Dr. Ian S. Zagon
Introduction to Low Dose Naltrexone (LDN)

As a scientist, educator, inventor, and university professor at a medical school and health center, it is not often that I get an opportunity to write something for a non-scholarly book or journal - much less to introduce a website listing of testimonials. However, the extraordinary scientific observations already made, along with the realized and unrealized clinical implications of the science insofar as the treatment of a variety of debilitating and often fatal illnesses, provides a compelling stimulus to say a few words about the subject of low dose naltrexone (LDN). And, quite frankly, the history of LDN, the biology revealed about the underlying mechanism of this drug, and the future of LDN deserve mention. Finally, something needs to be said about why it may be difficult to establish LDN as a medically condoned treatment for many diseases - and what it will take to do so.

First, let us discuss the history of what has been popularly called "LDN". Naltrexone is an opioid antagonist (it blocks exogenous (e.g., morphine, heroin, methadone) and endogenous (e.g., endorphins, enkephalins) from the opioid receptors in your body). When this was first discovered back in the 1960’s, the inventors were seeking a non-addictive opioid to relieve pain, and synthesizing a series of compounds that resembled morphine (an important exogenous opioid that is widely used for pain relief). At the time, the investigators (Drs. Blumberg and Dayton) concluded that naltrexone (along with other opioid antagonists such as naloxone) had little value. Only in the 1970’s, the utility of opioid antagonists such as naltrexone and naloxone become apparent in the reversal of opioid overdose, and in the management of patients with addiction to opioids. Today, naltrexone (trade names Revia and Depade) is widely used in the treatment of drug and alcohol dependency. The philosophy of using naltrexone is to employ a high enough dose (e.g., 50 mg) to block the elevated mood one gets with drugs such as heroin. Naltrexone, at an appropriate dosage, is capable of interfering with opioid-opioid receptor interactions which brings on the "high".

In 1979, my colleague Dr. Patricia J. McLaughlin, Professor of Neural & Behavioral Sciences at The Pennsylvania State University College of Medicine - and a coworker for over 3 decades, glimpsed the remarkable properties of the biological system influenced by opioid antagonists. It took a few years of scientific experiments, however, to arrive at an understanding of what LDN was doing. Basically, LDN - and this is also true for some other opioid antagonists such as naloxone - invokes an intermittent blockade of opioid receptors from native opioids for approximately 4-6 hours/day. During this interval, these native opioids are prevented from interacting with the opioid receptors present on cells in the body; these
Low Dose Naltrexone (LDN) Introduction

History

Naltrexone was originally synthesised in 1963 and patented in 1967. Early trials of naltrexone in rats, rabbits, dogs and monkeys had determined that the drug was non-toxic at therapeutic levels, with very few side effects. The US FDA approved in 1984 in a 50mg dose as a treatment for heroin addiction (Dupont were asked to run trials and develop the drug by the US government National Institute on Drug Abuse). The same year, DuPont’s Naltrexone patent expired.

In 1981 Dr Ian Zagon started research and published results on the use of LDN to retard tumour growth. In 1985, Dr Bernard Bihari in the US discovered that low doses of Naltrexone (LDN) (Typically 4.5mg) had a positive effect on the immune system. In 2007, Dr Jill Smith of Penn State University, USA, published results showing LDN was effective in inducing remission in Crohn’s patients in 67% of patients studied and had a positive effect in 90% of cases (Dr Smith is working on a larger trial at the time of writing).


Dr Chris Steele MBE’s Endorsment of LDN Now and the petition - http://tinyurl.com/DrCLDN

Glasgow LDN Pharmacist

Dickson Chemist
Home Delivery Pharmacy Services
J Stephen Dickson MRPharmS
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Published and on-going Research

http://www.lowdosenaltrexone.org/ldn_trials.htm
http://www.ldners.org/research.htm

Dr Jill Smith - http://fred.psu.edu/ds/retrieve/fred/investigator/jps12
Dr Ian Zagon - http://fred.psu.edu/ds/retrieve/fred/investigator/isz1


Further Reading

http://ldnnow.com
http://lowdosenaltrexone.org
http://glasgowldn2009.com
List of Conditions for Which LDN Has Been Successfully Used (Anecdotally)

Most reseach focussed on Crohn's, Multiple Sclerosis and Fibromyalgia but note that first results from Dr Ian Zagon in 1981 were with respect to tumour retardation and HIV/AIDS.

ALS (Lou Gehrig’s Disease)
Alzheimer’s Disease
Ankylosing Spondylitis
Autism Spectrum Disorders
Behcet’s Disease
Celiac Disease
Chronic Fatigue Syndrome
CREST syndrome
Crohn’s Disease
Emphysema (COPD)
Endometriosis
Fibromyalgia
HIV/AIDS
Irritable Bowel Syndrome (IBS)
Multiple Sclerosis (MS)
Parkinson’s Disease
Pemphigoid
Primary Lateral Sclerosis (PLS)
Psoriasis
Rheumatoid Arthritis
Sarcoidosis
Scleroderma
Stiff Person Syndrome (SPS)
Systemic Lupus (SLE)
Transverse Myelitis
Ulcerative Colitis
Wegener’s Granulomatosis
Cancers:
Bladder Cancer
Breast Cancer
Carcinoid
Colon & Rectal Cancer
Glioblastoma
Liver Cancer
Lung Cancer (Non-Small Cell)
Lymphocytic Leukemia (chronic)
Lymphoma (Hodgkin’s and Non-Hodgkin’s)
Malignant Melanoma
Multiple Myeloma
Neuroblastoma
Ovarian Cancer
Pancreatic Cancer
Prostate Cancer (untreated)
Renal Cell Carcinoma
Throat Cancer
Uterine Cancer
Naltrexone was licensed in 1984 by the FDA in a 50 mg dose as a treatment for heroin addiction. It is a pure opiate antagonist (blocking agent) and its purpose was to block the opioid receptors that heroin acts on in the brain. When it was licensed, Dr. Bihari, then involved in running programs for treating addiction, tried it in more than 50 heroin addicts who had stopped heroin use. None of the patients would stay on the drug because of side effects experienced at 50 mg such as insomnia, depression, irritability and loss of feelings of pleasure, all due to the effect of the drug at this dose in blocking endorphins. These are the hormones in the body that heroin resembles. Physicians treating heroin addicts therefore, for the most part, stopped prescribing naltrexone. In 1985, a large number of heroin addicts began to get sick with AIDS-studies showed that 50% of heroin addicts were HIV positive.

Dr. Bihari and his colleagues decided to shift their research focus to AIDS, in particular focusing on ways of strengthening the immune system. Since endorphins are the hormones centrally involved in supporting and regulating the immune system, levels of endorphins were measured in the blood of AIDS patients. They were found to average only 25% of normal.

Naltrexone, when given to mice and people at high doses, raises endorphin levels in the body’s effort to overcome the naltrexone blockade. This drug became the focus of Dr. Bihari’s research group. When the group discovered that endorphins are almost all produced in the middle of the night, between 2 AM and 4 AM, the studies focused on small doses (1.5-4.5 mg at bedtime) with the hope that a brief period of endorphin blockade before 2 AM might induce an increase in the body’s endorphin production. In fact, the drug did so in this dosage range. It had no effect below 1.5 mg and too much endorphin blockade at doses over 5 mg. A placebo-controlled trial in AIDS patients showed a markedly better outcome in patients on the drug as compared with those on placebo.

During the trial, a close friend of Dr. Bihari’s daughter had three acute episodes of multiple sclerosis over a nine-month period with complete spontaneous recovery from each. Because of his knowledge of MS as a neurologist and of recent evidence of an autoimmune component in the disease, Dr. Bihari started his daughter's friend on naltrexone at 3 mg every night at bedtime. She took it for five years with no further attacks. At that point, when a particular month’s supply ran out, she stopped it because of some denial that she had MS. Three and a half weeks later, she developed an episode of weakness, numbness, stiffness and spasms in her left arm and resumed LDN, which she has stayed on since. This episode
cleared and over the 12 years since, she has had no further disease activity.

The apparent mechanism of action of LDN in this disease parallels that in AIDS and other immune-related diseases. A small dose of the drug taken nightly at bedtime doubles or triples the endorphin levels in the body all of the next day restoring levels to normal. Since endorphin levels are low in people with MS, immune function is poorly orchestrated with significant impairment of the normal immune supervisory function of CD4 cells. In the absence of normal orchestration of immune function, some of the immune system cells "forget" their genetically determined ability to distinguish between the body’s 100,000 unique chemical structures (called "self") and the chemical structures of bacteria, fungi, parasites and cancer cells (called "non-self"). With this loss of immunologic memory, some cells begin to attack some of the body’s unique chemical structures. In the case of people with MS, the tissue attacked by immune cells (particularly macrophages) is primarily the myelin that insulates nerve fibers. These attacks result in scars in the brain and spinal cord called plaques. LDN in such patients works by restoring endorphin levels to normal, thereby allowing the immune system to resume its normal supervision and orchestration.

There exists a common notion that the immune system in a person with an autoimmune disorder is too strong and, in its exuberance, targets a body tissue for attack. Rather, the evidence is more consistent with autoimmunity resulting from immunodeficiency. Kukreja et al have demonstrated that multiple immunoregulatory T cell defects lie behind Type 1 diabetes both in humans and in non-obese diabetic mice.

Multiple scientific papers from various other research centers have demonstrated that an underlying immunodeficiency is characteristic of any tested autoimmune disease. Examples thus far reported include multiple sclerosis, rheumatoid arthritis, Crohn’s disease, and chronic fatigue syndrome.

Sacerdote et al measured low beta-endorphin levels in two animal examples of autoimmune disease - a mouse strain with a lupus-like syndrome and a strain of chicken with an autoimmune thyroiditis. They had significantly lower hypothalamic concentrations of the opioid than normal controls. In each case, the low levels of beta-endorphin were found well before the expression of autoimmune disease. This adds to considerable evidence of a key role for endorphins in regulating immune responses and suggests a therapeutic pathway.

Bihari et al found that a low oral dose of the opioid antagonist naltrexone, when taken at bedtime, led to a doubling or tripling of low
levels of circulating beta-endorphin. Bihari has since treated some 100 people with autoimmune disorders. None of them has progressed further while the patient continued taking low dose naltrexone each night at bedtime. Since no side effects are apparently associated with its use, this medication might well be studied as a possible preventive for Type I diabetes in those youngsters with beta-cell autoantibodies.

http://www.ldninfo.org/ldn_and_ ai.htm#Background
LDN Petition

“Low Dose Naltrexone (LDN) is a drug that is credited with helping those with HIV/AIDS, cancer, autoimmune diseases, and central nervous system disorders (including MS) by boosting the immune system.

As well as being effective it is cheap, costing less than one pound a day, and could save the NHS vast sums of money.

We therefore urge the Government to fund a trial of LDN on the NHS so that everyone in the UK can reap the benefits of this drug.”

(summary by S Crabb MP)

We have created a petition to No. 10 Downing Street to urge the government to take the necessary steps to trial this drug and achieve the licences necessary to make this drug available on the NHS. Currently, this lack of a licence is preventing many GPs from having the confidence to prescribe it.

Because of the lack of interest by the normal bodies who conduct trials - the drug companies - without political intervention, we will probably never see this generic drug trialled. Therefore, we need your help in this matter to overcome the apathy which is standing in the way.

Please sign the petition online by going to www.LDNNow.com and select ‘PETITION LINK’.

Or contact us below.

Please remember to click on the confirmation link in the return email after signing.

LDNNow

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Save Our Sick,
Save Our Economy
www.LDNNow.com
The Science
Low Dose Naltrexone is a therapy which has been in use for 25 years in the treatment of MS, HIV/AIDS, Cancer, Fibromyalgia, Crohn’s Disease, Rheumatoid Arthritis and many more conditions besides. A fuller list can be found on the LDNNow website. This versatility was discovered in clinical use by Dr Bihari after working with scientist Dr Zagon. It was Dr Zagon in 1979, who discovered that Naltrexone, taken once a day in low dosage, produced a surge in endorphin production of several hundred percent. Endorphins perform many functions in the body, one of which is to restore a healthy immune system and modulate it, allowing it to start working properly again. Endorphins also multiply cells that repair damage and act to remove free radicals. One of them, called met-5-enkephalin, can attach to cancer cells and inhibit them which stops a tumour from growing and allows the immune system to attack it. This theory is supported by the clinical success that has been observed. Cancers do stop growing, shrink and in some cases disappear, but not always. Sometimes other techniques must be used in addition to complete the job.

The Debate
Twenty five years is a long time for a successful drug therapy to be ignored by health services - so why?

Essentially, Naltrexone is a very low cost generic drug. Any company funding trials (costing millions of pounds) will be unable to secure exclusive right to manufacture. Cheap competition would cause them to lose their money, so this and all other generic drugs get shelved for further trials once the patent is due to expire. We expend huge effort and establish charities to defeat these chronic diseases but we now know that Low Dose Naltrexone saves lives and reduces disability! We should be taking this option very seriously - as well as saving our sick it can also save our economy. The drugs currently used to treat these diseases are very expensive and often dangerous. In medicine there is a rule, ‘First do no harm’. Naltrexone is safe with very few, short term side effects. It is even prescribed, in high doses, for pregnant mothers to treat addiction with no known risks to mother or foetus - so low dose usage must be risk free.

The Solution
We need to find a way for generic drugs - which find new uses and acquire proven track records in clinical use - to be licensed. Currently this means they must either be prescribable off license or they must be trialled. LDN can be prescribed off license for these conditions, but this is discouraged. Many drugs in use for many of these diseases are also not trialled for those uses, but they are allowed. However, using LDN for autoimmune conditions does not fit the standard protocol for treatment. There is only one way to end this controversy - to trial LDN properly. There are plenty of doctors now with good experience using LDN who can design a good trial, we just need the government to provide the funding. Nobody else has done or will do, but the UK government stands to reap huge savings in the NHS budget from the use of LDN. Therefore we have petitioned the government to fund the trials for Low Dose Naltrexone so that we can confirm, or otherwise, the clinical results being achieved with so many of our most dreaded illnesses. Please sign the petition and let’s get the government to resolve what is a tragedy of modern medicine where high tech business goals outweigh the needs of health.

Save our Sick, Save our Economy, Now!
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.

(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 tract 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). Additonally, 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). [Met5]-enkephalin is an endogenous pentapeptide that is located throughout the gastrointestinal tract (18). In addition to the growth characteristics of [Met5]-enkephalin, this endogenous opioid has also been shown to influence the immune system with effects on OK 10 cells, Leu13, and natural killer cells (19). A catarophan is an oral enkephalinase inhibitor that elevates endogenous enkephalin in 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%. Additonally, the symptoms of abdominal pain, anorexia, and nausea were also significantly reduced compared with placebo (22).

Zagon and M CLaughlin (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 [Met5]-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 the healing of corneal abrasions (25). Naltrexone has also been shown to block TNF 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 mechanism 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 endoscopic 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. Be cause 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. C-reactive protein (C-RP) was measured at baseline and at week 12. [Met5]-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- 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.

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>Mean age ± SEM (yr)</td>
<td>42.1 ± 2.3</td>
<td>(23–73)</td>
</tr>
<tr>
<td>Gender, N (of patients)</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (18)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (82)</td>
<td></td>
</tr>
<tr>
<td>Mean body weight ± SEM (kg)</td>
<td>72 ± 4</td>
<td>(53–101)</td>
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<td>Disease site</td>
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<tr>
<td>Small bowel</td>
<td>2 (12)</td>
<td></td>
</tr>
<tr>
<td>Small bowel colon</td>
<td>10 (59)</td>
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<tr>
<td>Colon</td>
<td>5 (29)</td>
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<td>Past resection performed, N (of patients)</td>
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</tr>
<tr>
<td>Prior anti-TNF- therapy, N (of patients)</td>
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<tr>
<td>Concomitant meds for Crohn’s, N (of patients)</td>
<td>11 (5)</td>
<td></td>
</tr>
</tbody>
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Aminosalicylates
Immunomodulators
Glucocorticoids
Antibiotics
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 enterocutaneous 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 neurological 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. Our weeks after discontinuation of therapy (wk 1), 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, 7 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. Our 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). Our weeks after discontinuation of LDN therapy, 33 of the subjects were in clinical remission. Therefore, at some point during the 1-wk trial, 89 of patients exhibited a response ($P \leq 0.001$), and 7 achieved a remission ($P \leq 0.07$) with LDN.

![Figure 1](image1.png)

**Figure 1.** Mean Crohn’s disease activity index (CDAI) scores \( \pm \) 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 1). Significantly different from baseline at $P \leq 0.0001$.

When the components of the CDAI scores were evaluated separately, the number of bowel movements and pain assessment both independently improved significantly ($P \leq 0.01$) from baseline at each 4-wk interval on LDN and 4 wk after discontinuing LDN. In addition, the CDAI score minus the number of bowel movements and pain was also statistically improved with LDN therapy ($P \leq 0.01$). 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 IBD (Fig. 3) and the S-3 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 IBD survey, signifi-

![Figure 2](image2.png)

**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 1).
significant 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 1–5 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 ( ) 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 1), all parameters except emotional health showed improvement ranging from 27 to an eightfold improvement over baseline.

**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 7 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 -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 IBD 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
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. Corticosteroids have short-term side effects of weight gain, emotional lability, glucose intolerance, and risk of secondary infections, especially fungal (34). Acute complications with some immunomodulators (azathioprine, mercaptopurine, idiquaporterip inductiopic pancreatitis and neutopenia (35). Acute allergic reactions have been reported with the new anti-TN- compounds, these drugs can also increase the risk of reactivation of tuberculosis (3) 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 diarrhoeal 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 I administration) (43). Naltrexone is a generic medication and the cost is therefore inexpensive. Moreover, effective mesalamine therapy (Pentasa) may require up to 8-1 tablets 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 , and have been identified on immune cells (44) and morphine has been shown to induce the release of proinflammatory cytokines from mouse peritoneal macrophages (45). Met5 -enkephalin has similarly been shown to stimulate peritoneal macrophages in rodents (44). In contrast, Philipp and coworkers have shown that stimulation of the opioid receptor with selective agonists reduces inflammation in the TNBS (24, -trinitrobenzene sul-
and CO -RR01 499 to the General Clinical Research Center and an Institutional Dean’s feasibility Grant.

STUDY HIGHLIGHTS

What Is Current Knowledge

The current medical therapy of Crohn’s disease includes medications that target the immune system or inflammatory modulators.

Pioioid 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 immune suppression 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.

Naltrexone therapy was well tolerated in Crohn’s disease with minimal side effects.

REFERENCES


CONFLICT OF INTEREST

The authors declared no conflicts of interest.
Preliminary Research

Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A Pilot Study

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Abstract

Objective. Fibromyalgia is a chronic pain disorder that is characterized by diffuse musculoskeletal pain and sensitivity to mechanical stimulation. In this pilot clinical trial, we tested the effectiveness of low-dose naltrexone in treating the symptoms of fibromyalgia.

Design. Participants completed a single-blind, crossover trial with the following time line: baseline (2 weeks), placebo (2 weeks), drug (8 weeks), and washout (2 weeks).

Patients. Ten women meeting criteria for fibromyalgia and not taking an opioid medication.

Interventions. Naltrexone, in addition to antagonizing opioid receptors on neurons, also inhibits microglia activity in the central nervous system. At low doses (4.5 mg), naltrexone may inhibit the activity of microglia and reverse central and peripheral inflammation.

Outcome Measures. Participants completed reports of symptom severity everyday, using a handheld computer. In addition, participants visited the lab every 2 weeks for tests of mechanical, heat, and cold pain sensitivity.

Results. Low-dose naltrexone reduced fibromyalgia symptoms in the entire cohort, with a greater than 30% reduction of symptoms over placebo. In addition, laboratory visits showed that mechanical and heat pain thresholds were improved by the drug. Side effects (including insomnia and vivid dreams) were rare, and described as minor and transient. Baseline erythrocyte sedimentation rate predicted over 80% of the variance in drug response. Individuals with higher sedimentation rates (indicating general inflammatory processes) had the greatest reduction of symptoms in response to low-dose naltrexone.

Conclusions. We conclude that low-dose naltrexone may be an effective, highly tolerable, and inexpensive treatment for fibromyalgia.

Key Words. Fibromyalgia; Chronic Pain; Naltrexone; Low-Dose; Novel Treatment; Microglia
dysregulations in the central nervous system [9–12], although the possibility of combined peripheral and central contributions has not been excluded [13]. Some researchers have classified fibromyalgia as a “central sensitivity syndrome,” perhaps sharing pathophysiological mechanisms with conditions such as irritable bowel syndrome, temporomandibular disorders, interstitial cystitis, and chronic fatigue syndrome [14]. This central sensitivity may be mediated in part by centrally acting proinflammatory cytokine activity that can produce the hyperalgesia, fatigue, and other symptoms of fibromyalgia [15–17].

There are currently three Food and Drug Administration-approved medications for fibromyalgia. The first medication, pregabalin, operates via alpha2delta voltage-dependent calcium channels [18]. The other two medications, duloxetine and milnacipran, are serotonin and norepinephrine reuptake inhibitors [19,20]. While many fibromyalgia sufferers respond to these medications, a significant number either do not respond adequately, or experience intolerable side effects [21,22]. There is, therefore, still a need to introduce additional effective treatments to adjunct conventional therapeutic approaches.

Naltrexone hydrochloride is a potential novel treatment for chronic pain. The drug is a competitive antagonist of opioid receptors, and has been used clinically for over 30 years to treat opioid addiction. More recently, naltrexone (and its shorter acting cousin, naloxone) has also been found to attenuate the production of proinflammatory cytokines and neurotoxic superoxides via suppressive effects on central nervous system microglia cells [23–27]. The reduction of proinflammatory cytokines can be achieved with ultra low doses, and can reduce thermal hyperalgesia in a rat model [28]. The effect is not due to opioid receptor activity, as the opioid nonactive isomers dextro-naloxone and dextro-naltrexone also exhibit neuroprotective benefits; it is instead potentially mediated by activity on toll-like receptor 4 [29,30]. Naltrexone has also been proposed to exert neuroprotective effects via modulation of mitochondrial apoptotic pathways [31].

Despite a solid base of basic science evidence suggesting a neuroprotective role for naltrexone, human studies are rare. One study found that naltrexone strongly attenuated the side effects associated with interferon-alpha treatment in cancer patients [32]. More recently, the drug has been used in dosages ranging from 3 mg to 4.5 mg per day to treat chronic pain and autoimmune disorders. Naltrexone used in this dosage range is typically referred to as low-dose naltrexone (LDN). Pilot trials for LDN in Crohn’s disease [33] and multiple sclerosis [34] have recently been conducted. Beneficial effects were reported in these trials; however, both were open label.

Given: 1) naltrexone’s demonstrated suppressing effect on centrally produced proinflammatory cytokine activity; and 2) the overlap in symptoms between fibromyalgia and cytokine-induced sickness behaviors, we hypothesized that LDN would successfully reduce the symptoms of fibromyalgia. We predicted a clinical response (30% improvement) in self-reported fibromyalgia symptom severity over placebo. We also predicted that LDN would relieve a number of specific symptoms (e.g., pain, fatigue, and sleep difficulty), and decrease pain sensitivity in quantitative sensory testing of mechanical, thermal, and cold pain thresholds. To test these hypotheses, we conducted a pilot clinical trial of LDN for the treatment of fibromyalgia, using a placebo-controlled, single-blind, crossover design.

**Patient Selection**

All individuals were required to meet the American College of Rheumatology’s 1990 [35] criteria for fibromyalgia. Current or recent use of opioids was exclusionary, but participants were allowed to continue other medications during their participation in the study. Participants must have held their drug dosages steady for at least the previous 2 months, and were asked not to modify their pain treatment regimen without notifying the study personnel. Participants were also screened out if they exhibited joint pain/inflammation or had ever been diagnosed with an autoimmune or rheumatologic condition. Exclusionary blood test results included rheumatoid factor (RF) over 20 IU/mL, antinuclear antibody over 1:80, and erythrocyte sedimentation rate (ESR) over 60 mm/h. Initial eligibility for study participants was determined over the phone, with further screening occurring at a laboratory visit.

**Study Design**

This study was a placebo-controlled, single-blind, crossover, pilot investigation of LDN for reducing symptoms of fibromyalgia. A crossover design was used to minimize the statistical demand for large sample sizes. A single-blind approach was used over the more typical open-label approach for an initial, signal-detecting study. Each participant...
received both LDN and placebo, thereby acting as their own control. Participants were not told when they would receive the placebo capsules. All participants provided informed consent, and all procedures were approved by the Institutional Review Board at Stanford University School of Medicine.

Each study participant followed the same schedule: baseline (2 weeks), placebo (2 weeks), LDN (8 weeks), and washout (2 weeks). In the baseline phase, daily self-reports of symptom severity were obtained, but no capsules were administered. In the placebo and LDN phases, capsules were consumed by mouth daily, and daily symptom measures were collected. In the washout phase, no capsules were administered, and participants continued to complete all study measures. Total time in the study for each participant was 14 weeks. Participants attended laboratory sessions every 2 weeks, for a total of eight visits.

Treatment

LDN capsules (4.5 mg naltrexone hydrochloride) were compounded by Preuss Pharmacy (Menlo Park, CA) using standard gelatin capsules and a microcrystalline cellulose filler (Avicel, FMC BioPolymer, Rockland, ME). A noncaloric sweetener was added to all capsules. Quality assurance was provided by Front Range Laboratories (Loveland, CO). Participants took LDN capsules once per day for a total period of 8 weeks. Capsules were taken approximately 1 hour before bedtime. At each laboratory visit, participants were given enough capsules to cover a 2-week period, plus four extra capsules in case of a delayed appointment. Participants returned bottles and extra capsules at each laboratory visit for drug accountability.

Assessments

One primary outcome measure and 13 secondary measures were assessed. The primary end point was daily, self-reported fibromyalgia symptom severity. Participants provided severity reports via a Palm Z22 handheld computer (Palm Inc., Sunnyvale, CA) and free Experiential Sampling Program (http://www.experience-sampling.org/). Participants responded on a 0–100 visual analog scale to the question, “Overall, how severe have your fibromyalgia symptoms been today?” Single-item, global outcome measures can demonstrate good reliability, validity, and responsiveness, especially when presented on a 101-point scale [36]. The system recorded the exact time and date of each response, thereby minimizing the impact of backfilling. The self-reported symptom severity measure was completed every night while participants were enrolled in the study.

A number of secondary end points were also collected via the handheld computer. These measures included: average daily pain, highest pain, fatigue, sadness, stress, sleep quality, ability to think and remember, gastrointestinal symptoms, and headaches. Additional questions were asked each night as a quality control measure, and were not tested as end points. These questions assessed if participants took their capsule each night, if any breakthrough pain medications were needed, if any highly stressful events occurred each day, the participants’ ability to tolerate the medication, and the severity of side effects.

In addition to the daily symptom sampling, participants attended brief (45-minute) visits to the laboratory every 2 weeks. In these lab visits, quantitative sensory testing protocols were performed to obtain mechanical, heat, and cold pain thresholds. For the mechanical pain tests, pressure was applied to each of the 18 tender points [35] at a rate of 1 kg/cm²/s until the participants indicated the first sensation of pain. Pressure was applied and measured using a JTech Commander Algometer (JTech Medical, Salt Lake City, UT). The kg/cm² pressure was recorded to the nearest tenth place and averaged for all 18 points to provide an overall score of mechanical pain threshold. Thermal pain was presented via a 3 cm × 3 cm Peltier-type, fast-ramping thermode driven by a Medoc Thermal Sensory Analyzer II (Medoc, Durham, NC) and placed on the palm (thenar eminence) of the right hand. From a baseline temperature of 32°C, heat was increased at a rate of 0.3°C/sec until the participant stopped the temperature increase at the first sensation of pain. The procedure was repeated three times, and all three resulting threshold temperatures averaged for a single estimate. Cold pain followed a similar protocol. From a baseline of 20°C, and placed on the left palm, the temperature was reduced at a rate of 0.3°C/sec until the participant stopped the decrease at the first sensation of pain. The procedure was repeated three times and all results averaged. The heat and cold pain tests were alternated, switching hands for each test, to allow adequate recovery time between stimulus repetitions. The fibromyalgia impact questionnaire (FIQ) [37] was also administered at each visit as a separate end point.

Finally, basic individual responder analyses were performed to determine if baseline participant characteristics could predict a positive
Drug response was defined as the reduction of severity symptoms in the drug condition, minus the reduction of symptoms in the placebo condition. This drug response variable was correlated with three predictors: ESR, fibromyalgia severity at baseline (measured with the FIQ), and duration of illness.

Statistical Analysis
All clinical outcome analyses were conducted with SPSS v17 (SPSS Inc., Chicago, IL), utilizing linear mixed models. Linear mixed models are superior over repeated-measures ANOVAs for estimating treatment effects when outcome measures are assessed frequently, when autocorrelation may be present, and when individual differences in treatment response are expected. For all outcomes tests (daily diary and laboratory), the subject identification number was entered as a random effect, so that results could be generalized to the larger population. Study condition (baseline, placebo, drug, washout) was entered as the primary predictor. For daily symptom tests, there was strong evidence of a lag-1 autocorrelation. A first-order autoregressive covariance type was confirmed to best fit the data using the Akaike’s information criterion (AIC) and Schwarz’s Bayesian criteria (BIC), and was used for all daily symptom tests. For tests conducted during laboratory visits, the AIC and BIC indicated the use of a compound symmetry covariance type. Individual responder analyses were conducted using Pearson’s correlations. All statistical tests were two-tailed. A total of 17 primary, secondary, and individual responder analyses were performed. All tests were controlled for multiple comparisons, using a method of false discovery rate modified for dependent outcomes (B-Y method) [38,39]. For all 17 tests, the adjusted statistical significance P value threshold of 0.014 was used.

For the primary outcome measure of daily fibromyalgia symptom severity, the clinical significance threshold for a positive drug effect was set at 30% reduction of symptoms over placebo. This degree of symptom reduction corresponds with “much improved” or “very much improved” on a patient global impression of change scale [40]. The crossover design, together with the high number of repeated observations, provided a high degree of statistical power for detecting drug effects. Power was estimated using G*Power 3.0 [41]. Assuming an adjusted P value of 0.014, moderate correlation between repeated measures, and four conditions, projected power for finding a 30% reduction of symptoms was calculated to be over 0.99.

Participants and Demographics
Twelve women were recruited, with an average age of 44.0 years (standard deviation [SD] = 10.3, range = 22–55). Participant demographics are presented in Table 1. The mean fibromyalgia severity at baseline, as scored by the FIQ, was 67.2 (SD = 15.0), indicating moderately severe symptoms. The average duration of illness was 9.6 years (SD = 6.5). All participants returned negative values for RF and normal values of ANA. Several participants returned slightly elevated or elevated ESR levels, but were not excluded from participation.

Two participants who began the study protocol were excluded from all analyses. One participant reported taking opioid medications during the study period. The participant also had a poor response rate on the handheld computer, including large periods of time (weeks) with no responses. Sampling was especially insufficient in

<table>
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BMI = body mass index; ESR = erythrocyte sedimentation rate; FIQ = fibromyalgia impact questionnaire.
the placebo period, preventing any type of meaningful comparison to the drug condition. The second excluded participant had a major physical accident that caused severe and prolonged pain, and required a major change in medication status.

Daily Symptom Reporting Entries were successfully completed on 92% of all study days. The primary outcome measure of daily, overall fibromyalgia symptom severity was first tested. The drug condition had a significant impact on fibromyalgia symptom severity ($F[3,254] = 8.67, P < 0.0005$). During placebo, symptoms were reduced by 2.3% in the entire cohort from baseline. In the drug condition, symptoms were reduced by 32.5% (Figure 1A). Post hoc pairwise comparisons (least squares differences) found that fibromyalgia symptoms were significantly lower during drug than both baseline ($P < 0.0005$) and placebo ($P = 0.003$) conditions. No difference was found between the drug and washout conditions ($P = 0.891$). Six individuals were classified as drug responders, given a 30%
greater reduction of symptoms during LDN compared with placebo. Figure 1B shows daily symptoms over the study period for drug responding (N = 6) and nonresponding (N = 4) groups.

The effects of naltrexone were then tested on the daily, self-reported secondary outcome measures. Drug condition had a significant impact on: daily pain (F[3, 287] = 5.6, P = 0.001), highest pain (F[3, 277] = 4.41, P = 0.005), fatigue (F[3, 224] = 4.05, P = 0.008), and stress (F[3, 236] = 4.67, P = 0.003). Statistical significance (using the adjusted P = 0.014 threshold) was not reached for sleep quality (F[3, 230] = 3.28, P = 0.022), gastrointestinal problems (F[3, 302] = 2.991, P = 0.031), headaches (F[3, 279] = 2.538, P = 0.057), thinking and concentration (F[3, 226] = 1.338, P = 0.263), or sadness (F[3, 229] = 1.016, P = 0.386). Post hoc, pairwise contrasts revealed that each of these symptoms followed the same pattern as the primary end point, with symptom severity being lower in the drug condition as contrasted with the baseline and placebo conditions.

Laboratory Visits
During baseline, participants had an average mechanical pain threshold of 1.02 kg/cm² at the fibromyalgia tender sites. Drug condition significantly predicted the secondary outcome of mechanical pain threshold (F[1, 67] = 5.88, P = 0.001). Pain thresholds were reduced by 0.07 kg in the placebo condition, and raised by 0.22 kg in the drug condition (Figure 2A). Post hoc, pairwise comparisons showed that mechanical threshold was significantly improved in the drug condition compared with both baseline (P = 0.012) and placebo (P = 0.010), but was not different than washout (P = 0.829). Drug condition was then tested on the lab measures of thermal and cold pain threshold. At baseline, participants first experienced thermal pain at 37.9°C. The drug significantly impacted heat pain threshold (F[1, 67] = 3.858, P = 0.013). During placebo, heat threshold was unchanged. During the drug condition, thermal pain thresholds were increased by 0.9°C (Figure 2B). For cold pain threshold, participants experienced the first sensation of pain at 17.7°C. The drug condition had no impact on cold pain thresholds (F[1, 67] = 1.49, P = 0.224).

The final secondary outcome variable tested was FIQ-rated symptom severity. FIQ scores were significantly affected by drug condition (F[1, 66] = 8.96, P < 0.0005). FIQ scores were reduced by 16.7% in the placebo condition and 31.7% in the drug condition. Post hoc contrasts showed that the drug condition was significantly different from baseline (P < 0.0005) and placebo (P = 0.042), but not washout (P = 0.160).

Side Effects
Average daily tolerability during the drug condition was 96.3% (compared with 89.7% during placebo). Two individuals in the study reported more vivid dreams. One individual reported transient nausea and insomnia for the first few nights of capsules. No other symptoms were reported. All side effects were reported as mild, and no change in dosage or dosing schedule was required.

Individual Responder Analysis
Three variables were used to predict positive drug responders: ESR, severity of fibromyalgia during baseline, and duration of illness. Baseline ESR values predicted over 82% of the variance in LDN response. The correlation between response and ESR was 0.91, P < 0.0005 (Figure 3). Those who had elevated ESR levels had the greatest positive response to LDN. Neither duration of illness (r = -0.48, P = 0.16) nor baseline symptom severity (r = 0.02, P = 0.95) predicted response to LDN.

is ssi n

This pilot study is the first to examine the effectiveness of LDN in reducing the symptoms of fibromyalgia. Overall symptom severity was significantly reduced in the drug condition, as contrasted to baseline and placebo conditions. In the entire group of participants, LDN reduced fibromyalgia symptoms by 30.2% over and above placebo. Specific symptoms, including average pain, highest pain, fatigue, and stress, were also significantly impacted by the drug. The observed effects were accompanied by a very low incidence of side effects, suggesting LDN may be an effective and well-tolerated treatment option for individuals with fibromyalgia.

Six of the 10 participants were significant responders to the drug, showing a greater than 30% reduction of symptoms over and above placebo. Daily symptom ratings (Figure 1B) showed that the nonresponding group demonstrated a significant placebo effect that was not maintained during LDN treatment. In the responding group, symptoms slowly and steadily decreased during placebo, but sharply decreased after the start of LDN administration. The time to peak effect was roughly 28 days, which is consis-
tent with reports of 4.5 mg LDN for Crohn’s disease [33]. That report also found a comparable responder rate (67%). During washout, nonresponders showed a rapid return to baseline levels of symptom severity. Drug responders showed a rapid but noncomplete return to baseline severity levels. A longer washout period (greater than 2 weeks) might show a complete return to baseline. Post hoc analyses on the outcome variables revealed no difference between drug and washout, potentially suggesting continued beneficial action following cessation of the drug, which has also been previously reported [33].

Qualitative sensory testing in the laboratory yielded interesting results. Mechanical pain thresholds rapidly increased after administration of LDN. These effects were maintained at the 2-week washout period. Similar results were found.
for thermal pain thresholds. These tests provide more objective support of sensory changes resulting from LDN administration. The changes in threshold levels, while small in absolute terms, represent significant improvements.

Individual responder analyses showed that baseline levels of ESR was strongly correlated with drug response, and predicted over 80% of the variance in response to LDN. These results, which suggest the presence of inflammatory processes in some fibromyalgia patients, must be viewed with caution because of low sample size. We note, however, that the LDN trial for Crohn’s disease found a significant reduction of ESR due to the drug [33]. It is unlikely that ESR can serve as a biomarker for fibromyalgia, given that our study and previous studies have found ESR levels to be normal or only mildly elevated in these patients [42–44]. Furthermore, ESR is found to be elevated in a number of conditions, such as rheumatoid arthritis, systemic lupus erythematosus, and acute infection. For these reasons, the ESR test may be most useful in defining an important subgroup of fibromyalgia patients who are experiencing low-level, systemic inflammation and are responsive to LDN. It is possible that the term fibromyalgia describes a discrete number of conditions with similar symptoms, but nonoverlapping pathophysiological mechanisms [8,45]. To our knowledge, there are no reports of ESR being used to predict treatment responders. By further attempting to identify treatment responders using physiological and psychological predictors, we may be able to define important subgroups and better understand the underlying pathophysiological mechanisms.

FM is a costly condition, both in terms of lost productivity and the cost of available treatments [46,47]. LDN is an inexpensive drug, with total costs usually running under $40 per month. There are several additional advantages to LDN. The drug is easily dosed, with a once-a-day schedule. Side effects are infrequent and mild. And, while safety of long-term administration for the low dose has not been assessed, the drug has a long history of safe use at much higher dosages. Liver functioning may need to be monitored, as elevated liver transaminases have been reported with 50 mg and greater dosages in opioid-addicted and alcohol-addicted patients [48]. Changes in these markers have not been found for the 4.5 mg dosage [32]. Also, because of the proposed mechanism of action (i.e., attenuation of microglia activity), there is a theoretical increased risk of infection. While no anecdotal reports suggest increased frequency of infections under naltrexone, this risk should continue to be monitored.

There are a few methodological limitations in this study that are associated with the exploratory nature of the project. First, as an initial signal-detecting study, a single-blind design was used. While this approach provides more scientific control than an open-label design, the results will need to be confirmed in a double-blind study. Second, placebo was administered before LDN in all participants, which could have led to confounding order effects. Third, while a rich dataset was obtained on participants, the subject size was small, and generalization to a larger population needs to be established. Fourth, the pooled data from responders and nonresponders show a slow decline of symptom reporting over the placebo period and continuing into the drug period. The slope of the line (Figure 1A) could suggest that the lower symptom reports given during the drug period were just a continuation of the placebo effect. Future studies may distinguish drug effects from placebo with longer conditions, and by utilizing crossover or parallel group research designs. Fifth, the lack of a difference between washout and the drug condition suggests that effects of the drug were sustained after cessation of capsules. The complete clinical picture of LDN for fibromyalgia will therefore be made clearer by utilizing a longer washout or follow-up period. Sixth, subsequent trials may use a validated scale for the primary outcome measure, rather than the single-item
Fibromyalgia Symptoms Reduced by Naltrexone

Fibromyalgia severity measure employed in this study. Seventh, more exploration of dose-response relationships are needed. Future studies employing stricter, double-blind designs could easily address all of these methodological concerns.

We propose here a microglia mechanism of action for naltrexone’s beneficial impact on fibromyalgia symptoms. While recent in vitro and in vivo work has highlighted the importance of those cells [23–31], there is no direct evidence available that links microglial activity to fibromyalgia symptoms. We are not aware of any method by which central microglia state can be assessed in peripheral blood, so investigating microglial activity in human patients is difficult. An exciting, minimally invasive method of assessing central microglia activity may involve positron emission tomography scans with the PK11195 or DAA1106 ligands [49,50].

We conclude that LDN is a drug that should be researched more thoroughly for the treatment of fibromyalgia, and perhaps more generally for conditions associated with elevated ESR.

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We would like to thank Jim and Connie Binns for their generous gift in support of this trial. We would also like to thank the American Fibromyalgia Syndrome Association for their financial and logistical support, and the Oxnard Foundation for their financial support. We also wish to thank the Arthritis Foundation for their support of Dr. Younger during the conduct of this study.

References

A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis

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A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis

M Gironi\textsuperscript{1,2}, F Martinelli-Boneschi\textsuperscript{1}, P Sacerdote\textsuperscript{1}, C Solaro\textsuperscript{4}, M Zaffaroni\textsuperscript{1}, R Cavarretta\textsuperscript{2}, L Moiola\textsuperscript{1}, S Bucello\textsuperscript{1}, M Radaelli\textsuperscript{1}, V Pilato\textsuperscript{5}, M E Rodegher\textsuperscript{1}, M Cursi\textsuperscript{3}, S Franchi\textsuperscript{3}, V Martinelli\textsuperscript{1}, R Nemni\textsuperscript{2}, G Comi\textsuperscript{1} and G Martino\textsuperscript{1}

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 \textd{-}endorphins (BE) and mRNA levels and allelic variants of the \textd{-}opioid 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. Multiple Sclerosis 2008; 14: 1076–1083. http://msj.sagepub.com

Key words: \textd{-}endorphins; efficacy; low-dose naltrexone; opioid receptors; primary progressive multiple sclerosis; safety

Introduction

Naltrexone is an orally semisynthetic opiate antagonist licensed in 1984 by the Food and Drug Administration (FDA) in a 50–100 mg daily dose as a treatment for heroin and alcohol addiction because it counteracts the effects of opioids by blocking opiate receptors [1]. However, when naltrexone is given at a lower dose, equal to or less than 5 mg/day [low-dose naltrexone (LDN)], its opiate antagonist activity turns into an agonist one so as to trigger a prolonged release of endogenous opioids such as \textd{-}endorphins (BE) [2]. BE is a peptide neurotransmitter produced by pituitary and hypothalamic neuronal cells, which has been traditionally considered as a regulator of nociception, mood, food intake, and endocrine secretion.

However, recent evidence indicates that such a peptide has a broader activity because when released by lymphocytes it also exerts peripheral anti-nociceptive action [3] and possesses an anti-inflammatory activity [4–6]. All together, these results have led to the widespread off-label use of LDN for the treatment of symptoms such as numbness, spasticity, fatigue, and bladder dysfunction as well as diseases with a dysimmune origin such as HIV, Crohn’s disease, lupus arthritis, fibromialgia, and multiple sclerosis (MS) (http://www.LDNers.org). However, most of the evidence so far accumulated is anecdotal, and the first phase II clinical trial assessing safety and efficacy of LDN has been completed only recently in patients with Crohn’s disease [7].

MS is an immune-mediated, inflammatory, demyelinating disease of the central nervous system...
in which pain, fatigue, and spasticity are among the more frequent and disabling symptoms [8]. Because these symptoms have a strong impact on occupational functioning, productive activity, and quality of life and could potentially benefit from LDN-induced secretion of endogenous opioids [9,10], we performed a pilot phase II (open label) uncontrolled clinical trial to first assess safety and tolerability of LDN in patients with MS. Symptomatic effect on pain, fatigue, spasticity, and depression was also measured as secondary outcome measures. Only patients with the primary progressive variant of the disease (PPMS) (affecting about 15% of patients with MS) [11] have been selected considering that no disease modifying treatments are available for this variant; spasticity is almost always present, and pain and fatigue are quite frequent. The biological impact on the opioid system of LDN administration [e.g., protein concentrations of BE and mRNA levels of its receptor, the -opioid receptor (MOR)] was also evaluated together with the allelic variants of the human MOR gene OPRM1 [12].

Materials and methods

Patients’ selection

Forty patients with a definite diagnosis of PPMS according to McDonald criteria [13,14] have been enrolled from December 2006 to March 2007 in four Italian MS clinical centers. At the time of inclusion, patients should be 18–65 years aged, had a disability level measured with the Expanded Disability Status Scale (EDSS) [15] between 3.0 and 6.5, had to have a disease duration longer than 2 years, and had a stable disease course in the 6 months before the enrollment. Patients were enrolled if they were affected by at least one of the following symptoms: spasticity (defined as a score between 2 and 4 in, at least, one limb on the Modified Ashworth Scale) [16], pain [defined as a score >2 at the Visual Analogue Scale (VAS)] [17], fatigue [measured with a score between 36 and 63 at the Fatigue Severity Scale (FSS)] [18], and/or depression [measured with a score >9 at the Beck Depression Inventory] [19]. Patients were excluded if they were treated with concomitant opioid-related drugs at the time of inclusion. Gabaergic and serotoninergic treatments were accepted if the dosage was maintained unmodified in the 2 months preceding and during the trial. Women of childbearing were asked to use contraceptives to prevent pregnancy. A negative pregnancy test was mandatory as well as a written informed consent. The study was approved by the ethical committees and the review boards of each of the participating institutions.

Methods

The design of the study was open, uncontrolled, 6-month duration. Primary outcomes of the study were the safety and tolerability of the drug, measured as the frequency of major and minor adverse events as well as the occurrence of neurological deterioration. The secondary outcome measures were the efficacy of the drug on fatigue, pain, spasticity, and depression measured using validated scales (FSS, VAS, Modified Ashworth Scale, and Beck Depression Inventory, respectively). We also monitored the quality of life, using the Italian-validated version of the SF-36. Four Italian centers participated to the clinical trial: San Raffaele Scientific Institute (Center 1; coordinating centre), Don Gnocchi Scientific Institute (Center 2), Gallerate Hospital (Center 3), and Micozzi Hospital (Center 4). Nineteen patients have been enrolled in Center 1, whereas seven in each of the other three centers. Once included, patients were given 2 mg as oral dose of naltrexone at bedtime for the first 4 weeks. Using phone call monitoring, the dose was increased up to 4 mg (referred as LDN) within the first 2 weeks of treatment until the end of the study. Physical examination and medical/neurological history were recorded at screening and baseline visits to determine patients’ eligibility. Follow-up visits were scheduled after 1, 3, and 6 months (end of the study) after the beginning of the therapy and 1 month after the end of the study. At each safety evaluation visit, assessment of the patients included history and physical/neurological examination, vital signs, adverse event monitoring, and complete biochemical tests [including blood cell count, liver and kidney function, electrolytes, plasma glucose, cholesterol, eritrosedimentation rate (ESR), and urinary analysis]. Adverse events were monitored at each visit according to Common Terminology Criteria for Adverse Events (CTCAE) (v3.0) (http://www.ctep.cancer.gov). Additional visits were performed at the time of adverse event occurrence. Disease progression was measured using EDSS. We considered as progressed any patient showing change in EDSS 0.5 between the final and baseline evaluation if the baseline EDSS was 5.5 and change in EDSS 1.0 and if the baseline EDSS was <5.5. EDSS changes had to be confirmed 1 month after treatment discontinuation.

BE and MOR studies

In all patients, peripheral blood samples were collected in the morning, between 9 and 10 a.m., in a tube containing ethylenediamine tetraacetic acid
(EDTA). BE level was measured in peripheral blood mononuclear cells (PBMC) using a previously described and validated radioimmunoassay procedure [6,20]. Sensitivity of the method was 10 pg per tube, and intra-assay and inter-assay variation coefficients were 8% and 11%, respectively. For the evaluation of mRNA expression levels of MOR, total RNA was purified from PBMC using TRIzol reagent (Invitrogen, Life Technologies, San Giuliano Milanese, Italy), resuspended in 6 L of diethylpyrocarbonate (DEPC) water, and treated with DNase (DNAfree-Ambion). Then, cDNA was synthesized using Moloney Murine Leukemia Virus Reverse Transcriptase (MMLV RT) (Invitrogen) and subjected to real-time polymerase chain reaction using ABI PRISM 7000 (Applied Biosystems, Forster City, California, USA). Probe/primer pairs specific for human GAPDH (code number Hs99999905_m1) and human MOR (code number Hs00168570_m1) were purchased from Taqman® Assays-on-Demand Gene Expression Products (Applied Biosystems). All PCR assays were performed in triplicate as previously shown [20]. To determine the genotypic variant of MOR, genomic DNA was isolated from peripheral blood of all but one of the patients with PPMS at baseline visit according to standard procedures. The Asn40Asp single nucleotide polymorphism in the human MOR gene OPRM1 was genotyped using the ABI Taqman assay for rs1799971. The primer sequences were forward, 5’-CTCTGGCGTACTCAAGTTGCTC-3’ (fluorescently labeled), and reverse, 5’-TTCGGACCGCATGGGA CCGAC-3’. Participants were grouped by OPRM1 status using the previously reported criteria [12].

Statistical analysis

An intention-to-treat analysis was performed. Data from all enrolled patients, including dropout when available, were included in the statistical analysis. Baseline values and end of the study values were mandatory; only one missing value over the 6-month period was tolerated. BE concentrations were analyzed by means of one-way analysis of variance for repeated measures followed by Bonferroni post hoc tests (Fisher’s exact test for categorical variables and Wilcoxon signed-rank test for quantitative data). The association between OPRM1 genotype category and clinical responsiveness to treatment was assessed using the Fisher’s exact test. SPSS statistical package (Chicago, Illinois, USA) was used for the analysis. No formal measurement of sample size was performed because the primary outcome of the study was the safety and tolerability of the drug.

Results

Patients’ demographic

Table 1 shows the baseline clinical and demographic characteristics of the PPMS patients enrolled in the study. No differences have been found between the different clinical centers in terms of gender ratio, age at enrollment, and time from symptom onset at the inclusion. Median baseline EDSS disability level was lower at Center 3 (3.5) than in the other MS centers (5.5, 5.5, and 6.0) (P<0.05). The gender proportion (females:males) ratio 1:1) and the age of disease onset (40.8 ±8.9 years) were comparable to previous population-based studies on PPMS [21]. Subacute or chronic walking impairment was the most common symptom at onset, the so-called spinal cord variant. In most of the cases, it was due to paraparesis and less frequently by hemiparesis. Mean disease duration (12.7 ±6.8 years) and disability levels (median EDSS 6.0, ranging from 3 to 6.5) of the enrolled patients were comparable to those of larger studies such as PROMISE [22], and MAGNIMS [23], and reflected the epidemiological characteristics of patients with PPMS [11,21]. Table 2 shows baseline levels of fatigue, pain, spasticity, and depression in our cohort of patients with PPMS. No differences have been found across clinical centers as regards to baseline levels of fatigue, pain, spasticity, and depression.

Safety and tolerability results

Thirty-five (87.5%) patients completed the 6 months of therapy. Five patients (12.5%) terminated pre-

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>MS (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female:Male</td>
<td>21:19 (52.5%)</td>
</tr>
<tr>
<td>Age at enrollment [mean (SD)]</td>
<td>53.4 (8.0)</td>
</tr>
<tr>
<td>Age of onset [mean (SD)]</td>
<td>40.8 (9.9)</td>
</tr>
<tr>
<td>Time from symptom onset to enrollment [mean (SD)]</td>
<td>12.7 (6.8)</td>
</tr>
<tr>
<td>Symptoms at presentation</td>
<td></td>
</tr>
<tr>
<td>Paraparesis/spinal cord</td>
<td>22 (55%)</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>10 (25%)</td>
</tr>
<tr>
<td>Cerebellar syndrome</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>Cerebrospinal fluid examination</td>
<td></td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>28 (70%)</td>
</tr>
<tr>
<td>Normal</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td>EDSS [median (range)]</td>
<td>6.0 (3-6.5)</td>
</tr>
<tr>
<td>Progression index [median (range)]</td>
<td>0.43 (0.12-1.65)</td>
</tr>
</tbody>
</table>

EDSS, Expanded Disability Status Scale. *Progression index represents the ratio between EDSS score and disease duration.
Table 2  Neurological status of patients with primary progressive multiple sclerosis as assessed at baseline

<table>
<thead>
<tr>
<th>Measure</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Analogue Scale [median (range)]</td>
<td>2 (0–10)</td>
</tr>
<tr>
<td>0-2</td>
<td>23 (57.5%)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Modified Ashworth Scale [median (range)]</td>
<td>0.875 (0–3)</td>
</tr>
<tr>
<td>&lt;2 in all limbs</td>
<td>19 (47.5%)</td>
</tr>
<tr>
<td>2 in at least 1 limb</td>
<td>21 (52.5%)</td>
</tr>
<tr>
<td>Fatigue Severity Scale [median (range)]</td>
<td>45 (9–63)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>36</td>
<td>33 (82.5%)</td>
</tr>
<tr>
<td>Beck Depression Inventory [median (range)]</td>
<td>5 (1–30)</td>
</tr>
<tr>
<td>&lt;9</td>
<td>28 (73.7%)</td>
</tr>
<tr>
<td>9–16</td>
<td>7 (18.4%)</td>
</tr>
<tr>
<td>&gt;16</td>
<td>3 (7.9%)</td>
</tr>
</tbody>
</table>

*When not specified, values represent the number of patients (%). 
*Two patients were not evaluated at baseline for mood alteration.

maturely the study. One patient (ID_1) decided to interrupt the treatment 48 days after the beginning due to the occurrence of enuresis. ID_13 decided to interrupt the treatment 5 months after the beginning due to a subacute clinical worsening of left upper and lower limb hyposthenia. Neurological worsening was not confirmed 1 month after treatment discontinuation. ID_16 exited the study 3 months after the beginning of the treatment because of a >2 fold increase of bilirubin (total 2.32; indirect 1.46). ID_38 exited the study 4 months after the beginning of treatment because of a urinary infection causing renal failure (creatinine 3.9 mg/dL) not requiring dialysis. ID_40 dropped out for a major protocol violation: 15 days after the beginning of the study, the patient admitted the use of an opioid-containing drug (tramadol) to treat pain.

Adverse events experienced during the trial are reported in Table 3. According to The National Cancer Institute CTCAE, we observed only two major adverse events of grade III (severe) or IV (life-threatening or disabling). One patient was the above-mentioned dropped-out patient suffering from renal failure not requiring dialysis (ID_38). Further analysis showed a previously unrecognized polycystic kidney disease. The other patient was diagnosed as having bone metastases presenting lung carcinoma (ID_36). In this latter case, the patient completed the trial because the diagnosis was made only at the end of the treatment.

All the other adverse events recorded during the trial were considered minor being of grade I (non-interfering with function) or II (not interfering with daily living activities).

Four grade II adverse events were recorded in four patients. Two patients (ID_12 and ID_13) had an increase of -glutamyl-transpeptidase levels (147 and 121 U/L, respectively) (>2.5–5.0 Upper Limit of Normal range [ULN]). In both patients, increased enzymatic levels occurred 3 months after the beginning of the treatment and normalized 1 month after the end of treatment. One patient (ID_16) showed increased levels of bilirubin (total 2.32; indirect 1.46) (>1.5–3.0 ULN) – despite normal levels of liver enzymes [aspartate aminotransferase (AST) 36; alanine aminotransferase (ALT) 50] – 3 months after the beginning of the treatment. The treatment was soon after discontinued, and the patient dropped out of the study. Three months after drug withdrawal, blood levels of bilirubin were still increased (total 1.80; indirect 1.31), hepatic enzymes remained within normal values (AST 27, ALT 40) but a liver ecography showed a liver ecostucture diffusely hyper reflecting as in hepatopathy. Eleven months after drug discontinuation, bilirubin levels and liver function returned to normal values and the liver ecostucture was ameliorated. We attribute this adverse event to a possible mild and transitory “Gilbert like-effect” induced by the investigational drug, as reported for other

Table 3  Number of patients experiencing major and minor adverse events during the trial

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Center 1</th>
<th>Center 2</th>
<th>Center 3</th>
<th>Center 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major (grade III or IV)</td>
<td>Lung carcinoma renal failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Minor (grade I or II)</td>
<td>Irritability</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hematological abnormalities</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Urinary infection</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4b</td>
<td>1c</td>
<td>2d</td>
<td>1a</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients experiencing at least one adverse event: 17/19 (84.2%) 4/7 (57.1%) 4/7 (57.1%) 3/7 (42.9%) 27/40 (67.5%)

*Adverse events were monitored according to the Criteria for Adverse Events v3.0 (CTCAE) (http://ctep.cancer.gov). Severe (grade III) or life-threatening (grade IV) events, requiring hospitalization, have been considered as major adverse events. Events not interfering with function (grade I) and events not interfering with activities of daily living (ADL) (grade II) have been considered as minor adverse events.
*Joint pain (1 patient), mood alteration (1 patient), asthenia (1 patient), enuresis (1 patient).
*Mood alteration (1 patient).
*Gastro-intestinal infection (1 patient), decrease of libido (1 patient).
*Facial peripheral palsy (1 patient).
treatments, such as rifampin [24]. We cannot exclude that the concomitant use in this patient of low-dose methotrexate – a labeled treatment for MS at 7.5 mg per week – might have contributed to hepatic toxicity. One month after the beginning of the therapy, ID_34 experienced a peripheral facial nerve palsy, which resolved after steroid treatment.

Forty-three grade I adverse events were recorded in 21/40 (52.5%) patients. Nine of 40 (22.5%) patients showed more than one grade I event during the trial. Leucopenia (<Lower Limit of Normal range = 3.0 109 /L) was measured in 14 patients. Increased levels of cholesterol (>ULN = 300 mg/dL) were recorded in six patients. Increased levels (2.5 ULN) of liver enzymes were measured in six patients. Such abnormalities were transient and in all cases subsided at the end of the trial. Asymptomatic urinary infections occurred in eight patients and mild irritability in five patients. Mood alteration (two patients), gastrointestinal infection (one patient), decrease of libido (one patient), joint pain (one patient), enuresis (one patient; ID_1, drop out), and asthenia (one patient) were the remaining grade I adverse events recorded during the trial. Such symptoms were transitory, did not interfere with function, and did not lead to any change in the dosage of the treatment.

Neurological disability was evaluated in 39/40 (97.5%) patients using the EDSS at different time points during the study. ID_40 was lost at follow-up. At the end of the study, only one (2.6%) patient experienced progression of the disease as measured by a 1-month confirmed 1.0 EDSS point increase (ID_30, from 3.5 to 4.5). In 35 (90%) patients, EDSS remained unchanged at the end of the trial compared with baseline values. In three patients, a 0.5 point EDSS improvement was measured at the end of the trial (ID_2 and ID_23, from 6.0 to 5.5; ID_26 from 5.5 to 5.0).

Secondary outcome (efficacy) measure results

Data are shown in Table 4. As of intention-to-treat analyses, a statistically significant reduction of spasticity, measured using Modified Ashworth Scale, was observed at 3 (P <0.001) and 6 months (P <0.01) after the beginning of the treatment when compared with baseline. The positive effect persisted up to 1 month after treatment discontinuation (P <0.05).

No significant changes were observed for fatigue at the 3- and 6-month evaluations. One month after treatment discontinuation, FSS data from 21 patients were available. In these patients with PPMS, FSS was significantly decreased compared with baseline value (median value, respectively, 37.0 vs 42.4; P <0.05).

VAS showed a significant increase of pain at 3 (median value 3.0; P <0.01) and 6 months (median value 3.0; P <0.05) after treatment beginning when compared with baseline values (median value 2.0). One month after treatment discontinuation, VAS data from 30 patients were available. Pain showed a significant decrease (median value 1.0; P <0.05) when compared to the 6-month evaluation.

Beck Depression Inventory did not change during the trial at any of the time points analyzed. As regards quality of life measured using SF-36, there was no statistically significant improvement in any of the items measured at the 6-month examination compared with baseline despite a trend of amelioration was observed for some items (Figure 1).

Protein and mRNA concentration of BE and MOR BE concentrations in PBMC from patients with PPMS at baseline, 3 months, and 6 months after the beginning of treatment and 1 month after the end of treatment are reported in Figure 2. As expected from previous studies [25], PBMC BE concentration in

---

Table 4: Effect of low-dose naltrexone administration in primary progressive multiple sclerosis patients on spasticity, fatigue, pain, and depression during the 6 months study

<table>
<thead>
<tr>
<th>Secondary outcome measures</th>
<th>No. of patients</th>
<th>Baseline value (median)</th>
<th>Final value (median)</th>
<th>% improved</th>
<th>% stable</th>
<th>% worsened</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasticity (Modified Ashworth Scale)</td>
<td>38</td>
<td>0.87</td>
<td>0.5</td>
<td>47.4%</td>
<td>42.1%</td>
<td>10.5%</td>
<td>0.008</td>
</tr>
<tr>
<td>Fatigue (Fatigue Severity Scale)</td>
<td>39</td>
<td>45</td>
<td>44</td>
<td>33.3%</td>
<td>25.6%</td>
<td>41%</td>
<td>0.01</td>
</tr>
<tr>
<td>Pain (Visual Analogue Scale)</td>
<td>39</td>
<td>2</td>
<td>3</td>
<td>28.2%</td>
<td>15.4%</td>
<td>56.4%</td>
<td>0.01</td>
</tr>
<tr>
<td>Depression (Beck Depression Inventory scale)</td>
<td>36</td>
<td>5</td>
<td>4.5</td>
<td>55.6%</td>
<td>11.1%</td>
<td>33.3%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

a The following patients were not included in the intention-to-treat analysis: ID_40 dropped out of the study for protocol violation 15 days after the beginning of the treatment (he had a baseline mean Ashworth Modified Scale of 2.3, Fatigue Severity Scale of 45, Visual Analogic Scale of 6, and Beck Depression Inventory scale of 5) and was lost at follow-up. ID_38 was evaluated at baseline (Ashworth modified scale of 1.5), at the 3-month visit (Ashworth Modified Scale of 1.5) but not at the end of the study. ID_12 and ID_14 had no baseline evaluation of the Beck Depression Inventory scale. ID_5 had no final evaluation of the Beck Depression Inventory scale.
patients with PPMS (48.3 ± 1.9 pg/10⁶ PBMC) were lower than in healthy controls at baseline. A significant (P < 0.05) increase of BE concentration (mean ± SEM) was measured either at 3 months (63.4 ± 4.8) and 6 months (76.9 ± 3.3) after the beginning of LDN treatment. BE concentration remained elevated up to 1 month (104.6 ± 12.4) after the end of treatment.

Figure 1  SF-36 health survey in patients with primary progressive multiple sclerosis treated with low-dose naltrexone (LDN). Mean scores (± SEM) are shown at baseline (BASAL) and after 6 months (6 Mo) of LDN therapy. Each item measured by the SF-36 health survey is represented.

Figure 2  -endorphin (BE) levels in peripheral blood mononuclear cells (PBMC) from patients with primary progressive multiple sclerosis. In panel A, a scatter plot reporting PBMC BE concentrations for each patient is depicted. In panel B, BE mean values (± SEM) are represented. BE concentrations are expressed as pg/10⁶ PBMC. Measurements have been performed at baseline, 1 month, and 3 months (Mo) after beginning of the treatment and 1 month after therapy discontinuation (Post Treatment). *P < 0.05 versus basal, #P < 0.05 versus 3 months, °P < 0.05 versus 6 months.
The mRNA levels of MOR - measured at 3 and 6 months after the beginning of LDN treatment and 1 month after the end of therapy - did not change in any of the patients compared with baseline values (data not shown).

We found 31 patients (79.5%) homozygous and 8 (20.5%) heterozygous for the more common A variant of OPRM1 gene, and no association was found between allelic variants and amelioration of spasticity (P =NS; OR and 95% C.I. of G carriers and efficacy on spasticity: 3.11; 0.6-16.8).

Discussion

To the best of our knowledge, here we report the first therapeutic trial aimed at assessing the safety and tolerability of a 6-month LDN therapy in patients with PPMS. Five patients dropped out during the study. None of the remaining 35 patients asked to discontinue the drug, missed the clinical scheduled visits, or was lost during the follow-up. The compliance was generally acceptable. The only two major adverse events (grade III and IV) reported were unlikely related to the drug. We hardly see any relationship between bone metastasis presenting lung carcinoma in patient ID_36 and the LDN mechanisms of action. The patient was a 40 cigarette/day smoker with a familial risk for cancer, and metastatic disease progressed in only one patient (2.5%) at the end of the study. This latter finding is reasonably attributable to the natural history of the disease [7], we had not to change LDN schedule of administration to solve irritability problems. Finally, disease progressed in only one patient (2.5%) at the end of the study. This latter finding is reasonably attributable to the natural history of the disease [11,21] and not to the treatment in itself considering the cohort of the patients enrolled in the study. All together, these data indicate that LDN is safe and well tolerated by patients with PPMS.

Assessment of LDN efficacy in our cohort of patients with PPMS was limited owing to the open uncontrolled design of the clinical trial. Nevertheless, we decided to assess LDN efficacy on pain, fatigue, depression, and spasticity because these are typical and frequent symptoms of the MS variant we studied and their responsiveness to LDN has been, although only anecdotally, reported (http://www.LDNers.org). Our preliminary results, based on intention-to-treat analysis, suggest a beneficial effect of LDN on spasticity only. Fatigue significantly ameliorated 1 month after treatment discontinuation but, owing to the uncontrolled nature of the trial, this is only barely attributable to the treatment itself. As regards quality of life, most of the items were improved at the end of the study but none of them at a statistically significant level.

We performed several experiments to evaluate whether or not improvement of spasticity was paralleled by an LDN-induced biological phenomenon. Because LDN is supposed (but never documented) to exert its efficacy by triggering the release of BE, we serially measured BE concentration in the PBMC of our patients. We were able to provide the first in-vivo demonstration that LDN treatment is able to increase the intracellular concentration of BE in PBMC of patients with MS. BE concentration started increasing 3 months after the beginning of the therapy and remained elevated (compared to baseline values) up to 1 month after therapy discontinuation. At this stage, we might only speculate that the symptom improvement is related to the increased circulating concentration of BE. Nevertheless, it is interesting to note that symptom amelioration paralleled increasing BE concentration during the trial and persisted 1 month after treatment discontinuation when BE level peaked. Furthermore, besides its own potential benefit, BE might exert its therapeutic effect in PPMS by interacting with the endocannabinoid system [26]. Although acting on two different receptor pathways, the synergistic activity between BE and cannabinoids can occur at different levels because of cross-tolerance and cross-sensitization as well as receptor co-localization in some brain areas [26-30]. BE release is, for example, critical for peripheral antinociceptive action induced by cannabinoid 2 receptor stimulation [3]. Administration of cannabinoids in patients with MS and experimental animals has been associated to an improvement in bodily pain and mental health as well as to an amelioration of symptoms such as spasticity, mood, sleep disturbances, tremor, and muscle cramps [31-36].

Our data clearly indicate that LDN is a relatively safe and well-tolerated drug in patients with PPMS. However, a randomized, double-blind, placebo-controlled trial needs to be performed to cogently assess the potential efficacy of this drug in patients with MS.

Acknowledgments

This trial was initiated and undertaken by the investigators. It has been entirely funded by the Multiple Sclerosis Italian Foundation (FISM) with a dedicated grant to M.G., and the Institute of Experimental Neurology (INSPE). The drug has been provided by Zambon Group (Italy), which produces the drug of interest, for heroin and alcohol addiction (licensed...
at 50–100 mg daily dose). Pharmaceutical companies had no involvement in the study design, collection, analysis, and interpretation of data, in the writing of the report, in the decision to submit the paper for publication, neither in study funding. None of the authors have any conflicts of interest to declare. We are indebted with all the physician and nurses operating within the involved MS centers for their help in recruiting and assessing enrolled patients. We thank F. Esposito and S. Lupoli for performing genotype analyses. We thank L. Licciardello and M. Motta from Zambon Group for providing LDN for the trial. We are grateful to all the patients participating to the trial.

References


The authors describe the long-term survival of a patient with pancreatic cancer without any toxic adverse effects. The treatment regimen includes the intravenous α-lipoic acid and low-dose naltrexone (ALA-N) protocol and a healthy lifestyle program. The patient was told by a reputable university oncology center in October 2002 that there was little hope for his survival. Today, January 2006, however, he is back at work, free from symptoms, and without appreciable progression of his malignancy. The integrative protocol described in this article may have the possibility of extending the life of a patient who would be customarily considered to be terminal. The authors believe that life scientists will one day develop a cure for metastatic pancreatic cancer, perhaps via gene therapy or another biological platform. But until such protocols come to market, the ALA-N protocol should be studied and considered, given its lack of toxicity at levels reported. Several other patients are on this treatment protocol and appear to be doing well at this time.

Keywords: pancreatic cancer; naltrexone; lipoic acid; survival

J.A. is a 46-year-old man diagnosed with poorly differentiated adenocarcinoma of the pancreas with metastases to the liver. In early October 2002, J.A. started to feel vague abdominal pains as well as complained of symptoms associated with hyperacidity and indigestion. After his symptoms became more pronounced, he presented to the local emergency department where, secondary to his complaint of right lower quadrant abdominal pain, a computed tomography (CT) was performed on October 8, 2002. It revealed a hyperdense mass at the junction of the second and third portions of the duodenum and the uncinate process of the pancreas (Figure 1).

The mass had infiltrative margins, without local adenopathy. Furthermore, within the liver, there were at least 3 hyperdense lesions that were thought to possibly represent hemangiomas; a fourth lesion, 5 to 6 cm in diameter, contained some areas of hypodensity, thus suggestive of a neoplastic process (Figure 2). Six days later, an esophagogastroduodenoscopy was performed, and an ulcerated Ampulla of Vater was biopsied; the pathology report was significant only for acute and chronic inflammation. One day later, magnetic resonance imaging (MRI) of the liver was performed in an attempt to classify the multiple hepatic lesions recognized on CT. The MRI suggested the lesions were not indicative of hemangiomas but rather of metastatic deposits. Subsequently, a 3.9 x 3.9 cm mass was located associated with the head and
uncinate process of the pancreas. This prompted a fine-needle aspiration of the largest liver lesion on October 22, 2002, and the diagnosis of poorly differentiated adenocarcinoma of pancreatic origin was made. Laboratory parameters reflecting J.A.’s functional hepatic status were at this time all within reference range; in addition, a common serum tumor marker for pancreatic cancer (CA 19-9) was within the reference range. Furthermore, this common marker has remained negative throughout the disease course.

Following this diagnosis, chemotherapy was prescribed. On November 7, 2002, J.A. began a 21-day course of gemcitabine (1000 mg/m$^2$; actual dose = 1800 mg; day 1 and day 8) and carboplatin (AUC 5; actual dose = 600 mg; half dose on day 1 and half dose on day 8). The patient, after becoming leukopenic and thrombocytopenic and demonstrating poor subjective tolerance for the chemotherapy, decided to seek another opinion and traveled to a well-respected oncology center. After a complete oncology workup and review of his previous records, J.A., per his historical account, was told essentially that, given his situation, any further treatment would ultimately be fruitless.

Given this prognosis, on November 25, 2002, J.A. presented to the Integrative Medical Center of New Mexico (IMCNM) and was seen in consultation by one of the authors (B.M.B.). At the time of presentation, his review of systems was positive for seasonal allergies, heartburn, tinnitus, decrease in force of urinary stream, sleeping difficulty, weight loss, abdominal pain, and severe emotional stress and anxiety. Medications at arrival were Prevacid 30 mg, trimethoprim/sulfamethoxazole, Mylanta, Pepto-Bismol, and Rolaids. B.M.B. added alprazolam 0.25 mg each bedtime as needed to help relieve J.A.’s nighttime anxiety.

An integrative medical program was then developed and prescribed for the patient. The purpose of this program was 3-fold: (1) nutritional support, (2) comfort and palliation, and (3) immune stimulation. The key therapeutic agents were intravenous L-lipoic acid (ALA) 300 to 600 mg 2 days per week and low-dose naltrexone (LDN), 4.5 mg at bedtime. In addition, a triple antioxidant regimen consisting of oral ALA (600 mg/d), selenium (200 g 2 times per day), and silymarin (300 mg 4 times a day) was added to scavenge the products of oxidative stress that inevitably result from any serious chronic medical disorder. J.A. was also placed on a lifestyle program that included specific dietary advice.

After the first intravenous (IV) administration of the ALA, the patient improved subjectively, prompting his volunteered comment, “I have increased energy and a sense of well-being.” The program was continued, and J.A. was extremely compliant.

On January 3, 2003, a repeat CT scan was performed using the same machine at the same diagnostic radiology department. Again, the mass at the head of the pancreas as well as the multiple hepatic lesions were demonstrated, and all lesions remained unchanged as compared to the scan of October 8, 2002 (Figure 3); furthermore, no new lesions were identified. The course of events was relatively uneventful as the patient continued on this integrative treatment plan.

On February 24, 2003, a repeat CT scan was performed (Figure 4; same CT machine, 51 days after the previous CT scan and 138 days after the initial CT scan), which again demonstrated unchanged pancreatic primary and metastatic hepatic lesions; no new lesions were identified.

As the patient continued on his treatment plan, follow-up CT scans were ordered at regular intervals. Both CT scans of April 21, 2003, and June 20, 2003 (Figure 5) revealed no changes in the existing lesions, nor any new lesions.

Another CT scan performed on August 19, 2003 (this time on a different machine at a different...
institution) revealed stable primary and hepatic lesions with the potential development of 2 new lesions. However, a caveat by the interpreting radiologist read, “Two new visible lesions that were not clearly evident on the prior scan [June 20, 2003, different institution], but again this could be an artifact of a different phase of contrast enhancement rate/hr than a definite new finding. Otherwise stable CT of the upper abdomen.” It is noted by the authors that no CT scan performed on J.A. has ever demonstrated evidence of biliary obstruction nor dilatation.

J.A. continued on his integrative protocol, without changes to his schedule, through March 2004, during which time CT images showed no changes in his disease status. The patient began to feel so well, with no symptoms of his disease, that he voluntarily discontinued his integrative treatment program. A positron emission tomography (PET)/CT fusion scan was performed on July 20, 2004, the results of which demonstrated disease advancement. Unfortunately, a subsequent CT scan performed in December 2004 demonstrated evidence of progressive disease at both the primary and metastatic sites (Figure 6). The lesion at the head of the pancreas had increased in size to 5 cm transversely, and 8 hepatic lesions became recognizable, while the previously identified hepatic lesions showed a general increase in their sizes. In December 2004, because of the unsatisfactory scan results, J.A. resumed the IMCNM program. Since that time, J.A. has continued to improve subjectively, and he realized no disease progression in a June 2005 CT scan.

The overall prognosis for patients with carcinoma of the pancreas is poor: the average length of survival after diagnosis ranges from 3 to 6 months. Surgical resection is generally not an option for people with metastatic pancreatic cancer, and patients with advanced metastatic disease rarely survive more than a few months. The current dogma concerning this issue is that treatment should concentrate on the alleviation of pain and the improvement of quality of life with participation from palliative medical personnel.

This leaves few options for such patients beyond chemotherapy and clinical trials. In this instance, J.A. chose to follow an integrative medical program that included intravenous ALA 300 to 600 mg twice a week, LDN 3 to 4.5 mg at bedtime, the oral triple antioxidant therapy protocol (developed by B.M.B.) consisting of (1) ALA 300 mg orally 2 times a day, (2) selenium 200 g orally 2 times a day, and (3) silymarin 300 mg 4 times a day, along with 3 professional-strength vitamin B complex capsules each day. It was also suggested that he follow the IMCNM lifestyle program including a strict dietary regimen along with a stress-reduction and exercise program.

That J.A. has had comparatively stable disease for more than a 3-year period is a remarkable clinical finding and prompts this report. It is the opinion of the
authors that the lack of progression of J.A.'s disease cannot be solely attributed to the single dose of chemotherapy he received. It has been reported that gemcitabine's effect on response rate and survival is disappointing. No data exist determining response to partial, moreover a single dose, of this drug either alone or in combination.

The stability of J.A.'s disease is thus attributable to the integrative program developed by one of the authors (B.M.B.). This is further evidenced by the quick progression of J.A.'s primary and hepatic lesions after his voluntary discontinuation of his integrative and successful treatment—an unfortunate but not uncommon decision. Many patients, despite strong encouragement from their physicians, will discontinue their treatments, in whole or in part, when faced with better health, diminishing financial resources, or both. The former is a subjective sensation often realized by patients when undergoing a treatment plan aimed at improving their overall health and as a result promoting an autogenous antitumor response. Nonmedically trained patients tend to associate improved sense of well-being and reduction of paraneoplastic symptoms with the notion that they are improving and that continued treatment may not, indeed, be necessary. In addition, because nonconventional medical treatments are generally not covered by most insurance plans, long-term care of this type can become a financial burden, forcing a discontinuation of their treatments despite their desires or those of the treating physician. Thus, it becomes the duty of integrative physicians to bring to public attention, via publication, cases in which such treatment plans have demonstrated success.

When J.A. first presented to the clinic (IMCNM), his quality of life was poor. He was losing weight, exhausted both physically and emotionally, and experiencing almost constant abdominal pain and nausea. However, as mentioned above, after only 1 treatment of intravenous ALA, his symptoms began to resolve. Improvement in quality of life is a particular strength of nutritional programs, and its inclusion in a treatment plan for someone with advanced pancreatic cancer may be essential.

People with metastatic pancreatic cancer often suffer from weight loss. The mechanism behind this is generally well understood and involves a complex interplay of proinflammatory biological response modifiers; however, such pathways will not be reiterated here. From a clinical point of view, and for J.A.'s case in particular, maintenance of body weight and provision of normal protein-calorie nutritional status is of paramount importance. As weight loss continues, an individual's appetite generally diminishes, thus accelerating the loss of lean body mass, which then leaves the patient with even less endogenous resources to maintain health and fight disease. It is probable, from the course of this case, that had J.A. continued on his course of chemotherapy, he quite possibly would have developed frank cachexia followed by the deleterious consequences of such a syndrome, including death.

The first key component in J.A.'s treatment protocol was ALA. It is a naturally occurring cofactor that is active in an assortment of enzymatic complexes that control metabolism. There have been a number of articles suggesting the utility of ALA in the treatment of various cancers. One article reported that ALA induced hyperacetylation of histones. In this study, human cancer cell lines became apoptotic after being exposed to ALA, while the same treatment of normal cell lines did not induce apoptosis.

Another indication of a mechanism whereby ALA might discourage the growth of cancer cells is its ability to stabilize NF- B transcription factor. Th1- and Th2-mediated immune system cells identify and react to pathogenic insults with various cell membrane receptors. Most of these receptors initiate a cascade of signal transduction events that eventually activate the master transcription factor NF- B. NF- B is able to bind to DNA after the phosphorylation and ubiquitin-mediated deactivation of its inhibitor I B and to affect the rate of transcription of certain deleterious genes that have NF- B binding sites. Because of this, NF- B plays a significant role in the regulation of inflammatory-induced gene function. High doses of ALA, when added to cell culture, have been shown to inhibit the activation of NF- B.

Additional data have demonstrated evidence of a mechanism by which ALA may contribute to the therapy for malignant disease: ALA can stimulate prooxidant-driven apoptosis in human colon cancer cells. This process is activated by an increased uptake of oxidizable substrates into the mitochondrion. In another study, ALA synergistically improved vitamin C cytotoxicity against cancer cells in tissue culture. Unlike ascorbate alone, ALA was equally effective against proliferating and nonproliferating cells.

One study evaluated an extensive population of people with advanced cancer for the biological considerations that are relevant to cancer cachexia. The parameters studied were serum levels of proinflammatory cytokines (IL-1, IL-6, TNF- ), IL-2, acute-phase proteins (C-reactive protein and fibrinogen), lepton, and others applicable to oxidative stress, such as reactive oxygen species, endogenous antioxidant

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enzymes such as glutathione peroxidase, and superoxide dismutase. The authors observed that patients with advanced cancer exhibit a chronic inflammatory state with high-grade oxidative stress. The article also suggests that antioxidant agents such as ALA can stimulate the development and maturation of cancer-fighting lymphocytes. Therefore, in this way, ALA can promote the functional restoration of the immune system in individuals suffering the oxidative stress that results from advanced cancer.

In another study, ALA was shown to increase homocysteine concentrations within cancer cells in certain established cancer cell lines. The increased homocysteine concentrations were toxic to the malignant cells.

Another study demonstrated the effects of ALA on the proliferation of mitogen-stimulated human peripheral blood lymphocytes in comparison to its nontumors. ALA therefore increased the proliferation of 2 leukemic T-cell lines. The discriminating toxicity of ALA toward the cancer cell lines was shown by electron microscopy and was due to the induction of apoptosis. In addition, ALA noticeably increased the induction of IL-2 mRNA and IL-2 protein secretion in cancer cells. The authors suggested that the differential effects of ALA on normal and leukemic T lymphocytes may specify a new pathway toward development of therapeutic agents for cancer.

Another relevant article demonstrated the ability of ALA to correct the most significant functional defects of peripheral blood mononuclear cells (PBMC) isolated from advanced-stage cancer patients. Twenty patients (mean age = 64.6 years) with advanced cancers of the lung, ovary, endometrium, and head and neck were examined. The serum levels of IL-1, IL-2, IL-6, TNF-α, and sIL-2R were significantly higher in those with cancer than in patients with no known cancers. The addition of ALA (0.001 mM) into the PBMC cultures significantly increased the response of PBMC isolated from cancer patients and healthy subjects. After 24 and 72 hours of culture, the expression of CD25 and CD95 on PBMC isolated from cancer patients was significantly lower than that of PBMC isolated from healthy subjects. The addition of ALA into these cultures significantly increased the percentage of cells expressing CD25 as well as those expressing CD95. ALA thus had a positive effect on several important T-cell functions in people with advanced-stage cancer.

LDN was the second key ingredient in this case. Nocturnally dosed LDN blocks endogenous opiate receptors, a short-lasting effect. During this receptor blockade, the body produces large amounts of opiates in response to the positive feedback, which become available to and saturate said receptors, once the LDN has been cleared from them. Opiates are powerful inducers of the Th1 immune response: in this sense, then, LDN produces an indirect immune response. LDN has a stimulatory effect on immune cells via an indirect interaction with their opiate receptors, whereas high-dose naltrexone has an inhibitory effect. The widely recognized pharmacologic effect of naltrexone is the competitive inhibition of membrane-based opiate receptors that consequently produce an opiate blockade. As a result of this action, patients who are addicted to opiates or are chronic ethyl alcohol users will not feel the normal "high" and should be inclined to discontinue these recreational activities.

For this reason, naltrexone is considered an opiate antagonist.

Zagon and McLaughlin reported that very low-dose naltrexone slowed the growth of neuroblastoma cells in culture and suggested that it therefore may have a role in the treatment of certain cancers. In a 2003 article, the same authors suggested that the modulation of cancer cell growth in tissue culture was not the result of alterations in apoptosis or necrosis but from some other pathway.

Malignant astrocytomas are believed to be incurable; therapy for such is aimed at palliation and overall survival. Lissoni et al reported on the treatment of malignant astrocytomas with the administration of naltrexone plus radiotherapy (RT). The tumor regression rate in patients treated with RT plus naltrexone was slightly higher than that of those treated with RT alone, but the percentage of those surviving at 1 year was significantly higher in patients treated with RT plus naltrexone than in those treated with RT alone (5/10 vs 1/1, P < .05).

In a later article, Lissoni et al reported escalation of IL-2-dependent anticancer immunity by the administration of melatonin (MLT) plus naltrexone. The researchers found that these 2 agents were able to stimulate the Th1 and suppress the Th2 lymphocyte response. The results of their study also suggested that NTX amplified the lymphocytosis obtained by IL-2 plus MLT. In addition, the authors wrote that in view of the fact that lymphocytosis represents the most important favorable prognostic variable predicting the anticancer efficacy of IL-2 immunotherapy, the addition of MLT and naltrexone to IL-2-containing regimens warrants further testing.

Bihari first used LDN to treat people with AIDS; given his promising results, he later used LDN for the treatment of people with cancer. Over the years, he administered LDN to 450 patients with cancer, most of whom had failed the standard treatments. According to Bihari, of 354 patients who had regular follow-ups, 86 showed signs of noteworthy tumor shrinkage (at least a 75% reduction in tumor bulk), and at least
125 others were reported to have stabilized and appeared to be moving toward remission.

In this case report, we describe the treatment of a 46-year-old man who was diagnosed with metastatic pancreatic cancer in October 2002. He was initially surveyed and staged by a local oncology team and treated with a standard chemotherapy regimen. After a single treatment of gemcitabine and carboplatin, the patient became leukopenic and thrombocytopenic and could not tolerate any further chemotherapy. In addition, even with the standard chemotherapy protocol, his cancer progressed.

J.A. then arrived at the office of one of the authors (B.M.B.) and was promptly started on a program of intravenous ALA, LDN, and a healthy lifestyle program. During the period from October 2002 to present (December 2005), J.A.’s pancreatic cancer with metastases to the liver was followed closely by regular office visits and CT and PET scans, and he has remained mostly stable (Figure 7). It is interesting to note that J.A.’s disease progressed rapidly when he went off the ALA-LDN therapy; however, it stabilized quickly when he resumed the treatment.

J.A. went back to work soon after he started the ALA-LDN integrative treatment protocol and remains free of symptoms at 3 years and 3 months. The authors believe that since most people with metastatic pancreatic cancer succumb to their disease miserably within a very short time, the 39-month survival time with non-progressive disease reported here represents a benchmark in oncology. People with metastatic pancreatic cancer more often die from their disease or complications thereof within 6 months and usually after a very stressful and painful course. The report above is thus of great importance.

In summary, the integrative therapy described in this article may have the possibility of extending the life of a patient who is customarily considered terminal. This was accomplished with a program of universal antioxidants, one that bears known antitumor activity (ALA) and an opiate-blocking agent that can stimulate an endogenous immune response. The authors believe that biomedical science will one day develop a cure for metastatic pancreatic cancer, perhaps via gene therapy or another biological-type platform. But until such protocols come to market, and moreover evolve and become realized, the ALA/LDN therapy should be considered given its lack of toxicity at levels reported herein, ready availability, and its effect on J.A., the true subject of this report.

B. Berkson declares no financial interest in the substances discussed in this paper but uses lipoic acid and naltrexone in his medical practice.

8. Wenzel U, Nickel A, Daniel H. Alpha-lipoic acid induces apoptosis in human colon cancer cells by increasing...


Summary for petition to Number 10 to fund trials for Low Dose Naltrexone, November 23rd 2009.

Low Dose Naltrexone is a therapy which was discovered in the beginning of the 1980’s and was first used to treat HIV/Aids by using it to boost the strength of the immune system to overcome the effects of HIV.

It was noticed that this action also restored a proper balance to a dysfunctional immune system, making it behave normally and hence put an end to auto immune conditions. It was also found to produce the endorphin that controls cancer growth in the body and combined with the functioning immune system, restores the body’s normal ability to control and prevent cancers.

If this were a patented and high tech drug, then it would have received funding, except that it might also see and end to many of these terrible diseases, which is not very profitable. Under these circumstances, it is the job of NIHR HTA to recognise that this situation exists and take on the responsibility to fund these trials, but LDN didn’t get from the USA – were it seems to have got locked in the financial poverty trap – until 2000 when Dr Lawrence introduced it to the UK, so up to now we can forgive NIHR HTA for missing it.

However, now over 100,000 people worldwide use LDN and over 3000 in the UK. Over 12500 people have signed this petition and several MP’s and AM’s in Wales and Scotland, Dr Chris Steele MBE and many doctors support its use in the UK. The time has come to face up to this issue and end the postcode lottery associated with getting LDN on the NHS. I say this, because while some GP’s are happy to prescribe LDN on the NHS, most will only prescribe it via a private prescription and they do this because they fear litigation if they prescribe it on the NHS.

LDN is a safe drug, safer than Paracetamol which can be purchased over the counter. The proof of this is in the fact that Naltrexone at high dose, which is used to treat heroine and alcohol addiction, is safe for pregnant women and routinely prescribed in this circumstance.

Therefore there is no reason for NICE not to write to all LHB’s/PCT’s telling them that it is legitimate to prescribe LDN off label. Note here that I was offered Mitoxantrone off label, a chemotherapy agent, not licensed for MS, costing £12000 a year and likely to cause heart valve failure, liver damage and brain damage, which is why I refused it. Many other drugs used for MS are off label but for some reason doctors feel unthreatened by their prescription. I assume that NICE have approved these uses off label.

LDN should be a safe front line ‘first do no harm’ option offered for all the conditions it can treat – see list at end – and we believe this could be approved without the need for expensive
phase 3 trials for all the conditions it can treat, although we feel research is needed to discover more about this treatment and clinical data should be collected once it is in use to form a better picture of the efficacy and use.

Therefore we expect the government to respond by helping to find researchers for this task and by negotiating with NICE for approval or for specific terms of reference for approval. We expect the government to fund this work via NIHR HTA and we expect this effort to become proactive once this petition is acknowledged.

LDNNow is a group of individuals who have worked extremely hard. Most of us have serious disability yet we have got out on the streets to garner support and spread the word about this vital therapy – the most important medical discovery since penicillin. We have lobbied many MP’s and AM’s as mentioned and have had almost 30 news articles published.