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LOW DOSE NALTREXONE

Contents

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What is low-dose naltrexone and why is it important?

> Low-dose naltrexone holds great promise for the millions of people worldwide with autoimmune diseases or central nervous system disorders or who face a deadly cancer.

> In the developing world, LDN could provide the first low-cost, easy to administer, and side-effect-free therapy for HIV/AIDS.

Naltrexone itself was approved by the FDA in 1984 in a 50mg dose for the purpose of helping heroin or opium addicts, by blocking the effect of such drugs. By blocking opioid receptors, naltrexone also blocks the reception of the opioid hormones that our brain and adrenal glands produce: beta-endorphin and metenkephalin. Many body tissues have receptors for these endorphins and enkephalins, including virtually every cell of the body's immune system.

In 1985, Bernard Bihari, MD, a physician with a clinical practice in New York City, discovered the effects of a much smaller dose of naltrexone (approximately 3mg once a day) on the body's immune system. He found that this low dose, taken at bedtime, was able to enhance a patient's response to infection by HIV, the virus that causes AIDS. *[Note: Subsequently, the optimal adult dosage of LDN has been found to be 4.5mg.]*

In the mid-1990's, Dr. Bihari found that patients in his practice with cancer (such as lymphoma or pancreatic cancer) could benefit, in some cases dramatically, from LDN. In addition, people who had an autoimmune disease (such as lupus) often showed prompt control of disease activity while taking LDN.

First Study of LDN Published in US Medical Journal

Dr. Jill Smith's original article, "Low-Dose Naltrexone Therapy Improves Active Crohn's Disease," in the January issue of the *American Journal of Gastroenterology* (2007;102:1–9), officially presents LDN to the world of scientific medicine. 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 treatment to some degree. She concluded that "LDN therapy appears effective and safe in subjects with active Crohn's disease."

How does LDN work?

> LDN boosts the immune system, activating the body's own natural defenses.

Up to the present time, the question of "What controls the immune system?" has not been present in the curricula of medical colleges and the issue has not formed a part of the received wisdom of practicing physicians. Nonetheless, a body of research over the past two decades has pointed repeatedly to one's own endorphin secretions (our internal opioids) as playing the central role in the beneficial orchestration of the immune system, and recognition of the facts is growing.

Witness these statements from a review article of medical progress in the November 13, 2003 issue of the prestigious New England Journal of Medicine: "Opioid-Induced Immune Modulation: .... Preclinical evidence indicates overwhelmingly that opioids alter the development, differentiation, and function of immune cells, and that both innate and adaptive systems are affected.[1,2] Bone marrow progenitor cells, macrophages, natural killer cells, immature thymocytes and T cells, and B cells are all involved. The

relatively recent identification of opioid-related receptors on immune cells makes it even more likely that opioids have direct effects on the immune system.[3]"

The brief blockade of opioid receptors between 2 a.m. and 4 a.m. that is caused by taking LDN at bedtime each night is believed to produce a prolonged up-regulation of vital elements of the immune system by causing an increase in endorphin and enkephalin production. Normal volunteers who have taken LDN in this fashion have been found to have much higher levels of beta-endorphins circulating in their blood in the following days. Animal research by I. Zagon, PhD, and his colleagues has shown a marked increase in metenkephalin levels as well. *[Note: Additional information for Dr. Zagon can be found at the end of this page.]*

Bihari says that his patients with HIV/AIDS who regularly took LDN before the availability of HAART were generally spared any deterioration of their important helper T cells (CD4+).

In human cancer, research by Zagon over many years has demonstrated inhibition of a number of different human tumors in laboratory studies by using endorphins and low dose naltrexone. It is suggested that the increased endorphin and enkephalin levels, induced by LDN, work directly on the tumors' opioid receptors — and, perhaps, induce cancer cell death (apoptosis). In addition, it is believed that they act to increase natural killer cells and other healthy immune defenses against cancer.

In general, in people with diseases that are partially or largely triggered by a deficiency of endorphins (including cancer and autoimmune diseases), or are accelerated by a deficiency of endorphins (such as HIV/AIDS), restoration of the body's normal production of endorphins is the major therapeutic action of LDN.

What diseases has it been useful for and how effective is it?

> Bernard Bihari, MD, as well as other physicians and researchers, have described beneficial effects of LDN on a variety of diseases:

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**

Autoimmune

Neurodegenerative:

- **ALS (Lou Gehrig's Disease)**
- **Alzheimer's Disease**
- **Autism Spectrum Disorders**
- **Hereditary Spastic Paraparesis**
- **Multiple Sclerosis (MS)**
- **Parkinson's Disease**
- **Post-Polio Syndrome**
- **Post-Traumatic Stress Disorder (PTSD) ⇉**
- **Primary Lateral Sclerosis (PLS)**
- **Progressive Supranuclear Palsy**
- **Transverse Myelitis**

Other Autoimmune Diseases:

- Pancreatic Cancer
- Prostate Cancer (untreated)
- Renal Cell Carcinoma
- Throat Cancer
- Uterine Cancer

Other Diseases

- Common Colds (URI's)
- Emphysema (COPD)
- HIV/AIDS
- Depression (Major; and Bipolar)
- Lyme Disease (LATE Stage)
- Ankylosing Spondylitis
- Behcet's Disease
- Celiac Disease
- Chronic Fatigue Syndrome
- CREST syndrome
- Crohn's Disease
- Dermatomyositis
- Dystonia
- Endometriosis
- Fibromyalgia
- Hashimoto's Thyroiditis
- Irritable Bowel Syndrome (IBS)
- Myasthenia Gravis (MG)
- Nephrotic Syndrome
- Pemphigoid

> LDN has demonstrated efficacy in thousands of cases.

Cancer. As of mid-2004, Dr. Bihari reported having treated over 300 patients who had a cancer that had failed to respond to standard treatments. Of that group, some 50%, after four to six months treatment with LDN, began to demonstrate a halt in cancer growth and, of those, over one-third have shown objective signs of tumor shrinkage.

Autoimmune diseases. Within the group of patients who presented with an autoimmune disease (see above list), none have failed to respond to LDN; all have experienced a halt in progression of their illness. In many patients there was a marked remission in signs and symptoms of the disease. The greatest number of patients within the autoimmune group are people with multiple sclerosis, of whom there were some 400 in Dr. Bihari's practice. Less than 1% of these patients has ever experienced a fresh attack of MS while they maintained their regular LDN nightly therapy.

HIV/AIDS. As of September 2003, Dr. Bihari had been treating 350 AIDS patients using LDN in conjunction with accepted AIDS therapies. Over the prior 7 years over 85% of these patients showed no detectable levels of the HIV virus — a much higher success rate than most current AIDS treatments, and with no significant side effects. It is also worth noting that many HIV/AIDS patients have been living symptom-free for years taking only LDN with no other medications.

Central Nervous System disorders. Anecdotal reports continue to be received concerning beneficial effects of LDN on the course of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS—Lou Gehrig's disease), and primary lateral sclerosis. Dr. Jaquelyn McCandless has found a very positive effect of LDN, in appropriately reduced dosage and applied as a transdermal cream, in children with autism.

> How is it possible that one medication can impact such a wide range of disorders?

The disorders listed above all share a particular feature: in all of them, the immune system plays a central role. Low blood levels of endorphins are generally present, contributing to the disease-associated immune deficiencies.

Research by others — on neuropeptide receptors expressed by various human tumors — has found opioid receptors in many types of cancer:

- Brain tumors (both astrocytoma and glioblastoma)
- Breast cancer
- Endometrial cancer
- Head and neck squamous cell carcinoma
- Myeloid leukemia
- Lung cancer (both small cell and non-small cell)
- Neuroblastoma and others...

These findings suggest the possibility for a beneficial LDN effect in a wide variety of common cancers.

What dosage and frequency should my physician prescribe?

The usual adult dosage is 4.5mg taken once daily at night. Because of the rhythms of the body's production of master hormones, LDN is best taken between 9pm and 3am. Most patients take it at bedtime.

Notable exceptions:

- People who have multiple sclerosis that has led to muscle spasms are advised to use only 3mg daily and to maintain that dosage.
- For intial dosage of LDN in those patients who have Hashimoto's thyroiditis with hypothyroidism and who are taking thyroid hormone replacement medication, please read Cautionary Warnings, below.

Rarely, the naltrexone may need to be purchased as a solution — in distilled water — with 1mg per ml dispensed with a 5ml medicine dropper. If LDN is used in a liquid form, it is important to keep it refrigerated.

The therapeutic dosage range for LDN is from 1.5mg to 4.5mg every night. Dosages below this range are likely to have no effect at all, and dosages above this range are likely to block endorphins for too long a period of time and interfere with its effectiveness.

> IMPORTANT: Make sure to specify that you do NOT want LDN in a slow-release form (see above).

Are there any side effects or cautionary warnings?

> Side effects:

LDN has virtually no side effects. Occasionally, during the first week's use of LDN, patients may complain of some difficulty sleeping. This rarely persists after the first week. Should it do so, dosage can be reduced from 4.5mg to 3mg nightly.

> Cautionary warnings:

1. Because LDN blocks opioid receptors throughout the body for three or four hours, people using medicine that is an opioid agonist, i.e. narcotic medication — such as Ultram (tramadol), morphine, dextromethorphan, Percocet, Duragesic patch or codeine-containing medication — should not take LDN until such medicine is completely out of one's system. Patients who have become dependant on daily use of narcotic-containing

pain medication may require 10 days to 2 weeks of slowly weaning off of such drugs entirely (while first substituting full doses of non-narcotic pain medications) before being able to begin LDN safely.

2. Those patients who are taking thyroid hormone replacement for a diagnosis of Hashimoto's thyroiditis with *hypo*thyroidism ought to begin LDN at the lowest range (1.5mg for an adult). Be aware that LDN may lead to a prompt decrease in the autoimmune disorder, which then may require a rapid reduction in the dose of thyroid hormone replacement in order to avoid symptoms of *hyper*thyroidism.
3. Full-dose naltrexone (50mg) carries a cautionary warning against its use in those with liver disease. This warning was placed because of adverse liver effects that were found in experiments involving 300mg daily. The 50mg dose does not apparently produce impairment of liver function nor, of course, do the much smaller 3mg and 4.5mg doses.
4. People who have received organ transplants and who therefore are taking immunosuppressive medication on a permanent basis are cautioned against the use of LDN because it may act to counter the effect of those medications.

When will the low-dose use of naltrexone become FDA approved?

> Although naltrexone itself is an FDA-approved drug, the varied uses of LDN still await application to the FDA after related scientific clinical trials.

The FDA approved naltrexone at the 50mg dosage in 1984. LDN (in the 3mg or 4.5mg dosage) has not yet been submitted for approval because the prospective clinical trials that are required for FDA approval need to be funded at the cost of many millions of dollars.

The successful results of the first US medical center research on LDN, an open-label trial that tested the use of LDN in Crohn's disease was presented in May 2006 by Professor Jill Smith of the Pennsylvania State University College of Medicine. The National Institutes of Health has granted $500,000 for Dr. Smith's group to continue the study as a larger placebo-controlled scientific trial of LDN in Crohn's disease.

All physicians understand that appropriate off-label use of an already FDA-approved medication such as naltrexone is perfectly ethical and legal. Because naltrexone itself has already passed animal toxicity studies, one could expect that once testing is able to begin, LDN could complete its clinical trials in humans and receive FDA approval for one or more uses within two to four years.