CLINICAL EVIDENCE ON THE USE OF LOW-DOSE NALTREXONE

IN PATIENTS WITH NUTRIENT AND VITAMIN IMBALANCE FOR THE TREATMENT OF AUTOIMMUNE DISEASES AND CANCER

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Preface

Dear Reader

Opioid receptors are groups of receptors (γ, κ-, δ- and ζ-opioid receptors) that are widely distributed in the nerve cells of the brain, the spinal cord and the digestive tract. Naltrexone is a type of general opioid receptor antagonist and has been used to treat chronic pain syndrome, autoimmune diseases, and cancer at a dose of 5 mg/day, which is often called Low Dose Naltrexone (LDN). This book analyzed the pharmacological functions of low-dose naltrexone, especially in anti-inflammation and immunoregulation, and its potential for immune-related diseases and cancer therapy. Low-dose naltrexone has immunomodulatory and therapeutic effects. Recent clinical studies have confirmed that low-dose naltrexone has played a significant role in the treatment and control of a variety of autoimmune diseases, for example, it prevents the recurrence and progression of multiple sclerosis, and low-dose naltrexone has been able to treat Crohn's disease. and mesentery panniculitis with little or no adverse reactions. Low-dose naltrexone regulates the production of inflammatory cytokines by influencing the level of endogenous opioid peptides in the body. Furthermore, low-dose naltrexone has an antitumor effect and can modulate the response of the neuroblastoma tumor, delaying the onset and reducing the incidence rate of tumors, significantly decreasing the volume and weight of the tumor and DNA synthesis in the tumor.

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SUMMARY

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INTRODUCTION

Opioid receptors are groups of receptors (γ-, κ-, δ-, and ζ-opioid receptors) that are widely distributed on nerve cells in the brain, spinal cord, and digestive tract. The main function of ζ receptors is related to growth and development. Therefore, the ζ receptor is also called the opioid growth factor receptor (OGFR) [1,2].

OGFR is also expressed on or in immune cells, indicating that OGFR agonists and antagonists may play immunoregulatory roles. Naltrexone is a general opioid receptor antagonist [1]. It has a strong blocking effect on OGFR [2]. It can be used for drug withdrawal and relapse prevention at the label dose of 50 mg/day.

Currently, naltrexone has been used to treat chronic pain syndrome and autoimmune diseases at a dose of 5 mg/day, commonly referred to as LDN [3]. Many studies have focused primarily on the traditional pharmacological effects of LDN on substance abuse and addiction disorders, with some success. LDN has been shown to alleviate symptoms of physical dependence [4-10], reduce withdrawal symptoms [11,12], and prevent relapse to drug addiction after detoxification [13,14], as well as provide supportive therapy for severe alcohol and tobacco dependence [15-17].

However, LDN's immunoregulatory activity should not be overlooked. In 1983, a paper in Science first reported [18] that LDN intermittently blocked OGFR and significantly inhibited neuroblastoma growth in tumor-bearing mice. Over the past three decades, the immunoregulatory actions of LDN have attracted increased attention, and increasing trials and experiments are still ongoing. Previous articles published by our research team indicate that LDN could modulate the function of immune cells, such as bone marrow dendritic cells (BMDCs) and macrophages [19,20].

Furthermore, naltrexone has a similar structure and mechanism of action to naloxone, but with greater oral bioavailability and a longer half-life [1,2]. It is used

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clinically in the treatment of alcohol and opioid dependence. Initially, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) approved its use for the treatment of alcoholism, in daily doses of 50 mg to 100 mg. Subsequently, the FDA also approved its use in combination with bupropion for the treatment of obesity, in doses of 8 mg/90 mg/day to 32 mg/360 mg/day, in individuals with at least one comorbidity related to excess weight [3-5]. In this context, naltrexone has been used at low doses (up to 5 mg/day) to treat chronic pain and autoimmune diseases. This therapy, known as low-dose naltrexone (LDN), is an off-label use practice, which involves the use of a drug for a condition other than that for which it was developed and approved [7]. However, this practice began in the 1980s (1985), when physician Bernard Bihari used LDN to treat immunosuppression in HIV patients. Since then, the off-label use of LDN has emerged as a promising pharmacotherapy for the treatment of autoimmune diseases, malignant tumors, inflammatory bowel diseases, and dermatological conditions, conditions often accompanied by chronic pain [9-16].

LDN has a paradoxical effect compared to usual doses, as it promotes analgesia and anti-inflammatory effects [11,17]. It is noteworthy that the pharmacological mechanism of low-dose naltrexone is not yet fully understood. It is essential to note that naltrexone is a potent opioid receptor antagonist, leading to a decrease in the proliferation of B and T cells, as well as macrophages. Blockade of the OGFR receptor by LDN promotes a compensatory increase in the production of endogenous opioids that activate kappa opioid receptors. Activation of kappa receptors induces an anti-inflammatory effect, decreasing interleukin 6 (IL-6) levels and neutrophil migration. Meanwhile, naltrexone acts selectively and potently on the δ receptor, which is associated with analgesia, cognitive functions, and physical dependence [10,19].

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At low doses (up to 5 mg/day), naltrexone also acts as a glial modulator [11,17,20], more specifically via antagonism of Toll-like receptor 4 (TLR4). This receptor is present in microglia, which make up approximately 70% of the central nervous system [21]. Its blockade by LDN inhibits cytokine release and Toll-like receptor 4 (TLR4) signaling from microglia, suppressing the release of pro-inflammatory cytokines, substance P, nitric oxide, glutamate, and decreasing the expression of chemokine receptors and adhesion molecules [11-14,17].

Furthermore, considering a potential indication for use, with its proposed few adverse effects, high adherence, low cost, and efficacy of the specific LDN dosage, this therapeutic approach may represent an option for patients unresponsive to conventional medications facing a multitude of chronic health conditions [11,13].

Therefore, this book analyzed the pharmacological functions of low-dose naltrexone, particularly in anti-inflammation and immunoregulation, and its potential for immune-related diseases and cancer therapy.

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CHAPTER I

Main Clinical Approaches and Outcomes

In 1987, Zagon and Melaughlin [22] discovered that the opioid growth factor-opioid growth factor receptor (OGF-OGFR) axis is composed of OGF and its specific receptor in the developing rat brain and a neuroblastoma cell line. Under physiological conditions, such as the developing cerebrum and cerebellum [23] and in the cornea [24], OGF-OGFR binding has been recorded by immunoelectron microscopy and confocal microscopy, playing an important role in supporting the growth and development of tissues and organs.

OGF and naltrexone can promote cell proliferation and wound healing. However, many physical diseases, including multiple sclerosis, Crohn's disease, diabetes, and cancer, as well as mental disorders, are linked to dysregulation of the OGF-OGFR axis. For example, the existence of the OGF-OGFR axis has been confirmed in many malignant tumor cells [25,26]. *In vitro* studies have shown that OGF significantly inhibits cell replication in squamous cell carcinoma of the head and neck (SCCHN) through a receptor-mediated mechanism [27]. As an OGFR antagonist, LDN has been found to regulate tumor cell proliferation through the OGF-OGFR axis in recent studies [2,28].

Evidence suggests that OGFR mediates the effect on cell growth and appears to be dose-dependent, but is related to the duration of action [29]. LDN inhibits tumor growth, while HDN accelerates tumor growth and somatic cell development. Continuous blockade by naltrexone can promote cell proliferation, while intermittent blockade by LDN can inhibit cell proliferation, which plays a therapeutic role in cancers and autoimmune diseases. During the window period of intermittent blockade caused by

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LDN, endogenous opioids and their receptors are compensatorily regulated. Therefore, receptor availability may be enhanced after intermittent antagonist blockade, and receptor availability was inhibited after continuous blockade. LDN treatment upregulates the expression of OGF and OGFR in SKov-3 cells [30], and LDN can reverse the altered homeostasis by exerting a partial inverse agonist effect.

Treatment with LDN or OGF fails to inhibit cell proliferation in OGFR-knockdown SKov-3 cells [31]. The effects of LDN on cell proliferation and DNA synthesis may be related to the cell cycle-dependent inhibitory proteins p16 and/or p21 [26, 30, 32]. Naltrexone, as a non-selective opioid receptor antagonist, can block the binding of endogenous opioids and opioid receptors. The mechanistic pathways of LDN remain unclear. Some studies indicate that LDN acts as an immunomodulatory agent, binding directly to the OGFR within immune cells [33,34].

Evidence suggests that naltrexone acts in the body through at least two receptors with different mechanisms. Microglia are considered resident macrophages of the CNS, which are activated by various triggers. In addition to antagonizing mu-opioid and other opioid receptors, naltrexone simultaneously blocked non-opioid receptors, such as TLR-4, on macrophages and microglia [35-37]. LDN is thought to exert its anti-inflammatory effects through non-opioid antagonist pathways.

By elevating endogenous opioids and inhibiting T and B lymphocyte proliferation, Zagon and colleagues found that the short-term effects of LDN could produce upregulation of opioid receptors. By increasing the production of endogenous opioids, LDN could inhibit the proliferation of B lymphocytes [38], T lymphocytes [39], and the corresponding immune responses. Bihari and colleagues [40] first used LDN to treat acquired.

LDN can increase β-endorphin levels *in vivo* and stabilize T cell numbers in HIV-

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infected individuals [41]. The results indicated that LDN could reduce opportunistic infections and increase the survival rate of AIDS patients. OGF and LDN had no significant effect on the number of mononuclear infiltrates in the central nervous system (CNS) in a model of established experimental autoimmune encephalomyelitis (EAE) [42], but both can limit the number of CD3+/CD4+ T cells in the lumbar spinal cord.

Another study reported that LDN reduced the proliferation rate of activated T cells in EAE mouse models [43]. The results of a study from our laboratory [20] revealed that LDN could improve the phagocytic capacity of macrophages by influencing the expression of surface markers and the secretion of several cytokines.

Also, LDN can increase the concentration of interleukin (IL)-2 and induce the secretion of tumor necrosis factor (TNF)-α [19]. At the same time, LDN could enhance the expression of MHC II, CD40, CD83, CD80, and CD86 molecules on the surface of dendritic cells. However, the mechanism of LDN is not fully understood. Because opioid receptors are widely distributed on many types of immune cells, research on the effects of different concentrations of naltrexone on immune cells is needed. Recent studies have shown that 4 to 10 mol/L of naltrexone has a suppressive effect on lymphocyte proliferation by blocking μ-opioid receptors and increasing the expression level of TLR-4 [44].

Besides, increasing studies have suggested that LDN may function not only through the OGF-OGFR axis [26,32,38,42,45], but also through immune-related signaling such as the Toll-like receptor 4 (TLR-4) pathway [36,44,46]. LDN may also regulate proteins by activating apoptotic pathways [47], alleviate glutamate neurotoxicity in nerve cells by inhibiting nitric oxide and inducing nitric oxide synthase (iNOS) activity [48], and reduce inflammation [49].

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CHAPTER II

LDN and Autoimmune Disease

In the 1980s, LDN was found to have immunomodulatory and therapeutic effects. Recent studies have confirmed that LDN plays a significant role in the treatment and control of a variety of autoimmune diseases. Ten years ago, LDN was first used spontaneously by multiple sclerosis (MS) patients worldwide, with substantial results before medical institutions conducted rigorous clinical trials [49].

LDN can not only prevent MS recurrence but also reduce disease progression [50]. A series of trials [51-54] in patients diagnosed with MS showed that LDN is well tolerated and does not cause adverse reactions, significantly improving the patient's quality of life and mental health. Similar results were obtained in animal models [55,56] and in MS patients [57]. These data suggested that LDN provides a non-toxic and inexpensive therapy and does not lead to further deterioration of disease symptoms [58].

A prospective study conducted by Zagon and colleagues [59] investigated for the first time the safety and efficacy of LDN in patients with Crohn's disease (CD). CD activity index scores significantly decreased, and quality of life assessments improved after LDN treatment. A number of studies [60,61] found that LDN was well tolerated and could reduce disease activity. Furthermore, LDN was able to treat CD and mesenteric panniculitis with little or no adverse reactions [62,63].

In this regard, LDN may regulate the production of inflammatory cytokines, influencing the level of endogenous opioid peptides in the body [64]. Treatment with sulfasalazine, LDN, or a combination significantly improved the measured parameters, including serum TNF-α and C-reactive protein levels, the disease activity index, and

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macroscopic and microscopic pathological scores, compared with those of the enteritis group.

Furthermore, Ploesser and colleagues [65] reviewed the therapeutic effects and side effects of LDN therapy in 206 patients with a variety of gastrointestinal disorders, including irritable bowel syndrome, chronic idiopathic constipation, or inflammatory bowel disease. LDN use had side effects, including neurological complaints such as anxiety, drowsiness, headache, dizziness, insomnia, muscle pain, mood swings, and concentration problems, and gastrointestinal reactions such as nausea, abdominal pain, diarrhea, and anorexia, which were tolerable in most cases. Intravenous administration of LDN reversed chronic opioid-induced constipation and transit changes [66], which indicated that LDN was beneficial for the treatment of opioid-induced bowel motility disorder in patients with chronic pain.

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CHAPTER III

LDN – Fibromyalgia, Type I Diabetes, Pruritus and AIDS

In crossover experiments with several female fibromyalgia patients, LDN was found to significantly relieve pain in more than half of the patients [67,68]. Some researchers [69] suggested that if fibromyalgia is an endocrine deficiency disease, LDN may be an effective medication for treating the condition. Subsequent studies found that LDN had a glial cell-modulating effect and thus improved the patient's fibromyalgia symptoms [35].

Furthermore, some researchers proposed using a dynamic prediction model to formulate the optimal dose curve for chronic fibromyalgia patients through engineering control to achieve personalized treatment of LDN patients, reduce costs, and improve efficacy [70]. LDN was found to improve fibromyalgia and prolong pain tolerance [71], which was thought to work through modulation of inflammatory mediators in plasma [72].

Although increasing numbers of fibromyalgia patients have used LDN off-label as a potentially useful drug, resulting in recovery of endorphin function to mitigate pain, further trials are needed to verify this observation before LDN can be recommended as first-line therapy [73,74].

Insulin-dependent diabetes mellitus (type I diabetes) is an autoimmune disease characterized by inflammation of the pancreatic islets and destruction of β cells by the immune system. Patients experience a complete lack of insulin and a variety of complications, such as dry eye and corneal disease. LDN could maintain a short period of tear secretion in dry eye mice and could restore a loss of corneal sensory sensitivity to

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normal [75], in addition to promoting the growth of corneal granulation tissue and angiogenesis [76,77]. LDN has been shown to accelerate the healing of damaged corneal lesions in mice [78]. Furthermore, LDN also affects diabetic neuropathy [79].

Regarding pruritus, systemic sclerosis is an autoimmune disease that causes skin, lung, and gastrointestinal fibrosis, vascular lesions, and pruritus as a common symptom. Treatment with LDN has achieved initial results for pruritus and pain in other inflammatory bowel diseases. Three case series reports [80] suggested that LDN was an effective, highly tolerated, and inexpensive treatment for pruritus symptoms in systemic sclerosis.

In terms of Acquired Immunodeficiency Syndrome (AIDS), LDN can induce the production of two endorphins (β-endorphin and enkephalin) *in vivo*. Serum β-endorphin levels in AIDS patients are at normal levels in people without AIDS. Taking 3 mg/day of LDN can increase endorphin levels without blocking them. Additional studies have shown a significant difference in the incidence of opportunistic infections with long-term use of LDN and a decrease in CD4+ T cell counts [40].

Some patients have taken LDN for up to 7 or 8 years without disease progression or CD4+ T cell decline [40]. LDN, as an immune-stabilizing agent for the treatment of AIDS, is effective. In Nigeria, LDN has been approved for the treatment of AIDS [20].

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CHAPTER IV

LDN and Cancer

LDN has an antitumor effect and can modulate the neuroblastoma tumor response, delaying tumor onset and reducing tumor incidence [18]. In ovarian tumor-bearing mice, LDN caused intermittent opioid receptor blockade and upregulated the expression of OGF and OGFR [32], inhibiting tumor progression in a cytotoxic manner by reducing DNA synthesis and angiogenesis. When tumor cells received intermittent LDN for a short period of time (4–6 h) followed immediately by LDN, there was an 18–20-h window during which tumor cell growth was significantly inhibited [28].

During this window, the number of endogenous OGF and intracellular OGFR in tumor cells was detected to increase, and the mechanism of the antitumor effect of intermittent naltrexone and the mechanism of the exogenous OGF antitumor effect were associated with the OGF-OGFR axis [1,81].

Tissue culture and nude mouse transplantation experiments with human ovarian cancer (SKOV-3) cells [31] confirmed that LDN significantly inhibited DNA synthesis in SKOV-3 cells, reduced tumor cell numbers, and inhibited angiogenesis. The OGFOGFR axis therapeutic approach not only inhibited the growth of breast cancer cell lines and their DNA synthesis but also alleviated the adverse effects of conventional chemotherapy by protecting non-tumor cells from death caused by paclitaxel [26].

In squamous cell carcinoma of the head and neck (SCCHN), OGF can reduce tumor size through the OGF-OGFR axis and delay tumor recurrence [82]. LDN can intermittently block the OGF-OGFR axis of OGF-OGFR, which plays a role in inhibiting tumor growth, extending the tumor incubation period by up to 1.6 times. LDN treatment significantly reduced tumor volume and weight, and reduced tumor DNA synthesis. As

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the number of weekly LDN administrations increased, the tumor growth-inhibiting effect improved [45]. Spleen weight and tumor volume in mice gradually decreased.

Berkson and colleagues reported that, after treatment with the combination of LDN and α-lipoic acid (ALA/N) [83,84], patients with metastatic and non-metastatic pancreatic cancer achieved long-term survival without adverse effects. Tumor marker levels decreased, and symptoms and physical examinations improved, with clinical manifestations disappearing. They also reported a patient with B-cell lymphoma whose signs and symptoms attenuated after use of LDN alone [85]. These cases not only highlighted the potential role of LDN therapy in cancer but also emphasized the good compliance with this therapeutic agent. Two sons, one with congenital hepatoblastoma and the other with polycystic kidney disease, predictive of congenital hepatoblastoma, had 10-year and 5-year disease-free survival rates after treatment with OGF/LDN. These two cases suggested that LDN could be a less toxic alternative to conventional chemotherapy when traditional chemotherapy for hepatoblastoma is impractical [86].

Clinical trials [87] followed 10 patients with chemoresistance in advanced metastatic cancer and 1 with hormone-refractory advanced prostate cancer. The combination of hydroxycitric acid (HCA) + α-lipoic acid (α-la) + LDN was found to be safe and effective for the treatment of refractory cancers and was able to modulate the metabolism of several cancer types. LDN reduces tumor growth by interfering with cell signaling and regulating immune system function.

LDN selectively affects genes involved in cell cycle regulation and immune regulation [88]. Furthermore, cells pretreated with LDN are more sensitive to the cytotoxic effects of common chemotherapeutic drugs. LDN not only works as a monotherapy for cancer but is also effective in combination with other agents such as aged garlic extract [89], vitamin D [90], and panobinostat [26] to inhibit tumor growth.

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Authors have previously used the combination of low-dose naltrexone and Menk (also called OGF) as an anticancer treatment that can inhibit DNA replication in pancreatic tumor cells, in addition to stimulating the activation and proliferation of immune cells, promoting the body's recovery [21]. LDN and OGF bind to opioid receptors on the surface of immune cells, stimulating the activation and proliferation of immune cells and improving immune function.

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CHAPTER V

LDN and Inflammatory Diseases

Autism is considered a hyperopioid-like disorder caused by endogenous disturbances of the opioid hormone system [71]. Furthermore, CNS demyelination can be observed in the brains of patients with autism, accompanied by increased NO levels *in vivo* [91]. LDN can reduce the *in vivo* activity of inducible nitric oxide synthase in patients and reduce inflammation.

Oral administration of 0.5 mg/kg of LDN daily improved clinical symptoms in children with autism, resulting in significantly increased plasma β-endorphin and normalized serotonin levels [92]. With its anti-inflammatory effect, LDN can be applied in the treatment of autism [48]. Furthermore, the use of LDN for complex post-traumatic dissociative disorder [93], short-term memory impairment caused by acute stress [94], self-biting behavior [95], and depressive disorder [96] has shown some benefit, and larger studies are needed for further confirmation. Furthermore, complex regional pain syndrome (CRPS) is a neuropathic pain condition characterized by glial activation and central sensitization of the central nervous system (CNS), which is associated with local or systemic inflammation. The mechanism by which LDN is used to treat chronic pain is not fully understood.

In addition to increasing endogenous opioid levels by blocking opioid receptors [97], LDN binds to receptors on the surface of immune-related cells (microglia) while reducing pro-inflammatory cytokine release and inflammation [98]. LDN can be used as an anti-inflammatory agent in the central nervous system and as a modulator of glial cells

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for the treatment of chronic pain syndromes. LDN can enhance the analgesic effect of acupuncture [99]. Acupuncture affects the opioid and cannabinoid systems, releasing endogenous receptor ligands, and LDN also acts on both systems and regulates opioid and cannabinoid receptors. Physical and pharmacological treatments have a synergistic effect, alleviating chronic pain syndrome.

Although no large randomized controlled trials have been conducted, the results of two case reports from 2013 [36] and 2016 [100] indicate that when conventional CRPS medications failed to suppress refractory CRPS symptoms, LDN was used in these patients by antagonizing the TLR-4 pathway, attenuating glial activation and central sensitization [37] and inducing the production of anti-inflammatory endorphins.

Another case of refractory chronic low back pain [101] treated with LDN received satisfactory treatment. Furthermore, a case was first reported in 2016 in which LDN was effective for an elderly man with a 30-year history of diabetes and a 7-year history of diabetes. He had neuropathic symptoms that were refractory to other available treatments [79].

In 2017, two case studies [102,103] simultaneously reported that patients with familial benign pemphigus (Hailey-Hailey disease) achieved satisfactory clinical symptom resolution with LDN treatment. LDN may be developed into a novel therapeutic agent for this disease. In addition to influencing the OGF-OGFR axis or the TLR signaling pathway, the possible mechanism may involve improving keratinocyte differentiation and wound healing.

The authors presented the immune-related pharmacological functions and potential mechanisms of LDN. LDN could modulate the body's immune system function to resist an abnormal immune response and has been widely accepted [104] by patients with MS, inflammatory bowel diseases (IBD) such as CD, and many types of malignant

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tumors. Successful reports of patients with fibromyalgia, ALS, and type 1 diabetes treated with LDN are increasing. Future studies and clinical work are needed to confirm the role of LDN in the treatment of immune-related diseases. LDN can be considered a novel immunomodulatory and tumor biotherapy agent, routinely recommended for people with autoimmune diseases and cancer. Meanwhile, researchers have also found that LDN can control appetite and the intake of high-sugar and high-fat foods [105-107], and that the effect and mechanism of LDN in controlling body weight are of great value. Furthermore, it is expected that LDN will have newer dosage forms, such as passive transdermal delivery [108], liquid nasal spray, and sustained-release preparations [109], shortly.

While LDN therapy offers many advantages, such as low cost, low adverse reactions, high safety, easy availability, and improved compliance, some issues remain to be noted. Because LDN is believed to play a role in regulating inflammatory mediators and upregulating endogenous opioid receptors, clinicians should be alert to patients who have previously used LDN chronically for pain management when using exogenous opioids to prevent hypersensitivity to exogenous opioids [110].

Furthermore, patient-funded research on LDN for the treatment of multiple sclerosis is good news for both clinicians and patients, but attention should be paid to issues such as program reviews and conflicts of interest [111]. Although LDN is still considered an off-label treatment in Brazil, the results demonstrate a growing increase in its dispensing in all Brazilian macroregions, particularly in the center-south region of the country. Among the 26 capitals and the Federal District analyzed, 15 showed increasing dispensing rates, while 12 showed stable dispensing [112-120].

It is worth noting the absence of decreasing LDN dispensing rates. The macroregional differences in LDN dispensing identified in this study may be related to both the higher prevalence of health conditions for which LDN is indicated and inequities

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in diagnosis and access to new treatment options [121-129], such as individualized LDN compounding, in Brazil's macroregions [130-139].

It should be noted that the prescription/dispensing/consumption of naltrexone in its use approved by National Health Surveillance Agency (ANVISA), as well as for the treatment of obesity, will not be discussed, as these are not part of the specific LDN dosage range. Focusing exclusively on the off-label use of LDN (up to 5 mg/day), few studies have evaluated the trend in the use of this pharmacotherapy [140,141]. A cohort study on drug use in Norway reported a sudden and unprecedented increase in the prescription of this drug following a television documentary on the alleged effects of LDN in a wide range of unapproved indications [140]. Regarding pharmacological use, the literature indicates its use in the treatment of autoimmune diseases, chronic pain, malignant tumors, inflammatory bowel diseases, and dermatological conditions, conditions that are generally accompanied by chronic pain [122-128].

However, it is known that for safe and effective clinical pharmacology of LDN, robust clinical trials are needed to establish evidence of the correct clinical indications and essential aspects, such as route of administration and dosage, making this process difficult and costly [129]. Thus, current reviews have highlighted the use of LDN pharmacotherapy in patients with fibromyalgia, inflammatory bowel diseases, and painrelated syndromes, although with limited evidence of efficacy and safety profile [125,129].

In this sense, a systematic review, including cross-sectional studies, identified the occurrence of chronic pain in Brazil's macroregions, revealing higher prevalence in the Central-West (56.25%), South (46.70%), and Southeast (42.2%) regions [141]. These data are consistent with the results of the present study, which demonstrate the greatest trends

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in LDN dispensing in these same macro-regions, with coefficients of 25.79 (Central-West), 19.76 (South), and 8.91 (Southeast).

Among the most studied conditions for LDN prescription are neuroinflammatory diseases such as fibromyalgia, multiple sclerosis, and Crohn's disease [125]. Regarding fibromyalgia, evidence points to LDN as an effective strategy [142,143], with a doubleblind, randomized, placebo-controlled study showing that fibromyalgia patients treated with LDN (4.5 mg/day) experienced improvements in pain and mood, without changes in fatigue or sleep quality [143]. However, according to the Brazilian Society for Pain Studies, this condition is difficult to diagnose, which limits the collection of accurate data on its magnitude in Brazil [144].

In the available literature, no nationwide studies investigating the prevalence of fibromyalgia were identified, and those that did exist were conducted in specific municipalities and regions. However, a study that used secondary data from a larger survey on the prevalence of chronic pain in Brazil revealed a 2% prevalence of fibromyalgia in the Brazilian population between 2015 and 2016, without demonstrating data stratified by macroregion [145].

Thus, what is known to date is that fibromyalgia affects populations of all ages, ethnic groups, and cultures, and that its pathophysiology is not fully understood, making it difficult to hypothesize a possible correlation between increased LDN and this chronic condition in Brazil. In this sense, LDN is an emerging pharmacological proposal also in multiple sclerosis, considering the immunomodulation of the OGF-OGFr axis [144].

This is a chronic condition that occurs more frequently in individuals located geographically farther from the equator, corresponding, in the case of Brazil, to the southernmost regions of the country. Therefore, it is plausible to infer that this condition is more prevalent in these regions, possibly leading to an increase in LDN prescriptions

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compared to the Northeast and North regions, the latter of which is intersected by the equator at the point where Macapá, the capital of the state of Amapá, is located [145].

A study involving this chronic condition indicates occurrence rates of 18, 15, and 27 per 100,000 inhabitants in cities in the Central-West, Southeast, and South regions, respectively [145]. Regarding the epidemiology of inflammatory bowel and dermatological diseases attributed to LDN pharmacotherapy [146-149], systematic literature reviews indicate that the incidence of Crohn's disease and ulcerative colitis has increased significantly in Brazil over the last two decades [147,148]. However, the available literature is still limited, and no data were found on the distribution of occurrence in the country's macro-regions.

The dermatology literature is also limited. However, a geographic survey using a telephone survey to estimate the prevalence of psoriasis in the country found higher prevalence in the South and Southeast regions, associated with the European ancestry characteristic of the colonization of these regions [150]. However, higher prevalence of chronic health conditions related to pharmacotherapy, as well as LDN dispensing, in the central-southern regions of the country could also be explained by socioeconomic indicators and access to diagnosis and treatment.

Covering an estimated territorial area of over 8.5 million square kilometers and subdivided into five macro-regions grouped by common characteristics, Brazil has regional inequalities, as evidenced by the Human Development Index (HDI), which encompasses three main indicators: education, health, and income. Data from the latest demographic census list the Southeast, Central-West, and South regions, with HDIs of 0.766, 0.757, and 0.754, as the most favored, in contrast to the North and Northeast regions, where HDIs are 0.667 and 0.663, respectively [151].

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Although the latest data for this indicator is for 2010, there is no expectation that these inequalities have changed, which may, from economic and social perspectives, contextualize the study's findings. In addition to the HDI, another indicator that could, to some extent, explain the differences in consumption trends in the North and Northeast regions, compared to the Central-South, is medical demography [151]. Data from the latest medical demographic survey indicate a marked disproportion of physicians in the North and Northeast regions compared to other regions of the country. It is plausible to assume that a smaller number of qualified prescribers leads to a smaller number of prescriptions. It is worth noting that this study describes the prescription/dispensing/consumption behavior of LDN and is not an association study with the aforementioned indicators. However, the hypothesis of a correlation between them cannot be ruled out [137].

Since LDN is an individualized and exclusively compounded preparation, it is also necessary to consider the number of compounding establishments and their distribution across Brazilian regions. By the end of 2020, Retail trade with compounding of formulas totaled 82.7% of establishments located in the central-south regions, compared to 17.3% in the North and Northeast regions [138,139].

Although it is not possible to state that all establishments are authorized to dispense naltrexone, the geographic distribution of compounding pharmacies in Brazil raises concerns that a greater number of establishments capable of compounding LDN may indicate a greater demand for the service [139]. It is important to emphasize that drug development involves a series of evaluations to ensure that the drug is safe and effective for its approved purpose; off-label practices do not guarantee that the drug will maintain these characteristics. Another consideration is the scarcity of data monitoring the longterm off-label use of medications [150].

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The literature attributes this use to a contribution to preventable adverse events and a potential lack of therapeutic gains compared to licensed use. In this sense, the emerging use of LDN dosages that still lack scientific evidence raises concerns, especially due to its action on the central nervous system, signaling, in addition to caution in its indication, the need to develop guidelines for prescribing practices that ensure patient safety, in line with the rational use of medications [152,153].

On the other hand, medication use is considered rational when it meets the patient's individual needs, within an appropriate timeframe, and at a lower aggregate cost [42]. Thus, off-label prescription of LDN may represent an option for individuals unresponsive to conventional medications, in the presence of serious or life-threatening conditions, and in rare diseases for which there are no regulated treatments. However, despite the possibility of outweighing benefits [153], the lack of scientific evidence on the topic supports the need for studies evaluating this type of prescription and medication use, with well-defined guidelines.

Although the SNGPC system does not address the reasons for LDN prescription, and the ecological design of the study does not allow for the inference of associations, the use of low-dose naltrexone highlights a public health concern that permeates the rational use of medications, since there is no data available on the long-term effects of LDN consumption [153]. Therefore, studies with primary data collection evaluating the potential effects of this specific dosage of naltrexone are necessary to elucidate the indications and determinants of low-dose naltrexone use. National coverage is needed, based on a publicly available system with a centralized, comprehensive, constantly updated, and still under-explored database that encompasses all Brazilian regions and allows for the addressing of a topic of great importance and concern: the off-label use of medications acting on the central nervous system [154].

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Due to the impossibility of using the defined daily dose (DDD) calculation, universally accepted in drug use studies, any calculation would imply a dosage other than 50 mg a strength of this study is the manual construction of successful strategies adopted in off-label data collection to support the robustness of low-dose naltrexone data, which could support future studies using SNGPC data [112].

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CHAPTER VI

Mechanism of Action of LDN Therapy

Naltrexone, administered in low doses, acts competitively as an antagonist to opioid receptors, which would normally bind to endorphins produced in the pituitary gland and exert their function on cells throughout the body. Thus, by occupying the receptors designated for endorphins, the body's production of these receptors increases in an attempt to capture more of this neurohormone [112].

The receptors tend to increase their sensitivity so they can more easily bind to endorphins. Thus, to compensate for the lack of endorphins, cells tend to increase the production of this endogenous opioid. This process results in better regulation of immunity and cell growth, as LDN is excreted within a few hours of administration (approximately 4 to 13 hours), resulting in the so-called rebound effect. This is the combination of a greater number of more sensitive receptors, with increased endorphin production, allowing for improved endorphin turnover by cells [155-159]. Unlike highdose naltrexone, which competes with endorphins by permanently binding to opioid receptors, LDN binds for a short period, which, in addition to conferring some of the effects of naltrexone, extends the half-life of endogenous opioids. When released, these opioid receptors activate κ, μ, and δ opioid receptors, which, when activated, induce an anti-inflammatory effect, decreasing IL-6 levels and neutrophil migration [160].

Low doses also activate the opioid growth factor receptor (OGFr), which regulates cell proliferation, and block non-opioid receptors, such as TLR4, which confer antiinflammatory and analgesic effects, as most are found in microglia (which constitute

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70% of the CNS). When blocked, they inhibit the release of pro-inflammatory cytokines, substance P, nitric oxide, excitatory amino acids, and tumor necrosis factor (TNF) [155-157].

According to the Electronic Medicines Compendium (EMC), not all patients who may benefit from LDN treatment should receive it. This is because some characteristics prevent some individuals from adhering to treatment. For example, LDN is contraindicated for patients with hypersensitivity to any of its pharmacological components, as well as for patients with severe renal failure, severe liver failure, acute hepatitis, and dependent patients currently using or co-using opioid-containing medications, as it can cause acute withdrawal syndrome. It is also contraindicated for use in combination with methadone for people with chronic pain [160,161]. Furthermore, the side effects of low-dose naltrexone are quite limited. Among the clinical trials conducted, the main adverse effects noted were difficulty sleeping (nightmares, insomnia, vivid dreams), anxiety or nervousness, cramps, asthenia, tachycardia, restlessness, joint, muscle, and abdominal pain, and headache [162].

The most promising research on the use of LDN is based on its role as an immune system regulator, as discoveries are made over the years about conditions in which LDN administration has proven effective in treating them. Therefore, physicians are permitted to prescribe it to their patients as an off-label use for conditions they consider appropriate for treatment. This immune system regulation provides relief to patients with central nervous system (CNS) disorders, autoimmune diseases, and others, as they benefit from increased endorphin levels [160-163].

Among the various contributions of LDN to the immune system that justify the treatments of different diseases, there is the reduction of inflammatory processes, decrease in oxidative stress, modulation of inflammatory cytokines, facilitation of wound

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repair and healing, release of neurotrophic factors in astroglia (regenerative process), restoration of CD4 lymphocyte levels, elevation of Natural Killer (NK) lymphocyte levels, increase in the amount of beta-endorphin, blockade of the Toll Like Receptor 4 (TLR4) receptor responsible for the reduction of inflammatory cytokines, alteration in the development and differentiation of the immune system [164]. In this sense, the benefits and successful uses of LDN have been reported in several clinical trials, case studies, and even in patient reports/testimonials for various pathologies, such as autoimmune diseases.

Adenoid carcinoma of the tongue, lymphomas, Complex Regional Pain Syndrome, refractory low back pain, fibromyalgia, systemic sclerosis pruritus, multiple sclerosis, pancreatic cancer, ankylosing spondylitis, Parkinson's disease, optic neuritis, multiple myeloma, psoriasis, Crohn's disease, ulcerative colitis, and irritable bowel syndrome, among others [162-164].

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CHAPTER VII

Clinical Approach to LDN

Several studies and therapeutic applications are being conducted using low-dose naltrexone, especially for those pathologies that cause inflammation and/or chronic pain. Recent results have shown a significant reduction in chronic pain in patients with fibromyalgia, as well as an improvement in their mood [165].

Small clinical trials have shown potential benefits of using LDN to improve the clinical and endoscopic response of patients with Crohn's disease. In autoimmune diseases, small studies have demonstrated the potential benefits of using low-dose naltrexone, through the reduction of some other medications used in rheumatoid arthritis (RA) and seropositive RA, as well as the use of LDN as a complement to pharmacotherapy or even as an alternative to conventional treatment [166-171].

Another study, cited by RAKNES (2018) [172], reports that a survey was conducted in an online community (CureTogether), in which patients with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis responded that of the 48 existing treatments, LDN was the most effective. It is also noteworthy that patients who continued to use the medication reduced the use of other essential medications in the treatment of these conditions, such as immunosuppressants, anti-inflammatories, and intestinal corticosteroids.

Clinical application of low-dose naltrexone studied was to aid in the treatment of obesity, which inhibits beta-endorphins, thus preventing the anorectic pathway and restricting the sensation of pleasure when eating. However, its use alone did not show significant effects. For these purposes, studies have shown that LDN should be combined

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with bupropion. These clinical trials demonstrated weight reduction in obese patients [173]. A study analyzing the application of LDN to assess the progression of ovarian cancer in humans showed an upregulation of the OGF-OGFr axes, in which the medication suppressed the development of this pathology. Continuous use of low doses of naltrexone inhibited tumor cell proliferation and angiogenesis, resulting in a decrease in the number of nodules and tumor weight/volume. Thus, it was observed that such application could significantly change the course of this cancer, as it could be an alternative treatment, since current chemotherapy agents are highly toxic to patients, unlike LDN, which has minimal side effects [168].

A case report showed that a patient used LDN as an adjunct to conventional treatment for Sjögren's syndrome, and she reported clinical improvements. Among the complaints observed were xerostomia, xerophthalmia, severe pain, asthenia, and myalgia. After using the medication for approximately two weeks, a reduction in pain, asthenia, and their inflammatory markers was observed. Therefore, at the end of the study, it was suggested that further research be conducted in this area, as the initial results suggested possible benefits [168].

Among current research, the use of LDN as a broad-spectrum antiviral stands out, demonstrating its potential therapeutic potential for patients infected with COVID-19. This is because the medication prevents SARS-CoV-2 viral proteins from binding to specific human cell receptors, thus reducing host cell infectivity [134].

Due to its low cost and low side effects, it has proven to be a potential complementary or even stand-alone treatment option, given that in conditions such as a pandemic, more immediate alternative therapies must be sought, as definitive treatments have not yet been established [174].

In this context, endogenous opioids inhibit the onset and progression of

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experimental autoimmune encephalomyelitis (EAE) within 30 days of treatment. A study examined the long-term effects of opioid growth factor (OGF, [Met(5)]-enkephalin) and a LDN on the expression of myelin oligodendrocyte glycoprotein (MOG)-induced EAE. C57BL/6 mice began receiving daily injections of 10 mg/kg OGF (MOG+OGF), 0.1 mg/kg naltrexone (MOG+LDN), or saline (MOG+Vehicle) at the time of EAE induction and continued for 60 days. In contrast to 100% of the MOG+Vehicle group with behavioral symptoms of EAE, 63% and 68% of MOG+OGF and MOG+LDN mice expressed disease. Both the severity and disease rates of EAE in OGF- and LDN-treated mice were markedly decreased in the MOG+Vehicle cohorts. At day 60, 6 and 3 times more animals in the MOG+OGF and MOG+LDN groups, respectively, had a remission compared to MOG+Vehicle mice. Neuropathological studies revealed i) astrocyte activation and neuronal damage as early as day 10 (before behavioral symptoms) in all MOG-injected groups, ii) a significant reduction of activated astrocytes in the MOG+OGF and MOG+LDN groups compared to MOG+Vehicle mice at day 30, and iii) no demyelination at day 60 in mice treated with OGF or LDN and which do not show disease symptoms. These results indicate that treatment with OGF or LDN had no deleterious long-term repercussions and did not exacerbate EAE, but i) halted disease progression, ii) reversed neurological deficits, and iii) prevented the onset of neurological dysfunction over a considerable period [175].

LDN is commonly used to manage pain and other symptoms, especially in patients with autoimmune diseases, but with limited evidence. One study analyzed the efficacy of LDN in reducing chronic pain in patients with osteoarthritis (OA) and inflammatory arthritis (IA), where existing approaches often fail to adequately control pain. In this randomized, double-blind, placebo-controlled, crossover clinical trial, each patient received 4.5 mg of LDN for 8 weeks and a placebo for 8 weeks. Outcome measures were

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reported by patients using validated questionnaires. The primary outcome was differences in pain interference during the LDN and placebo periods, using the Brief Pain Inventory (0-70 scale). Secondary outcomes included changes in mean pain intensity, fatigue, depression, and multiple domains of health-related quality of life. The painDETECT questionnaire classified pain as nociceptive, neuropathic, or mixed. Data were analyzed using mixed-effects models. Seventeen patients with OA and 6 with IA completed the pilot study. Most patients described their pain as nociceptive (n = 9) or mixed (n = 8) rather than neuropathic (n = 3). There was no difference in the change in pain interference after treatment with LDN (mean [SD], -23 [19.4]) versus placebo (mean [SD], -22 [19.2]; P = 0.90). No significant differences were observed in pain intensity, fatigue, depression, or health-related quality of life. In this small pilot study, the results do not support the efficacy of LDN in reducing nociceptive pain due to arthritis. Too few patients were included to rule out modest benefits or to assess inflammatory or neuropathic pain [176].

LDN is involved in the treatment of inflammatory and immune system diseases and may affect immune cells. Mesenchymal stem cells (MSCs) are known for their immunomodulatory effects and potential for treating certain types of autoimmune diseases. A study investigated the long-term effects of LDN on human adipose-derived mesenchymal stem cells (ASCs) to determine how their immunomodulatory properties are affected and how LDN-treated ASCs interact with other immune cells present in peripheral blood mononuclear cells (PBMCs). After 14 days of treatment, the ability of LDN-treated ASCs to modulate PBMC proliferation in a bidirectional mixed lymphocyte reaction (MLR) model was assessed using XTT. The relative expression of IDO, PD-L1, COX-2, HGF genes, and the level of cytokines IL-6 and TGF-β were measured in IFN-γ-stimulated and unstimulated ASCs (treated and untreated cells) using real-time PCR and ELISA, respectively. Unstimulated ASCs treated with 10-8 M Naltrexone (10-8 M

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NTX) showed higher levels of TGF-β compared to controls ($p<0.05$). Stimulated ASCs treated with 10-6 M NTX showed elevated expression of IDO, PD-L1 genes, and IL-6 level ($p<0.05$). The results demonstrated that various concentrations of LDN have different effects on the immunomodulatory properties of ASCs. A higher concentration of LDN induced a change in the immunomodulatory characteristics of ASCs [177]. Although the use of LDN in this context is still off-label, the studies currently reviewed show that this form of treatment should be explored to benefit patients with refractory fibromyalgia (FM) and refractory pruritus in cases of dermatomyositis and scleroderma [178-181]. In FM, it appears to not only relieve pain but also improve general symptoms, likely due to its anti-inflammatory properties at the CNS level, inhibiting the production of several cytokines locally [165].

In a systemic disease, an anti-inflammatory effect cannot be ruled out, as the work by Younger et al. [165] shows that the therapeutic response of LDN is proportional to the patient's baseline ESR, and the work by Parkitny et al. [161] demonstrated that the levels of several pro-inflammatory cytokines are decreased peripherally after its administration. Furthermore, animal studies have shown that naloxone suppresses the production of IL-6, TNF-alpha, monocyte chemoattractant protein-1, and superoxide in peripheral macrophages [173].

This is a fascinating aspect of LDN, since FM does not respond to common anti-inflammatories such as NSAIDs or glucocorticoids and cannot be considered an inflammatory disorder from a classical perspective [174,175]. Although some degree of inflammation may exist at the CNS level in microglial cells, the cytokine-induced sickness behavior that results from microglial inflammation overlaps with many FM symptoms [155].

Some possible explanations for the anti-inflammatory and immune regulatory

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properties of LDN may be that this drug could:

(1) regulate T lymphocyte subsets: CD4+/CD8+ T cells, Th1/Th2 cells, and Th17/Treg cells;

(2) decrease TNF-α, IL-6, IL-12 alpha, and IL-17 expression;

(3) increase the expression of IL-10, an anti-inflammatory cytokine;

(4) Regulate immune responses to rebuild the immune balance and alleviate inflammation [176].

Another point that needs to be explored is the action of LDN on pruritus, with beneficial aspects in dermatomyositis and scleroderma [169-172]. Pruritus is a symptom that can be associated with significant morbidity and loss of quality of life, which has limited treatment options.18 The pathophysiology of these symptoms is not fully understood, but it may involve amplified opioid-mediated neurotransmission in the brain [177].

Therefore, LDN may control pruritus through opioid-mediated actions or by decreasing inflammatory mediators. 18 Interestingly, in scleroderma, pruritus has been associated with gastrointestinal symptoms that also improved with LDN [171]. Finally, a controlled before-after study based on the Norwegian Prescription Database (NorPD) compared prescriptions for RA patients one year before and one year after starting LDN and found a reduction in the use of NSAIDs, opioids, and DMARDs such as methotrexate and anti-TNF-alpha [172].

In addition to its analgesic effect and anti-inflammatory properties, LDN may function as an immunomodulatory agent, binding directly to the opioid growth factor receptor (OGFr) on the immune system and tumor cells [178]. The advantages of this form of treatment are that LDN is affordable and has a low incidence of side effects, and is considered safe at low doses [170].

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Few comparisons between LDN and conventional treatments used in rheumatic diseases were available. The number of participants was low, and the follow-up was short. Future studies should include larger patient samples with longer follow-up; this would allow for a better understanding of the course of LDN in rheumatic conditions [171].

The strengths are:

(1) inclusion of studies with patients meeting international criteria for rheumatic diseases;

(2) Inclusion of all types of study designs on the use of LDN in rheumatic diseases.

The scientific rationale for LDN in cancer patients is compelling, both alone and in combination. Even so, the high cost of a clinical trial to justify registration, coupled with the fact that LDN is not protected, means that there have been no significant randomized studies to date. However, the numerous anecdotal responses justify further clinical studies [182].

Of particular note, a number of these reports of response to LDN have been reported, either as a single agent or more commonly in combination with another agent. Activity has been observed in lung adenocarcinoma, adenoid cystic carcinoma of the tongue (in combination with vitamin D3) [182], renal cell cancer (coupled with alpha lipoic acid (ALA)) [183], and pancreatic cancer (with ALA) [184,185].

The potential of the combination is even more intriguing from a clinical perspective. Lissoni et al. [186] reported four partial responses and one stable disease in nine patients with renal cell cancer treated with IL-2 and LDN. Significantly, however, these patients experienced disease progression when using IL-2 alone.

This small selection of examples highlights activity in a variety of cancer types,

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with no one type appearing to be more amenable to LDN treatment. This suggests a broad mechanism of action. However, a small number of processes appear to be impacted more frequently, suggesting that anticancer activity is achievable through modulation of immunity and activation of cellular signaling cascades that support cell proliferation and death [187].

Several articles have highlighted naltrexone's ability to suppress tumor growth [187]. These studies, both *in vitro* and in animals, have not established an explicit mechanism of action, but broadly, it may involve two areas. LDN may directly interfere with intracellular signaling pathways that result in the arrest of cell proliferation and the upregulation of proteins associated with the promotion of apoptosis.

LDN is also capable of modifying immune function, which may ultimately increase the cytotoxic activity of immunity. Complicating the narrative is the plethora of articles showing changes in cell signaling and immune modulation, similar to how LDN can improve cell growth performance [188,189].

Thus, considering the effects of LDN in isolation, it is difficult to establish the primary mechanism of action. What appears to be important, however, is that the outcome of naltrexone treatment is critically determined by the dose and timing of use. The effects of low and high doses of naltrexone on cancer gene expression profiles have been compared, showing that the profiles are completely different depending on the dose used [190].

Specifically, gene ontology analysis showed that low doses of naltrexone had a greater impact on genes associated with cell cycle control and immune responses, and that these effects were exclusive to this lower dose [190]. *In vivo* studies conducted in the 1980s highlighted the importance of dose in determining the overall effect, as rats treated with clinically conventional doses of 10 mg/kg induced continuous occupancy of opioid

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receptors, which was associated with increased tumor growth [191].

If doses were reduced to 1 or 0.1 mg/kg, receptor blockade was incomplete. Binding sites were therefore available to exogenous opioids and endogenous endorphins, resulting in the activation of their antitumor actions. In addition to dose, the naltrexone administration schedule was also crucial, with intermittent administration of low-dose naltrexone achieving the greatest antitumor response [192].

The reason for this remains unclear, but it has been suggested that the extent to which opioid receptors are antagonized may induce changes in the types and numbers of opioid receptors expressed. For example, a study in albino rats reported that LDN increased the expression of the opioid growth factor receptor (OGF-R), which was also associated with changes in key signaling pathways, some of which were directly linked to cell growth and death [192].

A compensatory increase in the expression of another type of receptor to compensate for the loss of another has been observed in other ligand: receptor relationships. Because this receptor is of a different type, its action would be different from that of the one it replaced, and ultimately, the ligand/receptor relationship at this level would change. Thus, it would be feasible that a particular ligand with a conventional set of actions elicited through a specific type of receptor could inadvertently activate other cellular processes through this compensatory change in receptor distribution [193].

Indeed, a 2016 study showed that a different set of genes can be activated, which differ fundamentally depending on the specific dose of naltrexone used and the level of receptor antagonism [190]. On a similar note, the effect of naltrexone may differ between individuals, as compensatory changes influencing intracellular signaling may differ.

Studies have also highlighted that LDN's anticancer action is associated in part with alterations in pERK and PI3-K signaling. Furthermore, as these cascades are

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inextricably linked to apoptosis and the mechanisms that regulate it, LDN is shown to alter the balance of pro- and anti-apoptotic proteins that regulate cell death. *In vitro* and *in vivo* models demonstrate how the pro-apoptotic proteins BAX and BAD can be enhanced by short-term exposure to LDN, which in turn can sensitize cancer cells to the cytotoxic effects of common chemotherapeutic agents [190].

Crucially, others have demonstrated similar apoptotic-enhancing effects through the involvement of parallel systems [193]. As discussed, there are good reasons to suggest that LDN has a potential role in anticancer therapeutic regimens. Indeed, its effects on intracellular signaling pathways that support oncogenesis are one means by which LDN could be used to halt aberrant cell growth. However, its effects on the immune system may also contribute to its anticancer action. Inflammation, particularly chronic inflammation, underlies a number of diseases [195].

Indeed, it has been described how chronic inflammation, arising as a result of chronic exposure to a non-infectious irritant, can support the development of cancer. Examples of this include long-term irritation and exposure to asbestos fibers leading to mesothelioma, chronic bronchitis, and emphysema as predisposing factors for lung cancer, and the association between chronic inflammatory bowel disease and colon cancer [194]. Medications that target specific elements of inflammation, such as cyclooxygenase (COX) inhibitors, have demonstrated activity and potential clinical benefit in the setting of cancer [195].

Similarly, there is considerable epidemiological evidence supporting the efficacy of the ubiquitous nonsteroidal anti-inflammatory drug aspirin as a preventative for cancer development [196]. LDN has potent anti-inflammatory qualities and appears to modulate and modify various elements of the immune system. *In vitro* investigations using models of individual immune components have described naltrexone's alteration of intracellular

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signaling and subsequent cytokine production by certain immune cells.

While immunity as a whole is more complex and cannot be simply considered a collection of individual cells working in isolation, it is interesting to note that in patients administered LDN, systemic levels of cytokines that drive humoral and cell-mediated inflammation, such as G-CSF, IL-4, IL-6, IL-10, IFN-alpha, and TNF-beta, were significantly reduced after eight weeks [197].

Furthermore, LDN has been reported to have a marked clinical effect on several clinical conditions whose common pathology is chronic inflammation, including Crohn's disease and psoriasis, as well as numerous autoimmune inflammatory diseases such as arthritis, SLE, and multiple sclerosis. Thus, the ability to dampen cytokines that drive key elements of immunity supports the growing view that LDN is immunomodulatory [198].

LDN is also believed to enhance the immune adaptation response by enhancing the maturation of professional antigen-presenting cells, as studies have demonstrated increased expression of maturation markers in dendritic cells (DCs) after culture with LDN. Most significantly, DCs were able to elicit responses in autologous T cells [198]. While it is unclear how naltrexone, which is fundamentally an opioid antagonist, might modify the levels of cytokines that influence immune function, what is clear is that opioids such as morphine have been known for some time to be immunosuppressive [199].

Opioid receptors have been found on immune cells [200], which play a role in regulating immunity [201]. Specifically, studies have indicated that opioid receptor antagonism can affect the activities of a number of immune cells. Indeed, the upregulation of OGF-R, discussed by Zagon's group, is closely associated with the ability to suppress colony formation, migration, and invasion in cervical cancer cells.

These effects were associated with reduced expression of P13-K, AKT, and

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mTOR *in vivo* and *in vitro*, which are central signaling cascades regulating immune function [202]. Similarly, LDN, by increasing OGF-R, can suppress the mesenchymal transition of cervical cancer cells, which has an indirect effect on tumor-associated macrophages with reduced IL-10 expression in mice [203].

The similarity between opioid receptors and other GPCRs suggests the possibility that other receptors are responsible for naltrexone's action. Therefore, disruption of signaling via receptors of the same superfamily or those that modify signaling through them is also believed to contribute to the mechanism by which naltrexone imparts its immunomodulatory effects [203].

One such receptor that has been described as part of this response is a distinct class of pattern recognition receptors called toll-like receptors. These play a central role in initiating immune responses, serving to recognize specific cellular and molecular patterns of cells damaged by pathogens. Activation of these TLRs, which exist in different classes and vary depending on the stimulus, ultimately leads to changes in the signaling cascades that orchestrate an immune response [204].

These responses, which are partially modulated by GPCRs, are an essential part of the innate immune system, providing a first line of defense against microbial invasion, and are present in all major cell types of the immune system. Activation of one TLR, of which there are ten, leads to the production of pro-inflammatory cytokines, often involving the production of NF-kappaB, a recognized target for autoimmune diseases and cancers [205].

NF-kappaB can increase cancer oncogene activity, an important mechanism by which it may enhance cancer progression. Importantly, naltrexone can disrupt immune responses by inhibiting cytokine production by peripheral blood mononuclear cells, antagonizing TLRs [205]. More specifically, we examined a panel of available

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inflammatory receptors and confirmed that naltrexone could completely block TLR-9 on immune cells, with some activity on TLR7 and TLR-8.

It was unable to detect activity on TLR-4 (which is on the cell membrane), an activity previously reported in glial cells but not in immune cells. TLRs 7, 8, and 9 are all intracellular receptors. An important relevance of TLR-9 inhibition is that it is associated with chronic inflammatory conditions such as Crohn's disease and psoriasis [205]. It is also accepted that chronic inflammation is a precursor to many types of tumors, whether caused by chronic infections (e.g., HBV, HCC, HPV, or EBV) or by chronic irritation (e.g., smoking or diet) [194]. Of greater relevance is that TLR-9 stimulation leads to the production of IL-6, which is the cytokine most closely associated with cancer progression.

Cancers are often associated with inflammation, which can lead to the suppression of cell-mediated immunity as well as angiogenesis. Therefore, LDN may exert a positive effect on cancer control by:

(i) inhibiting inflammation and NF-κB-activated oncogenic pathways through TLR antagonism;

(ii) upregulating immune responses through opioid modulation;

(iii) directly inhibiting cellular signaling pathways in tumor cells that support the oncogenic process.

In recent years, there has been a rapid increase in the number of reports highlighting a role for LDN in immunology and oncology. These reports offer tantalizing glimpses into the different ways the drug can be used. Although naltrexone was first employed as a means of supporting patients with addiction disorders, it was discovered, albeit serendipitously, that if used at lower dosage levels, it can also help with other indications [206].

However, the dose range was very narrow, typically between 3 and 5 mg per day

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for patients. Dosage did not appear to be dependent on body weight, but rather on daily dose, as patients using doses outside this range commonly reported a loss of activity, which was restored once the dose was readjusted to 3–5 mg/day [206]. Importantly, most of these conditions have a strong inflammatory component, and where the effect can be directly observed, such as in patients with psoriasis, the benefit observed at the commonly used dose of 4.5 mg disappears if increased to 6 mg. However, it is reassuring that clinical benefit and activity are rapidly restored when the dose is reduced to 4.5 mg.

The existence of real-world cases describing activity using LDN has led to a number of laboratory-based studies confirming an immunomodulatory element of LDN. The fact that so many cases have been recorded in which the addition of these agents improved and/or supported the actions of other treatments highlights the potential for using a drug that is both safe and cost-effective. Although there have been a number of randomized trials in some indications showing some benefit, none were large enough to lead to formal approval. The need for these larger trials would require industry support, and understandably, the risks associated with promoting a generic drug can be daunting [207].

It is expected that a greater understanding of the mechanisms of action will present IP and licensing opportunities that will attract the necessary support to deliver a therapeutic product. Genetic analysis of LDN action has identified mechanisms of action, which suggest new approaches to improving its activity. Cancer cells are often resistant to chemotherapy because they have dysfunctional apoptosis pathways [208].

Studies have shown that LDN can alter the balance of proteins that determine cell death in cancer cells. By directing apoptosis toward a pro-apoptotic environment, LDN has the ability to transform cancer cells into cytotoxic chemotherapy drugs. Studies have also shown that the sequence in which it is administered can influence overall activity,

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and the sensitization element of LDN activity is an area currently being explored in more depth. This has been highlighted and discussed previously, allowing for the development of new treatment regimens that can employ LDN more effectively. Ultimately, these combination approaches mean that LDN may be able to partner with a wide range of medications and potentially be employed as a universal adjuvant [204-206].

There are several conditions for which activity is difficult to explain based on LDN's ability to modulate opioid receptors. This led to a search for more receptors through which LDN could work, and it was discovered that naltrexone could inhibit IL-6 production through TLR-7, 8, and 9. This effect is also likely to explain the benefits of LDN in Crohn's disease and psoriasis, which both overexpress TLR-9. The fact that IL-6 is an important promoter of cancer progression and metastatic spread is yet another reason to explore LDN in a range of oncological conditions [208].

The initial findings showing that lower doses of naltrexone reduced the size of an experimentally implanted neuroblastoma tumor, while a higher dose of naltrexone produced exactly the opposite effects, opened the perspective of opioid-immune interactions and cancer growth, particularly about mechanisms involving low-dose naltrexone and opioid growth factor receptor signaling [205].

In contrast to other areas where LDN has been applied, pharmacological bench studies preceded clinical use for cancer treatment. A clinical group using LDN and a nutritional supplement containing α-lipoic acid reported some intriguing case reports [206,207]. The combination was administered to four patients with clinically and pathologically confirmed advanced pancreatic cancer who refused or were not suitable for conventional treatment.

Six months later, their cervical and inguinal lymph nodes, previously measured at a maximum size of 12.7 cm, had shrunk substantially, and subsequent positron emission

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tomography (PET) scans revealed no abnormalities. After one year of follow-up, at the time of publication, the patient was symptom-free. Low-dose naltrexone combined with opioid growth factor has been used as an adjuvant modality in the case of a pediatric patient born with severe hepatoblastoma. After surgical resection and only initial chemotherapy discontinued due to life-threatening toxicity, this non-toxic alternative treatment was shown to be effective, with the patient remaining disease-free at a 10-year follow-up examination [208].

In a prospective case series from a French group [208], a metabolic cancer treatment consisting of hydroxycitrate, α-lipoic acid, and LDN was administered to 11 patients undergoing multiple conventional cancer treatments with a life expectancy of between two and six months. Although some of the patients died relatively early due to advanced disease, or follow-up was too short at the time of publication to establish the long-term efficacy of the treatment, it was notable that the combination was well tolerated without side effects. In eight cases, disease progression was halted with symptom improvement, and the predicted six-month survival margin was exceeded. Recent *in vitro/in vivo* experimental studies expand the understanding of opioid growth factor signaling and point to the concomitant administration of met-enkephalin and LDN as a modality with translational value for clinical oncology practice. For example, cell preparation with LDN significantly increased the efficacy of standard chemotherapy drugs [209].

One study reported the case of a 50-year-old patient diagnosed with poorly differentiated non-small cell lung cancer stage T3N1MX who could not tolerate chemotherapy toxicity after undergoing mass resection. He suffered severe complications following surgery and radiotherapy; he then received LDN as adjunctive therapy for recovery and had high-quality rehabilitation with over four years of complete remission

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(CR) [210].

Clinical data showed that LDN as a supplemental regimen significantly increased patient survival at one year compared with radiotherapy alone ($p < 0.05$) [211]. Four patients with advanced pancreatic cancer with liver metastases who were not eligible for surgery or chemotherapy received alpha-lipoic acid (ALA) and LDN (ALA/N) for treatment [212,213]. ALA is an antioxidant that inhibits the NF-κB-induced inflammatory response, which is associated with malignant events. After ALA/N treatment, one patient achieved CR for 78 months, one had comparatively stable disease (SD) for over 3 years, one achieved CR for half a year, and one was symptom-free with improved physical condition [213].

The co-administration protocol was initiated as palliative treatment to improve the quality of life of people with advanced or terminal cancer. Furthermore, a patient with stage IV lung metastases who failed targeted treatment had mild complications; however, he subjectively reported rehabilitation with increased energy after ALA/N for one week and achieved CR for 11 months. He remained in good health for seven years after the ALA/N regimen [214].

Similarly, another report described a patient diagnosed with follicular lymphoma. The largest cervical node measured approximately 7.62 cm, and the left inguinal region approximately 12.7 cm. With the ALA/LDN approach, the sensations of pain and tension disappeared a week later. Furthermore, the nodules almost completely disappeared six months later, and she was symptom-free at one-year follow-up [215].

Furthermore, an infant and a 20-month-old child diagnosed with hepatoblastoma received OGF/LDN. The child suffered significant complications after neoadjuvant chemotherapy, and the parents refused further chemotherapy. After surgical resection and treatment with OGF/LDN, she achieved CR for approximately 10 years. Similarly, the

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child achieved CR for more than five years [216]. A multicenter study investigated 11 solid tumor patients treated with a combination of ALA, hydroxycitrate, and LDN. Primary data showed that six developed DS, two had regression, one had slow progression, and two died, all with indistinguishable toxicity [217].

ALA and hydroxycitrate, two dominant enzymes in glycometabolism, are used in combination as metabolic therapies in cancer [218,219]. Tumor propagation relies on aerobic glycolysis to perform DNA/RNA synthesis and the synthesis of associated compounds. Lipoic acid activates pyruvate dehydrogenase to convert pyruvate to lactate in the mitochondrial Krebs cycle, while hydroxycitrate decreases fat synthesis by inhibiting ATP citrate lyase and acetyl-CoA conversion.

The lack of tumor specificity limits the clinical utility of single-agent targeted metabolic agents; therefore, at least two or more metabolic therapeutic drugs are most commonly used in neoplasms to amplify antitumor efficacy. LDN binds to sirtuin-1 and reduces NFκB p65 transduction to eliminate insulin resistance; furthermore, the Sirtuin-1/LKB-1/AMPK pathway and downstream acetyl-CoA carboxylase are implicated in fat synthesis [220,221].

The synergistic effect of combining ALA, hydroxycitrate, and LDN consolidates tumor inhibition through a metabolic approach. Khan reported successful treatment of a patient with adenoid cystic carcinoma who experienced significant adverse effects with conventional methods and feared a loss of quality of life. He underwent combined LDN and vitamin D therapy and achieved CR for over 47 months without any complications [222].

Also, vitamin D protects normal cells by preventing caspase activation and can be used as a prognostic index in tumor patients. Vitamin D reduces chemical-induced pyroptosis and secondary inflammation, including gasdermin family protein E, IL-1β,

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caspase-1, and caspase-3, and restores Ca2+, attenuating nausea without weakening chemolethality [223,224].

In this sense, vitamin D may aid LDN in maintaining homeostasis and enhancing its antitumor effect. Furthermore, two hepatoblastoma patients administered OGF/LDN instead of chemotherapy after surgery achieved comparable OS, avoiding chemotherapy-induced side effects [216]. This is strong evidence consistent with preclinical trials confirming the tumor-inhibiting properties of LDN and opioids.

In preclinical trials, LDN demonstrated inhibitory efficacy in the progression of carcinogenesis and development [225]. Thus, LDN can be used as a prophylactic or therapeutic modality. However, reports of clinical administration are limited. Most patients who received LDN as adjuvant or palliative therapy experienced numerous treatments until the terminal phase of the disease, with intolerance to the side effects of traditional medicine. These patients were cachectic and painful, suffering both physically and emotionally.

Finally, in patients with advanced cancer with metastasis, LDN was shown to inhibit tumor growth (SD to CR), increase analgesic sensitivity, achieve recovery, and prolong survival time. LDN is a safe modality in infants and children. Clinical studies of LDN in cancer are limited to a few phase II trials [225].

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FINAL CONSIDERATIONS

Low-dose naltrexone has immunomodulatory and therapeutic effects. Recent clinical studies have confirmed that low-dose naltrexone plays a significant role in the treatment and control of a variety of autoimmune diseases. For example, it prevents the recurrence and progression of multiple sclerosis, and low-dose naltrexone has been shown to treat Crohn's disease and mesenteric panniculitis with few or no adverse reactions. Low-dose naltrexone regulates the production of inflammatory cytokines, influencing the level of endogenous opioid peptides in the body. Furthermore, low-dose naltrexone has an antitumor effect and can modulate the neuroblastoma tumor response, delaying the onset and reducing the incidence rate of tumors, significantly decreasing tumor volume and weight, and DNA synthesis in the tumor.

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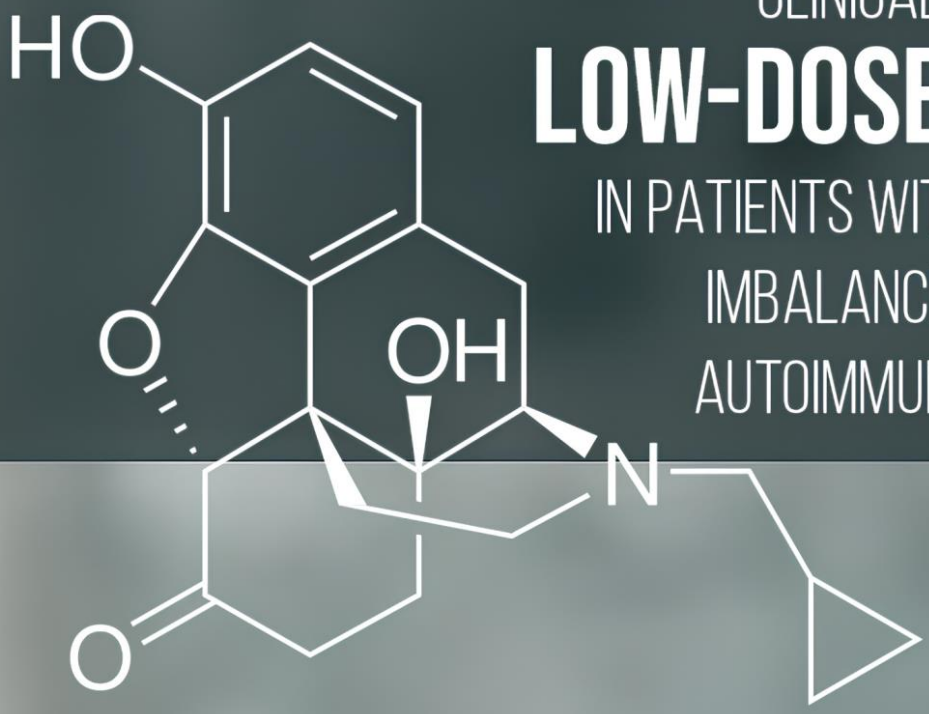
CLINICAL EVIDENCE ON THE USE OF LOW-DOSE NALTREXONE IN PATIENTS WITH NUTRIENT AND VITAMIN IMBALANCE FOR THE TREATMENT OF AUTOIMMUNE DISEASES AND CANCER



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