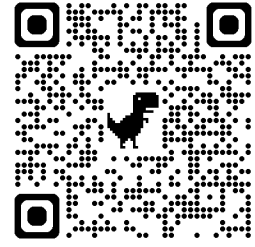


## Accurate Clinic

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## Accurate Education

OIH

Naltrexone for Pain

### ***Opioid-Induced Hyperalgesia, Opioid Analgesic Tolerance, and Central Sensitization:***

### **Clinical Overview and Naltrexone-Based Treatment Options**

Those who have chronic pain and have been taking potent, full agonist opioid medications (especially oxycodone, morphine and fentanyl patches) for a long time often encounter difficulties in achieving and maintaining adequate pain control. Aside from inevitable progression of disease processes and lack of effective alternatives to opioids, these difficulties can also arise from loss of efficacy of the maintenance opioids. Conditions leading to this loss of efficacy include Opioid-Induced Hyperalgesia (OIH), Opioid Analgesic Tolerance and Central Sensitization (CS).

New, safe and effective treatment options are now available to help offset these conditions, including ultra-low-dose naltrexone (ULDN) and low-dose naltrexone (LDN).

#### **A quick review:**

- **Opioid-Induced Hyperalgesia (OIH)** is a paradoxical increase in pain sensitivity caused by chronic opioid therapy. Patients may report worsening or spreading pain, new onset of allodynia or simply pain that is less responsive to opioid dose escalation. The prevalence of OIH in patients on long-term opioid therapy is likely in the range of 5% to 15%, [2][13][14]
- **Opioid Analgesic Tolerance (OAT)** is the need for increasing opioid doses to achieve the same analgesic effect, due to neuroadaptive changes in opioid receptor signaling. The expected prevalence of clinically significant opioid analgesic tolerance is very high—likely >50% and approaching 100% of chronic pain patients with increasing duration of therapy. [13][14]
- **Central Sensitization (CS)** refers to increased responsiveness of central nervous system neurons to normal or sub-threshold input, leading to amplified pain experience. This is a hallmark of many chronic pain syndromes (e.g. chronic headaches, chronic low back pain, fibromyalgia, CRPS,). In studies of mixed chronic pain populations, central sensitization was present in 43% - 80% of patients. [1][10][17][18]

#### **Patients most at risk for OIH and OAT:**

- Long-term, high-dose opioid therapy [13][15][19]
- Use of potent full agonist opioids (e.g., oxycodone, morphine, fentanyl)[13]
- History of escalating opioid requirements or diffuse, poorly localized pain [2][13]
- History of conditions like chronic headaches, chronic back pain, fibromyalgia CRPS, neuropathy, MS, chronic pelvic pain or other "centralized" pain syndromes [1][10]
- Co-morbidities such as sleep disturbance, mood disorders, or high baseline pain sensitivity [1][2][10][17][18]

## How are these conditions treated?

**Traditional painkillers** (like NSAIDs, acetaminophen, or even more opioids) are generally not effective for OIH, OAT or central sensitization and may even make things worse. New treatments focus on restoring the endogenous opioid system.

**Naltrexone** is an opioid antagonist that at standard doses (50 mg) is used to treat opioid and alcohol use disorders. At much lower doses, it works differently and offers unique opportunities for the management of OIH, OAT and central sensitization.

### Ultra Low Dose Naltrexone (ULDN)

- *Benefits:* Significantly improves pain tolerance (sometimes quadrupling it in OIH), reduces pain and improves quality of life. It can help facilitate opioid dose tapering over time.
- *Dose:* 0.001 mg (1 microgram) BID, co-administered with ongoing opioid therapy. [\[11\]](#)
- *Mechanism:* Prevents maladaptive mu-opioid receptor (MOR) Gs protein coupling, attenuates glial activation and restores endogenous opioid tone, reducing OIH and tolerance. [\[11\]](#)
- *Evidence:* Clinical trials (e.g., Oxytrex) show ULDN enhances opioid analgesia, reduces tolerance, and minimizes hyperalgesia, with an excellent safety profile. [\[11\]](#)
- *Side effects:* Minimal at ultra-low doses; no increased risk of withdrawal or opioid antagonism. [\[11\]](#)

### Low Dose Naltrexone (LDN)

- *Benefits:* Significantly improves pain tolerance (sometimes quadrupling it in OIH), reduces pain and improves quality of life
- *Dose:* 1.5 – 4.5 mg once daily (studies use up to 4.5 mg). [\[1\]\[2\]\[3\]\[4\]\[5\]\[6\]\[7\]\[8\]\[9\]\[10\]\[12\]](#)
- *Mechanism:* Transiently blocks opioid receptors, leading to up-regulation of endogenous opioids and receptors; modulates neuroinflammation via glial and TLR4 inhibition. [\[1\]\[4\]\[6\]](#)
- *Evidence:* Meta-analyses and clinical studies show LDN improves pain, pain tolerance, quality of life and sleep in fibromyalgia, OIH, and other centralized pain syndromes. In OIH, LDN quadrupled pain tolerance (cold pressor testing) and reduced pain by 32–44% in inflammatory and neuropathic pain conditions. [\[1\]\[2\]\[3\]\[4\]\[5\]\[6\]\[7\]\[8\]\[9\]\[10\]\[12\]](#)
- *Side effects:* Mild and infrequent (GI upset, headache, vivid dreams); serious adverse events are rare and rates are similar to active comparators. [\[3\]\[5\]\[7\]\[12\]](#)

### Clinical Pearls

- ULDN is preferred for OIH and OAT in patients who must remain on opioids. [\[1\]\[2\]\[11\]](#)
- LDN is especially effective for fibromyalgia and other centralized pain syndromes;
- Improvement in pain and function is often seen within 2–4 weeks of starting ULDN or LDN, but it may take longer for some. [\[2\]\[3\]\[4\]\[5\]\[6\]\[7\]\[8\]\[9\]\[10\]\[12\]](#)
- Ongoing therapy is recommended as long as opioids are continued; recurrence of OIH is common if LDN/ULDN is discontinued while opioid therapy persists. [\[2\]\[13\]](#)
- ULDN and LDN are well tolerated, with a safety profile comparable to placebo or active comparators. [\[3\]\[5\]\[7\]\[12\]](#)
- Cost: \$1-2/day at compounding pharmacies (not covered by insurance)
- LDN and ULDN are not FDA-approved for chronic pain but are supported by growing evidence for OIH, OAT, and centralized pain. [\[1\]\[2\]\[3\]\[4\]\[5\]\[6\]\[7\]\[8\]\[9\]\[10\]\[12\]](#)

## What else can help with OIH and OAT and Central Sensitization?

- Reducing opioid doses, if possible, can also help reverse OIH and tolerance.
- Acupuncture, physical therapy and exercise are important for long-term pain management.
- Supplements like Omega-3's (Lovaza), Magnesium (citrate or glycinate), Resveratrol, NAC, alpha-Lipoic Acid, and Acetyl-L-Carnitine have substantial preclinical evidence and some clinical support for chronic pain and CS, with limited but promising data for OIH/OAT.
- Non-opioid medications (gabapentin, pregabalin (Lyrica), or duloxetine (Cymbalta) may help with central sensitization.
- Buprenorphine: Butrans transdermal patches (Micro-Dose) & Belbuca buccal strips (Low Dose) may help OIH and OAT without interfering with current opioid therapy.
- Buprenorphine: Subutex (Standard Dose: 2-32mg/day) may help OIH and OAT but requires substitution of current opioid therapy. Micro-dosing Rotation protocol recommended.

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