Low Dose Naltrexone

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Low Dose Naltrexone (LDN)

Learning Objectives

1. **What is Naltrexone? Why Low Dose Naltrexone**
2. **What are the two mechanisms of action of Low Dose Naltrexone (LDN)?**
3. **What Conditions are Known to Be Treated Successfully with LDN?**
4. **What is the Efficacy and Safety of LDN vs. “Traditional” Therapies**
5. **How is LDN Dosed?**
6. **What are the three most common side effects of LDN**
7. **What are the Psychiatric Conditions Addressed by LDN?**
8. **Which herbal and/or homeopathic remedies enhance or mimic LDN**
9. **Identify Skin, Hair, and Pain Syndromes Amenable to LDN input.**

Disclosures

None

1985 New York City AIDS Crisis

Patients Present w Severe Atypical Infections/Inflammation

Etiology? A Virus

Treatment?

Noting Concrete- Anything Goes

Desperate Times Call for Desperate Measures

Enter Naltrexone

- **FDA approved in 1984**
- **50 mg. Naltrexone is an opioid receptor antagonist**
- **Treats alcohol and opioid dependence**
- **No agonist properties to naltrexone.**
- **Diminishing opioid receptors blocks pleasure derived from alcohol or narcotics.**

Opioid System and Opioid Receptors

- **Opioid receptors**
  - ***4 Major Subtypes***
    - **Delta, Kappa, Mu, Nociceptin receptor**

- **Sites:**
  - ***Brain***
  - ***Spinal Cord***
  - ***Periphery Neurons***
  - ***Digestive tract***
  - ***Immune system (80% of Immune System Resides in Small Intestine)***

Opioid System and Opioid Receptors

- **The endogenous opioid system mediates complex social behaviors including:**
  - ***Formation of stable, emotionally committed relationships.***
  - ***Pain Modulation***

- **Immune cells are significantly inhibited by morphine in a dose-dependent manner.**

- **IFN-alpha and IFN-beta production by normal lymphocytes and fibroblasts inhibited by morphine.**

  - ***Inhibition of IFN alpha production by morphine is reversed by opiate receptor antagonists.***
  - ***Immunomodulatory effects of morphine are mediated through the opioid receptor.***

How Does Naltrexone Work? (1)

- **Naltrexone binds to and blocks:**
  - **Pleasure-promoting μ(mu)-, (delta)-and (epsilon)-opioid receptors [endorphins] found on cell membranes**
  - **Opioid growth factor (OGF) receptors [met-enkephalin] found on the membrane of the cell nucleus.**
    - **Opioid system up-regulates NK and T cells, down-regulates TNF-alpha cells and alters cytokine and interferon signaling.**

Origin of Low Dose Naltrexone

- Immune enhancement and inflammatory
- First used in 1985 for the relief of symptoms of AIDS patients
- Originally referenced as LDN for 10 mg or fewer doses.
- Now prescribed in 0.25 to 4.5 mg increments, 10-to 50-fold lower than for opioid addiction.

High Dose Naltrexone vs. Low Dose Naltrexone [2]

High Dose Naltrexone (10 mg/kg)	Low Dose Naltrexone (0.1 mg/kg)
Blocks endogenous opioids, meta-enkephalin receptors continuously. No pleasure experience pleasure from alcohol or opioids. Decrease endorphins. Promotes Cell Growth Increases tumor growth	Blocks opioid receptors temporarily (2-6 hours) Leads to a rebound increase in: Endogenous opioids Endorphins Inhibits cell proliferation Decreases tumor growth

Pain Modulation and the Immune System

The Discovery of Opioid Growth Factors (3)

- **Opioid growth factors, (aka Met(5)-enkephalin, (OGF) and receptors.**

  Pain Modulators

  Regulates immune function & cell proliferation.

- **OGF**
  - **Suppress autoimmune reactions**
  - **Decreases inflammation**
  - **Anti-bacterial, Anti-fungal, Antiviral properties**
  - **Slows growth of malignant cells.**

Naltrexone and Opioid Growth Factors

- Naltrexone blocks OGF activity by attaching to OGF receptor sites.
  - High-dose naltrexone continuously block OGF.
    - Synthesis and sensitivity decrease.
  - LDN temporarily blocks OGF. Synthesis and sensitivity increase.
- Blocking OGF receptors renders cells temporarily deficient in OGF.
  - When unblocked, OGF and OGF receptors produced.

LDN and Opioid Growth Factors [4]

- **LDN Diminishes TNF, IL-6 Production**
  - **Increases endorphins**
  - **Decreases inflammatory cytokines**
  - **Effects shifts from TH-1 (proinflammatory) cells to TH-2 (anti-inflammatory) cells.**

A Brief Look at the Root Cause of Chronic Disease

True or False?

Atherosclerosis and All Chronic Disease

Are Manifestations of Chronic Inflammation

A Brief Look at the Root Cause of Chronic Disease

- Cholesterol is to Heart Disease as Police are to Burglaries
- After all when there is a burglary, there are Police
- Where there is Heart Disease there are Cholesterol Plaques

Biomarkers Elevated In Chronic Disease

Cytokines

C-reactive protein (CRP)

+ Relationship b elevated hs-cRP and cardiovascular (CVD) events.

Chemokines

Toll-like receptors

Fibrinogen

Lipoprotein-associated phospholipase A2

Psoriasis as a Clinical Marker of Inflammation

- **Psoriasis is associated with ⇧ risk for ASVD, CAD, and CVA**
- **Psoriasis Pt. has a 5-year shorter life expectancy due to CVD.**
- ***Psoriasis is associated with elevated CRP and other cytokines***
- **Patients with psoriasis represent an emerging risk population**
- **Moderate to severe psoriasis patients should be screened for CVD risk factors.**

Naltrexone and Psoriasis

LDN found safe and effective for psoriasis including pruritus. [5]

Interleukin 6 is expressed in high levels in psoriatic skin. [6]

Epidermal opioid systems, rather than hyperinnervation causes psoriatic pruritus. [7]

Naltrexone Topical Solutions
(Formulas in Addendum)

Psoriasis Plaque-1% Naltrexone Cream, Lotion or Gel

Alopecia Areata-Topical 1% in Scalp Solution

Topical Wound Care-Naltrexone facilitates closure of full-thickness wounds in diabetic rats.[8]

-Selective blockade of the OGF-OGFr pathway accelerates fibroblast proliferation and wound healing.[9]

Naltrexone Topical Solutions
(Formulas in Addendum)

- **Prevention of Scars and Keloid Treatment** [10]
  - *Fibroblasts regulate immune/inflammatory responses through Toll-like Receptors*
  - *Controls inflammation and manipulates TLR in skin cell receptors*
- **Burns and Contracture Scars**
- **Sjogren's Syndrome (1-4 drops, 50 uM/ml)**
- **Diabetic Neuropathy**
  - *Normalizes tear production and corneal sensitivity in type I diabetic rats.* [11]
- **Sinusitis**
  - *0.5% NTX Nasal Spray*

“TH-1” vs. “TH-2” Helper Cells

- **T cells exhibit "helper" and "suppressor or killer" functions.**
  - T cells sense the presence of infected cells and removes them directly.
  - T helper cells come in two varieties, TH-1 and TH-2.
  - Healthy individuals have more TH-1 cells than TH-2 cells. Injured patients find this ratio reversed. [12]

- **When TH-1 and TH-2 are properly balanced, the immune system is intact.**

“TH-1” vs. “TH-2” Helper Cells

T Helper 1 (TH-1) Cells

Responsible for killing intracellular parasites and perpetuating autoimmune responses

.

Excessive proinflammatory responses can lead to uncontrolled tissue damage.

Excess TH-1 results in cellular immunity issues, i.e. type 1 diabetes mellitus and Crohn’s Disease.

- **Interferon gamma is the main TH-1 cytokine.**

“TH-1” vs. “TH-2” Helper Cells

T Helper 2 (TH-2) Cells

- *The TH2-type cytokines include interleukins 4, 5, and 13,*
- *Associated with the promotion of IgE and eosinophilic responses in atopy*
- *Interleukin-10 (anti-inflammatory response)*
- *In excess, **TH-2 responses will counteract the TH-1 mediated microbicidal action.***
- *Excess of TH-2 or humoral immunity is present in autoimmune, infectious, allergies, and cancer issues.*

B cells assist killer T cells and keeping the immune response under control.

- *Once activated, helper T cells produce immune substances instructing B cells to produce antibodies.*

Conditions Treated by LDN

- Crohn's Disease
- Fibromyalgia
- Multiple Sclerosis
- Cancer
- Autism
- RA/SLE, etc.

- HIV/AIDs –the original use of LDN in 1985
- Parkinson's
- Gulf War Syndrome
- ALS
- Diabetes
- Hashimoto's thyroiditis
- Weight Loss

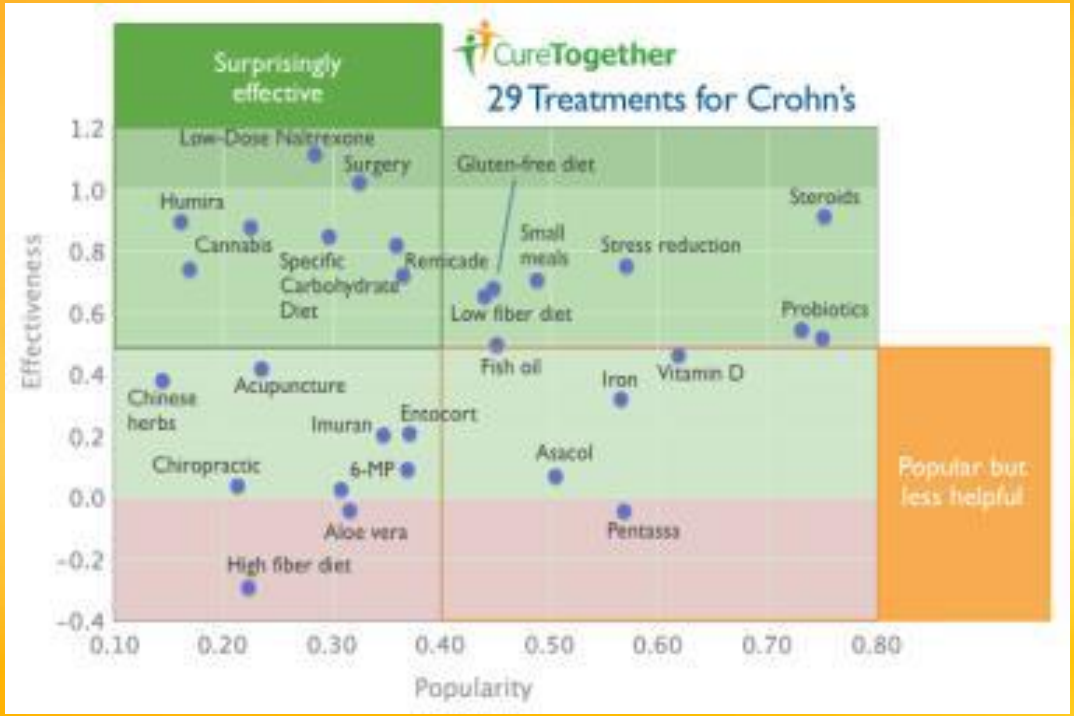
Crohn's Disease

- 17 Patient 2007 Pilot Study
  - Unresponsive or intolerant to conventional therapies
  - *R*eceived 4.5 mg LDN at bedtime.
  - **67% of treated patients vs. 23% in a placebo-controlled trial were in remission of their disease at 90 days.** [13]
    - Improved quality of life scores within four (4) weeks when given the Crohn's Disease Activity Index (CDAI) and Inflammatory Bowel Disease Questionnaire (IBDQ). [14]
- 40 Patient Follow-up Randomized, Double-Blind, Placebo-Controlled Study
- Rx: 4.5-mg Naltrexone or Placebo (Providers and patients masked):
  - **70-point decline in Crohn's Disease Activity Index score (CDAI).**
  - **Secondary outcome- >200% increase in mucosal healing based upon colonoscopy appearance and histology versus placebo.** [15]

LDN and Crohn's Disease

- 67% effective remission rate
- No reports of significant toxicity
- Cost effective (30-60$/mo)
  - "Standard" aminosalicylates (Asacol; Pentasa generics $985- 1200$/mo) or infliximab (4500$/mo). [16]

LDN and Crohn's Disease (17)



Fibromyalgia

Diffuse musculoskeletal pain & sensitivity to pressure at specific trigger points without a diagnosable cause.

“I hurt, I don’t know why, and nothing fixes it.”

It affects 1–2% of the general population, mostly women.

Conventional medical treatments are notoriously ineffective.

S/S

1. **Fatigue**

1. **Sleep disturbances**

1. **Deleterious effects on:**
   - ➢ **Thinking**
   - ➢ **Concentration**
   - ➢ **Memory.**

Pregabalin (Lyrica)

- **FDA approved.**
- **Effectiveness is hit or miss.**
- **Mechanism of Action: Diminishes Nerve Cell Discharges**
- **Ratings between 3.0 and 3.5 on a 5 point scale.**
- **Some rave, others curse it’s existence.**

Lyrica Side Effects [19]

Sleepiness

Vertigo

Feeling of being “Hung Over”

Blurred Vision

Dry Mouth

Swelling of hands, Feet, Mouth, Throat

Chest Tightness

Weight Gain

Loss of Concentration and Memory

Sudden Mood Changes

Unusual Thoughts or Behavior

Extreme happiness or depression

Suicidal thoughts

Bleeding

Bruising

Physical Weakness.

LDN Mechanism of Action in Fibromyalgia

- *A*ffects the microglia, the first line of defense in the central nervous system.
- Microglia activated by cell death, inflammation, and infection
  - Increase pro-inflammatory cytokines, excitatory amino acids, and nitric oxide (NO).
  - Stimulate NF-Kappa Beta, IL-6 to produce more even more proinflammatory cytokines
- Acts on neurons creating pain, fatigue, and the other S/S of fibromyalgia.
- LDN suppresses Microglial Activation.

Fibromyalgia Study [20]

- 12 women; average age 44; placebo controlled single blind crossover study. Exclusions included RF>20 IU/mL, ANA>1:80, and ESR>60.
- Recording parameters:
  - Subjective VAS 0-100, "How severe is your fibromyalgia symptoms been today?"
  - Average daily pain, highest pain, fatigue, sadness, stress, sleep quality, memory remember, GI symptoms & headache frequency and severity diary.
- Objective Findings:
  - Ashi (tender) point exam (via an algometer),
  - Hot and cold pain,
  - ESR.
- 50 % of patients perceived their fibromyalgia as "improved or much improved."
  - 10% of patients stated there was little to no change.

Follow Up Study[21]

- 31 women with fibromyalgia in randomized, double-blind, placebo-controlled, crossover trial.
- Materials:
  - Algometer,
  - Fibromyalgia Impact Questionnaire (FIQ),
  - Beck Depression Index (BDI-II).
- Treatment Arm: 4.5 mg. Naltrexone x 22 Weeks
  - The treatment arm included 4.5 mg of naltrexone for 22 weeks.
- Results:
  - Pain reduced 28.8% with LDN, 18.0% reduction with placebo (P= 0.016).
  - QOL improved (P= 0.045),
  - Mood improved (P= 0.039),
  - Fatigue or sleep did not improve significantly.
    - 32% of patients met the criteria for a significant reduction in pain plus a substantial decline in either fatigue or sleep problems vs. 11% placebo (P= 0.05)
- Side effects were similar to placebo with no serious side effects reported.

Multiple Sclerosis

Prevents excitatory neurotoxicity of glutamate on neuronal cells and oligodendrocytes

- ***Reduces*** **inducible nitric oxide synthase activity**
- ***D*****ecreases peroxynitrite formation**
- ***Inhibits*** **glutamate transporters.**

Reduces apoptosis of oligodendrocytes. [22]

Multiple Sclerosis Study[23]

60 (of 80) patients completed eight weeks of 4.5 mg LDN nightly.

- **Self-reported quality of life questionnaires.**
- **LDN well tolerated and exhibited no serious adverse events.**

Findings:

- **3.3-point improvement on the Mental Component of the SF-36 G.H. Survey (p = 0.04)**
- **6-point improvement on the Mental Health Inventory**
- **1.6-point improvement on the Pain Effects Scale (p =.04)**
- **2.4-point improvement on the Perceived Deficits Questionnaire (p = 0.05)**

Quality of Life Study

- Effects on spasticity, pain, fatigue, depression, and quality of life:

- Beta-endorphins (BE) and beta-endorphin concentration increased, resulting in a significant reduction of spasticity. [24]

Cancer

- **Opioid growth factors (OGF) are important regulators of the onset and progression of a variety of human cancers. OGFs bind to the OGF receptors (OGFr) to delay the interface of the cell cycle.**

- **Increasing OGF-OGFr activity in cancer cells by exogenous OGF depresses cell proliferation.[25]**

- **OGF suppresses cancer growth in hepatocellular and follicular thyroid carcinoma cell lines. [26-27]**

- **The opioid growth factor (OGF;[Met(5)]-enkephalin) and its receptor (OGFr) mediate the action of LDN on cell proliferation. LDN produces rebound OGF activity. LDN inhibits cell proliferation in vivo. [28]**

Cancer Studies

- **In vitro and in vivo experiments show increases IL-2, WBCs, NK cell activity, interferon, greater destruction of opportunistic organisms, and cancer cells. [29]**

- **LDN (0.1 mg/kg) reduced neuroblastoma tumor incidence in mice 66%, decreased tumor development 98% and increased survival 36%. [30]**

Cancer Studies 2

- Mice inoculated with ovarian tumors treated with short-term LDN combined with either cisplatin or taxol, revealed the **LDN + cisplatin,** but not taxol, mice, had less tumorigenesis and angiogenesis. **The LDN alleviated weight loss associated with cisplatin toxicity.** [31]

- A review of case reports of several **pancreatic cancer patients treated with IV lipoic acid + LDN reported all signs of cancer gone including liver metastases.** [32]

Cancer Studies 3

- A prospective phase II trial of 24 advanced pancreatic cancer patients who failed chemotherapy treated with 250 µg/kg OGF IV resulted in a three-fold increase in median survival time vs. untreated patients with tumor sizes stabilizing or shrinking in 62% of patients. (33)

- Although there is strong indications of benefits with little risk for LDN, there is limited support for its use in cancer, in the medical literature.

The Autistic Spectrum

- 18 children ages 3 –8 showed improvement with fidgeting and hyperactivity. There was no effect on learning. [34]

- Double-blind, placebo-controlled crossover study, 13 children 3 -8 years old improved in :
  - **Self-injurious behavior**
  - **Communication skills**
  - **Hyperactivity, Agitation**
  - **Social withdrawal**
  - **Stereotyped behaviors**
  - **Attention**
  - **Eye contact**

Low Dose Naltrexone in Anti-Aging

- **Immune system changes with aging are directly affected by low dose naltrexone.**
- **LDN increases opiate receptors, beta-endorphins (BE), and met-enkephalins(ME) shifting the balance from TH1 to TH2**
- **Improves autoimmunity,**
- **Downregulates NFk2**
- **Downregulates inflammatory cytokines TNF, IL-1, and IL-6. [37]**

LDN Modulates the Immune System and Brain Neurochemistry

- **LDN promotes health supporting immune-modulation.**
  - **Reduces oncogenic and inflammatory autoimmune processes.**
- **LDN upregulates endogenous opioid activity:**
  - **Promotes stress resilience, exercise, social bonding, and emotional well-being.**
  - **Ameliorates psychiatric problems such as autism and depression.**
- **LDN used effectively as a buffer.**
  - **Beneficially modulates the immune system and the brain neurochemistry that regulate positive affect." [38]**

Dosing

- *Initial Rx.*

- *First 2 Weeks*

Hashimoto's 0.5 mg
MS 1.0 mg
Others 1.5 mg

- *Week 3-4*

- **(Increase dose by the same amount)**
  - **Hashimoto's 1.0 mg**
  - **MS 2.0 mg**
  - **Others 3.0 mg**

- *Week 5-6*

- **Hashimoto's 1.5 mg**
- **MS 3.0 mg**
- **Others 4.5 mg**

Dosing

- ***Maintenance***
  - ***Week 6 and Beyond!***

- **See patient in follow-up six (6) weeks after beginning LDN**
- **If full dose tolerated, consider 3-6 month Rx, usually 3–4.5 mg**
- **May need to lower dose (as low as 0.5-1 mg) as symptoms improve.**

Rx. for Autoimmune Thyroid Disease

Hashimoto's Thyroiditis

Naltrexone 0.5 mg

#84

1 po qhs x 14 days then:

2 po qhs x 14 days then:

3 po qhs x 14 days then:

Evaluate effect on thyroid before increasing.

Maximum Dose: 3.0 mg

Multiple Sclerosis/Hashimoto's Maximum Dose

Naltrexone 3 mg

#90

1 po qhs

Refill x 1

Other Indications Maximum Dose

Naltrexone 4.5 mg

#90

1 po qhs

Refill x 1

LDN Dosage: Children [39]

Naltrexone liquid or topical 1 mg/mL

Begin at 0.1 mL (0.1 ml)

Increase by 0.1 mL q3-7 days up to maximum dose of 0.1mg/kg

Children > 40 kg Adult dosing

Effects/Side Effects[40]

- Increased sense of well-being
- Increased Energy
- Increased self-confidence
- Increased Muscle Strength
- Increased sex drive
- Drowsiness
- Body aches
- Muscle ache
- Sore joints
- Hypothyroidism
- Ulcer
- Difficulty sleeping

Most Common Side Effects

- **Insomnia**
  - *OGF activity has diurnal peak shortly after sleep*
  - *Typical recommendations are for LDN to be taken at bedtime*
- **“Vivid Dreams”**
  - *Start with lower doses and gradually increasing*
  - *Most resolve in a few weeks*
  - *LDN can be taken at suppertime, lunch or even in the morning*
- **Nausea**

LDN and Opioids

- **Do not use LDN with opioids as they blunt the effects of opiates.**
  - Result is headache, nausea or *frank* opioid withdrawal symptoms.
  - If opioids needed, discontinue LDN 2 days before until two (2) days after opiates administered.
- In emergency (fracture, etc.), the patient may need to take an increased dose of opioids.
- Long-term opioid users are at risk for severe and life-threatening reactions if started on LDN.
  - **The patient must have a seven (7) day washout of his or her opioid before beginning LDN**
  - *B*e careful being "white knight." Social service agencies, esp. hospice will cancel services if they cannot administer opioids. LDN Practitioner left doing preauths etc. for hospital beds, wheelchairs.

Low Dose Naltrexone Pearls

■ Hashimoto's Thyroiditis

■ Thyroid function normalizes requiring less supplemental thyroid.

■ Beginning doses should be in 0.5-1.0 mg range. Increase slowly.

■ Chronic Infectious Diseases

(Candida, EBV, Herpes 1 and 2, H. pylori, Yersinia (gastroenteritis), Lyme Disease)

Herxheimer's reactions can occur as immune function improves

Cancer Chemotherapy

- **LDN interferes with action of chemotherapy**
- **Stop LDN two (2) days before until two (2) days after chemo.**

Psychiatric Uses

- **Psychomotor Activity, Fatigue**
- **Medical Conditions Affected by Immune System or**
- **PTSD, Depersonalization Disorder**
- **Depression. Anxiety, OCD, Psychosis**
- **Autism**
- **Sex Drive, Fertility**
- **LDN Assisted Behavior Modification**
- **Addiction**
  - ***Substances: Etoh, Opioids***
  - ***Processes: Eating, Sex, Gambling, Internet***
  - ***Weight Control***

LDN, Weight Loss and Inflammation

Effects of Inflammation on Weight Gain

- Decreased T4 to T3 conversion (leading to a state of thyroid resistance)
- Increased insulin resistance (leading to weight gain)
- Low testosterone and increased expression of aromatase leading to high estrogen levels
- Increased leptin levels (leading to weight gain)
- Increased appetite

LDN for Weight Loss

1. **Naltrexone Reduces Insulin Resistance**
2. **Naltrexone Increases Growth Hormone**
    a. ***(Increased Insulin=Decreased GH)***
3. **Naltrexone Modulates Appetite**
4. **Naltrexone Acts as an Anti-Inflammatory Agent**
5. **Naltrexone Improves Sleep & Sleeping Patterns**
6. **Naltrexone** increases total T3 levels and improve T4 to T3 conversion.

Natural Remedies that Mimic/Enhance LDN

T Cell Regulators (Immune Enhancement)

Vitamin D3
Glutathione
Selenium
Zinc
Iodine
Probiotics
Butyrate (Prebiotics)
Vitamin A (Cod Liver Oil)

Anti-Inflammatory

Curcumin
Boswellia
Fish Oil
Green Tea Extract
Skullcap Root Extract
Quercetin
Bromelain

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LDN Topical Formulas[41]

- **Topical Naltrexone for Eczema, Psoriasis and Itch**
  - Naltrexone HCl 0.5%/Diphenhydramine HCl, 2%/Vitamin D3 5000 IU/Gm
  - Naltrexone HCl 1%, Tranilast 1%/Cyanocobalamin 0.07% Topical Cream
  - Melatonin 2.5%/Naltrexone HCl 1%/Tranilast 1% Topical Cream
  - Naltrexone HCl 1%/Pramoxine HCl 1% Topical Gel
- **Alopecia**

  Topical Naltrexone 1% in Scalp solution

  Can add Minoxidil 5%, Biotin 0.3% , Zinc 0.1%, B12 0.07%

LDN Topical Formulas

- **Wound Care**

  – Naltrexone HCl 0.5%/Arginine HCl 1%/Phenytoin 2%/Timolol 0.5% Topical Gel

  – Naltrexone 1%, Arginine 1%, Phenytoin 5%, Aloe Vera 0.2%, Nifedipine 1% in Spira Wash Gel

  – Naltrexone 1%, Arginine 1%, Phenytoin 5%, Aloe Vera 0.2%, Nifedipine 1%, (Clindamycin 2% +/-metronidazole 2%) in Spira Wash Gel

Scars

– Naltrexone HCl 1%, Aloe Vera 0.2% in Topical Gel
– Naltrexone HCl 1%/Pramoxine HCl 1% Topical Gel
– Naltrexone HCl 1%, Beta-Glucans 0.2% Topical Gel

Nasal Spray and Eye Drops

Naltrexone HCl 0.5% Nasal Spray

- Muco-adhesive spray
- Consider adding specific ABX required for infections
- Erosion of tissue? Add wound care components

Naltrexone 0.5% Eye drops

- Must be done in sterile conditions
- Bid-tid application into affected eye
- Have seen mixed in with ABX

Pain Formulas

Arthritis Pain

– Naltrexone HCl 3%/Magnesium Chloride 10%/Cetyl Myristoleate, 2% Topical Lipoderm® ActiveMax™

Neuropathic Pain

– Naltrexone HCl 3% Topical Lipoderm®

– Naltrexone HCl 3%, Ketamine HCl 5%/Gabapentin 10%/Clonidine HCl 0.2%/ Baclofen 2% Topical Lipoderm®

Migraine Pain

– Naltrexone HCl 3%, Ketamine HCl 5%/Amitriptyline 2%, Cyclobenzaprine 2% Lidocaine 2, Topical Lipoderm

Post-Herpetic Neuralgia

– Naltrexone HCl 1%/Deoxy-D-Glucose 0.2%/EGCg 0.2% Ketamine 3%, Lidocaine 5% Lipoderm®