LOW DOSE NALTREXONE

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Disclaimers

- None

What is Naltrexone

- Oral Opioid antagonist developed in 1963 by Endo pharmaceutical
- First approved use by the FDA was for Opioid addiction in 1984 (marketed by Dupont)
- In 1995 approved by the FDA to treat Alcoholism

Naltrexone

- Drinking alcohol enhances endogenous opioid activity
- Several research studies in animals showed that by giving small amounts of morphine this increased consumption of alcohol in rats
- It was concluded that the rewarding effects of alcohol are mediated at least partially through the opioid system

Naltrexone

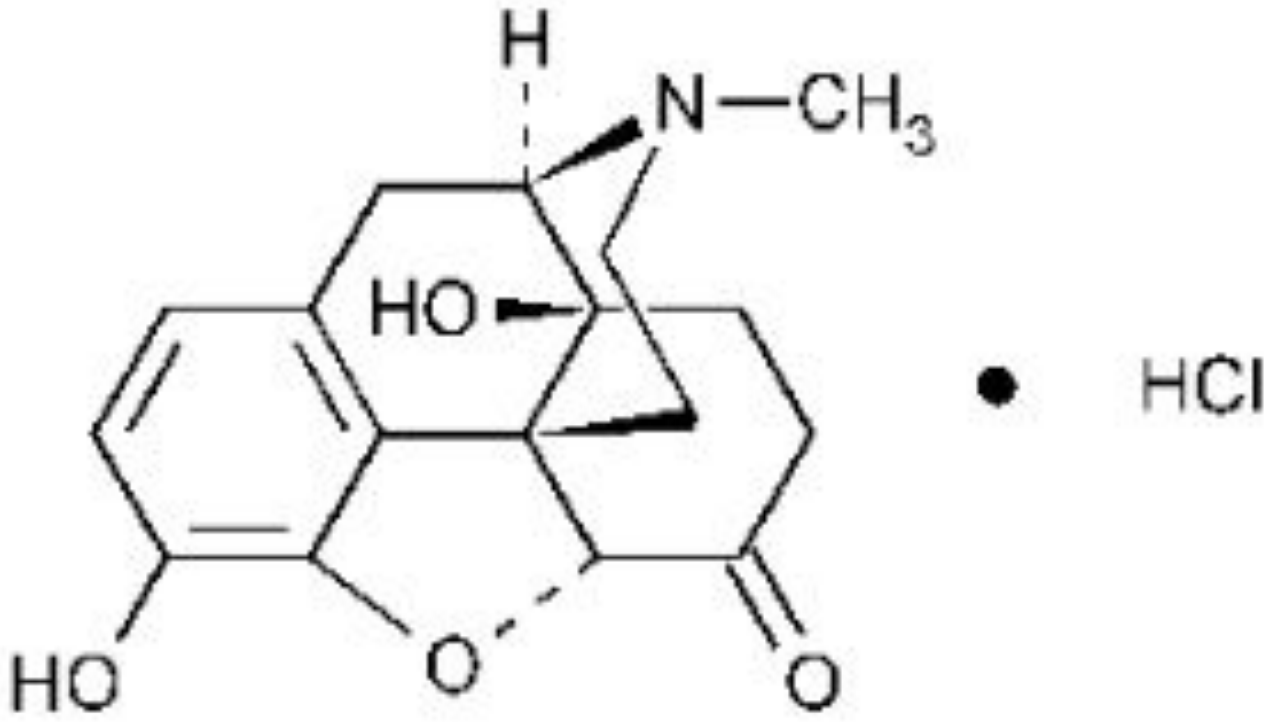
- Two separate research teams found that these rewarding effects were diminished by blocking the opiate receptor and thus decreasing dopamine release from the nucleus accumbens

Naltrexone Pharmacology

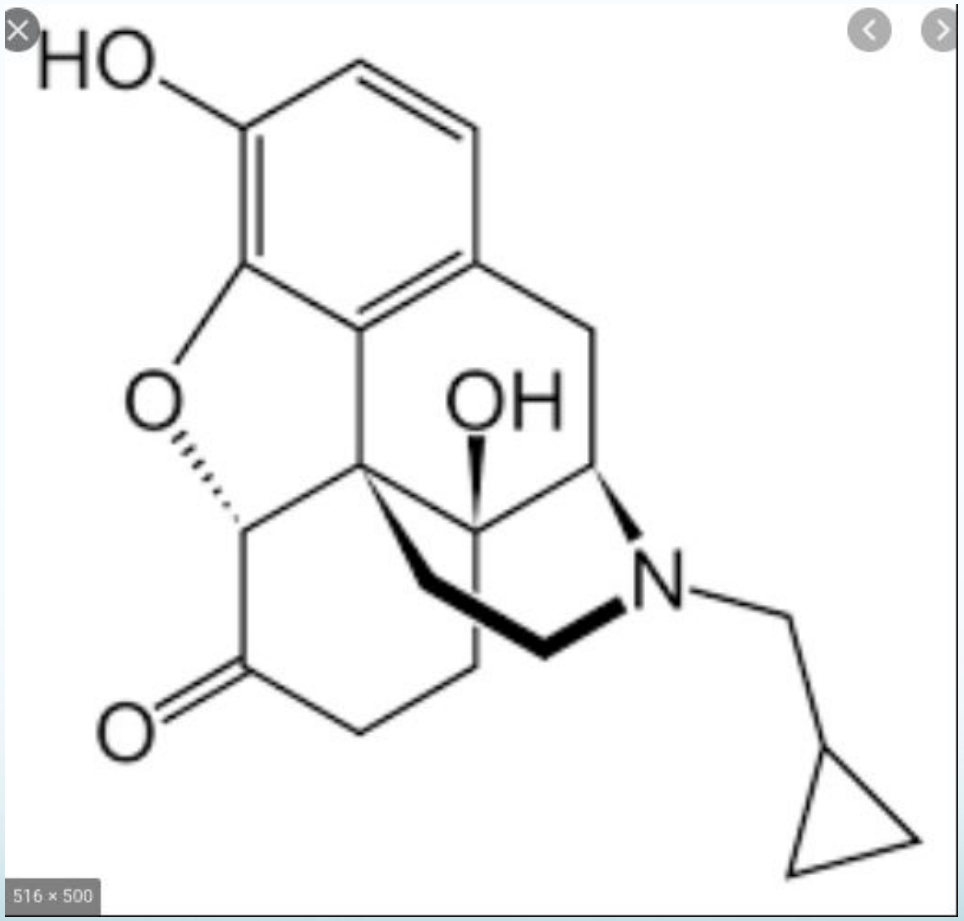
- Derived by the substitution of N-Methyl group of Oxymorphome with a Cycloproplymethyl group

- Oxymorphone is a metabolite of Oxycodone and is marketed as Opana

Oxymorphone



Naltrexone



Naltrexone Pharmacology

- High oral bio availability
- 96% absorbed but significant first pass metabolization
- 98% metabolized, the rest renal clearance
- Primary active metabolite 6-Beta naltrexol

Naltrexone Pharmacology

- Reaches peak plasma concentration in 1-2 hrs
- @1/2 life 14 hours (of the 6-Beta Naltrexol)

Naloxone

- Only available IV or Nasal spray
- Onset 1-2 minutes iv or 2-5 subcutaneously
- Duration @ 30-90 minutes
- Metabolized in the liver 98%

Mechanism of Action #1

- In low dose (.5-4.5mg) it has shown an anti-inflammatory effect on the CNS through glial cell modulation.

- Acts on Toll-like receptor 4 (TRL-4) as an antagonist

Mechanism of Action #1

- Toll like receptor family plays a fundamental role in the pathogen recognition and activation of innate immunity

Mechanism of Action #1

- Microglial TRL-4 activation results in the production and release of inflammatory end-products such as interleukin-1, tumor necrosis factor alpha, interferon-B and nitric oxide

Mechanism of Action #1

- The inflammatory milieu produced by these compounds leads to transduction sensitivity.

- Peripheral and central sensitization of nociceptor pathways leads to hyperalgesia and allodynia

Mechanism of Action #1

- Thus the proposed mechanism of action is that by blocking TRL-4 one has reduced inflammation around the nociceptive neural pathways, the initiation and propagation of central sensitization is attenuated.

Mechanism of Action #1

- Work with Dextro-Naltrexone helps to support this hypothesis
- Dextro-Naltrexone is a stereoisomer of naltrexone which is active at microglia receptors but has NO activity on opioid receptors
- Dextro-Naltrexone possesses analgesic and neuroprotective properties (in rat model)
- Therefore, the analgesic and, anti-inflammatory, and neuroprotective effects of naltrexone do not appear to be dependent on opioid receptors

Mechanism of Action #2

- Another proposed mechanism may involve up regulation of the basal opioid receptor signaling

- At low doses the antagonism leads to up regulation of physiological basal opioid signaling with observed increase in endorphins, met enkephalin and opioid growth factor

Mechanism of Action #2

- Up regulation leads to increases in Mu and Delta endogenous opioid expression

Mechanism of Action

- Very- low dose, .001-1mg
- Possibly same as low dose
- Used as add on for methadone taper

Mechanism of Action #2

- Ultra low dose <.001mg
- Binding to high affinity filamin-A site (scaffolding protein) and reducing Mu opioid receptor associated Gs coupling, thus analgesic effects of opioid potentiated and unwanted side effects mitigated

Mechanism of Action

- Activated Gs promotes Adenylyl Cyclase activity thus increase CAmp
- Activated Gi decreases Adenylyl Cylase thus decrease Camp
- In the presence of chronic opioid admission the Mu receptor shifts from Gi to Gs, thus possible cause of hyperalgesia/tolerance/dependence

Clinical Use

- First found by Dr. Bernard Bihari
- studied effects on AIDS patients 1985-6 at Downstate Medical Center in Brooklyn NY
- Immune system regulated by endorphins and he had found that naltrexone would increase endorphin production, thus boost the immune system
- Found 3mg would markedly increase endorphins when given at night, peak release of endorphin between 2-4am

Clinical Use

- 9 month placebo controlled study found that those AIDS patients taking the drug had fewer deaths many fewer opportunistic infections versus placebo.
- T helper cells dropped significantly less in those taking the naltrexone versus those who were on placebo

Clinical Use

- Fibromyalgia

  Now seen as a neuro inflammatory condition

  Younger et al 2014 Clin Rheumatology

  randomized placebo controlled cross over

  study.

Clinical Use

- Fibromyalgia

  Used 4.5 mg, 20 week study

  31 patients all noted significant improvement

  in pain, satisfaction with life and mood.

Clinical Use

- Fibromyalgia

  Parkitny L, Younger, J 2017 Biomedicines

  10 week single blind study 8 women.

  Outcomes showed significant decrease in Il-6,

  TNF-Alpha (inflammatory cytokines)

Fibromyalgia

- Younger J, Noor N et al 2013 Arthritis and Rheumatology

  Reported that is 38 patients they studied that the

  that fibromyalgia patients with a higher ESR at

  baseline tended to have a greater pain reduction

  when taking LDN (placebo cross over study)

Clinical Use

- Multiple Sclerosis

  prototypical Auto-Immune

  Neuro-Inflammatory disease

  Several studies with slightly mixed results

Clinical Use

- Multiple Scerlosis

  Gironi et al Multiple Scerlosis 2008

  open label pilot study 40 patients with progressive MS treated over 6 months.

  dosing started at 2mg and after two weeks 4mg

Clinical Use

- Multiple Sclerosis

  Gironi noted statistically significant decrease in spasticity, well tolerated, found significant increase levels of beta endorphins

Clinical Use

- Multiple Scerlosis

  Ludwig et al, Multiple Sclerosis Journal 2016

  retrospective study 215 patients over 10 yrs

  relapsing/remitting type

Clinical Use

Patient demographics, number and duration of visitation, and walking.

	LDN–Copaxone	LDN only
Number	32	27
Mean age, years	52.5 (M)	50.3 (M)
	46.7 (M)	55.7 (F)
Sex, % female	66	63
Number of visits (range)	6.4 ± 0.5 (2–10)	4.6 ± 0.5 (1–10)*
Mean length of LDN, days	1095 ± 113	1418 ± 97*
Range of LDN treatment, months	5–52	1–72

Clinical Use

- Multiple Sclerosis

  60% reported improvement with fatigue

  75% recalled improvement quality of life

  dosing 3-4mg qday

  77% no significant side effects

  6% insomnia

  5% nightmares

Clinical Use

- Multiple Sclerosis

  Sharafaddinzadeh et al Multiple Sclerosis

  2010

  randomized placebo controlled 17 weeks no

  statistical difference in quality of life measures

Clinical Use

- Multiple Sclerosis

  Cree et al Annuls of Neurology 2010

  8 week, 60 patients significant improvement

  mental health component of quality of life

  (4.5mg) x over placebo controlled

Clinical Use

- Inflammatory Bowel Disease (IBD) considered a Neuro-Inflammatory disease with symptoms of hyperalgesia/abdominal pain

Clinical Use

- IBD

  Parker et al in Cochrane Database Syst. Rev, 2018

  Identified two studies, 46 participants

  including 12 children

  placebo controlled studies, 12 wks adults

  8 wks children

Clinical Use

- IBD

  Smith et. al. , Am J Gastroenterol 2007

  Adults with Crohns disease used 4.5 mg

  89% response to therapy

  67% remission

  Improvement with quality of life vs baseline

Clinical Use

- IBD

  Smith et al. J Clinical Gastroenterology, 2013

  avg age 12.3 yrs

  first 8 weeks placebo vs LDN .1mg/kg followed

  by open labeled treatment with LDN

  25% considered remission

  67% improvement with mild disease activity

  Systemic and Social quality of life improved

Clinical Use

- Dermatology

Jaros, J et al, Journal of Drugs in Dermatology

primarily oral at 4mg but one study in atopic dermatitis topical (chronic pruritic disorder)

punch biopsy showed increasing staining of epidurmal mu-opioid receptors after 2 weeks,

Clinical Use

			ment at 12 months
Hailey-Hailey	Ibrahim *et al* (2017) [17]	Case series (3 patients)	>80% improvement at 2 and 3 months
Hailey-Hailey	Albers *et al* (2017) [8]	Case series (3 patients)	Clinical resolution of lesions at 2 months
Lichen planopilaris	Strazzulla *et al* (2017) [6]	Case series (4 patients)	Decreased pruritus and disease progression at 1 and 4 month follow-up
Systemic Sclerosis	Frech	Case series	Decrease in pruritus

Clinical Use

- Cancer

  thought is that LDN reduces tumor growth by interfering with cell signaling and by regulating immune system function.

  found that cells pre treated with LDN are more sensitive to the cytotoxic effects of common chemo-therapeutic drugs.

Clinical Use

- Case Reports

  Diabetic Nueropathy-1

  Chronic Low Back Pain-1

  CRPS-2

- All four reports, no patient side effects, decrease daily pain score

Clinical Use

- LDNresearchtrust.org
- Based in the UK, lists other conditions for use of LDN

Side Effects

- Generally very safe!!

most glaring side effect “vivid dreams”

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Side Effects

More common

- Abdominal or stomach cramping or pain (mild or moderate)
- anxiety, nervousness, restlessness or trouble sleeping
- headache
- joint or muscle pain
- nausea or vomiting
- unusual tiredness

Side Effects

Less common

- Chills
- constipation
- cough, hoarseness, runny or stuffy nose, sinus problems, sneezing, or sore throat
- diarrhea
- dizziness
- fast or pounding heartbeat
- increased thirst
- irritability
- loss of appetite
- sexual problems in males

Side Effects

- chest pain
- confusion
- discomfort while urinating or frequent urination
- fever
- hallucinations or seeing, hearing, or feeling things that are not there
- itching
- mental depression or other mood or mental changes
- ringing or buzzing in the ears

Dosing

- NO FDA APPROVED DOSING OR USE!!!!
- All the uses are technically off label!!
- Commercial Carriers do NOT pay for this medication
- Must be compounded (pharma does not make this!)

Dosing

- Go low go slow
- I will start with 1mg in the evening, holding dose for at least three weeks prior to titrating
- Maximum dose from literature is 5 mg

Shameless Plug!!!


RUTGERS
New Jersey Medical School