ARCHIVES OF HELLENIC MEDICINE: ISSN 11-05-3992

REVIEW
ΑΝΑΣΚΟΠΗΣΗ

ARCHIVES OF HELLENIC MEDICINE 2026, 43(4):474–479
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2026, 43(4):474–479

The role of naltrexone in the management of chronic pain in patients with multiple sclerosis

A. Panagi,
P. Theodosis-Nobelos,
C. Triantis

Department of Pharmacy,
School of Health Sciences,
Frederick University Nicosia,
Nicosia, Cyprus

Ο ρόλος της ναλτρεξόνης στη διαχείριση του χρόνιου πόνου σε ασθενείς με σκλήρυνση κατά πλάκας

Περίληψη στο τέλος του άρθρου

Chronic pain is a significant concern in multiple sclerosis (MS), particularly in the extremities, trigeminal neuralgia, back pain, and headaches. Pain management in MS patients is challenging due to the disease's progressive and relapsing-remitting nature. Naltrexone, an opioid receptor antagonist, has demonstrated the ability to inhibit T and B cell proliferation at low doses, exhibiting anti-inflammatory and analgesic effects against chronic pain. The aim of this article is to highlight the potential of naltrexone in addressing the underlying pathological mechanisms in MS, particularly chronic pain. A series of studies involving MS patients across different forms of the disease has shown that naltrexone, administered in doses of 3–5 mg daily, is both tolerable and safe. Additionally, it can enhance patients' quality of life (QoL) and reduce fatigue, especially in those with relapsing-remitting multiple sclerosis (RRMS), with many of its effects considered to be dose-dependent. However, concrete evidence regarding its impact on inflammation markers are lacking. In primary progressive MS (PPMS), low-dose naltrexone (LDN) has been shown to increase peripheral β-endorphin levels in blood and significantly reduce spasticity, with these effects retaining even up to one-month post-treatment. Although many of these results are preliminary, and much more clinical findings are in need, naltrexone seems promising as an active substance that could aid in the management of the progression and the symptoms of MS, with pain reducing effects.

Key words

Chronic pain
Inflammation
Multiple sclerosis
Naltrexone

Submitted 12.6.2025
Accepted 25.6.2025

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune inflammatory and degenerative disease that affects the central nervous system (CNS).[1] It was first described in 1868 by the French neurologist Jean Martin Charcot. The hallmark of this disease is the loss of myelin which leads to the formation of plaques. MS results from inflammation occurring in areas of the brain and spinal cord. This inflammation is associated with the entry of activated lymphocytes from the periphery into the CNS without the identification of an antigen, triggering the activation of the immune system. As a result, neuronal myelin is destroyed, ultimately leading to axonal degeneration. These lesions are located in various parts of the CNS depending on the patient's symptoms.[2,3] Chronic inflammation, characterized by the activation of microglia and the ongoing involvement of T and B cells after the blood-brain barrier, is a key pathophysiological feature of MS. This inflammatory process can exacerbate mitochondrial damage in neurons, leading to an energy deficit that further compromises axonal health.[4]

According to the third edition of the Atlas of MS, compiled in collaboration with the World Health Organization (WHO), using data from 115 countries, covering 87% of the world's population, it is estimated that 2.8 million people are living with MS globally. The Atlas reveals a significantly higher number of children and young people under 18, living with MS and confirms the high proportion of females affected by the disease, with variations observed across different regions.[5] MS typically manifests between the ages of 15 and 35, and its symptoms vary widely, lacking a specific set of definite characteristics.[6] It is noteworthy that it often takes several years to diagnose MS, after the first symptoms appearance, since its symptoms could resemble those of other conditions.[7]

The diagnosis of MS is based on a combination of clinical and laboratory findings, since there is no specific diagnostic test for the disease. Since 2001, established clinical guidelines known as the McDonald criteria have been in place. These guidelines have been revised over time to ensure earlier and more reliable diagnosis.[8,9] The symptomatology

of MS is highly heterogeneous, making it challenging to categorize the disease uniformly. Some of the most common symptoms of this disease are sensory, which often complicates the evaluation of each case and raises issues of differential diagnosis. Frequent clinical symptoms of the disease include hypoesthesia and paresthesia, observed in 80–90% of patients in the face, limbs, trunk, or even in combination, Lhermitte's sign, visual disturbances, optic neuritis, tremor in the hands due to cerebellar damage, spasticity, diplopia, gait disturbances, nystagmus, fatigue and pain, which is quite common, with the most frequent form being neuropathic pain characterized by a burning sensation and deep pain, and trigeminal neuralgia presenting with pain in the facial area or the skull.[10] Another common symptom is sexual dysfunction that is more prevalent among patients with MS compared to the healthy population, particularly among females.[11] The progression of the disease in each patient also significantly depends on their adherence to prescribed treatments. The prolonged nature of the disease, combined with medication side effects, frequently results in poor adherence to treatment regimens.[12,13]

Currently, there is extensive research in this field, with numerous therapeutic approaches already in practice and several others undergoing clinical trials. The available disease-modifying drugs aim to reduce the frequency of relapses and slow disease progression, including neurological decline and loss of mobility, thereby improving patients' quality of life (QoL). For MS patients experiencing neuropathic pain, pharmacological treatments include cannabinoids, muscle relaxants, anticonvulsants, benzodiazepines, gabapentin, antidepressants, and opioids. Additionally, neurosurgical methods and non-pharmacological approaches are being explored.[14–16]

Opioids are natural, semi-synthetic, or synthetic substances that produce effects similar to morphine. All opioids act by binding to specific receptors in the CNS, mimicking the action of endogenous opioid peptide neurotransmitters such as endorphins. The result of their administration is relief from severe and intense pain, offering a better QoL. Many well-known substances can act as agonists or antagonists of opioids. In this review, we will analyze the action of naltrexone regarding its effect on the relief of chronic pain, and other disorders, in individuals suffering from MS.

2. NALTREXONE AND PAIN

Pain significantly impacts the quality of life in palliative care patients, with most research traditionally focusing on opioid-based pain management. However, opioids and nonsteroidal anti-inflammatory drugs have limitations, due to their risk of adverse effects. Naltrexone, a reversible, semi-synthetic, competitive antagonist of opioid receptors, has effects that vary depending on its dose. At high doses of 50–100 mg oral daily dose, it has been initially used to treat opioid, heroin and alcohol abuse disorders as it can neutralize the effects of opioids, acting as inhibitor of these receptors.[17] At low doses (1–5 mg), it follows an alternative mechanism, acting as a glial modulator with neuroprotective effects, inhibiting microglial activation. Naltrexone binds to Toll-like receptor 4 (TLR4), antagonizing it and thus reducing the pro-inflammatory cytokine response. Additionally, its transient opioid receptor blockade, at low-dose, leads to up-regulated opioid signaling and increased endogenous opioid production, known as opioid rebound effect.[18]

Naltrexone was developed in 1963 as a principal representative of antagonists, since it acts as a long-term antagonist of opioid receptors in CNS, having higher affinity to the μ receptors. Naltrexone, by blocking the μ and δ opioid receptors, prevents relapse, by reducing the desire for opioid consumption, and also reduces the withdrawal symptoms. However, it is a partial agonist of the κ opioid receptors and also affects opioid receptor families such as nociceptin (nociceptin/orphanin FQ receptor).[19] In a study on collagen-induced arthritis (CIA) in rat models, naltrexone (10 mg/kg *per os* daily) was found to relieve arthritis severity by regulating T lymphocyte subsets and cytokine expression. Naltrexone inhibited the TLR4/NF-κB (nuclear factor kappa B) signaling pathway, targeting opioid receptors, regulating the systemic immune response, reducing osteoclast differentiation, and thereby alleviating inflammation and erosion of articular cartilage and bone tissue.[20] Respectively, it has been shown that at lower daily doses (5 mg per day), naltrexone can relieve pain and regulate neuroinflammatory processes caused by inflammation in the glial cells. It can also act as a weak opioid antagonist showing partial agonistic action, thus reducing the activation of dorsal root ganglia cells and up-regulating the activation of the basic opioid receptors.[21] As a result, endogenous opioid substances such as β-endorphins can be released. β-endorphins can regulate mood, thinking, the feeling of well-being, food intake, and endocrine secretion. All these together led to the use of naltrexone as an off-label treatment for symptoms such as numbness, spasticity, fatigue, and bladder dysfunction, as well as in individuals suffering from HIV, Crohn's disease, lupus erythematosus arthritis, fibromyalgia, and MS.[22] A recent study indicated that low-dose naltrexone (LDN) resulted in a 33% reduction in pain, with patients suffering from neuropathic pain being of higher benefit than those with nociceptive or inflammatory pain.[23] However, ambivalent results concerning its activity in diverse chronic pain conditions have been recorded for

low dose administration, rendering its further analysis at *in vivo* and clinical level required.[24]

Although typical dose of naltrexone is 4.5 mg per day, a recent study of 41 eligible patients showed that naltrexone dose range for pain relief may be from 0.1 to 4.5 mg per day.[25] In cases where the dose is characterized as very low (100 μg per day), an opposite effect is caused, with the duration of action potential being extended, enhancing the anti-stimulatory action of morphine and reducing its observed tolerance.[21] Conversely, its oral or intravenous administration could enhance the analgesic effects of opioids, acting on filamin A, which is involved in the signaling of μ-opioid receptors[26] and can be used for the post-surgical analgesia control, leading to reduction of the need for opioids. Thus, at dosage lower than 1 μg per day, orally, naltrexone, or intravenous naloxone, being referred as ultra-low-dose naltrexone/naloxone (ULDN), enhance opioid analgesia, through interaction with filamin A and involvement of μ-opioid receptor signaling.[26]

Naltrexone, as a TLR4 antagonist, leads to decrease in inflammatory cytokine and various other markers production (such as interleukin-1, interferon-β, tumor necrosis factor-alpha, and nitric oxide) and the activation of the innate immune system.[21] Administration of LDN can regulate different types of pain, such as central neuropathic or inflammatory pain, enhancing endogenous opioids causing pre-stimulation, which regulates pain sensitivity, without the adverse effects of opioid use. LDN also inhibits the activation of microglial cells and reduces the fatigue, pain sensitivity, sleep disturbance, and weakness. Over time, it even has the ability to address the source of pain instead of just ameliorating it.[17] Additionally, naltrexone has the ability to act peripherally and centrally, affecting algogenic receptors that cause hyperalgesia and allodynia, since it is able to reduce the inflammation around the CNS and the proliferation of T and B cells that are responsible for the pain transmission.[27]

LDN used off-label, has shown promising results in alleviating symptom severity in various autoimmune conditions, such as MS, fibromyalgia, complex regional pain syndrome, Crohn's disease, and inflammatory bowel disease. Additionally, LDN may improve mood disorders and enhance QoL.[27,28] LDN treatment in fibromyalgia is linked to a reduction in several key pro-inflammatory cytokines and associated symptoms.[29,30] Moreover, LDN may serve as a low-cost, low-risk alternative or adjunct in treating Hailey-Hailey disease (HHD).[31,32]

3. NALTREXONE AND INFLAMMATION

As mentioned above, naltrexone is responsible for the proliferation of T and B lymphocytes, as well as the differentiation of macrophages and the production of cytokines, which are responsible for inflammation. Naltrexone is a cell growth regulator and interacts with opioid receptors to inhibit abnormal cell proliferation and growth by modulating inflammation. It competes with antagonists to bind to the respective exogenous or endogenous opioid receptors producing immunomodulatory effects. LDN antagonizes the Toll-4 receptor expressed by primary sensory neurons and neuroimmune cells that can activate glial cells and release proinflammatory cytokines.[33] At low dose, it can reduce DNA synthesis and inhibits cell growth by reversing the immune activation,[20] and reversing neuroinflammation, inhibiting the activation of microglia and consequently the release of pro-inflammatory cytokines. In MS patients, it was observed that the levels of enkephalin in their body are reduced, being more prone to the development of autoimmune diseases. In patients with acute and relapsing multiple sclerosis, there is a massive leakage of T and B lymphocytes in the blood-brain barrier, specifically in the white matter, which lead to demyelination of the plaques. Small dose of naltrexone was able to restore enkephalin levels in mice in 7 days; thus reducing inflammation.[34]

4. NALTREXONE AND ITS POTENTIAL BENEFITS FOR MULTIPLE SCLEROSIS

Naltrexone emerges as a potentially useful agent for MS, based on recent evidence (fig. 1). A thorough analysis of the PubMed, Web of Science, Scopus and Google Scholar databases, from 2000 to 2025, was performed concerning MS and the application of naltrexone.

LDN appears promising as a safe and effective treatment option for preventing disease progression and improving the quality of life in patients with neurological conditions, such as MS.[35,36] Although initial reports suggest that naltrexone might benefit MS patients, primary research on this topic is limited, but with encouraging elements on several fronts.

In a phase II multicenter open-label pilot study, involving 40 patients with primary progressive MS (PPMS), participants received a LDN (ranging from 2 mg to 4 mg, orally, every night for six months) to evaluate its tolerability and safety.[22] The study demonstrated that LDN was safe and well-tolerated in PPMS patients, with a clinical benefit observed in one aspect of physical function. Specifically, there was a significant reduction in spasticity and an increase in beta-endorphin level during the trial. However, no association was found between mu-opioid receptor gene *(OPRM1)* variants and spasticity improvement.

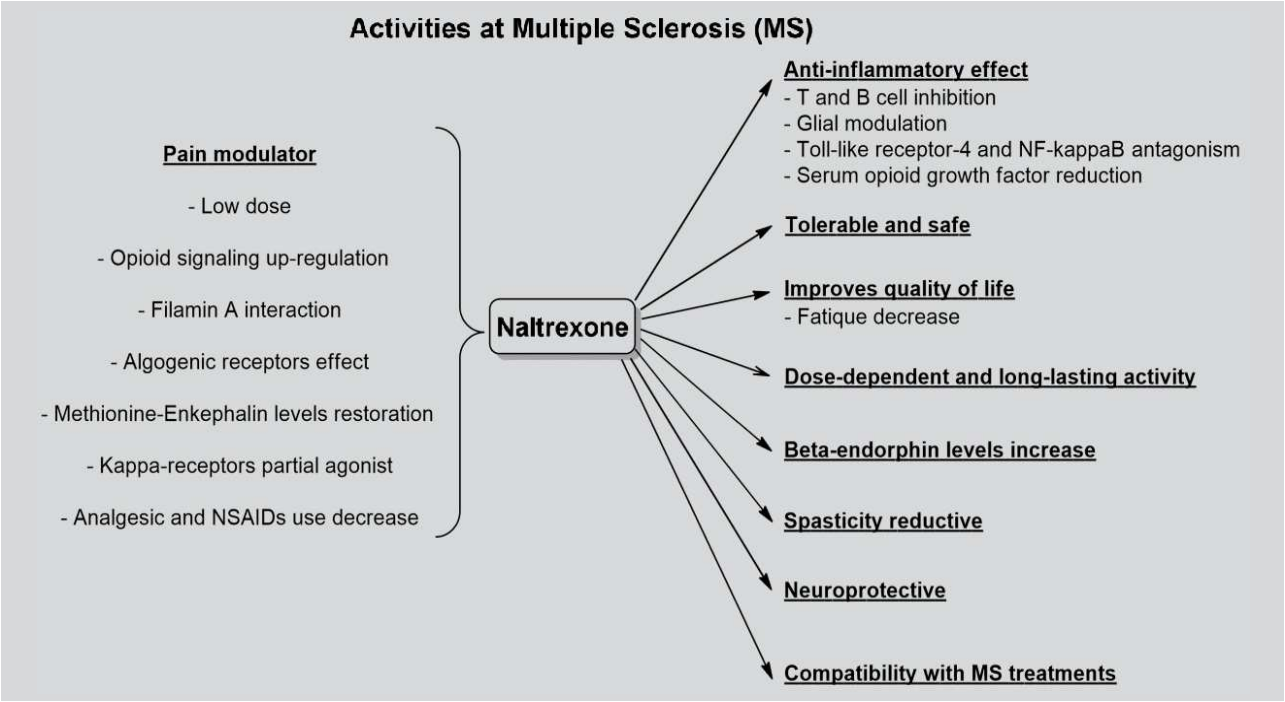

Figure 1. The multi-functional characteristics of naltrexone in multiple sclerosis.

Regarding QoL improvement, a 17-week randomized, double-blind study[19] evaluated the impact of LDN on the QoL, in 96 adult patients, with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS). Using the MSQoL-54 questionnaire, the study found that LDN led to improvements in patients' health perception. However, no improvements were noted in pain, energy, emotional well-being, social, cognitive, and sexual functions, posing limitations due to physical and emotional problems, health distress, and overall QoL. Despite its safety and tolerability, the study suggested that longer trials are needed to confirm efficacy.

A similar pattern of reduced side effects and improved QoL, particularly in terms of fatigue and pain reduction, was also observed in another study involving patients with long-term RRMS or SPMS. To determine the safety, tolerability, and effectiveness of LDN on fatigue, a retrospective analysis of 215 MS patients prescribed LDN (3.5 mg orally, once daily) found that 77% reported no side effects. Additionally, no increased side effects were observed when LDN was combined with other immunomodulators. About 60% of patients receiving LDN reported a reduction in fatigue with LDN therapy. Regarding their quality of life and the perception of LDN's effects on MS, 60% of patients stated that LDN stabilized or improved their condition, with 75% reporting stabilized or improved QoL.[37] A double-blind, placebo-controlled, cross-over study was conducted to evaluate the safety and efficacy of LDN on the QoL, in patients with MS.[38] The study initially enrolled 80 participants, of which 60 completed the trial and evaluated the efficacy of 4.5 mg naltrexone over 8 weeks. The study found that LDN was well-tolerated and significantly improved mental health QoL.

Another study examined the long-term use of naltrexone in patients with MS and its impact on health status and disease progression, including its combined action with other active substances. Two cohorts of patients were established based on their RRMS therapy: One group of patients (n=23) received only LDN, and the second group (n=31) was treated with glatiramer acetate (Copaxone), along with LDN, as an adjunct therapy. Both groups showed no significant differences in clinical laboratory values, timed walking tests, or magnetic resonance imaging (MRI) changes. Despite the small sample size, the study suggested that LDN is non-toxic and safe, with no exacerbation of disease symptoms.[34] Furthermore, research has presented human and animal data suggesting that naltrexone reduces serum levels of opioid growth factor (OGF), which in turn inhibits cell proliferation and reduces inflammation.[39] In MS patients, naltrexone restored methionine-enkephalin levels, reducing inflammation. In mice, naltrexone normalized enkephalin levels before disease onset, but had no effect on beta-endorphin levels in humans or mice.

A quasi-experimental study involving 341 patients and 20,921 prescriptions, investigated the impact of increasing

LDN use on the dispensing of other MS medications. The study found no significant changes in systemic glucocorticoid dispensing, but observed a significant reduction in opioid use, 42% in the cumulative dose and 9% in the number of users. Nonsteroidal anti-inflammatory drugs (NSAIDs) use was also significantly decreased by 8%. While no significant correlation between naltrexone and disease modification or QoL improvement was found, its co-administration with other drugs appeared feasible and beneficial.[40]

5. CONCLUSIONS

In conclusion, naltrexone, an orally administered opioid antagonist, appears to be a promising agent for the management of MS, based on current literature and available studies. At low doses, it has shown significant anti-inflammatory and analgesic properties, leading to the improvement of symptoms and QoL in patients with MS, particularly in cases of chronic pain. It is well-tolerated, safe, and can improve patients' QoL by reducing fatigue, spasticity, and pain. It may also be beneficial as an adjunct therapy. However, the current findings are preliminary and sometimes inconsistent, indicating the need for more studies in the future to confirm and verify its efficacy, particularly regarding its potential to modulate disease progression and inflammation.

ΠΕΡΙΛΗΨΗ

Ο ρόλος της ναλτρεξόνης στη διαχείριση του χρόνιου πόνου σε ασθενείς με σκλήρυνση κατά πλάκας

Α. ΠΑΝΑΓΗ, Π. ΘΕΟΔΟΣΗΣ-ΝΟΜΠΕΛΟΣ, Χ. ΤΡΙΑΝΤΗΣ

Τμήμα Φαρμακευτικής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Frederick, Λευκωσία, Κύπρος

Αρχεία Ελληνικής Ιατρικής 2026, 43(4):474–479

Ο χρόνιος πόνος αποτελεί σημαντικό πρόβλημα στη σκλήρυνση κατά πλάκας (ΣΚΠ), ιδιαίτερα στα άκρα, στη νευραλγία τριδύμου, στον πόνο στη μέση και στους πονοκεφάλους. Η αντιμετώπιση του πόνου στους ασθενείς με ΣΚΠ είναι δύσκολη λόγω της προοδευτικής και υποτροπιάζουσας φύσης της νόσου. Η ναλτρεξόνη, ένας ανταγωνιστής των οπιοειδών υποδοχέων, έχει αποδειχθεί ότι σε χαμηλές δόσεις μπορεί να αναστείλει τον πολλαπλασιασμό των Τ και Β λεμφοκυττάρων, επιδεικνύοντας αντιφλεγμονώδεις και αναλγητικές ιδιότητες έναντι του χρόνιου πόνου. Σκοπός του άρθρου είναι η ανάδειξη των δυνατοτήτων της ναλτρεξόνης στην επηρεασμένη παθοφυσιολογία της ΣΚΠ, και ειδικά στον χρόνιο πόνο. Μια σειρά μελετών σε ασθενείς με διάφορες μορφές ΣΚΠ έδειξαν ότι η ναλτρεξόνη, σε ημερήσιες δόσεις των 3–5 mg, είναι ανεκτή και ασφαλής. Επί πλέον, μπορεί να βελτιώσει την ποιότητα ζωής (QoL) και να μειώσει την κόπωση, ιδιαίτερα σε ασθενείς με υποτροπιάζουσα-διαλείπουσα σκλήρυνση κατά πλάκας (RRMS), μέσω μηχανισμών που φαίνεται να σχετίζονται με τη δοσολογία. Ωστόσο, δεν υπάρχουν επαρκή δεδομένα για την επίδρασή της σε δείκτες φλεγμονής. Στην πρωτοπαθώς προϊούσα ΣΚΠ (PPMS) η χαμηλή δόση ναλτρεξόνης (LDN) έχει αποδειχθεί ότι αυξάνει τα επίπεδα των β-ενδορφινών στο περιφερικό αίμα και μειώνει σημαντικά τη σπαστικότητα, με τα αποτελέσματα αυτά να διατηρούνται έως και ένα μήνα μετά τη θεραπεία. Αν και πολλά από τα εν λόγω αποτελέσματα είναι προκαταρκτικά και απαιτούνται περισσότερα κλινικά δεδομένα, η ναλτρεξόνη φαίνεται να αποτελεί μια υποσχόμενη δραστική ουσία που μπορεί να συμβάλλει στην αντιμετώπιση της εξέλιξης και των συμπτωμάτων της ΣΚΠ, με αναλγητική δράση.

Λέξεις ευρετηρίου: Ναλτρεξόνη, Σκλήρυνση κατά πλάκας, Φλεγμονή, Χρόνιος πόνος

References

1. COMPSTON A, COLES A. Multiple sclerosis. *Lancet* 2008, 372:1502–1517
2. REICH DS, LUCCHINETTI CF, CALABRESI PA. Multiple sclerosis. *N Engl J Med* 2018, 378:169–180
3. NOSEWORTHY JH, LUCCHINETTI C, RODRIGUEZ M, WEINSHENKER BG. Multiple sclerosis. *N Engl J Med* 2000, 343:938–952
4. FAISSNER S, PLEMEL JR, GOLD R, YONG VW. Progressive multiple sclerosis: From pathophysiology to therapeutic strategies. *Nat Rev Drug Discov* 2019, 18:905–922
5. THE MULTIPLE SCLEROSIS INTERNATIONAL FEDERATION. Atlas of MS. 3rd ed. Part 1: Mapping multiple sclerosis around the world – key epidemiology findings. MSIF, London, 2020. Available at: https://www.msif.org/wp-content/uploads/2020/12/Atlas-3rd-Edition-Epidemiology-report-EN-updated-30-9-20.pdf
6. DOSHI A, CHATAWAY J. Multiple sclerosis, a treatable disease. *Clin Med (Lond)* 2016, 16(Suppl 6):s53–s59
7. WALLIN MT, CULPEPPER WJ, CAMPBELL JD, NELSON LM, LANGER-GOULD A, MARRIE RA ET AL. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology* 2019, 92:e1029–e1040

8. McDONALD WI, COMPSTON A, EDAN G, GOODKIN D, HARTUNG HP, LUBLIN FD ET AL. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001, 50:121–127
9. THOMPSON AJ, BANWELL BL, BARKHOF F, CARROLL WM, COETZEE T, COMI G ET AL. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018, 17:162–173
10. THEODOSIS-NOBELOS P, REKKA EA. Efforts towards repurposing of antioxidant drugs and active compounds for multiple sclerosis control. *Neurochem Res* 2023, 48:725–744
11. HADJIMICHAIL K, ASIMAKOPOULOU E, CHARALAMBOUS D, PANTZARIS M, THEODOSIS-NOBELOS P, TRIANTIS C. The prevalence of sexual dysfunction in patients with multiple sclerosis in Cyprus: A cross-sectional Study. *J Neurosci Nurs* 2020, 52:302–307
12. BRUCE JM, LYNCH SG. Multiple sclerosis: MS treatment adherence – how to keep patients on medication? *Nat Rev Neurol* 2011, 7:421–422
13. THEODOSIS-NOBELOS P, ASIMAKOPOULOU E, RIKKOU-KALOURKOTI M, TRIANTIS C. Adherence to medical treatment. Evaluation methods and enhance strategies. *Hellenic Journal of Nursing (HJNS)* 2019, 58:317–327
14. TRIANTIS C, CHATZIMICHAIL K, THEODOSIS-NOBELOS P, ASIMAKOPOULOU E. New pharmaceutical approaches to the treatment of multiple sclerosis. *Arch Hellen Med* 2020, 37:602–611
15. JAWAHAR R, OH U, YANG S, LAPANE KL. A systematic review of pharmacological pain management in multiple sclerosis. *Drugs* 2013, 73:1711–1722
16. SHKODINA AD, BARDHAN M, CHOPRA H, ANYAGWA OE, PINCHUK VA, HRYN KV ET AL. Pharmacological and non-pharmacological approaches for the management of neuropathic pain in multiple sclerosis. *CNS Drugs* 2024, 38:205–224
17. POLIWODA S, NOSS B, TRUONG GTD, CREECH ZA, KOUSHIK SS, URITS I ET AL. The utilization of low dose naltrexone for chronic pain. *CNS Drugs* 2023, 37:663–670
18. TROFIMOVITCH D, BAUMRUCKER SJ. Pharmacology update: Low-dose naltrexone as a possible nonopioid modality for some chronic, nonmalignant pain syndromes. *Am J Hosp Palliat Care* 2019, 36:907–912
19. SHARAFADDINZADEH N, MOGHTADERI A, KASHIPAZHA D, MAJDINASAB N, SHALBAFAN B. 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
20. XU N, WANG Y, ZHAO S, JIAO T, XUE H, SHAN F ET AL. Naltrexone (NTX) relieves inflammation in the collagen-induced-arthritis (CIA) rat models through regulating TLR4/NFκB signaling pathway. *Int Immunopharmacol* 2020, 79:106056
21. KIM PS, FISHMAN MA. Low-dose naltrexone for chronic pain: Update and systemic review. *Curr Pain Headache Rep* 2020, 24:64
22. GIRONI M, MARTINELLI-BONESCHI F, SACERDOTE P, SOLARO C, ZAFFARONI M, CAVARRETTA R ET AL. A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis. *Mult Scler* 2008, 14:1076–1083
23. MARTIN SJ, McANALLY HB, OKEDIJI P, ROGOSNITZKY M. Low-dose naltrexone, an opioid-receptor antagonist, is a broad-spectrum analgesic: A retrospective cohort study. *Pain Manag* 2022, 12:699–709
24. RASSI-MARIANI V, BARRETO ESR, ANTUNES CR, ALENCAR VB, LINSKUSTERER LEF, AZI LMTA ET AL. The use of naltrexone in the treatment of chronic pain: A systematic review. *Pain Manag* 2024, 14:453–463
25. MARCUS NJ, ROBBINS L, ARAKI A, GRACELY EJ, THEOHARIDES TC. Effective doses of low-dose naltrexone for chronic pain – an observational study. *J Pain Res* 2024, 17:1273–1284
26. TOLJAN K, VROOMAN B. Low-dose naltrexone (LDN) – review of therapeutic utilization. *Med Sci (Basel)* 2018, 6:82
27. 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
28. 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
29. PARKITNY L, YOUNGER J. Reduced pro-inflammatory cytokines after eight weeks of low-dose naltrexone for fibromyalgia. *Biomedicines* 2017, 5:16
30. BRUUN-PLESNER K, BLICHFELDT-ECKHARDT MR, VAEGTER HB, LAURIDSEN JT, AMRIS K, TOFT P. Low-dose naltrexone for the treatment of fibromyalgia: Investigation of dose-response relationships. *Pain Med* 2020, 21:2253–2261
31. ALBERS LN, ARBISER JL, FELDMAN RJ. Treatment of Hailey-Hailey disease with low-dose naltrexone. *JAMA Dermatol* 2017, 153:1018–1020
32. IBRAHIM O, HOGAN SR, VIJ A, FERNANDEZ AP. Low-dose naltrexone treatment of familial benign pemphigus (Hailey-Hailey disease). *JAMA Dermatol* 2017, 153:1015–1017
33. HUMMIG W, BAGGIO DF, LOPES RV, DOS SANTOS SMD, FERREIRA LEN, CHICHORRO JG. Antinociceptive effect of ultra-low dose naltrexone in a pre-clinical model of postoperative orofacial pain. *Brain Res* 2023, 1798:148154
34. LUDWIG MD, TUREL AP, ZAGON IS, McLAUGHLIN PJ. Long-term treatment with low dose naltrexone maintains stable health in patients with multiple sclerosis. *Mult Scler J Exp Transl Clin* 2016, 2:2055217316672242
35. BROWN N, PANKSEPP J. Low-dose naltrexone for disease prevention and quality of life. *Med Hypotheses* 2009, 72:333–337
36. AGRAWAL YP. Low dose naltrexone therapy in multiple sclerosis. *Med Hypotheses* 2005, 64:721–724
37. 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, 35:609–611
38. CREE BAC, KORNYEYEVA E, GOODIN DS. Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. *Ann Neurol* 2010, 68:145–150
39. LUDWIG MD, ZAGON IS, McLAUGHLIN PJ. Featured article: Serum [Met^5]-enkephalin levels are reduced in multiple sclerosis and restored by low-dose naltrexone. *Exp Biol Med (Maywood)* 2017, 242:1524–1533
40. RAKNES G, SMÅBREKKE L. Low dose naltrexone in multiple sclerosis: Effects on medication use. A quasi-experimental study. *PLoS One* 2017, 12:e0187423

Corresponding author:

C. Triantis, 7 Y. Frederickou street, Nicosia 1036, Cyprus
e-mail: hsc.tc@frederick.ac.cy