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# Low Dose Naltrexone: Side Effects and Efficacy in Gastrointestinal Disorders

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## INTRODUCTION

Naltrexone is U.S. Food and Drug Administration (FDA)-approved for relapse prevention of alcohol dependence, and it plays a role in relapse prevention of narcotic abuse.<sup>1-2</sup> The dose of oral naltrexone for these purposes is 50 mg daily.

Use of low dose naltrexone (LDN) (1.75 to 4.5 mg daily) has been advocated on the Internet for a variety of medical problems.<sup>3</sup> Only a few articles on LDN or ultra-LDN have been published in peer reviewed journals.<sup>4-6</sup> A recent review elucidated the potential mode of action including immune-modulation and anti-inflammatory processes.<sup>7</sup> Manipulation of opioid receptors has potential application in gastrointestinal disorders. Opioid neurons exhibit tonic restraint on intestinal motility; opioid antagonists stimulate peristalsis and increase transit. Anti-inflammatory effects are also desirable for both inflammatory bowel disease and irritable bowel syndrome (IBS).

Naltrexone is a water soluble compound which crosses the blood brain barrier, and this increases the potential for neurologic side effects. Reported adverse effects of standard dose naltrexone include anxiety, nervousness, confusion, drowsiness, hallucinations, skin crawling, blurred vision, muscle or joint pain, vomiting, diarrhea, stomach pain, liver disease, and skin rash. There were no significant adverse reactions using ultra-LDN (0.5 mg) in one study.<sup>4</sup> Recent FDA approval of subcutaneously injected methylated formula-

## ABSTRACT

Use of low dose naltrexone has been advocated for a variety of medical problems. Only a few articles published in peer reviewed journals have documented side effects of low dose naltrexone. The purpose of this study was to determine the frequency of adverse effects of low dose naltrexone in patients who have been treated for a variety of gastrointestinal disorders. The secondary purpose was to determine global efficacy in a retrospective survey. Patients (206) from a single gastroenterologist's clinical practice who had been prescribed naltrexone were mailed a survey to evaluate the side effects and efficacy of naltrexone. Patients had either irritable bowel syndrome without evidence for small intestinal bacterial overgrowth, irritable bowel syndrome with evidence of small intestinal bacterial overgrowth, chronic idiopathic constipation, or inflammatory bowel disease. Patients with diarrhea were given 2.5 mg daily, constipation 2.5 mg twice daily, and inflammatory bowel disease 4.5 mg daily. In the patients who returned the survey, 47/121 (38.8%) had no side effects. Of the 74/121 (61.2%) patients who had side effects, 58 had one or more neurological complaints, and 32 had one or more gastrointestinal side effects. In the patients with side effects, 24/74 (32.4%) had short lived symptoms. Low dose naltrexone was terminated owing to side effects in 20/74 patients (27.0%). In 13 patients with idiopathic irritable bowel syndrome, 2 were markedly improved, 5 were moderately improved, 2 were unchanged, and 3 were markedly worse. In 85 patients with irritable bowel syndrome-small intestinal bacterial overgrowth, 15 were markedly improved, 32 were moderately improved, 11 were mildly improved, 23 were unchanged, 3 were moderately worse, and 1 was markedly worse. In 12 patients with chronic constipation, 7 were markedly improved, 1 was moderately improved, 3 were mildly improved, and 1 was unchanged. Two of 8 patients with inflammatory bowel disease were markedly improved, 1 was moderately improved, 1 was mildly improved, and 4 were unchanged. Low dose naltrexone frequently has side effects but in most is tolerable. It appears to be helpful for a number of patients with gastrointestinal disorders.

tion, methylnaltrexone (Relistor), allows for safe use of this compound in patients who are on narcotics. Methylnaltrexone is effective for opioid-induced constipation by reversing peripheral opioid receptors.<sup>8</sup>

At this point in time, methylnaltrexone is not available in oral formulation and thus the role of oral LDN needs to be further defined. The purpose of this study was to determine the frequency of adverse effects of LDN in patients who have been treated for a variety of gastrointestinal (GI) disorders. The secondary

purpose was to determine global efficacy in a retrospective survey.

## MATERIAL AND METHODS

LDN was compounded in 2.5-mg and 4.5-mg capsules. The source of naltrexone was Spectrum Chemical Manufacturing Corporation. Compounding began by first calculating the ingredient filling constants. Ingredients other than naltrexone included microcrystal-

line cellulose as a filler and some food color powder to assure proper blending of powders. Formulas for batches of 100 and 300 capsules were calculated using the filling constants; and powders were mixed using an electronic mortar and pestle. The final powder mixture was then placed into empty size #3 gelatin capsules which were locked into capsule machines. Once the capsules were appropriately packed, the capsule tops were locked onto the capsule bottoms.

Patients from a single gastroenterologist's clinical practice who had been prescribed naltrexone in a two-year period were mailed a letter asking if they would participate in a survey to evaluate the side effects and efficacy of naltrexone. If they did not return the survey they were called once to remind them to fill out the survey. The majority of the patients had received prescriptions in the previous six months.

Patients (206) with the following GI conditions were given prescriptions for LDN: IBS without evidence for small intestinal bacterial overgrowth (SIBO) (i.e., patients with a normal lactulose breath test), IBS with evidence of SIBO (using naltrexone as a second phase of treatment in efforts to improve motility and reduce inflammation), chronic idiopathic constipation, and patients with inflammatory bowel disease. Patients with diarrhea were given 2.5 mg daily, constipation 2.5 mg twice daily, and inflammatory bowel disease 4.5 mg daily.

In the survey they were asked about the duration and dose of naltrexone administered. They were asked if they had any of the following side effects: trouble sleeping, nightmares or vivid dreams, jitteriness, nervousness, dizziness, headache, drowsiness, anxiety, vomiting, decrease in appetite, diarrhea, stomach pain, muscle pain, nausea, or other symptoms. They were asked if the side effects improved with continued use of the naltrexone and if they had to stop using naltrexone because of a side effect. If they were no longer taking naltrexone, they were asked what made them stop taking it: condition improved, unacceptable side effects, or the medicine did not work. They were asked if their overall GI symptoms were markedly improved, moderately improved, slightly improved, unchanged, slightly worse, moderately worse, or markedly worse. If they had SIBO, they were asked if they needed to take another antibiotic since being placed on naltrexone.

## RESULTS

Surveys were returned by 121/206 (58.7%) of the patients. The mean age ( $\pm 1$  standard deviation) was  $53.0 \pm 16.8$ . Of these 92 women and 29 men, 85 had IBS with SIBO, 14 had idiopathic IBS, 12 had slow transit chronic constipation, 8 had inflammatory bowel disease (Crohn's disease in 4 and ulcerative colitis in 4), and 2 had small bowel pseudoobstruction. The daily dose of naltrexone was 2.5 mg in 67, 5.0 mg in 46, and 4.5 mg in 8 patients.

In the patients who returned the survey, 47/121 (38.8%) had no side effects. Of the 74/121 (61.2%) patients who had side effects, 58 had one or more neurological complaints, and 32 had one or more GI side effects. The profile of the side effects is shown in the accompanying Table. In the patients with side effects, 24/74 (32.4%) had short-lived symptoms. In twenty of the 74 patients (27.0%), naltrexone was terminated owing to side effects. The rest of the patients were able to tolerate the side effects. The frequency of side effects for the group treated with 2.5 mg compared with the group treated with 5.0 mg daily differed in three symptoms, respectively:

1. Anxiety (11.9 vs. 21.7%)
2. Muscle pain (4.5 vs. 15.2%)
3. Diarrhea (6.0 vs. 13.0%)

The efficacy of naltrexone was determined a global assessment of overall clinical improvement:

- Markedly improved
- Moderately improved
- Mildly improved
- Unchanged
- Mildly worse
- Moderately worse
- Markedly worse

Naltrexone was used to supplement stable existing therapy in IBD patients or act as sole treatment in the cases of IBS-SIBO and idiopathic IBS. Patients with chronic constipation were treated with LDN alone or as an adjunct to other partially effective medications.

Of the 13 patients with idiopathic IBS (3 with diarrhea, 5 with constipation, and 5 with alternating bowel habits), the results were:

- 2 (15.3%) were markedly improved
- 5 (38.5%) were moderately improved
- 2 (15.3%) were unchanged
- 3 (23.1%) were markedly worse

Of the 3 that were worse, the results were:

- 1 had IBS-constipation
- 2 had IBS-alternating bowel habits

The 85 patients with IBS-SIBO were treated for a mean of 14.2 weeks (58 with 2.5 mg and 27 with 2.5 mg twice daily LDN), with the following results:

- 15 (17.6%) were markedly improved
- 32 (37.6%) were moderately improved
- 11 (12.9%) were mildly improved
- 23 (27.0%) were unchanged
- 3 (3.5%) were moderately worse
- 1 (1.2%) were markedly worse

A second course of antibiotics were administered in 38% of these patients during the 14 weeks to retreat recurrent symptoms of SIBO.

LDN (2.5 mg twice daily) was administered for a mean of 10.8 weeks in 12 patients with chronic constipation. Of these patients, the results were:

- 7 (58.3%) were markedly improved
- 1 (8.3%) was moderately improved
- 3 (25.0%) were mildly improved
- 1 (8.3%) was unchanged

Eight patients with inflammatory bowel disease (4 Crohn's and 4 ulcerative colitis) were treated with 4.5 mg naltrexone daily for a mean of 16.8 weeks, with the following results:

- Two were markedly improved
- 1 was moderately improved
- 1 was mildly improved
- 4 were unchanged

Two of those who stated they were unchanged were in clinical remission prior to starting naltrexone.

## DISCUSSION

The current study shows that side effects of LDN occurred frequently (61%) and led to cessation of the treatment in a quarter of those with adverse effects. The retrospective nature of the study and incomplete return of the surveys would likely bias the frequency to a higher number of adverse effects. There are few studies that have evaluated side effects of LDN. In 40 multiple sclerosis patients treated with 3.0 mg naltrexone, 3 reported having trouble concentrating and 1 reported having fatigue.<sup>6</sup> In 42 IBS patients

**TABLE. Side Effects of Low Dose Naltrexone in 121 Patients.**

| Neurological Side Effects            | Number of Participants with Side Effects | Percentage of Participants with Side Effects |
|--------------------------------------|--|--|
| Anxiety                              | 19                                       | 15.7   |
| Drowsiness                           | 14                                       | 11.6   |
| Headache                             | 14                                       | 11.6   |
| Dizziness                            | 13                                       | 10.7   |
| Insomnia                             | 10                                       | 8.3  |
| Muscle pain                          | 10                                       | 8.3  |
| Vivid dreams                         | 6  | 5.0  |
| Mood change                          | 4  | 3.3  |
| Trouble concentrating                | 2  | 1.7  |
| <b>Gastrointestinal Side Effects</b> |  |  |
| Nausea                               | 15                                       | 12.4   |
| Abdominal pain                       | 14                                       | 11.6   |
| Diarrhea                             | 10                                       | 8.3  |
| Anorexia                             | 10                                       | 8.3  |
| <b>Other Side Effects</b>            |  |  |
| Rash                                 | 1  | 0.1  |
| Hot flashes                          | 1  | 0.1  |
| Weight gain                          | 1  | 0.1  |

treated with ultra-LDN (0.5 mg), no side effects were reported.<sup>4</sup>

There is theoretic value to use of LDN in GI disorders, but few articles have been published. One study of 50 mg naltrexone to affect GI motility failed to show efficacy in treatment of constipation in IBS.<sup>9</sup> In an open-label study, 89% of 17 Crohn's disease exhibited a response to LDN (4.5 mg daily), and 67% achieved a remission ( $P < 0.001$ ).<sup>6</sup> In another open-label study, 42 IBS patients participated and received ultra-LDN (0.5 mg daily).<sup>5</sup> During treatment, the mean weekly number of pain-free days increased from  $0.5 \pm 1$  to  $1.25 \pm 2.14$  ( $P = 0.011$ ).

In the present study, the global responses to LDN appeared to show promise in IBS, IBS-SIBO, chronic constipation, and inflammatory bowel disease. The nature of this study did not allow for quantitative analysis. Retrospective nature and incomplete data collection further reduced the conclusions that can be reached. Further study appears to be warranted to determine the efficacy of LDN in GI diseases.

## ACKNOWLEDGMENT

*This study was approved by a human studies committee (Sterling Institutional Review Board, Georgia, Alabama).*

## CONCLUSION

LDN is not without potential for side effects. Future use of methyl naltrexone may be better tolerated since it does not cross the blood brain barrier.

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