Ultralow Dose Naltrexone:
Exploring microgram doses of LDN

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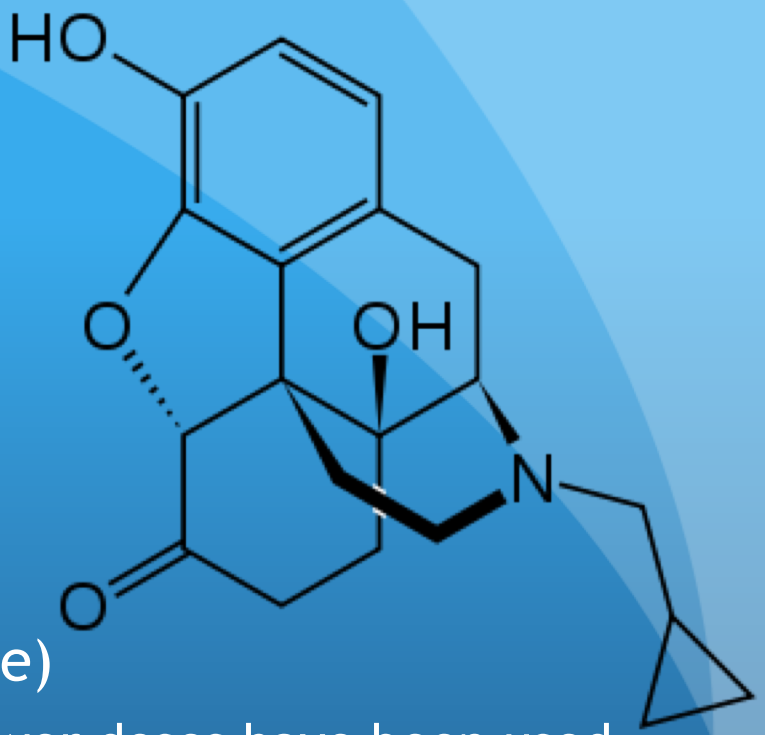
LDN v. U-LDN



- LDN
  - 1.5 mg to 4.5 mg
- U-LDN (ultra-low dose naltrexone)
  - 1 microgram and higher (even lower doses have been used in the laboratory).
  - Compounding pharmacies may have technical difficulties of creating 1 microgram.
  - However, there are 1 some compounding pharmacies where 1 microgram can be compounded.

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U-LDN (micro-dose naltrexone)

- LDN is contraindicated in patients who are on opioid medication
  - LDN while on opioid medication can precipitate an opioid withdrawal.
  - Symptoms include extreme discomfort including heightened anxiety, nausea, vomiting, or abdominal pain.
  - Embeda (Morphine + encapsulated LDN)
    - LDN normally is not released if ingested by mouth
    - LDN released if pill is crushed and ingested
    - Case reports of opioid withdrawal with crusing Embeda have been reported

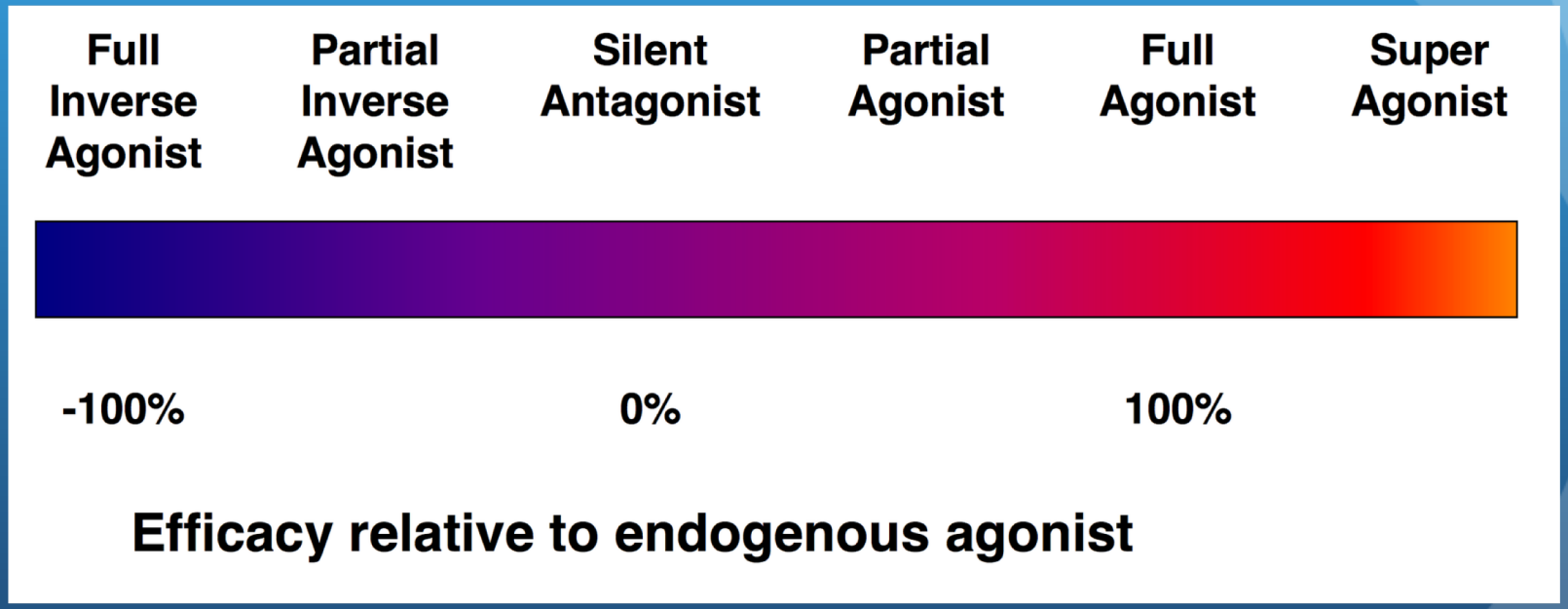
Helping patients on opioid medication

- U-LDN – 1 microgram may offer additional benefits for patients on opioid medication
  - Improved pain control
  - Lessen side effect

ULDN Mechanism?

- Hormesis
  - Hormesis refers to non-linear effect
  - Inhibitor at high concentration may be a weak stimulator at much lower concentration
  - Originally referred as Arndt-Schulz rule - small doses of poison stimulated growth of yeast
  - The Arndt-Schutlz rule fell out of favor due to limited reliability
- Receptor-Antagonist Interaction
  - At first inhibitors inhibit receptor-ligand interaction
  - In response to decreased stimulation, more receptors are produced and deployed to the cell membrane
  - Net effect - overcome the inhibition over time

Agonist v. Antagonist



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Naltrexone @ “normal dose”

- Naltrexone at regular dose 50 mg to 150 mg – can block narcotic medication through antagonistic action (receptor blocker or competitive inhibitor)
- This means naltrexone will bind to the opioid receptor but the receptor remains turned off.
- The receptor remains turned off and naltrexone denies opiods to bind to receptor.

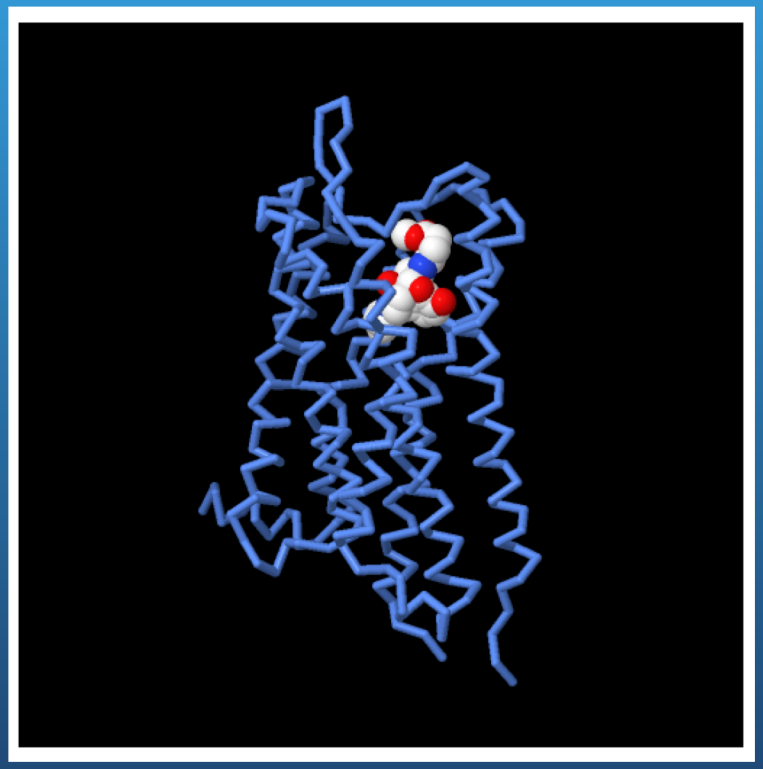
LDN Mechanism

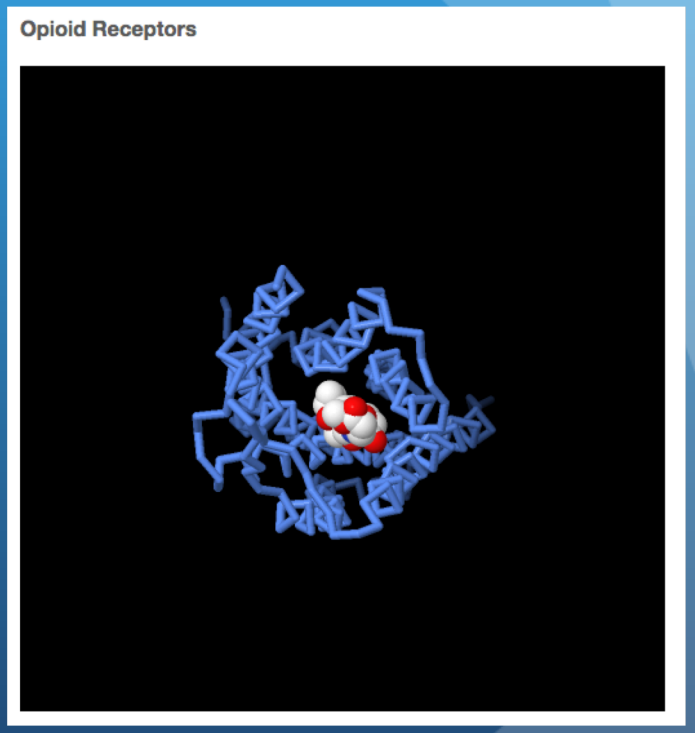
- LDN at 1.5 mg to 4.5 mg can partially block endorphin actions
  - At which points multiple possibilities may happen
  - 1. Increased production of endorphin (negative feedback)
  - 2. opioid receptor resetting resulting in increased sensitivity to endorphins
  - 3. Receptor up regulation (more receptors are produced and deployed to cell membrane) resulting in increased sensitive to endorphins
  - 4. LDN found to have CNS anti-inflammatory actions by regulating glial cells.

U-LDN Mechanism

- U-LDN at 1 microgram can bind the opioid receptors but at that concentration not likely to overwhelm opioid medication
  - Instead opioid receptor appears to be reset which results in sensitization
  - Normally, opioid medication unopposed has receptor down regulation (less receptors are produced)
  - Some authors theorize unopposed opioid stimulation of receptor results in

Mu Opioid Receptor and Ligand





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Oxytrex

- Therapeutic doses of oxycodone + 1 microgram of naltrexone

Oxytrex Clinical Trial 1

- Chindalore et al (2005)
  - N = 360 patients with chronic pain cause by osteoarthritis of hip x 3 weeks
    - Group 1 Placebo
    - Group 2 Oxycodon QID (40 mg of Oxycodone per day)
    - Group 3 Oxycodon QID (40 mg of Oxycodone + 4 µg of Naltrexone
    - Group 4 Oxycodon BID (40 mg of Oxycodone + 2 µg of Naltrexone
  - Group 4 Oxytrex BID group produced a 39% reduction in pain intensity greater than group 1, group 2, and group 3.

Oxytrex Clinical Trial 2

- Wester et al. (2006)
- N = 716 patients with chronic back pain x 12 weeks
  - Group 1 Placebo
  - Group 2 Oxycodon QID (Oxycodone 80 mg/day)
  - Group 3 Oxytrex QID (Oxycodone 80 mg/day + naltrexone 4 µg/day)
  - Group 4 Oxytrex BID (Oxycodone 80 mg/day + naltrexone 2 µg/day)
- Group 4 reported 55% less physical dependence than group 2 and reported decreased constipation, somnolence, while achieving comparable analgesia.
- U-LDND (2 microgram) may minimize physical dependence

U-LDN – Oxytrex project

- Unfortunately, the manufactures of Oxytrex, Pain Therapeutics, subsequently abandoned this project and has returned the rights for Oxytrex to Albert Einstein College of Medicine.
- Therefore, ultralow dose naltrexone is not available through conventional pharmacies. However, licensed medical practioners may prescribe ultralow dose naltrexone through compounding pharmacies capable of compounding ultralow dose naltrexone.
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Uses of U-LDN

- Endorphin depleted sub-population:
- Personal observation
  - Endorphin reserve of people should be estimated.
  - Some patients may benefit from microgram dosing of naltrexone
    - Endorphin reserve
      - Questions:
        - Energy level
        - Sleep
        - Restorative Sleep
        - Resilience

Use of U-LDN

- Neuroanatomical/Pharmacological Approach to Pain
- Developed by Yoon Hang Kim MD
  - U-LDN on patients using opioid medication
    - Step 1: (entry): reduce pain through neuroanatomical acupuncture or other techniques
    - Step 2: (disrupt pain): start microgram dosing of naltrexone (or increase microgram dosing of naltrexone, if already started)
    - Step 3: (advance) if pain level continues to decrease, trial of decreasing pain medication.

Conclusions

- Microdosing of naltrexone 1 – 2 microgram per day range in the presence of narcotic medication has been shown to decrease side effect and increase pain control.
- While commercialization of this aspect of medication has failed, this approach may still have clinical significance especially when combined with non-pharmacological pain management.
- For non-narcotic dependent patients, microgram dosing of naltrexone also useful for patients who are endorphin depleted.

Conclusions

- Given the epidemic of opioid crisis in the US, microgram dosing naltrexone should be explore in depth.

LDN 2018 Conference Presentation

By Dr John Kim