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been used in several randomized controlled trials^{48,54-69} and have been shown to provide relief

and reduce pain in IBS, both with a number needed to treat of 4.¹ However, common adverse events such as dry mouth and drowsiness limit the use of TCAs.

Serotonergic agents

There are different types of serotonin (5-HT) receptors in the gut, two of which have targeted therapies in the treatment of IBS symptoms. Visceral pain and intestinal transit are targeted by 5-HT₃ antagonism using alosetron (Lotronex™). While alosetron has shown efficacy, it has also shown instances of severe constipation and ischemic colitis.⁷⁰ This adverse effect has caused the FDA to restrict its use to women suffering with severe diarrhea-predominant IBS. Gastrointestinal transit and secretion are targeted by 5-HT₄ agonists such as tegaserod (Zelnorm™). Unfortunately, while it has been proven to be effective in women with IBS-C,⁷¹ it was withdrawn from the market in 2007 due to possible cardiovascular adverse events⁷². No new agents in this class have efficacy or safety data available.

Prosecretory agents

Linaclotide (Linzess™) and lubiprostone (Amitiza™) have shown efficacy in IBS-C as prosecretory agents.⁷³⁻⁷⁸ Linaclotide results in an increase in chloride and bicarbonate, which draws sodium and water into the intestinal lumen. Lubiprostone is similar but results in chloride and water being drawn into the lumen decreasing transit time. The most commonly reported adverse event with each agent is diarrhea.

MELATONIN

General Information, Traditional and Alternative Uses

Melatonin is a hormone known mostly for its release by the pineal gland located in the center of the brain. Melatonin is released at high concentrations during darker times of the day (eg. night), and is secreted to a much lesser extent when there is light. Its primary function involves maintaining the body's circadian rhythm, or the 24-hour clock that keeps our sleep cycle stable and allows us to fall asleep and wake up at the appropriate time, as well as, adjusts to seasonal changes in light. Melatonin has been successfully used in the treatment of sleep disorders such as insomnia.^{5,79} In addition, melatonin has also been utilized in several other areas such as contraceptive use, fibromyalgia, certain types of cancer, and irritable bowel syndrome.⁸⁰

The Role of Melatonin in Irritable Bowel Syndrome

Research shows that melatonin is also secreted in the gastrointestinal tract and has strong antioxidant properties, anti-inflammatory properties and is involved with intestinal motility regulation.⁸¹⁻⁸⁴ All these methods contribute to the possibility of melatonin to induce symptom relief in patients with IBS. Melatonin has been shown to inhibit smooth muscle motility possibly

by stimulating certain receptors in the GI tract, as well as regulating calcium activated potassium channels in cells and blocking nicotinic receptors.⁵⁻⁶ Melatonin also may be involved in visceral sensation of the gut.⁸ While the exact mechanism is unknown, studies do show symptom relief in patients with IBS who take melatonin.^{5, 6, 79, 86}

SCIENTIFIC DATA

A search was conducted using PubMed (keywords: melatonin and irritable bowel syndrome, no limits) and resulted in five small,^{5,6,79,85,86} double-blind, placebo-controlled trials (four of which were randomized) utilizing melatonin in irritable bowel syndrome. Four of the five studies tested symptom improvement; whereas, one study tested colonic transit time changes induced by the use of melatonin. Of these four studies, all showed a significant improvement in IBS symptoms. The study that focused on colonic transit time noticed an increase in colonic transit time with those who used melatonin. Each of the five studies was limited by small sample size, and 4 of the studies did not differentiate which IBS subtypes (IBS-C or IBS-D) benefited the most from the use of melatonin. These studies have been summarized in the next sections. A randomized, double-blinded, placebo-controlled study was conducted by Song *et al*⁶ in forty IBS patients aged 20-64 years. Of the forty patients, 24 were female (8 male and 12 female in each study group) and patients with IBS-C as opposed to IBS-D was similar in both groups. Patients completed several questionnaires before the first administration of medication (or placebo) and immediately after two weeks of either placebo or study drug treatment. The drug regimen was either melatonin 3 mg or placebo at bedtime for two weeks. All forty patients completed the study, and no adverse events were reported. Results have been summarized in table 1.

Table 1. Irritable Bowel Syndrome Symptom Scores Before and After Two Weeks of Treatment

| Parameter | Baseline score | Decrease in score after 2 weeks of treatment | | | |
|----------------------------------|----------------|--|---------|----------------|---------|
| | | Melatonin 3mg | Placebo | Melatonin 3 mg | Placebo |
| Abdominal pain | 4.05 | 3.85 | 2.35 | 0.70 | <0.001 |
| Abdominal distension | 4.00 | 3.15 | 1.05 | 0.15 | NS |
| Frequency of defecation | 3.25 | 3.15 | 1.85 | 0.85 | NS |
| Stool type | 6.15 | 6.25 | 0.65 | 0.55 | NS |
| Abnormal sensation of defecation | 7.10 | 7.70 | 1.30 | 1.35 | NS |
| Quality of life | 5.80 | 5.45 | 1.25 | 0.95 | NS |
| Total score [#] | 30.35 | 29.55 | 7.30 | 3.95 | NS |

*Significance of the comparison between the melatonin and placebo groups

[#]A score of > 20 suggests the presence of significant bowel dysfunction

This was the first study to address the role of melatonin in IBS. The results showed a decrease in IBS symptoms evaluation score questionnaire (IBSSESQ) scores from baseline to two weeks which was not deemed as significant compared to placebo. However, as seen in Table 1, the decrease of abdominal pain in patients was found significant. Lu et al⁷⁹ conducted a randomized, double-blinded, placebo-controlled, 16-week crossover study that examined improvement in IBS symptoms (using IBSSESQ scores) in 17 women aged 24-66. Patients received either melatonin 3 mg or placebo at bedtime for 8 weeks, followed by a washout period for 4 weeks, melatonin and placebo in reverse order for an additional 8 weeks. Patients were required to suffer from IBS symptoms at the time of the study, and have a score of at least moderate severity. Adverse events were not noted while on the study drug. Results are shown in Table 2.

Table 2: Irritable Bowel Syndrome Symptom Scores at Baseline and After Study Completion

| Parameter | Melatonin 3 mg (n=17) | Placebo (n=17) | p-value |
|---|--------------------------|-------------------|---------|
| Mean baseline IBS symptom scores (s.d.)* | 11.1 (4.2) | 11.8 (3.4) | 1.0 |
| Change in mean IBS symptom scores (s.d.) | 3.9 (2.6) | 1.3 (4.0) | 0.037 |
| Change in mean abdominal pain scores (s.d.) | 1.17 (1.2) | 0.47 (1.6) | 0.045 |
| Change in mean abdominal distension scores (s.d.) | 0.62 (0.6) | 0.12 (0.7) | 0.019 |
| Change in mean abnormal sensation of defecation scores (s.d.) | 1.15 (1.1) | 0.24 (1.3) | 0.04 |
| Change in mean stool consistency scores (s.d.) | 0.45 (0.7) | 0.41 (0.9) | 0.9 |
| Change in mean frequency of defecation scores (s.d.) | -0.7 (1.1) | -0.9 (1.4) | 0.7 |

* s.d. stands for standard deviation

While this study included patients with less severe disease than the patients who were enrolled in the previous study,⁶ there was still significant improvement in areas including overall improvement in symptoms, improvement in abdominal pain scores, improvement in abdominal distension scores, and improvement in abnormal sensation of defecation scores. In a third study, Saha et al⁸⁵ conducted a randomized, double-blinded, placebo-controlled trial in 18 patients aged 18-65 over the course of 8 weeks. Nine patients were given melatonin 3 mg at bedtime, and nine patients were given an identical placebo. Adverse events were reported in each group: one patient from the melatonin group and one patient from the placebo group reported drowsiness. An unspecified IBS score was used to assess severity of symptoms in the 18 patients, and results were reported as median values expressed in Table 3.

Table 3: IBS Scores at Baseline and After Eight Weeks of Treatment

| Parameter | Melatonin (n=9) | | | Placebo (n=9) | | |
|----------------------------------|-----------------|--------------|-------------------------------|--------------------|---------------|---------|
| | Baseline | After | p-Value | Baseline | After | p-Value |
| Pain severity | 50 (40-80) | 35 (10-50) | <0.001* <0.05 [#] | 60 (10-100) | 60 (0-100) | >0.05 |
| Pain frequency | 50 (30-90) | 35 (10-50) | <0.001* <0.01 [#] | 70 (5-100) | 80 (0-100) | >0.05 |
| Bloating | 70 (10-100) | 30 (10-50) | <0.001* | 70 (20-100) | 60 (10-100) | >0.05 |
| Bowel habit dissatisfaction | 60 (10-85) | 30 (0-50) | <0.01* | 50 (10-90) | 45 (0-100) | >0.05 |
| Life interference | 70 (40-100) | 40 (10-50) | <0.001* <0.05 [#] | 60 (10-90) | 50 (0-80) | >0.05 |
| Overall IBS score | 300 (250-365) | 170 (75-200) | <0.001* <0.05 [#] | 240 (160-450) | 200 (100-400) | >0.05 |
| Improvement in overall IBS score | 45% (39 to 71) | | | 16.7 (-16 to 47.3) | | |

*When compared with baseline values

[#]When compared between groups

†Scoring system used not specified

The results of this study showed clinically significant improvement in the patients treated with melatonin as compared with placebo. While the results seem promising, this study had a very small sample size, and the scoring system used was not revealed. Also, it does not appear to be the same scoring system used in the previous two studies. The previous studies used an adapted model of the IBS symptoms evaluation score questionnaire (IBSSESQ) which at most could have had a maximum point value of 70.⁸⁷ This study uses a scoring system which exceeds a score of 400. The range in scores, as compared to the reported median is also something to note, especially with such a small sample size as this could skew the results. Lu et al⁸⁶ conducted a randomized, double-blinded, placebo-controlled 16-week crossover study with a 4-week washout period to evaluate the colonic transit time (CTT) in 17 individuals taking either melatonin 3 mg or placebo once daily as compared with 17 matched healthy controls. CTT measurements included the radio-opaque, blue dye, and Bristol stool form score methods. The aim of the study was to see if melatonin would affect the CTT in individuals with IBS. Results showed that in normal healthy patients, melatonin increased the CTT (mean \pm SD: from 27.4 \pm 10.5 to 37.4 \pm 23.8 hours; p=0.04). However, IBS patients did not show a significant change in CTT after treatment. Regardless, investigators of this study concludes that melatonin may still be beneficial in IBS patients despite their results due to the other studies that have been conducted.^{6, 79, 8.} Finally, Chojnacki et al⁵ conducted a double-blinded, placebo-controlled but not randomized

study. This was the largest of the five studies, with 80 participants: 40 participants with IBS-D, and 40 with IBS-C. All 80 participants were post-menopausal women aged 48-65. Patients were chosen based on the premise that melatonin secretion in the gastrointestinal tract decreases with age, particularly in post-menopausal women. Each group, the 40 women with IBS-D and the 40 women with IBS-C were stratified into two arms: melatonin 3mg in the morning upon awakening and 5mg at bedtime, or placebo in a double-blinded fashion. A ten-point scale was used to assess clinical improvement by distinguishing disease severity: mild stage (1-4 points), moderate stage (5-7 points) and severe stage (8-10 points). Patients were to keep an observation diary in which they noted intensification of visceral pain, abdominal bloating, and constipation or diarrhea. The results have been summarized in Table 4.

Table 4: Differences in Symptom Scores from Baseline to Month 6

| Parameter | IBS-C Patients (n=40) | | IBS-D Patients (n=40) | |
|----------------------------|-----------------------|-----------|-----------------------|-----------|
| | Placebo | Melatonin | Placebo | Melatonin |
| Symptoms score at baseline | 7.05 | 7.40 | 7.60 | 7.75 |
| Symptoms score at month 6 | 5.75 | 3.55 | 6.55 | 6.10 |

Results showed the patients who benefited the most from melatonin were the patients with IBS-C, who had clinically and statistically significant decreases in symptoms compared to placebo. Patients with IBS-D did not show significant improvement. Melatonin was well tolerated in both groups with only two patients with complaints of fatigue in the first week of treatment with melatonin. This was the first study to distinguish between the subtypes of IBS patients and utilize that distinction before melatonin was given.

CONCLUSION

Although several studies^{5-6, 79, 85-86} support the use of melatonin in IBS, their small sample size and lack of differentiation in type of IBS limits its clinical use. Studies specific to IBS-C and IBS-D can help to optimize therapy. Doses of 3 to 8mg have been proven to be effective in patients with IBS-C.^{5,6, 79, 85} Doses of 3mg of melatonin prolonged colonic transit time, which could prove beneficial in patients with IBS-D.⁸⁶ Available literature shows a positive correlation between the use of melatonin and symptom relief in IBS symptoms, thereby identifying it as a promising future treatment.

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