LDN-- History

Around the globe, there has been a quantum leap forward in the number of ongoing research studies on LDN.

Before it was first used to treat cancer, LDN had been in use in the treatment of HIV/AIDS. A double-blinded placebo-controlled trial in 1986 showed significant immune system protection from HIV in a group of patients given the active drug. The development of LDN was based on several biological facts. One was the fact that naltrexone, which had been licensed in 1984 as an adjunct in treating heroin addiction, has the ability to induce increases in the endorphin levels in the body. Another was the fact that endorphins are the primary supervisors or (homeostatic) regulators of the immune system, representing 90% of immune system hormonal control. *Ninety percent of the day's endorphins are produced by the pituitary and adrenal glands between 2a.m. and 4a.m.*

Dr. Bihari and his colleagues then showed that endorphin blood levels averaged less than 25% of normal in people with AIDS. These facts all provided the background for the discovery of the value of LDN in HIV/AIDS. The nocturnal production of endorphins allowed Dr. Bihari and his colleagues to experiment with small doses of naltrexone taken at bedtime in order to jump-start endorphin production. They found that LDN increased endorphin production when taken at bedtime in doses of 1.5mg to 4.5mg. Doses lower than 1.5mg had no effect on endorphin production. Doses higher than 4.5mg produced no more of an endorphin boost, but did block endorphins for significantly longer, thereby reducing the benefit of increased endorphin levels.

During the course of the placebo-controlled trial of LDN in people with AIDS in 1986, a friend of Dr. Bihari's called him when she discovered that she was experiencing an exacerbation of non-Hodgkin's lymphoma which had gone into remission five years earlier after treatment with chemotherapy. Because of her awareness

of the decreased likelihood of a long-term remission with a second round of chemotherapy, she called to ask if his AIDS drug might help her cancer.

Dr. Bihari agreed to treat her with LDN, and used the three golf-ball-sized tumors in her groin as markers of response. All three shrank and disappeared over the next six months. She stayed on LDN and had no further exacerbations of her malignancy. She died six years later in her mid-seventies from her third heart attack.

Several months later, Dr. Bihari, while in Paris to present the LDN AIDS results at an International AIDS Conference, met a woman in her early forties who was quite ill with metastatic malignant melanoma. This had spread from a malignant mole on her arm to her brain, which showed four metastases on C-T scan. Her speech was slurred, her balance and handwriting impaired, and she suffered from headache and recent memory impairment. Her oncologist in Paris said the malignancy was untreatable, and believed that she had perhaps three to six months of life remaining. On his return to New York, Dr. Bihari shipped LDN to her daughter, who started the patient on it. Nine months later, with all neurological signs and symptoms having cleared, she had a repeat C-T scan that showed no residual tumor.

She remained on LDN for the succeeding 12 years, stopping it without her family's knowledge in late 1999. Until that time, she had remained in complete remission, without any recurrence of her malignancy. Eight or nine months after stopping LDN she developed nodules under her skin and began to cough up blood. A C-T scan of the chest showed multiple metastatic lesions. Biopsy of one of the subcutaneous nodules confirmed recurrence of malignant melanoma. Dr. Bihari shipped LDN to the patient's family and she resumed it in early 2000. Eight months later, the nodules in the skin had cleared and a repeat C-T scan of the chest showed no residual tumor. She appears to be, once again, in remission.

Over the years encompassed by these two cases, 1986 to 1999, Dr. Bihari focused his research energy on the study of LDN's effect on immune function and on immunological approaches to the treatment of HIV/AIDS. In 1999, however, conversations with three small pharmaceutical companies revealed some interest in the development of LDN, with a goal of getting FDA approval for immune-related diseases including cancer. With this development possibility, Dr. Bihari decided to revisit the potential value of treating cancer with LDN.

Dr. Bihari began an informal private-practice-based evaluation of the effects of LDN with a variety of types of cancer in February 1999. He had seen positive results with a small but growing number of patients with cancer during the preceding 14 years, while developing the drug as an immune modulator for HIV/AIDS. The drug was compounded by pharmacists in 3mg capsules and taken once a day at bedtime. Most patients have recently had their LDN dose increased to 4.5mg daily. It is nontoxic and has no side effects. Its only interaction with other drugs is with narcotics (such as morphine), which it briefly blocks.

Mechanisms

The mechanisms involved in the apparent beneficial effect of LDN on cancer have three main elements.

- The first is the effect of LDN, when taken late at night, in inducing a sharp increase in pituitary and adrenal production of beta-endorphin and metenkephalin, respectively, in the pre-dawn hours, when 90% of the day's manufacture of these hormones occurs. Most studies have shown that naltrexone induces a two to three-fold increase in production of metenkephalin, the endorphin that most specifically activates delta-opioid receptors, the primary endorphin-related anti-growth factor on cancer cells. The low dose of naltrexone, which in higher doses would block endorphin and enkephalin

action on the receptor, is gone from the body in about three or four hours — whereas the elevated levels of endorphins and enkephalins persist all day.

- The second step involved in the anti-cancer effect of these hormones results from *direct* activation of opioid receptors of cancer cells by the increased endorphins. If this activation occurs while the cell is dividing, it dies. In fact, relatively small concentrations of metenkephalin, when added to human pancreatic cancer cells or human colon cancer cells growing in the test tube, have been shown to kill both. The apparent mechanism of cell killing is called apoptosis (programmed cell death). This appears to be one of the mechanisms by which endorphins and enkephalins combat cancer.
- A third element, which may play a major role in controlling cancer, involves the cells of the immune system, which is regulated/orchestrated to a great extent by endorphins. In particular, endorphins raise the circulating levels of natural killer cells and lymphocyte-activated CD-8 cells, the two immunological cell types that prevent cancer by killing cancer cells as they arise.

It should be emphasized that Dr. Bihari's patients were all treated in a private practice setting without the scientific rigor of a prospective clinical trial. This precludes any scientific claims about the drug's efficacy in treating any of the above-mentioned types of cancer.

The results thus far do, however, raise the possibility that the manipulation of opioid receptors on cancer cells as anti-growth factors through the use of endorphins and endorphin-inducing opioid antagonists may eventually prove to have considerable merit, particularly in view of the many years of published, supportive laboratory research findings.

Those cancer cells that have opioid receptors on their cell membranes, and that may, therefore, respond to LDN, include all of those that arise from the gastrointestinal tract. This includes the

mouth, esophagus, liver, pancreas, stomach, small intestine, colon and rectum. Lymph glands and the spleen have large numbers of opioid receptors, suggesting that Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma and lymphocytic leukemia should respond to LDN. Other malignancies with sizable numbers of opioid receptors on their cell membranes include breast cancer, neuroblastoma, prostate cancer, malignant melanoma, renal cell carcinoma, glioblastoma, astrocytoma, endometrial cancer and small cell and large cell cancers of the lung.

Research History

Ian Zagon, Ph.D., whose research group has done much of the basic animal work in the area of cancer treatment and endorphins, showed in 1981 in a mouse neuroblastoma model that very small doses (0.1 mg. /kg) of naltrexone, given once a day, inhibit tumor growth, prolong survival in those mice that develop tumors and protect some mice from developing tumors altogether.

Zagon had hypothesized that the small daily doses of naltrexone work to enhance the endorphin-related protective effect against cancer in mice by increasing the number and density of opiate receptors on tumor cells. He hypothesized as well that the increase in endorphins known to be induced by naltrexone might play a part in the protective effect of the small daily dose by working directly on the tumors' opiate receptors.

In 1996 and 1997, Zagon and his co-workers, reported on laboratory research using specially-bred mice that had no immune system (so-called 'nude mice'). They transplanted, in separate experiments, human colon cancer and human pancreatic cancer into the animals and compared the growth of the cancer between those mice that received daily injections of metenkephalin and a control group that received placebo. In each experiment, metenkephalin acted as a negative regulator of tumorogenesis and was significantly able to suppress tumor appearance and growth in the treated group.

Of special importance, in 1996 the same group of researchers demonstrated that by utilizing LDN to induce an intermittent blockade of opioid receptors in similar laboratory animals (nude mice), the growth of inoculated human colon cancer was markedly retarded.

"At the time (10 days) when all control mice had tumors, 80% of the mice in the 0.1 mg/kg NTX group had no signs of neoplasia." When measurements of metenkephalin plasma levels were made, the group that received LDN had metenkephalin levels that were elevated 2.5-fold compared with the control group. The researchers concluded that the results suggested "that daily intermittent opioid receptor blockade with low dose naltrexone provokes the interaction of opioids and receptors in the interval following drug availability, with opioids serving to inhibit tumorogenicity of human colon cancer".

New findings by Zagon and colleagues at The Pennsylvania State University in Hershey were published in the December 1999 issue of the journal Brain Research. They had identified the specific cell receptor for one of the endorphins, metenkephalin (the levels of which are increased by LDN).

Zagon stated that the opioids act as growth inhibitors, as well as neurotransmitters, and that this feature has implications for cancer treatment. Metenkephalin is found in all tissues, and appears to be associated with cells undergoing renewal or proliferation. Zagon's group was described as having mounted Phase I trials using metenkephalin in an attempt to control the growth of pancreatic cancer in humans. Pancreatic tumors appear to have low levels of the metenkephalin receptor. Low peptide [metenkephalin] or [opioid] receptor levels may exist in cancer cells in general since they want to stimulate their own growth, Zagon said.

LDN for MS

A long-awaited pilot study of low dose naltrexone therapy in multiple sclerosis was run by the Milan neurological researcher, Dr. Maira

Gironi and colleagues. Dr. Gironi's research team in Milan has long been a locus for significant research on endorphins in relation to illness, and this study has been tracking accurate assessments of the patients' beta-endorphin levels in response to their LDN treatment.

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

Results were published in September 2008:

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

Our data clearly indicate that LDN is safe and well tolerated in patients with PPMS.

Clinical Trials in Progress or Awaiting Publication

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

Dr. Jill Smith's original article, "Low-Dose Naltrexone Therapy Improves Active Crohn's Disease," was published in the Jan 11, 2007

online edition of the American Journal of Gastroenterology (2007;102:1–9) [print edition Apr '07].

This was the first clinical study of LDN published by a US medical journal. Dr. Smith, Professor of Gastroenterology at Pennsylvania State University's College of Medicine, found that two-thirds of the patients in her pilot study went into remission and fully 89% of the group responded to LDN treatment to some degree. She concluded that "LDN therapy appears effective and safe in subjects with active Crohn's disease." That open-label Penn State trial demonstrated the efficacy of LDN in a small group of patients.

Dr. Smith's most recent research on the effects of LDN is a double blind placebo controlled Phase ll study of youngsters from ages 6 to 17 with active Crohn's disease. It was launched at Penn State in July 2008 and is expected to run until July 2010. Participants "will be treated with either naltrexone or placebo for the first 8 weeks then all subjects will receive active naltrexone drug the last 8 weeks."

LDN for HIV

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

The study, which is placebo controlled and should last for some 9 months, involves 3 study groups: LDN treatment only; LDN plus antiretroviral drugs; and only antiretroviral drugs.

Because of the severe stigma attached to HIV infection in Mali, as of October 2008 the total number of participants who had reached 6 months time in all 3 groups combined amounted only to 16 people. However, Dr. McCandless reported that sign-ups were beginning to

improve markedly. The volunteer subjects must be 18 years of age or older and must have reduced CD4 counts in the 350 to 600 cells range at the outset for the LDN treatment only group. The other two groups must begin with CD4 counts below 350 and must be asymptomatic at that time. Laboratory studies are being rechecked at 12-week intervals.

The research team is led by Dr. Abdel Kader Traore and other health officials at the University Hospital in Bamako. Irmat Pharmacy of Manhattan supplied all of the original 4.5mg LDN and matching placebo capsules at no cost. [Another supplier is Skip Pharmacy, Boca Rotan]. In addition, the plans include careful attention to counseling aimed at improving preventive health practices for women and children. Both Dr. McCandless and her colleague husband, Jack Zimmerman, plan to be in Mali from time to time to supervise the study.

LDN for Fibromyalgia

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

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

Additional information can be found at clinicaltrials.gov.

Research on Neuro-degeneration at NIEHS Suggests a Protective Naltrexone Role

J.S. Hong, Ph.D., head of the Neuro-pharmacology Section of the Laboratory of Pharmacology and Chemistry at the National Institute of Environmental Health Sciences, finds that 'morphinan' drugs, including naltrexone and naloxone, are able to reduce inflammatory reactions in microglia brain cells in animal studies. Such inflammation is believed to be central to the progressive neurodegenerative effects seen in disorders such as Parkinson's disease and Alzheimer's disease. Hong's report, summarizing the role of microglia in inflammation-related neurodegeneration and the potential of therapy using morphinans, appears in a January 2007 issue of *Nature Reviews Neuroscience*.

LDN for an Animal Model of MS

The National Multiple Sclerosis Society "awarded a small Pilot Award to Dr. Ian Zagon at Pennsylvania State University. The title of his project is *'Role of opioid peptides and receptors in MS.'* This study is based on an animal model of MS daily with either a high dose of naltrexone or a low dose of naltrexone to determine whether naltrexone influences disease course.

Zagon described the project as follows:

This research project raises the question of whether endogenous opioids and opioid receptors influence the course of MS. This is a novel and innovative concept that is valuable to explore. To test this hypothesis, we will subject [rodents] to experimental autoimmune encephalomyelitis (EAE), a model that mimics MS. Animals will be treated daily with a high dose of [naltrexone] (HDN) or a low dose of [naltrexone] (LDN)....Our expectations are that continuous opioid receptor blockade will exacerbate the progression of MS, whereas a low dose of naltrexone will retard the course of this disease.

Evidence for the involvement of endogenous opioids and opioid receptors in MS will open a new field of research related to the pathogenesis of this disease, and will contribute to the development of strategies for treatment.

Dr. Zagon's expectations were met, as is clear in the titles of the two poster presentations, which he gave to the World Congress on Treatment and Research in Multiple Sclerosis, held in September 2008 in Montreal, Canada. The actual data still awaited journal publication at that date.

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

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