Autoimmune Disease and Low Dose Naltrexone

There is growing recognition in the scientific community that autoimmune diseases result from immunodeficiency, which disturbs the ability of the immune system to distinguish ‘self’ from ‘non-self’. The normalization of the immune system induced by LDN makes it an obvious candidate for a treatment plan in such diseases.

The experience of people who have autoimmune diseases and who have begun LDN treatment has been remarkable. Patients with diagnoses such as systemic lupus, rheumatoid arthritis, Behcet’s syndrome, Wagener’s granulomatosis, bullous pemphigoid, psoriasis, and Crohn’s disease have all benefited.

Because LDN clearly halts progression in multiple sclerosis, its use has been more recently extended to other neurodegenerative diseases, such as Parkinson’s disease and amyotrophic lateral sclerosis (ALS or Lou Gehrig’s disease) whose etiology remains unknown but for which there is suggestive evidence of a possible autoimmune mechanism.

In addition, people with fibromyalgia and chronic fatigue syndrome have had marked improvement using LDN, suggesting that these entities probably have an important autoimmune dynamic as well.

Parkinson’s disease

As of September 2003, Dr. Bihari reported that there were seven patients with Parkinson’s disease (PD) in his practice, all of whom have shown no progression since beginning LDN. Indeed, two of them have shown clear evidence of improvement in signs and symptoms.

Two people with PD, the first patients with that disorder known to have been treated with LDN, have had good results that persist after more than two years on LDN. One patient, a man in his mid-60’s from New Jersey, had his first annual revisit to Dr. Bihari for a
check-up in April 2002. His wife reported that, in contrast to all the other members of his PD monthly group meeting, he seemed to have shown no deterioration in his functional abilities throughout the prior year. On a thorough neurological examination, Dr. Bihari found improvement in some signs of his Parkinson’s disease. Among these was now the absence of the glabellar sign, a primitive reflex that is consistently found in those with PD and which the patient had demonstrated the year before on his initial examination.

Another patient with PD is a 48-year-old male who began LDN in December 2000. Because he was seeing no improvement in his condition (although he was not getting any worse), he discontinued LDN in early March 2002. He called Bihari in mid-May 2002 because he was now beginning to see, for the first time in over a year, worsening of his PD symptoms. In those three months, the disease manifested increased tremor and rigidity in the involved arm. He resumed LDN and over the following two months experienced reversal of the progression that had occurred off of the drug. He was also able to reduce his dopamine-analogue medication by two-thirds, relieving the depression that it was producing.

**Amyotrophic Lateral Sclerosis**

In the spring of 2002, several people with amyotrophic lateral sclerosis, asked their physicians to prescribe LDN for their ALS. Two patients with advanced disease showed significant improvement in their breathing, as measured by a forced vital capacity (FVC). One had a 25% improvement within two months of beginning LDN and the other 11% improvement. A third patient who also has advanced ALS and an impaired FVC has had significant subjective improvement in his ability to breathe and a reduction in his resting pulse from 96 to the low 80’s.

Subsequently, in early fall 2002, the first patient, who had been taking only 3mg of LDN nightly, notified us that both his FVC and that of the second patient, who was using the 4.5mg dose, had reverted to
their usual baseline capacities, but that their FVC's appeared to be remaining stable for a prolonged period.

Note: Given the repeated demonstration of LDN’s efficacy in halting progression in virtually all cases of MS (see LDN and MS), and the possibility of its having a therapeutic effect in Parkinson’s Disease and in ALS, it may be timely to consider LDN in treating the full spectrum of neurodegenerative diseases whose etiology is unknown—all of which may well have a significant underpinning of immunodeficiency/autoimmunity causing their neurological syndromes. Alzheimer’s disease also suggests itself as an important possibility.

Crohn’s Disease

As of September 2002, Dr. Bihari was following eight patients with Crohn’s Disease on LDN. In all eight cases, within 14-21 days the signs and symptoms of disease activity stopped. All eight had remained stable since anywhere from 2 months to 36 months.

Rheumatoid Arthritis

Ten patients with this disease have been treated with LDN in recent years. In all ten patients the joint pain and swelling cleared, in some, leaving residual joint distortion. Two of the patients stopped LDN for several weeks because of travel. Both had an immediate exacerbation. One patient who was responding well on LDN had a mild exacerbation during a period of severe marital stress.

Pemphigoid

A 82-year-old woman who, over a period of three months, developed blisters on her ankles, the soles of her feet, her arms and her neck, which on biopsy proved to be pemphigoid. She was referred to a dermatologist specializing in this disease who treated her with prednisone 40 mg/day, which slowed disease progression but did not clear her blisters. When LDN was added by Dr. Bihari, her blisters cleared and slowly healed over a 6-week period, during which time she slowly tapered her prednisone. On her last visit, she was on both
LDN each night and prednisone 5mg every other day with no exacerbation.

**Background**

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.

*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.

*[Note: Optimal adult dosage of LDN has been found to be 4.5mg.]*

**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.”
Endoscopic improvement in Crohn’s Colitis with Naltrexone

Figure A: Shown is the rectum of a subject with active Crohn’s Disease before starting therapy with naltrexone 4.5 mg/day. The mucosa is ulcerated, edematous, and inflamed.

Figure B: Shows the same area of the rectum in the same patient four weeks after naltrexone therapy. The lining is now healed, ulcers resolved, and the mucosa is healthy.

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. 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.”

www.healthoracle.org
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.

Dr. 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 Dr. 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:

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<th>Cancers:</th>
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<td>• Bladder Cancer</td>
<td>• ALS (Lou Gehrig's Disease)</td>
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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
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
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, 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 have 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.

**IMPORTANT:** LDN in a ‘slow-release’ or ‘time-release’ form has proved to be ineffective.

Unless the low dose of naltrexone is in an unaltered form, which permits it to reach a prompt ‘spike’ in the blood stream, its therapeutic effects may be inhibited.

*Fillers.* Capsules of LDN necessarily contain a substantial percentage of neutral inactive or active filler. Experiments by the compounding pharmacist, Dr. Skip Lenz, have demonstrated that the use of
calcium carbonate as a filler will interfere with absorption of the LDN capsule. Therefore, it is suggested that calcium carbonate filler not be employed in compounding LDN capsules.

What is the dosage and frequency?

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 initial 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 1.75mg 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.

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, 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 hypothyroidism 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 hyperthyroidism.

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.

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.

What You Can Do

Cancer. Anyone with cancer or a pre-cancerous condition should consider LDN. Many use LDN as a preventive treatment. Post-treatment, others have been using LDN to prevent a recurrence of their cancer. LDN has been shown in many cases to work with virtually incurable cancers such as neuroblastoma, multiple myeloma, and pancreatic cancer.

HIV/AIDS. As an AIDS drug, LDN leads to far fewer side effects than the standard ‘AIDS cocktail.’ When used in conjunction with HAART therapies, LDN can boost T-cell populations; prevent disfiguring lipodystrophy, and lower rates of treatment failure.

Low-dose naltrexone has the potential to reduce the terrible human loss now taking place throughout the globe. It is a drug that could be a powerful ally in the war against cancer.

For more information:

www.lowdosenaltrexone.org

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