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REVIEW ARTICLE

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Major clinical evidence on the use of low-dose naltrexone in the treatment of cancer: a systematic review

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Abstract

Introduction: Opioid receptors are groups of receptors (γ-, κ-, δ-, and ζ-opioid receptors) that are widely distributed in nerve cells in the brain, spinal cord, and digestive tract. Naltrexone is a type of general opioid receptor antagonist. It has been used to treat chronic pain syndrome, autoimmune diseases, and cancer at a dose of 5 mg/day, which is generally called low-dose naltrexone (LDN). **Objective:** It was to analyze the pharmacological functions of low-dose naltrexone, especially in anti-inflammation and immunoregulation, and its therapeutic potential against cancer. **Methods:** The research and development of the work were carried out from June to July 2024 in the Scopus, PubMed, Science Direct, and Scielo databases, using scientific articles from the last 15 years, following the PRISMA rules. The quality of the studies was based on the GRADE and AMSTAR2 instruments, and the risk of bias was assessed using the Cochrane instrument (Funnel Plot). **Results and Conclusion:** Fifteen studies were included in the systematic review out of 30. Most studies showed homogeneity in their results, with X^2=94.5%>50%. Low-dose naltrexone has immunomodulatory and therapeutic effects. 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 cancer.

Keywords: Cancer. Immunity. Naltrexone. Low Dose.

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 opioid growth factor receptor (OGFR) **[1,2]**.

OGFR is also expressed on or in immune cells, which indicates that OGFR agonists and antagonists may play immunoregulatory roles. Naltrexone is a kind of 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.

In addition, naltrexone has been used to treat chronic pain syndrome and autoimmune diseases at a dose of 5 mg/day, which is commonly referred to as LDN **[3]**. Many studies have mainly focused on the traditional pharmacological effects of LDN on substance abuse and addiction disorder, which have achieved some success. LDN could alleviate the symptoms of physical dependence **[4-7]**, reduce withdrawal symptoms **[6,7]**, and prevent relapse of drug addiction after detoxification **[8,9]**, as well as provide supportive therapy for heavy alcohol and tobacco dependence **[10-12]**.

The immunoregulatory activity of LDN should not be overlooked. In 1983, a paper in Science first reported **[13]** that LDN intermittently blocked OGFR and significantly inhibited the growth of neuroblastoma in tumor-bearing mice. In the past three decades, the immunoregulatory actions of LDN have attracted more attention, and increasing trials and experiments are still ongoing. Previous papers published by our research team indicate that LDN could modulate the function of immune cells, such as bone marrow dendritic cells (BMDCs) and macrophages **[14,15]**.

Furthermore, naltrexone has a structure and mechanism of action similar to naloxone, but with greater oral bioavailability and a longer half-life **[1,2]**. It is used 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 in 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 patients with HIV. 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 diseases, conditions often accompanied by chronic pain **[9-11]**.

LDN has a paradoxical effect concerning usual doses, as it promotes analgesia and anti-inflammatory effects **[11,12]**. It is interesting to note that the pharmacological mechanism of low-dose naltrexone has not yet been fully elucidated. It is important to emphasize that naltrexone is a strong antagonist of OGFr, inducing a decrease in B and T cell proliferation of immune cells and 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 levels of interleukin 6 (IL-6) and neutrophil migration. On the δ receptor, naltrexone acts selectively and potently. This type of receptor is related to analgesia, cognitive functions, and physical dependence **[10,14]**. At low doses (up to 5 mg/day), naltrexone also acts as a glial modulator **[11,12,15]**, 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 **[16]**. Its blockade by LDN inhibits the release of cytokines and Toll-like macrophage (TRL4) signaling from microglia, suppressing the release of pro-inflammatory cytokines, substance P, nitric oxide, glutamate, and decreasing the expression of the chemokine receptor and adhesion molecule **[6-9,12]**.

Also, considering a possible indication for use, with a proposal for few adverse effects, high adherence, low cost, and efficacy of the specific dosage of LDN, this therapeutic approach may represent an option for patients who are unresponsive to conventional drugs in the face of a multitude of chronic health conditions **[6,8]**.

Therefore, the present systematic review study analyzed the pharmacological functions of low-dose naltrexone, especially in anti-inflammation and immunoregulation, and its potential for cancer therapy.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 06/18/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 06/18/2024. Table 1 shows the main variables of this

study that were addressed, according to the designation of the PICOS (Patients; Intervention; Control; Outcomes, and Study Design) literary search strategy.

Table 1. Literary search strategy - PICOS.

PATIENTS	Cancer patients
INTERVENTIONS	Low-dose naltrexone therapy
CONTROL	Conventional treatments
OUTCOMES	Cancer control and even elimination
TYPES OF STUDIES	Randomized, prospective and retrospective observational clinical trials.

Source: Own Authorship.

Instruments for Study Eligibility

Studies that rigorously presented the results of the search process in Table 1 and that presented scientific quality according to the GRADE classification, and that did not present a significant risk of bias, that is, that could compromise the safety of the results, according to the Cochrane instrument, were selected.

Data Sources, Search Strategy, and Study Time

The search strategies for this study were based on the health science descriptors of the DeCS platform (available at: https://decs.bvsalud.org/) with the keywords (MeSH Terms): "Cancer. Immunity. Naltrexone. Low Dose". Search filters designated as clinical studies were used. The research and development of the work were carried out from June to July 2024 in the Scopus, PubMed, OVID, Science Direct, LILACS, and EBSCO databases, using previous articles to the present. In addition, a combination of keywords with the Boolean operators "OR", AND, and "NOT" operator was used to target the scientific articles of interest. The title and abstracts were examined in all conditions. Table 2 presents an example of the search structure in PubMed. The same search strategy was used in the other databases.

Table 2. For example, in the search structure in PubMed, the same search strategy was used in the other databases.

PubMed	*Cancer* ***OR*** *Naltrexone* ***OR*** *Immunity*
	AND
PubMed	*Naltrexone* ***OR*** *Treatments* ***OR*** *Microglia*
	AND
PubMed	*Prospective Clinical studies* ***OR*** *Retrospective Clinical studies* ***OR*** *Randomized clinical trials* ***OR*** *Clinical case series* ***OR*** *Review studies*
	NOT
PubMed	*Editorials* ***OR*** *Short communications* ***OR*** *Case Report*

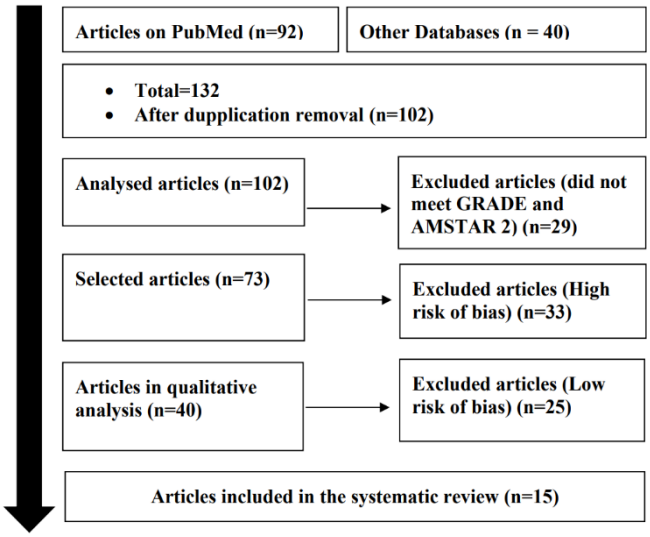
Source: Own Authorship.

Results and Discussion

Summary of Findings

As a corollary of the literature search system, a total of 132 articles were found that were submitted to eligibility analysis and, subsequently, 15 of the 30 final studies were selected to compose the results of this systematic review. The listed studies presented medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=94.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 33 studies with a high risk of bias and 29 studies that did not meet GRADE and AMSTAR-2.

Figure 1. Flowchart showing the article selection process.

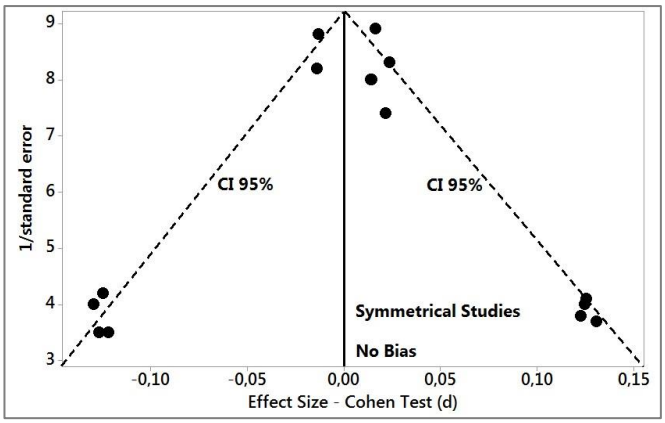


Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample size (lower precision) that are shown at the bottom of the graph and in studies with large sample size that are shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample size that are shown at the bottom of the graph. High confidence

and high recommendation studies are shown above the graph (n=15 studies).



Source: Own authorship.

Main Clinical Findings – Low-Dose Naltrexone and Cancer

LDN has an antitumor effect and can modulate the neuroblastoma tumor response, delaying the onset and reducing the incidence rate of tumors **[13]**. In ovarian tumor-bearing mice, LDN caused intermittent opioid receptor blockade and upregulated the expression of OGF and OGFR **[17]**, inhibiting tumor progression in a cytotoxic manner by reducing DNA synthesis and angiogenesis. When tumor cells received intermittent LDN for a short period (4–6 h) followed immediately by LDN, there was a window of 18–20 h during which tumor cell growth was significantly inhibited **[18]**.

During this window, the number of endogenous OGF and intracellular OGFR in tumor cells was found to increase, and the mechanism of the antitumor effect of intermittent naltrexone and the mechanism of exogenous OGF antitumor effect was associated with the OGF–OGFR axis **[1,19]**. Tissue culture and nude mouse transplantation experiments with human ovarian cancer cells (SKOV-3) **[20]**. Both confirmed that LDN could significantly inhibit the DNA synthesis of SKOV-3 cells, significantly reduce the number of tumor cells, and inhibit angiogenesis.

The therapeutic approach of the OGF-OGFR axis not only inhibits the growth of breast cancer cell lines and their DNA synthesis but also alleviates the adverse effects of conventional chemotherapy by protecting non-tumor cells from death caused by paclitaxel **[21]**. In squamous cell carcinoma of the head and neck (SCCHN), OGF can reduce tumor size through the OGF-OGFR axis and delay tumor appearance **[22]**. 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 the number of weekly LDN administrations increased, the effect of inhibiting tumor growth was enhanced **[23]**.

The mouse spleen weight and tumor volume gradually decreased. Berkson and colleagues reported that after treatment with the combination of LDN and α-lipoic acid (ALA/N), patients with metastatic or nonmetastatic pancreatic cancer achieved long-term survival without adverse effects. The levels of tumor markers decreased, the symptoms and physical examinations improved, and the clinical manifestations disappeared. They also found a patient with B-cell lymphoma whose signs and symptoms attenuated after the use of LDN alone **[24]**. These cases not only led to the potential role of LDN therapy in cancer but also emphasized good compliance with this therapeutic agent. Two sons, one with congenital hepatoblastoma and the other with polycystic kidney disease, predictive 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 **[25]**.

Clinical trials **[26]** of 10 patients with chemoresistance in advanced metastatic prostate cancer and 1 with hormone-refractory advanced prostate cancer were followed. The use of hydroxy citric 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 by regulating the function of the immune system.

LDN selectively affects genes involved in cell cycle regulation and immune regulation **[27]**. 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 **[28]**, vitamin D **[29]**, and panobinostat **[30]** to inhibit tumor growth. Authors have previously used the combination of low-dose naltrexone and Menk (also called OGF) as an anticancer treatment that can inhibit DNA replication of pancreatic tumor cells, as well as stimulate the activation and proliferation of immune cells and promote the body's recovery. LDN and OGF bind to opioid receptors on the surface of the body's immune cells, stimulating the activation and proliferation of immune cells and improving immune function **[16]**.

Conclusion

It was concluded that low-dose naltrexone has immunomodulatory and therapeutic effects. Low-dose naltrexone regulates the production of inflammatory

cytokines, influencing the level of endogenous opioid peptides in the body. In addition, 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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Conflict of Interest

The authors declare no conflict of interest.

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