LOW DOSE NALTREXONE
SAHAR SWIDAN PHARMD
SEBASTIAN DENISON RPH
PAMELA W. SMITH M.D., MPH, MS
NALTREXONE

FDA-approved indications

▪ Treatment of alcohol dependence
▪ For the prevention of opioid dependence relapse after opioid detoxification

Dose

▪ 12.5 mg to 150 mg PO
OPIOID RECEPTORS

4 Major Sub-types
- Delta, Kappa, Mu, Nociceptin receptor
- Distributed throughout body, Brain, Spinal Cord, Periphery Neurons, Digestive tract
The ligand will act like a key in a lock, with different ligands activating different ‘tumbler/protein’ sequences.

It was not meant for opioid class of drugs.

Opioids happen to turn the key a specific way.
The immuno-modulatory effects of morphine have been characterized in animal and human studies. Morphine decreases the effectiveness of several functions of both natural and acquired immunity, interfering with important intracellular pathways involved in immune regulation.

NALTREXONE

Naltrexone is a competitive antagonist at opiate receptors mu, kappa, and delta.

Naltrexone can either displace opiate agonists from binding at these receptors or prevent opiate binding.

By turning the key in the opposite direction---the immuno-modulatory effects of naltrexone can be used to help patients in a unique way.
MECHANISM OF ACTION

Antagonist of opiate receptors

Highest aff
CONTRAINDICATIONS

Acute hepatitis
Liver failure
Recent or current opioid/alcohol ingestion
LOW DOSE NALTREXONE
USES

Crohn’s Disease
Multiple Sclerosis
Fibromyalgia
Complex Regional Pain Syndrome
Cancer
Lyme Disease
Amyotrophic Lateral Sclerosis
AIDS/HIV
Itching
Eczema and Psoriasis
Irritable Bowel Syndrome
Weight loss
Dry Eyes

Younger, J, Parkitny, L, Mclain, D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment
LOW DOSE NALTREXONE (LDN)

Dose: 3 to 4.5 mg qhs

LDN is hypothesized to increase the production of endogenous opioids during short term blockade of opioid receptors.

LDN has anti-inflammatory effects.

LDN is a positive effect on the immune system and affects immune modulation.
Effects of Opioids on the Immune System

Schematic representation of the hematopoietic system showing the differentiation pathways sensitive to opioids.

NALTREXONE

High Dose

δ-Opioid Receptor Antagonist

- Inhibition of
  - T, B and NK function
  - IFN-γ and IL-2 production

Low Dose

δ-Opioid Receptor Agonist

- Stimulation of
  - T, B and NK function
  - IFN-γ and IL-2 production
MECHANISM OF ACTION OF LDN

LDN

- Increase in endogenous enkephalin and endorphin
- Inhibition of proinflammatory cytokines
- Interaction of the nuclear opioid growth factor receptor
- Blockade of opiate-R in GI tract
- Regulation of TReg and production of IL-10 and TGF-β

Promotion of DNA synthesis

- Effect on no. of liquid bowel movements
- Healing & repair of mucosal tissue

- Improvement in Crohn’s disease activity
- Down regulation of TH-17

- Enhancement of immune function
- Improvement in inflammatory reaction
- Healing of corneal ulcers
POTENTIAL SHORT-TERM SIDE EFFECTS

- Insomnia—most common
- Vivid dreams
- Fatigue
- Loss of appetite
- Nausea
- Hair thinning
- Mood swings
- Mild disorientation
POTENTIAL LONG-TERM SIDE EFFECTS

Possible liver and kidney toxicity

Possible tolerance to the beneficial rebound effect

Other unknown sequelae

- There is a long history of use of naltrexone at FDA approved doses (much higher than used in LDN)
CROHN’S DISEASE
CROHN’S DISEASE AND LDN

Small study showed that LDN was both safe and effective in the treatment of Crohn’s disease.

Patients were allowed to continue on aminosalicylates, immunomodulators, corticosteroids, or antibiotics if stable.

Eighty-nine percent of patients exhibited a response to therapy and 67% achieved a remission.

Fast onset of symptom benefit, 4 weeks where immunomodulators take up to 3-4 months to work and the patients may relapse immediately after stopping treatment. This was not the case with LDN: continued benefit was see up to 4 weeks post therapy.
CROHN’S DISEASE AND LDN: FOLLOW-UP STUDY

Prospective, double-blind, randomized, placebo controlled trial of patients with Crohn’s disease and the use of LDN. Concomitant medications allowed at same dose throughout study were aminosalicylates, steroids, and thiopurines. Anti-TNF-alpha medications and Lomotil were not allowed.

Eighty-eight percent of those treated with naltrexone had at least a 70-point decline in CDAI scores compared to 40% of placebo-treated patients.

After 12 weeks, 78% of subjects treated with naltrexone exhibited an endoscopic response as indicated by a 5-point decline in the Crohn’s disease endoscopy index severity score (CDEIS) from baseline compared to 28% response in placebo-treated controls and 33% achieved remission with a CDEIS score <6, whereas only 8% of those on placebo showed the same change.
This study was conducted on indomethacin-induced Crohn's disease in rats.

Treatment with sulfasalazine, low dose of naltrexone or their combination resulted in significant improvement of all measured parameters compared with enteritis group.

MULTIPLE SCLEROSIS
MULTIPLE SCLEROSIS AND LDN

Study examined the use low doses naltrexone in patients with multiple sclerosis.

It found LDN not only prevents relapses in MS but also reduces the progression of the disease.

It is proposed that naltrexone acts by reducing apoptosis of oligodendrocytes. It does this by reducing inducible nitric oxide synthase activity. This results in a decrease in the formation of peroxynitrites, which in turn prevent the inhibition of the glutamate transporters.

A pilot study that was a single-center, double-masked, placebo-controlled, crossover study evaluated the efficacy of 8 weeks of treatment with 4.5mg nightly LDN on self-reported quality of life of MS patients.

LDN significantly improved mental health quality of life indices.

FIBROMYALGIA
FIBROMYALGIA

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.

Younger reviewed the evidence that LDN may operate as a novel anti-inflammatory agent in the central nervous system, via action on microglial cells.

FIBROMYALGIA AND LDN

Patient Global Impression of Change after LDN

- 37% very much improved
- 20% much improved
- 13% minimally improved
- 20% no change
- 10% minimally worse
Study examined the use of LDN at 4.5 mg qhs for the treatment of fibromyalgia in a small randomized, double-blind, placebo-controlled, counterbalanced, crossover trail which assessed daily pain levels.

The preliminary evidence showed that low-dose naltrexone had a beneficial impact on fibromyalgia pain. The medication was inexpensive, safe, and well-tolerated.

LDN has a great anti-inflammatory effect.

Small medical trial of 8 women with fibromyalgia.

The trial found that LDN was associated with reduced plasma concentrations of interleukin (IL)-1β, IL-1Ra, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p40, IL-12p70, IL-15, IL-17A, IL-27, interferon (IFN)-α, transforming growth factor (TGF)-α, TGF-β, tumor necrosis factor (TNF)-α, and granulocyte-colony stimulating factor (G-CSF).

The study also found a 15% reduction of fibromyalgia-associated pain and an 18% reduction in overall symptoms.

A resent study showed the efficacy of LDN for fibromyalgia patients that were not effectively treated with conventional therapies.

CHRONIC PAIN
NALTREXONE

High Dose

\( \delta \)-Opioid Receptor Antagonist

Inhibition of
- T, B and NK function
- IFN-\( \gamma \) and IL-2 production

Low Dose

\( \delta \)-Opioid Receptor Agonist

Stimulation of
- T, B and NK function
- IFN-\( \gamma \) and IL-2 production
LOW-DOSE NALTREXONE FOR THE TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME

Study reviewed the evidence that LDN may operate as a novel anti-inflammatory agent in the central nervous system, via action on microglial cells.

They found that 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.

CANCER
LDN AND OVARIAN CANCER: ANIMAL STUDY

Female mice were implanted with human ovarian cancer cells (SKOV-3 cells).

Mice with confirmed ovarian cancer were randomly assigned to receive either IP LDN, cisplatin, taxol, LDN and taxol, LDN and cisplatin, or saline.

Results: “Mice with established ovarian tumors and treated with a low dosage of NTX (LDN), which invokes a short period of opioid receptor blockade, repressed tumor progression in a non-toxic fashion by reducing DNA synthesis and angiogenesis but not altering cell survival. The combination of LDN with cisplatin, but not taxol, resulted in an additive inhibitory effect on tumorigenesis with enhanced depression of DNA synthesis and angiogenesis. LDN combined with cisplatin alleviated the toxicity (e.g. weight loss) associated with cisplatin.”

LDN AND PANCREATIC CANCER: 3 CASE HISTORIES

Three case histories are presented in this article of patients treated with IV alpha-lipoic acid and oral LDN. Patients are doing well. Authors call for a clinical trial.

LYME DISEASE
LDN AND LYME DISEASE

Anecdotal Reports show benefit

Proposed immuno-modulatory, anti-inflammatory effects

Needs further study

- Some have raised concerns of immuno-modulation causing greater problems for Lyme patients
- Use may be beneficial in Lyme “flare’s”
AMYOTROPHIC LATERAL SCLEROSIS (ALS)
ALS

Study showed that low-dose naltrexone is beneficial in patients with ALS.

Naltrexone offers short term blockade which causes an increase in endogenous opioid release.

Naltrexone has anti-nociceptive and anti-inflammatory action.

Naltrexone may help with fatigue, pain, spasticity, and depression.

LDN AND HIV

Researchers found that LDN is both safe and free of side effects and that it appears to be efficacious in strengthening the immune system of HIV+ individuals. In this study’s patients, who all had HIV infection but whose CD4 levels were not yet low enough to warrant antiretroviral (ARV) drug therapy, the mean CD4 % count remained unchanged throughout the study.

LDN group showed a significantly higher increase in CD4 count by 6 months of treatment and it was concluded that “further exploration of LDN as part of an HIV+ treatment regimen is warranted.”

ITCHING
Pruritus is a common symptom in systemic sclerosis which is an autoimmune disease which causes fibrosis and vasculopathy in skin, lung, and gastrointestinal tract.

Study of three case reports of patients that had significant improvement in pruritus and total gastrointestinal symptoms as measured by the 10-point faces scale and the University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract questionnaire.

This small case series suggests LDN may be an effective, highly tolerable, and inexpensive treatment for pruritus and gastrointestinal symptoms in patients with systemic sclerosis.

NALTREXONE FOR ITCHING IN ELDERLY PATIENTS

Naltrexone is a pure opioid antagonist that blocks the effects of opioids and it could be an effective, relatively tolerable and safe alternative treatment option for controlling severe intractable pruritus in old patients.

- Jungsoo Lee, et al, “The clinical efficacy of naltrexone with severe pruritus in old patients,” Department of Dermatology and Cutaneous Biology Research Institute, Yonsei University College of Medicine, Seoul, Korea.
NALTREXONE FOR ITCHING IN BURN PATIENTS

In this study the authors observed a significant decrease in itching sensations in burn patients after 2 weeks of treatment with naltrexone. Scratching activity was also decreased in 44.5% of the subjects.

The objective of the first open study was to correlate the clinical efficacy of topically applied naltrexone in different pruritic skin disorders to a change of epidermal μ-opiate receptor (MOR) expression. This finding is supported by the biopsy results from the open studies, showing a regulation of MOR expression in epidermis after treatment with topical naltrexone.

ECZEMA AND PSORIASIS
LDN ECZEMA AND PSORIASIS

- Take the patient off of gluten
- Fix the GI tract using the 4R program for gut restoration
- Use topical naltrexone to affect immune system: 1% for itching
- Consider combining with other immuno-modulatory drugs.
IRRITABLE BOWEL SYNDROME
IRRITABLE BOWEL SYNDROME (IBS)

Study involving patients with either irritable bowel syndrome without evidence for small intestinal bacterial overgrowth, chronic idiopathic constipation, or inflammatory bowel disease were treated with LDN.

Results revealed that a significant number of patients were helped with LDN. However some patients symptoms worsened with the treatment.

One of the “side effects” of LDN is decreased appetite.

LDN has been shown to be an effective adjunct to weight loss which includes exercising and a healthy eating program.

LDN promotes weight loss by the following mechanisms:

- Decreases appetite
- Improves insulin resistance
- Increase growth hormone
- Decreases inflammation
DRY EYES
LDN AND DRY EYES: ANIMAL STUDY

Study looked at using topical naltrexone for dry eyes in lab animals.

Eye drops of 10(-5)M naltrexone or sterile vehicle were administered either once only or 4 times a day for 1 or 5 days.

Topical treatment with naltrexone normalizes tear production and corneal sensitivity in type 1 diabetic rats.

Human trials should be considered.

LDN DOSING
**LDN DOSING**

Most common dosing schedule of compounded LDN:

- One 1.5 mg capsule qhs x 7 days
- Two 1.5 mg capsules qhs x 7 days
- Three 1.5 mg capsules qhs x 7 days
- Then 4.5 mg thereafter as a single capsule
SUMMARY

Low dose naltrexone (LDN) is a novel approach to helping patients.

Its use should be considered in patients with autoimmune and inflammatory conditions along with other disease processes.
USE OF LDN IN PATIENTS WITH MULTIPLE SCLEROSIS
CONVENTIONAL THERAPIES FOR MS

Human recombinant interferon-B

Glatiramer acetate
- Random polymer of four amino acids that stimulates protective T cells

Fingolimod
- Prevents activated lymphocytes from entering the CNS by sequestration in lymph nodes

Monoclonal antibody against alpha-4 integrin

Novantrone

Steroids
REFERENCES

REFERENCES


REFERENCES (CONT.)


FUNCTIONAL THERAPIES FOR MULTIPLE SCLEROSIS

Diet
EPA/DHA/GLA
Antioxidants
Vitamin D
Alpha lipoic acid
Ginkgo biloba
Hyperbaric oxygen
FUNCTIONAL THERAPIES FOR MULTIPLE SCLEROSIS (CONT.)

Vitamin B12
Phosphatidylserine
Coenzyme Q-10
L-carnitine/acetyl-L-carnitine
Chlamydia treatment
Candida treatment
FUNCTIONAL THERAPIES FOR MULTIPLE SCLEROSIS (CONT.)

Folic acid
Exercise
Stress management
Mind-body-spirit
Low dose naltrexone
Liver detoxification
Estriol/testosterone/progesterone
Summary of all the studies on diet and MS reveal a modest influence on the development of MS but a major influence on how well the patient did that had MS.

Low-saturated fat diet (<20 grams qd)

Whole milk, cheese, margarine, and other forms of hydrogenated oils and shortenings were forbidden in the trial.

Red meat was prohibited.
DIET (CONT.)

After 34 years, 70 of the patients that consumed 20 grams of saturated fat intake a day or less, the morality rate was 31% vs. those who consumed more than 20 grams of fat a day where serious disability was common and the mortality rate was 80%.

The positive results of these trials may be due to the low saturated diet but may also be due to the omega-3-fatty acids, omega-6 fatty acids, and vitamin D that was contained in the cod liver oil.

Consequently, place the patient on a low saturated fatty diet and supplement with omega-3-fatty acids, vitamin D, and omega-6-fatty acids.
Studies have shown an association between inflammatory cytokines and the disease activity in MS.


REFERENCES


A study looked at giving 6 grams qd of EPA/DHA to patients with MS.

Levels of IL-1-B, TNF-alpha, IL-2, IFN-γ, PGE2 and LTB4 secreted from immune cells that were un-stimulated and stimulated were examined.

Study revealed a decrease in levels of inflammatory markers after 3 and 6 months with the use of EPA/DHA vs. controls.
VITAMIN D

This study showed that higher levels of vitamin D in patients with MS correlated with lower disability rates related to MS.

ALPHA LIPOIC ACID (ALA)

Excellent brain nutrient
Both fat and water soluble
Able to cross the blood brain barrier
Helps regenerate vitamins E, C, glutathione, and coenzyme Q-10
Stimulates the sprouting of new nerve fibers on nerve cells
REFERENCES

In animal studies, lipoic acid has been shown to suppress the development of MS by preventing inflammatory T cells from entering the CNS.


A double-blind, placebo-controlled pilot study used lipoic acid in RRMS.

Study showed that 1,200 mg given once a day was the best dose.

Study also showed that higher serum levels of ALA (which were achieved with 1,200 mg as a once a day dose instead of 600 mg BID) were associated with an increased immunomodulatory activity.

Doses of alpha lipoic acid above 600 mg a day can negatively affect the conversion of T4 to T3.


Please advise the patient and chart that you have discussed this with them.
GINKGO BILOBA

A randomized, placebo-controlled, 12 week trial looked at the effects of Ginkgo on cognition in patients with MS.

A standardized extract was used of Ginkgo biloba of 120 mg BID vs. placebo.

Study showed that the patients that used Ginkgo had improvement in cognitive function tests compared to placebo.

VITAMIN B12

Vitamin B12 deficiency is commonly seen in the serum and/or cerebrospinal fluid of patients with MS.

B12 deficiency enhances the destruction of myelin during an MS attack.

B12 deficiency compromises the body’s ability to repair the damaged myelin since B12 plays a role in the synthesis and integrity of myelin.

REFERENCES

PHOSPHATIDYLSEERINE

Phosphatidylserine is part of the nutrient lecithin. Is one of the important building blocks for neuronal membranes. Deficiencies of intracellular communication are the ultimate functional flaws in MS. Phosphatidylserine is need to preserve and enhance the ability of nerves to transmit information.

Dose: 300 mg qd
COENZYME Q-10

Inadequacies of CoQ10 threaten the fundamental process of cellular energy production and enhances the damaging effects of naturally occurring free radicals.

Supplementation with Q-10 has been shown to be helpful in patients with MS (500 mg qd)

Supplementation with L-carnitine improved fatigue caused by medications in patients with MS.

Patients took 3-6 grams a day of L-carnitine. Dosage for patients with normal kidney function.

67% of the patients had improvement in fatigue within 3 months.

Treatment with acetyl-L-carnitine relieved fatigue related to MS in another trial.

Dose: 1 gram BID (normal renal function)

Study found acetyl-L-carnitine was more effective than amantadine for MS fatigue.

In one study, some of the patients with MS had low folic acid levels.


No studies have been down to show that low folic acid levels will exacerbate MS symptoms, but levels should be checked and supplemented when low.
L-THREONINE

Studies have shown that L-threonine supplementation in doses of 3-7.5 grams qd for 2-8 weeks produced moderate improvement in patients with spasticity due to MS.

L-threonine can be converted to glycine in the brain which is an inhibitory neurotransmitter. Glycine levels have been shown to be low in animals with spasticity.
REFERENCES

One year study evaluated the course of a group of MS patients receiving hyperbaric oxygen therapy compared to a control group. This was a randomized, double-blinded, and placebo-controlled study.

Worsening of symptoms was observed in 55% of the untreated group, while only 12% of the patients treated with hyperbaric oxygen experienced a deterioration of function.
HYPERBARIC OXYGEN (CONT.)

The treated group experienced improvements in a variety of symptoms including mobility, fatigability, tremor, bladder control, and visual symptoms.

This bacterium may be related to MS.

Consider empiric treatment for Chlamydia pneumoniae using doxycycline.
- Doxycycline 100 mg twice a day for 14 days
- Probiotics
CANDIDA

This organism has been associated with hyperimmune diseases and specifically MS.

- Fluconazole 100 mg a day for 14 days, followed by 100 mg every other day for another 14 days.
Infection with an overgrowth of Candida in the GI tract can result in the formation of autoantibodies that cross-react with other tissues and organs which may exacerbate MS.

Studies have shown that regular exercise is helpful in patients with MS in helping with quality of life, sense of well-being, and ability to ambulate.


A medical panel in review of the medical literature found there was a possible association between antecedent stress and MS onset or exacerbations of MS.

A prospective longitudinal study found that increased conflicts and disruptions in the daily routine of life were followed by an increased risk of developing new MS brain lesions 8 weeks later as evidenced by MRI.

Perceived stress by patients with MS has been correlated with MS exacerbations in other studies.

Mindfulness-based stress reduction in mind-training approach was shown in this trial to improve nonphysical quality of life issues, depression, fatigue, and anxiety in patients with MS.

Study showed that mediation, yoga, and prayer were helpful in patients with MS.

ACUPUNCTURE

Study showed that acupuncture was being used commonly in patients with MS.

LOW DOSE NALTREXONE (LDN)

Studies showed that low-dose naltrexone is beneficial in patients with MS.

Naltrexone offers short term blockade which causes an increase in endogenous opioid release.

Naltrexone has anti-nociceptive and anti-inflammatory action.

Naltrexone may help with fatigue, pain, spasticity, and depression.
LOW DOSE NALTREXONE (CONT.)

Dose:
- One 1.5 mg capsule qhs x 7 days
- Two 1.5 mg capsules qhs x 7 days
- Three 1.5 mg capsules qhs x 7 days
- Then 4.5 mg thereafter as a single capsule

LIVER DETOXIFICATION

Since there is an increased risk in the development of MS if the patient is exposed to organic solvents, liver detoxification may be helpful.

Studies have shown that estriol can help both women and men benefit if they have MS.

Estriol causes an immune shift from TH1 to Th2 helper cells.


Studies showed a reduction in symptoms and a decrease in gadolinium-enhancing lesions on MRI in women and men with MS who were treated with estriol.

- Ibid., Soldan.
In male patients testosterone and estriol has also been shown to help with multiple sclerosis.

TESTOSTERONE

In this study testosterone replacement was shown to aid in MS symptoms in both men and women.