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METHOD

Effective Doses of Low-Dose Naltrexone for Chronic Pain – An Observational Study

Norman J Marcus[1,2], Lexi Robbins[1], Aya Araki[1], Edward J Gracely[3,4], Theoharis C Theoharides[5,6]

[1]Norman Marcus Pain Institute, New York, NY, USA; [2]Department of Anesthesiology and Neurological Surgery, Weill Cornell Medicine, New York, NY, USA; [3]Family, Community & Preventative Medicine, Drexel University College of Medicine, Philadelphia, PA, USA; [4]School of Public Health, Epidemiology and Biostatistics, Drexel University, Philadelphia, PA, USA; [5]Department of Immunology, Tufts University School of Medicine, Boston, MA, USA; [6]Institute for Neuro-Immune Medicine, Nova, Southeaster University, Clearwater, FL, USA

Correspondence: Norman J Marcus, Private Practice, Norman Marcus Pain Institute, 30 E. 40th Street, Ste 1100, New York, NY, 10016, USA, Tel +01 (212) 532-7999, Email njm@nmpi.com

Purpose: Despite the availability of a wide variety of analgesics, many patients with chronic pain often experience suboptimal pain relief in part related to the absence of any medication to address the nociplastic component of common pain syndromes. Low-dose naltrexone has been used for the treatment of chronic pain, typically at 4.5 mg per day, even though it is also noted that effective doses of naltrexone for chronic pain presentations range from 0.1 to 4.5 mg per day. We performed an observational analysis to determine the range of effective naltrexone daily dosing in 41 patients with chronic musculoskeletal pain.

Methods: Charts of 385 patients, 115 males, 270 females, ages 18–92, were reviewed. Two hundred and sixty patients with chronic diffuse, symmetrical pain were prescribed a titrating dose of naltrexone to determine a maximally effective dose established by self-report of 1) reduction of diffuse/generalized and/or severity level of pain and/or 2) positive effects on mood, energy, and mental clarity. Brief Pain Inventory and PROMIS scales were given pre- and post-determining a maximally effective naltrexone dose.

Results: Forty-one patients met all criteria for inclusion, successfully attained a maximally effective dose, and completed a pre- and post-outcome questionnaire. Hormesis was demonstrated during the determination of the maximally effective dosing, which varied over a wide range, with statistically significant improvement in BPI.

Conclusion: The maximally effective dose of low-dose naltrexone for the treatment of chronic pain is idiosyncratic, suggesting the need for 1) dosage titration to establish a maximally effective dose and 2) the possibility of re-introduction of low-dose naltrexone to patients who had failed initial trials on a fixed dose of naltrexone.

Plain language summary: Low-dose naltrexone (LDN) has been used to treat chronic pain. There is, however, no agreed on effective dose, leaving clinicians without guidelines on initiating treatment with naltrexone. It appears that the dose of LDN for any patient is idiosyncratic, and in a small study, ranges from 0.1 to 6.0 mg/day. Understanding the various possible mechanisms of action of LDN may help the clinician to understand how and why it can effectively reduce chronic pain. A titration schedule to establish the maximally effective dose for chronic myofascial pain is presented.

Keywords: myalgia, low-dose naltrexone, chronic pain, hypermobile Ehlers Danlos syndrome, nociplastic pain, musculoskeletal pain

Introduction

Background and Purpose

In contrast to the FDA-approved use of naltrexone for addiction and naloxone for drug overdose, low-dose naltrexone (LDN)'s paradoxical effect on the μ receptor of increasing the analgesic effect of opioids has been reported in the literature for decades.[1] In addition, effects on pain and chronic disease for a variety of diagnoses have been claimed for LDN.[2,3] LDN has been shown to produce enhanced opioid analgesia, reduced tolerance to opioids,[4] suppression of the release of proinflammatory substances from microglia, and inhibition of mast cells, which uninhibited can further stimulate microglia to release proinflammatory

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cytokines.[5,6] LDN dose is an important variable when considering effectiveness, with reports of patients responding to only very specific doses.[7] There are numerous postulates of the pathophysiological mechanisms based on off-label use, as well as case reports discussing the clinical effectiveness of LDN for various chronic pain syndromes.[8] Although it has been noted that there may be a wide range of effective doses when LDN is used for chronic pain presentations, no protocols are available to establish a maximally effective dose (MED). One study of fibromyalgia patients was done to establish a dose–response relationship[9] by varying doses up or down starting with 0.75 mg/day and increasing or decreasing by 0.75 mg increments. The conclusion was that ED50 was 3.88 mg and ED95 was 5.4 mg, yet out of 25 subjects, only 11 were classified as responsive to the LDN. Another fibromyalgia syndrome study found that 9 of 28 patients responded to LDN at a dose of 4.5 mg or 3.0 mg/day.[10] The wide range of possible dosing, high failure rate, and inconsistency of results with a fixed standard dose in these studies and numerous others suggests that preset average doses may not be the best method to find an MED for LDN. No protocols have been published to guide clinicians in establishing an MED of LDN.

Objectives: The primary purpose of the study is to demonstrate the presence of idiosyncratic MEDs of LDN in the treatment of patients with chronic pain. We present the first study of effective dose ranges of LDN in a population of chronic pain patients and propose a protocol for clinicians to initiate LDN treatment with appropriate patients.

Variation in Dosing of LDN Related to Different Treatment Targets

The absence of studies to explore effective LDN dosing and frequency of dosing was noted by Younger et al.[10] There are large variations in effective doses of LDN, which appear to be related to putative receptors and their associated mechanisms of action. For example, effective doses of LDN in various chronic pain syndromes are generally reported between 1.0 mg and 4.5 mg/day to suppress Toll Like Receptor-4 on microglia, in contrast to opioid enhancement with doses of <0.001 mg/day and facilitation of ease of opioid withdrawal at 0.001–1.0 mg/day, facilitated through effects on the μ-opioid receptors.

A comprehensive review of the putative mechanisms of LDN-related analgesia[11] is beyond the scope of this paper, however a basic overview of LDN's physiologic effects is important in appreciating the putative complex mechanisms of its effectiveness in treating chronic pain.

Historical Observations of Naltrexone and Hormesis

In 1988, Shen and Crane[12] demonstrated that low concentrations of opioid could produce an excitatory effect on dorsal root ganglion cells, an effect which could be blocked by low concentrations of naloxone (ie, small doses of opioids could paradoxically cause increased pain – opioid-induced hyperalgesia – which could be blocked by small doses of naloxone). Larger doses of naltrexone would abolish the pro-analgesic effects of lower doses. This bimodal effect was found to be mediated by the mu-opioid receptor.[13] The concept of paradoxical responses to different doses of the same drug is called hormesis.[14]

Hormesis

Hormesis is the quality of a chemical to exert a beneficial effect at low doses and to lose the effect or to have an opposite effect at higher doses. Kendig[14] suggests a definition that encompasses many of the variables in the literature:

> Hormesis is a dose-response relationship for a single endpoint that is characterized by reversal of response between low and high doses of chemicals, biological molecules, physical stressors, or any other initiators of a response.

This definition, however, does not consider the possibility of a "re-reversal"[15] of the response so that additional dosing may once again be beneficial.

Ultra and Very Low-Dose Naltrexone

The hormetic effect of LDN can be appreciated at pico- and nano-doses affecting μ-opioid receptors signaling, where it seems to be mediated through binding with filamin A, a scaffolding protein found in the cytoplasm.[16] The high-affinity filamin A-LDN complex is presented to a G-protein coupled receptor on the μ-opioid receptors.

G-Protein Coupled Receptors

When stimulated by low doses of opioids, G-protein coupled receptors are operationally transformed so that their signaling to the dorsal root ganglion is stimulating vs inhibitory, thus blocking the analgesic effects of the opioid. This switch in function from the typical inhibition of dorsal root ganglion firing to stimulating activity can be blocked by a very specific low dose of naltrexone. In a phase three study of a drug that combined LDN with an opioid,[17] 2 mcg but not 4 mcg/day of LDN produced enhanced analgesia. It is suggested that when the low affinity receptor on filamin A is activated at the higher LDN dose, the high-affinity filamin A receptor is blocked through physical alteration of filamin A, resulting in loss of the analgesic effect.

The Role of Filamin A

The doses of LDN that prevent the G-protein coupled receptors switch are less than the threshold to block the μ-opioid receptors, therefore an intermediate step facilitating the effects of LDN on the μ-opioid receptors was postulated. The discovery that LDN binds to a protein found in the cytoskeleton, filamin, explains the process. Filamins (classified as filamin A, B, and C) are scaffolding proteins that have many functions in the cell,[16] one of which is the capacity to bind and present ligands to receptors. Filamin A has two binding sites with which LDN can interact – a high-affinity site and low-affinity site. Low doses of LDN will be sufficient to bind to the filamin A high-affinity site but not the low-affinity site.[7] Doses higher than those adequate to bind the high-affinity site will bind to the low-affinity site. Binding to the low-affinity site produces a change in the shape of filamin A that eliminates the pro-analgesic effect of the LDN- filamin A complex.

Immune and Inflammatory Conditions

Various studies[2] have been published on the use of LDN for a variety of inflammatory and immune-related diseases, including multiple sclerosis, Crohn's disease, sarcoidosis, fibromyalgia syndrome, complex regional pain syndrome, diabetic neuropathy, cancer, autism, wound healing, and myalgia encephalitis/chronic fatigue syndrome.

A central feature of the effectiveness in these conditions is the ability of LDN to block the activation of microglia.[18] LDN has been termed a glial modulator[19] and has been shown to block toll-like receptor 4 activation and prevent the switch of microglia from an anti-inflammatory to a pro-inflammatory state, by preventing secretion of pro-inflammatory cytokines.[20] Microglial suppression may operate protectively as well by preventing downstream cascades affecting neurodegenerative diseases.[21]

A study of the effect of Naltrexone on inflammation in the collagen-induced arthritis rat model[22] suggests that Naltrexone's beneficial effect on signs and symptoms of arthritis was mediated through opioid receptors on lymphocytes, suggesting the possible role of neuroimmune modulation in chronic pain states.[23,24] Interestingly, the MED of 10 mg/kg/day, was significantly superior to 5 and 20 mg/kg/day doses, once again suggesting a dose specificity being key to successful regulation of the inflammatory biochemical pathways involved, and beneficial effects overall.

LDN and Opioid Growth Factor

Single daily dosing of LDN produces blockade of the opioid growth factor for about 6 hours/day, which apparently results in a rebound effect of opioid growth factor and an increased production of beta endorphins. This mechanism has been demonstrated in animal models of cell proliferation,[25,26] but proposed specific analgesic and mood elevating effects[27] based on this intermittent blockade mechanism of action have not been tested. Multi-dose LDN throughout waking hours would theoretically diminish or eliminate this effect.

Mast Cell Activation Disorder (MCAD)

Mast cells are inflammatory cells that when activated may release substances that cause or enhance clinical pain syndromes. Increased numbers of mast cells are present in Systemic Mastocytosis. Patients that have normal numbers of mast cells that are productive of increased amounts of inflammatory substances may be diagnosed as Mast Cell Activation Syndrome.[28] When Mast Cell Activation Syndrome criteria are not fulfilled but mast cell involvement is possible, the [provisional] diagnosis MCAD, not otherwise specified, may be present.[3,29] Approximately 30% of patients (12/41), all of whom had hEDS, were diagnosed with MCAD, not otherwise specified. There is general recognition of the increased incidence of MCAD in hEDS.[30]

Mediators released from the mast cells may further stimulate microglia.[47] Pathological activity of mast cells could be suppressed through the effect of LDN on various Toll-Like Receptors on mast cells.[32,33]

Methods

All patients seen at the lead author's (NM) private practice in New York City from 2018 to 2022 with diffuse musculoskeletal pain were evaluated for the presence of diffuse sensitization of muscles as a contributing source of their pain complaints.[34,35] Sensitization is defined as a lowered threshold to produce an action potential in a muscle nociceptor. Muscle nociceptors are high threshold mechanoreceptors and chemoreceptors. Various noxious stimuli can lower the threshold to produce an action potential, thus facilitating pain from non-noxious stimuli. Palpation is commonly used to establish the presence of sensitization. We established the presence of sensitization by using a small electrical stimulus presented through a proprietary instrument (Patent #11707222), to which a normal muscle will not respond. The instrument produces a beat frequency (a slow frequency embedded in a fast frequency) allowing electrical stimulation through the skin without stimulation of cutaneous sensory fibres and so small in amplitude as to be incapable of producing any muscle contraction. In a non-sensitized muscle, no sensation is produced. In a putative sensitized muscle, the patient reports varying degrees of discomfort (eg, sensation of increased pressure and/or tenderness) which are recorded as reflective of sensitization in that muscle.

Inclusion criteria: Patients, ages 18 and older, presenting with pain for more than 6 months with sensitization in at least 15 muscles where at least 55% were identified bilaterally (ie, muscle pair on right and left side), were considered to have nociplastic pain.[36] Nociplastic pain is defined as

> Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing pain.[37]

Most of these patients could have been diagnosed as having Fibromyalgia Syndrome, presenting with diffuse pain, fatigue and difficulties concentrating, but the diagnostic assessment was based on the centrality of the presentation of treatable peripheral muscle nociceptor sensitization and coexisting central sensitization, now referred to as nociplastic pain. All included patients had the diagnosis myalgia, and 70% had enthesopathies of multiple sites. Animal studies reveal that the greatest density of nociceptors is in the attachment sites vs the muscle tissue.[38] Simons reports on the importance of attachment site Trigger Points.[39]

Exclusion criteria: Patients were excluded from the study if they were taking opioids with a daily morphine equivalent dose of greater than 90 mg/day, or if they were pregnant at the time of the study.

All patients seen at the author's private practice were assessed at baseline (initial visit and physical examination) with the Brief Pain Inventory (BPI), used routinely until 8/19/2020, when the Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 and Physical Function measures were implemented in place of the BPI. Baseline measures were collected at the initial visit and collected again at a minimum of four weeks after establishing a LDN MED.

See Figure 1 for patient flow chart.

An IRB review was conducted by BRANY, a Central IRB Company, issuing a waiver of Exempt Status. The data accessed complied with relevant data protection and privacy regulations.

Treatment Construct Addressing Nociplastic Pain Prior to Peripherally Generated Soft Issue Pain

If nociplastic pain is present, it would be reasonable to provide a treatment plan that included a trial of LDN to address the phenomenon of central sensitization, where pain may be related to the putative effects of non-neuronal cells producing generalized pain, prior to receiving more localized, targeted treatments of specific muscles, such as various muscle injections or laser treatments. This approach requires the explanation to patients that their centrally mediated pain may be the result of activation of non-neuronal cells such as microglia and mast cells and to suggest that they may be able to differentiate it from

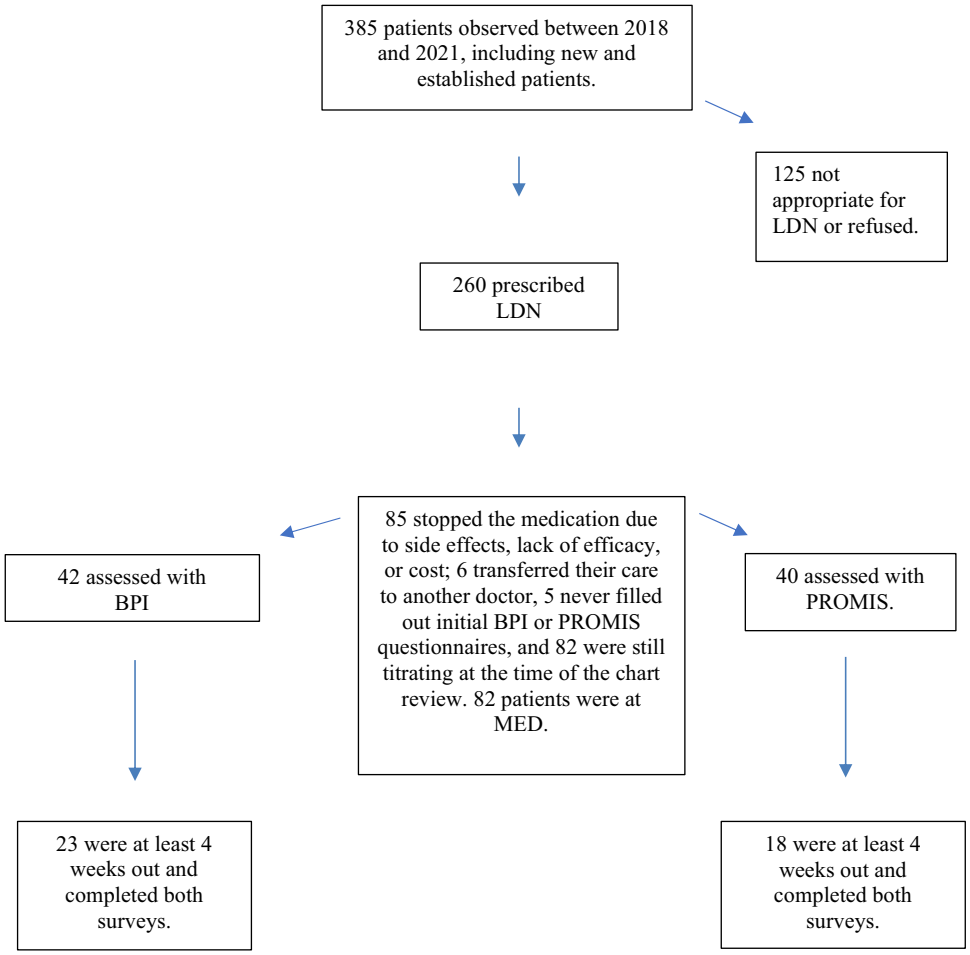

Figure 1 Flowchart of Patient Inclusion.

peripheral muscle sensitization causing regional pain with non-noxious stimulation (eg, simple movements like bending or walking). If centrally mediated pain can be suppressed, it will be easier to identify and treat specific sensitized muscles.

Methods and Rationale for Titration

The LDN protocol since 2012 at the principal author's practice has been based on a titration schedule to establish a MED. We chose to provide the LDN in divided doses based on the non-published experience of a colleague, Hugo Franco, M.D., who found that when side effects occurred, smaller aliquots were better tolerated. LDN capsules were compounded by a local compounding pharmacy. Titration of LDN begins at 0.1 mg per day and increases by 0.1 mg on every third day. Patients remain at a dose for two days before increasing the daily dose, to allow for self-assessment and reflection on induced changes. Patients continue titrating until a maximum of 6.0 mg/day, at which point if no improvement has occurred, the LDN trial is discontinued. After establishing an MED, patients could reduce the frequency of dosing (eg, two or three times per day, or once a day) if tolerated and equally effective while maintaining the total daily dose of LDN.

Dosing Protocol for LDN

Day 1: 0.1mg
Day 2: 0.1mg
Day 3: 0.1mg bid (0.1, 0.1)
Day 4: 0.1mg bid (0.1, 0.1)
Day 5: 0.1mg tid (0.1, 0.1, 0.1)

Day 6: 0.1mg tid (0.1, 0.1, 0.1)
Day 7: 0.1mg qid (0.1, 0.1, 0.1, 0.1)
Day 8: 0.1mg qid (0.1, 0.1, 0.1, 0.1)
Day 9: 0.2mg, 0.1, 0.1, 0.1
Day 10: 0.2mg, 0.1, 0.1, 0.1
Day 11: 0.2mg, 0.2, 0.1, 0.1

This process continues until a positive effect or no effect at a total dose of 6.0 mg/day.

When G.I. complaints of abdominal pain and/or nausea were present, patients were instructed to take LDN with food and remain on the lowest dose that caused any G.I. upset until the discomfort no longer occurred and then to resume the titration. If difficulties falling asleep or disturbing vivid dreams occurred, patients were instructed to take the last dose of the day no later than 4 PM and if problems persisted, to take the last dose earlier and if necessary, eventually take all the LDN in the AM on awakening.

Establishing the MED

Patients were told that if LDN was effective they might notice diminished generalized pain, hyperalgesia, and/or increased mood and energy. If this occurred, it signaled the entry into a "window of effectiveness". Doses below or above the window are not effective. Therefore, patients were instructed to carefully monitor the response to subsequent increases in dose and if 2 successive doses did not produce additional improvement, they were to go back to the dose prior to the last 2 increases which would be their MED. See Figure 2. There was no suggestion that any specific dose or range would be established.

Summary of statistical methods: To compare scales before initiation of LDN and after establishing the MED, paired t-tests were used. To compare groups (notably Hypermobile Spectrum Disorder [HSD]/Hypermobile Ehlers-Danlos Syndrome [hEDS] and non-HSD/hEDS) on established dose, unpaired t-tests were used. Scales were tested for change also in the combined HSD and hEDS group, which had a large enough sample size for that analysis.

Results

The final analyses and summary were based on results from 41 patients (see Table 1), who took LDN as prescribed, had pre- and post-MED outcome results, and were at least four weeks post establishment of MED.

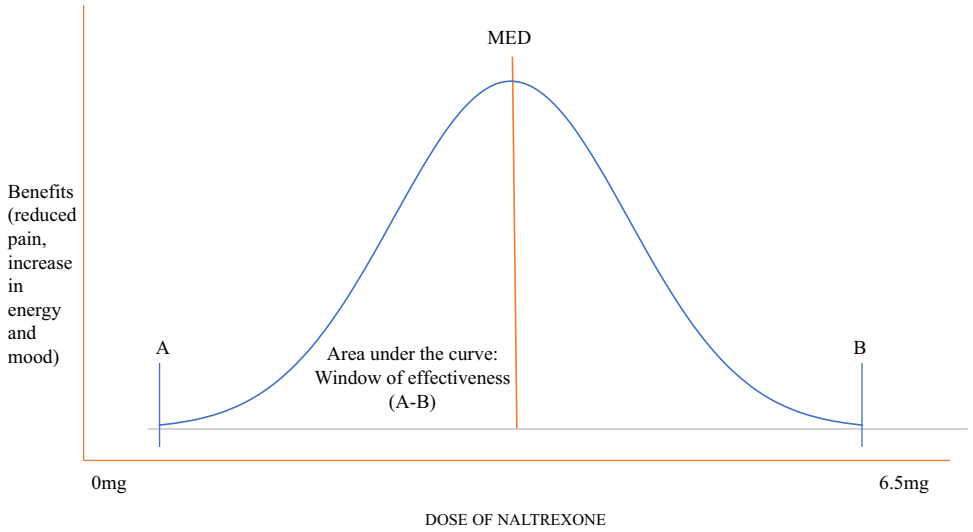

Figure 2 Effectiveness Curve. Diagram used only to discuss possible sequence of events for a patient with an MED around 3.25. Other patients would have different maximum points. This exact symmetrical pattern of response has not been experimentally demonstrated. The area under the curve (AUC) is the window of effectiveness and is the point in the titration that the patient is obliged to carefully observe any response to dose increments. The apogee of the curve is the MED. Moving beyond the MED produces no additional improvement or actually a decrement in improvement.

Table 1 Patient Selection

Variable	Count (%) Unless Indicated
Gender[a]	
Male	7 (17.1%)
Female	34 (82.9%)
Age Mean (SD)	40.05 (14.4)
Min – Max	18 to 76
Age, <40 years old	21 (51.2%)
Age, >40 years old	20 (48.8%)
Diagnosis	
Myalgia	41 (100%)
Enthesopathy of multiple sites	29 (70.7%)
hEDS or HSD	30 (73.2%)
MAST cell activation disorder, unspecified	12 (29.3%)
Post-operative pain	3 (7.3%)
Number of sensitized muscles	13–147
Percentage of symmetrical sensitization	58.8%–96.6%

Notes: [a]One patient identified as nonbinary, four females were in the process of gender reassignment to male, one male was in the process of gender reassignment to female.
Abbreviations: hEDS, hypermobile Ehlers-Danlos syndrome; HSD, hypermobility spectrum disorder.

As shown in Table 1, they were disproportionately female and averaged around 40 years of age. By design, all had a diagnosis of myalgia. Most had been diagnosed with enthesopathy (dysfunction of muscle attachment sites) of multiple sites and hEDS or HSD.

Both BPI scales improved from pre to post as shown in Table 2 with p <0.001 by paired *t*-test. The effect sizes are large (over 1 SD of change).

The PROMIS scales did not show as strong of an improvement, but the overall scale and mental health both improved significantly. The effect sizes are less than 1 (0.67 SD's for mental health is the largest). At a few time points, several scales showed evidence of non-normality, but a Wilcoxon Signed Ranks test returned p-values in all cases that confirmed those from the paired *t*-test.

Table 2 Outcome Data

Scale	Pre-Mean (SD)	Post-Mean (SD)	p-value (One-Tailed)	Mean Improvement and 95% CI
BPI Pain n = 23	5.78 (1.7)	3.16 (1.60)	< 0.001	2.62 (1.83 to 3.41)
BPI Interference n = 23	6.26 (2.1)	2.63 (1.7)	< 0.001	3.63 (2.74 to 4.51)
PROMIS n= 18	38.8 (8.8)	42.2 (8.5)	0.029	−3.4 (−6.93 to 0.13)
PROMIS: physical health n= 17	41.4 (8.8)	44.3 (6.2)	0.12	−2.93 (−8.07 to 2.21)
PROMIS: mental health n= 17	44.5 (8.8)	49.8 (6.8)	0.017	−5.27 (−10.1 to −0.44)

Notes: Mean improvement is a decrease for BPI and an increase for PROMIS. These are shown as a positive change for BPI and negative change for the PROMIS.
Abbreviations: BPI, Brief Pain Inventory; PROMIS, Patient-Reported Outcomes Measurement Information System; CI, confidence interval.

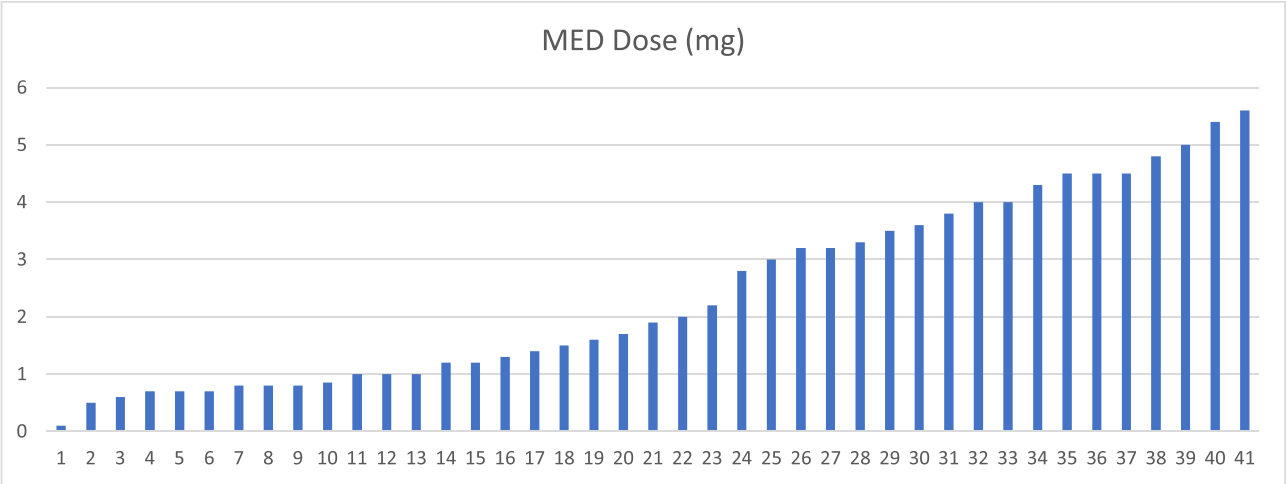

Figure 3 Histogram of individual MEDs. Individual MEDs for each patient in the study clearly suggesting idiosyncratic doses.

The hEDS or HSD subgroup, with 30 patients, was large enough for a separate analysis. All 5 scales changed in the same way as for the complete sample, with similar p-values for the BPI (data not shown). Although all three PROMIS scales improved by a similar degree to the overall sample, none of the PROMIS scales attained significance in the hEDS or HSD subgroup.

Patients in the HSD/hEDS subgroup (n = 30) did not differ significantly (p = 0.25 by unpaired *t*-test) in mean established dose (2.23, SD = 1.5) from the 11 other patients (3.02, SD = 1.99).

Established doses ranged from 0.1 to 5.6 with the most frequent doses near the low end of the distribution (2 mg or less). Figure 3 shows the individual MEDs of each patient.

Examples of hormesis (see below) where higher doses clearly resulted in decreased effectiveness were found in 13 patients. One patient had titrated to 0.7 mg for her MED. She was running out of LDN and cut back to 0.6/day finding it was less effective than 0.7. When she received her renewal, she restarted 0.7 and found it more effective. She then increased to 1.0 resulting in pain worse than prior to LDN, with restoration of analgesic effect with reduction back to 0.7.

Effect of BMI on Dosing

A correlation coefficient between BMI and established dose (using Spearman's rho due to some high BMI values) returned rho = 0.028, p = 0.87, n = 35. This is effectively a correlation of 0 with no evidence of association.

Opioid Intake

Ten of 41 patients were taking opioids during this study. Seven did not change their medication dose after attaining their MED. Two decreased their dose (one by 20% and one who went off entirely, thus a 100% drop). The remaining patient increased from a morphine equivalent of 15 to 67.5 (which was related to acute pain in her foot and surgery for a Lisfranc fracture).

Mast Cell Activation Disorder (MCAD) Medications

All patients diagnosed with MCAD were on or were prescribed some or all of famotidine, cetirizine, and montelukast, to antagonize receptors for mast cell products – histamine and leukotrienes.

Adverse Effects

Gastrointestinal: one patient of the 41 reported an upset stomach (other patients assessed but not eligible also complained of cramping, constipation, acid reflux, and loss of appetite).

Sleep issues: 2 patients with drowsiness, one with drowsiness at 1.4 mg which was eliminated with return to MED of 1.3 mg; 2 patients had difficulty sleeping, and their dosing was altered to provide all LDN by noon; two patients noted vivid dreams.

Other: 1 patient was agitated, relieved with tizanidine, resolved with an established MED.

Discussion

Our results indicate idiosyncratic MEDs of LDN for patients with chronic musculoskeletal pain. The effective doses are widely distributed, and no dose is most often the MED, supporting the utility of a titration protocol to establish the MED. BMI was not associated with the MED.

Approximately 30% of the patient population at the lead author's practice are diagnosed as HSD or hEDS, which are thought to be clinically indistinguishable[40] (hEDS in this paper going forward will represent both HSD and hEDS) and was present in 30 of 41 patients in our study. This is an expected skew as patients with hEDS were found in a retrospective review[41] of 220 patients, in 2019–20 at the lead author's private practice, to have 4.5 times the number of sensitized muscles as the non-hEDS group.

We did not find significant MED differences between the hEDS and the non-EDS group. A larger patient sampling may reveal different dosing and outcome characteristics. Most of our patients were diagnosed with hEDS which often presents challenging pain problems related to multiorgan dysfunction found in this patient population,[42,43] which would have an impact on quality-of-life issues. One case series showed that LDN was useful in alleviating pruritus[44] that is commonly associated with mast cell activation. Moreover, age and genetics of naltrexone biotransformation could play a role in the variable response to LDN.[45]

The measures of effectiveness, the BPI and PROMIS scales, reflect different aspects of improvement. Whereas the BPI is measuring pain intensity and interference in function, the PROMIS scale measures secondary outcomes. Our results of clear improvement with the BPI suggest that it may be more useful in assessing analgesic effectiveness. The finding of less effectiveness in the PROMIS scales with hEDS may also be related to the multiorgan dysfunction contributing to chronic pain in this subset of patients compared to patients with solely musculoskeletal presentations. It may also be a function of a smaller sample size than the total study group.

Knowledge of the importance of dose specificity and the complexities associated with various dose ranges facilitates the appreciation for the need to establish a specific MED that may be missed by arbitrary assignment of a fixed dose of LDN, eg, 1.0, 1.5, 3.0, 4.5. It appears that the MED of all patients, prior to being prescribed LDN, should be considered as unknown.

Limitations of This Study

LDN has been used for symptom management for a wide variety of conditions; however, no well-controlled large-scale studies have been performed to validate either symptom management or disease modification.[46] Multiple mechanisms of action are postulated to explain the complexities of chronic pain and the clinical analgesic effects of LDN, without rigorous translational studies. These studies should be done. The purpose of this study was only to demonstrate that various idiosyncratic doses of LDN could be the MED for patients in chronic pain.

The specificity of dosing for each patient studied is empiric. The inclusion group was unusual. We chose patients who evidenced diffuse symmetrical tenderness to trivial electrical stimuli and defined this as a manifestation of central sensitization and nociplastic pain. hEDS patients in our practice are found to have significantly more diffuse sensitized muscles than in non-h EDS patients,[47] accounting in part for the predominance of hEDS patients in our study. This makes the outcome difficult to generalize to other patient populations, although no significant difference was seen in MED between hEDS and non-hEDS groups.

Some successful subjects had prior failures with different dosing of LDN. However, many patients in our study were prescribed and/or started the titration without continuing. Poor patient compliance has been reported by others.[48] For some of those patients, providing an arbitrary dose (like 3.0 or 4.5mg) could have resulted in a rapidly apparent effective treatment. Conversely, based on achieving successful dosing with patients who had previously failed at specific doses, choosing fixed doses alone may have resulted in failure to find an effective dose. Patients may have dropped out because

of the rigor and cost (compounding costs are based on the number of capsules) demanded of a titration with small dose increases.

Conclusions

LDN with idiosyncratic dosing appears to effectively suppress chronic pain. LDN may be a useful medication for patients with pain related to hEDS. The findings of this small study suggest that the current standard of care of utilizing a fixed dose, often 4.5 mg/day as the LDN dose, may be ill-advised.[9,10] We present patients who achieved an effective dose utilizing our titration schedule but had prior multiple unsuccessful trials of LDN at fixed or variable doses using large dose adjustments. All patients who have failed LDN trials at standard fixed doses could be retreated with a titration schedule to find an MED. A lengthy titration schedule may result in frequent non-compliance, perhaps justifying an arbitrary fixed dose which, if successful, could be followed by micro adjustments above or below the effective dose to establish a MED. Selecting the right subgroup of patients may enhance the possibility of success.[33]

Abbreviations

LDN low-dose naltrexone; MED maximally effective dose; BPI Brief Pain Inventory; PROMIS Patient-Reported Outcomes Measurement Information System; HSD hypermobile spectrum disorder; hEDS hypermobile Ehlers-Danlos syndrome; MCAD mast cell activation disorder.

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Disclosure

The authors report no conflicts of interest in this work.

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