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The Uses of Low-Dose Naltrexone in Clinical Practice [6]

Potential benefits for a wide range of conditions

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Abstract

The purpose of this paper is to review low-dose naltrexone (LDN) for use in clinical practice. The known or theoretical mechanism of action of LDN, clinical research findings in relation to various medical conditions including pain, autoimmune conditions, cancer, and mood disorders will be discussed. Recommended doses and forms of LDN will also be summarized.

Introduction

Naltrexone, in oral form, was patented by Endo Laboratories in 1967 and approved by the US Food and Drug Administration (FDA) in 1984 for the treatment of opioid addiction.[1] Referred to in early research as "ENDO1639A," the drug would become what we know as naltrexone. In recent years, the use of buprenorphine and methadone have been recommended over naltrexone to reduce undesirable side effects and/or counter the effect of morphine partly due to lack of patient compliance with naltrexone.[2]

The use of oral naltrexone for opioid addiction requires detoxification from the opioid drug and has been associated with low adherence and high level of relapse back to opioid use after discontinuation of naltrexone.[3,4] The typical daily oral dose of naltrexone is 50 mg but may vary depending on the addiction. An extended-release injectable naltrexone that only needs to be administered every 4 weeks is now available. This new method of naltrexone treatment produces better compliance rates in opioid-addicted individuals.[5]

Low-dose naltrexone was first used clinically in 1985 by Bernard Bihari, MD, a Harvard University physician and Director of the Division of Alcoholism and Drug Dependence, SUNY/Health Science Center at Brooklyn. He became the City Addiction Commissioner of New York in 1974 and continued working with drug addicts at the New York City Health Department and King's County Hospital in Brooklyn, New York. Given his posts, he was steeped in the upcoming use of drugs such as methadone and naltrexone to treat addictions. He was aware of data indicating that naltrexone led to immune effects, an observation that was merely incidental to its approved use. In 1984, Bihari observed the

therapeutic effects of the use of full-dose naltrexone (50 mg/dose) when given to heroin addicts. While naltrexone successfully blocked heroin's ability to bind the opioid receptors, the complete blockage led to side effects so severe that the former addicts would not comply with continued use. Side effects such as severe anxiety, depression, irritability, and sleep disturbance hampered the adoption of naltrexone for long-term use.[6]

Meanwhile, while working for the Public Health Department in New York City in 1985, Bihari naturally became worried about the human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic that was surfacing. He turned his research attention and his knowledge of naltrexone's effect on the immune system in that direction. Realizing that naltrexone's effects included increasing endorphins—and that this raises immune competence—he began research into the use of naltrexone for the HIV-positive (HIV+)/AIDS population. He began with testing innate endorphin levels in individuals with HIV+/AIDS and found they were low in endorphin production compared to patients who did not have AIDS.[7]

> Unlike higher doses of naltrexone, LDN acts on β-endorphin receptors to stimulate the release of endorphins in the body.

In an effort to find the minimal dose of naltrexone needed to raise endorphins, Bihari and his colleagues did a dose-ranging study comparing 50, 20, 10, 5 and 3.0 mg of naltrexone.[6] They found that while all of these doses raised endorphins equally, a dose as low as 1.0 mg had no effect on endorphins. He then compared various doses of LDN between 1.75 and 4.5 mg and verified that a dose of 3.0 mg of LDN increased levels of endorphins during the night and even throughout the next day.[8,9] At the International AIDS Conference in 1988 Bihari reported fewer opportunistic infections in a group of AIDS patients using LDN as compared to the placebo group. He also found a reduction in the level of interferon-alpha (IFN-α) in those taking the LDN.[10] Increased levels of IFN-α have been implicated in comorbidities in HIV patients such as vascular and kidney disease.[11] In addition, patients with HIV infections often have reduced levels of CD4+ T cells. Bihari found that CD4+ T cells did not decrease in patients who received LDN, compared to the placebo group (who were not treated with LDN). These findings and other clinical trials led to the approval of LDN in April 2016 for management of HIV patients in the country of Nigeria by the National Agency for Food and Drug Administration and Control (NAFDAC),[12] Nigeria's equivalent to the US Food and Drug Administration (FDA).

The FDA has not approved LDN for use for any medical conditions in the United States at doses below 5.0 mg, so it is only available from compounding pharmacies.

Mechanism of Action

Several mechanisms of action of LDN have been reported in the literature. The following are 3 of the most prominent actions of LDN: 1) action on opioid receptors to increase release of β-endorphins; 2) ability to reduce pro-inflammatory cytokines and increase anti-inflammatory cytokines; and 3) regulation of the opioid growth factor (OGF)/opioid growth factor receptors (OGFr) axis.

Endorphin production and opioid receptor activation

Bihari stated in his research that endogenous endorphins were released in the body between 2:00 am and 4:00 am; however, other research has shown that beta (β)-endorphins are released in healthy adults between 4:00 am and 10:00 am.[13] Beta-endorphins bind to mu (μ) opioid receptors. This interaction between β-endorphins and μ receptors is thought to be responsible for the analgesic effects in the body.[14] The word endorphin comes from the term “endogenous morphine.” Endorphins are found in the human body originating from the amino acid L-tyrosine and the methyl group of L-methionine.[15]

Morphine, the drug, is the exogenous equivalent to our own endogenous opioids. Morphine is derived from the opium poppy plant *Papaver somniferum* and has been used for many years for its analgesic properties.[16] Endogenous morphine has been found in the adrenal gland, and secretion from the liver has been shown to increase following physical stress such as sepsis and surgery.[17-19] In addition to increased levels of endogenous morphine following physical stress, levels of anti-inflammatory cytokines are released as a response to stresses such as surgery.

As mentioned, naltrexone in higher doses is classified as an opioid receptor antagonist and blocks the receptors to counteract the side effects of medication like morphine. Higher doses of naltrexone have also been shown to blunt the release of endorphins following physical activity.[20] Unlike higher doses of naltrexone, LDN acts on β-endorphin receptors to stimulate the release of endorphins in the body.[21] Low-dose naltrexone is still considered an opioid receptor antagonist, but only for a short duration, and research has shown that LDN increases levels of endogenous opioids.[22] In addition, LDN stimulates the body’s own production of endorphins, even after the LDN is no longer in the system. In a 2008 study, researchers found elevations in endorphins even 1 month after discontinuation of LDN doses of less than 5.0 mg.[23] So, the analgesic effects attributed to LDN, in part at least, most likely come from its ability to stimulate β-endorphin release in the body.

Anti-inflammatory activity

The increase of β-endorphins to reduce pain levels is only one aspect of the use of LDN in pain management, especially when the source of the pain is related to an inflammatory process. It has been shown that LDN reduces inflammation by reducing multiple pro-inflammatory cytokines.[24] Cytokines are chemical messengers, often made by immune cells, whose net effect can be to either increase or decrease immune function. The coordination of the immune system rests on the body's ability to keep a balance between cytokines that promote inflammation and those that reduce it. Cytokines are produced by various cells in the body and are associated with the physiologic experience of pain.[25] However, the cytokine system isn’t simple. For example, tumor necrosis factor alpha (TNF-α) is associated with both increased inflammation and neuroprotection when the body is presented with an insult such as nerve damage.[26,27] Excess synthesis or upregulation of TNF-α is associated with certain conditions such as cerebral ischemia, Alzheimer’s disease, and atherosclerosis, and reducing levels of this cytokine may be of benefit in treatment.[28,29]

In an 8-week single-blinded pilot study using 4.5 mg of LDN each night, serum levels of

numerous proinflammatory cytokines including interleukin (IL)-1, IL-2, IL-12, IL-18, interferon gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), and TNF-α were significantly reduced when compared to baseline in patients suffering from fibromyalgia.[30]

Regulation of the opioid growth factor

Low-dose naltrexone has been shown to upregulate the OGF/OGFr axis. Opioid growth factor is an opioid peptide also known as [Met^5]-enkephalin. The name was changed to OGF due to the association of [Met^5]-enkephalin with growth and cell proliferation. Cell growth cycles are classified as G1 (before DNA synthesis), S (DNA synthesis), G2 (before mitosis), and M (mitosis or cell division). OGF has been found to delay the G1/S phase of cell growth.[31,32] In addition, there is evidence that the OGF/OGFr axis pathway is involved in the regulation of tumor growth.[33] The use of LDN to regulate this pathway is of interest in cancer research and in the treatment of neurodegenerative diseases such as multiple sclerosis.[34,35] In addition, research has shown that cell proliferation is altered when OGF binds to the OGF receptors. When the OGF/OGFr axis pathway is upregulated, tumor growth may be decreased.[36]

The treatment of pain is a complex challenge and can benefit from an approach that includes attention to both biological and psychological aspects of a patient's symptoms. Healthcare practitioners have multiple tools available when facing the challenge of pain management. Treating the symptoms of pain using LDN as a monotherapy does not always work; however, if the patient's condition is highly inflammatory (eg, rheumatoid arthritis) using LDN can be extremely helpful by itself.[37]

Of course, the use of opioids in this country has risen to an unprecedented level. It was reported in 2016 that 90 individuals die of opioid overdose in this country each day.[38] The model of using a low dose of an opioid antagonist such as LDN is paradoxical. The benefit of using LDN for pain management has its foundations in the ability of this formulation to increase endogenous endorphins and decrease pro-inflammatory cytokines.

There have been several published articles on the use of LDN in patients suffering from fibromyalgia. In a 2013 placebo-controlled, crossover pilot study involving 31 women with fibromyalgia, a 4.5 mg dose of LDN at bedtime reduced daily pain levels (P=0.016) and improved mood (P=0.039) and overall reported quality of life (P=0.045). In this study, neither sleep nor fatigue improved.[39] However, in a study conducted in 2009 by the same researchers, the same dose of LDN reduced pain levels and improved symptoms of fatigue (P=0.008) and stress (P=0.003) in 10 women with fibromyalgia.[40]

Autoimmune Conditions

Some of the more prevalent autoimmune conditions conducive to LDN therapy include rheumatoid arthritis (RA) and inflammatory bowel disease (predominately Crohn's disease). Many autoimmune conditions present quite a challenge to physicians. Based on the scientific literature, LDN can offer a good option for those seeking pain relief along with a low side effect profile for some autoimmune conditions.

Rheumatoid arthritis is an autoimmune condition characterized predominantly by joint pain. Although not always present, this condition is frequently associated with a positive rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) antibodies. Proinflammatory cytokines such as TNF-α and some interleukins such as IL-1 are often associated with RA. Using TNF inhibitors has been an option for treatment; however, in patients for whom treatment is unsuccessful, researchers have found elevated T-helper type 17 (Th17) cells, which do not respond to this therapy.[41] Inhibitors of TNF include medications such as adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade). Other options for treating RA include nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, steroids such as prednisone, disease-modifying antirheumatic drugs (DMARDs) like methotrexate, and biological agents like the TNF inhibitors. T-helper 17 cells are responsible for the production of IL-17, a proinflammatory cytokine. In general, Th1/Th17 type cells are considered pro-inflammatory and Th2/regulatory T cells (Tregs) are anti-inflammatory. T-helper 2 activity has been shown to be reduced in patients with RA.[42] To further explore the effectiveness of LDN on inflammatory conditions, clinical trials are currently ongoing to study the effects of LDN on adults with osteoarthritis and inflammatory arthritis.[43]

Crohn's disease is characterized by abdominal pain, severe diarrhea, fatigue, weight loss, and malnutrition. It is considered an autoimmune disease because of the presence of serum and mucosal autoantibodies acting against intestinal epithelial cells. Results from research using LDN on patients with Crohn's Disease have been mixed. In a 2014 article published in the *Cochrane Data Base of Systematic Reviews*, the authors stated that there was "insufficient evidence to allow any firm conclusions regarding the efficacy and safety of LDN used to treat patients with active Crohn's disease."[44] This conclusion was based on 2 cited studies in which there was a significant positive clinical response; however, according to the authors of the Cochrane review, the number of remissions was not significant. In the one study mentioned, 25% of the 12 pediatric patients studied achieved clinical remission and 67% had a significant positive response to LDN therapy. In reviewing the actual study, which was called a "pilot study," the authors conceded that the small sample size was a weakness. Also of note, the dose of LDN was based on body weight (0.1 mg/kg, up to 4.5 mg) and not a standard dose (eg, 4.5 mg).[45] An adult study of the use of LDN on 17 patients with Crohn's disease showed a 67% remission rate and a significant improvement in Crohn's Disease Activity Index (CDAI) scores. In addition, both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were significantly reduced (P=0.03).[46]

Multiple sclerosis (MS) is an autoimmune disease that damages myelin, the protective sheath that covers nerve fibers. The most common type of MS is called relapsing-remitting because it cycles between periods of remission and active destruction. Because there is no cure for MS, the focus of treatment is to reduce inflammation and slow the progression of the disease. Corticosteroids are used to reduce inflammation and a class of drugs known as disease-modifying therapies (DMTs) is used to try to slow the progression. Disease-modifying therapies include interferon beta (IFNB) 1-a and 1-b, glatiramer acetate (GA), mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, and alemtuzumab.[47,48] Researchers have found that a larger number of IL-17 cells are found in the cerebrospinal fluid of patients suffering from MS compared to other noninflammatory neurological diseases. The inflammatory role of IL-17 cells is also important in Parkinson's Disease and Alzheimer's Disease.[49] In addition, TNF-α, IFN-γ, and IL-1b have been

shown to play a major role in neurodegenerative conditions, including MS.[27]

A retrospective study published in 2016 reviewed medical records from patients with relapsing-remitting MS who used either LDN only or LDN with glatiramer acetate, over a 10-year period (2006-2015). The study compared 3 parameters between the groups: laboratory values (eg, kidney function, liver enzymes); time to walk a 25-foot course unassisted; and changes in the brain based on MRI. Researchers concluded that there was no significant difference in the group that was treated with LDN alone vs those using the combination of LDN and glatiramer acetate.[50] Even though there was no difference between the 2 groups, the authors concluded that LDN should be considered when treating MS patients because of the low cost. The average annual cost of LDN is around $212 per patient, while the annual cost of DMTs ranges from $41,078 to $53,032 per patient.[51]

Cancer

To this author's knowledge, there have not been any randomized clinical trials on the use of LDN as a monotherapy, or adjunctive therapy, for the treatment of cancer. However, there have been case reports, theoretical research, and in vitro studies.[52,53] An in vitro study of triple-negative breast cancer (TNBC) cells revealed that the OGF/OGFr axis is diminished in these tumor cells. Since enhancing this pathway has been shown to have an inhibitory effect on cancer cells, LDN, which upregulates the OGF/OGFr axis, may offer some benefit in treating cancer such as TNBC.[33] Triple-negative breast cancer is usually a more aggressive type of breast cancer with a poor prognosis. Because the cancer does not respond to hormone-based therapies, LDN is worth investigating for viability as an adjunctive therapy for TNBC.

In an attempt to determine the effects of modulating the OGF/OGFrc axis on cancer outcomes, researchers at Penn State College of Medicine studied the effects of infused OGF on patients with advanced unresectable pancreatic cancer and found that OGF increased survival time and, in 2 cases, resolved liver metastases.[54] Another study looked at the use of OGF in patients failing standard chemotherapy for pancreatic cancer. Patients who received OGF therapy had a threefold increase in survival time compared to those who did not receive OGF therapy. In addition, patients on OGF therapy had significantly elevated blood levels of enkephalin after a month of treatment.[55] Because LDN upregulates the expression of OGF and OGFr, these same researchers are exploring the use of LDN in the treatment of ovarian, pancreatic, and other types of cancer.[56] There have also been 2 published reports (in 2006 and 2009) of long-term survival using LDN and infused alpha-lipoic acid in patients suffering from pancreatic cancer.[52,53]

In a study published in 2016, researchers compared standard doses of naltrexone with LDN on various genes involved in cell turnover. They found that genes responsible for apoptosis were upregulated by LDN but not by standard doses of naltrexone.[57] In an in vitro study using ovarian cancer cells, investigators were able to demonstrate that LDN inhibited tumor growth when used with the chemotherapeutic agent cisplatin.[35]

Depression

There are no clinical studies evaluating the effectiveness of LDN as a monotherapy for depression. LDN has been studied, however, in patients with a history of using dopamine-enhancing medication for depression with history of relapse. Many factors are involved in the relapsing of major depressive disorders, and trying to develop ways to prevent relapses is a challenge.[58] In a small study of 12 individuals using dopamine-enhancing medications for depression, the addition of 1.0 mg of LDN 2 times a day for 3 weeks appeared to improve relapsing symptoms of depression. Scores on the Hamilton Depression Rating Scale fell, on average, from 21.2 (severe depression) to 11.7 (mild depression) in patients who were on LDN.[59]

Dissociative Disorders and Post-Traumatic Stress Syndrome

There is limited information, mostly from case studies, on the use of LDN for post-traumatic brain injury syndrome and post-traumatic stress syndrome. One published study looked at using 2.0 to 6.0 mg of LDN when working with individuals with a history of repetitive, prolonged childhood trauma such as sexual abuse or cruelty. According to the author of the study, Wiebke Pape, MD, most of the people suffered from dissociative disorder, which she described at the 2017 LDN conference as the act of “shutting down” or where the “brain goes blank.” Of the 12 inpatients studied with LDN, most reported favorable benefits of taking LDN, including better regulation of traumatic memories and reduction of self-destructive impulses.[60,61]

Dosing Recommendations and Methods of Delivery

The recommended dose of LDN is typically 0.5 mg at bedtime for several weeks, followed by 0.5 to 1.0 mg incremental increases over a 1- to 3-month period. When using LDN for pain management, a thorough patient evaluation prior to each dosage increase is important. A thorough medical history including medications, nutritional supplements, and herbal formulas must be obtained before any LDN prescription. The decision to prescribe LDN as an adjunct to chemotherapy or other molecular or biologic agents for cancer treatment should be a joint decision that involves the prescribing physician, the oncologist, and the patient.

If a patient is at the typical maximum dose of 4.5 mg and symptoms return, the clinician should consider reducing or discontinuing LDN for 1 to 2 weeks, then reinitiating medication at a lower dose and building back up to a maximum effective dosage. When inflammatory markers are used to diagnose or follow a patient’s progress (eg, ESR, CRP) it is important to track these levels and correlate them with changes in symptomatology.

Oral use

Capsules and tablets can be prepared in any prescribed dose but the most common is 0.5 to 4.5 mg, typically taken at bedtime. Be sure to ask the pharmacist what fillers are used because patients might be sensitive to such things as lactose. Also, the size of the capsule can vary from pharmacy to pharmacy and many patients prefer the smallest capsule available. Tablets are usually very small and well-tolerated by patients, but not all pharmacies distribute tablets. Liquids or sublingual preparations can be made for those who want or need to avoid using capsules or tablets. Typical solutions are a 1.0 mg LDN per 1.0 mL glycerol solution. Liquids are often preferred over capsules or tablets for young

children, or adults with swallowing difficulties.

Most LDN is prescribed at bedtime; however, if patients report nightmares, then taking the dose in the morning can be an alternative. Vivid dreams are the most commonly reported side effect in clinical trials but this seems to decrease after a few nights. Another less common side effect is headaches, but these are reported as mild in severity. No side effects of stomach ulcers, renal impairment, or interference with anticlotting medications have been reported in research.[62]

Summary

Considering its low cost and low side effect profile, LDN in oral form has potential clinical utility in the treatment of a wide variety of conditions including inflammatory diseases, fibromyalgia, neurological conditions, cancer, and mood disorders.

About the Author

Timothy Schwaiger, ND, received his naturopathic degree from Southwest College of Naturopathic Medicine in Tempe, Arizona, and completed a 2-year residency there in Family Medicine. Schwaiger recently served as Chief Medical Officer at Bastyr University in California before moving to Prescott, Arizona with his wife, Debra. Schwaiger has been in practice since 1999 and loves being a naturopathic physician. He uses naturopathic modalities as well as an integrative approach to family care, pain management and cancer therapy.

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