LOW DOSE NALTREXONE
LDN FACT SHEET

An informational guide for practitioners on the many benefits of low dose naltrexone (LDN) either alone or in combination with a patients regular medication regimen. This document was also created with the intention to provide science based evidence to support the use of compounded LDN.

Naltrexone:

Naltrexone is in a class of drugs known as opiate antagonists. It was approved by the FDA in 1984 and is indicated in the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. The usual dosage ranges from 50 to 300mg per day.

Low-dose Naltrexone (LDN)

Low-dose Naltrexone (LDN) has been used "off-label" in the treatment of many diseases and conditions since 1985. The typical dose is between 1.5mg and 4.5mg. The use of LDN was pioneered by the late Dr. Bernard Bihari, M.D., a board certified physician in Psychiatry and Neurology. He was originally doing research with AIDs, M.S. and Parkinson's disease patients.

How does LDN work? Multiple mechanisms of action:

Recent research has identified multiple mechanisms by which LDN exerts its effects in the body. Understanding these mechanisms is extremely beneficial in understanding how LDN can be effective in so many diseases and conditions.

1. LDN up regulates the opioid system:
    a. Levo-Naltrexone is an antagonist for the opiate/endorphin receptors. This temporary blockade appears to result in a compensatory increase in endorphins and enkephalins, which potentially stimulates an increase in the number of opiate receptors and an up-regulation of the entire opioid system.
2. This increases endorphins and enkephalins results in:
    a. -Promoting tissue repair, wound healing and mucosal repair
    b. –Regulating cell growth and Inhibiting tumor growth
    c. –Increasing cytotoxic T cells and natural killer (NK) cells
    d. --Restoring T-helper/CD4 levels
    e. –Restoring balance of Th1 and Th2 lymphocytes
    f. –Down regulating inflammatory cytokines
    g. –Reducing inflammation and oxidative stress

h. –Positively augmenting the immune system by modulating T and B lymphocyte production
i. –Providing a sense of euphoria- “endorphin rush”
j. –Providing a sense of well-being and satisfaction
k. –Providing “natural” analgesia

3. LDN increases [Met(5)]-Enkephalin which is also known as Opioid Growth Factor (OGF):
    a. This up-regulation of the OGF-OGFr (OGF receptor) system results in of cell growth in normal and **abnormal cells** (WOUND HEALING & CANCER).
    b. It also regulates cell proliferation through the p16 and p21 cyclin dependent inhibitory kinases.
4. Dextro-Naltrexone blocks Toll Like Receptor 4 (TLR4) which down regulates microglia hyper activation and blocks TLR9 which augments immune response.
    a. This suggests LDN is actually a glial cell modulator which could be beneficial in most known neurodegenerative conditions. Glial cells are the immune cells in your central nervous system (brain & spinal cord). They are very involved in dysregulation of pain systems, neuroinflammation, and some neurological diseases such as Multiple Sclerosis, Alzheimer’s, Parkinson ’s disease, Autism, ALS, infections of the brain, etc.”
    b. This modulation results in reduced production of inflammatory cytokines including IL-6, IL-12, TNFα and NF-κB.
5. LDN may exert antidepressant effects by enhancing dopaminergic signaling.

REF:

https://www.ldnresearchtrust.org/sites/default/files/LDN_Mechanism_Of_Action_Pradeep_Chopra_MD.pdf
http://www.sciencedirect.com/science/article/pii/S0090825811002708
https://link.springer.com/article/10.1007/s10067-014-2517-2
http://www.sciencedirect.com/science/article/pii/S0165032716304499
https://www.frontiersin.org/articles/10.3389/fimmu.2017.00809/full
https://www.mdpi.com/2076-3271/6/4/82

Suggested Dosing of Therapy:

The typical starting dose for LDN starts at 1.5mg daily for 2 weeks and is increased to 3mg daily for 2 weeks and then 4.5mg daily as the usual maintenance dose.

If a patient experiences any side effects during this ramp up period it may be advisable to decrease the dose to the prior level and remain here for an additional week or two before increasing to the next level or increasing in 0.5mg increments.

However, in certain circumstances, such as with overly sensitive patients or for certain conditions such as Hashimoto's Thyroiditis, the starting dose can be 0.5mg

(or lower) and can be increased by 0.5mg a week until a daily dose of 3mg or 4.5mg is reached. The maintenance dose is based on patient response but is typically 3 to 4.5mg daily at bedtime. Patients on thyroid replacement or diabetics may see a very quick response, which may necessitate a dosage adjustment and should be monitored very closely from the start. (see below)

It is important to advise patients at the start of therapy that some may not improve right away and in rare instances, some symptoms may actually get worse before getting better. Patience is recommended and a minimum 6-12 month trial may be necessary to obtain desired results.

For Cancer treatment, LDN can be taken at similar doses, but must be avoided the week before and the week after cancer chemotherapy. This does not include tamoxifen or certain daily medications for prostate cancer. Recent evidence supports the "pulsing" of LDN when used in cancer treatments.

Taking LDN at night is often recommended, but there are many patients who take it in the morning and get excellent benefits. This appears to be patient specific.

It is important to note, that these guidelines for dosing and conditions are truly just guidelines. The various conditions and ultimate dosing is extremely patient specific and may require various adjustments unique to the individual patient. It appears that the use of LDN, through its many mechanisms, has the ability to optimize immune function and decrease inflammation at a very foundational level in human physiology. It is extremely important to not self-medicate with any other dosages of LDN unless specifically recommended by your health care provider.

Contraindications and Special Precautions:

- LDN is contraindicated in patients who are currently on opioids (including Tramadol) as it blocks the opioid receptor and could initiate immediate and severe withdrawal.
- LDN may also be contraindicated in patients who have undergone transplant procedures and are on immunosuppressive medication.
- LDN is compatible with most other therapies. It does not directly interact with steroids
- CAUTION: As mentioned previously, patients who start LDN and are on Thyroid replacement or possibly diabetics may see a rapid response and a dosage adjustment may be necessary.

Side Effects and patient experience:

- Vivid Dreams
- Sleep Disturbance
- Nausea (generally will last for about 1-2 weeks)
- Headache
- Dry Mouth (over 95% acceptable)

Many patients who start LDN do not experience any severe side effects. It is interesting and important to note that in some patients their symptoms may become worse. In less than ten percent of cases treated, increased symptoms may be more prolonged or even more severe than usual, lasting sometimes for several weeks. In rare cases, symptoms may persist for two or three months before the appropriate beneficial response is achieved. In MS, this can be characterized by increased fatigue, or increased spasticity. In CFS/ME, this can be the onset of apparent 'flu-like' symptoms. It has been observed that patients who withstand this increase in symptoms and stay on the therapy for at least 6 to 12 months will eventually see benefits.

Examples of conditions in which LDN has shown benefit:

NOTE: This list is just an example of conditions in which LDN has been shown to be beneficial and is by no means all-inclusive. For a more complete list you might visit the references listed at the end of this fact sheet.

In Autoimmune disease:

There are a number of mechanisms relating to the benefits seen in the use of LDN. It has recently been shown in studies that by temporarily blocking the opioid receptor with LDN there is a resulting compensatory increase in endorphins and enkephalins which are known to have a very positive influence on optimizing immune function. Increased levels of endorphins should stimulate the immune system, promoting an increase in the number of T lymphocytes. This effect was observed in Dr. Bihari's research. This increase in T-cell numbers apparently restores a more normal balance of the T-cells such that the effects of the diseases' progress are significantly reduced. It may also act directly on these immune cells to stimulate or restore normal function.

There is research currently underway, to prove the hypothesis that naltrexone improves or modulates the immune system by acting on a receptor called TLR4, which is involved in activating glial cells in the nervous system. This glial cell hyper-activation is now implicated in early degenerative disease and many neuro-degenerative conditions and pain syndromes. Several published papers have shown that naltrexone binds to the TLR4 receptor, and has a clinically measurable effect. This is evident in Crohn's disease and Ulcerative Colitis.

REF:
http://www.ncbi.nlm.nih.gov/pubmed/22850250
http://www.ncbi.nlm.nih.gov/pubmed/22826216
http://www.ncbi.nlm.nih.gov/pubmed/23188075
http://www.ncbi.nlm.nih.gov/pubmed/17222320

In Crohn's Disease:

In a recent study, Dr. Jill Smith at Penn State University reported that 89% of patients showed a significant response to therapy using LDN in active Crohn's disease while 67% achieved remission.

In a follow up randomized, placebo controlled 12 week study, Dr. Smith reported 88% of LDN patients had at least a 70 point decline in CDAI vs 40% of placebo patients (p = 0.009) and 78% of LDN patients had an endoscopic response (5 point reduction in Crohn's disease endoscopy index severity score (CDEIS) from baseline) vs 28% in placebo patients (p = 0.008).
In another 2018 study: Naltrexone directly improves epithelial barrier function by improving wound healing and reducing mucosal ER stress levels. Low dose Naltrexone treatment is effective and safe, and could be considered for the treatment of therapy refractory IBD patients.

REF:
https://www.nature.com/articles/ajg2007152
https://link.springer.com/article/10.1007/s10620-011-1653-7
https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-018-1427-5

In Multiple Sclerosis:

There is a significant amount of anecdotal evidence supporting the benefits of LDN in Multiple Sclerosis. Some reports indicate that symptoms may actually get worse at the initiation of therapy; however if patients are able to stay the course the results can be very impressive. A recent study showed that serum Opioid Growth Factor aka [Met^5]-Enkephalin levels were lower in humans with multiple sclerosis relative to non-multiple sclerosis patients, and low-dose naltrexone restored their levels.

REF:
http://www.sciencedirect.com/science/article/pii/S030698770400578X
http://journals.sagepub.com/doi/abs/10.1177/1352458508095828
http://journals.sagepub.com/doi/abs/10.1177/1535370217724791
https://www.nationalmssociety.org/Treating-MS/Complementary-Alternative-Medicines/Low-Dose-Naltrexone
https://journals.sagepub.com/doi/abs/10.1177/1535370217724791
https://www.ncbi.nlm.nih.gov/books/NBK470156/
https://journals.sagepub.com/doi/abs/10.1177/1535370217749830

In Thyroid Disease:

Patients with thyroid disease often have a strong auto-immune component.
Using LDN to optimize the immune system often leads to a reduction in hypothyroidism and an improvement in symptoms. Patients with Thyroid disease must always be very careful when starting LDN as the results can be very fast – and rapidly cause hyperthyroidism if they do not reduce their thyroid replacement

medication. Recently, one of our practitioners, who has been using LDN for autoimmune thyroid patients, stated: *" In my experience, if a patient with elevated Thyroid antibodies, stays on LDN long enough, they will see a decrease in those antibodies!"*

Ref:
http://www.stopthethyroidmadness.com/ldn/

In Cancer:

Recent research by Dr. Ian Zagon in Multiple Resistant Breast Cancer, has shown that it can stop breast cancer cells from dividing by acting on a new pathway; the "p21 cyclin-dependent inhibitory kinase pathway".

REF:
http://www.sciencedaily.com/releases/2013/08/130810063639.htm
https://www.sciencedirect.com/science/article/pii/S1567576918302315
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6126779/

An interesting study on LDN immune response, qualtity of life and survival of dags with mammary carcinoma. The results showed higher serum concentrations of beta-endorphin and met-enkephalin, fewer chemotherapy-related side effects, and better quality of life and survival rates in the LDN-treated groups than in LDN-untreated groups ($P < 0.05$).

REF:
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0204830

This pathway is present in many solid tumors as well as a large proportion of breast cancers. The article seems to offer some hope for people with Multiple Resistant Breast Cancer.

Multiple centers around the UK are quietly using LDN for all types of cancer. Prof. Angus George Dalgleish (Bsc, MD FRACPath FRACP FRCP FMedSci), professor of oncology at University College London is extremely experienced in using LDN for cancer. Recent examples where it has been beneficial in anecdotal cases include lung, bowel and malignant melanoma. Dr. Zagon's study points to a mechanism of action in these, and other solid tumor types relating to LDN's influence on the Opioid Growth Factor which acts on the p21 cyclin kinase pathway.

There is also a combination therapy called the Berkson Method – using Alpha-Lipoic Acid and LDN in pancreatic cancer. Dr Berkson talks about it in the reference below:

REF:
http://www.anticancer.org.uk/2011/10/q-with-dr-burt-berkson-low-dose.html

http://journals.sagepub.com/doi/abs/10.1177/1534735409352082
https://journals.sagepub.com/doi/abs/10.1177/1534735417747984

In Chronic Pain:

Recent studies have shown tremendous benefit in various chronic pain conditions including conditions as difficult as Complex Regional Pain Syndrome (CRPS). LDN blocks the TLR4 which is known to stimulate glial cells and mediate hyperalgeis and certain types of neuropathic pain.

- "*Low-dose naltrexone (LDN) has been demonstrated to reduce symptom severity in conditions such as fibromyalgia, Crohn's disease, multiple sclerosis, and complex regional pain syndrome. We reviewed the evidence that LDN may operate as a novel anti-inflammatory agent in the central nervous system, via action on microglial cells. These effects may be unique to low dosages of naltrexone and appear to be entirely independent from naltrexone's better-known activity on opioid receptors. As a daily oral therapy, LDN is inexpensive and well-tolerated.*" Ref A

- *"The totality of the basic and clinical research to date suggests that LDN is a promising treatment approach for chronic pain conditions thought to involve inflammatory processes."* Ref A

- *"LDN may emerge as the first of many glial cell modulators that could be used to treat chronic conditions."* Ref A

- *"Provide evidence that a multi-modal interventional approach, which includes low-dose naltrexone (a known glial attenuator), should be considered as a treatment option for the treatment of CRPS patients, particularly those patients with dystonic movement disorders."* Ref B

REF:

A. https://link.springer.com/article/10.1007/s10067-014-2517-2
B. https://link.springer.com/article/10.1007/s11481-013-9451-y

In Fibromyalgia:

Recent research by Dr. Jared Younger showed in a small trial of 10 women that LDN reduced fibromyalgia symptoms in the entire cohort, with a greater than 30% reduction of symptoms over placebo. Side effects (including insomnia and vivid dreams) were rare, and described as minor and transient. Interestingly, individuals with higher sedimentation rates (indicating general inflammatory processes) had the greatest reduction of symptoms in response to low-dose naltrexone.
In a follow-up study, thirty-one women with fibromyalgia participated in the randomized, double-blind, placebo-controlled, counterbalanced, crossover study where 32% of patients met the criteria for response compared to placebo.

REF:
https://academic.oup.com/painmedicine/article/10/4/663/1829894
http://onlinelibrary.wiley.com/doi/10.1002/art.37734/full
https://www.ingentaconnect.com/content/ben/crr/2018/00000014/00000002/art00014
https://www.mdpi.com/2227-9059/5/2/16/htm

In Autism, Depression and Gulf War Illness:

LDN has been used by many physicians, usually after expert assessment – in children with Autism. This has been widely discussed and the mechanism is probably a mixture of inflammation and direct neurological effects. Interestingly, dosage does not seem to be weight related. Transdermal (cream) can be compounded for children with many benefits reported.

"Since LDN can upregulate endogenous opioid activity, it may also have a role in promoting stress resilience, exercise, social bonding, and emotional well-being, as well as amelioration of psychiatric problems such a autism and depression. It is proposed that LDN can be used effectively as a buffer for a large variety of bodily and mental ailments through its ability to beneficially modulate both the immune system and the brain neurochemistries that regulate positive affect." Ref C

LDN has been *"found to be predominantly effective in decreasing self-injurious behavior. Naltrexone may also attenuate hyperactivity, agitation, irritability, temper tantrums, social withdrawal, and stereotyped behaviors. Patients may also exhibit improved attention and eye contact. Transient sedation was the most commonly reported adverse event."* Ref D

"This pilot trial suggests low-dose naltrexone may be effective for some with GWI." Ref E

REF:
C. http://www.sciencedirect.com/science/article/pii/S0306987708005070
D. http://journals.sagepub.com/doi/abs/10.1345/aph.1G499
E. https://www.tandfonline.com/doi/abs/10.1080/21641846.2018.1477034

In Alcohol craving:

We have had 2 patients who are in alcohol recovery programs and have used LDN. In both cases they have struggled personally and socially with alcohol cravings. Both patients reported a significant reduction in these cravings shortly after starting their LDN.

In Hay fever/Allergy/Dermatitis/Psoriasis/Dermatmyositis:

Many patients who experience severe hay fever have noticed that their hay fever symptoms resolve after LDN treatment is given for another completely different

condition. This has led to many patients with severe allergies trying LDN as an adjunct to their existing treatments, such as anti-histamines.
“In this article, we describe the successful use of a compounded formulation of oral low-dose naltrexone to manage guttate psoriasis in a 75-year-old white male patient“ Ref C
The patient's psoriatic lesions were significantly improved at 3 months, and the affected BSA had decreased from 10% to 1% after 6 months of treatment. The calculated PASI (psoriasis area severity index) score decreased from 7.2 to 0.9 after 6 months of treatment. Symptoms of pruritus also improved with naltrexone. No other adjuvant medications were used during this period. No side effects from the treatment were reported. Ref D
We present two cases in which low-dose naltrexone proved an effective therapy for dermatomyositis (DM), an idiopathic inflammatory myopathy Ref E

REF:
A.
http://www.gidoctor.net/client_files/File/successful-treatment-of-adultonset-dermatitis-herpetiformis-withlow-dose-naltrexone.pdf
B. https://europepmc.org/abstract/med/29141063
C. https://europepmc.org/abstract/med/30021181
D. https://www.jaadcasereports.org/article/S2352-5126(18)30147-4/abstract
E. https://onlinelibrary.wiley.com/doi/full/10.1111/dth.1272
F. https://jamanetwork.com/journals/jamadermatology/fullarticle/2716295

In Postural Orthostatic Tachycardia Syndrome (POTS) and Mast Cell Activation Syndrome (MCAS):

A patient with severe postural orthostatic tachycardia syndrome (POTS) and mast cell activation syndrome (MCAS) received immunotherapy with low-dose naltrexone (LDN) and intravenous immunoglobulin (IVIg) and antibiotic therapy for small intestinal bacterial overgrowth (SIBO). A dramatic and sustained response was documented

REF:
https://casereports.bmj.com/content/2018/bcr-2017-221405.full

In Conclusion:

“In summary, we conclude that low-dose naltrexone presents a safe and promising approach to prevention and/or treatment of many autoimmune diseases and cancer variants, as well as potentially various viral (e.g., AIDS) and neurological diseases (Multiple Sclerosis) that are exacerbated by compromised immunity.” Ref E

“There are solid reasons to believe LDN can also promote positive emotional states through the endogenous opioid amplification of positive affect and energy. From a psychiatric perspective, the facilitation of endogenous opioids should alleviate

depression since, to some degree, that multifaceted problem reflects reduced ability to experience pleasure." Ref E

"The use of low-dose naltrexone (LDN) for the treatment and prophylaxis of various bodily disorders is discussed. Accumulating evidence suggests that LDN can promote health supporting immune-modulation which may reduce various oncogenic and inflammatory autoimmune processes. Since LDN can upregulate endogenous opioid activity, it may also have a role in promoting stress resilience, exercise, social bonding, and emotional well-being, as well as amelioration of psychiatric problems such a autism and depression. It is proposed that LDN can be used effectively as a buffer for a large variety of bodily and mental ailments through its ability to beneficially modulate both the immune system and the brain neurochemistries that regulate positive affect." Ref E

REF:

E. http://www.sciencedirect.com/science/article/pii/S0306987708005070

Resources and Credits:

LDN Research Trust
https://www.ldnresearchtrust.org
LDN.org homepage
http://www.lowdosenaltrexone.org
Norway TV2 Documentary: "Unknown Medicine LDN Gives Hope to Thousands of Patients."
https://www.youtube.com/watch?v=rBd2gv8UGU0
"The LDN Book" by Linda Elsegood

The cost for LDN is approximately $1.00 per day when a 90 day supply is ordered.

Pioneer Health Compounding Pharmacy, LLC
520 Hartford Turnpike Unit D
Vernon, CT 06066
P: 860-979-0089
F: 860-979-0091
www.pioneerhealthcenter.com

This information has been assimilated and provided to you courtesy of Gene Gresh, R.Ph., FIACP, IFMCP of Pioneer Health as no doctor or pharmaceutical company benefits from the prescribing of LDN. It is an extremely valuable tool that can benefit many patients as this referenced fact sheet demonstrates.