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Acute Precipitated Opioid Withdrawal With Akathisia, Delirium, and Lactic Acidosis from Low-Dose Naltrexone for Chronic Pain: Case Report

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Background: Low-dose naltrexone (LDN) is an increasingly popular medication to enhance analgesia and decrease opioid reliance in patients with chronic pain.

Case Report: We present the case of a 66-year-old man on long-term opioids for chronic pain who was initiated on 1 mg of LDN for enhanced analgesia and subsequently went into severe precipitated opioid withdrawal (POW), a reaction understood to be rare at such low doses.

Conclusion: LDN has been introduced into pain medicine as a safe and effective adjunct for the treatment of chronic pain conditions in both opioid-naive patients and those on concomitant opioid therapy. While this is generally considered a safe practice, LDN initiation can cause acute precipitated withdrawal in certain individuals already on opioids, even at low doses previously thought to be free from this risk. We recommend pain providers consider this effect and be prepared to manage POW when prescribing LDN.

Key words: Low-dose naltrexone, LDN, chronic pain, precipitated opioid withdrawal, case report

BACKGROUND

Between 18% to 34.5% of Americans live with chronic pain, making it one of the most significant public health problems in the United States (1). The toll on those with chronic pain has increased even more during the COVID-19 pandemic both due to preexisting chronic pain conditions and the development of COVID-19-related pain disorders and COVID-19-induced barriers to treatment (2-4). As novel medical treatments for pain management emerge, it will be important to track and address adverse impacts related to their use. One of these treatments involves low-dose naltrexone (LDN), which is emerging as a novel tool for treating many chronic pain disorders (5-11,13). When combined with oxycodone, naltrexone generates greater pain relief, prolongs opioid analgesia, and attenuates opioid tolerance and withdrawal compared to oxycodone alone (14-16).

First utilized in the 1980s during exploration of treatments for HIV/AIDS, naltrexone is a nonselective opioid receptor antagonist traditionally used to reduce cravings and treat patients with opioid use disorder and alcohol dependence (6-8). A daily dose of 50-100 mg is commonly prescribed for these conditions. LDN involves providing 1.5-4.5 mg once daily for the alternative treatment of chronic pain. Studies suggest it is most effective for pain associated with multiple sclerosis (MS), Crohn's disease, fibromyalgia, complex regional pain syndrome (CRPS), and chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), but has also been utilized

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for chronic musculoskeletal pain (5,7,10,13). It also has a low cost from a compounding pharmacy, which is an important feature given the financial burden of many who are disabled by chronic pain.

The hypothesized mechanisms of LDN for chronic pain conditions are unique from its more widely known effects as an opioid receptor antagonist. Its pain-reducing action results from multiple mechanisms (7,10-12). It is thought to work via a short half-life (6 hours) suppression of mu-opioid receptors with a subsequent rebound of systemic endogenous opioid production (10,12). It is also understood to cause antinociceptive effects by promoting anti-inflammatory signals among central nervous system (CNS) microglial cells through antagonizing toll-like receptor 4 (TLR4) (7,11,12). TLR4 contributes to pain by activating glial cells and stimulating the release of proinflammatory cytokines. Blockage of TLR4 by LDN helps explain both its nociceptive effects on pain, as well as its effects on CNS disorders like MS, CRPS, and CFS/ME (7,10-12). These combined actions result in naltrexone being considered an opioid receptor antagonist, a TLR4 antagonist, and a "glial cell and immune modulator" (7,10-12,18).

LDN has a relatively low side-effect profile limited primarily to sleep disorders, appetite changes, and nausea in a minority of patients (7,9,10). This being true, there are reports of reactions, including precipitated withdrawal in individuals simultaneously taking opioids (18,20). However, these instances occurred during use of Vivitrol, which is a significantly greater dose of extended-release intramuscular naltrexone (XRNTX). To the best of our knowledge, there are no reports to date of acute precipitated withdrawal following initiation of low-dose oral naltrexone (< 1.5 mg). We present the case of a 66-year-old man who experienced acute precipitated withdrawal following initiation of 1 mg oral naltrexone.

CASE

Our patient is a 66-year-old man with a past medical history of gouty arthritis, hypertension, gastritis, necrotizing pancreatitis status post partial pancreatectomy, pseudogout, hemochromatosis, depression, fibromyalgia, diabetic neuropathy, and chronic low back pain from multilevel degenerative facet arthropathy and spinal stenosis. The patient presented to the Comprehensive Pain Program (CPP) at the University of Vermont (UVM) Medical Center for a follow-up appointment for his chronic pain. He reported a 40-year history of pain initiated by work-related injuries and enhanced over the years by his chronic conditions. When the patient began his care at CPP in 2018, he arrived on 480 morphine milligram equivalents (MME) daily of fentanyl and oxycodone. He had been chronically dependent on opioids for pain for over 10 years. Despite extremely high doses of opioids, he still had significant pain.

During the 2 years leading up to the events reported here, the patient's opioids were reduced by 50% by his primary care physician and pain physicians from 480 MME to 240 MME in an effort to reduce his total opioid burden and to spur efforts to find alternative ways of addressing his chronic pain. Multiple medications were trialed including gabapentin, Lyrica, Cymbalta, ketamine, nonsteroidal anti-inflammatory drugs (NSAIDs), as well as marijuana in an attempt to find even a marginal reduction in pain.

Gabapentin resulted in somnolence. Lyrica, Cymbalta, and ketamine had no impact on the intensity of his pain. NSAIDs were stopped due to gastrointestinal intolerance and worsening of his preexisting gastritis, and marijuana caused anxiety, restlessness, and discomfort. He received epidural steroid injections (L4-S1) and sacral radiofrequency ablation that resulted in only a transient minimal decrease in pain. He was offered a spinal cord stimulator, but declined out of concern about engaging in a procedure so invasive and felt it would unlikely help his symptoms. Though the realistic analgesic potential of these adjuncts is variable, they were nonetheless trialed to search for even minimal pain reduction. The patient found that self-medicating with alcohol was his most effective analgesic. He stopped drinking just 18 months ago and though he remains abstinent for now, he reports frequent temptations to return to drinking particularly when his pain is severe. At the time of these events, his current pain regimen consisted of a total of 240 MME of fentanyl and oxycodone.

To find a way to reduce his total pain burden, LDN was suggested by his pain physician. The patient was prescribed oral LDN at 1 mg per day for the first week with plans to gradually increase to 4.5 mg daily. At around 12:00 pm, he took his first 1 mg dose of LDN and within 30 minutes began experiencing excessive perspiration, temperature instability, tinnitus, and worsening of his restless leg syndrome. He further experienced anxiety, panic, muscle tremors and spasms, akathisia, chest pain, and abdominal pain and ultimately called 9-1-1 for assistance.

The patient arrived at the University of Vermont's Emergency Department (ED) with a chief complaint of abdominal pain and restlessness and was found to be unable to sit or lay still. His vital signs were stable (blood pressure 137/95, heart rate 83). He had mild leukocytosis, hypomagnesemia of 1.5, and severe lactic acidosis with a lactate of 4.2. Over the course of 3 hours, he received 2 liters of intravenous (IV) fluids, 5 mg IV droperidol, 50 mg IV diphenhydramine, 1 mg IV Ativan, 5 mg IV morphine, 0.1 mg clonidine, 2 g IV magnesium sulfate, an additional 0.3 mg IV clonidine, and an additional 0.5 mg of IV Ativan. He also received a computed tomography of the abdomen/pelvis to rule out ischemic bowel disease that showed signs of only a mild terminal ileitis. He had a normal electrocardiogram. As his stay lengthened, his abdominal pain resolved, and his primary issue continued to be hyperactivity with akathisia and altered mental status. His behavior was disruptive. He removed his IV, and the ED interventions were ineffective in reducing his hyperactivity. A security officer was called to assist in his agitation and be stationed outside his hospital room. He eventually fell asleep around 3:00 AM in the morning with a total symptom duration of approximately 15 hours. The patient was admitted for management of his symptoms and ultimately discharged the day after presentation with complete resolution of his symptoms and a final diagnosis of acute precipitated opioid withdrawal secondary to naltrexone administration and severe lactic acidosis due to hyperactivity. The only change in his care and his daily routine had been the initiation of LDN.

Discussion of Existing Literature

Precipitated opioid withdrawal because of naltrexone administration is well understood, but this effect may be overlooked when naltrexone is used off-label at significantly lower doses for chronic pain. This is understandable given the current literature reporting on the use of LDN for chronic pain, particularly in "legacy" patients on high MME who cannot realistically taper their opioid medications before undergoing a trial of LDN. While recommendations suggest an opioid-free period prior to initiation of naltrexone, recent literature states that "LDN rarely, if ever, precipitates opioid withdrawal in patients on opioids" and that "one of the major side effects listed is opioid withdrawal for this opioid antagonist, but [remember] that at low doses, we do not see this effect clinically" (9). Similarly, a 2023 study (17) from the Mayo Clinic reports that "at low doses of naltrexone, we do not see opioid withdrawal symptoms" and "current chronic opioid use should not contraindicate a trial of LDN." This literature, combined with an increasing practice of using LDN for chronic pain with minimal side effects in a majority of patients may provide false reassurance when using naltrexone (9,17). This practice can result in patient harm if not appropriately considered by prescribing physicians.

Current literature (19) emphasizes the potential for precipitated opioid withdrawal, but highlights this principle only during the use of higher-dose extended-release naltrexone (XRNTX; Vivitrol). For example, a 2018 case series (19) describes 2 patients who became acutely ill requiring intensive care intervention and monitoring after intramuscular XRNTX-induced precipitated opioid withdrawal. Both of these patients had concurrent substance use disorder with recent illicit opioid use, and both received a single 380 mg intramuscular dose of naltrexone. A similar case (20) described a 17-year-old woman who received XRNTX for opioid dependence several days after using oxycodone for recreational purposes and subsequently experienced precipitated opioid withdrawal. In these papers, the authors highlight the importance of adhering to the manufacturer's protocol in performing a naloxone challenge test and ensuring an opioid-free period in order to minimize the risk of precipitated opioid withdrawal (19,20). These recommendations are helpful to prescribers using intramuscular XRNTX, but the existing literature fails to highlight the importance of considering this effect in patients with chronic pain receiving much lower doses of oral naltrexone who cannot have their opioids tapered. While there are general recommendations and discussions in the literature about the possibility of precipitated withdrawal, to the best of our knowledge, there are no existing reports of this clinical effect in patients initiated on low-dose oral naltrexone as in the case of our patient.

In summary, our patient developed severe, acute precipitated opioid withdrawal with resulting altered mental status, lactic acidosis, and severe akathisia secondary to initiation of 1 mg oral naltrexone induction. Though care was taken to start this patient on a low dose (1 mg) with the goal of increasing to the desired dose (4.5 mg) over 2-3 weeks, the patient still experienced this acute side effect. While a single case does not constitute evidence of causation or a consistent pattern, it does highlight the possibility of such an outcome. Therefore, this effect must be considered as a potential

harm when utilizing naltrexone in this context. Others may wish to explore this principle further with higher grades of evidence.

CONCLUSIONS

As we search for more novel ways to treat chronic pain, especially for those "legacy" patients who have been on high doses of opioids for years, we can expect more patients being prescribed LDN to reduce total pain burden. There is an ongoing need to continue to search for meaningful ways to treat these patients due to the challenging nature of tapering their chronic opioid medications, with reports of the destabilizing effects of doing so (21-23). At the CPP at the UVM Medical Center, we utilize a full repertoire of integrative therapies in combination with standard Western medical therapies to achieve the highest reduction of pain. LDN is part of that regimen for some patients, even those who have been on opioids for years and cannot be tapered. Some patients find a reduction in their pain when LDN is added. This practice is generally considered safe and well tolerated when initiated at a dose of 1.5 mg once daily and increased to 4.5 mg over a period of 2-3 weeks, even in those on high MME.

The experience of the patient in this case shows that acute precipitated opioid withdrawal with just 1 mg of naltrexone is possible, can be significant, and may be more prevalent than reported. Providers initiating LDN for patients with chronic pain must consider this effect and be prepared to manage it.

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