"NALTREXONE, IT'S NOT JUST FOR DRUG DEPENDENCE ANYMORE"

Presenter: Mark Jurovich, RPh, PharmD
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1. Define “Low Dose” Naltrexone (LDN)
2. Give a brief history on Naltrexone
3. Briefly Discuss the current areas of study on the use of “Low Dose” Naltrexone (LDN)
4. Learn how LDN is being used to treat pain.
5. Review dosing and clinical considerations of LDN.
1. Naltrexone was FDA approved in 1984 as a 50 mg tablet for use in treating alcohol dependence and opioid dependence.

2. Low Dose Naltrexone (LDN) – refers to the use of naltrexone at doses of less than 10 mg per day. (most commonly 0.5 to 4.5 mg)

3. Ultra Low Dose Naltrexone – Uses doses in the microgram, nanogram and picogram administered with opioids therapy to increase the efficacy and reduce side effects.
HISTORY OF NALTREXONE

- 1962 Naltrexone discovered by Endo Laboratories in Long Island, NY
- 1980 “Low Dose” Naltrexone (LDN) discovered. LDN effects against cancer discovered by Dr. Ian Zagon at Penn State University
- 1984 Naltrexone (50 mg dose) approved for treating heroin and opiate dependence
- 1985 LDN first used for MS
- 1987 LDN used in AIDS patients
- 2003 LDN Clinical Trial for Crohn’s Disease
- 2009 LDN for Fibromyalgia Trial Published
- 2010 US FDA Grants Orphan Designation for LDN for pediatric Crohn’s disease
- 2015 LDN case reports on Pain and Neuropathy
History and Pharmacology of LDN

Opiate receptors in specific

- **AGONIST**
  - Fits and Activates (Variable)

- **Partial agonist**
  - Fits but doesn't fully activate

- **Antagonist Blocks**
CHEMICAL STRUCTURE

AGONIST

ANTAGONIST

Morphine

Naltrexone
Naltrexone when produced for human consumption, consists of a 50:50 mix of levo- and dextro-isomers (mirror images of each other.

Many drugs have only one active isomer, both isomers of Naltrexone have activity.
MECHANISM OF ACTION
(LEVO-NALTREXONE)

- Naltrexone blocks activity at the opioid receptor (mu, delta and kappa).

- LDN will also block opioid growth factor (OGF) receptors for a short time (3-4 hours)
  - This blockade by LDN causes a “rebound effect” to
    1. increase production of endorphin receptors
    2. increase the sensitivity of these receptors
    3. increase production of endogenous endorphins specifically OGF aka [Met5]-enkephalin
  - This leads to immunomodulation and reduction in cell proliferation via endorphins
MECHANISM OF ACTION
(DEXTRO-NALTREXONE)

- Naltrexone can block toll-like receptor 4 (TLR4) peripherally and no microglial cells in the Central Nervous System
- The inhibition of these non-opioid receptors (TLR4) on macrophages (such as microglia) may decrease inflammatory cytokine release.
- This is thought to be the mechanism behind naltrexone’s anti-inflammatory effects.

Peripheral nerve injury

Excitotoxic neuronal death

Traumatic & hemorrhagic brain injury

Neuronal damage

Endogenous TLR4 agonist

Glia activation & neuroinflammation

Neurodegeneration

Neuropathic pain
MECHANISM OF ACTION OF LDN

LDN

- Increase in endogenous enkephalin and endorphin → Enhancement of immune function
- Inhibition of proinflammatory cytokines → Improvement in inflammatory reaction
- Interaction of the nuclear opioid growth factor receptor → Promotion of DNA synthesis → Healing of corneal ulcers
- Blockade of opiate-R in GI tract → Effect on no. of liquid bowel movements → Healing & repair of mucosal tissue → Improvement in Crohn’s disease activity
- Regulation of TReg and production of IL-10 and TGF-β → Down regulation of TH-17
<table>
<thead>
<tr>
<th>LOW DOSE NALTREXONE</th>
<th>OFF LABEL USES</th>
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<tbody>
<tr>
<td>✓ Multiple Sclerosis</td>
<td>✓ Cancer</td>
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<tr>
<td>✓ Crohn’s Disease</td>
<td>✓ HIV/AIDS</td>
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<tr>
<td>✓ Fibromyalgia</td>
<td>✓ Autism Spectrum Disorder</td>
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<tr>
<td>✓ Rheumatoid Arthritis</td>
<td>✓ Ulcerative Colitis</td>
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<td>✓ Irritable Bowel Syndrome</td>
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Acute disseminated encephalomyelitis
Acute hemorrhagic leukoencephalitis
Addison's Disease
Agammaglobulinemia
Amyotrophic Lateral Sclerosis
Ankylosing Spondylitis
Anti-GBM/TBM Nephritis
Antiphospholipid syndrome
Antisynthetase syndrome
Asthma
Atopic allergy
Atopic dermatitis
Autoimmune aplastic anemia
Autoimmune cardiomyopathy
Autoimmune enteropathy
Autoimmune hemolytic anemia
Autoimmune hepatitis
Autoimmune inner ear disease
Autoimmune lymphoproliferative syndrome
Autoimmune pancreatitis
Autoimmune peripheral neuropathy
Autoimmune polyendocrine syndrome
Autoimmune progesterone dermatitis
Autoimmune thrombocytopenic purpura
Autoimmune urticaria
Autoimmune uveitis
Balo disease/Balo concentric sclerosis
Behcets Syndrome
Berger's disease
Bickerstaff's encephalitis
Blau syndrome
Bullous pemphigoid
Cancers
Castleman's disease
Celiac disease
Chronic Fatigue Syndrome (CFS)
Chronic inflammatory demyelinating polyneuropathy
Chronic recurrent multifocal osteomyelitis
Chron's disease (CD / IBD)
Churg-Strauss syndrome
Cicatricial pemphigoid
Cogan syndrome
Cold agglutinin disease
Complement component 2 deficiency
Cranial arteritis
CREST syndrome
Crohn's Disease (one of two types of idiopathic inflammatory bowel disease "IBD")
Cushing's Syndrome
Cutaneous leukocytoclastic angiitis

Dego's disease
Depression
Dercum's disease
Dermatitis herpetiformis
Dermatomyositis
Diabetes mellitus type 1
Diffuse cutaneous systemic sclerosis
Discoid lupus erythematosus
Dressler's syndrome
Eczema
Enthesitis-related arthritis
Eosinophilic fasciitis
Eosinophilic gastroenteritis
Epidermolysis bullosa acquista
Erythema nodosum
Essential mixed cryoglobulinemia
Evans's syndrome
Fibrodyplasia ossificans progressiva
Fibromyalgia (FB)
Fibrosing aevolitis
Gastritis
Gastrointestinal pemphigoid
Giant cell arteritis
Glomerulonephritis
Goodpasture's syndrome
Graves' disease
Guillain-Barré syndrome (GBS)
Haemolytic anaemia
Hailey – Hailey Disease
Hashimoto's encephalitis
Hashimoto's thyroiditis
Henoch-Schonlein purpura
Herpes gestationis
HIV
Hypogammaglobulinemia
Idiopathic Inflammatory Demyelinating Diseases
Idiopathic pulmonary fibrosis
Idiopathic thrombocytopenic purpura
Autoimmune thrombocytopenic purpura
IgA nephropathy
Inclusion body myositis
Inflammatory demyelinating polyneuropathy
Interstitial cystitis
Juvenile idiopathic arthritis
Juvenile rheumatoid arthritis
Kawasaki's Disease
Lambert-Eaton myasthenic syndrome
Leukocytoclastic vasculitis
Lichen planus
Lichen sclerosus
Linear IgA disease (LAD)
Lou Gehrig's disease (Also Amyotrophic lateral sclerosis)
Lupoid hepatitis
Lupus erythematosus
Lyme Disease
Majeed syndrome
Meniere's disease
Microscopic polyangitis
Miller-Fisher syndrome
Mixed Connective Tissue Disease
Morpha
Mucosa-Habermann disease
Multiple Sclerosis (MS)
Myalgic Encephalomyelitis (ME)
Myasthenia gravis
Myositis
Neuromyelitis optica (Also Devic's Disease)
Neuro-myelitis optica
Ocular cicatricial pemphigoid
Opsoclonus myoclonus syndrome
Orb thyroiditis
Parkinson's Disease
Painful rheumatism
PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcus)
Paraneoplastic cerebellar degeneration
Parkinson’s Disease
Paroxysmal nocturnal hemoglobinuria (PNH)
Parry Romberg syndrome
Pars planitis
Parsonage-Turner syndrome
Peliosis
Pemphigus
Pemphigus vulgaris
Perivenous encephalomyelitis
Pernicious anaemia
POEMS syndrome
Polyarteritis nodosa
Polymyalgia rheumatica
Polymyositis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Progressive inflammatory neuropathy
Psoriasis
Psoriatic arthritis
Pure red cell aplasia
Pyoderma gangrenosum
Rasmussen's encephalitis
Raynaud phenomenon
Reiter's syndrome
Relapsing polychondritis
Restless leg syndrome
Retroperitoneal fibrosis
Rheumatoid arthritis
Rheumatoid fever
Sarcoidosis
Schmidt syndrome
Schnitzler syndrome
Scleritis
Scleroderma
Sjogren's syndrome
Spondyloarthropathy
Stiff person syndrome
Still's disease
Subacute bacterial endocarditis (SBE)
Sue’s syndrome
Sweet’s syndrome
Sydenham chorea
Sympathetic ophthamia
Takayasu's arteritis
Temporal arteritis (also known as "giant cell arteritis")
Tolosa-Hunt syndrome
Transverse myelitis
Ulcereative colitis (one of two types of idiopathic inflammatory bowel disease "IBD")
Undifferentiated connective tissue disease
Undifferentiated spondyloarthropathy
Vasculitis
Vitiligo

Due to LDN’s ability to modulate the immune system and decrease inflammation, it has been used and studied in many chronic pain conditions.
Fibromyalgia symptoms were reduced by low dose naltrexone in two recent studies.

A 2009 single blind randomized crossover pilot study (N=10) compared placebo and LDN in patients with moderately severe fibromyalgia.

- Naltrexone reduced symptoms compared to baseline by 33% vs 2.3% with placebo
- Naltrexone daily tolerability was 96% vs 90% with placebo

In a 2013 double blinded placebo controlled study of 31 patients, significantly greater reduction of baseline pain was seen in the LDN group vs placebo (28.8% reduction versus 18.0%, P=0.016).

Secondary endpoints in the study of general satisfaction with life (P=0.045) and improved mood (P=0.039) also showed improvement over placebo.

Younger, Noor, McCue, Mackey, Low-Dose Naltrexone for the Treatment of Fibromyalgia. Arthritis and Rheumatism Vol 65 No 2 Feb. 2013 pp 529-538
REDUCED PRO-INFLAMMATORY CYTOKINES WHEN STARTING LDN

Parkitny, Younger. Pro-inflammatory Cytokines after Eight weeks of Low-Dose Naltrexone for Fibromyalgia. Biomedicines 2017, 5, 16
LDN is thought to antagonize TLR4 on activated glial cells
  - This could have an indirect inhibitory action on AMPA and NMDA receptors in sensitized glutamate-receptive neurons

In 2013 two case reports were published looking at the use of LDN in CRPS.

Chopra, P, Cooper, M Treatment of Complex Regional Pain Syndrome (CRPS) Using Low Dose Naltrexone (LDN) J Neuroimmune Pharmacol (2013) 8:470-476
CRPS CASE 1

- A 48 year-old male developed CRPS after an injury to his right leg.
  - After having cardiac bypass surgery the CRPS spread to upper chest and arms.
  - He developed significant dystonia of both arms.
- After years of multiple treatments, the patient was started on Naltrexone 4.5 mg once daily (one week after discontinuing opioids).
- Within 2 months of starting the LDN the patient's dystonic spasms discontinued and his reported pain decreased from an average of 8-10 on a pain scale to an average of 5-6.
This case involved a 12 year-old female patient with CRPS in her right foot in 2008 who also developed dystonic muscle spasms in her upper extremities in 2009. The patient had been on multiple medications and rated her pain an 8/10 at its lowest and 10/10 on the worst days. In June 2011 the patient was started on LDN at 3 mg once daily and ketamine troches 10 mg on a prn basis.

- The LDN was increased to 4.5 mg 4 weeks after initiation.
- Pain scores dropped from 7-10/10 to 3-5/10.

The patient later had multiple invasive procedures including surgery with no spread of CRPS. Her CRPS symptoms have since resolved completely.

Chopra, P, Cooper, M Treatment of Complex Regional Pain Syndrome (CRPS) Using Low Dose Naltrexone (LDN) J Neuroimmune Pharmacol (2013) 8:470-476
Naltrexone, through interacting with opioid/endorphin receptors, has an immunomodulation effect.

Naltrexone antagonizing TLR, suppresses cytokine modulated immune system.

Due to these effects, LDN has been used and studied in many autoimmune disease states such as:

- Multiple Sclerosis, Crohn’s Disease, Rheumatoid Arthritis, Ulcerative Colitis, Lupus, etc.
- CRPS may have autoimmunity involved as a recent study found 90% of adult CRPS patients had either autoantibodies against the beta-2 adrenergic receptor, or the M2 muscarinic acetylcholine receptor.

Kohr D, Autoimmunity against the b(2) adrenergic receptor and muscarinic-2 receptor in complex regional pain syndrome. Pain 2011, 152: 2690-2700
**LDN IN MULTIPLE SCLEROSIS**

- It was recently found that [Met5] enkaphalin (i.e. opioid growth factor) levels are low in MS patients and that these can be restored by LDN.

- The author speculated that serum OGF (opioid growth factor) levels may be a new and novel biomarker for onset and progression of MS, as well as a response to therapy.

Ludwig, M Serum [Met5]-encephalin levels are reduced in multiple sclerosis and restored by low-dose naltrexone. Experimental Biology and Medicine 2017; 242; 1524-1533
What IS an Endorphin?
- A chemical peptide made inside the brain and nervous system that binds to opiate receptors to produce pharmacological effects such as pain relief

Symptoms of Endorphin Deficiency Syndrome (EDS)
- Chronic Pain and low pain threshold
- Lack of response to pain medications
- Emotional sensitivity, depression, weepy, lack of joy
- Craves foods that release endorphins such as chocolate, sugar and wine
- Addicted to gluten/dairy (natural opioids)
CLINICAL APPLICATION
Initiation of oral doses

- 0.5-1.5 mg once daily usually at bedtime
- This is increased by 0.5 – 1.5 mg every 1-2 weeks
- Normal doses are up to 4.5 mg once daily

Side Effects

- Vivid Dreams
- Sleep disturbances
Naltrexone can induce withdrawal in chronic, opioid dependent patients, which can be very severe and last up to 3 days.

Patients taking thyroid hormone replacement for the diagnosis of Hashimoto’s thyroiditis should start at lower LDN doses such as 0.5 mg
- Monitor for hyperthyroidism due to LDN reduction of the autoimmune effects.
- The patient’s dose of thyroid may need to be reduced.
Patients who have received organ transplants who are taking immunosuppressive medication are cautioned against the use of LDN because it may counter the effects of these medications.

Patients with type 1 diabetes should monitor blood sugar levels very closely upon initiation.
- Mitigate potential for hypoglycemic events resultant of immune modulation with LDN.

Patients undergoing a surgical procedure should discontinue their LDN at least 72 hours prior to surgery.
NALTREXONE AND UNEXPECTED ACUTE PAIN

Due to potential block of the opioid receptors while on naltrexone (full strength or low dose) alternatives for pain control are needed in acute pain situations

- Acetaminophen (po or IV)
- NSAIDS
- Ketamine IV
- Local anesthetic block per anesthesia
- Epidural analgesia per anesthesia

COMPOUNDING
DOSAGE FORMS

- Capsule – various strengths from 0.5 to 4.5 mg
- Oral solutions
- Transdermal Creams 0.5 – 10%
QUESTIONS?