tipSC Timely Information for Providers in South Carolina

NOTES – SUMMER 2022

LOW-DOSE NALTREXONE
Is there a role for *ORAL* LDN in chronic pain management?

LDN Recent Evidence

OFF-LABEL use of low-dose naltrexone (LDN) in chronic pain management in adults is primarily supported by small clinical trials, case reports, and literature reviews. Fibromyalgia, Crohn's Disease, and Multiple Sclerosis (MS) are among the most studied conditions and growing evidence points to efficacy among specific chronic pain conditions, including those with neuropathic and inflammatory components (See TABLE on back page). In contrast, benefit has been inconsistent in the management of MS. Collectively, LDN has been safe and well tolerated.

LDN Candidates

Chronic pain conditions are a challenge to manage. Based on published data, a trial of LDN may be reasonable in patients with chronic pain, particularly those with symptoms of central sensitization, as well as in patients with limited options due to age and co-morbidities (e.g., CV, renal, GI, liver disease). It is key to remember that any pharmacotherapy, including LDN, should always be part of a multi-modal pain care strategy that includes other therapies (e.g., psychological, rehabilitative, interventional, and complementary/alternative care).

LDN Use and Dosing

Naltrexone (NTX) is FDA approved to treat opioid use disorder (OUD) and alcohol use disorder (AUD). At a standard treatment dose of 50 - 100 mg, NTX is a non-selective opioid receptor antagonist primarily affecting mu opioid receptors. This effect on mu opioid receptors is not reported with LDN. The term LDN refers to a total daily dose between 1 and 5 mg, approximately 1/10th of the dose used to treat OUD. At low doses, NTX demonstrates anti-inflammatory, immunomodulatory, and antinociceptive effects via several potential mechanisms of action. LDN is typically administered at bedtime, beginning with a lower dose and gradually titrated up as tolerated according to patient response. Discerning the onset of clinical benefit can be difficult early on and may not be observed until at least 1 month after beginning LDN. Some early data suggest that 2 months of treatment are generally needed to estimate efficacy.

LDN and Opioids

Little data exist on co-administration of NTX 4.5 mg with opioids. It is suggested to use caution if initiating LDN within 1 week of chronic opioids and that patients stop opioids before initiating LDN due to unknown risk of acute withdrawal. There are case reviews that have successfully used LDN to reduce opioid-induced hyperalgesia. It has been recommended to use NTX doses < 0.5 mg in patients on chronic opioid therapy. Of interest to note, NTX has been used in very low doses (0.1 – 0.25 mg) in the management of opioid withdrawal in patients on methadone.

Be alert when considering an opioid dose for a patient on chronic LDN, as opioid overdose requiring reversal with naloxone and overnight hospitalization has been reported in a single case report on an adult taking only NTX 2 mg/day who received a single oxycodone 5 mg dose for pain due to the theorized upregulation of opioid receptors.

LDN Safety

The incidence of adverse effects reported in clinical trials and practice is low. Most commonly reported adverse effects of nausea/vomiting, dizziness, sleep disturbance, vivid dreams, and nightmares were considered minimal and diminished over time. Vivid dreams and nightmares also seemed to improve if the dose was given in the morning instead of the evening. Slowing the titration, lowering the dose, or pausing a few days before reinitiating LDN at a lower dose are considerations if adverse effects are an issue. In patients who have experienced adverse effects from NSAIDs (e.g., ulcers, renal dysfunction, bleeding due to interactions with anticoagulants), LDN may be a good option because existing evidence suggests it does not cause these effects. In addition, LDN has demonstrated low potential for abuse or misuse in clinical trials. LDN dosing adjustments are not required for renal or hepatic impairment.

Writing an LDN Prescription

LDN has no commercially available products and must be compounded. You may wish to contact your local pharmacy before writing the prescription.

LDN Compounding Information

Capsules containing the appropriate low dose of NTX in powder form are the typical dosage form for compounded LDN in South Carolina and cost, on average, $47 for a month's supply (30 capsules). This information is based on feedback from four compounding pharmacies located throughout the state. Another compounding option is to make a 1 mg/ml oral solution by crushing ten naltrexone 50 mg tablets and adding enough water to equal 500 ml. Counsel patients to keep solution refrigerated, shake well before use, and discard after 90 days (or less per policy). Patients need a measuring device dispensed with the solution that accurately measures the correct low dose. If bitter or gritty taste is a problem, experience from use in dermatology suggests mixing the dose in a favorite juice (orange juice was referenced).

Published Literature Evaluating Low-Dose Naltrexone (LDN) and Chronic Pain Conditions			
Use[1]	**Typical Dose (Dose Range, including initial titration dose)**	**Clinical Benefit**	**Evidence**
Fibromyalgia	4.5 mg daily (0.1 mg – 6 mg daily)	Potentially Favorable	Ongoing RCT (2), Dose-response single-arm study (1), Crossover trial (1), RCT (1), Single-Blind pilot (1), REVIEWS (6)
Gastrointestinal Disorders – Crohn's Disease, Irritable Bowel Syndrome	4.5 mg daily (2 mg – 4.5 mg daily) Pediatric: 0.1 mg/kg up to 4.5 mg max daily	Potentially Favorable	RCT (2), REVIEWS (4)
Diabetic Neuropathy	4 mg daily (1 mg – 4 mg daily)	Inconclusive	RCT (1), Case reports (1), REVIEWS (3)
Complex Regional Pain Syndrome (CRPS)	4 – 4.5 mg daily (1.5 mg – 4.5 mg daily)	Inconclusive	Case report, REVIEWS (6)
Multiple Sclerosis	4 – 4.5 mg daily (2 mg – 4.5 mg daily)	Inconsistent[2]	RCT (2), REVIEWS (5)
Neuropathic Corneal Pain	4.5 mg at bedtime	Inconclusive	Case series (1)
Chronic Fatigue	4.5 mg daily (0.25 mg daily – 7.5 mg twice daily)	Inconclusive	Case series (1)
Rheumatoid & Seropositive Arthritis	Not given	Inconclusive	Quasi-experimental study (1)

REVIEWS of LDN and Chronic Pain Conditions		
Author/Year	**Study Design**	**General Findings**
Soin 2021	Systematic review (29 studies)	Growing body of literature supporting use in chronic pain; more studies needed
Hatfield 2020	Systematic review (8 studies)	Beneficial in pain reduction and improved QOL across fibromyalgia, CRPS, chronic pelvic pain, and interstitial cystitis
Kim 2020	Systematic review (6 studies)	Low-dose and ultra-low-dose naltrexone reasonable option in chronic pain
Trofimovitch 2019	Narrative review	Appears to have potential as a therapeutic option (focused on nonmalignant pain in palliative setting). There is some suggestion that LDN may also improve QOL and emotional well-being through mechanisms other than just pain reduction.
Toljan 2018	Systematic review (85 studies)	Reasonable option in fibromyalgia or Irritable Bowel Disease
Patten et al 2018	Narrative review	Safety and tolerability displayed in all human studies; evidence for objective measures of efficacy is limited
Younger et al 2014	Review article	Appears to have potential as a therapeutic option "for chronic pain conditions thought to involve inflammatory processes"

1. Case reports have also been published for chronic low back pain, burning mouth syndrome, and stiff-person syndrome. **2.** May improve health perception & spasticity.

KEY: QOL Quality of Life; **RCT** Randomized Controlled Trial

References for this tipSC NOTES and additional tipSC information are available at **https://schealthviz.sc.edu/tipsc-1/**