Systematic Review

Low-Dose Naltrexone Use for Patients with Chronic Regional Pain Syndrome: A Systematic Literature Review

Amol Soin, MD[1,2], Yasmeen Soin, JD[2], Tammy Dann, DO[3], Ricardo Buenaventura, MD[4], Kris Ferguson, MD[5], Sairam Atluri, MD[6], Harsh Sachdeva, MD[7], Gururau Sudarshan, MD[8], Humam Akbik, MD[9], and Jordan Italiano, BS[1]

From: [1]Wright State University Boonshoft School of Medicine, Fairborn, OH; [2]Ohio Pain Clinic, Dayton, OH; [3]Pain Evaluation Management Center of Ohio, Dayton, OH; [4]Pain Relief of Dayton, Dayton, OH; [5]Aspirus Health Care, Wausau, WI; [6]Interventional Spine Specialists, Cincinnati, OH; [7]University of Cincinnati, Cincinnati, OH; [8]UC Physicians: University of Cincinnati Physicians, Cincinnati, OH; [9]Cincinnati Comprehensive Pain Center, Fairfield, OH

Address Correspondence:
Amol Soin, MD
Ohio Pain Clinic
7076 Corporate Way,
Dayton, OH 45458
E-mail:
ohiopainclinic@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Dr. Amol Soin is the founder and CEO of Soin Theraputics which may be doing a clinical trial on low-dose naltrexone in the future.

Manuscript received: 08-30-2020
Revised manuscript received: 11-08-2020
Accepted for publication: 11-12-2020

Free full manuscript:
www.painphysicianjournal.com

Background: Complex regional pain syndrome is a rare, neuropathic disorder that affects fewer than 200,000 individuals in the United States annually. Current treatments often focus on pain management and fall short of relieving symptoms of pain and dystonia in patients.

Objective: The goal of this systematic qualitative review is to evaluate the evidence for the use of low-dose naltrexone in the treatment of chronic pain syndromes.

Study Design: This is a systematic review.

Methods: PubMed, Embase, and Web of Science were searched for articles containing the keywords "low-dose naltrexone" AND ("pain" OR "chronic pain" OR "fibromyalgia" OR "complex regional pain syndrome" OR "neuropathic pain" OR "nociceptive pain") between 1950 and July 17, 2020. A total of 30 publications were systematically reviewed. Exclusion criteria were articles that were unavailable in English, focused on acute pain only, and evaluated only animal models. Case studies were included for the purposes of our qualitative review.

Results: Out of 29 articles, we reviewed 11 prospective studies, 10 case studies, 3 systematic reviews, 2 retrospective studies, 2 simulation models, and one combination study. Articles focused on chronic pain syndromes as well as painful rheumatologic disorders and neurological disorders. We found that low-dose naltrexone treatment was positively associated with symptom relief in patients experiencing chronic pain, dystonia, and sleep disturbances.

Limitations: Due to the limited number of available articles focusing on the treatment of complex regional pain syndrome with low-dose naltrexone, the majority of studies analyzed focused on other chronic pain syndromes.

Conclusions: There is a need for additional prospective and interventional studies addressing the use of low-dose naltrexone in the treatment of complex regional pain syndrome symptoms.

Key words: Complex regional pain syndrome, reflex sympathetic dystrophy, low-dose naltrexone, chronic pain, opioid antagonist

Pain Physician 2021: 24:E393-E406

Complex regional pain syndrome (CRPS) is a rare, chronic pain disorder affecting only 200,000 individuals each year. It is divided into 2 categories: CRPS type 1, also known as reflex sympathetic dystrophy (90% of cases) and CRPS type 2. The prevalence of CRPS type 1 is low, with 5.46 out of 100,000 individuals affected in the United States annually (1). Indeed, fewer than 200,000 people experience CRPS each year (2). Consequently, the National Organization of Rare Diseases (NORD) has classified CRPS as a rare or orphan disease (i.e., a disease that affects fewer than 200,000 people) (2).

While CRPS type 2 is typically diagnosed following nerve damage, CRPS type 1 lacks nerve injuries (3). The characteristic feature of CRPS is hyperalgesia, or hypersensitivity to painful stimuli, with pain that is out of proportion to the original stimulation. CRPS is a neuroinflammatory condition and patients frequently experience autonomic, sensory, vasomotor, and motor dysfunction (such as pain in their limbs and dystonia) (3). The cause of CRPS is likely multifactorial and the exact mechanism is still unclear. Evidence suggests, however, that Toll-like receptors and inflammatory cytokines play key roles in the mechanistic pathway (3). Toll-like receptor 4 (TLR4) is believed to be upregulated during neuroimmune activation, which triggers the production of proinflammatory cytokines, leading to allodynia and hyperalgesia (4).

Current treatment of CRPS includes physical and occupational therapy, pharmacotherapies, and interventional procedures. Pharmacologic treatments focus on pain management, steroids, and opioids. Much of the research on opioid treatments have, thus far, fallen short in efficacy for CRPS treatment. Low-dose naltrexone (LDN) represents a promising avenue for CRPS treatment due to its unique mechanisms.

Naltrexone is approved for use in the treatment of alcohol use disorders (AUD) and other addictions, such as opioid dependence (5). In this context, naltrexone functions as an opioid antagonist targeting the mu and delta opioid receptors (6). Off-label uses of naltrexone have explored its use at lower doses through a different mechanism for the treatment of inflammatory, rheumatologic, and neurologic conditions. These include multiple sclerosis, fibromyalgia, Crohn disease, chronic fatigue syndrome (CFS), and—more recently—CRPS. At the low doses used for these conditions, naltrexone is thought to act as an immune modulator. Some speculate that this mechanism is caused by reduced neuroinflammation in the case of disorders like CFS (7). Evidence suggests that, at low doses, naltrexone antagonizes TLR4 on activated glial cells without the previously mentioned function as a mu opioid receptor antagonist (3). Thus, LDN presents a promising therapeutic avenue for the treatment of CRPS, a condition in which TLR4 upregulation is a primary pathway through attenuation of glial activation and direct targeting of TLR4 activity (4).

While previous systematic reviews have examined the use of oral naltrexone at higher doses and the prevalence of serious adverse events (SAEs), the widespread usages of LDN for chronic pain and inflammatory conditions have not yet been analyzed (5). The goal of this qualitative review is to examine the existing literature supporting the use of LDN in the treatment of pain in various disorders and, specifically, the evidence for LDN to treat chronic pain syndromes, such as CRPS. Furthermore, we will explore current gaps in knowledge on the use of LDN for CRPS, where further study is required.

Methods

Search Strategy

PubMed, Embase, and Web of Science were searched for the following keywords: "low-dose naltrexone" AND ("pain" OR "chronic pain" OR "fibromyalgia" OR "complex regional pain syndrome" OR "neuropathic pain" OR "nociceptive pain"). Publications between 1950 and July 17, 2020, were selected. Case studies, reviews, clinical trials, and animal studies were included in the initial review.

Abstract and Full-Text Review

Authors reviewed the abstracts and full-length articles. Microsoft Excel was used to manage all citations. Reasons for exclusion during abstract review included the following: conference abstract; not related to LDN; foreign language with English translation unavailable; not related to pain; review article; and duplicate. Exclusion criteria for full-length articles included the following: acute pain only; patients with chronic pain were excluded; lack of data relating to pain; animal model; in vitro study; and duplicate. Exclusion criteria were determined by authors and discrepancies were addressed through discussion.

Data Abstraction

Data were systematically collected from full-length articles and recorded in Microsoft Excel. A standard abstraction table was created to summarize the following information on study characteristics and demographics: author name(s), publication date, title, study type, objective(s), data source(s), population, sample size, mean age (in years), gender (% women), and race (% African American). Full-length articles were further analyzed to systematically collect and qualitatively summarize the type of disorder studied, symptoms of study patients, symptoms alleviated, time to resolution of symptoms, dose, adverse events, and SAEs. Risk of bias was informally assessed in all publications, including the risk for selection, performance, detection, and

attrition bias according to the Cochrane Back Review Group (8). This qualitative review relied on summary data and anecdotal reports included in case studies for analysis. Due to the inclusion of case studies, this report may be affected by selective reporting within the published studies.

Results

Search Results and Trial Flow

Details of the systematic review process are provided in the PRISMA flow diagram (Fig. 1). Electronic searches of PubMed, Embase, and Web of Science identified a total of 336 citations. PubMed returned 89 results; Embase returned 95 results; and Web of Science returned 152 results. A total of 268 citations remained after 68 duplicates were removed, of which 232 abstracts were reviewed. A total of 51 abstracts were included after the first round of abstract evaluation, and full-text articles were reviewed. Of these, 2 citations were found to be a duplicate. In the remaining 49 full-text articles which were removed, 14 animal studies, one in vitro study, and 3 studies focusing on acute pain were excluded. Upon further review, 2 additional studies were excluded after it was determined that effects of LDN on chronic pain were not assessed. A total of 29 studies were included for further qualitative analysis, including 11 prospective clinical trials, 10 case studies, 3 systematic reviews, 2 retrospective studies, 2 simulation/ predictive model studies, and one prospective 2-part study involving in vitro analysis with humans and animals (Table 1) (3,5,7,9-34).

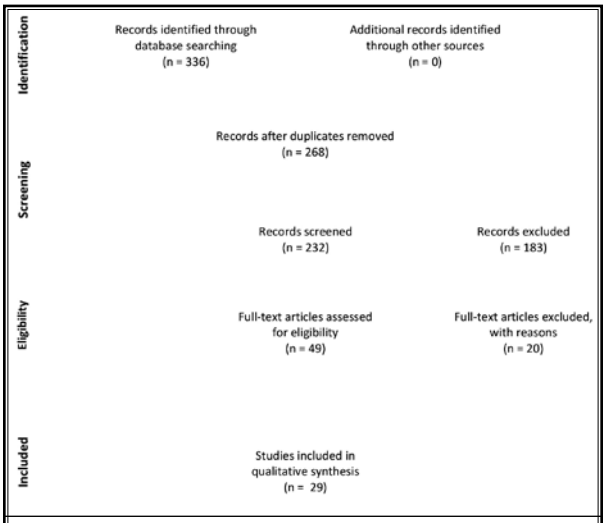

Fig. 1. *Selection of studies displayed in a PRISMA flow diagram.*

Characteristics of Included Studies

Of the 3 systematic reviews, one examined adverse events and SAEs from LDN treatment, and 2 evaluated the effects of naltrexone on opioid-induced conditions (opioid-induced pruritus and opioid-induced bowel dysfunction [OIBD]) (5,11,22). The remaining studies examined LDN use in the treatment of chronic pain in chronic pain syndromes, neurologic diseases, and rheumatologic disorders. Only 3 studies directly involved chronic pain syndromes, all of which were case studies on CRPS, highlighting the need for more detailed analysis of the effects of pain alleviation by LDN in CRPS patients (3,30,31). The majority of included studies focused on neurologic or rheumatologic disorders. There were 2 studies on myalgic encephalomyelitis and CFS (ME/CFS): one case study and one retrospective analysis of medical records (7,26). Fibromyalgia was the most commonly reported disorder, with 8 included studies (5 prospective, 2 predictive models, and one case study) (10,14,15,23-25,27,28). A total of 4 studies examined LDN effects on multiple sclerosis (all prospective) (12,18,23,29). Two studies assessed the effects of opioid consumption and antagonists (11,27). One prospective trial assessed the efficacy of LDN on treating Gulf War Illness (GWI), of which chronic pain is a characteristic symptom (9), and one study only included healthy patients (19). The remaining 5 studies were case reports analyzing various syndromes with pain as a primary symptom (polyneuropathy, neuropathic pain, refractory chronic low back pain, Hailey-Hailey Disease, and Stiff-Person Syndrome) (13,17,20,21,34).

Demographics

There was a tendency for fibromyalgia studies to focus on women, with 95 women patients out of 97. Study populations for CFS were slightly biased towards women, with 77% women out of 218 patients analyzed in a retrospective study and 2 out 3 women in the included case study (7,26). Three out of 4 patients were women in CRPS case studies (3,30,31). Age was not particularly biased in any of the study populations. The majority of included studies did not report on race; only 2 prospective studies directly reported race (11% African American in Brewer et al [9]; 12.5% African American in Parkitny et al [25]). Study populations for 5 of the studies were located outside of the U.S., with studies from Norway, Australia, Iran, Denmark, and Italy (10,16,18,19,27).

Table 1. *Characteristics of included studies.*

Author (year)	Study type	Objective(s)	Data source(s)	Population	Sample size	Mean age (years)	Gender (% female)	Race (% African American)
Bolton et al (2019)(5)	Systematic review	To evaluate the safety of oral naltrexone in randomized controlled trials comparing naltrexone with placebo	89 randomized controlled trials	Participants from trials of AUD (n = 38), various psychiatric disorders (n = 13), impulse control disorders (n = 9), other addictions (n = 18), obesity or eating disorders (n = 6), Crohn disease (n = 2), FM (n = 1), and cancers (n = 2)	10,957	NR	NR	NR
Bolton et al (2020)(7)	Case study	To report on the effects of LDN for CFS	Patient diaries and previous medical records	Patients with long-term ill-health due to CFS	3	53.6	66.70%	0%
Brewer et al (2018)(9)	Prospective	To assess the efficacy of LDN to treat GWI	Behavioral and laboratory assessments	Veterans who met the Kansas Case Definition of GWI, with moderate to severe symptoms in at least 3 of the 6 categories. Comorbidities were not excluded.	37	51	2.70%	11% of responders and non-responders
Bruun-Plesner et al (2020)(10)	Prospective	To assess dose-response relationships of LDN to treat FM	Questionnaire	Caucasian females with a diagnosis of FM in Southern Denmark	25	47	100%	0%
Candy et al (2018)(11)	Systematic review	To assess the effectiveness and safety of MOA for OIBD in people with cancer and people receiving palliative care	8 clinical trials	Patients with cancer (any stage) or patients at a palliative care stage of any disease	1022	NR	NR	NR
Chopra et al (2013)(3)	Case study	To report the effectiveness of LDN in patients with CRPS previously treated with conventional therapies	Clinical evaluation	Patients who meet the IASP criteria for CRPS diagnosis, with failed conventional CRPS pharmacotherapy	2	30	50%	0%
Cree et al (2010) (12)	Prospective	To evaluate the efficacy of 4.5mg nightly naltrexone on the quality of life of MS patients	Questionnaire/ survey	Patients between the ages of 18 and 75 years old with a diagnosis of MS according to the International Panel criteria in San Francisco, CA	60	49	60%	NR
Cruciani et al (2003)(13)	Case study/ letter	To report the effectiveness of ultra-low–dose naltrexone in a patient with painful diabetic neuropathy	Clinical evaluation	Patient with painful diabetic polyneuropathy	1	61	0	NR
Deshpande et al (2014)(14)	Simulation study/ predictive model	To develop an adaptive intervention model for LDN in FM	N/A	N/A	N/A	N/A	N/A	N/A
Deshpande et al (2014)(15)	Predictive model	To develop a predictive model for assigning dosages of naltrexone for FM	N/A	N/A	N/A	N/A	N/A	N/A
Farahmand et al (2012)(16)	Prospective	The present study aims to assess the influence of ultra-low doses of opioid antagonists on the analgesic properties of opioids and their side effects	Survey, laboratory assessment	Patients between the ages of 18 and 45 years old with closed single-bone fractures or soft tissue injuries in extremities and a pain level of 5 or greater (out of 10), in Tehran, Iran	267	26.5	27%	NR

Table 1. *Characteristics of included studies (continued).*

Author (year)	Study type	Objective(s)	Data source(s)	Population	Sample size	Mean age (years)	Gender (% female)	Race (% African American)
Ghai et al (2014) (17)	Case study	To report the effectiveness of LDN for a patient with chronic low back pain	Clinical evaluation	Patient with 2-year history of nonspecific chronic low back pain	1	35	0	NR
Gironi et al (2008)(18)	Prospective	To assess the safety and tolerability of a 6-month LDN course in patients with PPMS	Survey, laboratory assessment	Patients between the ages of 18 and 65 years old, with diagnosis of PPMS according to McDonald criteria in Italy	40	53.4	52.50%	NR
Hay et al (2011) (19)	Prospective	To determine whether, like naloxone, ultra-low dose naltrexone could potentiate the antinociceptive effects of buprenorphine in healthy humans	Cold pressor test	Healthy patients between the ages of 18 and 33 years old, without a history of chronic pain, in Adelaide, Australia	10	23	50%	NR
Hota et al (2016) (20)	Case study	To report the effectiveness of LDN in a patient with painful diabetic neuropathy	Clinical evaluation	Patient with a 30-year history of T2D and a 7-year history of painful diabetic neuropathy	1	76	0	NR
Ibrahim et al (2017)(21)	Case study	To assess LDN in treatment of recalcitrant HHD	Clinical evaluation, patient report	Patients with HHD treated at the Cleveland Clinic	3	40s, 60s, 60s	33%	NR
Kjellberg et al (2001)(22)	Systematic review	To identify pharmacotherapies that have been used to control opioid-related pruritus in the surgical setting, and to report their relative efficacies	22 trials	Patients from trials in surgical settings, including Caesarean sections, labor, hysterectomy, and orthopedic surgery	1477	NR	NR	NR
Ludwig et al (2017)(23)	Prospective; two-part with humans and animals	To measure endogenous opioids in MS patients	Human serum samples	MS patients receiving LDN therapy	10 control and 19 patients with MS	NR	45%	NR
Metyas et al (2017)(24)	Prospective	To evaluate the uses of LDN in a community practice–based setting	Survey, clinical evaluation	Patients with fibromyalgia diagnosis	25	55.4	96%	NR
Parkitny et al (2017)(25)	Prospective	To test the immune effects of LDN in patients with FM	Survey, laboratory assessment	Women ages 18 to 65 years old who met the ACR 2010 criteria for FM, near Palo Alto, CA	8	45.6	100%	12.50%
Polo et al (2019) (26)	Retrospective	To assess safety and efficacy of LDN alleviation of ME/CFS symptoms	Medical records	Patients who consulted the Unesta Sleep and Breathing Clinic during 2010-2014 and had a diagnosis of ME/CFS and LDN treatment	218	48.4	77%	NR
Raknes et al (2017)(27)	Retrospective	To examine changes in opioid consumption after starting LDN therapy	Pharmacy records	All Norwegian patients with at least one recorded LDN prescription in 2013 and at least one opioid prescription dispensed during the preceding 365 days	3775	53	78%	NR

Table 1. *Characteristics of included studies (continued).*

Author (year)	Study type	Objective(s)	Data source(s)	Population	Sample size	Mean age (years)	Gender (% female)	Race (% African American)
Ramanathan et al (2012)(28)	Case study	To report the treatment course and effectiveness of LDN in a patient with FM	Clinical evaluation and medical records	Patient with FM	1	37	0	NR
Sharafaddinzadeh et al (2010)(29)	Prospective	To assess the effect of LDN on quality of life in patients with MS	Survey	Patients between ages 15 and 65 years old with relapse-remitting or secondary progressive MS longer than 6 months, in Iran	106	34.81	76%	NR
Sturn et al (2016) (30)	Case study	To report the effectiveness of LDN in a patient with CRPS	Clinical evaluation	CRPS patient	1	17	100%	NR
Weinstock et al (2016)(31)	Case study	To report the effectiveness of LDN in a patient with CRPS	Clinical evaluation	Long-standing CRPS patient with Ehlers-Danlos syndrome	1	56	100%	0%
Younger et al (2009)(32)	Prospective	To test the efficacy of LDN to treat FM	Survey	Patients who met the ACR criteria for FM	10	44	100%	NR
Younger et al (2013)(33)	Prospective	To determine efficacy of LDN on reducing FM severity compared to placebo	Survey	Patients registered with the Fibromyalgia Network in Northern California between 2008 and 2010, between 18 and 65 years old, who met the ACR criteria for FM	28	42.7	100%	NR
Zappaterra et al (2020)(34)	Case study	To assess LDN in patient with stiff-person syndrome	Clinical evaluation	Patient with stiff-person syndrome	1	59	100%	NR

Effects of LDN on Chronic Pain

Complex Regional Pain Syndrome

LDN has been shown to alleviate symptoms of pain in patients with chronic pain (Table 2). Chopra et al (3) reported 2 patient case studies with CRPS who experienced significantly less pain with 4.5 mg daily LDN treatment. In another CRPS case study, Sturn and Collin (30) found alleviation of pain symptoms as early as 2 days after beginning LDN therapy, with significantly less pain at 4 weeks. Weinstock et al (31) reported alleviation of pain symptoms within one month of LDN treatment, with complete remission of CRPS leg symptoms by 16 months. LDN has been reported to have benefits related to other symptoms of chronic pain syndromes as well, including dystonic spasms, CRPS flares, energy, sleep disturbances, and mood.

Chronic Fatigue Syndrome and Fibromyalgia

Bolton et al (7) identified 3 case studies with chronic fatigue syndrome (CFS) who reported reduced pain from LDN use. In a retrospective study, Polo et al (26) found that 16.9% of patients with myalgic encephalitis CFS (ME/CFS) reported pain relief after beginning LDN therapy.

Reduction of pain has also been found in a number of reports involving fibromyalgia patients. Parkitny et al (25) published the results of a small, pilot, prospective study with a 15% reduction in fibromyalgia-associated pain. Ramanathan et al (28) reported a case study for a patient who experienced a significant reduction in spot pain and generalized body ache, with an improved time for the cold pressor test. This improvement in pain symptoms was not straightforward, and the patient experienced recurrence in pain symptoms while optimizing LDN dosage. Younger and Mackey (32) conducted a prospective, pilot study on 10 fibromyalgia patients who reported alleviated pain symptoms within 12 weeks of LDN treatment. In a second, prospective study of fibromyalgia patients, Younger et al (33) reported reduced mechanical and heat pain, in addition to reduction in daily pain and highest pain, following LDN treatment. Bruun-Plesner et al (11) assessed dose-response relationships in patients

Table 2. *Efficacy of low-dose naltrexone treatment.*

Author (year)	Disorder studied	Symptoms	Symptoms alleviated	Time to alleviation of symptoms	Dose	AEs	SAEs
Bolton et al (2019)(5)	AUD, various psychiatric disorders, impulse control disorders, other addictions, obesity or eating disorders, Crohn disease, FM (n = 1), and cancers.	NR	NR	NR	3 – 250 mg	Dizziness, nausea, and vomiting	No increase in SAEs compared with placebo
Bolton et al (2020)(7)	CFS	Headaches, fatigue, postexertional malaise, migraines, food intolerances, mood, abdominal pain, mobility, flu-like symptoms, cognitive impairment, widespread pain, and sleep disturbances, light and sound sensitivity, depression	Fatigue, food intolerances, pain, mobility, sleep disturbances, depression/mood	NR in detail. Case 1 – 3: < 2 yrs; 6 months; < 2 yrs	Case 1 – 3: 6 mg (1.5 -> 12 mg test range); 4 mg (0.25 – 4 mg); 4.5 mg (1 – 4.5 mg)	Case 1 – 3: Increased headaches (resolved with different dose); none reported; none reported	None
Brewer et al (2018)(9)	GWI	Overall condition via CGIS: physical limitations, physical wellbeing, emotional limitations, emotional wellbeing, energy/fatigue, social function, pain, general health	Overall condition (partial benefit only): emotional wellbeing and energy/fatigue were P = 0.05	< 3 months	4.5 mg/day	Dizziness	NR
Bruun-Plesner et al (2020)(10)	FM	FIQR survey, pain, energy, stiffness, depression, anxiety, cognitive impairment, sleep disturbances, tenderness to touch, imbalance	Patient Global Impression of Improvement Scale (PGI-I)	2 – 3 weeks	0.75 – 6 mg	Gastrointestinal symptoms, headache, vivid dreams, mood disturbance, pain, fatigue, dizziness, palpitations, increased appetite, sleeping difficulty	None
Candy et al (2018)(11)	OIBD	Bowel movements, pain	Bowel movements	< 14 days	0.15 mg/kg or 0.30 mg/kg; 8 mg to 12 mg	Abdominal pain, flatulence, nausea, vomiting, diarrhea, peripheral edema, restlessness, falls, somnolence	Aneurysm ruptured, respiratory arrest, exacerbation of dyspnea, suicidal ideation, aggression, malignant neoplasm, concomitant disease progression, myocardial ischemia, aggravation of coronary artery disease, and aggravation of congestive heart failure

Table 2. *Efficacy of low-dose naltrexone treatment (continued).*

Author (year)	Disorder studied	Symptoms	Symptoms alleviated	Time to alleviation of symptoms	Dose	AEs	SAEs
Chopra et al (2013)(3)	CRPS	swelling, allodynia, color change, temperature change, some weakness, blisters, skin ulceration, dystonic spasms, dysesthesia	Dystonic spasms, CRPS flares, energy, pain tolerance, sleep disturbances, pain, mood	< 2 months	4.5 mg/day	None	None
Cree et al (2010)(12)	Multiple sclerosis	MSQLI scores (mental health, pain effects, perceived deficits, fatigue, visual impairment, bowel and bladder control, sexual satisfaction)	Mental health outcome measures	8 weeks	4.5 mg/day	Vivid dreaming; other AEs equal between placebo and LDN	None
Cruciani et al (2003) (13)	Polyneuropathy	Pain and paresthesias in feet, distal legs, and fingers, mood, chronic nausea,	Pain, chronic nausea, fatigue	< 24 hours	1 mg	None	None
Deshpande et al (2014) (14)	FM	Data extracted from Younger et al trial on FM	N/A	N/A	4.5 mg/day	N/A	N/A
Deshpande et al (2014) (15)	FM	N/A	N/A	N/A	N/A	N/A	N/A
Farahmand et al (2012)(16)	Trauma patients in ER	Upper or lower extremity injury or fracture	Measured dose of morphine needed to treat pain	Inpatient	100 ng	None	None
Ghai et al (2014)(17)	Refractory chronic low back pain	Non-specific left-side chronic low back pain,	Pain	2 weeks (after 4 mg dose was started; 4 weeks from initial 2 mg dose of LDN)	2 – 4 mg	None	None
Gironi et al (2008)(18)	PPMS	Spasticity, pain, fatigue, depression, quality of life	Spasticity	< 3 months	2 – 4 mg	Irritability, hematological abnormalities, urinary infection, other	lung carcinoma renal failure
Hay et al (2011)(19)	Healthy subjects	Nociception	Nociception	N/A	100:1, 133:1, 166:1. 200:1 for buprenorphine: naltrexone	Nausea, dizziness, vomiting, difficulty concentrating	None
Hota et al (2016)(20)	Diabetic, neuropathic pain	Pain in both legs, numbness, sleep disturbances, hyperalgesia, decreased vibration perception in both feet	Pain, sleep disturbances, hyperalgesia	< 4 weeks (partial improvement on 2 mg dose), < 6 weeks (greater improvement on 4 mg dose)	1 – 4 mg	Mild diarrhea, nausea, somnolence	None

Table 2. *Efficacy of low-dose naltrexone treatment (continued).*

Author (year)	Disorder studied	Symptoms	Symptoms alleviated	Time to alleviation of symptoms	Dose	AEs	SAEs
Ibrahim et al (2017) (21)	HHD	Erosions, erythema, pain	Quality of life, depression, erosions, pain, ulcerations, erythema	3 months; 3 months; 4 months	1.5 – 3 mg/day	None	None
Kjellberg et al (2001) (22)	Opioid-induced pruritus	Pruritus and other AEs (e.g., nausea, vomiting)	Duration of anesthesia	NR	3 – 9 mg naltrexone	NR	NR
Ludwig et al (2017) (23)	MS	N/A	N/A	N/A	N/A	N/A	N/A
Metyas et al (2017)(24)	FM	FIQR survey: physical function, functional ability, pain, stiffness, restorative sleep, energy, anxiety, depression, memory, and balance	FIQR survey	90 days	1.5 – 4.5 mg/day	Diarrhea	None
Parkitny et al (2017) (25)	FM	Inflammation, pain	Inflammation, pain	2-week blocks	3 – 4.5 mg	None	None
Polo et al (2019)(26)	ME/CFS	Unrefreshing sleep and PEM	Vigilance/ alertness, physical performance, cognition, pain, fever, other symptoms	Unclear	1.5 – 4.5 mg/say	Nausea, anxiety, dizziness, headache, nightmares, GI symptoms, sleepiness, hot flashes/sweating, tachycardia, depression, paresthesias, muscle and joint pain	None
Raknes et al (2017)(27)	Opioid consumption (after LDN treatment)	Opioid use	N/A	N/A	Median, 3.7 mg	N/A	N/A
Ramanathan et al (2012)(28)	Fibromyalgia	Generalized dull pain throughout body, stiff cervical muscles, pain on soles of feet and unsteadiness while walking, dryness and itchiness of eyes, pain in eye muscles, fatigue, sleep abnormalities, difficulty concentrating, anxiety	"Spot" pain (1 week), dull pain in back and neck and gait unsteadiness (1 month), subjective pain (1 month)	1 week*	1 – 4.5 mg	Dry mouth and increased thirst, increased fatigue, lower quality of life (dependent on timing of dose/treatment)	None
Sharafaddinzadeh et al (2010)(29)	MS	Pain, energy, emotional well-being, social, cognitive, and sexual functions, role limitations, health distress, and quality of life	No statistical difference for LDN vs placebo on symptoms	< 17 weeks	4.5 mg/day	Nausea, epigastric pain, mood alteration, mild irritability, headache, and joint pain	None
Sturn et al (2016)(30)	CRPS	Pain	Pain	2 days	1.5 mg	None	None

Table 2. *Efficacy of low-dose naltrexone treatment (continued).*

Author (year)	Disorder studied	Symptoms	Symptoms alleviated	Time to alleviation of symptoms	Dose	AEs	SAEs
Weinstock et al (2016) (31)	CRPS	Severe leg pain, episodic pain in arms and nose, asymmetric and shiny skin with fluctuating temperature changes, color change, edema, IBS, atypical chest pain and fatigue, edema, blue discoloration, tenderness, joint hypermobility with EDS diagnosis	Leg and bowel symptoms; all CRPS pain, bowel symptoms, and fatigue	< 1 month	4.5 mg/day	None	None
Younger et al (2009) (32)	FM	Pain, mood, fatigue, life satisfaction, sleep quality	Pain, mood	< 12 weeks	4.5 mg/day	Dryness, tinnitus, vivid dreams, headaches, heartburn, irritability	None
Younger et al (2013) (33)	FM	Average daily pain, highest pain, fatigue, sadness, stress, sleep quality, ability to think and remember, gastrointestinal symptoms, and headaches	Mechanical pain, heat pain, daily pain, highest pain, fatigue, stress		4.5 mg/day	Insomnia, vivid dreams, nausea	None
Zappaterra et al (2020) (34)	Stiff-person syndrome	Diffuse muscle pain, anxiety, agoraphobia, muscle tightness and discomfort	Pain levels, anxiety, agoraphobia, muscle tightness and discomfort	6 weeks	1.5 – 4.5 mg	None	None

AUD, alcohol use disorder; CFS, chronic fatigue syndrome; CGIS, Clinical Global Impression Scale; CRPS, complex regional pain syndrome; EDS, Ehler-Danlos syndrome; FIQR, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; GWI, Gulf War illness; HHD, Hailey-Hailey disease; IBS, irritable bowel syndrome; LDN, low-dose naltrexone; ME, myalgic encephalomyelitis; MS, multiple sclerosis; MSQLI, Multiple Sclerosis Quality of Life Inventory; N/A, not applicable; NR, not reported; OIBD, opioid-induced bowel dysfunction; PEM, postexertional malaise; PPMS, primary progressive MS.

with fibromyalgia. Deshpande et al (14,15) published 2 simulation studies with predictive models for the use of LDN in fibromyalgia patients.

Other Conditions with Pain Symptoms

Cruciani et al (13) reported a case study for a diabetic patient with polyneuropathy, who experienced pain relief in less than 24 hours after the addition of 1 mg LDN to existing therapies. Ghai et al (17) published a case study of a patient with refractory chronic low back pain who responded to LDN therapy within 4 weeks. A case study published by Zappaterra et al (34) described a patient with stiff-person syndrome reported reduced pain levels as early as 6 weeks after starting LDN therapy. Hay et al (19) conducted a prospective study in 10 healthy patients who reported LDN as an antinociceptive.

Symptoms Alleviated by LDN Treatment

Fatigue and Sleep Disturbances

A total of 5 studies reported significantly less fatigue in patients receiving LDN treatment (7,9,13,31,33). Among these was the case study by Weinstock et al (31), reporting less fatigue in a CRPS patient. An additional 2 studies reported increased energy with LDN treatment (3,26). Furthermore, 4 studies reported alleviation of sleep disturbances (3,7,10,20).

Mood, Anxiety, and Depression

Poor emotional wellbeing was a commonly analyzed symptom and was present in nearly all patient populations at baseline (CRPS, CFS, GWI, polyneuropathy, fibromyalgia, and multiple sclerosis). This included reports of overall emotional wellbeing, mood, depression, or anxiety. A total of 8 studies reported significant

improvements in these measures following LDN treatment (3,7,12,21,24,32-34).

Overall Condition

A number of studies reported improvement in overall condition, using patient surveys that included questions about pain. Brewer et al (9) found that 38% of patients responded to treatment, using the 7-point Clinical Global Impression Scale (CGIS) to determine improvements in patient condition. A prospective study by Metyas et al (24) found an overall reduction of 19.5% in the Revised Fibromyalgia Impact Questionnaire (FIQR), with 50% of patients reporting average improvements of 41% (24).

Common CRPS Symptoms

Chopra et al (3) reported positive effects of LDN on dystonic spasms, CRPS flares, pain tolerance, sleep disturbances, and mood. Weinstock et al (31) described a patient with CRPS (including severe leg pain) who experienced relief from all CRPS pain, leg and bowel symptoms, and fatigue.

Side Effects

One systematic review evaluated occurrence of adverse events (AEs) and SAEs with LDN use. Bolton et al (5) found only mild AEs reported among the included studies (89 studies), including nausea, vomiting, and dizziness. Although 119 patients reported at least one SAE in the naltrexone study arm, meta-analysis found no difference between occurrence of SAEs in naltrexone and placebo groups. Furthermore, secondary analysis found only 6 AEs that were statistically significant: decreased appetite, dizziness, nausea, sleepiness, sweating, and vomiting.

Across the other studies included here, the most commonly reported AEs were dizziness (4 studies), vomiting (4 studies), nausea (8 studies), and vivid dreams (4 studies). Other reported AEs included headaches, abdominal pain, gastrointestinal issues, peripheral edema, restlessness, falls, somnolence, irritability, hematological abnormalities, urinary infection, difficulty concentrating, anxiety, sleepiness, hot flashes/sweating, tachycardia, depression, muscle and joint pain, fatigue, tinnitus, heartburn, dry mouth, and joint pain. The majority of AEs were reported as mild, and only 2 studies reported SAEs that were significant compared with placebo. Gironi et al (18) reported 2 patients with progressive MS who developed lung carcinoma and renal failure; however, the authors speculated that these diagnoses were due to pre-existing conditions. In a systematic review, Candy et al (11) reported SAEs from methylnaltrexone use (dosages between 0.15 mg/kg and 0.30 mg/kg) and naloxone use (120 – 160 mg dosages).

Dose

Dosages varied widely between studies, with 4.5 mg frequently used as a target dose. A total of 11 of the included studies utilized a range of LDN dosages to find optimal alleviation of symptoms (7,10,11,17,19-22,24-26,28,34). The dosages ranged from 1 to 9 mg, with 4.5 mg per day as a common end point. One systematic review examined dosages from 3 to 250 mg naltrexone (5). Only one study assessed the dose-response relationship of LDN to the treatment of symptoms (10). In a prospective study of 25 fibromyalgia patients, Bruun-Plesner et al (10) tested doses from 0.75 to 6 mg and reported an ED50 of 3.88 mg and ED95 of 5.40 mg.

Time to Alleviation of Symptoms

There was a large range in both the time points at which patient symptoms were assessed and the time to efficacy of LDN, particularly in reported case studies. Patients with CRPS reported pain relief as early as 2 days after beginning LDN treatment (1.5 mg dose) to less than 2 months, dependent on clinical evaluation of symptoms (3,30,31). Furthermore, LDN treatment reportedly increased in efficacy with time, according to Weinstock et al (31), who reported complete remission of CRPS symptoms at 16 months.

Cruciani et al (13) reported a case study of a patient with polyneuropathy who experienced symptom relief within 24 hours of LDN initiation). The time to resolution of symptoms varied in other studies from one week to 2 years. An accurate estimation of time required to resolve symptoms was limited by patient reports (in the case studies) and time points for clinical evaluation. Since many of the case studies included graded doses, with little to no effect after beginning initial dose, there was an inherent bias in the length of time until symptoms were resolved. Optimization of study dose introduced bias into the evaluation of time for LDN efficacy, with multiple studies instructing patients to begin LDN treatment at lower dosages (1 – 1.5 mg) and gradually increase the dosage every 2 weeks until reaching the effective dose.

Risk of Bias in Included Studies

The risk of bias within and across included studies was compounded by the presence of case studies

and lack of clinical trials. Our analysis returned 10 case studies (14 patients), 11 prospective studies (616 patients), and 2 retrospective studies (3993 patients) (3,5,7,9-34). As such, selection bias was common as was performance bias (8). No direct comparison of bias was made across studies. The majority of prospective studies focused on fibromyalgia, for which there are overlapping symptoms (pain, energy, sleep disturbances, mood) with CRPS; however, the majority of included fibromyalgia studies utilized the patient FIQR survey, whereas all 3 included CRPS studies were case studies based on clinical evaluation and patient reports. One prospective study (267 patients) measured the dose of morphine needed to treat pain in trauma patients in the ER, in contrast to other studies analyzing the effects of LDN on chronic pain (16). The 3 systematic reviews and 2 predictive models/simulation studies did not directly address pain relief from LDN treatment (5,11,14,15,22).

Discussion

Although case studies present compelling anecdotal evidence for the use of LDN to treat CRPS, there is a profound lack of prospective interventional studies assessing the effects of LDN on chronic pain. Given its prevalent off-label use in clinical settings, there is a need for further study on the safety and efficacy of LDN in inflammatory conditions. In many of the analyzed studies, pain was at least partially alleviated by LDN treatment. Fatigue, sleep dysfunction, and mood were also improved by LDN treatment.

The data presented in this review highlight both the advantages and pitfalls of previous studies. There is a need for further study on safety, efficacy, dosing, and expansion of usage for LDN. Four of our included prospective, interventional studies took place outside of the United States, suggesting a need for more interventional studies within the United States (10,16,18,19). Furthermore, no interventional studies have been published on CRPS and LDN. These data indicate an urgent need for prospective, interventional studies conducted in diverse populations.

Many studies discussed 4.5 mg as a feasible target dose; however, the included studies utilized dosages ranging from 1 to 9 mg, with case study efficacy as low as 1.5 mg. Furthermore, reports address the complicated necessity of dose optimization, as patients have been reported to experience increases or decreases in symptom relief and AEs, dependent on dose. Indeed, in one of the presented case studies, a CFS patient experienced headaches as an AE, which resolved when dose was increased (7). Another case study presented a diabetic patient with neuropathic pain who experienced partial improvement at a 2-mg dose and greater improvement at 4 mg (20).

The length of time required for symptom relief was another factor that was extremely variable, depending on the condition studied, the time points for analysis, and the dosage. One patient reported partial improvement at 4 weeks (2-mg dose) and greater improvement at 6 weeks (4-mg dose) (20). Another patient reported improvement at one week, with further improvement at later time points and recurrence of symptoms following (along with dose optimization throughout the process) (28). Multiple interventional studies utilized graded doses to assess the efficacy of LDN treatment, frequently in 2-week blocks per dose. Thus, graded dosages may extend the length of time required for resolution of pain symptoms; however, it is unknown whether patient adherence or LDN efficacy would change in a fixed-dose trial. Furthermore, the time required to alleviate symptoms varied significantly among studies and disorders. CRPS patients reported pain relief as early as 2 days or as long as 2 months (dependent on clinical evaluation visits) (3,30). One CRPS patient reported relief in less than one month with complete remission of CRPS symptoms at a 16-month follow-up (31). Thus, further study of dosages and time are required to fully assess the efficacy of LDN in the treatment of not only CRPS, but other inflammatory and chronic pain conditions as well. There was an inherent limitation in AEs and SAEs to those reported, particularly for case studies dependent on patient recall and prospective studies dependent on patient surveys.

The antinociceptive effects of LDN have been shown by several animal studies, in addition to one prospective study on healthy patients included in this review (19). In mice, LDN has been shown to block acute thermal hyperalgesia (35,36). Furthermore, when used in combination with LDN, morphine's analgesic effects may be increased (37,38). This mechanism was evaluated in one of our included studies, which measured the dose of morphine needed to treat pain in ER patients receiving LDN (16).

In a case study of polyneuropathy, Cruciani et al (13) also found potentiation of an opioid's effects when used in combination with LDN. These effects were corroborated by antinociceptive effects in mice receiving LDN with intermittent morphine and in other

studies evaluating the effects of opioid use with LDN (39-41). There is evidence that the synergistic effects of LDN are similar to cannabinoids as well (42). LDN has also been shown to enhance antiallodynic effects of anticonvulsants in the treatment of neuropathic pain in a rat model (43). Further studies are required to dissect the mechanism of LDN and relevance for CRPS patient treatment. These synergistic effects are critically important for the widespread uses of LDN because of added incentive it provides for the funding of clinical trials. Naltrexone is currently approved for use in AUD, and LDN's use in clinical practice to treat chronic pain has been primarily off-label. As a compound with potentially viable synergistic effects, the synergistic effects of LDN with opioids open new avenues for patentability (44).

Conclusions

There is a growing body of literature supporting the use of LDN for the treatment of chronic pain. A number of case studies have reported positive effects for LDN in the treatment of CRPS. While many of the studies presented here address the effects of LDN on pain, the majority focus on rheumatologic or neurologic conditions, rather than chronic pain syndromes. Consequently, there is a significant need for interventional studies assessing the efficacy and safety of LDN in the treatment of chronic pain syndromes.

Acknowledgments

Jessica Martin, PhD, and Hannah Ledford, PhD, provided assistance in the development of this manuscript.

References

1. Sandroni P, Benrud-Larson LM, McClelland RL, et al. Complex regional pain syndrome type I: Incidence and prevalence in Olmsted county, a population-based study. *PAIN* 2003; 103:199-207.
2. Diseases NOfR. Complex regional pain syndrome. https://rarediseases.org/rare-diseases/reflex-sympathetic-dystrophy-syndrome/ Accessed August 16, 2020.
3. Chopra P, Cooper MS. Treatment of complex regional pain syndrome (CRPS) using low dose naltrexone (LDN). *J Neuroimmune Pharmacol* 2013; 8:470-476.
4. Del Valle L, Schwartzman RJ, Alexander G. Spinal cord histopathological alterations in a patient with longstanding complex regional pain syndrome. *Brain Behav Immun* 2009; 23:85-91.
5. Bolton M, Hodkinson A, Boda S, et al. Serious adverse events reported in placebo randomised controlled trials of oral naltrexone: A systematic review and meta-analysis. *BMC Med* 2019; 17:10.
6. Cant R, Dalgleish AG, Allen RL. Naltrexone inhibits IL-6 and TNFalpha production in human immune cell subsets following stimulation with ligands for intracellular toll-like receptors. *Front Immunol* 2017; 8:809.
7. Bolton MJ, Chapman BP, Van Marwijk H. Low-dose naltrexone as a treatment for chronic fatigue syndrome. *BMJ Case Rep* 2020; 13:e232502.
8. Furlan AD, Pennick V, Bombardier C, et al. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941.
9. Brewer KL, Mainhart A, Meggs WJ. Double-blinded placebo-controlled cross-over pilot trial of naltrexone to treat Gulf War Illness. *Fatigue: Biomedicine, Health & Behavior* 2018; 6:132-140.
10. Bruun-Plesner K, Blichfeldt-Eckhardt MR, Vaegter HB, et al. Low-dose naltrexone for the treatment of fibromyalgia: Investigation of dose-response relationships. *Pain Med* 2020; 21:2253-2261.
11. Candy B, Jones L, Vickerstaff V, et al. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. *Cochrane Database Syst Rev* 2018; 6:CD006332.
12. Cree BA, Kornyeyeva E, Goodin DS. Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. *Ann Neurol* 2010; 68:145-150.
13. Cruciani RA, Lussier D, Miller-Saultz D, et al. Ultra-low dose oral naltrexone decreases side effects and potentiates the effect of methadone. *J Pain Symptom Manage* 2003; 25:491-494.
14. Deshpande S, Rivera DE, Younger JW, et al. A control systems engineering approach for adaptive behavioral interventions: Illustration with a fibromyalgia intervention. *Transl Behav Med* 2014; 4:275-289.
15. Deshpande S, Nandola NN, Rivera DE, et al. Optimized treatment of fibromyalgia using system identification and hybrid model predictive control. *Control Eng Pract* 2014; 33:161-173.
16. Farahmand S, Ahmadi O, Dehpour A, et al. Does adding low doses of oral naltrexone to morphine alter the subsequent opioid requirements and side effects in trauma patients? *Am J Emerg Med* 2012; 30:75-78.
17. Ghai B, Bansal D, Hota D, et al. Off-label, low-dose naltrexone for refractory chronic low back pain. *Pain Medicine* 2014; 15:883-884.
18. Gironi M, Martinelli-Boneschi F, Sacerdote P, et al. A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis. *Mult Scler* 2008; 14:1076-1083.
19. Hay JL, La Vincente SF, Somogyi AA, et al. Potentiation of buprenorphine antinociception with ultra-low dose naltrexone in healthy subjects. *Eur J Pain* 2011; 15:293-298.
20. Hota D, Srinivasan A, Dutta P, et al. Off-label, low-dose naltrexone for refractory painful diabetic neuropathy. *Pain Med* 2016; 17:790-791.
21. Ibrahim O, Hogan SR, Vij A, et al. Low-dose naltrexone treatment of familial benign pemphigus (Hailey-Hailey disease). *JAMA Dermatol* 2017; 153:1015-1017.
22. Kjellberg F, Tramer M. Pharmacological control of opioid-induced pruritus: A quantitative systematic review of

randomized trials. *Eur J Anaesthesiol* 2001; 18:346-357.

23. Ludwig MD, Zagon IS, McLaughlin PJ. Serum [Met(5)]-enkephalin levels are reduced in multiple sclerosis and restored by low-dose naltrexone. *Exp Biol Med (Maywood)* 2017; 242:1524-1533.
24. Metyas S, Chen CL, Yeter K, et al. Low dose naltrexone in the treatment of fibromyalgia. *Curr Rheumatol Rev* 2018; 14:177-180.
25. Parkitny L, Younger J. Reduced pro-inflammatory cytokines after eight weeks of low-dose naltrexone for fibromyalgia. *Biomedicines* 2017; 5:16.
26. Polo O, Pesonen P, Tuominen E. Low-dose naltrexone in the treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Fatigue: Biomedicine, Health & Behavior* 2019; 7:207-217.
27. Raknes G, Smabrekke L. Low-dose naltrexone and opioid consumption: A drug utilization cohort study based on data from the Norwegian prescription database. *Pharmacoepidemiol Drug Saf* 2017; 26:685-693.
28. Ramanathan S, Panksepp J, Johnson B. Is fibromyalgia an endocrine/endorphin deficit disorder? Is low dose naltrexone a new treatment option? *Psychosomatics* 2012; 53:591-594.
29. Sharafaddinzadeh N, Moghtaderi A, Kashipazha D, et al. The effect of low-dose naltrexone on quality of life of patients with multiple sclerosis: A randomized placebo-controlled trial. *Mult Scler* 2010; 16:964-969.
30. Sturn KM, Collin M. Low-dose naltrexone: A new therapy option for complex regional pain syndrome type I patients. *International Journal of Pharmaceutical Compounding* 2016; 20:197-201.
31. Weinstock LB, Myers TL, Walters AS, et al. Identification and treatment of new inflammatory triggers for complex regional pain syndrome: Small intestinal bacterial overgrowth and obstructive sleep apnea. *A A Case Rep* 2016; 6:272-276.
32. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: A pilot study. *Pain Med* 2009; 10:663-672.
33. Younger J, Noor N, McCue R, et al. Low-dose naltrexone for the treatment of fibromyalgia: Findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis Rheum* 2013; 65:529-538.
34. Zappaterra M, Shouse E, Levine RL. Low-dose naltrexone reduces symptoms in stiff-person syndrome. *Med Hypotheses* 2020; 137:109546.
35. Crain SM, Shen KF. Low doses of cyclic AMP-phosphodiesterase inhibitors rapidly evoke opioid receptor-mediated thermal hyperalgesia in naive mice which is converted to prominent analgesia by cotreatment with ultra-low-dose naltrexone. *Brain Res* 2008; 1231:16-24.
36. Crain SM, Shen K-F. Acute thermal hyperalgesia elicited by low-dose morphine in normal mice is blocked by ultra-low-dose naltrexone, unmasking potent opioid analgesia. *Brain Res* 2001; 888:75-82.
37. Crain SM, Shen K-F. Ultra-low concentrations of naloxone selectively antagonize excitatory effects of morphine on sensory neurons, thereby increasing its antinociceptive potency and attenuating tolerance/dependence during chronic cotreatment. *Proceedings of the National Academy of Sciences* 1995; 92:10540-10544.
38. Mattioli TA, Milne B, Cahill CM. Ultra-low dose naltrexone attenuates chronic morphine-induced gliosis in rats. *Mol Pain* 2010; 6:22.
39. Norouzi Javidan A, Yazdi Samadi F, Latifi S, et al. A novel controlled release drug delivery system for naltrexone administration combined with intermittent morphine to induce antinociception. *Journal of Drug Delivery Science and Technology* 2014; 24:413-417.
40. Largent-Milnes TM, Guo W, Wang HY, et al. Oxycodone plus ultra-low-dose naltrexone attenuates neuropathic pain and associated mu-opioid receptor-Gs coupling. *J Pain* 2008; 9:700-713.
41. Leonard JB, Nair V, Diaz CJ, et al. Potential drug interaction with opioid agonist in the setting of chronic low-dose opioid antagonist use. *Am J Emerg Med* 2017; 35:1209 e1203-1209 e1204.
42. Paquette J, Olmstead M. Ultra-low dose naltrexone enhances cannabinoid-induced antinociception. *Behav Pharmacol* 2005; 16:597-603.
43. Pineda-Farias JB, Caram-Salas NL, Salinas-Abarca AB, et al. Ultra-low doses of naltrexone enhance the antiallodynic effect of pregabalin or gabapentin in neuropathic rats. *Drug Dev Res* 2017; 78:371-380.
44. Holman CM, Minssen T, Solovy EM. Patentability standards for follow-on pharmaceutical innovation. *Biotechnology Law Report* 2018; 37:131-161.