

Low Dose Naltrexone (LDN)

Naltrexone is a drug that blocks the effect of morphine and other related drugs. It is usually prescribed for treating addictions to 'opiate' drugs such as heroin or morphine. The dose used for this purpose is usually between 50 and 300mg daily. The standard available form of naltrexone is a 50mg tablet.

However, using very small doses of naltrexone (less than a tenth of the standard 50mg tablet) has been found to be helpful in treating a number of clinical conditions. In this form it is referred to as Low-Dose-Naltrexone (LDN). LDN has been used mainly in the treatment of autoimmune diseases and cancer in the USA since 1985, but is relatively new in the United Kingdom and Europe. This form of treatment was developed by the late Dr Bernard Bihari, a neurologist from New York, USA.

How does LDN work?

How LDN works is poorly understood. The benefits of the drug are possibly due to the temporary blocking of the body's natural painkillers, known as endorphins. This results in a reactive increase in the production of endorphins when the LDN wears off. Increased levels of endorphins are thought to stimulate the immune system, increasing in the number of a particular type of white cells called T-lymphocytes. This increase in T-cell numbers apparently restores a more normal immune function, so that the effects of the disease process are significantly reduced. It may also act directly on these immune cells to stimulate or restore normal function.

There is also research showing that naltrexone improves the immune system by acting on a Toll-Like Receptor called TLR4. Several published papers have shown that naltrexone binds to the TLR4 receptor and blocks the formation of unnecessary inflammation.

What dose of LDN is recommended?

The therapeutic dosage range for LDN is from 1.5mg to 4.5mg daily. It is usual to start treatment at an ultra-low dose and increase this gradually over a period of weeks, until you are stable and side-effect free. The usual adult starting dose is 1mg a day, increasing by 1.0mg each week, to a maximum of 4.5mg a day. However, some patients with Chronic Fatigue Syndrome or Fibromyalgia who are severely affected, the starting dose is usually 0.5mg, and it is increased by 0.5mg a week until 4.5mg is reached.

Possible side effects of LDN

Many patients who start LDN do not experience any side effects at all. Initially, however, your symptoms may become worse. In MS, it can cause increased fatigue, or increased spasticity. In CFS/ME, this can cause the onset of apparent 'flu like symptoms'. LDN can occasionally cause sleep disturbances. These disturbances can take the form of vivid dreams, or insomnia. Taking LDN at night is often recommended, but there are many patients who take it in the morning and still get excellent benefits.

In various studies, the number of T-lymphocytes has been shown to dramatically increase when a patient starts on LDN. This may account for some of the benefits patients feel when they are being treated for an autoimmune disease or cancer. In less than five percent of cases treated, increased introductory symptoms may be more severe or more prolonged than usual, lasting sometimes for several weeks. Rarely, symptoms may persist for two or three months before the appropriate beneficial response is achieved. If side effects are troublesome, then reducing your dose by 0.5mg for 7 days, before increasing it again, can be helpful.

Very rarely, some patients experience gastro-intestinal side effects, such as nausea and/or constipation or diarrhea. The reason for this is currently unknown, but may be due to the presence of large numbers of TLR4 receptors in the gut. Patients who have these side effects should increase their dose by no more than 0.5mg per week, and should consult with their GP or pharmacist for appropriate treatment, if necessary.

Contraindications and special precautions

LDN is compatible with most other drugs. However, there are interactions with the following:

- Immunosuppressant steroids (> 20mg prednisolone equivalent daily)
- Opiate medications (Morphine, Codeine, Tramadol, Oxycodone, and similar)
- Certain antidepressants (Monoamine Oxidase Inhibitors)
- Interferon alpha and beta.
- Gilenya
- Any immunomodulator medication, such as Azathioprine or Sulfasalazine.
- Warfarin
- Heparin (Clexane)
- Anti-epilepsy medications, such as Sodium Valproate or "Epilim".
- Certain anti-cancer chemotherapies – i.e. Fluorouracil, Cisplatin.
- Anti-TNF medications (tumor necrosis factor)
- Clozapine

If you are taking any of these drugs, or drug classes, you must be sure that the prescribing doctor is aware of the fact. You may need added blood tests during treatment.

1. Because LDN blocks opioid receptors throughout the body for three or four hours, people using a medicine that is an opioid agonist, ie a narcotic medication, such as tramadol, morphine, Duragesic patch or codeine-containing medication, should not take LDN until such medicine is completely out of the body. Patients who

have become dependant on narcotic-containing pain medication may require 10 days to 2 weeks to 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 *hypothyroidism* ought to begin LDN at the lowest range (1.5mg for an adult). LDN may lead to a prompt decrease in the underlying autoimmune disorder, which then may require a rapid reduction in the dose of thyroid hormone replacement in order to avoid symptoms of *hyperthyroidism*. They should have their thyroxine and TSH levels checked after 28/56 and 84 days if starting LDN.
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. But those with advanced liver or kidney failure should not take LDN.
4. People who 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.
5. Patients with Type 1 insulin dependent diabetes may require alterations to their insulin dose.
6. Patients who are breastfeeding are advised not to take LDN.
7. If you are going into hospital for an operation, LDN should be completely stopped at least 24 hours before the operation. It can be commenced again as soon as you are released from hospital, or on the advice of your doctor.

LDN has been used to treat many conditions, including:

Alzheimer's disease	Irritable Bowel Syndrome (IBS)
Ankylosing spondylitis	Multiple sclerosis
Autistic Spectrum Disorder	Obsessive compulsive disorder (OCD)
Certain cancers (see below)	Parkinson's disease
Celiac disease	Premenstrual syndrome
Chronic Fatigue Syndrome/ME	Polycystic ovary syndrome (PCOS)
Crohn's disease	Polymyalgia rheumatica (PMR)
Chronic obstructive pulmonary disease (COPD)	Psoriasis
Depression	Rheumatoid arthritis
Endometriosis	Sarcoidosis
Fibromyalgia	Scleroderma
HIV/AIDS	Systemic lupus erythematosus (SLE)
Infertility	Ulcerative colitis

Dr Bihari's experience with LDN:

Cancer By 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. Dr Bihari and others have described beneficial effects of LDN on a variety of cancers including:

Bladder Cancer	Malignant Melanoma
Breast Cancer	Multiple Myeloma
Carcinoid	Neuroblastoma
Colon & Rectal Cancer	Ovarian Cancer
Glioblastoma	Pancreatic Cancer
Liver Cancer	Prostate Cancer
Lung Cancer (Non-Small Cell)	Renal Cell Carcinoma
Lymphocytic Leukemia (chronic)	Throat Cancer
Lymphoma (Hodgkin's and Non-Hodgkin's)	Uterine Cancer

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

HIV/AIDS By 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.

Low Dose Naltrexone - Key clinical studies

Compiled by Dr Tom Gilhooly

Low Dose Naltrexone has been the subject of much debate but actually very few clinical trials. Dr Ian Zagon, from Penn State University, has been studying LDN for over 20 years and conducted many preclinical studies investigating LDN in cancer and in the animal model of MS (1,2).

Dr Zagon has also been involved in two clinical studies into Crohn's disease with his colleague Professor Jill Smith from Penn State University. These demonstrated a significant improvement in symptoms and in bowel mucosal appearance with LDN treatment (3,4). In the randomised controlled trial, LDN patients were twice as likely to have a 70 point decline in the Crohn's Disease Activity Index. 78% of the LDN group achieved an endoscopic response compared to 28% with placebo.

Dr Jarred Younger, from Stanford University, has studied LDN in Fibromyalgia, firstly in a small pilot study and more recently in a yet to be published randomised controlled trial. The pilot study showed significant improvement in symptoms of pain in these patients(5).

Multiple sclerosis is one of the conditions in which LDN has been used most frequently. There are three published studies, one in primary progressive MS(6) and two on quality of life (7,8). The results of two studies were positive, with improved quality of life in one and reduced spasm in the PPMS study. The third showed no significant difference between the treatment and placebo groups but found the treatment to be safe. A review of the available studies into LDN and MS was published in 2009 (9).

All studies have confirmed the safety of the drug, and there is enough positive evidence to merit greater investigation.

Key references:

1. Rahn KA, McLaughlin PJ, Zagon IS. Prevention and diminished expression of experimental autoimmune encephalomyelitis by low dose naltrexone (LDN) or opioid growth factor (OGF) for an extended period: Therapeutic implications for multiple sclerosis. *Brain Res*. 2011 Mar 24;1381:243-53. Epub 2011 Jan 20.
2. Donahue RN, McLaughlin PJ, Zagon IS. The opioid growth factor (OGF) and low dose naltrexone (LDN) suppress human ovarian cancer progression in mice. *Gynecol Oncol*. 2011 Aug;122(2):382-8. Epub 2011 Apr 30.
3. Smith JP, Stock H, Bingaman S, Mauger D, Rogosnitzky M, Zagon IS. Low-dose naltrexone therapy improves active Crohn's disease. *Am J Gastroenterol*. 2007 Apr;102(4):820-8. Epub 2007 Jan 11.
4. Smith JP, Bingaman SI, Ruggiero F, Mauger DT, Mukherjee A, McGovern CO, Zagon IS. Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn's disease: a randomized placebo-controlled trial. *Dig Dis Sci*. 2011 Jul;56(7):2088-97. Epub 2011 Mar 8.
5. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. *Pain Med*. 2009 May-Jun;10(4):663-72. Epub 2009 Apr 22.
6. Gironi M, Martinelli-Boneschi F, Sacerdote P, Solaro C, Zaffaroni M, Cavarretta R, Moiola L, Bucello S, Radaelli M, Pilato V, Rodegher M, Cursi M, Franchi S, Martinelli V, Nemni R, Comi G, Martino G. A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis. *Mult Scler*. 2008 Sep;14(8):1076-83.
7. Cree BA, Kornyeveva E, Goodin DS. Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. *Ann Neurol*. 2010 Aug;68(2):145-50.
8. Sharafaddinzadeh N, Moghtaderi A, Kashipazha D, Majdinasab N, Shalbafan B. The effect of low-dose naltrexone on quality of life of patients with multiple sclerosis: a randomized placebo-controlled trial. *Mult Scler*. 2010 Aug;16(8):964-9. Epub 2010 Jun 9.
9. Gilhooly TC. Low-dose naltrexone as a treatment for multiple sclerosis. *British Journal of Neuroscience Nursing* 13 Nov 2009, 5, (11), 494.

For more information about LDN, see the following internet websites:

www.lowdosenaltrexone.org (or to the same site: www.ldninfo.org)

www.ldnresearchtrust.org

www.ldnnow.co.uk

www.dicksonchemist.co.uk

www.prescribe4me.co.uk

And for a number of lectures, talks and presentations about LDN by researchers and clinicians, see:

www.youtube.com/user/TheLDNresearchtrust

Despite all the positive information about LDN, it is important to remember that LDN is not a miracle drug or a cure, and doesn't work for everyone.

Obtaining a prescription for LDN:

Do NOT buy LDN on the internet. There is no guarantee that the drug is genuine or safe.

The only way to safely and legally obtain LDN, is with a registered doctor's prescription.

LDN is prescribable on the NHS on an "individual patient" basis (see the letter below from Mike O'Brien MP, the Minister of State for Health Services, dated 10 March 2010).

Take this factsheet to your NHS GP. But please note that since your NHS GP does not have any requirement to prescribe an unlicensed product such as LDN on the NHS, you may need to see a private doctor for prescriptions.

Prescriptions for LDN will pass for payment on the NHS in Scotland, England, N. Ireland and Wales when written in the following manner:

Liquid form

On the **NHS**, GPs should specify on the prescription:

Rx Naltrexone tablets 50mg

Extemp disp **in pharmacy** to liquid 1mg/1ml

Directions: Take X mls daily at bedtime for 7 days, then increase by 0.5mg/0.5ml a week until taking 4.5mg/4.5ml

Send: 28 days supply (the doctor will need to calculate the volume according to the dosage regime)

Note, a typical starting regime of 1mg for 1 week, then 2mg for 1 week, 3mg for 1 week, 4mg for 1 week, and 4.5mg for a final week, will require 101.5mls, so a suggested dispensed volume would be 105mls.

On a **private** prescription, the doctor should specify:

Rx LDN Liquid 1mg/1ml. Repeat X times"

Directions: Take X mls daily at bedtime for 7 days, then increase by 0.5mg/0.5ml a week until taking 4.5mg/4.5ml

Send: 28days supply (the doctor will need to calculate the volume according to the dosage regime)

(?Also add "Repeat X times")

Note, a typical starting regime of 1mg for 1 week, then 2mg for 1 week, 3mg for 1 week, 4mg for 1 week, and 4.5mg for a final week, will require 101.5mls, so a suggested dispensed volume would be 105mls.

Capsules

For both **NHS and Private** prescriptions:

Rx Low dose Naltrexone capsules 3mg/4.5mg, capsules

Directions: Take one capsule daily at bedtime

Send: 28 days' supply

(?Also add "Repeat X times" if a private prescription)

Prescriptions, whether NHS or Private, should be posted to the following chemist to be dispensed:

Dickson Chemist, Private Rx Dept

35 Mitchell Arcade

Rutherglen

Glasgow

G73 2LS

Tel: 0141 647 8032

(Website: www.dicksonchemist.co.uk)

Please remember to include a cover letter with your prescription, giving them your Name, Address, Postcode, Telephone number, Date of birth, and a list of any other medication you take.

Signed prescriptions may also be faxed **by the signing doctor** to tel: 0141 647 8032, or sent as a scanned email attachment to homedeliverypharmacy@yahoo.co.uk. The signing doctor must also agree in writing with Dicksons that he/she will not provide you with a copy of the prescription (which could be taken to another chemist for dispensing).

When they dispense the LDN, Dicksons will post it directly to your home, usually within 2 working days of receiving the prescription. If you are paying privately, the liquid costs £17.50 for 130mls (ie 4.5mls for 28 days), and capsules £30 for 28 days supply (whether 3mg or 4.5mg). Costs include Royal Mail, 1st Class, 'Recorded Signed For Mail' postage. The first time Dicksons send the prescription to you, they will send you an invoice and you can call them by phone to pay and to register your credit card details with them (for any future prescriptions).

When Dicksons dispense for the NHS, they only charge the NHS £17.50 / £30. Many other pharmacies that may legally dispense LDN may have it made up specially and they have been known to charge the NHS in excess of £150 for 28 days supply. This may end up making the NHS reluctant to pay for it. However, if it is sent to Dicksons, the price charged is so low that the NHS is unlikely to flag it up as a problem item.