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

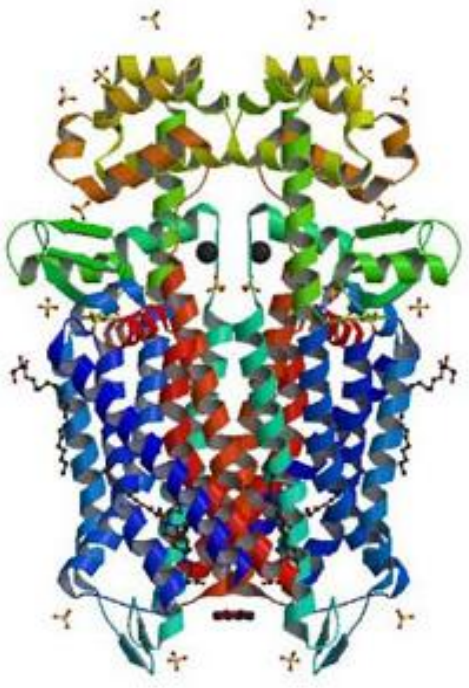
Dose

- 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

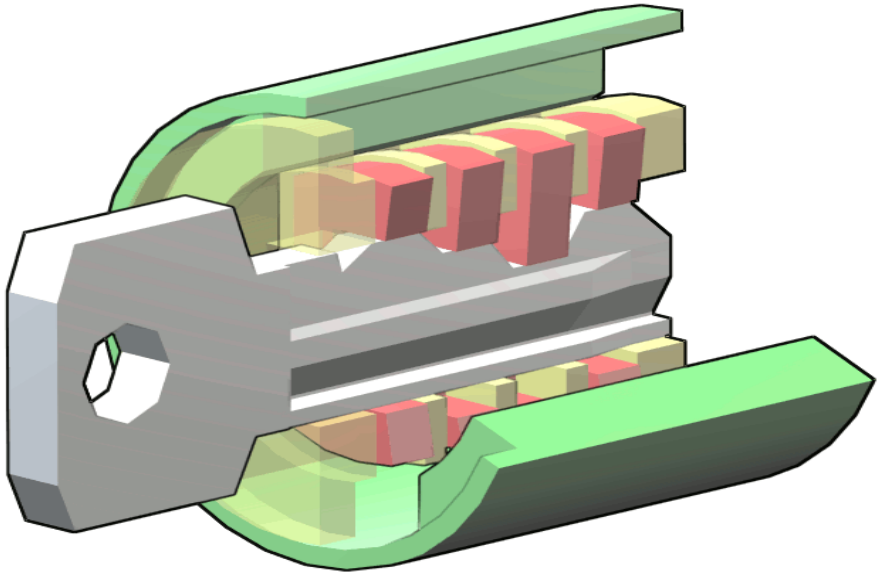


RECEPTOR AND LIGANDS

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.



OPIOID IMMUNO-MODULATION

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.

- Sacerdote, P., "Opioid-induced immunosuppression," Curr Opin Support Palliat Care 2008; 2(1):14-8.
- Eisenstein, T., "Opioids and the immune system: what is their mechanism of action?" Brit Jour Pharmacol 2011; 164(7):1826-28.

NALTREXONE

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

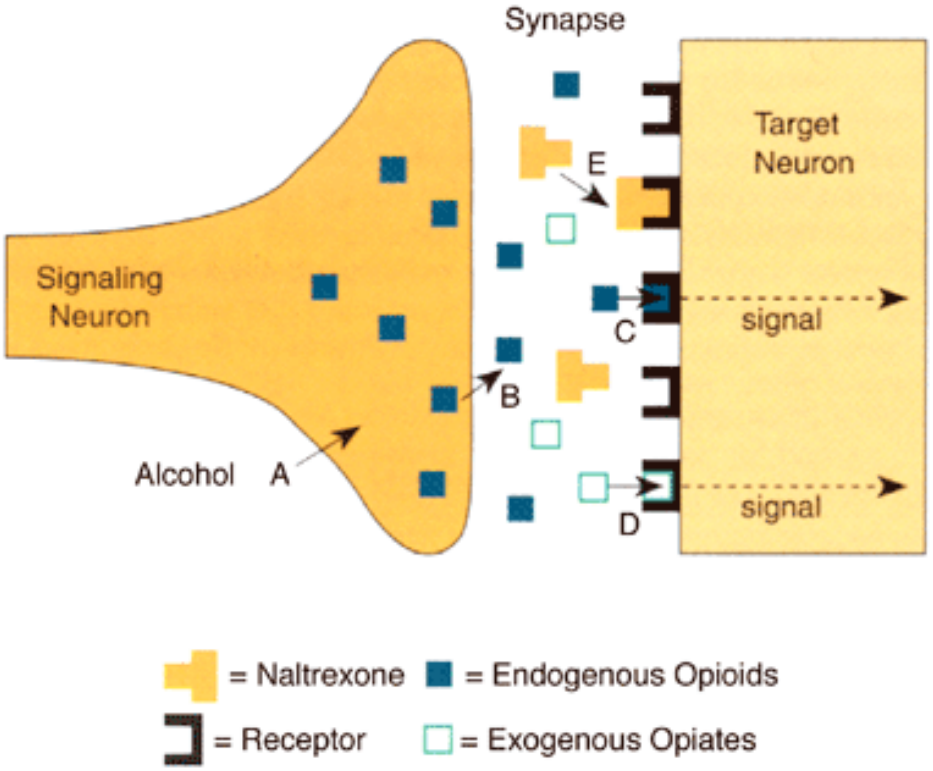
Naltrexone can either displace opiate agonists from binding at these receptors or prevent opiate binding.

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

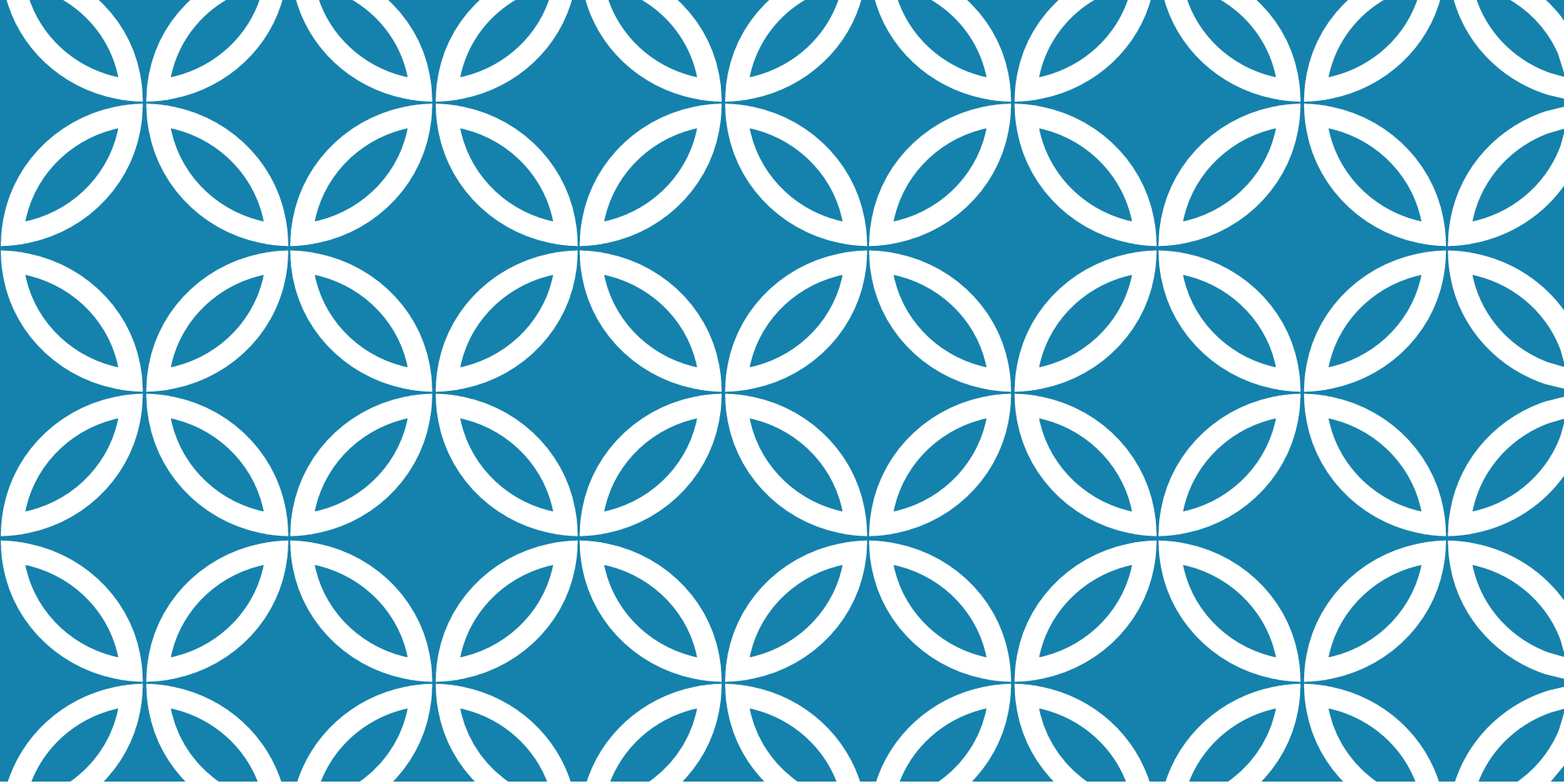


CONTRAINDICATIONS

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

Bihari B (2013) Bernard Bihari, MD: low-dose naltrexone for normalizing immune system function
Younger, J, Parkitny, L, Mclain, D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment

LOW DOSE NALTREXONE (LDN)

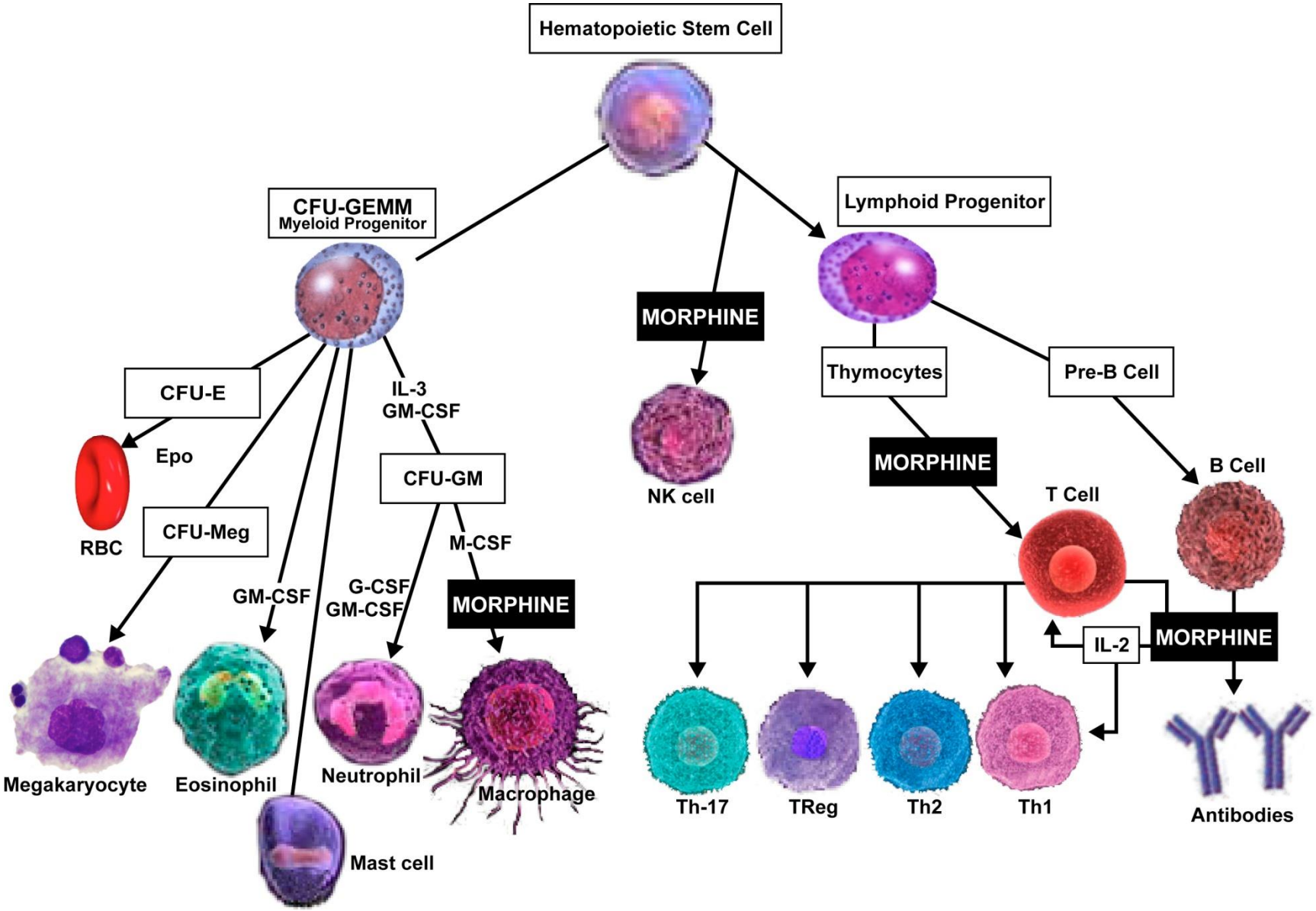
Dose: 3 to 4.5 mg qhs

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

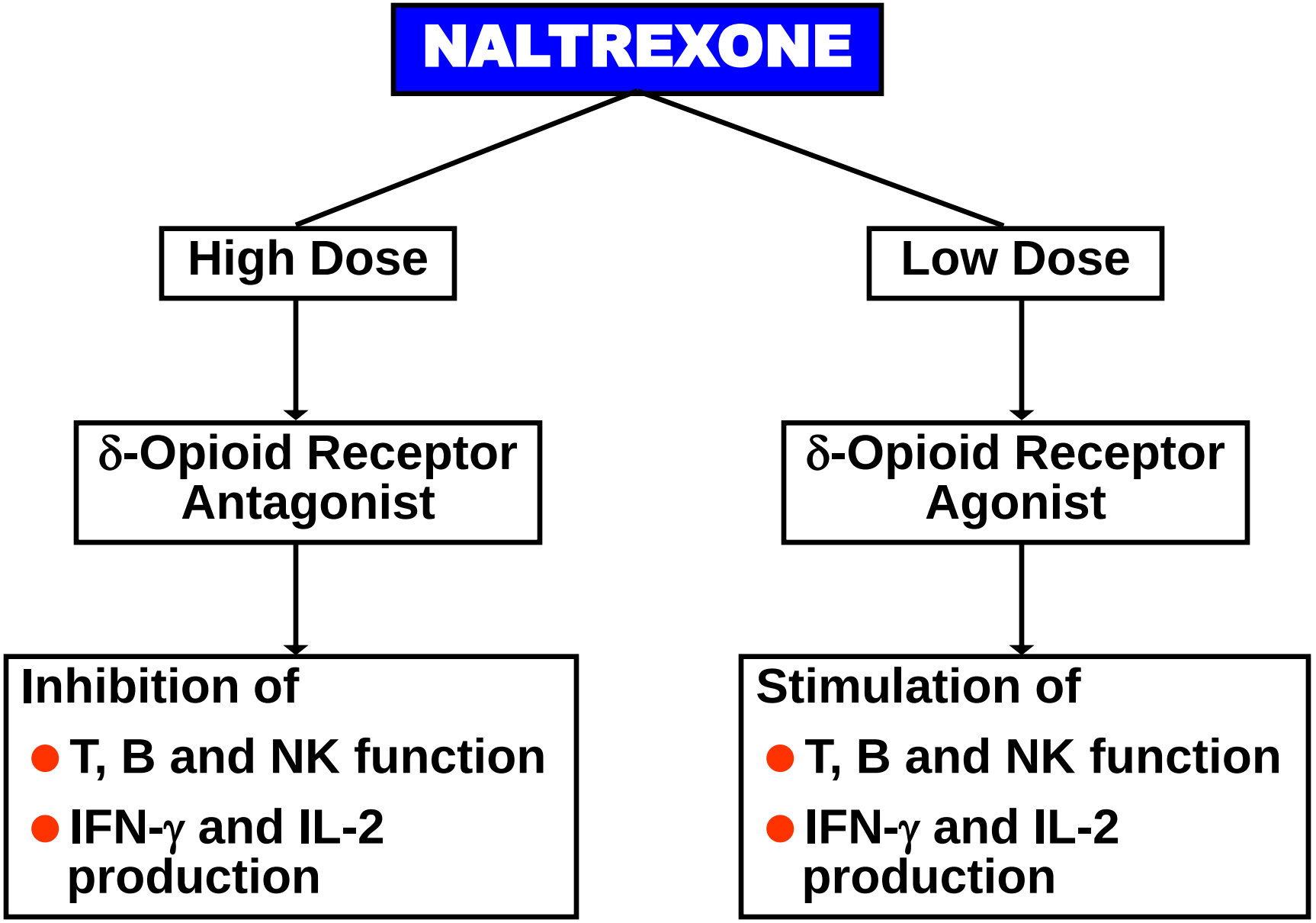
LDN has anti-inflammatory effects.

LDN is a positive effect on the immune system and affects immune modulation.

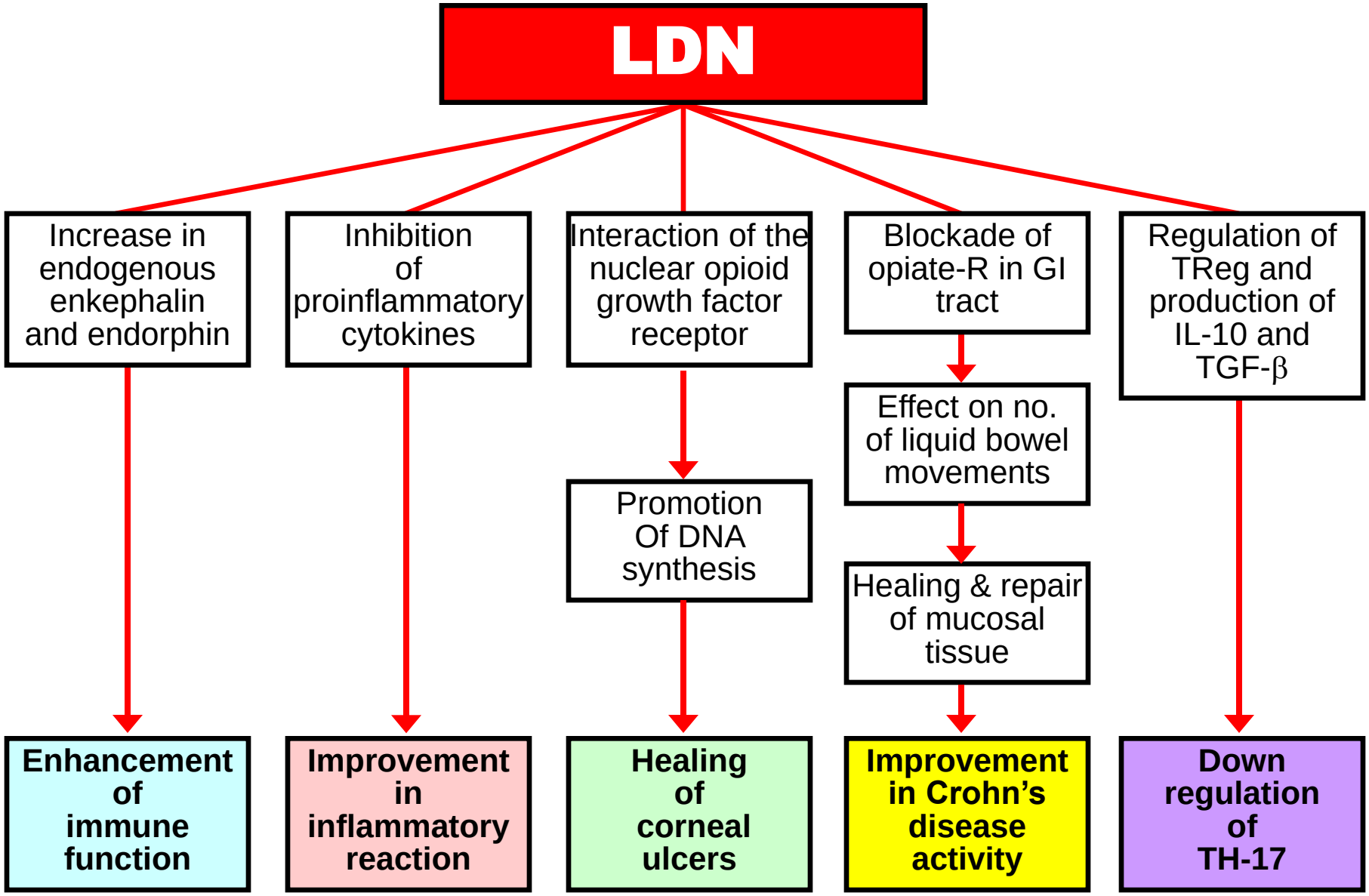
Effects of Opioids on the Immune System



Schematic representation of the hematopoietic system showing the differentiation pathways sensitive to opioids.
from Effects of Opioids on the Immune System – Roy S. and Loh H.H., Neurochemical Research, 21:1375-1386, 1996


NALTREXONE
High Dose
Low Dose
δ-Opioid Receptor Antagonist
δ-Opioid Receptor Agonist
Inhibition of
T, B and NK function
IFN-γ and IL-2 production
Stimulation of
T, B and NK function
IFN-γ and IL-2 production

MECHANISM OF ACTION OF LDN



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.

REFERENCE

- Smith, J., et al., “Low-dose naltrexone therapy improves active Crohn's disease,” Amer Jour Gastenterol 2007; 102(4):820-28.

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.

REFERENCE

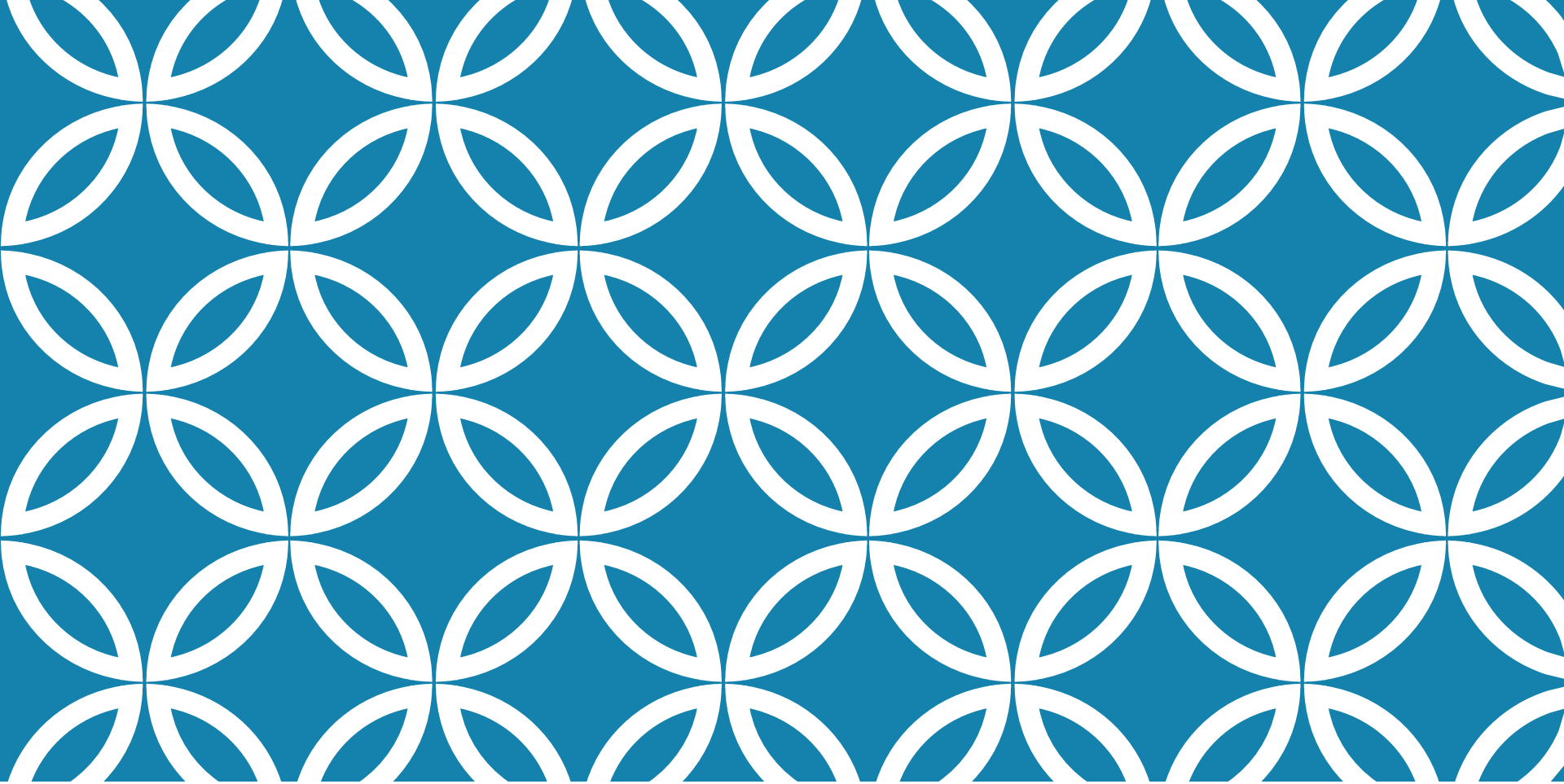
- Smith, J., et al., “Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn's disease: a randomized placebo-controlled trial,” Dig Dis Sci 2011; 56(7):2088-97.

CROHN'S DISEASE AND LDN: ANIMAL STUDY

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.

- Tawfik, D., et al., "Evaluation of therapeutic effect of low dose naltrexone in experimentally-induced Crohn's disease in rats," Neuropeptides 2016; 59:39-45.



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.

Agrawal, Y., "Low-dose naltrexone therapy in multiple sclerosis," Med Hypotheses 2005; 64(4):721-24.

MULTIPLE SCLEROSIS AND LDN (CONT.)

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.

Cree, B., "Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis," Ann Neurol 2010; 68(2):145-50.

- Gironi, Maira, et al. "A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis." *Multiple Sclerosis Journal* 14.8 (2008): 1076-1083.

FIBROMYALGIA

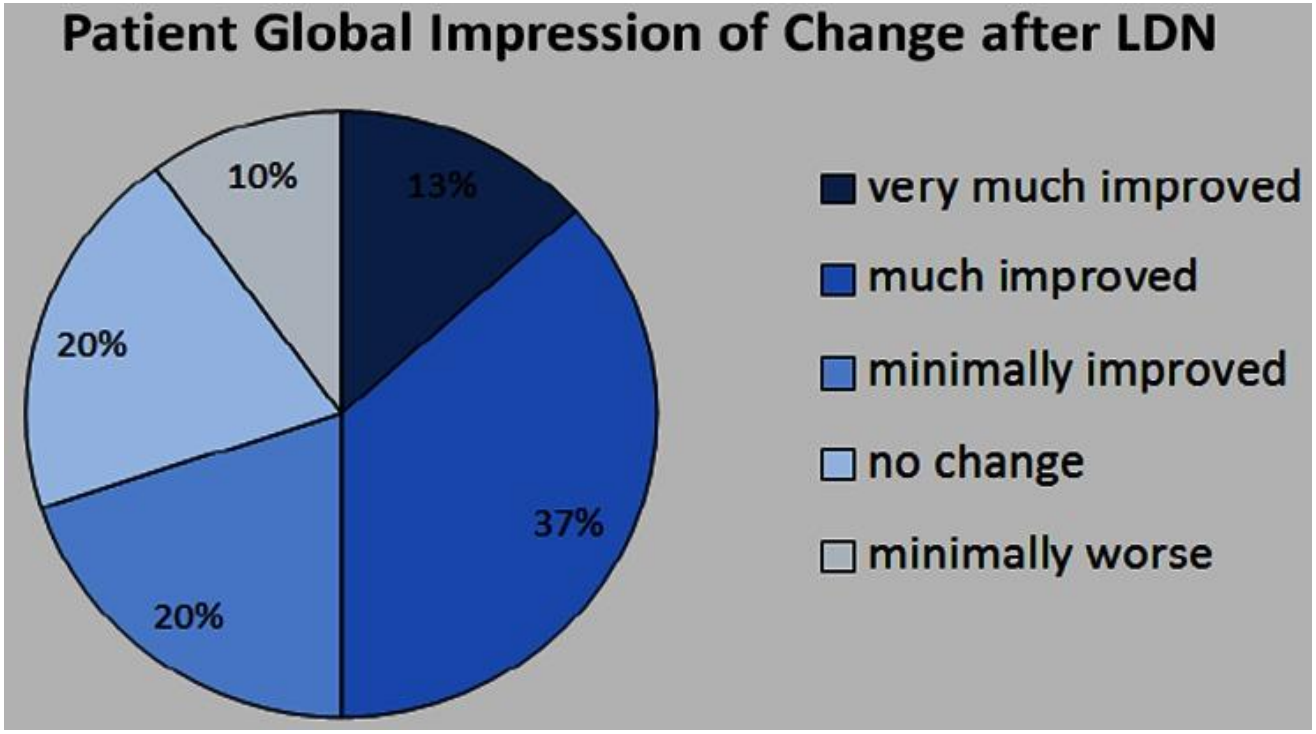
FIBROMYALGIA

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.

- Younger, L., et al., "The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain.," Clin Rheumatol 2014; 33(4):451-59.

FIBROMYALGIA AND LDN



FIBROMYALGIA AND LDN (CONT.)

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 assed 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.

- Younger, J., et al., "Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels," Arthritis Rheumatol 2013; 65(2):529-38.

FIBROMYALGIA AND LDN (CONT.)

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).

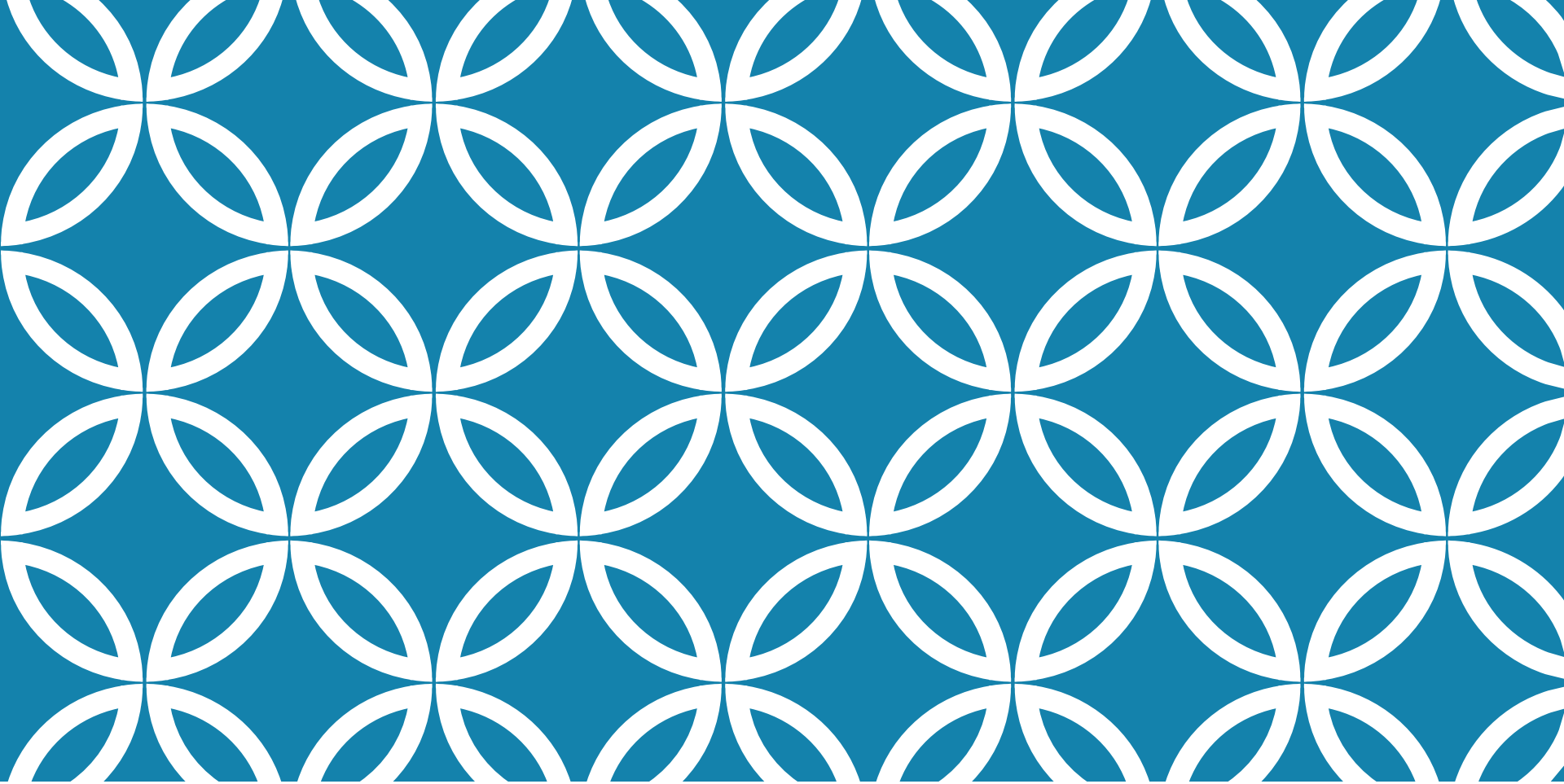
The study also found a 15% reduction of fibromyalgia-associated pain and an 18% reduction in overall symptoms.

Parkthy, L., et al., "Reduced pro-Inflammatory cytokines after eight weeks of low-dose naltrexone for fibromyalgia," Biomedicines 2017; April 5(2):DOI: 3390/biomedicines5020016.

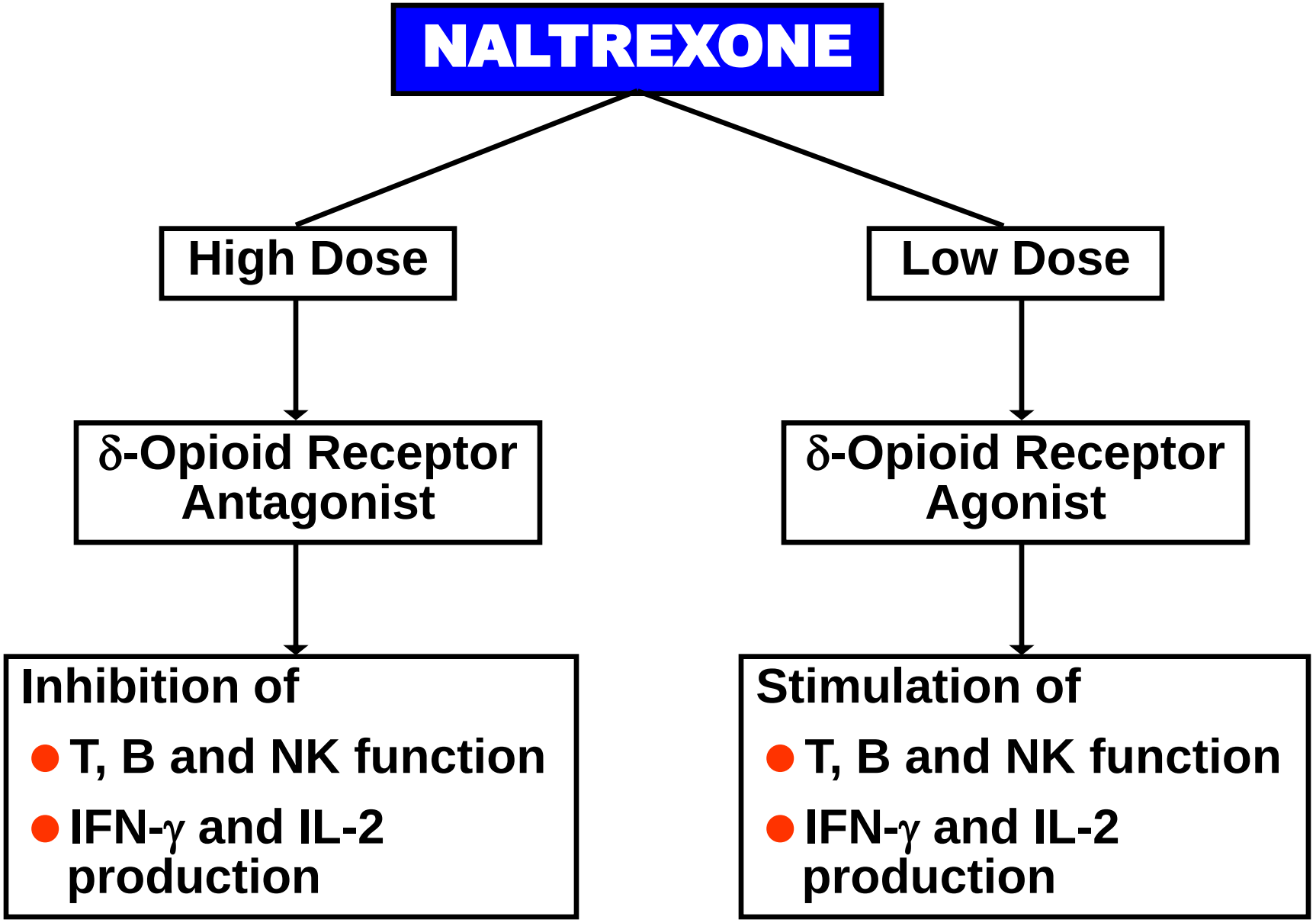
FIBROMYALGIA AND LDN (CONT.)

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

- Metvas, S., "Low dose naltrexone in the treatment of fibromyalgia," Curr Rhematol Res 2017; March DOI: 102174/1573397 Epub ahead of print



CHRONIC PAIN

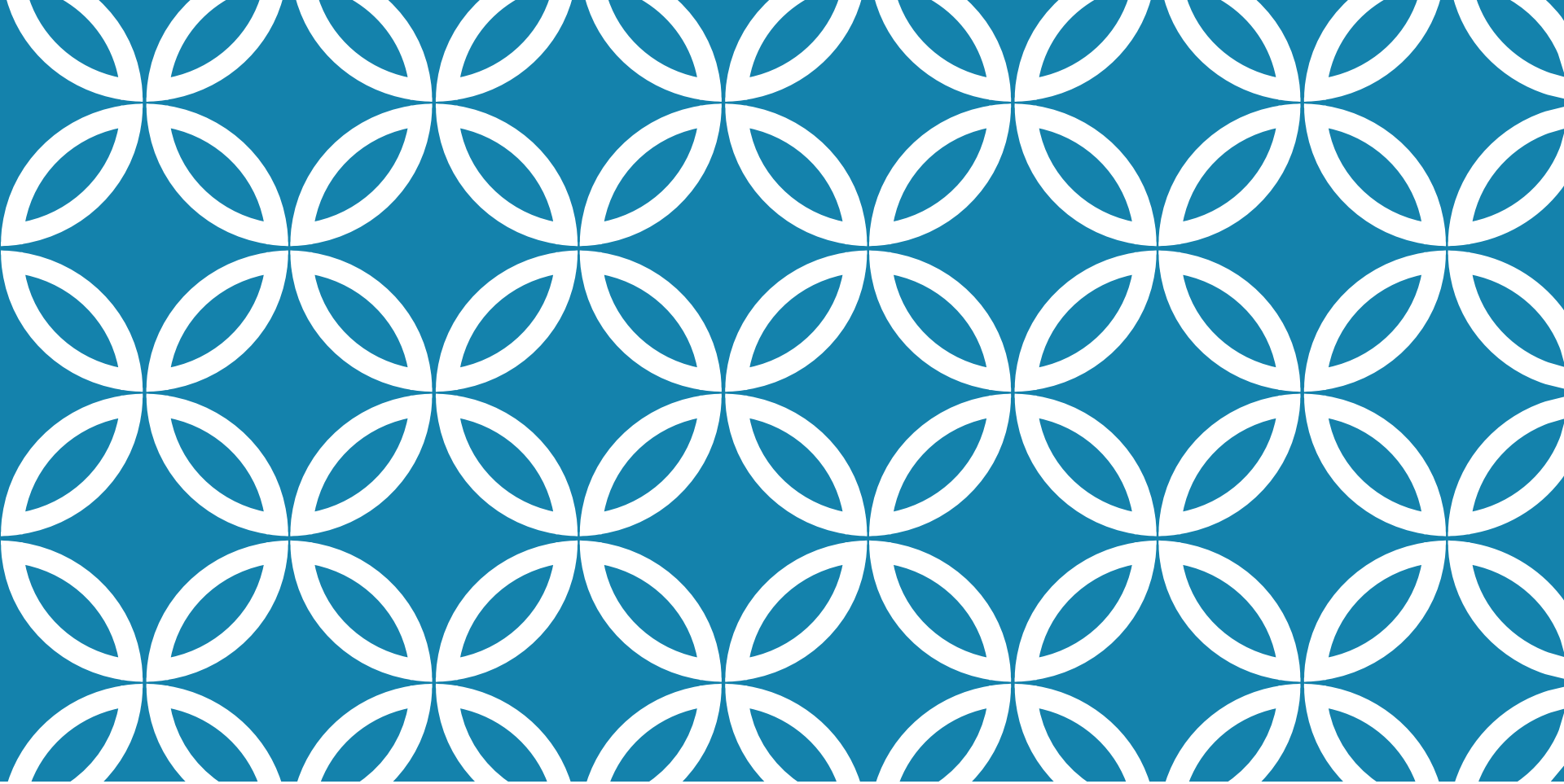

NALTREXONE
High Dose
Low Dose
δ-Opioid Receptor Antagonist
δ-Opioid Receptor Agonist
Inhibition of
T, B and NK function
IFN-γ and IL-2 production
Stimulation of
T, B and NK function
IFN-γ and IL-2 production

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.

- Younger, J., et al., "The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain," Clin Rheum 2014; 33(4):451-59.



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 tumorgenesis with enhanced depression of DNA synthesis and angiogenesis. LDN combined with cisplatin alleviated the toxicity (e.g. weight loss) associated with cisplatin."

- Donahue, R., et al., **Low-dose naltrexone suppresses ovarian cancer and exhibits enhanced inhibition in combination with cisplatin," Exp Biol Med (Maywood) 2011; 236(7):883-95.**

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.

- Berkson, B., "Revisiting the ALA/N (alpha-lipoic acid/low-dose naltrexone) protocol for people with metastatic and nonmetastatic pancreatic cancer: a report of 3 new cases," Integr Cancer Ther 2009; 8(4):416-22.

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

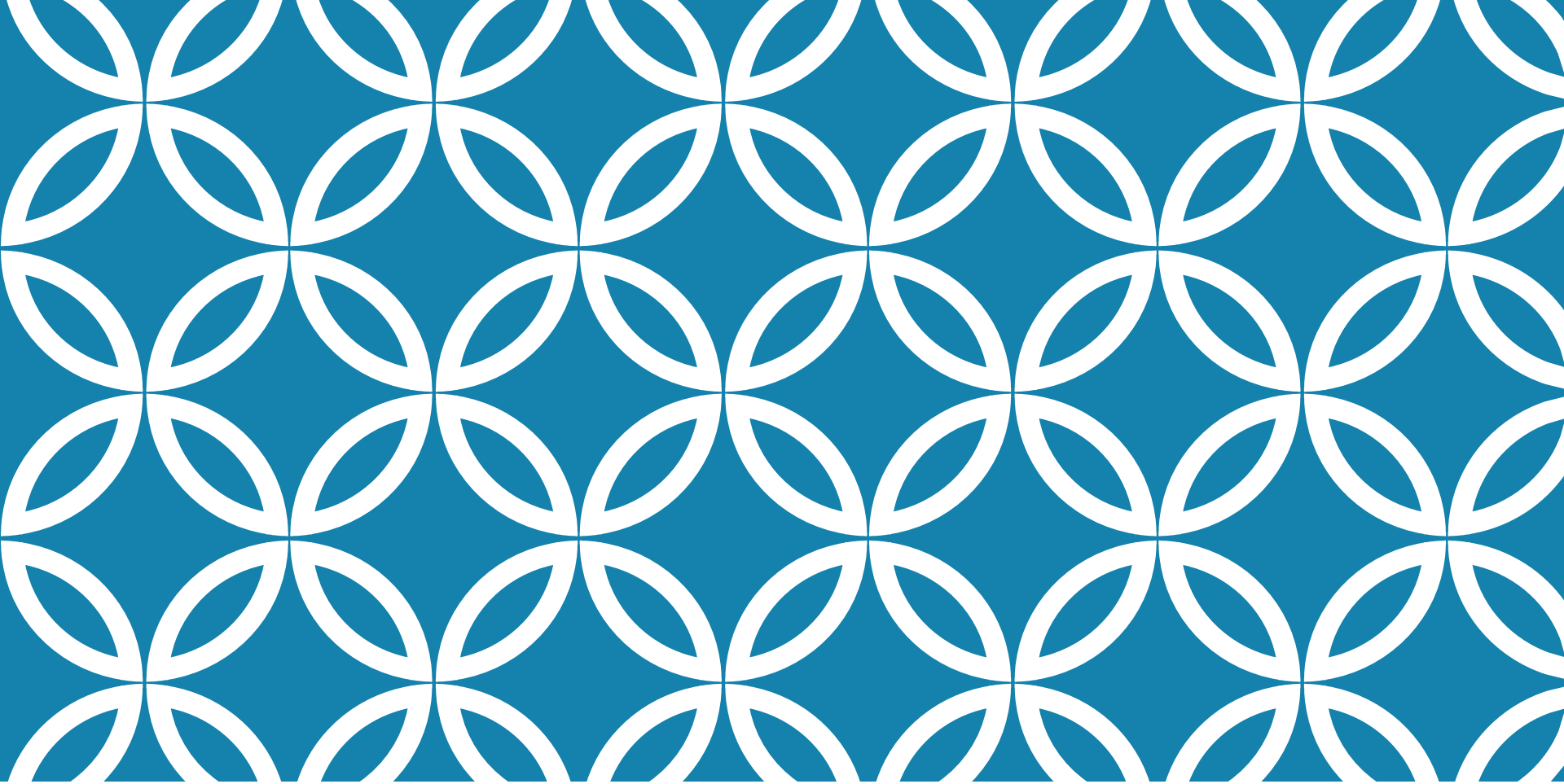
Study showed that low-dose naltrexone is beneficial in patients with ALS.

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.

- ALS Untangled Group, "Low-dose naltrexone for amyotrophic lateral sclerosis," Amyotroph Lateral Scler 2011; 12(1):76-8.



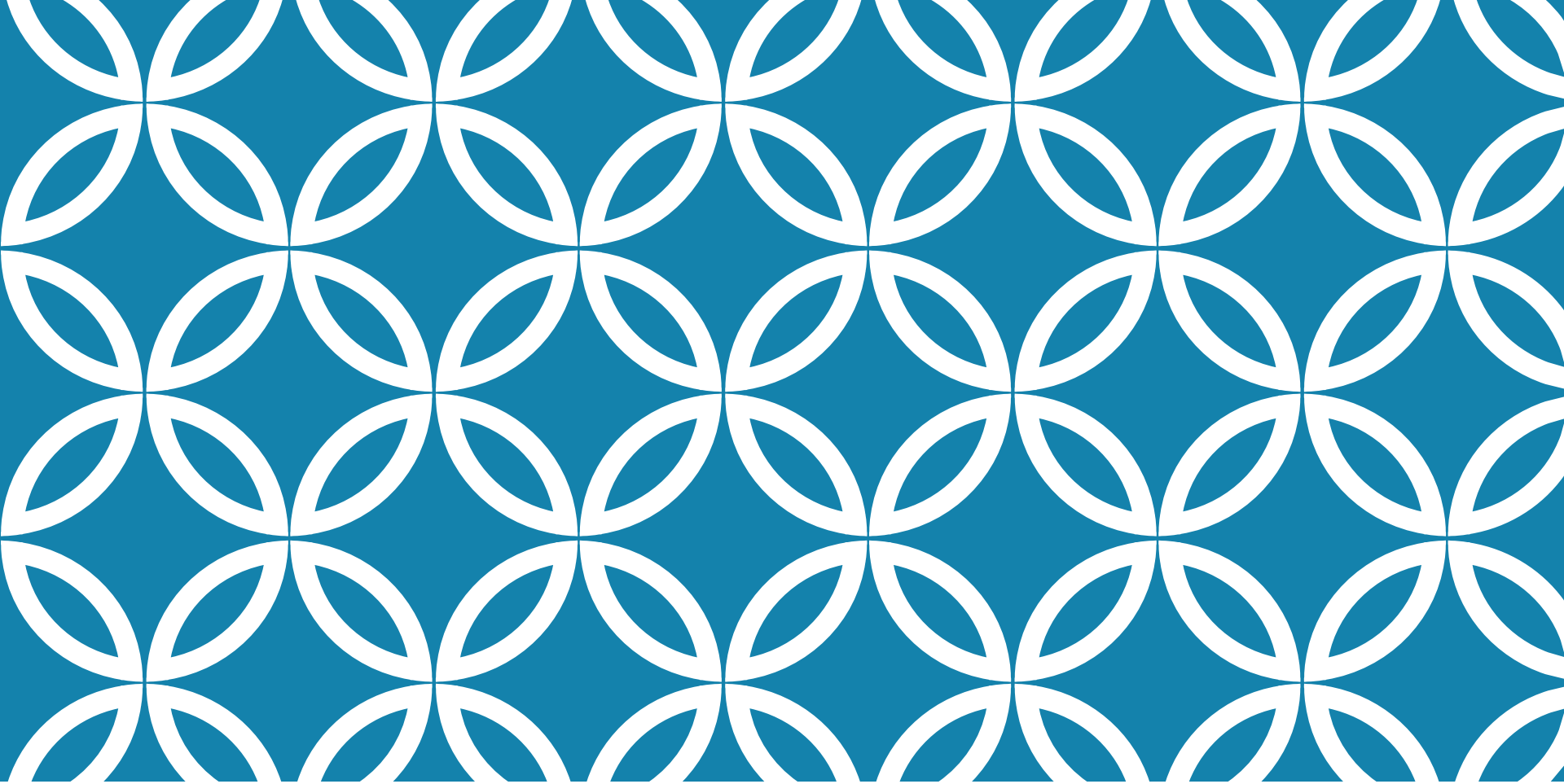
HIV

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."

- Bihari, B., "Efficacy of low dose naltrexone as an immune stabilizing agent for the treatment of HIV/AIDS," AIDS Patient Care1995; 9(1):3.



ITCHING

LDN AND SYSTEMIC SCLEROSIS

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.

- Frech, Tracy, et al. "Low-dose naltrexone for pruritus in systemic sclerosis." Int Jour Rheumatol 2011; 2011:804296.

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.

- Jung, S., et al., "Efficacy of naltrexone in the treatment of chronic refractory itching in burn patients: preliminary report of an open trial," Jour Burn Care Res 2009; 30(2):257-60.

TOPICALLY FOR ITCHING

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.

- Bigliardi, P., et al., "Treatment of pruritus with topically applied opiate receptor antagonist," Jour Amer Acad Derm 2007; 56(6):979-88.

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.

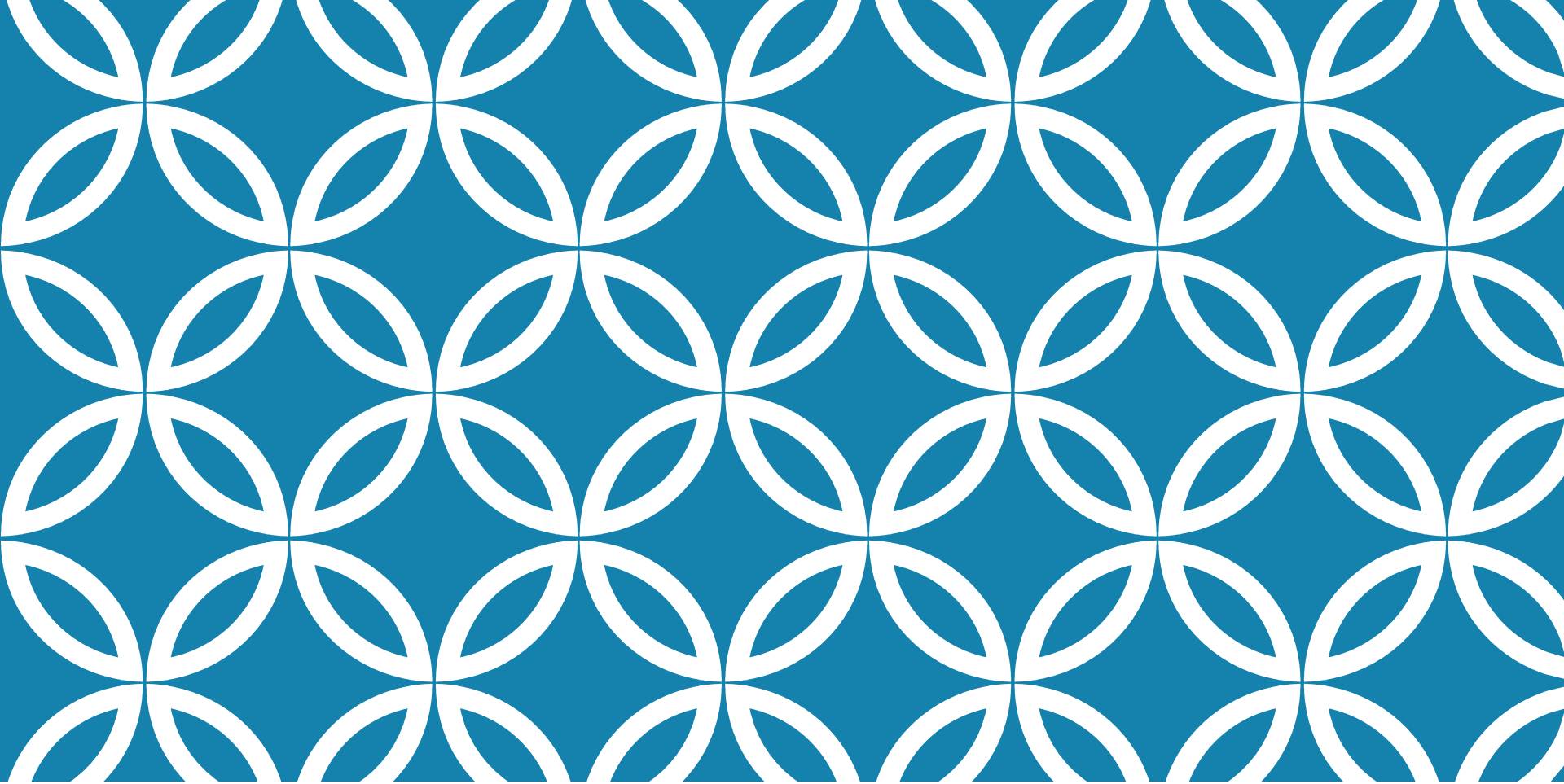
IRRITABLE BOWEL SYNDROME

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.

- Ploesser, J., et al., "Low dose naltrexone: side effects and efficacy in gastrointestinal disorders," Int Jour Pharm Compd 2010; 14(2):171-73.



WEIGHT LOSS

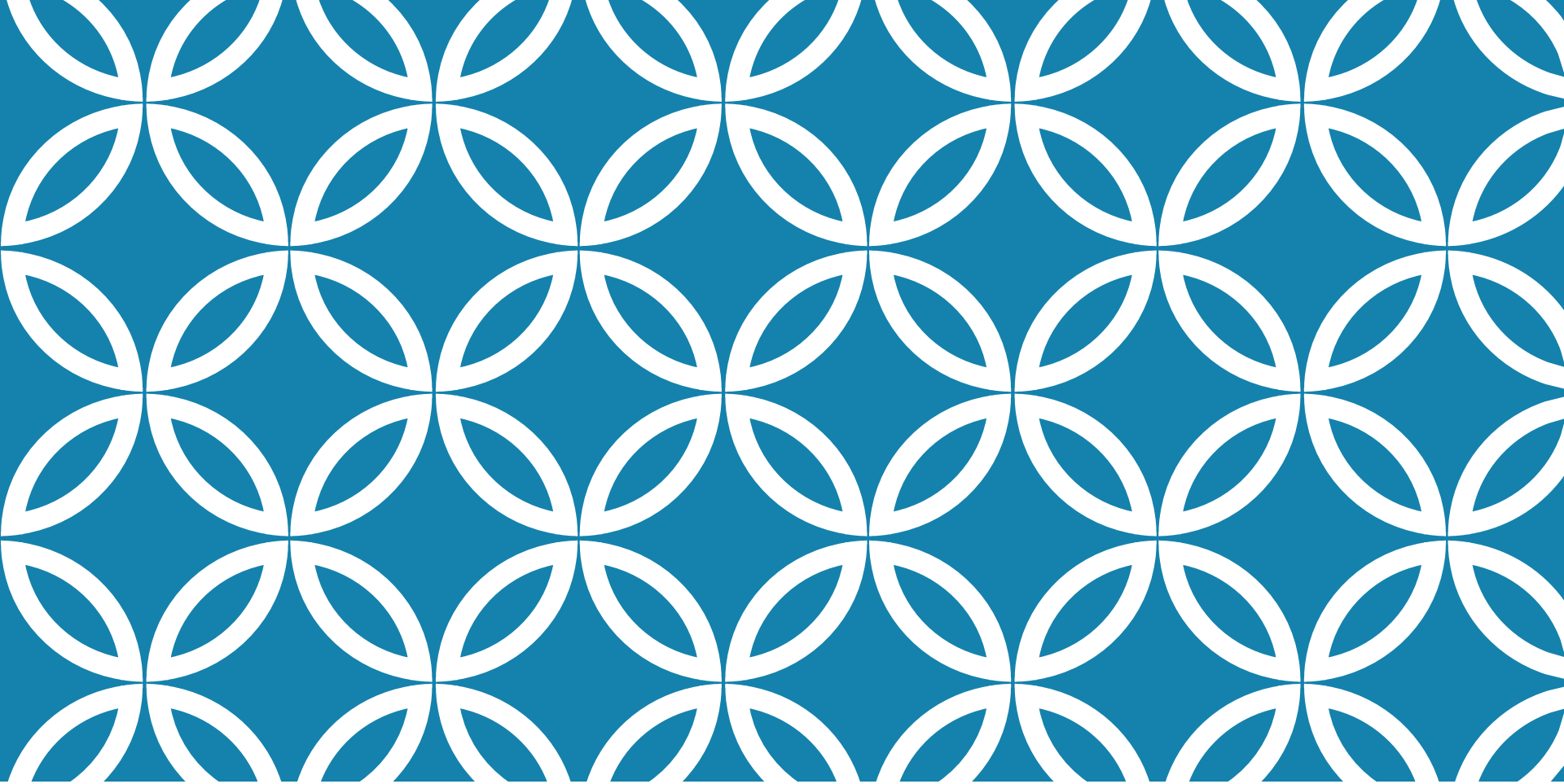
WEIGHT LOSS AND LDN

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.

- Zagon, I., et al., "Topical naltrexone reverses dry eye and restores corneal sensation in diabetes mellitus," Arch Ophthalmol 2009; 127(11):1468-73.

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

- Shinto, L., et al., Multiple Sclerosis in Pizzorno, J., and Murray, M., Textbook of Natural Medicine. St. Louis: Elsevier, 2013, p. 1628-37.
- O'Connor, P., et al., "Oral fingolimod (FTY720) in multiple sclerosis: two year results of a phase II extension-study," Neurology 2009; 72(1):73-9.
- Kappos, L., et al., "A placebo-controlled trial of oral fingolimod in relapsing remitting multiple sclerosis," NEJM 2010; 362(5):387-401.
- Polman, C., et al., "A randomized, placebo-controlled trial of natalizumab for relapsing remitting multiple sclerosis," NEJM 2006; 354(9):899-910.

REFERENCES

- Miller, D., et al., "MRI outcomes in a placebo controlled trial of natalizumab in relapsing MS," Neurology 2007; 68(17):1390-1401.
- The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. 1. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial," Neurology 1993; 43:655-61.
- Lauer, K., "Diet and multiple sclerosis," Neurology 1997; 49(Suppl 2):S55-S61.

REFERENCES (CONT.)

- Johnson, K., et al., "Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial." The copolymer 1 Multiple Sclerosis Study Group. Neurology 1995; 45:1268-76.
- Jacobs, L., et al., "Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis," The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996; 39:285-94.

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

DIET

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.)

- Swank, R., "Treatment of multiple sclerosis with low-fat diet: result of seven years of experience," Ann Intern Med 1956; 45:812-24.
- Swank, R., "Multiple sclerosis: twenty years on low fat diet," Arch Neurol 1970; 23:460-74.
- Swank, R., "Multiple sclerosis: fat-oil relationship," Nutrition 1991; 7:368-76.
- Swank, R., et al., "Effect of low saturated fat diet in early and late cases of multiple sclerosis," Lancet 1990; 336:37-39.

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%.

- Swank, R., et al., "Review of MS patient survival on a Swank low saturated fat diet," Nutrition 2003; 19:161-62.

DIET (CONT.)

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.

OMEGA-3-FATTY ACIDS

Studies have shown an association between inflammatory cytokines and the disease activity in MS.

- Sharief, M., et al., "Association between tumor necrosis factor-alpha and disease progression in patients with multiple sclerosis," NEJM 1991; 325:467-72.
- Hartung, H., et al., "Circulating adhesion molecules and inflammatory mediators in demyelination: a review," Neurology 1995; 45(6 Suppl 6):S22-S32.

REFERENCES

- Hauser, S., et al., "Cytokine accumulations in CSF of multiple sclerosis patients: frequent detection of interleukin-1 and tumor necrosis factor but not interleukin-6," Neurology 1990; 40:1735-39.
- Rudick, R., et al., "Cytokine secretion by multiple sclerosis monocytes: relationship to disease activity," Arch Neurol 1992; 49:265-70.

OMEGA-3-FATTY ACIDS (CONT.)

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-y, 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.

REFERENCE

- Gallai, V., et al., "Cytokine secretion and eicosanoid production in the peripheral blood mononuclear cells of MS patients undergoing dietary supplementation with n-3 polyunsaturated fatty acids," Jour Neuroimmunol 1995; 56:143-53.

VITAMIN D

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

- Wingerchuk, D., et al., "A pilot study of oral calcitriol (1,25-dihydroxyvitamin D3) for relapsing-remitting multiple sclerosis," Jour Neurol Neurosurg Psychiatry 2005; 6(9):1294-96.

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

- Packer, L., et al., “Alpha lipoic acid as a biological antioxidant,” Free Radic B iol Med 1995; 19:227-50.
- Busse, E., et al., “Influence of alpha-lipoic acid on intracellular glutathione in vitro and in vivo,” Arzneimittelforschung 1992; 42:829-31.

ALPHA LIPOIC ACID (CONT.)

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

- Marracci, G., et al., "Alpha lipoic acid inhibits T cell migration into the spinal cord and suppresses and treats experimental autoimmune encephalomyelitis," Jour Neuroimmunol 2002; 131:104-14.
- Schriebelt, G., et al., "Lipoic acid affects cellular migration into the central nervous system and stabilizes blood-brain barrier integrity," Jour Immunol 2006; 177:2630-37.

ALPHA LIPOIC ACID (CONT.)

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.

- Yadav, V., et al., "Lipoic acid in multiple sclerosis: a pilot study," Mult Scler 2005; 11:159-65.

ALPHA LIPOIC ACID (CONT.)

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

- Segermann, J., et al., "Effect of alpha-lipoic acid on the peripheral conversion of thyroxine to triiodothyronine and on serum lipid-, protein- and glucose levels," Arzneimittelforschung 1991; 41(12):1294-98.

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.

- Lovera, J., et al. "Ginkgo biloba for the improvement of cognitive performance in multiple sclerosis: a randomized, placebo-controlled trial," Mult Scler 2007; 13:376-85.

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.

- Reynolds, E., et al., "Multiple sclerosis and vitamin B12 metabolism," Jour Neuroimmun 1992; 40:225-30.

REFERENCES

- Reynolds, E., et al., "Vitamin B12 deficiency, demyelination, and multiple sclerosis," Lancet 1987; 2:920.
- Reynolds, E., "Multiple sclerosis and vitamin B12 metabolism," Jour Neuroimmunol 1992; 40:225-30.

PHOSPHATIDYLSERINE

Phosphatidylserine is part of the nutrient lecithin.

Is one of the important building blocks for neuronal membranes.

Deficiencies of intracellar 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)

- Sanoobar, M., et al., "Coenzyme Q-10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with relapsing-remitting multiple sclerosis," Int Jour Neurosci 2013; 123(11):776-82.

L-CARNITINE/ACETYL-L-CARNITINE

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.

- Lebrun, C., et al., "Levocarnitine administration in multiple sclerosis patients with immunosuppressive therapy-induced fatigue," Mult Scler 2006; 12:321-24.

L-CARNITINE/ACETYL-L-CARNITINE (CONT.)

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 amandatine for MS fatigue.

- Tomassini, V., et al., "Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial," Jour Neuro Sci 2004; 218:103-08.

FOLIC ACID

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

- Isager, H., "Serum folate in patients with multiple sclerosis," Acta Neurol Scand 1970; 46:238-42.

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

- Lee, K., et al., The Antispastic Effect of L-Threonine. In Lubec and Rosenthal (eds.) Amino Acids: Chemistry, Biology and Medicine. 1990, p. 658-63.
- Lee, A., et al., "A double-blind study of L-threonine in patients with spinal spasticity," Acta Neurol Scand 1993; 88:334-38.
- Hauser, S., et al., "An antispasticity effect of threonine in multiple sclerosis," Arch Neurol 1992; 49:923-26.

HYPERBARIC OXYGEN

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.

- Fisher, B., et al., "Hyperbaric-oxygen treatment of multiple sclerosis. A randomized placebo-controlled, double-blind study," NEJM 1983; 308(4):181-86.

CHLAMYDIA PNEUMONIAE

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

  - Srira, S., et al., "Chlamydia pneumoniae infection of the central nervous system in multiple sclerosis," Ann Neurol 1999; 46:6-14.

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.
  - Perlmutter, D., "Fatigue in multiple sclerosis," Townsend Letter for Doctors 1995; 148:49-50.

CANDIDA (CONT.)

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.

- Zouali, M., et al., "Evaluation of auto-antibodies in chronic mucocutaneous candidiasis without endocrinopathy," Mycopathologia 1983; 84:87-93.

EXERCISE

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.

- Petajan, J., et al., "Recommendations for physical activity in patients with multiple sclerosis," Sports Med 1999; 27:179-91.
- Andreasen, A., et al., "The effect of exercise therapy on fatigue in multiple sclerosis," Mult Scler 2001; 17:1041-54.
- Sutherland, G., et al., "Exercise and multiple sclerosis: physiological, psychological, and quality of life issues," Jour Sorts Med Phys Fitness 2001; 41:421-32.
- Mostert, S., et al., "Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis," Mult Scler 2002; 8:161-68.

STRESS

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.

- Goodin, D., et al., "The relationship of MS to physical trauma and psychological stress: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology," Neurology 1999; 52:1737-45.

STRESS (CONT.)

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.

- Mohr, D., et al., "Psychological stress and the subsequent appearance of new brain MRI lesions in MS," Neurology 2000; 55:55-61.

STRESS (CONT.)

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

- Mohr, D., "Stress and multiple sclerosis," Jour Neurology 2007; 254(Suppl 2):1165-68.
- Mohr, D., et al., "Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis," BJM 2004; 328:731-35.
- Schwarz, C., et al., "Stress and course of disease in multiple sclerosis," Behav Med 1999; 25:110-16.

STRESS (CONT.)

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.

- Grossman, P., et al., "MS quality of life, depression, and fatigue improve after mindfulness training: a randomized trial," Neurology 2010; 75:1141-49.

MIND/BODY/SPIRIT

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

- Wahbeh, H., et al., "Mind-body interventions: applications in neurology," Neurology 2008; 70:2321-28.

ACUPUNCTURE

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

- Olsen, S., "A review of complementary and alternative medicine (CAM) by people with multiple sclerosis," Occup Ther Int 2009; 16:57-70.

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

- Agrawal, Y., "Low dose naltrexone in multiple sclerosis," Med Hypotheses 2005; 64(4):721-24.
- Sharafaddinzadeh, N., et al., "The effect of low-dose naltrexone on quality of life with multiple sclerosis: a randomize , placebo-controlled trial," Mult Scler 2010; 16(8):964-69.

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.

- Crinnion, W., "Results of a decade of naturopathic treatment for environmental illnesses: a review of clinical records," Jour Naturopathic Med 1997; 7(2):21-7.

ESTRIOL

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.

- Sicotte, N., et al., "Treatment of multiple sclerosis with pregnancy hormone estriol," Ann Neurol 2002; 52:421-28.
- Kim, S., et al., "Estriol ameliorates autoimmune demylinating disease: implications for multiple sclerosis," Neurology 1999 52(6):1230-38.

REFERENCES (CONT.)

- Palaszynski, K., et al., "Estriol treatment ameliorates disease in males with experimental autoimmune encephalomyelitis: implications for multiple sclerosis," Jour Neuro Immunol 2004; 149(1-2):84-9.
- Draea, S., "Estriol and progesterone: a new role for sex hormones," Int Jour Biomed Sci 2006; 2(4):305-07.
- Soldan, S., et al., "Immune modulation in multiple sclerosis patients treated with the pregnancy hormone estriol," Jour Immunol 2003; 171(11):6267-74.

ESTRIOL (CONT.)

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.

- Voskuhl, R., "Gender issues and multiple sclerosis," Curr Neurol Neurosci Rep 2002; 2:277-86.
- Ibid., Soldan.

ESTRIOL AND TESTOSTERONE

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

- Gold, S., et al. "Estrogen and testosterone therapies in multiple sclerosis," Prog Brain Res 2009; 175:239-51.
- Spence, R., et al., "Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration," Front Neuroendocrinol 2012; 33(1):105-15.

TESTOSTERONE

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

- Voskuhl, R., et al., "Sex hormones in experimental autoimmune encephalomyelitis: implications or multiple sclerosis," Neuroscientist 2001; 7:258-70.