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Management of Pediatric Complex Regional Pain Syndrome with Low-Dose Naltrexone

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Background: Complex regional pain syndrome (CRPS) is a chronic, orphan neurologic condition that affects the extremities after nerve trauma or injury. Management of CRPS can be challenging due to a paucity of evidence surrounding treatment options. Low-dose naltrexone (LDN) has been used for the management of other types of chronic pain. LDN is believed to exert its activities through inhibition of Toll-like receptor 4, which attenuates microglial activation. This case report describes the use of LDN in an 11-year-old boy with CRPS.

Case Report: Prior to initiating LDN, this patient was treated with gabapentin and amitriptyline, which were associated with undesirable adverse effects. Initiation of LDN allowed for successful discontinuation of gabapentin and amitriptyline. With LDN treatment, the patient's pain severity improved by 70%, and self-reported functional status improved by 60%.

Conclusion: This case report adds to the growing body of evidence that suggests LDN is an effective treatment for chronic pain.

Key words: CRPS, pain, naltrexone, chronic pain, limb pain

BACKGROUND

Complex regional pain syndrome (CRPS) is a chronic, orphan neurologic condition that can cause severe pain (1). CRPS diagnostic criteria are outlined in Table 1 (2). CRPS type I (previously known as reflex sympathetic dystrophy syndrome [RDS]) occurs when there is no confirmed nerve injury, while CRPS type II (previously known as causalgia) occurs when there is a confirmed nerve injury. CRPS is considered a rare disease, affecting an estimated 20.6 per 100,000 people (3). Because of the rarity of CRPS, little high-quality research has been performed to evaluate optimal management strategies. In the 2013 Reflex Sympathetic Dystrophy Syndrome Association (RSDSA) guidelines, the authors noted that CRPS is currently treated in an "evidence vacuum" (4). As such, the RSDSA encouraged clinicians to "utilize empirical drug trials in each patient based on consideration of what mechanisms seem most germane" (4).

Low-dose naltrexone (LDN) has emerged as a potential treatment option for patients with chronic pain syndromes, including CRPS. LDN is defined as a daily dose of naltrexone of 1 to 5 mg, which is 10- to 100-fold lower than the dose used to manage alcohol and opioid use disorders (Table 2) (5,6). At a standard dose of 50 to 100 mg, naltrexone has been shown to function as a nonselective opioid antagonist with high affinity for μ opioid receptors, which decreases addiction cravings (7).

In contrast with standard-dose naltrexone, LDN is believed to exert its mechanism of action through interaction with and antagonism of Toll-like receptor 4 (TLR4) (8-10). TLR4 has been shown to be a key mediator of microglial activation, which has been identified as a causal mechanism

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of neuropathic pain. Microglial activation is associated with the release of proinflammatory cytokines, reactive oxygen species, and prostaglandins, which amplify the inflammatory response (11). Another potential mechanism of action of LDN treatment is a paradoxical upregulation of opioid signaling. LDN leads to transient opioid receptor blockade, which triggers a positive feedback mechanism that increases the production of endogenous opioids and opioid signaling (5,12). Together, these mechanisms may work to alleviate pain associated with CRPS.

This report reviews a case of pediatric CRPS successfully managed with LDN. Prior to initiating LDN, the patient was unsuccessfully treated with gabapentin and amitriptyline and was suffering quality of life (QoL) deficits and pharmacotherapeutic adverse events (AEs). Here, we report improvements in the patient's symptoms and functional status following treatment with LDN.

Table 1. Budapest criteria for complex regional pain syndrome (2).

1. Continuing pain, which is disproportionate to any inciting event	
2. Must report at least one symptom in 3 of the 4 following categories	
Sensory	• Hyperesthesia • Allodynia
Vasomotor	• Temperature asymmetry • Skin color changes and/or asymmetry
Sudomotor/edema	• Edema • Sweating changes and/or asymmetry
Motor/trophic	• Decreased range of motion • Motor dysfunction (i.e., weakness, tremor, dystonia) • Trophic changes (i.e., hair, nails, skin)
3. Must display at least one sign at time of evaluation in 2 or more of the following categories:	
Sensory	• Evidence of hyperalgesia (to pinprick) • Allodynia (to light touch, deep somatic pressure, or joint movement)
Vasomotor	• Evidence of temperature asymmetry • Evidence of skin color changes and/or asymmetry
Sudomotor/edema	• Evidence of edema • Evidence of sweating changes and/or asymmetry
Motor/trophic	• Evidence of decreased range of motion • Evidence of motor dysfunction (i.e., weakness, tremor, dystonia) • Evidence of trophic changes (i.e., hair, nails, skin)
4. There is no other diagnosis that better explains the signs and symptoms	

CASE

An 11-year-old boy presented to a pain specialist with diagnosed CRPS. Symptoms began when the patient suffered a twisted right ankle while playing basketball. Initially, the injury was routine, with normal expected pain and swelling. After one month of persistent pain and swelling, the patient's mother became concerned and sent the patient to a pediatric orthopedic surgeon. X-rays and magnetic resonance imaging (MRI) of the right lower extremity came back normal, and the orthopedist recommended a soft ankle brace. With time, the pain subsided slightly, and there were days when the child did not experience any symptoms.

The patient experienced another ankle injury when a child stomped on his right ankle on the playground, which resulted in an immediate and severe pain response accompanied by swelling. This time, the pain did not subside, despite trialing nonsteroidal anti-inflammatory drugs, ice, rest, and elevation of the foot. The patient again presented to an orthopedist, who noted no major anatomic damage. However, the surgeon did document significant allodynia and hypersensitivity to touch, as

Table 2. Clinical use and mechanism of action of naltrexone by dose (5,6).

Dose range	Dose category	Clinical use	Proposed mechanism of action
50-100 mg	Standard	• Alcohol use disorder • Opioid use disorder	Opioid receptor antagonism
1-4.5 mg	Low dose	• CRPS • Fibromyalgia • Multiple sclerosis • Crohn disease • Cancer	Toll-like receptor 4 antagonism and opioid growth factor antagonism
0.001-1 mg	Very low dose	• Add-on to methadone detoxification taper	Toll-like receptor 4 antagonism and opioid growth factor antagonism
< 0.001 mg, dosed twice daily	Ultra low dose	• Potentiating opioid analgesia	Binding to high-affinity filamin-A site and reducing μ opioid receptor-associated Gs-coupling

well as vasomotor and pseudomotor changes. At this time, CRPS was diagnosed, and the child was referred to a pediatric pain specialist.

The patient was started on 100-mg gabapentin once daily at night, which was titrated up to 600 mg, 3 times per day. Additionally, the patient was enrolled in physical therapy (PT) to improve his range of motion. Although the gabapentin helped his symptoms, his mother and 5th-grade teacher noted difficulty concentrating at school, poor grades, and fatigue. The mother also noted that, when the child was emotionally stressed, his pain seemed to get worse. The patient's physical therapist also reported irritability in the child.

The pain specialist added amitriptyline (12.5 mg) once daily to the treatment regimen, which modestly improved the patient's mood and pain. Over the next 18 months, the patient's pain was stable, with continued allodynia and hypersensitivity to touch and with some edema and decreased range of motion. However, the patient's QoL continued to decline, with poor school performance and an inability to be physically active in sports or during recess.

The patient's mother sought a second opinion from another pain specialist and requested alternative treatment options. At this time, a lumbar sympathetic nerve block was discussed as a diagnostic and therapeutic regimen, which was declined due to the invasive nature of the procedure. A spinal cord stimulator trial was also declined for the same reason. The patient was offered a trial of intravenous (IV) ketamine, which was ultimately declined due to the experimental nature of the treatment and lack of strong supporting data.

At this time, the pain specialist recommended a trial of LDN. This recommendation was based on anecdotal evidence of the beneficial effect of LDN for CRPS and other chronic pain syndromes. Case studies have shown that LDN can improve pain in patients with long-standing, intractable CRPS affecting multiple extremities and limiting activities of daily living (13-15). For example, LDN treatment has been reported to improve pain severity enough for patients with CRPS to resume some activities of daily living (15). Furthermore, these case studies have indicated relatively rapid treatment responses, with improvement in pain severity occurring within 1 to 2 months (14). Based on past case reports in CRPS and evidence from other pain states, the pain specialist thought that LDN may improve CRPS symptoms and allow the patient to discontinue the gabapentin and amitriptyline. The patient's mother—who held a PhD degree—researched LDN. She decided that, since the gabapentin and amitriptyline side effects were impacting her son's QoL, they would trial LDN.

A dose titration schedule was developed to ensure medication tolerability. One mg of LDN was prescribed to be taken at night. After one month, the patient did not report any AEs, and the LDN was titrated up to 2.5 mg daily at night.

After 2 weeks of 2.5-mg LDN, the mother reported that she noticed an improvement in the child's pain symptoms. The patient confirmed this by self-reporting fewer pain symptoms and indicating that he felt the medication was helping. At that point, the patient was weaned off of gabapentin according to the following dose schedule: 600 mg twice daily for one week; 600 mg once daily in the morning for 2 weeks; 300 mg twice daily for one week; 300 mg once daily in the morning for 2 weeks; and discontinuation. During the weaning process, the patient did not report changes in pain symptoms. Once the gabapentin was discontinued, the patient was weaned off of amitriptyline by decreasing the dosage to 12.5 mg every other day for one month prior to discontinuation.

After 3 months of 2.5-mg LDN, the patient's mother enquired whether a higher dose would improve pain symptoms more. The LDN dose was increased to 4 mg per day. After one month, the patient noted continued improvement, less edema, less hypersensitivity to touch, and less allodynia. On a pain assessment, pain symptoms had improved by 70% from baseline. Patient self-reported a 60% improvement in functional status. Furthermore, following discontinuation of gabapentin and amitriptyline, the patient reported improved concentration, reduced fatigue, and better performance in school, suggesting improved mood and behavior. The patient's mother noted that the patient was able to successfully complete an indoor basketball season on his school team, which had not been noted by the mother before.

No AEs related to LDN were reported by the patient or his mother. The lack of AEs reported in this study may be attributable to the initial use of doses in the lower range for LDN (1 and 2.5 mg) prior to titrating up to 4 mg. This dosing regimen was intentionally selected to mitigate AEs based on the pain specialist's past experience with LDN in pediatric populations and the published literature on adult LDN dosing.

DISCUSSION

In this case, LDN resulted in remission of CRPS after gabapentin and amitriptyline led to inadequate pain alleviation

and QoL-limiting AEs. Treatment with LDN allowed the patient to discontinue both gabapentin and amitriptyline and resulted in improvement in pain scores and functional status. The outcomes reported here are in line with past case reports of LDN in adults with intractable CRPS (13-15). In these case studies, LDN alleviated pain symptoms as early as 2 days after beginning LDN, with significantly less pain reported after 4 weeks of treatment (13). In one case, 16 months of LDN resulted in complete remission of leg symptoms (14). Furthermore, LDN use has been shown to reduce pain and improve function in patients with other chronic pain and inflammatory syndromes, including fibromyalgia (16-18), multiple sclerosis (19-21), and Crohn disease (22), among others (23-25).

Several inflammatory and neurogenic mediators have been shown to be upregulated in patients with acute CRPS, including C-reactive protein, soluble tumor necrosis factor (TNF) receptor, and substance P (26). Most studies of acute CRPS have shown a preferential increase in mediators of local inflammation over systemic inflammation (26,27). In chronic CRPS, the inflammatory signature shifts, with elevations in TNF-α, IL-2, and IL-4, among others (28). Plasma concentrations of many of these proinflammatory cytokines have been shown to be reduced by LDN in patients with fibromyalgia, including IL-2, IL-4, and TNF-α (29). Decreases in plasma markers of inflammation are likely exerted through the effects of LDN on TLR4 and the cytokine cascades that result from nerve injury and subsequent microglial activation in patients with CRPS.

CRPS is classically divided into 3 stages: acute, dystrophic, and atrophic (Table 3) (30,31). On initial presentation to the first pain specialist, this patient had been experiencing symptoms for about 4 weeks, suggesting acute CRPS when gabapentin was initiated, which resulted in stable pain symptoms. It is unclear whether CRPS treatment is more effective when initiated earlier in the disease process, but it stands to reason that prompt initiation of LDN may lead to the greatest level of benefit due to early interference with microglial activation and the resultant inflammatory processes that drive neuropathy and can lead to sustained cell damage. This idea is further supported by the differences in inflammatory signatures between acute and chronic CRPS and the observation that serum levels of proinflammatory cytokines decrease within 6 months of analgesic treatment, even in the presence of continued symptoms (28,32). Therefore, as CRPS progresses, it is possible that inflammation decreases while irreversible cell and tissue damage remains (33), underscoring the potential importance of early intervention.

The limitations of this study are shared with those of other case reports. This is a retrospective report of real-world usage of LDN and is unblinded and nonrandomized. Patient and caregiver reports of symptom improvement could have been biased by initiation of a new medication. It is possible that the patient's CRPS spontaneously resolved; however, the resolution of symptoms occurred only after initiation of LDN. Furthermore, evidence for the efficacy and safety of LDN is limited to case reports and small studies in CRPS and other pain syndromes. Nonetheless, given the functional improvements reported for the patient, including participation in a sport and improved school performance, LDN should be considered as a treatment option for patients with CRPS.

CONCLUSION

This report adds to the current body of literature supporting the use of LDN in pediatric pain syndromes, and, to the authors' knowledge, represents the fifth reported case of LDN success in CRPS (13-15). Currently, a single registered clinical trial of LDN in CRPS is ongoing, with results anticipated in 2021 (NCT02502162). The results

Table 3. CRPS staging (30,31).

	Stage I Acute	Stage II Dystrophic	Stage III Atrophic
Time Frame	Usually within weeks of injury, but can last up to 6 months	Within months of injury	Within 6-8 months of injury and can last indefinitely
Pain	Can span severity spectrum, from tenderness to severe and burning	Constant, burning, throbbing, increased by stimuli	Intractable, diffuse, can span severity spectrum
Pain Spread	Near site of original injury	Throughout limb	Throughout and beyond limb
Skin	Warm, dry, red, mottling	Cool, diaphoretic, mottling	Pale, shiny, irreversible atrophy
Edema	Nonpitting	Extensive, with indurated and brawny character	Limited

Abbreviations: CRPS, complex regional pain syndrome

of this placebo-controlled study are eagerly awaited, and additional clinical trials and prospective studies evaluating the use of LDN in patients with CRPS should be considered. Until that time, empirical use of LDN may be an effective, inexpensive, and safe treatment option for patients with CRPS.

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