

Naltrexone as Therapy for Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's Disease

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A relatively unknown approach to inflammatory bowel disease is the use of low dose naltrexone. Reports of naltrexone for Crohn's disease first started in 2007 from Pennsylvania State University. As with any Crohn's disease therapy it is rare to get more than 70% efficacy from any medicine since there are many pathways for inflammation. The same is true for ulcerative colitis treatment.

An article (below) that was published in 2014 in the Journal of Clinical Gastroenterology provides detailed information how naltrexone works in inflammatory bowel disease and what was found in my practice in both ulcerative colitis and Crohn's disease. The experience of the Penn State group is summarized as well.

Cautionary warnings

1. Because LDN blocks opioid receptors throughout the body for three or four hours, people using medicine that is an opioid agonist, i.e. narcotic medication — such as Ultram (tramadol), morphine, Percocet, Duragesic patch or codeine-containing medication — should not take LDN until such medicine is completely out of one's system. Patients who have become dependent on daily use of narcotic-containing pain medication may require 10 days to 2 weeks of slowly weaning off of such drugs entirely (while first substituting full doses of non-narcotic pain medications) before being able to begin LDN safely.
2. LDN should not be taken during pregnancy until research into that question is completed.
3. Those patients who are taking thyroid hormone replacement for a diagnosis of Hashimoto's thyroiditis with *hypothyroidism* ought to begin LDN at the lowest range (1.5mg for an adult). Be aware that LDN may lead to a prompt decrease in the autoimmune disorder, which then may require a rapid reduction in the dose of thyroid hormone replacement in order to avoid symptoms of *hyperthyroidism*.
4. Full-dose naltrexone (50mg) carries a cautionary warning against its use in those with liver disease. This warning was placed because of adverse liver effects that were found in experiments involving 300mg daily. The 50mg dose does not apparently produce impairment of liver function nor, of course, do the much smaller 3mg and 4.5mg doses.
5. People who have received organ transplants and who therefore are taking immunosuppressive medication on a permanent basis are cautioned against the use of LDN because it may act to counter the effect of those medications.

FDA approval status

Naltrexone itself is an FDA-approved drug, but the varied uses of LDN still await application to the FDA.

The FDA approved naltrexone at the 50mg dosage in 1984. LDN (in the 3mg or 4.5mg dosage) has not yet been submitted for approval because the prospective clinical trials that are required for FDA approval need to be funded at the cost of many millions of dollars. Physicians understand that appropriate off-label use of an already FDA-approved medication such as naltrexone is ethical and legal. Because naltrexone itself has already passed animal toxicity studies, one could expect that once testing is able to begin, LDN could complete additional clinical trials in humans and receive FDA approval for one or more uses within two to four years.

More information about naltrexone: www.LDNscience.org

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BACKGROUND & AIMS: Low dose naltrexone reduces Crohn's disease activity and mucosal inflammation. Naltrexone treatment of ulcerative colitis has not been reported.

METHODS: This open-label retrospective study reports on adults with moderate to severe ulcerative colitis failing 5-aminosalicylates with mercaptopurine and/or infliximab. Naltrexone was added as adjunctive therapy. Adverse events were queried. Preliminary evidence for clinical efficacy was determined by self-assessed questionnaires. Positive responses included "markedly or moderately improved". Failed responses were "mild or temporary help", "not helped" or "withdrew due to side effects".

RESULTS: Twelve patients received naltrexone 4.5 mg/day. Duration (mean \pm SD) of naltrexone treatment was 46 \pm 75 weeks (maximum 270 weeks). One patient withdrew after 8 weeks owing to insomnia. Positive clinical responses were reported in 6/12 patients. Two clinical responders had colonoscopy before and after naltrexone and each had complete mucosal healing.

CONCLUSIONS: Adjunctive low dose naltrexone is safe and may be effective in ulcerative colitis patients who are failing conventional therapy. A double blind study is required owing to a high placebo rate in ulcerative colitis.

Ulcerative colitis and Crohn's disease are the most common types of inflammatory bowel disease and share similar pathophysiology and medical therapy (1). Many inflammatory bowel disease patients have partial response or difficulty maintaining remission to one or more medications and addition of alternative treatment is often required (2,3). Addition of immunosuppressive medication to biologics ("combination therapy") is one example where additional therapy reduces flares and corticosteroid dependence (4-6). Options for combination therapy failure includes: excluding alternative diseases and disorders, escalating medication doses, checking therapeutic levels and antibody levels, changing to a different immunomodulator, manipulating thiopurine levels with allopurinol, switching to a different biologic agent or adding

adjunctive therapy. Commonly used adjunctive therapies include: different formulations of 5-aminosalicylates, corticosteroids, antibiotics, probiotics, opioids, bile salt binders, restricted diets, elemental diets and total parenteral nutrition. Combination of immunomodulators, biologics and/or corticosteroids is associated with an increased relative risk of opportunistic infections and neoplasms (5) and thus a safer combination therapy is desirable.

Neuropeptides may play a role in inflammatory bowel disease and these molecules (e.g., enkephalins and endorphins) are present in the gastrointestinal tract and these modulate immune responses (7,8). Up-regulation of met-enkephelin (opioid growth factor - OGF) and opioid receptors can be induced by a rebound effect from administration of the short-acting, low dose naltrexone (9). Naltrexone displaces endogenous endorphins bound to the OGF receptor. Affected cells become deficient in OGF which results in a rebound in receptor production. Receptor sensitivity is increased to capture more OGF and production of OGF is also increased to compensate for the perceived shortage of this molecule (9). Higher levels of endogenous opioids and receptors inhibit cell proliferation which suppress B and T lymphocyte responses (10,11). Naltrexone acts to reverse a mouse colitis model by decreasing the pro-inflammatory interleukins 6 and 12 (12). Another theoretical mechanism of action for naltrexone in inflammatory bowel disease is through the pro-inflammatory relationship of Toll-like receptors which can be abnormal in Crohn's disease (13). When altered this receptor allows for increase in bacterial translocation and the negative effects are enhanced from long-term administration of exogenous opioids (which suppress the endogenous opioid system) (14). An up-regulated endogenous opioid system might have positive effects on the Toll-like receptors. The general effects of exogenous and endogenous opioids are different where the latter are suspected to worsen inflammatory bowel disease.

Both open label and double blind clinical studies have shown that low dose naltrexone (4.5 mg daily) reduces Crohn's disease clinical activity and leads to mucosal healing up to 24 weeks (15-18). To date there have been no published reports of naltrexone therapy in ulcerative colitis. A case is presented and data from 11 other patients are summarized.

Cases

Patient 1

A 45-year-old man with a 25-year history of ulcerative colitis was in clinical and endoscopic remission for over six years on 5-aminosalicylate until September 2011. At that time he was admitted to the hospital for bloody diarrhea and joint pain that progressively worsened over a month. Colonoscopy showed severe colitis (Figure 1), biopsies showed active colitis and fecal studies were negative. He responded well to addition of intravenous methylprednisolone and increasing the 5-aminosalicylate dose. Slight tapering of 40 mg prednisone as an outpatient led to recurrent bleeding and joint pain. In the distant past, mercaptopurine was terminated owing to elevated liver chemistries. Infliximab 5 mg/kg was started in October 2011 (0, 2, 6 weeks and then every 8 weeks) and 5-aminosalicylate was continued. He went into a clinical remission that lasted for 9 months. In July 2012 he developed progressively worsening low grade fevers, joint aches and diarrhea with blood. In December 2012, naltrexone 4.5 mg/day was added to his regimen. He had a prompt response in all symptoms within a month.

Colonoscopy was repeated in March 2013 and there was complete mucosal and histologic healing (Figure 2). As of his last clinical follow up in September 2013 he has had no symptoms on 5 mg/kg infliximab every 8 weeks, 5-aminosalicylate 2.4 gm per day and naltrexone 4.5 mg per day.

Patients 2-12

The clinical data for the 11 other patients treated are summarized on Table 1. In total the 12 patients received naltrexone 4.5 mg as adjunctive therapy when biologic therapy (N=7), mercaptopurine (N=6), combined therapy (N=3) and prednisone (N=2) failed to control ulcerative colitis symptoms. One patient dropped out owing to insomnia as an AE after 8 weeks and is counted as a treatment failure. Six of 12 patients reported moderate to marked improvement. Clinical responders continued naltrexone for 69 ±88 weeks. Patient #2 was prescribed naltrexone 5 ½ years ago when infliximab, mercaptopurine and 5-aminosalicylates were failing. She had a dramatic response to addition of naltrexone and since that time she has maintained remission on all four medications.

Discussion

In the present study adjunctive use of low dose naltrexone was safe and appeared to have a positive clinical response in ulcerative colitis patients who were failing conventional therapy. Naltrexone is an emerging therapy with promising efficacy and safety in Crohn's disease (15-18). The mechanism of action may be modulation of T and B cell responses through up-regulation of the endogenous opioids and receptors (9). In the present study the duration of naltrexone use was up to 5 times longer in the responders compared to the subjects in the prior Crohn's disease publications. The outcome of these ulcerative colitis patients was similar to the author's experience seen in his moderate to severe Crohn's disease patients who failed conventional therapy. A chart review of 33 CD patients with moderate to severe disease who had been treated with naltrexone 4.5 mg/day as adjunctive therapy over a mean of 40 weeks was performed (2008-2013). Regarding safety, 5/33 patients stopped therapy owing to AEs and all of these mild to moderate AEs rapidly improved. Preliminary evidence of efficacy determined by self-assessed questionnaires (as defined for the ulcerative colitis patients above) showed that 15/33 (46%) had a positive clinical response and 18/33 (54%) failed therapy. Of the 15 clinical responders, 11 had colonoscopy or ileoscopy before and after addition of naltrexone: 8/11 had complete mucosal healing, 1/11 had partial mucosal improvement and 2/11 was unchanged. In the adult Crohn's disease randomized, placebo-controlled study, naltrexone was also used as adjunctive therapy (although biologic therapy was an exclusion for enrollment). The results of this study showed that 88% of the naltrexone group (N=18) had at least a 70-point decrease in Crohn's disease activity index scores compared to 40% of the placebo group (N=16). After 12 weeks, 78% of the naltrexone group had a significant response in the Crohn's disease endoscopy index severity score compared to a 28% response in the placebo controls; 33% of the naltrexone group had endoscopic remission compared to 8% of the placebo group (17).

Adverse events from naltrexone are thought to result from a withdrawal reaction from endogenous brain opioids since this antagonist is water soluble and crosses the blood-brain-barrier. In the authors experience with 45 inflammatory bowel disease patients and over 250 other gastrointestinal patients, LDN-induced AEs have rapid improvement

with cessation of therapy and the AEs are mild to moderate in severity (19). In the open-label adult Crohn's disease naltrexone study, 7 of 17 patients had sleep disturbances (15). In the double blind adult study, sleep disturbances were common in both naltrexone and placebo but the only statistically significant different AE was fatigue which was more common in placebo subjects (17).

Adjunctive therapy with low dose naltrexone appeared to be a safe and possibly effective therapy in ulcerative colitis. Double blind studies of naltrexone for ulcerative colitis therapy are required to make any firm conclusions since there is a high placebo response (23-32%) (20). Limitations of the present study include use of open-label therapy, retrospective surveys, lack of validated measures of clinical activity, small cohort and a limited number of the clinical responders (2 of 6) who had endoscopic activity assessed before and after addition of the naltrexone.

Table 1. Clinical characteristics and outcome of the 12 ulcerative colitis patients treated with low dose naltrexone as adjunctive therapy when conventional therapy was failing.

| Patient no. (Gender/Age) | IFX | 6MP | Pred | 5ASA | LDN use (wks) | Marked improved | Moderately improved | LDN failure | AE |
|-----------------------------|--------------|--------------|----------|----------|---------------------|--------------------|------------------------|----------------|----------|
| 1 (M/45) | 1 | ^b | | 1 | 32 | 1 | | | |
| 2 (F/38) | 1 | 1 | | 1 | 270 | 1 | | | |
| 3 (F/50) | 1 | ^b | | | 6 | | | 1 | |
| 4 (M/25) | 1 | 1 | | 1 | 8 | | | 1 | |
| 5 (M/60) | | 1 | | 1 | 8 | | | 1 | 1 |
| 6 (M/53) | | 1 | | 1 | 8 | | 1 | | |
| 7 (F/21) | 1 | ^b | | | 105 | 1 | | | |
| 8 (M/56) | 1 | 1 | 1 | 1 | 24 | | | 1 | |
| 9 (F/70) | ^a | 1 | | | 54 | | 1 | | |
| 10 (F/42) | | ^b | | 1 | 28 | | | 1 | |
| 11 (M/31) | 1 | ^b | | 1 | 8 | | | 1 | |
| 12 (F/35) | | ^b | 1 | 1 | 6 | | 1 | | |
| X=43 ±16yrs | 7 | 6 | 2 | 9 | X=48±76wks | 3 | 3 | 6 | 1 |

^a Allergic reaction to infliximab. ^b Failed or had AE from mercaptopurine. AE, adverse event; IFX, infliximab; LDN, low dose naltrexone 4.5 mg daily; no., number; Pred, prednisone; SD, standard

deviation; X, mean; 5-ASA, 5-aminosalicylates; 6MP, mercaptopurine. LDN failure included those not helped, temporarily or slightly helped or those who withdrew owing to an AE.

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