German Journal of Veterinary Research

eISSN:2703-1322

Review article

Current pharmacotherapeutic properties of low-dose naltrexone therapy in humans and possible therapeutic and prophylactic indications in cats and dogs

Reza G. MARANGALOO[1*], Orhan PINAR[2], Tandzhu MEHMEDOV[3] and Mehmet E. Or[1]

[1] Istanbul University-Cerrahpaşa, Faculty of Veterinary Medicine, Department of Internal Medicine, Istanbul, Turkey
[2] Equine and Equine Education Program, School of Veterinary Medicine, Istanbul University-Cerrahpaşa, Istanbul, Turkey
[3] Forestry University, Faculty of Veterinary Medicine, Sofia, Bulgaria

Article History:
Received: 03-Jan-2024
Accepted: 20-Feb-2024
***Corresponding author:**
Reza G. MARANGALOO
humavet20@gmail.com

Abstract

Naltrexone was first developed in 1963 as an opioid antagonist for therapeutic use in opioid-dependent individuals (alcohol, narcotics, and tobacco) with a 50 mg/day dose approved by the Food and Drug Administration (FDA). In 1985, Dr. Bernard Bihari explained that when naltrexone is taken in very low doses (1-5 mg/day) before bedtime, it blocks opioid receptors for 2- 4 hours and leads to the release of endorphins in the early morning hours, serving as an opioid agonist and immunomodulatory agent. This extra endorphin secretion has been proven to enhance the immune system response in AIDS patients. Endogenous opioids that affect cell development are referred to as opioid growth factor (OGF) and met-enkephalin (ME). Low-dose-naltrexone (LDN) pharmacotherapeutically possesses immunomodulatory, anticarcinogenic, antiviral, antibacterial, antiparasitic, and antifungal properties. LDN also increases the production and sensitivity of OGF, ME, and OGF receptor (OGFr) in the bloodstream, thereby enhancing quality of life. Based on these pharmacotherapeutic properties, LDN application is believed to be effective in the treatment or prophylaxis of various infectious diseases in cats and dogs, particularly vasculitis-related diseases such as feline infectious peritonitis (FIP) and infectious canine hepatitis (ICH), hypothyroidism, gastrointestinal disorders, spondylosis, rheumatoid arthritis, autoimmune diseases, pneumonia, atopic and allergic dermatitis, pyodermas, resistant pyodermas, methicillin-resistant *Staphylococcus aureus* (MRSA) or various gastrointestinal disorders, alopecia, stubborn dermatomycosis, stubborn demodicosis, various geriatric and oncogenic diseases, and deep depressions or obsessive-compulsive disorders. Thus, this review aims to evaluate the pharmacotherapeutic properties of LDN therapy usage and mechanisms of action in detail and assess the potential indications in cats and dogs based on these mechanisms.

Keywords: Immunomodulators, Therapy, Low-dose-naltrexone, LDN, Cats, Dogs

Citation: MARANGALOO, R. G., PINAR, O., MEHMEDOV, T. and Or, M. E. 2024. Current pharmacotherapeutic properties of low-dose naltrexone therapy in humans and possible therapeutic and prophylactic indications in cats and dogs. Ger. J. Vet. Res. 4 (1): 39-45. https://doi.org/10.51585/gjvr.2024.1.0070

Introduction

Naltrexone (NLX), an FDA-approved opioid receptor antagonist, has been used in the treatment of opioid addiction since 1984 at a daily dose of 50-150 mg. The intramuscular injection formulation of NLX was approved by the FDA in 2006 for the treatment of alcohol addiction and in 2010 for opioid addiction (Bihari, 1995). The phenomenon of Hormesis best explains the pharmacotherapeutic mechanism of low-dose naltrexone (LDN). The phenomenon of Hormesis essentially refers to the conversion of the antagonist effect to an agonist effect when any substance with antagonist activity is used at low doses. When the same active substance is used in very low doses, it can exhibit biphasic action; in other words, when an antagonist substance is used in low doses, it causes weak stimulation, but when given in high doses, it results in the same inhibition as the antagonist (Kim and West, 2019).

In a study conducted by Dr. Bernard Bihari in 1986, it was reported that when NLX is taken in very low doses (1-5 mg/day) before bedtime, it blocks opioid receptors for 2-4 hours. However, after the temporary blockade, it leads to the release of endorphins in the early morning hours. Consequently, the application of LDN results in the secretion of endorphins during this time frame, contributing to the regulation and functional development of the immune system. Research has demonstrated that the immunomodulatory effect of LDN application can enhance the immune system response in patients with Acquired Immune Deficiency Syndrome (AIDS). Dr. Bihari further proved the significant effectiveness of LDN use in the treatment of autoimmune diseases like lupus and patients with cancer, such as lymphoma or pancreatic cancer (Bihari, 1995).

Naltrexone is also administered in much-reduced dosages. When NLX is administered at a dosage ranging from 1 to 0.001 mg per day, it is classified as very-low-dose NLX (VLDN). If the dosage is below 0.001 mg per day, it is referred to as ultra-low-dose NLX (ULDN). The efficacy of ULDN treatment in reducing seizures has been demonstrated in individuals with epilepsy (Honar et al., 2004). Furthermore, ULDN treatment has been documented to decrease postoperative adverse effects and the necessary opioid consumption following surgery (Toljan and Vrooman, 2018).

This article aims to comprehensively analyze the pharmacotherapeutic properties and therapeutic mechanisms of LDN therapy in human subjects across a range of diseases. The evaluation of potential indications for LDN therapy in feline and canine pets will be conducted through the examination and analysis of relevant mechanisms (Figure 1).

Pharmacotherapeutic characteristics of LDN

The Micro/μ-opioid receptors (MOR), Delta/Δ-opioid receptors (DOR), Kappa/κ-opioid receptors (KOR), and Epsilon/ϵ-opioid

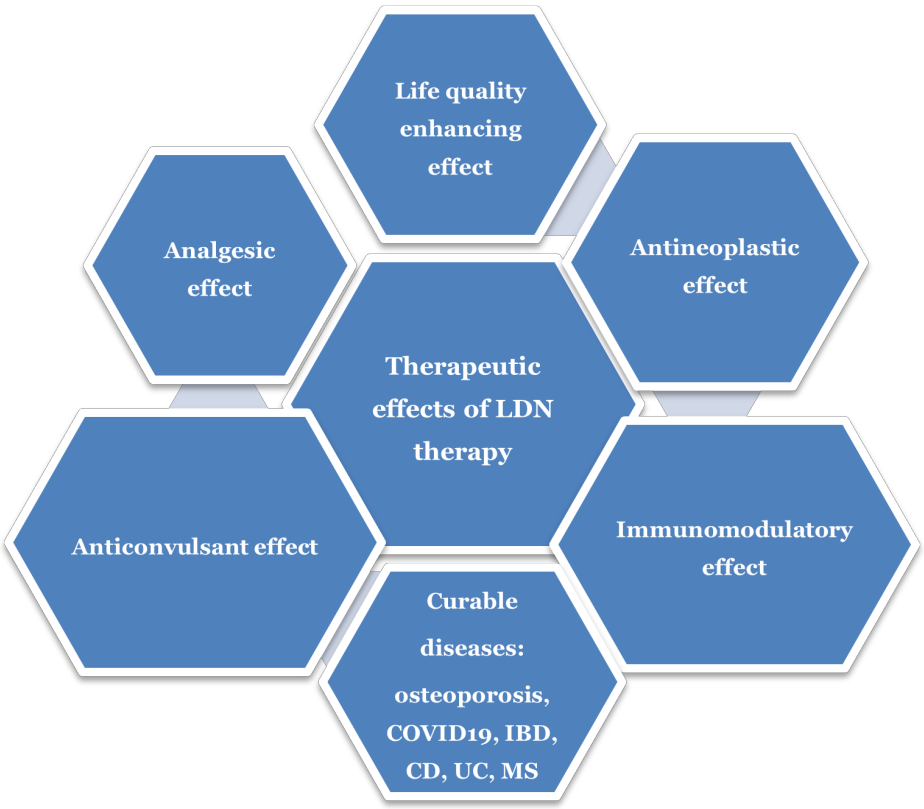

Figure 1: Therapeutic effects of low-dose naltrexone. Abbreviations: COVID-19; Coronavirus Disease-19, IBD; Irritable Bowel Disease, CD; Crohn's Disease, UC; Ulcerative Colitis, MS; Multiple Sclerosis.

receptors (EOR) are the many types of cell receptors that are found throughout the human body. Studies have shown that NLX, which is a nonselective opioid antagonist, has a significant inhibitory effect on EOR, MOR, and DOR receptors when administered at normal dosages. However, it has a less significant effect on KOR receptors. In addition, recent studies have demonstrated that NLX has an antagonistic impact on the recently discovered member of the opioid family known as orphanin FQ or nociceptin (N/OFQ) (Gharagozlou et al., 2006; Brown and Panksepp, 2009). When LDN activates these receptors, it can enhance the secretion of met-enkephalin (ME) and beta-endorphin (BE) both in the central nervous system and in the bloodstream via acting on MOR, DOR, and EOR receptors. This process enhances psychological well-being positively (Brown and Panksepp, 2009; Clauw et al., 2011; McCusker and Kelley, 2013).

Data suggests that individuals with rheumatic disorders, such as arthritis, lupus erythematosus, and gut-related ailments, have a low concentration of BE in their blood. Moreover, a notable negative link has been discovered between body mass index (BMI) and rheumatoid factor, erythrocyte sedimentation rate (ESR), and, therefore, the probability of inflammation. In conditions such as fibromyalgia, Crohn's disease, multiple sclerosis (MS), persistent migraines, and endometriosis, the levels of BE in the blood are reduced by around 1/8 to 1/4 compared to the standard levels. Hence, the utilization of LDN therapy has been scientifically demonstrated to be highly productive in treating these conditions through the augmentation of BE release (Brown and Panksepp, 2009).

LDN temporarily inhibits opioids and opioid receptors, leading to an increase in the synthesis and sensitivity of endogenous opioids such as methionine, ME, OGF, and OGFr. This method effectively suppresses the growth and multiplication of cancer cells (Zagon et al., 2009; Hammer et al., 2015). A study conducted on mice found that the administration of NLX at a dosage of 0.1 mg/kg resulted in a delay of clinical symptoms and a reduction in the severity of progressive experimental autoimmune encephalomyelitis within a few days (Ibrahim et al., 2017; Parkitny and Younger, 2017; Ekelem et al., 2019) (Figure 2).

Quality of life-enhancing therapeutic mechanisms

The LDN treatment stimulates a correlation between MOR and central dopamine, resulting in heightened energetic functions and ultimately improving the overall quality of life (Zagon and McLaughlin, 1983). Psychiatrists have observed that an increase in endogenous opioids can help alleviate different types of depression and improve the body's ability to handle cardiovascular stressors. This can lead to an overall improvement in quality of life (McCubbin et al., 1992, 1996).

Research endeavors have positioned LDN therapy as a promising, safe, cost-effective modality, exhibiting a quality-of-life augmenting effect in various viral, e.g., AIDS, autoimmune, neurological diseases such as multiple sclerosis, and cancer variants. LDN is thus presented as a prospective approach for the prophylaxis or treatment of these conditions, demonstrating both safety and affordability (Alcaro et al., 2007; Brown and Panksepp, 2009). The therapeutic basis of LDN is in its ability to stimulate energy-enhancing mechanisms, consequently improving the overall quality of life. This molecular phenomenon arises from the interaction between MU-opioid receptors and central dopamine neurons in the mesencephalon (Alcaro et al., 2007).

In a previous study, the therapeutic, prophylactic, and quality-of-life enhancing effects of LDN therapy across a spectrum of illnesses have been explained. According to this elucidation, LDN therapy emerges as a reliable and promising approach among novel treatments, serving as an alternative therapeutic option with a quality-of-life augmenting impact. It is asserted that LDN therapy represents a dependable and hopeful approach for the treatment and prophylaxis of numerous autoimmune, viral, cardiovascular, and neurological diseases, as well as depression and various cancer treatments (Brown and Panksepp, 2009). In another study, it has been demonstrated that the administration of carboplatin chemotherapy in 60 female dogs with mammary carcinoma not only elevates the quality of life but also reduces the side effects of chemotherapy, resulting in a significant increase in the survival rate of these dogs (Machado et al., 2018). Fibromyalgia is recognized as a chronic pain condition characterized by widespread musculoskeletal pain, profound fatigue, cognitive impairment, and sleep difficulties (Clauw et al., 2011; Metyas et al., 2018). Clinical studies have reported that

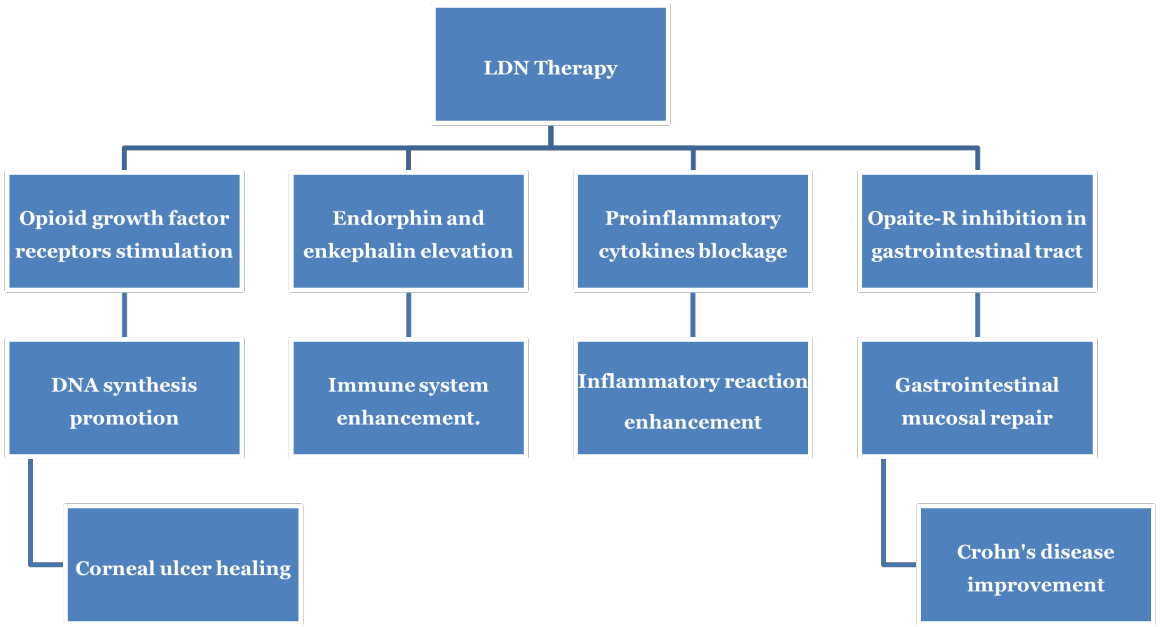

Figure 2: Low-dose naltrexone therapy mechanism of actions.

the application of LDN is beneficial in increasing the quality of life, improving motor activity, and alleviating fatigue in patients with fibromyalgia, Crohn's disease, or multiple sclerosis (Zagon and McLaughlin, 2018).

Anticonvulsant therapeutic mechanisms

The efficacy of ULDN therapy in treating chronic seizure problems is demonstrated by its ability to block G_S receptors, decrease sensitivity, and provide analgesic and anticonvulsant effects. Thus, ULDN medication is employed as a highly successful therapeutic strategy for persistent seizures (Honar et al., 2004; Roshanpour et al., 2009). A study done by Bahremand et al. (2008) has shown that the combination of ULDN (500 pg/kg), which is ineffective when administered alone, with Cannabinoids, leads to a substantial reduction in tonic seizures. Additional research has confirmed that both LDN and opioids possess notable properties that can either suppress or induce seizures. The anticonvulsant mechanism works by delaying the spontaneous depolarization and firing of nerve cells, which in turn prevents the early onset of seizures (Mihály et al., 1990; Montaser-Kouhsari et al., 2011).

Analgesic effect in chronic pain mechanisms

Microglia are immune cells of the central nervous system (CNS) activated by a wide range of triggers. When toll-like receptor-4 (TLR-4) on macrophages like microglia is triggered, it has been determined that microglia produce inflammatory and stimulating factors, leading to behavioral disorders such as pain sensitivity, cognitive impairment, sleep disturbances, mood disorders, and overall malaise. Previous studies have demonstrated that the administration of LDN inhibits TLR-4 activity (Tejwani et al., 1991; Chang et al., 2000; Kelley et al., 2003; McCusker and Kelley, 2013; Younger et al., 2014). LDN therapy exerts analgesic and neuroprotective effects through the suppression of microglial activation, resulting in the inhibition of the production of anti-inflammatory mediators such as C-reactive protein, reactive oxygen species, and other potentially neurostimulatory or neurotoxic chemicals (Younger et al., 2014).

Mechanisms of immunomodulation

An increase in the activity of natural killer (NK) cells is acknowledged as a critical factor in the mitigation of viral infections. It has been demonstrated that LDN therapy can increase the quantity and functionality of NK cells during viral infections by increasing the sensitivity of ME and beta-endorphin to MU-opioid receptors (Tseng et al., 2005). The administration of LDN regulates the innate and adaptive immune responses by activating the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). LDN treatment has been demonstrated to improve the activity of T cells and macrophages while also dramatically boosting the production of NK cells, TNF-α, IL-6, and IL-1β (Yi et al., 2016). LDN therapy was explained to significantly improve patients with sarcoidosis by regulating the abnormally high activity of lymphocytes (Weinstock et al., 2017).

Antineoplastic mechanisms

An extensive demonstration of the effectiveness of LDN therapy in the treatment of cancer was made (Zagon and McLaughlin, 1983). The results of this investigation demonstrated that administering 0.1 mg/kg NLX to mice resulted in significant improvements, including a 36% increase in survival rate, a 66% reduction in the incidence of neuroblastoma tumors, and a substantial 98% delay in tumor development. ME is recognized as an anti-neoplastic agent and is known as the most potent and long-acting opioid in the body (Hytrek et al., 1996). The application of LDN has been reported to induce remission in breast, ovarian, lung, and prostate cancers, Hodgkin and non-Hodgkin lymphoma, multiple myeloma, and neuroblastoma.

Additionally, it has been explained that the intravenous administration of ME or its combination with LDN is effective in the treatment of certain cancers. LDN therapy has been substantiated to increase the activity of NK cells by modulating the release and activity of ME, BE, and MUR and binding to the receptors of cancer cells (Brown and Panksepp, 2009). Another study has provided evidence that LDN therapy induces the activation of OGF and its receptor (OGFr) in mice with ovarian cancer, leading to an increase in the quantity and functionality of T and NK cells. As a consequence, the proliferation of tumor cells and angiogenesis have been impeded, leading to a decrease in the incidence of cancer. Human ovarian cancer cells were transplanted into the peritoneal cavity of female mice in this study. The mice were subjected to a daily treatment of OGF (10 mg/kg) and LDN (0.1 mg/kg) for 40 days. These findings revealed a substantial decrease in the volume of ovarian tumors, as measured by the number and weight of tumor nodules (Donahue et al., 2011).

In another research conducted on squamous cell carcinoma (SCC) cancer in the head and neck region, which has a high mortality and recurrence rate in humans, LDN therapy has been documented as a highly effective therapeutic strategy without leaving any toxic side effects. According to this research, LDN application as a new approach, even with just once-a-week administration, has been proven to reduce DNA synthesis in these tumors significantly (up to 1.6 times), reducing the tumor volume and weight. The results indicate that LDN application, which

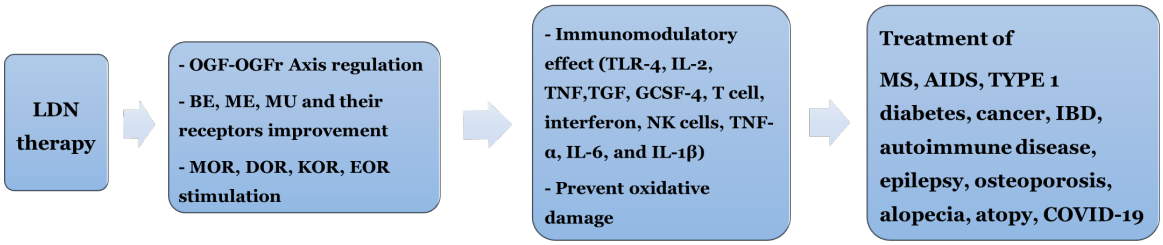

Figure 3: The outline mechanism actions and the list of treatable diseases of Low-dose-naltrexone (LDN) therapy. Abbreviations: opioid growth factor receptor (OGFr), Beta-Endorphin (BE), Met-Enkephalin (ME), Micro Opioid Receptors (MOR), Delta Opioid Receptors (DOR), Kappa Opioid Receptors (KOR), Epsilon Opioid Receptors (EOR), Toll-Like Receptor-4 (TLR-4), Interleukin-2 (IL-2), TGF (Transforming Growth Factor), TNF (Tumor Necrosis Factor), G-CSF (Granulocyte-Colony Stimulating Factor), Multiple Sclerosis (MS), Acquired Immunodeficiency Syndrome (AIDS), Irritable Bowel Disease (IBD), Coronavirus disease19 (COVID-19).

modifies the OGF– OGFr axis, is reported as both safe and cost-effective, serving as a topically applicable method (McLaughlin et al., 2012).

Methylnaltrexone (MNTX), reported as a selective peripheral MOR antagonist, has been indicated to inhibit angiogenesis and prevent *in-vivo* tumor growth (Yi et al., 2016). In another research project, it has been proven that LDN therapy triggers the OGF–OGF OGFr axis, inhibiting DNA synthesis and angiogenesis in tumoral structures. This inhibition has been demonstrated to halt or slow the development of type 2 diabetes, immune system diseases (MS, IBS, AIDS, etc.), and tumors (Li et al., 2018). In a published case report, a fifty-year-old male with non-small cell lung cancer (NSCLC, Lung Adenocarcinoma) demonstrated that LDN therapy, without leaving any side effects, strengthened the immune system at the cellular level, improved the quality of life, significantly reduced the severity of symptoms, and additionally documented the painless and successful outcome of chemotherapy and radiotherapy (Miskoff and Chaudhri, 2018). In a scholarly inquiry conducted on mice in 2020, the LDN therapy has been indicated to have a restricting effect on the progression of cervical cancer, which is known as one of the most challenging cancers to treat metastasis. According to this research, the administration of LDN in cervical neoplasia triggered apoptosis in tumoral cells, suppressed their migration and invasion abilities, and additionally demonstrated the proliferation of HeLa cells and an increase in the number and activity of macrophages. Consequently, LDN therapy has been identified as a therapeutic potential method for the treatment of cervical cancer through these mechanisms (Choubey et al., 2022).

Therapeutic indications and mechanisms of LDN therapy in diseases

Irritable bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC)

The LDN therapy method was applied in the treatment of patients with IBD, which is generally refractory to existing routine medications, with approximately 30% showing resistance or recurring symptoms over time. After administration of LDN in IBD patients, the serum cytokine levels decreased, the mucosal endoplasmic reticulum stress level decreased, and the epithelial barrier function directly improved. Consequently, clinical symptoms disappeared, remission rates increased, and the repair of intestinal ulcerative lesions accelerated. In conclusion, LDN therapy has been proven to be an effective, cost-efficient, and safe method in the treatment of resistant IBD patients (Lie et al., 2018) (Figure 3).

A two-year empirical investigation was conducted to examine the efficacy of LDN therapy in 582 patients diagnosed with CD, UC, and IBD. The results determined that LDN treatment was significantly beneficial. Based on the findings of this research, the concurrent administration of LDN and other intestinal immunosuppressive drugs induces a synergistic effect by stimulating intestinal motility and opioid-immunological receptors, which expedites the treatment process, owing to the abundance of opioid receptors in the gastrointestinal system (Raknes et al., 2018).

Autoimmune diseases

LDN therapy has been associated with elevated levels of ME and T-cells in patients diagnosed with AIDS or AIDS-related complex (ARC). Furthermore, it has been proposed that LDN therapy may provide early-stage immunomodulatory benefits to patients who have undergone chemotherapy, radiation, or surgery (Wybran et al., 1987). In an *in-vitro* and*in-vivo* investigation, the administration of LDN demonstrated a significant augmentation in ME, white blood cell (WBC) count, NK cell activity, gamma-interferon, active T-cells, and other constituents of the immune system in cancer patients afflicted with various forms of pain, encompassing lung cancer, Kaposi's sarcoma, melanoma, and hypernephroma. Furthermore, LDN therapy exhibited a substantial elevation in the expression of IL-2 (Interleukin-2) receptors, concomitant with a marked increase in IL-2 blood levels (Plotnikoff et al., 1987).

In a clinical investigation involving a cohort of 60 individuals diagnosed with multiple sclerosis (MS), the application of LDN at a dosage of 4.5 mg per day over 8 weeks yielded noteworthy improvements in various facets of quality of life. Specifically, discernible benefits were observed in mental health, pain perception, and cognitive functionality. Importantly, the LDN intervention exhibited an admirable safety profile, with no discernible adverse effects reported during treatment (Cree et al., 2010). OGF– OGFr axis is ubiquitously present in both normal and pathological cellular contexts, where it intricately regulates the essential function of maintaining homeostatic cell replication. Individuals afflicted with conditions such as multiple sclerosis or other neurological disorders exhibit notably reduced levels of serum enkephalin (SE). The strategic administration of LDN is documented to effectively elevate SE levels by selectively inhibiting OGFr, thereby facilitating bioregulatory reactions. In a meticulously conducted clinical investigation involving murine subjects with experimental autoimmune encephalomyelitis (EAE), a well-established model for MS, it was empirically evidenced that both BE and enkephalin levels were markedly diminished. Subsequent LDN therapy manifested the rectification of SE levels and a consequential amelioration in clinical behaviors, underscoring the therapeutic potential of LDN in neurologically mediated disorders (Zagon and McLaughlin, 2018) (Figure 3).

In the period spanning from 2006 to 2019, an extensive examination of case reports across diverse geographical locations has underscored the therapeutic efficacy of LDN in the context of chronic and refractory pemphigus. Particularly notable is LDN's ability to manifest a substantial anti-inflammatory and anti-pruritic impact, devoid of any overt side effects. This was observed prominently in cases where conventional treatments such as antibiotics or steroids exhibited inadequate or negligible responses. The documented outcomes reveal LDN as a promising intervention, fostering notable improvements in patient conditions (Mashiko et al., 2006; Ibrahim et al., 2017; Parkitny and Younger, 2017; Garayar Cantero et al., 2019). A research investigation carried out at the University of Alabama showcased the effectiveness of LDN in reducing inflammation, specifically in cases of fibromyalgia. The blood concentrations of inflammatory

markers, such as IL-2, IFN, transforming growth factor (TGF), tumor necrosis factor (TNF), and granulocyte-colony stimulating factor (G-CSF), were found to be substantially diminished by this intervention. The results of the study indicate that LDN prevents pro-inflammatory responses in fibromyalgia patients with efficacy (Ekelem et al., 2019).

Therapeutic mechanisms in osteoporosis cases

The LDN therapy has been proven to make significant improvements in bone-related metrics, such as increased bone mass, heightened bone production rate, increased number of osteoblasts, and improved values for bone surface (Seitz et al., 2010; Thakur et al., 2016). Research conducted on mice showed that LDN treatment augmented the signaling of OGF and its receptor (OGFr), hence controlling the proliferation of osteoblasts and leading to a notable increase in bone mass and density (Tanaka et al., 2019) (Figure 3).

Coronavirus Disease-19 (COVID-19)

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is known as the cause of the global pandemic COVID-19. SARS-CoV-2 infection leads to profound pro-inflammatory cytokine storm, causing lung tissue damage and respiratory failure and ultimately forming the basis for multiple organ failure. LDN therapy against COVID-19 has been demonstrated to act as a treatment and adjuvant treatment protocol by blocking both Extracellular Signal-Regulated Kinases (ERK) 1/2 and the interaction of angiotensin-converting enzyme2 (ACE2) with receptor binding domain (RBD), the receptor-binding domain, in coronavirus infection (Choubey et al., 2022) (Figure 3).

Possible indications for LDN therapy in cats and dogs

In a conducted investigation involving 60 female dogs diagnosed with mammary carcinoma tumors and undergoing mastectomy, concurrent administration of LDN therapy and chemotherapy with carboplatin was implemented. The comprehensive assessment of clinical and preclinical parameters after the study unveiled a noteworthy correlation between LDN usage and both prolonged survival and enhanced quality of life. These findings provide evidence that LDN therapy serves as a therapeutic approach, preserving the quality of life and extending survival rates in female dogs undergoing chemotherapy (Liu et al., 2020).

Analyzing the findings derived from studies conducted on humans, dogs, and experimental animals revealed that LDN therapy showed a spectrum of pharmacotherapeutic properties, including immunomodulatory, analgesic, anticarcinogenic, anticonvulsant, antiviral, antibacterial, antiparasitic, and antifungal effects. Each of these properties is thought to act agonistically, potentially elevating the quality of life in diverse diseases. The multifaceted nature of LDN effects across different therapeutic domains highlights its potential as a versatile and impactful intervention in various medical contexts (Bilgiç et al., 2020). In considering the mechanisms of LDN therapy mentioned above, this method is envisaged to have various applications in both cats and dogs. Due to its anti-viral, anti-bacterial, and immunomodulatory properties, LDN is considered for the treatment of infectious diseases such as feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), parvo, distemper, etc. Also, LDN therapy is considered to be effective in the treatment of infectious diseases characterized by vasculitis, such as FIP and ICH, due to its anti-inflammatory, immunomodulatory, anti-vasculitic, and antiviral pharmacotherapeutic properties.

Additionally, the opioid-stimulating effect of LDN therapy suggests its potential use in the treatment of various psychogenic disorders, including deep depression or obsessive-compulsive disorders. Furthermore, LDN's anti-inflammatory, immunomodulatory, and anticarcinogenic properties make it a potential candidate for both solid and parallel treatments of various oncogenic diseases. Moreover, considering the anti-inflammatory and immunomodulatory characteristics of LDN therapy, it is anticipated to be effective in the treatment of autoimmune diseases such as hypothyroidism, spondylosis, rheumatoid arthritis, autoimmune hemolytic anemia (AIHA), pemphigus, or lupus erythematosus. Furthermore, LDN therapy may find applications in the treatment of various pneumonias, atopic and allergic dermatitis, alopecia, as well as stubborn dermatomycosis, resistant demodicosis, resistant pyodermas, methicillin-resistant *Staphylococcus aureus* (MRSA), or various gastroenteritis diseases, given its anti-parasitic, anti-bacterial, and antifungal pharmacological characteristics.

Conclusion

In conclusion, it is proposed that integrating LDN therapy with conventional treatments could present a more cost-effective, secure, and efficient approach with minimal side effects for diseases characterized by treatment resistance, complexity, or chronicity. This synergistic approach may pave the way for enhanced therapeutic outcomes and improved patient experiences, emphasizing the potential of LDN as a valuable adjunct in comprehensive healthcare strategies. Further research and clinical studies are warranted to explore the full scope of LDN's therapeutic efficacy and its application in diverse medical contexts.

Article Information

Funding. This research received no external funds.

Conflict of Interest. The authors declare no conflict of interest.

Authors contribution. All authors contributed equally to the work.

References

Alcaro, A., Huber, R., Panksepp, J., 2007. Behavioral functions of the mesolimbic dopaminergic system: An affective neuroethological perspective. Brain Research Reviews 56, 283–321. 10.1016/j.brainresrev.2007.07.014.

Bahremand, A., Shafaroodi, H., Ghasemi, M., Nasrabady, S.E., Gholizadeh, S., Dehpour, A.R., 2008. The cannabinoid anticonvulsant effect on pentylenetetrazole-induced seizure is potentiated by ultra-low dose naltrexone in mice. Epilepsy Research 81, 44–51. 10.1016/j.eplepsyres.2008.04.010.

Bihari, B., 1995. Efficacy of low dose naltrexone as an immune stabilizing agent for the treatment of HIV/AIDS. AIDS Patient Care 9, 3. URL: https://www.ncbi.nlm.nih.gov/pubmed/11361353.

Bilgiç, B., Baysal Bakay, B., Ülgen Saka, S., Or, M.E., 2020. Therapeutic helminths in inflammatory bowel disease in cats and dogs. Turkiye Klinikleri Journal of Veterinary Sciences 11, 92–98. 10.5336/vetsci.2020-75067.

Brown, N., Panksepp, J., 2009. Low-dose naltrexone for disease prevention and quality of life. Medical Hypotheses 72, 333–337. 10.1016/j.mehy.2008.06.048.

Chang, R.C., Rota, C., Glover, R.E., Mason, R.P., Hong, J.S., 2000. A novel effect of an opioid receptor antagonist, Naloxone, on the production of reactive oxygen species by microglia: A study by electron paramagnetic resonance spectroscopy. Brain Research 854, 224–229. 10.1016/s0006-8993(99)02267-2.

Choubey, A., Dehury, B., Kumar, S., Medhi, B., Mondal, P., 2022. Naltrexone a potential therapeutic candidate for COVID-19. Journal of Biomolecular Structure & Dynamics 40, 963–970. 10.1080/07391102.2020.1820379.

Clauw, D.J., Arnold, L.M., McCarberg, B.H., 2011. The science of fibromyalgia. Mayo Clinic Proceedings 86, 907–911. 10.4065/mcp.2011.0206.

Cree, B.A.C., Kornyeyeva, E., Goodin, D.S., 2010. Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. Annals of Neurology 68, 145–150. 10.1002/ana.22006.

Donahue, R.N., McLaughlin, P.J., Zagon, I.S., 2011. The opioid growth factor (OGF) and low dose naltrexone (LDN) suppress human ovarian cancer progression in mice. Gynecologic Oncology 122, 382–388. 10.1016/j.ygyno.2011.04.009.

Ekelem, C., Juhasz, M., Khera, P., Mesinkovska, N.A., 2019. Utility of naltrexone treatment for chronic inflammatory dermatologic conditions: A systematic review. JAMA Dermatology 155, 229–236. 10.1001/jamadermatol.2018.4093.

Garayar Cantero, M., Canseco Martín, M., Aguado García, , Ruiz-Sánchez, D., Valtueña, J., Manchado López, P., 2019. Use of low-dose naltrexone in the treatment of severe Hailey–Hailey disease: One case report. Dermatologic Therapy 32. 10.1111/dth.12892.

Gharagozlou, P., Hashemi, E., DeLorey, T.M., Clark, J.D., Lameh, J., 2006. Pharmacological profiles of opioid ligands at kappa opioid receptors. BMC Pharmacology 6, 3. 10.1186/1471-2210-6-3.

Hammer, L.A., Zagon, I.S., McLaughlin, P.J., 2015. Low dose naltrexone treatment of established relapsing-remitting experimental autoimmune encephalomyelitis. Journal of Multiple Sclerosis 02. 10.4172/2376-0389.1000136.

Honar, H., Riazi, K., Homayoun, H., Sadeghipour, H., Rashidi, N., Ebrahimkhani, M.R., Mirazi, N., Dehpour, A.R., 2004. Ultra-low dose naltrexone potentiates the anticonvulsant effect of low dose morphine on clonic seizures. Neuroscience 129, 733–742. 10.1016/j.neuroscience.2004.08.029.

Hytrek, S.D., McLaughlin, P.J., Lang, C.M., Zagon, I.S., 1996. Inhibition of human colon cancer by intermittent opioid receptor blockade with naltrexone. Cancer Letters 101, 159–164. 10.1016/0304-3835(96)04119-5.

Ibrahim, O., Hogan, S.R., Vij, A., Fernandez, A.P., 2017. Low-dose naltrexone treatment of familial benign pemphigus (Hailey-Hailey disease). JAMA Dermatology 153, 1015–1017. 10.1001/jamadermatol.2017.2445.

Kelley, K.W., Bluthé, R.M., Dantzer, R., Zhou, J.H., Shen, W.H., Johnson, R.W., Broussard, S.R., 2003. Cytokine-induced sickness behavior. Brain, Behavior, and Immunity 17 Suppl 1, S112–8. 10.1016/s0889-1591(02)00077-6.

Kim, Y.H.J., West, K., 2019. Treating chronic pain with low dose naltrexone and ultralow dose naltrexone: A review paper. Journal of Pain Management and Therapy 3, 1–5.

Li, Z., You, Y., Griffin, N., Feng, J., Shan, F., 2018. Low-dose naltrexone (LDN): A promising treatment in immune-related diseases and cancer therapy. International Immunopharmacology 61, 178–184. 10.1016/j.intimp.2018.05.020.

Lie, M.R.K.L., van der Giessen, J., Fuhler, G.M., de Lima, A., Peppelenbosch, M.P., van der Ent, C., van der Woude, C.J., 2018. Low dose naltrexone for induction of remission in inflammatory bowel disease patients. Journal of Translational Medicine 16, 55. 10.1186/s12967-018-1427-5.

Liu, N., Ma, M., Qu, N., Wang, R., Chen, H., Hu, F., Gao, S., Shan, F., 2020. Low-dose naltrexone inhibits the epithelial-mesenchymal transition of cervical cancer cells *in-vitro* and effects indirectly on tumor-associated macrophages *in-vivo*. International Immunopharmacology 86, 106718. 10.1016/j.intimp.2020.106718.

Machado, M.C., da Costa-Neto, J.M., Portela, R.D., D'Assis, M.J.M.H., Martins-Filho, O.A., Barrouin-Melo, S.M., Borges, N.F., Silva, F.L., Estrela-Lima, A., 2018. The effect of naltrexone as a carboplatin chemotherapy-associated drug on the immune response, quality of life and survival of dogs with mammary carcinoma. Plos One 13, e0204830. 10.1371/journal.pone.0204830.

Mashiko, M., Akiyama, M., Tsuji-Abe, Y., Shimizu, H., 2006. Bacterial infection-induced generalized Hailey-Hailey disease successfully treated by etretinate. Clinical and Experimental Dermatology 31, 57–59. 10.1111/j.1365-2230.2005.01948.x.

McCubbin, J.A., Cheung, R., Montgomery, T.B., Bulbulian, R., Wilson, J.F., 1992. Aerobic fitness and opioidergic inhibition of cardiovascular stress reactivity. Psychophysiology 29, 687–697. 10.1111/j.1469-8986.1992.tb02047.x.

McCubbin, J.A., Wilson, J.F., Bruehl, S., Ibarra, P., Carlson, C.R., Norton, J.A., Colclough, G.W., 1996. Relaxation training and opioid inhibition of blood pressure response to stress. Journal of Consulting and Clinical Psychology 64, 593–601. 10.1037//0022-006x.64.3.593.

McCusker, R.H., Kelley, K.W., 2013. Immune-neural connections: how the immune system's response to infectious agents influences behavior. Journal of Experimental Biology 216, 84–98. 10.1242/jeb.073411.

McLaughlin, P.J., Stucki, J.K., Zagon, I.S., 2012. Modulation of the opioid growth factor ([met(5)]-enkephalin)-opioid growth factor receptor axis: Novel therapies for squamous cell carcinoma of the head and neck. Head & Neck 34, 513–519. 10.1002/hed.21759.

Metyas, S., Chen, C.L., Yeter, K., Solyman, J., Arkfeld, D.G., 2018. Low dose naltrexone in the treatment of fibromyalgia. Current Rheumatology Reviews 14, 177–180. 10.2174/1573397113666170321120329.

Mihály, A., Bencsik, K., Solymosi, T., 1990. Naltrexone potentiates 4-aminopyridine seizures in the rat. Journal of Neural Transmission 79, 59–67. 10.1007/{BF01251001}.

Miskoff, J.A., Chaudhri, M., 2018. Low dose naltrexone and lung cancer: A case report and discussion. Cureus 10, e2924. 10.7759/cureus.2924.

Montaser-Kouhsari, L., Payandemehr, B., Gholipour, T., Ziai, P., Nabavizadeh, P., Ghasemi, A., Bahremand, A., Ghasemi, M., Dehpour, A.R., 2011. A role for opioid system in the proconvulsant effects of sildenafil on the pentylenetetrazole-induced clonic seizure in mice. Seizure 20, 409–413. 10.1016/j.seizure.2011.01.014.

Parkitny, L., Younger, J., 2017. Reduced pro-inflammatory cytokines after eight weeks of low-dose naltrexone for fibromyalgia. Biomedicines 5. 10.3390/biomedicines5020016.

Plotnikoff, N.P., Miller, G.C., Nimeh, N., Faith, R.E., Murgo, A.J., Wybran, J., 1987. Enkephalins and T-cell enhancement in normal volunteers and cancer patients. Annals of the New York Academy of Sciences 496, 608–619. 10.1111/j.1749-6632.1987.tb35821.x.

Raknes, G., Simonsen, P., Småbrekke, L., 2018. The effect of low-dose naltrexone on medication in inflammatory bowel disease: A quasi experimental before-and-after prescription database study. Journal of Crohn's & Colitis 12, 677–686. 10.1093/ecco-jcc/jjy008.

Roshanpour, M., Ghasemi, M., Riazi, K., Rafiei-Tabatabaei, N., Ghahremani, M.H., Dehpour, A.R., 2009. Tolerance to the anticonvulsant effect of morphine in mice: Blockage by ultra-low dose naltrexone. Epilepsy Research 83, 261–264. 10.1016/j.eplepsyres.2008.10.011.

Seitz, S., Barvencik, F., Gebauer, M., Albers, J., Schulze, J., Streichert, T., Amling, M., Schinke, T., 2010. Preproenkephalin (Penk) is expressed in differentiated osteoblasts, and its deletion in Hyp mice partially rescues their bone mineralization defect. Calcified Tissue International 86, 282–293. 10.1007/s00223-010-9344-5.

Tanaka, K., Kondo, H., Hamamura, K., Togari, A., 2019. Systemic administration of low-dose naltrexone increases bone mass due to blockade of opioid growth factor receptor signaling in mice osteoblasts. Life Sciences 224, 232–240. 10.1016/j.lfs.2019.03.069.

Tejwani, G.A., Gudehithlu, K.P., Hanissian, S.H., Gienapp, I.E., Whitacre, C.C., Malarkey, W.B., 1991. Facilitation of dimethylbenz[a]anthracene-induced rat mammary tumorigenesis by restraint stress: role of beta-endorphin, prolactin and naltrexone. Carcinogenesis 12, 637–641. 10.1093/carcin/12.4.637.

Thakur, N.A., DeBoyace, S.D., Margulies, B.S., 2016. Antagonism of the Met5-enkephalin-opioid growth factor receptor-signaling axis promotes MSC to differentiate into osteoblasts. Journal of Orthopaedic Research 34, 1195–1205. 10.1002/jor.23135.

Toljan, K., Vrooman, B., 2018. Low-dose naltrexone (LDN)- Review of therapeutic utilization. Medical Sciences 6. 10.3390/medsci6040082.

Tseng, R.J., Padgett, D.A., Dhabhar, F.S., Engler, H., Sheridan, J.F., 2005. Stress-induced modulation of NK activity during influenza viral infection: Role of glucocorticoids and opioids. Brain, Behavior, and Immunity 19, 153–164. 10.1016/j.bbi.2004.07.001.

Weinstock, L.B., Myers, T.L., Shetty, A., 2017. Low-dose naltrexone for the treatment of sarcoidosis. Sarcoidosis, Vasculitis, and Diffuse Lung Diseases 34, 184–187. 10.36141/svdld.v34i2.5303.

Wybran, J., Schandené, L., Van Vooren, J.P., Vandermoten, G., Latinne, D., Sonnet, J., De Bruyère, M., Taelman, H., Plotnikoff, N.P., 1987. Immunologic properties of methionine-enkephalin, and therapeutic implications in AIDS, ARC, and cancer. Annals of the New York Academy of Sciences 496, 108–114. 10.1111/j.1749-6632.1987.tb35753.x.

Yi, Z., Guo, S., Hu, X., Wang, X., Zhang, X., Griffin, N., Shan, F., 2016. Functional modulation on macrophage by low dose naltrexone (LDN). International Immunopharmacology 39, 397–402. 10.1016/j.intimp.2016.08.015.

Younger, J., Parkitny, L., McLain, D., 2014. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Clinical Rheumatology 33, 451–459. 10.1007/s10067-014-2517-2.

Zagon, I.S., McLaughlin, P.J., 1983. Naltrexone modulates tumor response in mice with neuroblastoma. Science 221, 671–673. 10.1126/science.6867737.

Zagon, I.S., McLaughlin, P.J., 2018. Intermittent blockade of OGFr and treatment of autoimmune disorders. Experimental Biology and Medicine 243, 1323–1330. 10.1177/1535370218817746.

Zagon, I.S., Rahn, K.A., Turel, A.P., McLaughlin, P.J., 2009. Endogenous opioids regulate expression of experimental autoimmune encephalomyelitis: A new paradigm for the treatment of multiple sclerosis. Experimental Biology and Medicine 234, 1383–1392. 10.3181/0906-{RM}-189.