# Mirtazapine in diarrhea-predominant irritable bowel syndrome: an open-label study.

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## Abstract

**Background and objective: Antidepressant drugs including tricyclic antidepressants and selective serotonin reuptake inhibitors are established for use in the management of irritable bowel syndrome, but their efficacy over placebo remains modest. Mirtazapine is a novel antidepressant with multimodal mechanism of action. We aimed to study its efficacy in diarrhea-predominant irritable bowel syndrome (IBS-D).**

**Methods: Sequential IBS-D patients were administered oral mirtazapine for 12 weeks. Dosage commenced at 15 mg daily, increasing to 30 mg if tolerated. Outcomes included change in IBS symptom severity score, Hospital anxiety and depression scale and diary-derived symptom scores (diarrhea, pain, urgency) post-treatment compared with baseline.**

**Results: 16 patients (13 female, mean age 39) were included. Eleven patients received 15 mg while five received 30 mg mirtazapine. 11 patients (69%) were deemed responders, classified as those in whom IBS symptom severity score reduced by >50 points post-treatment. Significant reductions from pre- to post-therapy in mean hospital anxiety (difference -2.0, P=0.04) and depression (difference - 0.7, P=0.04) scales were noted. The mean IBS symptom severity score also reduced severity with therapy, from 313 to 215 (P<0.01). Significant reduction in symptom scores for abdominal pain, urgency, diarrhea and bloating were noted (all $P \leq 0.01$). No serious adverse events occurred, but minor adverse effects were noted in 9 subjects.**

**Conclusions: In this open-label study, mirtazapine demonstrated efficacy in improving both gastrointestinal and psychological symptoms in IBS-D. Its potential utility should be further evaluated in larger controlled trials.**

**Keywords**: Diarrhea, Irritable bowel syndrome, Mirtazapine.

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## Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder in which recurrent abdominal pain is typically associated with disordered bowel habits [1]. There is a worldwide prevalence of approximately 11% [1]. Antidepressant drugs and psychological therapies are often used when first-line measures such as education and reassurance, dietary modification and symptom-directed pharmacotherapy are unsuccessful [2]. Antidepressant drugs, in particular tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), have been shown to be superior to placebo in improvement in global symptom relief IBS as well as for improving pain [2]. However, the incremental benefit over placebo is still relatively small, and a significant portion of patients, approximately 40%, do not derive any benefit from antidepressants [2] highlighting the unmet need for new effective therapies in IBS.

Mirtazapine is an atypical antidepressant drug that has a more complex action compared to TCAs and SSRIs. By blockade of α2-adrenoceptors, it enhances both serotonergic and noradrenergic systems [3]. In depression, it has demonstrated advantages compared to other antidepressants including rapid onset of action, and more favorable safety profile when compared to TCAs [4]. The efficacy of mirtazapine specifically in IBS has not been extensively studied, and the little data that exists is limited to case reports [5,6]. The present study aimed to examine the effect of mirtazapine in subjects with diarrhea-predominant IBS (IBS-D).

## Methods

### *Patients*

We report on an uncontrolled open-label study of mirtazapine amongst 19 sequential patients with IBS-D referred to University College Hospital, a tertiary referral center for functional gastrointestinal disorders. Three patients were excluded due to failing diary data criteria for the diagnosis of IBS-D, leaving 16 valid patients.

Participants had undergone prior testing for exclusion of other disorders as deemed clinically appropriate; such testing included exclusion of any or all of coeliac disease (by either tissue transglutaminase antibody testing or histological examination of endoscopic biopsy obtained from the second part of the duodenum), microscopic colitis by histological examination of endoscopic biopsy obtained from colonoscopy or flexible

sigmoidoscopy, bile acid malabsorption by radio labelled SeHCAT testing or empirical bile-sequestration treatment, and small intestinal bacterial overgrowth by hydrogen breath test. All fulfilled criteria for IBS-D according to Rome III guidance [7]. All study subjects had previously failed to respond to dietary therapy for IBS; diets tried included the low-FODMAP diet (n =13), gluten-free (n=6) and lactose-free (n=5). All subjects had failed to respond (n=11) or failed to tolerate (n=9) adequate doses of loperamide and tricyclic antidepressant to treat their IBS-D symptoms. Fifteen patients had previously used other antidepressants including TCAs (n=11) and SSRIs (n=4), and 2 patients were currently using other antidepressants (TCAs n=1, SSRIs n=1) and these were continued. Five patients were using on-demand antispasmodic drugs at study entry and continued to do so during the study.

### *Intervention*

Subjects were administered regular mirtazapine, commenced at the dosage of 15 mg once daily. If the drug had been well tolerated and there was no response, the dose was increased to 30 mg at clinic review after 28 days (mean 28, range 26-33). Treatment continued for 12 weeks (mean 12.2, range 12-13) when final assessments were made.

### *Outcomes*

Subjects completed questionnaires at baseline and end of treatment including the Hospital Anxiety and Depression Scale for depression (HADS-D) and anxiety (HADS-A), as well as the IBS Severity Scoring System (IBS-SSS), instruments validated in outpatients with IBS [8,9]. Responders were defined by a reduction in IBS-SSS by 50 points, as per the original description of the tool [8,9].

All study subjects kept symptom diaries for a 14-day period at baseline and also at the end of treatment, documenting variables including Bristol Stool Form Scale (BSFS), bowel motion frequency, and the number of days with abdominal pain, bloating, diarrhea and urgency. Confirmation of Rome III criteria was established by the diary data confirming abdominal pain and altered bowel function with a temporal association between the two.

Outcome measures of interest include change in HADS and IBS-SSS scores post treatment, as well as change in the abovementioned diary-based symptoms scores post treatment compared to baseline. This was a retrospective analysis of prospectively collected data according to standard clinical practice in the Unit. Patients were made aware that use of mirtazapine for this indication is off-label.

### *Statistics*

Statistical analysis was undertaken using STATA. Normally distributed data were expressed as mean and standard deviation, and median and interquartile range (IQR) were measured for nonparametric data. For comparison of normally distributed data, paired two-tailed t-tests were used. For non-parametric data, Mann-Whitney U tests were used. Chi squared test was used to compare quantitative data. A P-value of <0.05 was considered significant.

## Results

### *Baseline patient characteristics*

Sixteen patients (13 female) were included in the study. Mean age at study entry was 39 years (range 19-57, SD 12.6). Mean BMI at study entry was 24.1 (range 16.5-28.8, standard deviation 3.4). Eleven patients took 15 mg for all 12 weeks of the study and five increased to 30 mg after a mean 28 days (range 26-29).

Eleven patients (69%) were classified as responders given a reduction in IBS-SSS score of >50 (mean 123, range 52 to 276). Of the 11 responders, ten were taking 15 mg mirtazapine and one 30 mg; of the five non-responders one was taking 15 mg and four 30 mg.

### *Questionnaires*

The mean HADS scores were significantly lower post-treatment compared with baseline (Table 1). Mean HADS-A reduced from 8.6 at baseline to 6.6 at the end of therapy (difference -2.0, P=0.043). Similarly, mean HADS-D reduced from 4.9 at baseline to 4.0 at the end of therapy (difference -0.7, P=0.044). The IBS-SSS was also significantly lower post therapy; it reduced from a mean of 313 at baseline to 215 post-therapy (P<0.01).

### *Diary symptom scores*

All of the diary-derived symptom scores assessed were improved after therapy (Table 1). The mean BSFS amongst all study subjects reduced from 5.3 at baseline to 3.8 (P<0.01). After therapy, there was a significant reduction from baseline in mean number of days of abdominal pain (from 6.3 to 4.3), mean number of days of urgency (5.9 to 3.9), mean number of days with diarrhea (6.1 to 3.7) and mean number of days with bloating (6.7 to 5.4) ($P \leq 0.01$ for all comparisons).

With only five non-responders, it was not possible to undertake analysis of predictive factors associated with beneficial outcome after mirtazapine.

### *Adverse effects*

No subjects experienced any severe adverse events. Nine

***Table 1.*** *BSFS, Bristol stool form scale; HADS-A, Hospital anxiety and depression scale (anxiety subscale); HADS-D, Hospital anxiety and depression scale (depression subscale); IBS-SSS, Irritable bowel syndrome severity scoring system*

| Outcome measure | Baseline | End of Treatment | Change from baseline to end of treatment | |
|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | Estimate (95% CI) | P value |
| **Questionnaires** | | | | |
| HADS-A | 8.6 (3.4) | 6.6 (2.5) | -2.0 | 0.043 |
| HADS-D | 4.9 (3.4) | 4.0 (2.7) | -0.9 | 0.044 |
| IBS-SSS | 312.6 (72.4) | 215.3 (69.9) | -97.2 | <0.01 |
| **Symptom diaries** | | | | |
| BSFS | 5.3 (0.4) | 3.8 (0.9) | -1.4 | <0.01 |
| Bowel frequency (per week) | 15.1 (3.7) | 9.9 (5.1) | -5.2 | 0.01 |
| Days with pain | 6.3 (0.6) | 4.3 (2.0) | -2.0 | 0.01 |
| Days with urgency | 5.9 (0.8) | 3.9 (2.0) | -1.8 | <0.01 |
| Days with diarrhea | 6.1 (0.7) | 3.7 (2.0) | -2.4 | <0.01 |
| Days with bloating | 6.7 (0.9) | 5.4 (1.8) | -1.2 | 0.01 |

subjects experienced minor adverse effects, but none were of a severity to require discontinuation of daily dosing with the drug. Adverse effects included increased appetite (n=5), dizziness (n=4), increased somnolence (n=4) and headache (n=2). No subjects reported constipation. There was an increase in weight of > 1 kg in 4 out of 16 patients, three of whom were non-responders.

## Discussion

In this open-label study, patients in a tertiary care unit with IBS-D who received mirtazapine demonstrated significant improvements in not only objective measures of symptom burden, but also in subjective measures of wellbeing related to IBS as well as psychological symptoms. This is the first series to assess the efficacy of mirtazapine in IBS and helps provide pilot data for a future prospective study. The majority of patients responded to a 15 mg dose.

Importantly, the drug was well-tolerated in this setting, with no severe adverse effects, and no drug discontinuation observed. Its benign side effect profile has been described previously and there have been no significant safety signals to date from its use in psychiatry and other functional disorders [4]. This compares favorably to conventional antidepressants such as TCAs as well as alosetron, the other 5HT3 antagonist that showed promise for IBS but was withdrawn from the market due to significant adverse effects, including ischemic colitis [10,11]. One quarter of patients increased weight by more than 1 kg in the 12 weeks of the study, a finding consistent with other studies of mirtazapine in functional gut disorders [12,13].

The hypothesis that mirtazapine could be efficacious in improving the symptoms of IBS is a plausible one. Dysfunction of the brain-gut axis is well established as a component of the pathogenesis of IBS, and psychosocial factors modulate the clinical expression of IBS [14-17] Based on these observations, antidepressants were first introduced into the management of IBS. As a class they are now an established part of the treatment paradigm for a relatively small group of IBS patients refractory to other treatments [18,19]. High quality evidence supports the use of TCAs and SSRIs in particular [2,20], and their use has been incorporated into the NICE Guidance on IBS. However, the effect size is moderate, and a significant proportion of patients do not derive any benefit from either. Clearly, a need still exists for further therapeutic options.

Some of the beneficial effects of antidepressants in IBS seem to occur via alteration of gastrointestinal motility [21]. Compared to conventional antidepressants, mirtazapine has a novel mechanism of action, antagonizing both 5HT2 and 5HT3 receptors, so only 5HT1A mediated serotonergic transmission is enhanced [3] These 5HT receptors have differing but important modulatory roles in the gastrointestinal tract [22,23] human and mammalian studies have reached differing conclusions as to the subsequent effect of mirtazapine on gastric, intestinal and colonic motility, with one animal study in fact demonstrating accelerated gut transit [24,25]. In clinical experience however, the effect usually seen is of reduction in gastrointestinal motility, similar to that seen with other potent 5HT3 antagonists, such as alosetron [26] and this effect on gastrointestinal motility is consistent with the reduction in diarrhea and improvements in stool form observed in the present study.

Like other conventional antidepressants, mirtazapine modulates aspects of noradrenergic and serotonergic transmission at the synapse, reinforcing descending inhibitory pain pathways, and so could be conceivably be expected to provide a similar benefit in IBS through pain modulation [3,27,28]. Furthermore, mirtazapine has also been shown in an animal model to, in a dose-dependent fashion, ameliorate colonic visceral hypersensitivity [29] which is well recognized to play an important role in the development of pain in IBS [14,30,31]. These effects probably underlie the significant improvements in pain that we demonstrated and are also in keeping with the evidence demonstrating the efficacy of mirtazapine in other functional gut syndromes such as functional dyspepsia, and non-gastrointestinal functional syndromes such as fibromyalgia [12,13,32].

The original licensed indication for mirtazapine was for treatment of depression, and therefore it is not surprising that along with exerting gastrointestinal physiological effects, mirtazapine produces beneficial effects on mood and wellbeing in IBS, in a similar fashion to other antidepressants [33]. Small but significant improvements in anxiety and depression scores were demonstrated in the present study. Because of the small numbers, it was not possible to differentiate between a general antidepressant effect and an improvement in mood secondary to reduced symptom burden, but this could be assessed in a larger study. Certainly, in a recent study of mirtazapine in functional dyspepsia, its beneficial mood effects did not correlate with improvement in physical symptom scores [12].

A strength of this study is its use of a number of both subjective and objective outcome measures to assess for any benefit of the intervention. It is the first published trial to assess the efficacy of mirtazapine in IBS. The main limitations of the study prohibiting generalizability of the results are the lack of a placebo control group, and the small sample size. In addition, given that patients were only treated and followed for three months, no comment can be made about the long-term use of mirtazapine as a maintenance treatment in IBS. However, being a pilot open-label study, the trial was not designed to make definitive conclusions about the efficacy of mirtazapine, and it would be premature to use the results of the study to recommend the routine use of mirtazapine in patients with IBS-D. Instead, in the first instance, it is important to replicate these results in a larger, placebo-controlled randomized controlled trial.

## Conclusion

In conclusion, this open-label study of mirtazapine in patients with IBS-D demonstrated benefit for its use through improvement in both gastrointestinal and psychological symptoms. Future studies should focus on re-evaluating the efficacy of mirtazapine in this setting through a larger controlled trial.

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