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Clinical Trials for Low Dose Naltrexone

Updated: Nov 10, 2008

"LDN may well be the most important therapeutic breakthrough in over fifty years. It provides a new method of medical treatment by mobilizing the natural defenses of one's own immune system." — David Gluck, MD

FDA-approved naltrexone, in a low dose, can boost the immune system — helping those with **HIV/AIDS, cancer, autoimmune diseases,** and **central nervous system disorders.**

Source: *www.lowdosenaltrexone.org/* *www.ldninfo.org/*

In Brief

Around the globe, there has been a quantum leap forward in the number of ongoing research studies on LDN. Here is a capsule look at a number of such projects.

Developments that are detailed below:

- *A multi-institutional clinical trial of LDN for PPMS in Italy, which includes endorphin measurements, completed in fall 2007, published in September 2008.*
- *A Phase II placebo-controlled clinical trial of LDN for Crohn's disease at Penn State.*
- *A Phase II placebo-controlled clinical trial on the efficacy of LDN for children and adolescents with Crohn's disease at Penn State.*
- *A clinical trial of LDN in HIV-infected citizens of Mali—the first scientific study of LDN for HIV/AIDS in Africa—implemented in October 2007.*
- *A study of LDN in the treatment of MS at the University of California, San Francisco, implemented in early 2007.*
- *A clinical trial of LDN in the treatment of fibromyalgia at Stanford Medical Center implemented in October 2007.*
- *A study by the MindBrain Consortium in Akron, Ohio of, especially, the affective changes in MS treated with LDN, begun late 2007.*
- *An animal research study at Penn State of naltrexone in a model of a disease that mimics MS, under a small grant from the National MS Society.*
- *Animal research on neurodegeneration at NIEHS, suggesting a protective role for naltrexone.*

Recently Published Clinical Trials of LDN

> LDN for MS—Milan, Italy

A long-awaited pilot study of low dose naltrexone therapy in multiple sclerosis was run by the Milan neurological researcher, Dr. Maira Gironi and colleagues. Several northern Italian hospitals began enrolling patients for the study during the first week of December 2006. Dr. Gironi reports that the 6 months of LDN treatment was completed in August 2007. Importantly, Dr. Gironi's research team in Milan has long been a locus for significant research on endorphins in relation to illness, and this study has been tracking accurate assessments of the patients' beta-endorphin levels in response to their LDN treatment.

The subjects were 40 patients affected with Primary Progressive MS. PPMS is an uncommon form of multiple sclerosis that progresses inexorably and for which neurologists have never had an approved treatment to offer.

Results were published in September 2008:

Multiple Sclerosis. 2008 Sep;14(8):1076-83.
A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis.

Gironi M, Martinelli-Boneschi F, Sacerdote P, Solaro C, Zaffaroni M, Cavarretta R, Moiola L, Bucello S, Radaelli M, Pilato V, Rodegher M, Cursi M, Franchi S, Martinelli V, Nemni R, Comi G, Martino G.

Institute of Experimental Neurology (INSPE) and Department of Neurology, San Raffaele Scientific Institute, Via Olgettina 58, Milan, Italy; Fondazione Don Carlo Gnocchi, IRCCS, Milan, Italy.

Abstract: A sixth month phase II multicenter-pilot trial with a low dose of the opiate antagonist Naltrexone (LDN) has been carried out in 40 patients with primary progressive multiple sclerosis (PPMS). The primary end points were safety and tolerability. Secondary outcomes were efficacy on spasticity, pain, fatigue, depression, and quality of life. Clinical and biochemical evaluations were serially performed. Protein concentration of **beta-endorphins (BE)** and mRNA levels and allelic variants of the mu-opiod receptor gene (OPRM1) were analyzed. Five dropouts and two major adverse events occurred. The remaining adverse events did not interfere with daily living. **Neurological disability progressed in only one patient. A significant reduction of spasticity was measured at the end of the trial. BE concentration increased during the trial,** but no association was found between OPRM1 variants and improvement of spasticity. **Our data clearly indicate that LDN is safe and well tolerated in patients with PPMS.**

[Editor's Note: That only one patient showed any progression of PPMS during the six-month period of this trial is extraordinary, as is the occurrence of a statistically significant reduction in spasticity. Two major adverse events were reported but were unassociated with MS or with LDN: one patient had previously unrecognized polycystic kidney disease and the other was diagnosed with metastatic lung cancer.]

Clinical Trials in Progress or Awaiting Publication

> LDN for Crohn's disease—Penn State College of Medicine, Hershey, PA

Dr. Jill Smith's original article, "Low-Dose Naltrexone Therapy Improves Active Crohn's Disease," was published in the Jan 11, 2007 online edition of the American Journal of Gastroenterology (2007;102:1–9) [print edition Apr '07]. This was the first clinical study of LDN published by a US medical journal. Dr. Smith, Professor of Gastroenterology at Pennsylvania State University's College of Medicine, found that two-thirds of the patients in her pilot study went into remission and fully 89% of the group responded to LDN treatment to some degree. She concluded that "LDN therapy appears effective and safe in subjects with active Crohn's disease." That open-label Penn State trial demonstrated the efficacy of LDN in a small group of patients.

As a result, Dr. Smith received an NIH grant that permitted a more definitive Phase II placebo-controlled clinical trial, which by September 2008 had already studied almost all of the 40 patients it plans to include. With just a few patients yet to be added to the study, Dr. Smith is very optimistic about the usefulness of LDN in inflammatory bowel diseases, such as Crohn's disease. (See the trial website.)

Dr. Smith's most recent research on the effects of LDN is a double blind placebo controlled Phase ll study of youngsters from ages 6 to 17 with active Crohn's disease. It was launched at Penn State in July 2008 and is expected to run until July 2010. Participants "will be treated with either naltrexone or placebo for the first 8 weeks then all subjects will receive active naltrexone drug the last 8 weeks." For information about joining the trial, contact Sandra Bingaman, RN, at 717-531-8108 or sbingaman@psu.edu. (Please see the trial website.)

> LDN for HIV—Mali, Africa

In September 2007, after years of preparatory efforts by many advocates, the Institutional Review Board in Bamako, the capital of Mali, finally approved plans for a clinical trial of LDN in people who are HIV-infected—the first scientific study of LDN for HIV/AIDS in Africa. Signing up of the volunteer subjects has already begun. The neurologist Dr. Jaquelyn McCandless has taken on the responsibilities of "Expatriate Clinical Monitor" for the medical aspects of the trial.

The study, which is placebo controlled and should last for some 9 months, involves 3 study groups: LDN treatment only; LDN plus antiretroviral drugs; and only antiretroviral drugs. Because of the severe stigma attached to HIV infection in Mali, as of October 2008 the total number of participants who had reached 6 months time in all 3 groups combined amounted only to 16 people. However, Dr. McCandless reported that sign-ups were beginning to improve markedly. The volunteer subjects must be 18 years of age or older and must have reduced CD4 counts in the 350 to 600 cells range at the outset for the LDN treatment only group. The other two groups must begin with CD4 counts below 350 and must be asymptomatic at that time. Laboratory studies are being rechecked at 12-week intervals.

The research team is led by Dr. Abdel Kader Traore and other health officials at the University Hospital in Bamako. Irmat Pharmacy of Manhattan supplied all of the original 4.5mg LDN and matching placebo capsules at no cost. However, due to untranslated English-French communications, the study was approved for 3mg LDN dosage, and that is being supplied by Skip's Pharmacy of Boca Raton. In addition, the plans include careful attention to counseling aimed at improving preventive health practices for women and children. Both

Dr. McCandless and her colleague husband, Jack Zimmerman, plan to be in Mali from time to time to supervise the study.

Dr. McCandless is actively seeking philanthropic donations (e-mail her here). The Fourth LDN Conference of October 2008 was proud to be able to donate $5,595 dollars from voluntary individual contributions.

For further details about this project, please see the linked Developing Nations Project page.

> LDN for MS—University of California, San Francisco, CA

A study of LDN in the treatment of MS at the University of California, San Francisco, was implemented in early 2007 by neurological researcher Bruce Cree, MD, and colleagues. Some 80 patients with MS were involved in this double-blind, "Randomized, Placebo-Controlled, Crossover-Design Study of the Effects of Low Dose Naltrexone on Quality of Life as Measured by the Multiple Sclerosis Quality of Life Inventory." Each subject received either LDN or a placebo for 8 weeks, followed by one week without either, and then a further 8 weeks on the the alternate capsule. A substantial contribution toward the study has been made by the the LDN for MS Research Fund.

Dr. Cree reported the conclusions as follows in a poster presentation to the World Congress on Treatment and Research in Multiple Sclerosis, held in September 2008 in Montreal, Canada. His report still awaited publication at that date:

Conclusions

- *8 weeks of treatment with LDN significantly improved quality of life indices for mental health, pain, and self-reported cognitive function of MS patients as measured by the MSQLI [MS Quality of Life Inventory]*
- *An impact on physical quality of life indices including fatigue, bowel and bladder control, sexual satisfaction, and visual function was not observed*
- *The benefits of LDN were not affected by disease course, age, treatment order, or treatment with either interferon beta or Copaxone*
- *The only treatment related adverse event reported was vivid dreaming during the first week of the study drug in some patients*
- *Potential effects of LDN beyond 8 weeks of treatment were not addressed in this study*
- *Multicenter randomized clinical trials of LDN in MS are warranted*

Dr. Cree also included the following in his Acknowledgment:

We are grateful to the MS patients for participating in this study and wish to specially acknowledge the efforts of SammyJo Wilkinson of ldners.org and the other fundraisers who made this trial possible. To our knowledge, this is the first patient-funded clinical trial in MS.

> LDN for Fibromyalgia—Stanford, California

A single-blind, small clinical trial of LDN for the treatment of fibromyalgia was begun at Stanford Medical Center in June 2007; principal Investigator Sean Mackey and sub-investigator Jarred Younger. In September 2008, Younger advised us as follows:

The LDN trial on 10 individuals gave us encouraging results, which we hope to publish in the next 2-3 months. The findings warrant a larger, double-blind trial, planning for which is currently ongoing. We are actively recruiting individuals with fibromyalgia in the San Francisco Bay area to participate in the second study. **We are also pursuing a small trial of LDN for pediatric fibromyalgia patients.** While I can't talk about specific results, I will say that the majority of our study participants asked to continue taking LDN after the conclusion of the study. Side-effects were virtually non-existent, with 2 reports of increased vividness of dreams, and 1 report of transient insomnia.

Additional information can be found at clinicaltrials.gov.

> LDN for MS—Akron, Ohio

In May 2007, the MindBrain Consortium and the Department of Psychiatry of Summa Hospital System of Akron, Ohio, along with the nearby Oak Clinic for the treatment of Multiple Sclerosis, announced a new scientific study of the effects of treating MS with low dose naltrexone. Psychologist David Pincus and his colleagues coordinated the study. It was a 16 week, double-blind, randomized, placebo-controlled, crossover-design analysis of 36 patients with either progressive or relapsing-remitting MS. The study examined symptom severity as well as any changes in quality of life, sleep patterns, and affective states.

In early October 2007, Dr. Pincus wrote as follows:

We have enrolled more than 20 of the 36 people intended; we expect to be fully recruited within the next 3 or 4 weeks, and, three months following the end of enrollment we will have all the data. The study is going well, a couple of people have dropped out or been removed for one reason or another, but none because of a problem with sleep. One patient had sleeping issues for a few nights, but then has been ok. We are looking at the psychoactive properties of LDN as well as assessing improvement of MS symptoms, and hope to find some changes in perception of energy level that correlate with personality type and amount of dreaming reported.
One year later, Dr. Pincus reported problematic outcomes in his study, with little apparent differences between the placebo and treatment groups. After lengthy consideration with his colleagues, he wrote as follows:
We did not exclude patients on existing immunosuppressants....The existing immunosuppressants may have inhibited the LDN effects in this population.

Past Completed Clinical Trials of Low Dose Naltrexone

> Penn State Trial for Crohn's Disease

Endoscopic Improvement in Crohn's Colitis with Naltrexone

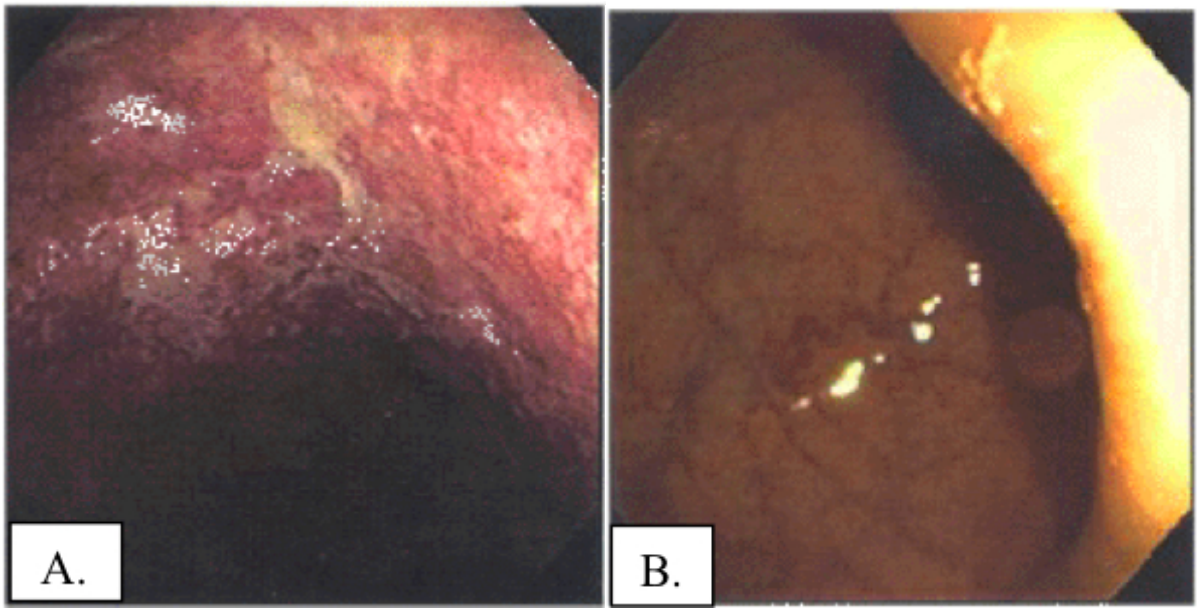


Figure A: Shown is the rectum of a subject with active Crohn's Disease before starting therapy with naltrexone 4.5 mg/day. The mucosa is ulcerated, edematous, and inflamed.
Figure B: Shows the same area of the rectum in the same patient four weeks after naltrexone therapy. The lining is now healed, ulcers resolved, and the mucosa is healthy.

The report on this groundbreaking research—**"Low-Dose Naltrexone as a Treatment For Active Crohn's Disease"**—was presented on May 23, 2006 at Digestive Diseases Week, a prestigious gastrointestinal conference, by Professor Jill Smith of the Pennsylvania State University College of Medicine. Dr. Smith's research paper, "Low-Dose Naltrexone Therapy Improves Active Crohn's Disease," has been published by the *American Journal of Gastroenterology* in its January 11, 2007 edition.

Dr. Smith and her colleagues concluded that "LDN therapy offers an alternative safe, effective, and economic means of treating subjects with active Crohn's disease."

According to the news from Penn State, the National Institutes of Health has already granted $500,000 for Dr. Smith's group to continue the study. This funding should help assure a full-fledged placebo-controlled scientific trial of LDN in Crohn's disease. (Notably, Dr. Smith and her research teams are also involved in exploring the direct effects of using a form of endorphin by infusion in order to treat pancreatic and colon cancer.)
For further details, see Penn State's online news, and our multimedia coverage of Dr. Smith's keynote address at the Second Annual LDN Conference, April 7, 2006.

Below are some extracts from the trial summary that was published online by the gastroenterology conference:

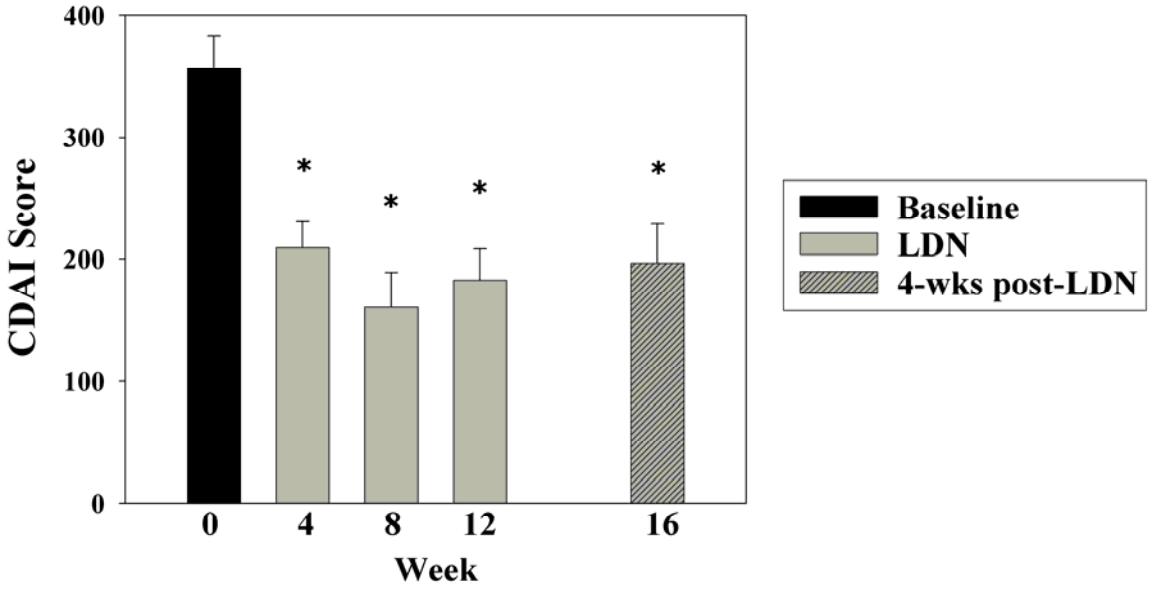
Low-Dose Naltrexone as a Treatment For Active Crohn's Disease

J. P. Smith[1]; H. E. Stock[1]; S. I. Bingaman[1]; D. T. Mauger[2]; I. S. Zagon[3]

1. Medicine, The Pennsylvania State University College of Medicine, Hershey, PA, USA.
2. Health Evaluation Sciences, The Pennsylvania State University College of Medicine, Hershey, PA, USA.
3. Neural and Behavioral Sciences, The Pennsylvania State University College of Medicine, Hershey, PA, USA.

Methods: Eligible subjects with histologically and endoscopically confirmed active Crohn's disease with a Crohn's Activity Index (CDAI) score of 220-450 were enrolled in a study using 4.5 mg naltrexone/day. Subjects were required to be off infliximab for at least 8-weeks, and this medication was not allowed during the trial. Other drug therapy for Crohn's disease utilized 4 or more weeks prior to enrollment was continued at the same dosages.... Drug [LDN] was administered orally each evening for a 12-week period. Laboratory tests, erythrocyte sedimentation rates, C-Reactive protein, and CDAI scores were assessed monthly and 4 weeks after discontinuing the medication.

Results: Seventeen patients with a mean initial CDAI* score of 356 ± 27 were enrolled in the study. CDAI scores decreased significantly ($p<0.01$) with LDN, and remained statistically lower than baseline 4-weeks after completing therapy (see Figure).



Eighty-nine percent of patients exhibited a response to therapy (>70-point decrease in CDAI, $p<0.001$) and 67% achieved remission (CDAI score <150). QOL* surveys indicated marked improvement with LDN. No laboratory abnormalities were noted. One subject undergoing routine endoscopic procedures showed healing of the intestinal mucosa. In both subjects with open fistulas, closure was noted with LDN. The most common side effect of LDN was sleep disturbances (7 patients).

Conclusions: **LDN therapy offers an alternative safe, effective, and economic means of treating subjects with active Crohn's disease.** **[Editor's Note: CDAI = Crohn's Disease Activity QOL = Quality of Life] Index;*

> Pain Therapeutics Ends Irritable Bowel Syndrome Trials of Ultra-low Naltrexone Dosage

In December 2005, Pain Therapeutics, Inc. announced results of its Phase III study with PTI-901. *[Editor's Note: PTI-901 contains only 0.5mg of naltrexone, which is well below the therapeutic dosage range for LDN—normally from 1.75mg to 4.5mg every night. LDN in the normal dosage range has been anecdotally reported quite beneficial in halting IBS.]* Excerpt from PTI's announcement:

This randomized, double-blinded, multi-center U.S. study compared a daily dose of PTI-901 against placebo in 600 women with documented IBS over a three-month treatment period. PTI-901 showed a favorable safety profile and patients reported statistically meaningful relief of IBS symptoms in the second month of treatment ($p<0.02$), but the drug did not demonstrate a meaningful benefit in the third month of treatment, which was defined as the primary endpoint. According to current regulatory standards, an experimental drug for chronic IBS needs to show efficacy at the end of a three-month treatment period.

The Company believes this study was well designed to detect any durable benefits of PTI-901 versus placebo in a large patient population with IBS. Based on the adequacy of the study itself, coupled with today's clinical results, the Company is discontinuing all further clinical development activities with PTI-901.

> Dr. Evers Trial in Germany for Multiple Sclerosis (MS)

Conducted in the Multiple Sclerosis Clinic of Dr. Evers Hospital in Sundern, Germany, the starting date was October 15, 2004. It is described as a short-term scientific, randomized, placebo-controlled, double-blind study involving patients with either secondary-progressive MS (SPMS) or primary-progressive MS (PPMS).

[Editor's Note: Unfortunately, because of some early complaints of sleep disturbance, the principal investigator of this trial switched all of the study group to taking LDN at 9am in the morning, a questionable dosage time. It is generally recognized that the most effective time to take LDN is at bedtime, between 9pm and 3am, due to the fact that the endorphins for each day are always produced at their peak rate in the pre-dawn hours. A 9am dosage time, as was used in this trial, might conceivably suppress—rather than boost—a patient's immune system.]

The purpose of the study was to investigate what MS-associated symptoms are positively influenced by LDN (low dose naltrexone, 3 mg per day). The principal investigator, Dr. Mir, reported his findings at the First Annual LDN Conference in 2005, as well as on his website.