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Low-Dose Naltrexone Therapy Improves Active Crohn's Disease

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OBJECTIVES: Endogenous opioids and opioid antagonists have been shown to play a role in healing and repair of tissues. In an open-labeled pilot prospective trial, the safety and efficacy of low-dose naltrexone (LDN), an opioid antagonist, were tested in patients with active Crohn's disease.

METHODS: Eligible subjects with histologically and endoscopically confirmed active Crohn's disease activity index (CDAI) score of 220–450 were enrolled in a study using 4.5 mg naltrexone/day. Infliximab was not allowed for a minimum of 8 wk prior to study initiation. Other therapy for Crohn's disease that was at a stable dose for 4 wk prior to enrollment was continued at the same doses. Patients completed the inflammatory bowel disease questionnaire (IBDQ) and the short-form (SF-36) quality of life surveys and CDAI scores were assessed pretreatment, every 4 wk on therapy and 4 wk after completion of the study drug. Drug was administered by mouth each evening for a 12-wk period.

RESULTS: Seventeen patients with a mean CDAI score of 356 ± 27 were enrolled. CDAI scores decreased significantly ($P = 0.01$) with LDN, and remained lower than baseline 4 wk after completing therapy. Eighty-nine percent of patients exhibited a response to therapy and 67% achieved a remission ($P < 0.001$). Improvement was recorded in both quality of life surveys with LDN compared with baseline. No laboratory abnormalities were noted. The most common side effect was sleep disturbances, occurring in seven patients.

CONCLUSIONS: LDN therapy appears effective and safe in subjects with active Crohn's disease. Further studies are needed to explore the use of this compound.

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INTRODUCTION

Chronic relapsing and remitting inflammation of the gastrointestinal tract is the hallmark of ulcerative colitis and Crohn's disease, conditions termed inflammatory bowel diseases (IBD) (1). The peak age of onset of this disease is between the first and fourth decades of life, with a prevalence of 100–200 per 100,000 in Europe and North America. IBD accounts for significant morbidity and lower quality of life, and is responsible for nearly $2.0 billion in annual medical costs in the United States (2). Crohn's disease is characterized by transmural, patchy, granulomatous inflammation of any part of the gastrointestinal tract, although it is most common in the ileocecal area (3). The major symptoms of Crohn's disease include abdominal pain, diarrhea, gastrointestinal bleeding, malabsorption, and weight loss. Although the etiology of Crohn's disease is unknown, research suggests it involves a complex interplay of environmental, genetic, microbial, immune, and nonimmune factors. Biopsies obtained from the bowel in subjects with Crohn's disease reveal inflammatory cells suggesting that the bowel is either reacting immunologically to a stimulus or the endogenous immune system of the gastrointestinal track is off balance (4).

Although there has been progress in defining the pathogenesis of these diseases, their cause remains obscure. The current most comprehensive hypothesis is that IBD is a heterogeneous group of diseases that have a final manifestation, which is mucosal inflammation, and that several genetic and environmental factors are implicated in the pathogenesis of the disease (5–8). The result of these events in some way leads to a disordered immune response to one or more mucosal antigens or bacteria in a genetically determined host (9, 10).

Traditionally, treatment of Crohn's disease includes compounds designed to reduce the inflammatory response, such as corticosteroids, cyclosporine, and azathioprine, which often lead to serious side effects (11, 12). Major advances in the understanding of the pathogenesis of IBD have led to the development of novel immunotherapies. Such treatments include the administration of chimeric antibodies specific for

molecules such as cytokines known to be central to the pathogenesis of mucosal inflammation (antitumor necrosis factor [TNF], interleukin [IL]-2, IL-10) (13, 14). Although this specific immunotherapy has helped those with Crohn's disease, still about 20% do not respond to this treatment (14) and many cannot continue this therapy due to untoward side effects (15, 16). Additionally, treatment with the monoclonal antibody infliximab is expensive with each infusion costing thousands of dollars.

Endogenous opioid systems (*i.e.*, opioids and opioid receptors) have been shown to participate in a wide variety of functions including growth and immunity (17). [Met^5]-enkephalin is an endogenous pentapeptide that is located throughout the gastrointestinal tract (18). In addition to the growth characteristics of [Met^5]-enkephalin, this endogenous opioid has also been shown to influence the immune system with effects on OK10 cells, Leu^{11}, and natural killer cells (19). Acetorphan is an oral enkephalinase inhibitor that elevates endogenous enkephalin blood levels and has been used in Europe and elsewhere to treat diarrheal disorders such as cholera (20) and AIDS diarrhea (21). In a clinical study (22), 193 subjects with diarrhea received either acetorphan or placebo for 10 days, and the incidence of diarrhea was reduced by 30%. Additionally, the symptoms of abdominal pain, anorexia, and nausea were also significantly reduced compared with placebo (22).

Zagon and McLaughlin (23) have reported in an animal model that a low dose of naltrexone can produce an intermittent blockade of the opioid receptor. This short-term blockade resulted in a rise in the endogenous tissue levels of [Met^5]-enkephalin and endorphins and results in the same effects on growth as exogenous enkephalin (23). It is presumed that too high a dose of receptor antagonist would block the receptor completely and obliterate the effects of the endogenous opioids (24). In fact, naltrexone therapy has been used to aid in the healing of corneal abrasions (25). Naltrexone has also been shown to block TNF-α synthesis and induction of septic shock in LPS/D-galactosamine-treated mice (26), suggesting that perhaps naltrexone itself may have anti-inflammatory effects.

In this pilot study, we investigated the effects of low-dose naltrexone (LDN) in patients with active Crohn's disease. It was hypothesized that LDN would improve activity of Crohn's disease in patients by showing a decline in the Crohn's disease activity index (CDAI) scores and blood inflammatory markers (C-reactive protein and ESR), and improve quality of life. It is proposed that the mecahnism by which LDN will improve Crohn's disease will be by causing an elevation in endogenous opioid levels.

PATIENTS AND METHODS

Patient Selection

Eligible patients were both male and female, at least 18 yr of age, and with the confirmed diagnosis of Crohn's disease by either endocopic or radiographic procedures. Patients had moderate to severely active disease as defined by a CDAI score of >220 and <450(27). Patients taking stable doses of aminosalicylates, immunomodulators, corticosteroids, or antibiotics were permitted to enter the study, and were continued at the same dosage throughout the trial. Women of childbearing age were permitted to enroll and, if not surgically sterile, were required to use adequate contraception (defined as oral or depot contraceptive, IUD, or barrier plus spermicide) for the duration of the study. These women were required to continue adequate contraception for 3 months after the completion of the study. Exclusion criteria included: women who were pregnant or breastfeeding, subjects with an ileostomy, colostomy, ileorectal anastomosis, or short bowel syndrome from surgery, and patients with abnormal liver function tests. Subjects taking tacrolimus, cyclosporine, mycophenolate, or infliximab within 8 wk of enrollment were excluded.

Approval for the study was granted by the Institutional Review Board of the Human Subjects Protection Office at the Pennsylvania State University Milton S. Hershey Medical Center. The LDN was assigned an Investigational New Drug Number 67,442 by the Food and Drug Administration (FDA).

Study Design

The study was designed as an open-labeled pilot investigation to evaluate response, safety, and toxicity to LDN in subjects with active Crohn's disease. Eligibility was assessed by telephone, and potential candidates were scheduled for a screening visit in the General Clinical Research Center (GCRC). At the screening visit, patients were subjected to a history and physical examination and laboratory testing (chemistry panel, complete blood count [CBC], urinalysis, and erythrocyte sedimentation rate [ESR]). Patients were dispensed a 7-day diary to record symptoms of frequency of diarrhea, abdominal pain, and general well-being. Within 14 days, patients returned for assessment and calculation of the CDAI score. Qualifying subjects were dispensed medication and given a new diary in order to calculate the subsequent month's CDAI score at the conclusion of this visit (baseline). Patients returned after 2 wk for an interim visit to evaluate side effects and perform a CBC. Follow-up visits were scheduled for weeks 4, 8, 12, and 16.

Treatment

Naltrexone hydrochloride was compounded into capsules containing 4.5 mg by GMP-approved standards at Williams Apothecary in Lancaster, PA. Because the dosage used in this study was lower than the FDA-approved dose of 50 mg, it will be referred to as "low-dose naltrexone" or LDN. Quality assurance of packaging and purity were confirmed by Analytical Research Laboratories (Oklahoma City, OK). Patients were treated with LDN orally each evening for 3 months. A monthly supply of medication was dispensed to patients by the Investigational Pharmacy of the Pennsylvania State University Milton S. Hershey Medical Center. On the first

visit, an additional 10-day supply of LDN was provided in the event of an appointment delay. Subjects were required to bring the vials to each appointment for counting and drug accountability; extra capsules were returned to the Investigational Pharmacy the day of the visit and another month's supply dispensed.

Assessments

In order to assess LDN's effect on disease activity, patients kept a Crohn's symptom diary for the 7 days preceding each visit for calculation of the CDAI score (27). A response to therapy was defined as a 70-point decline in the CDAI score and remission was defined as attaining a CDAI score of 150 or less. To assess quality of life, patients completed two standardized quality of life surveys, the inflammatory bowel disease questionnaire (IBDQ) (28) and SF-36 health survey (29). Appropriate licensure was purchased through contractual agreement for the use of these surveys from each facility.

Routine blood work including CBC, chemistry panel, and ESR were assessed monthly. In addition, urine tests and pregnancy tests were done for monitoring and safety purposes pretreatment and at each monthly visit. C-reactive protein (C-RP) was measured at baseline and at week 12. [Met^5]-enkephalin levels were determined by radioimmunoassay (RIA) at baseline and wk 4, 8, 12, and 16 (Peninsula Laboratories, San Carlos, CA).

Safety Measures

The study was monitored by the data safety monitoring board (DSMB) at the Pennsylvania State University Milton S. Hershey Medical Center. The safety and toxicity of LDN were assessed by adverse events, laboratory parameters, and vital signs. Nonhematologic and hematologic toxicities were determined by the WHO criteria (30). All adverse events were reported to the Institutional Review Board according to the guidelines established by the Pennsylvania State University Milton S. Hershey Medical Center.

Patients who required rescue medication based on an increase in CDAI score of 100 points were terminated from the study. These subjects were given a tapering regime of LDN, involving dose reduction to every other day for 10 days before discontinuing the medication. Patients necessitating discontinuation from the study were required to return for follow-up visits and analyzed as intent-to-treat subjects.

Statistical Analysis

Data were entered into a secure computer in the GCRC by a nurse assigned to this project and analyzed by the Department of Health Evaluation Sciences. An intent-to-treat analysis was performed in which the available data from all evaluable patients were included in the statistical analysis. The parameters of measurement (CDAI scores, laboratory values, and quality of life surveys) were analyzed by SAS statistical software system (version 8.1) computer program by the biostatistician comparing baseline values to those obtained monthly and 4 wk post-therapy. Data from laboratory results and quality of life surveys were entered into an Excel spreadsheet. A longitudinal data analysis, based on the linear mixed-effects model was applied using PROC MIXED program. The Bonferroni statistical method was used to adjust significance, where analysis including multiple comparisons to the baseline were made. *P* values for binary outcomes of response and remission were calculated using the exact test for binomial proportions.

RESULTS

Patients and Demographics

Twenty-one subjects were screened for the study and seventeen were eligible to participate. Of the four who were screened that did not participate: one was a screening failure due to elevated liver enzymes, one failed the screen secondary to severe psychiatric illness, and the other two subjects opted for other therapy and declined before receiving drug. Of the seventeen subjects who enrolled in the study, only one subject terminated before wk 12 secondary to a flare-up in Crohn's disease when she discontinued her concomitant medications. This subject was followed and data included throughout the study as an intent-to-treat subject. The characteristics of the patients at enrollment are shown in Table 1, including age, gender, and body weight. Most patients had both small bowel and colonic disease, and two patients had active perianal fistulas. Eight patients had prior surgical resection performed for their Crohn's disease. Seventy-six percent of patients had prior treatment with anti-TNF-α therapy, and were either allergic, intolerant, or unresponsive to this medication. Concomitant medications for Crohn's disease taken by patients throughout the study are also shown in Table 1.

General

Statistical analysis showed that there was no significant change in body weight from screening visit through wk 16 of

Table 1. Patient Demographics

Mean age ± SEM (yr)	42.1 ± 2.6
(range)	(23–63)
Gender, N (% of patients)	
Male	3 (18%)
Female	14 (82%)
Mean body weight ± SEM (kg)	72 ± 4
(range)	(53–101)
Disease site	
Small bowel	2 (12%)
Small bowel & colon	10 (59%)
Colon	5 (29%)
Past resection performed, N (% of patients)	8 (47%)
Prior anti-TNF-α therapy, N (% of patients)	13 (76%)
Concomitant meds for Crohn's, N (% of patients)	
Aminosalicylates	11 (65%)
Immunomodulators	8 (47%)
Glucocorticoids	4 (24%)
Antibiotics	1 (6%)

the study (data not shown). Two patients elected to discontinue taking routine medications for Crohn's disease prior to wk 12 and symptoms of Crohn's disease recurred in one of them. Data from both patients were analyzed with an intent-to-treat paradigm. The two subjects with entercutaneous and rectovaginal fistulas had closure of the fistulas with LDN therapy. Unexpectedly, one study subject with Crohn's disease and multiple sclerosis was found also to have improvement in her neuological symptoms and manifestations of multiple sclerosis with LDN.

Inflammatory Response (CDAI Scores)

CDAI scores were used to measure the patient's disease activity and inflammatory response to LDN therapy. Mean CDAI scores (Fig. 1) at wk 4, 8, and 12 following the initiation of LDN therapy were 41, 55, and 49%, respectively, decreased from baseline. Four weeks after discontinuation of therapy (wk 16), the mean CDAI score was 45% less than baseline and not statistically different from the mean scores measured during the therapy. Figure 2 shows the percentage of patients responding to therapy (Fig. 2A), as well as the percentage of subjects achieving a remission of disease (Fig. 2B). At 1 month after treatment, 76% had achieved a response to therapy (a decrease in the CDAI score by 70 points), and at 8 and 12 wk, 88% showed a response. Four weeks after discontinuation of LDN, 73% continued to show a response. At 1 month after starting LDN therapy, 29% of the patients had achieved a remission (a CDAI score of 150 points or less), and at wk 8 and 12 of LDN therapy, 53 and 47%, respectively, had achieved remission (Fig. 2B). Four weeks after discontinuation of LDN therapy, 33% of the subjects were in clinical remission. Therefore, at some point during the 16-wk trial, 89% of patients exhibited a response ($P < 0.001$), and 67% achieved a remission ($P = 0.07$) with LDN.

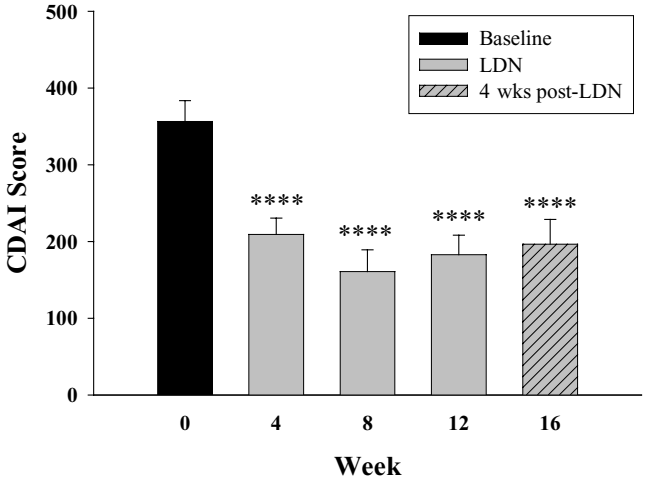

Figure 1. Mean Crohn's disease activity index (CDAI) scores ± SEM are shown at baseline (wk 0), wk 4, 8, and 12 after initiation of LDN therapy and 4 wk after discontinuation of LDN therapy (wk 16). ****Significantly different from baseline at $P < 0.0001$.

When the components of the CDAI scores were evaluated separately, the number of bowel movements and pain assessment both independently improved significantly ($P < 0.01$) from baseline at each 4-wk interval on LDN and 4 wk after dicontinuing LDN. In addition, the CDAI score minus the number of bowel movements and pain was also statistically improved with LDN therapy ($P < 0.01$). These results indicate that both pain and number of bowel movements are important markers in the CDAI score; however, they were not the only parameters contributing to the improved response found.

Quality of Life

Two standardized quality of life surveys, the IBDQ (Fig. 3) and the SF-36 health survey (Fig. 4), were administered to patients receiving LDN treatment. By both measures, patients experienced a significant improvement in their quality of life on LDN therapy. With regard to the IBDQ survey, signifi-

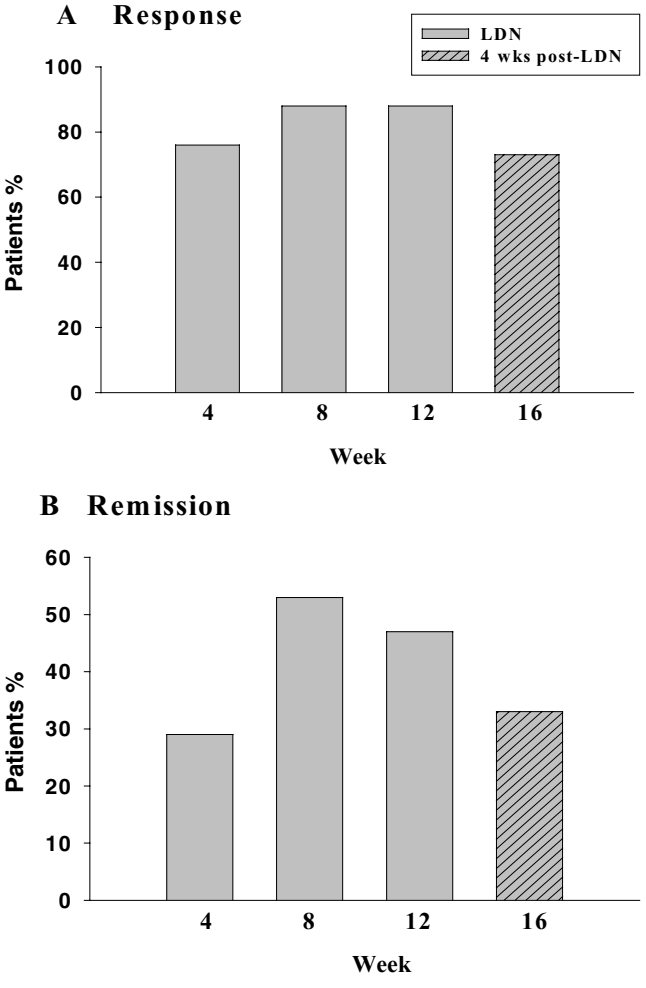

Figure 2. The percent of patients responding with a decline in CDAI score of at least 70 points (*A*), and the percent of patients achieving remission by a CDAI score of 150 or less (*B*), to LDN therapy are shown at wk 4, 8, and 12 and 4 wk after discontinuation of LDN therapy (wk 16).

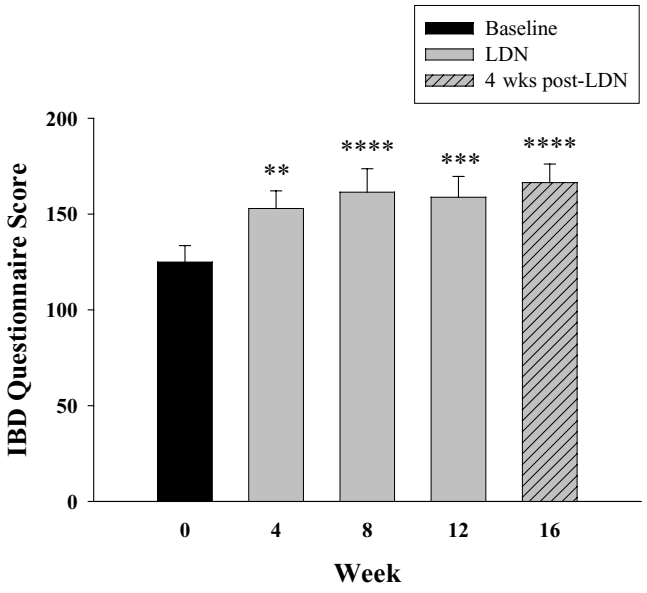

Figure 3. Mean inflammatory bowel disease questionnaire (IBDQ) scores ± SEM are shown at baseline (wk 0), wk 4, 8, and 12 after initiation of LDN therapy, and 4 wk after discontinuation of treatment (wk 16). Significantly different from baseline at $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$.

cant improvement in quality of life was noted compared with baseline at wk 4, 8, and 12 on LDN, as well as 1 month after completion of treatment.

Patients experienced a significant improvement in quality of life in a variety of parameters as measured by the SF-36 health survey (Fig. 4A–H). At wk 4, 8, and 12 of therapy with LDN there was, a five- to eightfold improvement in physical role scores (A) and a 61–65% improvement in bodily pain (B). Energy scores at wk 8 and 12 of LDN treatment (C) were at least twofold greater than at the time of initiation of therapy, whereas the scores for health perception (D) were 33% and 49%, respectively, greater than baseline. At 4 and 8 wk of LDN therapy, the physical function (E) was 23% greater than baseline values. Social function (F) was 70% greater than baseline at wk 4, 8, and 12, but was only statistically different at wk 8. Role–emotional (G) and emotional health (H) were comparable to baseline values at wk 4, 8, and 12 of LDN treatment.

At 4 wk after termination of LDN (*i.e.*, wk 16), all parameters except emotional health showed improvement ranging from 27% to an eightfold improvement over baseline.

Laboratory Data

At wk 4, 8, and 12 of LDN therapy, there was no change from baseline in CBC or chemistry values. Liver panels were not altered from baseline levels at wk 12. Assessment of CBC at wk 2 of LDN therapy was comparable to baseline values. C-reactive protein levels decreased from a median value of 2.6 (normal <0.8) at baseline to a value of 0.9 by the 12th week of treatment, and this change was statistically significant ($P = 0.03$). The ESR decreased from a mean baseline value of 23.3 ± 0.4 mm/h to 17.9 ± 0.3 mm/h, which was also significant ($P = 0.04$). Baseline plasma enkephalin levels were 9.5 ± 2.8 pg/mL, and decreased to a value of 3.6 ± 1.0 pg/mL at wk 12 of LDN therapy, but this difference in plasma enkephalin levels was not statistically significant.

Side Effects

The most frequently reported side effect with LDN therapy was sleep disturbances, and this was noted in seven patients; one reported unusual dreams. Five subjects changed the timing of LDN from the evening to morning due to insomnia. In no instance was a dose reduction necessary for sleep disturbances. Other rare reported events included nausea (N = 1), hair thinning (N = 1), blurred vision (N = 1), irritability (N = 1), mood swings (N = 1), and mild disorientation (N = 1).

DISCUSSION

The results of this pilot study are the first to show that LDN therapy significantly decreases symptoms and improves quality of life in patients with active Crohn's disease. In fact, two-thirds of enrolled patients achieved remission at some point during LDN treatment. It is known in a condition such as Crohn's disease that remissions of activity occur spontaneously (31); therefore, it is possible the remission occurred by chance. In a recent large randomized placebo-controlled trial for Crohn's disease, the remission rate with a placebo was recorded at 23% at wk 12 with even lower placebo remission rates earlier in the study (32). Therefore, in the present study, with 67% achieving remission, it would appear that LDN is effective; however, a randomized placebo-controlled trial is warranted.

Another finding in this trial was the fairly rapid onset of effect from LDN in that by 4 wk there was significant improvement. Corticosteroids may be effective in decreasing symptoms of Crohn's patients in 7–10 days, but other medications such as the immunomodulators (azathioprine and 6-mercaptopurine) may take 3–4 months to demonstrate improvement in symptoms (33). Often symptoms recur within 1 month after discontinuing corticosteroids or aminosalicylates (31, 33). However, in the present study, continued improvement in CDAI scores and quality of life was reported even 4 wk after discontinuing LDN. Longer studies are needed to evaluate the long-term effects of LDN and whether it can be used for maintenance therapy as well as induction therapy.

Another finding in this pilot study was that LDN improved the quality of life of subjects with active Crohn's disease. The baseline value on the IBDQ was similar to that reported in other clinical trials (32), indicating that our subject group did not differ from those used in other studies. Statistical analysis indicated that for two separate quality of life surveys, a significant difference from baseline occurred in those individuals on LDN. Moreover, even 1 month after discontinuation of LDN therapy, the quality of life remained better in almost

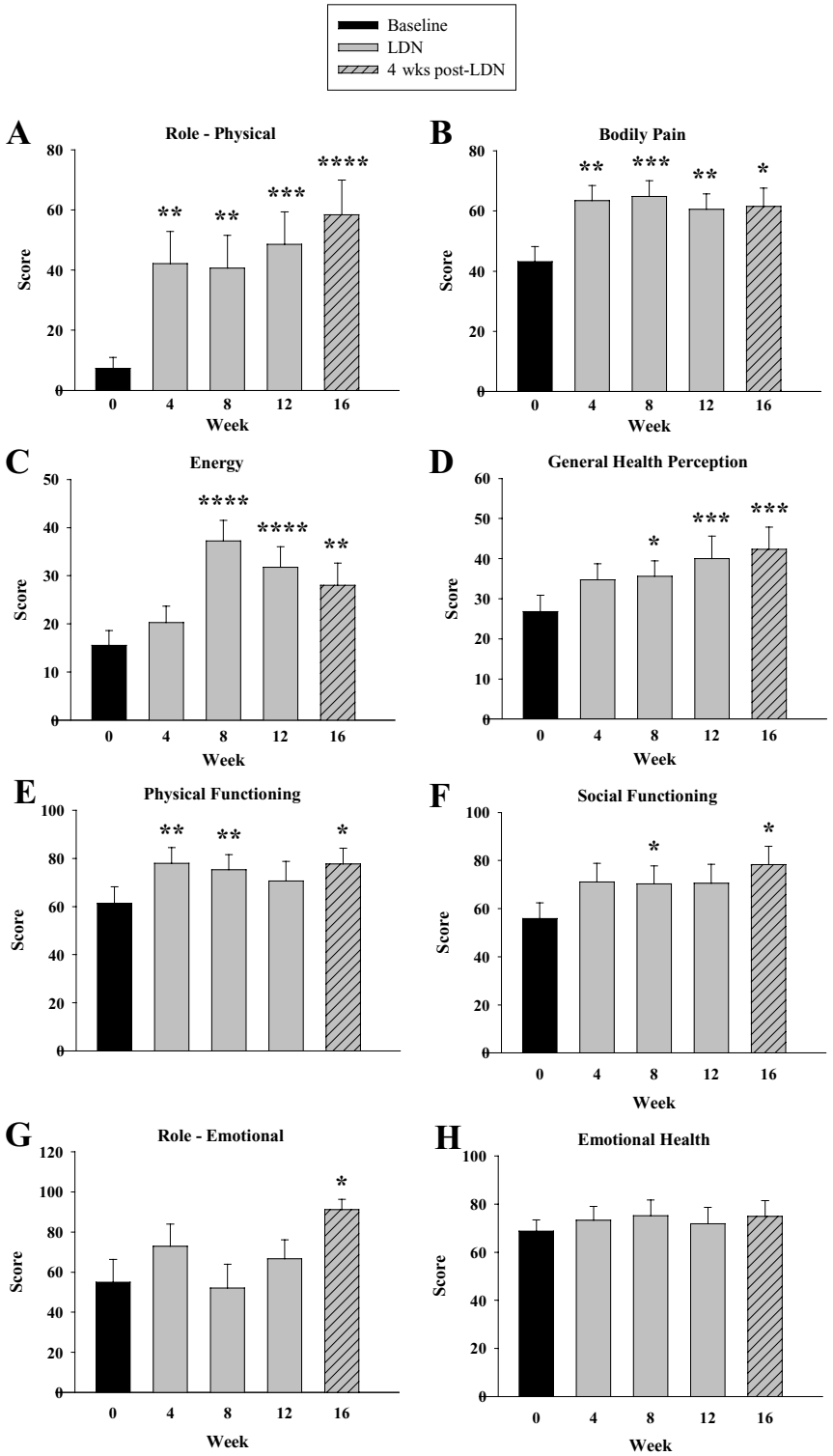

Figure 4. Mean SF-36 health survey scores ± SEM are shown at baseline (wk 0), wks 4, 8, 12 of LDN therapy, and 4 wk after discontinuation of treatment (wk 16) for each of the parameters measured by the SF-36 health survey. Significantly different from baseline values included the following: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

all parameters measured for these patients. It is unknown at this time, how long the quality of life benefit of LDN persists after discontinuing therapy, but this observation merits further investigation for duration of response.

Treatment with LDN may provide some advantages over other standard therapy for Crohn's disease. Although the long-term safety profile of LDN in Crohn's patients is unknown, the safety profile of LDN appears to be excellent in

this short-term study, with infrequent and minor side effects and no known suppression of immunity or greater risk of secondary infections. Cortiocosteroids have short-term side effects of weight gain, emotional laibility, glucose intolerance, and risk of secondary infections, especially fungal (34). Acute complications with some immunomodulators (azathioprine, 6-mercaptopurine) include idiopathic pancreatitis and neutopenia (35). Acute allergic reactions have been reported with the new anti-TNF-α compounds; these drugs can also increase the risk of reactivation of tuberculosis (36) and induce a lupus-like reaction, serum sickness syndrome, and/or anaphylaxis (37). Higher doses of naltrexone (*i.e.*, 50 mg) used for alcohol and opioid abuse have been reported to elevate liver transaminases (38). In contrast, the use of LDN herein at 4.5 mg daily did not change liver transaminases during treatment.

Infliximab has become the standard medical therapy for patients with fistulizing disease associated with Crohn's disease (39). It is of interest that the two subjects in our study with enterocutaneous fistulas noted closure with LDN when they had not previously responded to infliximab. Perhaps closures of the fistulas may be related to lower intestinal secretions or mucosal healing. Naltrexone has been reported to promote healing of corneal abrasions and epithelial wound healing by stimulating DNA synthesis (25); therefore, this compound may promote healing. Perhaps, the fistulas closed as a result of a lower number of bowel movements and improved mucosal fluid absorption as reported in diarrheal disorders of other etiologies that respond to enkephalins (22).

It was of interest that one study subject with multiple sclerosis and Crohn's disease in our study also had improvement of her neurologic symptoms with LDN. Although the etiology of both disease processes is unknown, another monoclonal antibody, natalizumab, has been useful in treating both of these conditions (40), suggesting perhaps a similar underlying defect. If so, perhaps evaluation of LDN in other inflammatory conditions such as multiple sclerosis would be warranted.

Medical care for IBD is costly (41, 42). Aminosalicylate therapy can cost several hundred dollars per month, and an infliximab infusion generally exceeds several thousand dollars (not to mention the time away from the workplace for IV administration) (43). Naltrexone is a generic medication and the cost is therefore inexpensive. Moreover, effective mesalamine therapy (Pentasa) may require up to 8–16 tables per day. Another advantage of LDN is the once-a-day dosing, which may improve patient compliance.

The mechanism by which LDN improves symptoms and reduces inflammation of those individuals with active IBD is unknown. Opioid receptors for μ, κ, and δ have been identified on immune cells (44) and morphine has been shown to induce the release of proinflammatory cytokines from mouse peritoneal marcrophages (45). [Met^5]-enkephalin has similarly been shown to stimulate peritoneal macrophages in rodents (46). In contrast, Philippe and coworkers have shown that stimulation of the μ opioid receptor with elective agonists reduces inflammation in the TNBS (2,4,6-trinitrobenzene sulfonic acid) murine model of colitis (47). Plasma enkephalin levels were not altered in this study; however, the enkephalin levels were only obtained monthly at the time of the AM clinic appointment. Because enkephalin levels have been shown to increase in animals administered LDN through transient receptor blockade, it is possible that the plasma enkephalin levels were increased by the compound, but the time of the blood sampling was inappropriate. Peptide levels usually are short-lived in the peripheral blood and frequent sampling postingestion would be necessary to perform accurate pharmacokinetic assays. Another possible explanation for the unchanged enkephalin levels in this study may be that perhaps the dose used in this study was too low and did not effect a sufficient blockade to stimulate upregulation of [Met^5]-enkephalin.

LDN may also be acting by another mechanism unrelated to changes in enkephalin levels such as through a reduction in cytokine activity or promotion of direct growth and mucosal repair. In fact, opioids have been shown to increase release of peritoneal cytokines (45) and naltrexone has been shown to block TNF-α production in a murine model (26). Another possibility is that therapy with the low-dose opioid antagonist may have affected a different endogenous opioid substance, such as endorphins, which were not measured.

Naltrexone may be playing a role in direct mucosal healing unrelated to its effects on cytokines. Opioids have been shown to decrease cell growth (48) through the interaction with the nuclear opioid growth factor receptor (49), and indeed blockade of the opioid receptor with naltrexone has been shown to promote DNA synthesis and healing of corneal ulcers (25). Lastly, there are opioid receptors throughout the gastrointestinal tract that are involved in analgesia, fluid, and water absorption. Because the CDAI scores are partially calculated with the patient's number of liquid bowel movements and perceived pain, naltrexone may have improved the CDAI scores in these individuals through another opioid-mediated mechanism.

The results of this feasibility study support the need for further investigation with a randomized controlled Phase 2 trial of LDN therapy and comparison to a placebo group. Because the present study found that subjects were still unchanged and improved 4 wk after stopping naltrexone therapy, a longer follow-up period should be observed to determine the durability of response. Extended treatment periods in future studies would further define optimal naltrexone treatment parameters. It is unknown whether naltrexone may be beneficial in reducing the amount of additional Crohn's medications required, *i.e.*, steroid sparing. Future studies are needed to further explore these interesting results and perhaps provide hope for a common frequently debilitating disease.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- The current medical therapy of Crohn's disease includes medications that target the immune system or inflammatory modulators.
- Opioid systems (peptides and receptors) play an integral role in gastrointestinal fluid regulation, pain perception, and inflammation.
- Many of the current drugs for treatment of Crohn's disease carry a greater risk of infection from immunosuppression or allergic reactions, and some must be administered parenterally.

What Is New Here

- An opioid antagonist, naltrexone 4.5 mg, administered by mouth once daily significantly improved Crohn's disease activity index (CDAI) scores and symptoms in subjects with active Crohn's disease.
- Quality of life significantly improved with low-dose naltrexone therapy and remained improved after discontinuation of the drug.
- Naltrexone therapy was well tolerated in Crohn's disease with minimal side effects.

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CONFLICT OF INTEREST

The authors declared no conflicts of interest.