PAIN MEDICINE CASE REPORTS

ISSN 2768-5152

Volume 7, Number 8, pp. 377-383

Retrospective Analysis of Naltrexone for Persistent Neuropathic Pain Case Series

Michael T. Lee, BS, and Maxim S. Eckmann, MD

Background: Persistent neuropathic pain (NP) is a prevalent and debilitating problem, often resistant to first-line treatment. Low-dose naltrexone (LDN) has shown promise in treating fibromyalgia and other forms of chronic pain.

Case Report: Retrospective analysis was performed on 14 of 18 patients with diverse forms of NP who met inclusion criteria by using LDN (1.5-4.5 mg) as a second-line medical pain therapy. Pain Numeric Rating Scale (NRS-11) in all patients decreased from 6.29 ± 2.20 to 3.71 ± 2.89 (P = 0.001) from initiation to final visit. Median treatment length was 252 days with longest being 1,054 days. All 6 patients who remained on LDN > 1 year reported reduced pain NRS-11 at last visit. Side effects were mild and did not result in cessation of therapy.

Conclusions: LDN may show promise in treating persistent NP.

Key words: Case series, naltrexone, neuropathic pain, chronic pain syndrome

BACKGROUND

Naltrexone is primarily a mu-opioid antagonist (1) used for long-term treatment of alcohol and opioid use disorders (2). Naltrexone has a similar biochemical structure to naloxone, with a higher bioavailability and longer half-life (3). However, low-dose naltrexone (LDN) has recently been used as an alternative therapy for pain in chronic pain disorders, such as multiple sclerosis and painful diabetic neuropathy (4,5). LDN has also shown anti-inflammatory properties, useful in the treatment of Crohn's disease and complex regional pain syndrome (6). Previous studies (7-9) have shown LDN having a significant improvement in pain for fibromyalgia. LDN is also used for trigeminal neuralgia and other chronic pain syndromes (10). Its low cost (11), favorable side-effect profile, and high safety hold promise as an inexpensive long-term solution for persistent neuropathic pain (NP).

NP can be defined as the secondary changes to the nociceptive system due to a lesion or disease (12), featuring symptoms, such as allodynia, hyperalgesia, and paresthesia. Prevalence is likely between 7% to 10%, with higher prevalence in women (60.5%) (13). NP is often difficult to treat with first-line medications; therefore, investigation into other options is warranted.

Naltrexone is thought to be part of a class of therapeutic agents called glial cell modulators (14). Glial cells are hypothesized to contribute to chronic pain, and targeting these cells could provide an alternate avenue in approaching persistent NP (14). Naltrexone modulates the toll-like receptor 4 (TLR4), a transmembrane protein part of the toll-like receptor family that leads to inflammatory cytokine production and immune system activation (15). TLR4 responds to stress, opioids, injury, and bacterial cell wall proteins (16). TLR4 activation results

From: UT Health San Antonio, San Antonio, TX

Corresponding Author: Michael T. Lee, BS, E-mail: leem13@livemail.uthscsa.edu
Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.
Patient consent for publication: Institutional policy exempts authors from obtaining informed consent.
Authors adhere to the CARE Guidelines for writing case reports and have provided the CARE Checklist to the journal editor.
Accepted: 2023-09-28, Published: 2023-12-31

in the secretion of glutamate from microglia, and therefore persistent reduction in the nerve-firing threshold and increase in frequency (17). The (+) enantiomer of naltrexone, present in the commercially available drug, modulates TLR4 and reduces neuropathic phenomena (18). LDN has been shown to have a paradoxical (i.e., positive) effect on analgesia when used in low doses of 1-6 mg (19).

The use of LDN for conditions other than fibromyalgia is understudied. We investigated the efficacy and tolerability of LDN in patients with persistent NP. We hypothesized symptomatic improvement in patients using LDN could be achieved after failure of first-line antineuropathic medications due to the mechanisms previously proposed. We analyzed patients who received LDN, from January 2020 to January 2023, to evaluate for reduction in pain and improvement in function.

CASE PRESENTATION

Methods

Patients with persistent or chronic NP who received naltrexone as part of their treatment at the University of Texas Health San Antonio Pain Clinic, from January 2020 to January 2023, were included in the study in retrospective analysis. The study met institutional review board criteria for protection of patients and did not require obtaining informed consent, as this study falls under the Health Insurance Portability and Accountability Act of 1996. Patients were required to be seen in the clinic for at least 2 visits with at least one follow-up visit after initiation of therapy. Patients who received naltrexone for indications besides pain treatment (e.g., weight loss, alcohol/substance use disorder treatment) were excluded from the study. In total, 18 patients were identified; 14 remained after applying exclusion criteria. Of the 14 included patients,

Numeric Rating Scale (NRS-11, 0-10) scores, basic demographics, pain diagnoses, side effects, adjacent therapies, and current and past medications were tabulated. A decrease in pain NRS-11 ≥ 2 is considered clinically significant for the purposes of this study (20).

RESULTS

The average age of patients was 53.29 ± 14.34, with the median age of 51.5. Thirty-six percent of patients were men. Eight patients were on LDN for ≤ 1 year. Six patients were on LDN for > 1 year, with the longest being 1,054 days. The median treatment length was 252 days. All patients began dosing at 1.5 mg or 3 mg daily, with subsequent increases to 3 mg or 4.5 mg daily.

Each patient had one or more pain diagnoses attributed to them. The diagnoses recorded included spondylosis without myelopathy, diffuse myofascial pain syndrome, poststreptococcal disorder, trigeminal neuralgia, chronic pain syndrome, status migrainosus, fibromyalgia, peripheral demyelinating neuropathy, NP, chronic post-COVID-19 syndrome, atypical facial pain, Eagle's syndrome, glossopharyngeal neuralgia, and failed back surgical syndrome. The most common diagnoses were trigeminal neuralgia, fibromyalgia, and NP (Table 1).

The mean starting pain NRS-11 score for all patients (n = 14) was 6.29 ± 2.20, and the pain NRS-11 score at the last recorded visit was 3.71 ± 2.89 (Fig. 1). The average change between starting pain score and last pain score was 2.57 ($P = 0.001$, paired Student's t test, one-tailed).

The mean starting pain NRS-11 for patients taking LDN for < 1 year (n = 8) was 6.13 ± 2.53, and the pain NRS-11 score for these patients at the last recorded visit was 3.88 ± 3.36 (Fig. 2). The average change between starting pain score and last pain score was 1.8 ($P = .025$, paired Student's t test, one-tailed.)

The mean starting pain NRS-11 for patients taking LDN for > 1 year (n = 6) was 6.50 ± 1.87, and the pain NRS-11 score for these patients at the last recorded visit was 2.83 ± 1.17 (Fig. 3). The average change between starting pain score and last pain score was 3.67 ($P = .004$, paired Student's t test, one-tailed.)

Besides LDN, other medications were trialed (Table 2). Classes of medications that patients had attempted or continued to use include opioids (e.g., tramadol, hydrocodone), benzodiazepines, anticonvulsants (e.g., gabapentin, pregabalin, carbamazepine), nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, celecoxib), muscle relaxants (e.g., tizanidine, baclofen), antidepressants (e.g., amitriptyline, venlafaxine), and antiheadache (e.g., sumatriptan, ubrogepant). All patients attempted at least one anticonvulsant before starting LDN. The most prescribed first-line medications were gabapentin and pregabalin.

Additionally, half the cohort (7/14) received procedural treatments in addition to medication and other multimodal treatments (Tables 3 and 4). The most common procedure was peripheral nerve block (n = 7); patients received multiple nerve blocks over the duration of treatment. Other procedures included corticosteroid injections, trigger point injections, and botulinum toxin injections.

Besides medications and procedures, therapeutic modalities were also used (Table 4). The most common were heating, ice, and physical therapy, but other modalities, such as massage, acupuncture, and stretching, were also tried.

Patients were asked about side effects at each clinic visit through a review of the system's questionnaire. Side effects of LDN described in the literature are vivid dreams and nightmares (21), which one of the patients described. Other side effects are listed in Table 5. Of the patients that experienced side effects, none felt it necessary to discontinue treatment or require a dose reduction. Half of the patients experienced no side effects.

DISCUSSION

In this observational study, patients with NP from a variety of diagnoses received improvement in pain NRS-11 after starting LDN. The improvement in pain occurred alongside other medications and therapeutic procedures.

In previous studies (22) on pain intensity, a decrease of 2.4 on the NRS-11 corresponded to "much" improvement. Another study (20) noted that on average, approximately a 2-point reduction or 30% reduction represented a clinically important difference. In this study, we decided on a 2-point reduction as clinically significant. Statistically significant reduction in pain NRS-11 was seen, while 8 of the 14 patients achieved clinically significant reduction in pain scores (pain NRS-11 decrease ≥ 2.) Three patients had no change in pain NRS-11. When examining treatment length, these 3 patients had received LDN for < 100 days. In current literature, LDN has been studied in diseases, such as multiple sclerosis and fibromyalgia, for treatment lengths from as little as 4 weeks to as long as 4 years (19,23). The latest study protocol (24) on LDN has a one-year follow-up design, setting the new standard for the window of observation. We wanted to examine the effectiveness of LDN beyond one year of treatment. Five of the six patients taking LDN for > 1 year achieved

Table 1. List of diagnoses of patients. Tabulation of all diagnoses listed above.

Diagnoses	# Patients
Spondylosis Without Myelopathy	2
Diffuse Myofascial Pain Syndrome	1
Poststreptococcal Disorder	1
Trigeminal Neuralgia	5
Chronic Pain Syndrome	3
Status Migrainosus	2
Fibromyalgia	4
Peripheral Demyelinating Neuropathy	1
NP	4
Chronic Post-COVID-19 Syndrome	1
Atypical Facial Pain	2
Eagle's Syndrome	1
Glossopharyngeal Neuralgia	1
Failed Back Surgical Syndrome	1

Abbreviation: NP, neuropathic pain.

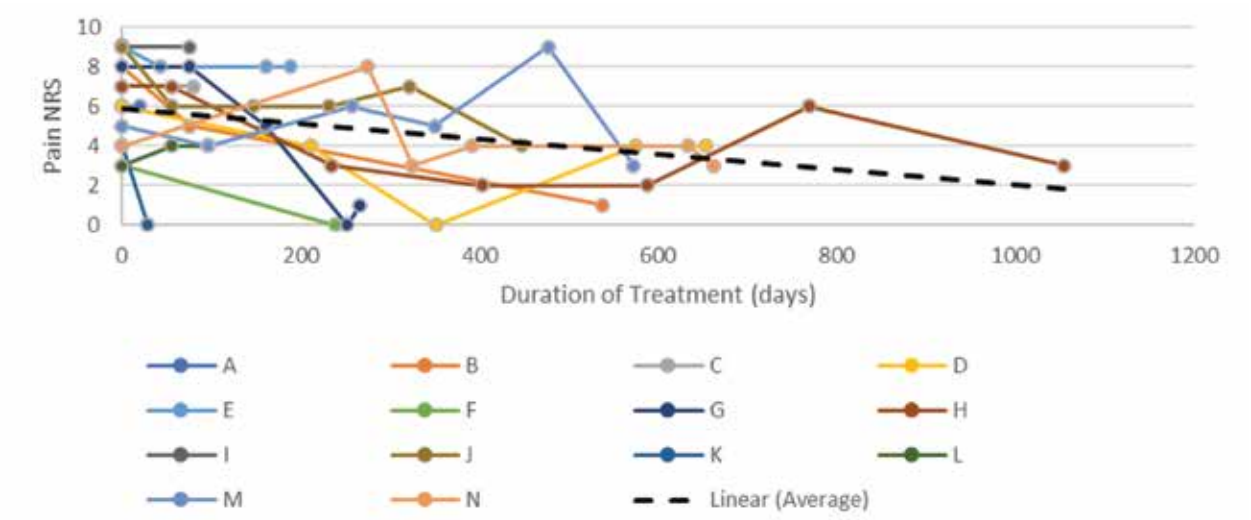

Fig. 1. Pain NRS-11 of all patients on LDN. Pain NRS-11 on the first day of treatment through the last available visit. Overall average pain NRS-11 (dotted line) decreased.

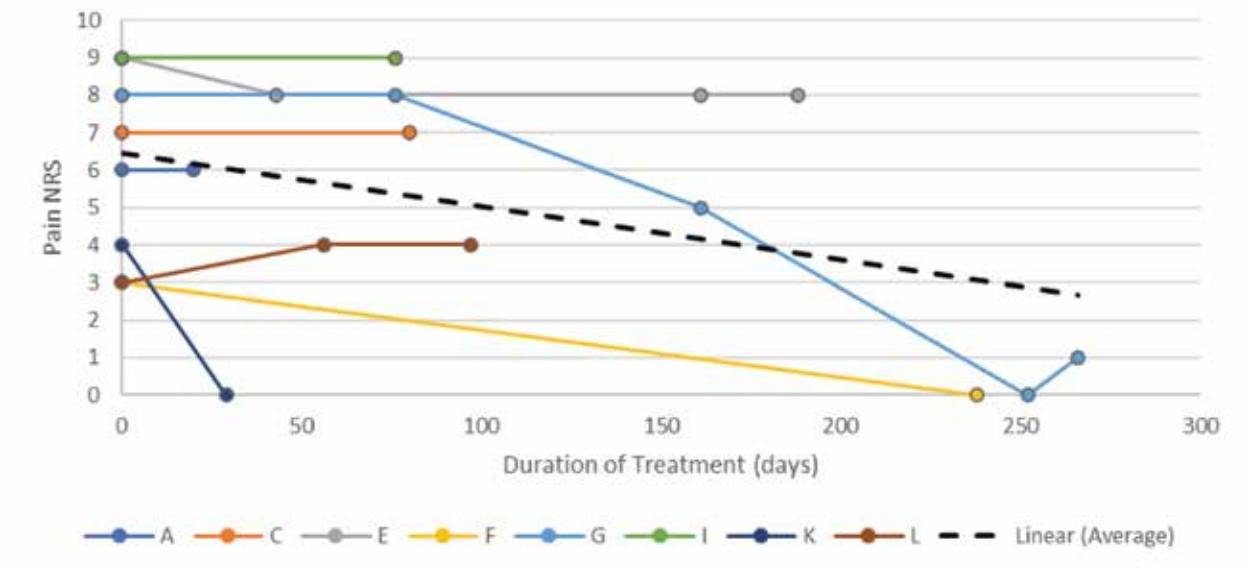

Fig. 2. Pain NRS-11 in patients with LDN treatment < 1 year (n = 8). Pain NRS-11 on the first day of treatment through the last available visit. A number of patients (patients A, C, E, I) had no change in pain NRS-11, while other patients experienced a decrease in pain scores (patients F, G, K). Overall average pain NRS-11 (dotted line) decreased.

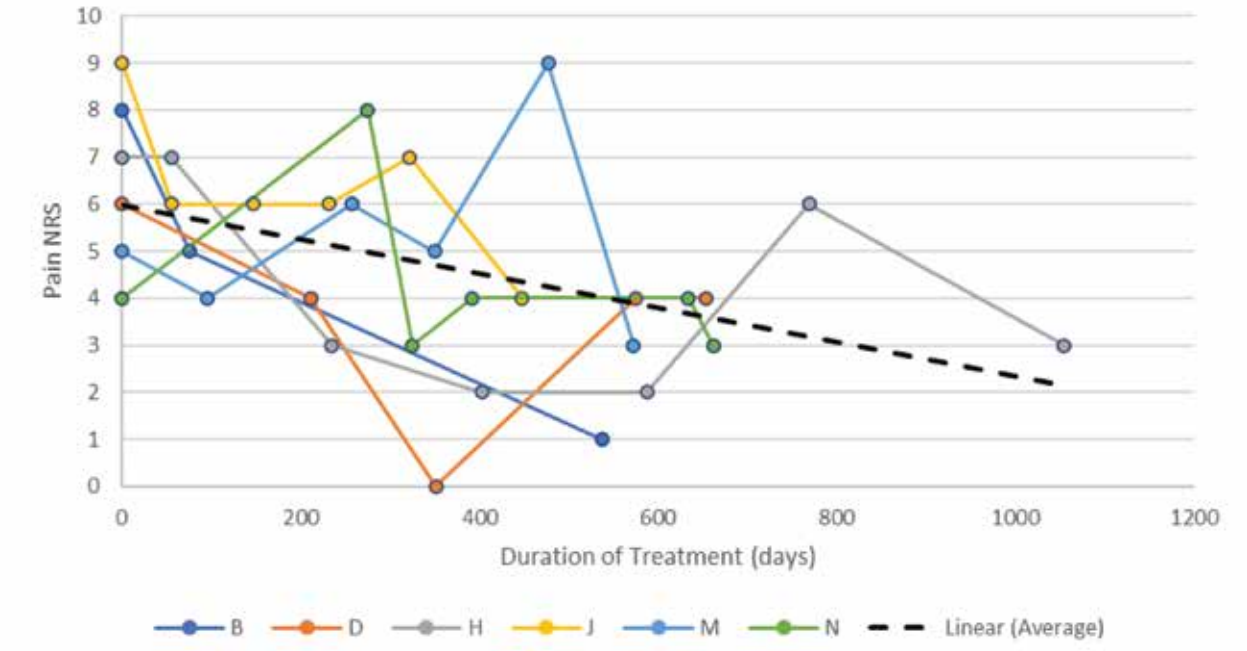

Fig. 3. Pain NRS-11 in patients with LDN treatment > 1 year (n = 6). Pain NRS-11 on the first day of treatment through the last available visit. All patients in the subgroup taking LDN for > 1 year experienced eventual decrease in pain NRS-11 (average denoted by dotted line).

Table 2. Prior attempted or coprescribed medications. This is a list of medications that patients used prior to or in addition to LDN.

Adjunct Meds	Name	# Ever Used	# Currently Using	% Total
Narcotics				
	Tramadol	7	1	7.1%
	Hydrocodone w/ Acetaminophen	6	1	7.1%
	Clonazepam	2	2	14.3%
	Tapentadol	1	0	0.0%
	Codeine w/ Acetaminophen	1	0	0.0%
	Oxycodone Extended Release	1	0	0.0%
Anticonvulsants				
	Gabapentin	9	4	28.6%
	Pregabalin	8	4	28.6%
	Carbamazepine	4	2	14.3%
	Topiramate	7	2	14.3%
	Oxcarbazepine	3	0	0.0%
NSAIDs				
	Ibuprofen	6	4	28.6%
	Celecoxib	1	1	7.1%

Table 2 cont. Prior attempted or coprescribed medications. This is a list of medications that patients used prior to or in addition to LDN.

Adjunct Meds	Name	# Ever Used	# Currently Using	% Total
Muscle Relaxants				
	Tizanidine	2	2	14.3%
	Baclofen	2	0	0.0%
	Methocarbamol	1	0	0.0%
	Cyclobenzaprine	1	0	0.0%
Antidepressants				
	Amitriptyline	1	1	7.1%
	Nortriptyline	2	1	7.1%
	Venlafaxine	1	0	0.0%
	Duloxetine	4	0	0.0%
Antiheadache				
	Butalbital-Aspirin-Caffeine	2	2	14.3%
	Ubrogepant	1	1	7.1%
	Galcanezumab	1	0	0.0%
	Erenumab	1	0	0.0%
	Sumatriptan	1	0	0.0%
Other				
	Botulinum Toxin	1	1	7.1%
	Magnesium	2	2	14.3%
	Vitamin B	1	1	7.1%
	Promethazine	1	1	7.1%
	THC Cream	1	1	7.1%
	Acetaminophen	4	1	7.1%

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; THC, tetrahydrocurcumin; LDN, low-dose naltrexone.

Table 3. Procedural treatments received by patients.

Procedure Type	No of Patients
Nerve Blocks	7
Corticosteroid Injections	1
Trigger Point Injections	1
Botulinum Toxin	1

Table 4. Multimodal treatments.

Treatment Modality	No of Patients
Physical Therapy	5
Heating	7
Ice	4
Acupuncture	1
Massage	3
TENS	1
Stretching	2
None	3
Lidocaine Patch	3
Voltaren Gel	2
Biofeedback	1
Meditation	1

Abbreviation: TENS, transcutaneous electrical nerve stimulation.

Table 5. Adverse effects experienced by patients taking LDN.

Side-Effect Type	%
None	50.0%
Nausea	7.1%
Diarrhea	14.3%
Constipation	14.3%
Tinnitus	21.4%
Night Sweats	7.1%
Insomnia	7.1%
Nightmares	7.1%
Anxiety	7.1%

Abbreviation: LDN, low-dose naltrexone.

a significant reduction in pain NRS-11, while 3 of the 8 patients taking LDN for < 1 year achieved a significant reduction in pain NRS-11.

All patients included in this study had persistent NP. Their failure to respond to extended multimodal therapy methods, such as oral medications and nerve blocks, prompted a search for alternatives in a tertiary referral center. LDN was selected by practitioners due to recent success reported in the treatment of fibromyalgia, the applicability of the proposed mechanisms, and the robust safety (4) of LDN. Given that persistent NP may, in part, be due to neuroexcitation from microglia following prior injuries or medical insults, LDN may potentially reverse this process (17,18). Notably, the median duration of therapy was 252 days with 43% of patients receiving treatment > 1 year. Future studies of LDN should consider the potential need to follow patients for at least 1 to 2 years to evaluate treatment effectiveness.

Despite the encouraging outcomes, our study has several limitations. Retrospective analysis limits the ability to attribute the duration of LDN treatment to improvement in outcome. For example, patients who stop LDN early may do so because of no perceived benefit. Additionally, the diversity of diagnoses limits the power to draw conclusions on any single form of NP. However, considering the difficulty in treating NP generally, the current study observed that LDN was well tolerated, with mild side effects that did not preclude long-term use. LDN did show promising efficacy over time in this cohort. As different forms of NP and chronic pain likely have diverse mechanisms, LDN should be studied in other major forms of chronic pain in a controlled prospective fashion.

CONCLUSIONS

Patients with persistent NP may receive benefits from LDN. Side effects of LDN are modest and tolerable. LDN should be further evaluated in controlled studies for various types of NP and other forms of chronic pain. Improvement from treatment with LDN may take up to one year or more.

REFERENCES

1. Verebey K. The clinical pharmacology of naltrexone: Pharmacology and pharmacodynamics. *NIDA Res Monogr* 1981; 28:147-158.
2. Valenta JP, Job MO, Mangieri RA, et al. μ-Opioid receptors in the stimulation of mesolimbic dopamine activity by ethanol and morphine in Long-Evans rats: A delayed effect of ethanol. *Psychopharmacology (Berl)* 2013; 228:389-400.
3. Crabtree BL. Review of naltrexone, a long-acting opiate antagonist. *Clin Pharm* 1984; 3:273-280.
4. Patten DK, Schultz BG, Berlau DJ. The safety and efficacy of low-dose naltrexone in the management of chronic pain and inflammation in multiple sclerosis, fibromyalgia, Crohn's disease, and other chronic pain disorders. *Pharmacotherapy* 2018; 38:382-389.
5. Hota D, Srinivasan A, Dutta P, Bhansali A, Chakrabarti A. Off-Label, low-dose naltrexone for refractory painful diabetic neuropathy. *Pain Med Malden Mass* 2016; 17:790-791.
6. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol* 2014; 33:451-459.
7. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: A pilot study. *Pain Med Malden Mass* 2009; 10:663-672.
8. Younger J, Noor N, McCue R, Mackey S. 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.
9. Parkitny L, Younger J. Reduced pro-inflammatory cytokines after eight weeks of low-dose naltrexone for fibromyalgia. *Biomedicines* 2017; 5:16.
10. Dieckmann G, Ozmen MC, Cox SM, Engert RC, Hamrah P. Low-Dose naltrexone is effective and well-tolerated for modulating symptoms in patients with neuropathic corneal pain. *Ocul Surf* 2021; 20:33-38.
11. Fairley M, Humphreys K, Joyce VR, et al. Cost-Effectiveness of treatments for opioid use disorder. *JAMA Psychiatry* 2021; 78:767-777.
12. Bouhassira D. Neuropathic pain: Definition, assessment and epidemiology. *Rev Neurol (Paris)* 2019; 175:16-25.
13. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: A systematic review of epidemiological studies. *Pain* 2014; 155:654-662.
14. Gillman MA, Lichtigfeld FJ. A pharmacological overview of opioid mechanisms mediating analgesia and hyperalgesia. *Neurol Res* 1985; 7:106-119.
15. Bruno K, Woller SA, Miller YI, et al. Targeting toll-like receptor-4 (TLR4) - emerging therapeutic target for persistent pain states. *Pain* 2018; 159:1908-1915.
16. Lee CC, Avalos AM, Ploegh HL. Accessory molecules for toll-like receptors and their function. *Nat Rev Immunol* 2012; 12:168-179.
17. Liu T, Gao YJ, Ji RR. Emerging role of toll-like receptors in the control of pain and itch. *Neurosci Bull* 2012; 28:131-144.
18. Tanda G, Mereu M, Hiranita T, Quarterman JC, Coggiano M, Katz JL. Lack of specific involvement of (+)-naloxone and (+)-naltrexone on the reinforcing and neurochemical effects of cocaine and opioids. *Neuropsychopharmacology* 2016; 41:2772-2781.
19. Toljan K, Vrooman B. Low-Dose naltrexone (LDN)-review of therapeutic utilization. *Med Sci Basel Switz* 2018; 6:82.
20. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94:149-158.
21. Lie MRKL, van der Giessen J, Fuhler GM, et al. Low dose naltrexone for induction of remission in inflammatory bowel disease patients. *J Transl Med* 2018; 16:55.
22. Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? *Pain* 2003; 105:151-157.
23. Turel AP, Oh KH, Zagon IS, McLaughlin PJ. Low dose naltrexone for treatment of multiple sclerosis: A retrospective chart review of safety and tolerability. *J Clin Psychopharmacol* 2015; 35:609.
24. Colomer-Carbonell A, Sanabria-Mazo JP, Hernandez-Negrin H, et al. Study protocol for a randomised, double-blinded, placebo-controlled phase III trial examining the add-on efficacy, cost-utility and neurobiological effects of low-dose naltrexone (LDN) in patients with fibromyalgia (INNOVA study). *BMJ Open* 2022; 12:e055351.