UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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TODAY'S TOPIC:

The Newest Kid on the Block: Naltrexone's Surprising Role in Analgesia

Background:

Traditionally used for opioid use disorder, naltrexone in low doses (1-5mg) is gaining attention for off-label use in chronic pain and inflammatory conditions via unique mechanisms of action. It has shown promise in reducing symptom severity in chronic conditions such as fibromyalgia, Crohn's disease, multiple sclerosis, and complex regional pain syndrome (CRPS). In this week's issue of the Tablet, we will explore the current evidence on low-dose naltrexone (LDN), including the mechanisms of action, pharmacokinetic data, and currently studied patient populations.

Mechanism of Action:

High-dose naltrexone (50mg-150mg) is a high-affinity mu- and delta- opioid receptor antagonist and is used in treating substance use disorder. However, at low doses (1-5mg), naltrexone exhibits unique paradoxical properties, offering analgesic and anti-inflammatory effect.

At low doses, naltrexone inhibits Toll-like receptor 4 (TLR4) on microglial cells, reducing neuroinflammation and central sensitization – mechanisms relevant to pain, fatigue, cognitive dysfunction, and mood disturbances. At ultra-low-doses (2-4 mcg/kg), naltrexone has been used concomitantly with full opioid agonists; naltrexone is thought to partially, temporarily block opioid receptors, potentially triggering a rebound increase in endogenous opioids and receptor sensitivity.

Pharmacokinetics & Safety:

Naltrexone has variable oral bioavailability (5-40%) and is hepatically metabolized and renally excreted. Its half-life is 4 hours. LDN is well tolerated, with mild side effects like vivid dreams or headache, often dose dependent.

Clinical Pearls:

- No standardized, evidence-based dosing regimen. Most common regimen is 4.5 mg PO nightly with dose reductions (i.e. 3mg) for tolerability
- Onset: 2-4 weeks for clinical effect
- Must be compounded as it is not commercially available in low doses
- Not FDA-approved for pain, insurance coverage may vary

Anecdotally, our pediatrics team has used LDN for a patient with systemic sclerosis with neuropathic pain due to nerve fibrosis. The patient reported significant pain benefit since initiation of LDN.

The Literature:

LDN literature continues to evolve, and as of now, it has been studied in fibromyalgia, multiple sclerosis, inflammatory bowel disease, and CRPS, with differing degrees of available evidence.

***Fibromyalgia*:**

Pain Med. 2009 May-June;10(4):663-72.
Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study
- Single-blind, crossover trial (n=10 women) received LDN (4.5mg nightly) and placebo over a 14-week study period
- Outcomes: daily, self-reported fibromyalgia symptom severity
- Methods: No concomitant opioids, 2 on neuropathic agents, and 2 on muscle relaxants.
- Results: Six out of ten had 30% reduction in symptom severity with LDN over placebo.

Arthritis Rheum. 2013 Feb;65(2):529-38.
Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels
- To help validate the findings of study above, the author expanded to a double-blind, crossover trial (N= 30 women) with similar study design over 22 weeks. Average reduction in pain after 12 weeks of LDN was 28.8%, with 57% of participants with a ≥30% reduction in symptoms.

Pain Rep. 2023 Jun 15;8(4):e1080.
Low-dose naltrexone for treatment of pain in patients with fibromyalgia: a randomized, double-blind, placebo-controlled, crossover study
- Randomized, double-blind, crossover trial (n=52 patients) received LDN (4.5mg nightly) and placebo with a washout period over 8 weeks
- Outcomes: scoring on fibromyalgia impact questionnaire (FIQR), reported pain intensity scale (SPIR)
- Methods: No concomitant opioids, 18 on neuropathic agents, 14 on muscle relaxants
- Results: No statistically significant difference between placebo or LDN in FIQR or SPIR

Lancet Rheumatol. 2024 Jan;6(1):e31-e39.
Naltrexone 6 mg once daily versus placebo in women with fibromyalgia: a randomised, double-blind, placebo-controlled trial
- Single-center, randomized, double-blind trial (n=99 women) received LDN (6mg daily) vs. placebo in 12-week study period
- Outcomes: change in pain intensity on numeric rating scale
- Results: No statistically significant difference in pain intensity after LDN vs placebo

***Multiple Sclerosis*:**

Ann Neurol. 2010 Aug;68(2):145-50.
Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis
- Randomized, double-blinded, crossover pilot trial (n=60 adults with MS) received LDN (4.5mg nightly) and placebo over 8 weeks
- Outcomes: scoring on self-reported MS QOL inventory (MSQLI)
- Methods: No concomitant opioids, no new disease-modifying therapies
- Results: statistically significant improvement on mental health QOL indices on MSQLI, not on physical symptoms/pain QOL indices

Mult Scler. 2010 Aug;16(8):964-9.
The effect of low-dose naltrexone on quality of life in patients with multiple sclerosis: a randomized placebo-controlled trial
- Double-blind, placebo-controlled, crossover clinical trial (n=96 adults with MS) received LDN (4.5mg nightly) and placebo over 17 weeks
- Outcomes: scoring on self-reported MS QOL inventory (MSQoL-54 questionnaire)
- Results: No statistically significant difference in any perceived QOL indices

CLINICAL PEARL: Though efficacy data is mixed, low-dose naltrexone offers a well-tolerated, low-risk option for managing refractory pain, fatigue, or neuroinflammation in select palliative care patients—particularly when standard therapies fall short.

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***Crohn's Disease*:**

Dig Dis Sci. 2011 Jul;56(7):2088-97.
Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn's disease: a randomized placebo-controlled trial
- Randomized, double-blind trial (n=34 adults with moderate-severe Crohn's) comparing LDN (4.5mg nightly) vs placebo
- Outcomes: 70 point decline in Crohn's Disease Activity Index score
- Methods: participants on stable amino salicylates and steroids, no concomitant opioids
- Results: 88% in LDN arm achieved primary outcome compared to 40% in placebo arm (p=0.009).

***Complex Regional Pain Syndrome*:**

J Neuroimmune Pharmacol. 2013 Jun;8(3):470-6.
Treatment of Complex Regional Pain Syndrome (CRPS) using low dose naltrexone (LDN)
- Case report: 48-year-old M who developed CRPS after a leg injury c/b dystonic spasms. Multiple pain modalities tried, including opioids, anticonvulsants, and low-dose IV ketamine.
- Started LDN 4.5mg PO nightly and had less frequent requirements for IV ketamine, improved mobility, and reduction in pain severity.

***Opioids with Low-Dose Naltrexone*:**

Med Sci (Basel). 2018 Sep 21;6(4):82.
Low-Dose Naltrexone (LDN) – Review of Therapeutic Utilization
- Two clinical trials assessed the combination of opioids with ultra-low-dose naltrexone (2 µg or 4 µg daily naltrexone) in treatment of low back pain and osteoarthritis
- High dropout rates call for serious caution in interpreting clinical significance

There are no studies yet that show the degree of opioid receptor blockade from LDN doses of 1-5mg. Some studies in surgical settings are looking at low-dose opioid antagonism in addition to opioid agonists will improve post-op analgesia.

Bottom Line:

- While existing studies of LDN focus on non-palliative populations, many of the target symptoms—neuropathic pain, fatigue, sleep disturbance, and inflammation—are highly relevant to palliative care.
- Most studies showed general safety and tolerability of LDN, with a rather benign adverse effect profile
- Onset 2-4 weeks for clinical effect, so more relevant for chronic pain rather than acute pain
- LDN is a promising subject for further research, and may, in the future, offer a nonopioid approach to chronic pain. As of right now, efficacy data is very mixed, with small sample sizes and poor generalizability across indications
- Given its favorable safety profile and plausible mechanism, LDN may be a reasonable adjunct to trial in select patients with refractory neuropathic or mixed pain, coexisting autoimmune disease, or chronic inflammatory disorders, especially when standard therapies are ineffective or poorly tolerated
- More research is needed on its use alongside opioids and in patients with advanced illness before broader adoption in palliative settings

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