ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 12 | December - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

LOW-DOSE NALTREXONE: A REVIEW OF ITS PLEIOTROPIC PHARMACOLOGICAL ACTIONS AND THERAPEUTIC POTENTIAL.

Pharmaceutical Science

Dr. Boda Srikanth Nayak* MD, Senior Resident, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri. *Corresponding Author

Dr. Madhavrao Chavan MD, Additional Professor, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri.

Dr. Gaurav Manikrao Rangari MD, Associate Professor, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri.

Dr. Arup Kumar Misra MD, DNB, Associate Professor, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri.

Dr. Katiboina Srinivasa Rao Assistant Professor, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri.

ABSTRACT

Naltrexone, an opioid receptor antagonist traditionally prescribed for opioid and alcohol dependence, has recently gained attention for its pleiotropic pharmacological properties when administered at substantially lower doses. The concept of low-dose naltrexone (LDN), typically ranging from 1 to 5mg per day, has evolved from its conventional high-dose use, demonstrating unique immunomodulatory, anti-inflammatory, and neuroprotective effects. This review synthesizes evidence from experimental and clinical studies published in PubMed-indexed journals, highlighting the molecular mechanisms and therapeutic implications of LDN across diverse disease spectra. Data were obtained through an extensive literature search from 2000 to 2025, focusing on mechanistic and clinical evaluations of LDN in autoimmune, inflammatory, neurodegenerative, and pain-related disorders. Findings reveal that transient opioid receptor blockade by LDN enhances endogenous endorphin production and attenuates Toll-like receptor-4-mediated microglial activation, resulting in reduced neuroinflammation and cytokine dysregulation. Clinical studies indicate symptomatic improvement in conditions such as multiple sclerosis, rheumatoid arthritis, fibromyalgia, Crohn's disease, psoriasis, and certain psychiatric and malignant disorders. Furthermore, emerging reports suggest potential benefit in post-viral syndromes, including long-COVID. Adverse effects are mild and self-limiting, predominantly involving sleep disturbances or vivid dreams. Collectively, low-dose naltrexone represents an inexpensive and well-tolerated adjunctive therapy with multifaceted biological actions. Despite promising preliminary outcomes, the current evidence remains limited by small sample sizes and heterogeneous methodologies. Large-scale randomized controlled trials are essential to validate these findings, optimize dosing regimens, and establish evidence-based clinical recommendations for its broader therapeutic use.

KEYWORDS

Low-dose Naltrexone, Pleiotropic effects, Immunomodulation, Neuroinflammation, Autoimmune diseases, TLR-4 antagonism, Endorphin up-regulation.

INTRODUCTION

Historical Background and Evolution of Naltrexone

Naltrexone, a long-acting competitive antagonist of μ-, κ-, and δ-opioid receptors, was developed in the early 1960s as a derivative of oxymorphone and was approved by the U.S. Food and Drug Administration (FDA) in 1984 for the management of opioid and alcohol dependence.[1,2] It functions primarily by blocking the euphoric and reinforcing effects of exogenous opioids, thereby reducing cravings and relapse rates.[3] The standard oral dose of 50 mg/day effectively maintains continuous opioid receptor blockade. However, during the late 1980s, experimental observations revealed that significantly lower doses of naltrexone (1 to 5 mg/day) produced unexpected beneficial effects on pain, fatigue, and immune dysregulation-effects not explained by classical opioid antagonism.[4]This marked the beginning of the Low-Dose Naltrexone (LDN) concept, pioneered by Dr. Bernard Bihari, which has since evolved into a potential therapeutic paradigm across diverse pathological conditions.[5]

Concept and Pharmacological Rationale of Low-Dose Naltrexone

Unlike its conventional high-dose application, LDN exhibits a biphasic pharmacodynamic profile. At low doses, naltrexone induces a transient blockade of opioid receptors lasting 3–4 hours, leading to a compensatory upregulation of endogenous opioids—β-endorphins, metenkephalins, and opioid growth factor (OGF)—once receptor antagonism subsides.[6,7] This "rebound" phenomenon enhances endorphinergic signaling, promoting immunoregulation, mood stabilization, and analgesia.[8]

In addition to opioid receptor modulation, LDN exerts non-opioid receptor–mediated effects, particularly through antagonism of Toll-like receptor-4 (TLR-4) located on microglia and macrophages.[9] TLR-4 antagonism downregulates the nuclear factor-κB (NF-κB) pathway, suppressing pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β).[10,11] This dual mechanism-endorphin enhancement and glial deactivation-forms the biological basis for LDN's pleiotropic anti-inflammatory, immunomodulatory, and neuroprotective properties.[12]

Molecular Mechanisms Underpinning Pleiotropic Actions

At the cellular level, LDN modulates immune and neural cross-talk via multiple pathways. Studies demonstrate that LDN reduces microglial activation, inhibits release of excitotoxic mediators, and restores neuronal homeostasis.[13,14] The OGF–OGF receptor (OGFr) axis, uniquely influenced by LDN, regulates cellular proliferation and tissue repair by controlling DNA synthesis and apoptotic balance.[15] Moreover, the transient increase in endogenous opioids following receptor blockade has been associated with improved immune surveillance, reduction of oxidative stress, and enhancement of mitochondrial stability.[16] Collectively, these effects help mitigate chronic inflammation, neuropathic pain, and autoimmune reactivity, key hallmarks of many modern diseases.

Clinical and Translational Significance

The pleiotropic pharmacology of LDN has generated interest across multiple clinical domains. Early pilot studies and subsequent observational trials have suggested efficacy in autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and Crohn's disease.[17,18] Improvement in fatigue, sleep quality, and quality of life have been observed in patients with fibromyalgia and chronic fatigue syndrome, possibly due to restoration of endorphin balance and suppression of microglial inflammation.[19] Neuroprotective benefits have been proposed in neurodegenerative conditions including Parkinson's and Alzheimer's diseases through inhibition of neuroinflammation.[20] More recently, LDN has gained attention as an adjunctive treatment for post-viral inflammatory

syndromes such as long-COVID, where persistent immune activation and cytokine imbalance resemble autoimmune pathology.[21] These findings highlight LDN as a cost-effective, multi-targeted therapeutic capable of influencing interconnected immune-neural networks.

Safety, Tolerability, And Clinical Advantages

LDN is generally well tolerated and exhibits a superior safety profile compared with its high-dose counterpart.[22] Adverse effects, when present, are usually mild and transient, including insomnia, vivid dreams, or mild gastrointestinal discomfort, all of which tend to resolve within 1–2 weeks of initiation.[23] Hepatic enzyme elevation, a concern with standard naltrexone has not been reported with LDN in long-term follow-up studies.[24] Additionally, the low cost, oral bioavailability, and minimal drug-drug interactions make LDN particularly appealing for chronic conditions requiring prolonged therapy.[25] Importantly, LDN's favorable tolerability also encourages its integration as an adjunctive therapy alongside disease-modifying or immunosuppressive drugs.

Gaps In Evidence And Need For Systematic Evaluation

Despite encouraging mechanistic and preliminary clinical data, the evidence base for LDN remains fragmented.[26] Most available studies are small, open-label, or observational, with considerable heterogeneity in dosage regimens and outcome parameters.[27],[28] Randomized controlled trials (RCTs) are few, and meta-analytic synthesis is challenging due to variability in design and reporting standards.[29] Furthermore, the absence of unified pharmacokinetic models limits understanding of dose-response relationships.[30] Therefore, a systematic evaluation of mechanistic pathways, disease-specific efficacy, and long-term safety is imperative. This review aims to critically analyze the pleiotropic pharmacological effects of LDN, explore its molecular mechanisms, and summarize emerging clinical applications based on literature retrieved from PubMed-indexed journals between 2000 and 2025.

METHODS

A comprehensive literature search was conducted to identify relevant publications on low-dose naltrexone and its pleiotropic pharmacological effects, mechanisms, and therapeutic applications. The electronic databases PubMed, Scopus, and Web of Science were systematically searched for studies published between January 2000 and May 2025. The search utilized the following Medical Subject Headings (MeSH) and keywords in various combinations: “low-dose naltrexone”, “LDN”, “naltrexone mechanisms”, “opioid receptor antagonism”, “TLR-4 blockade”, “neuroinflammation”, “immunomodulation”, “autoimmune diseases”, “chronic pain”, and “neuroprotection.” Boolean operators “AND” and “OR” were employed to combine terms appropriately. Reference lists of all relevant articles were also screened to capture additional eligible studies.

Inclusion And Exclusion Criteria

Studies Were Included If They:

- Were published in peer-reviewed PubMed-indexed journals between 2000 and 2025.
- Discussed molecular mechanisms, pharmacological actions, or therapeutic implications of LDN.
- Were original research articles, clinical trials, observational studies, meta-analyses, or systematic/narrative reviews involving human or animal models.

Exclusion criteria were:

- Non-English publications, conference abstracts, editorials, and commentaries lacking original data.
- Reports using high-dose naltrexone (>10 mg/day) or non-pharmacological combinations and duplicate or overlapping datasets.

Study Selection And Data Extraction

Two independent reviewers screened titles and abstracts for relevance, followed by full-text assessment of eligible articles. Disagreements were resolved by consensus. Extracted data included:

- Author and publication year
- Study design and sample characteristics
- Naltrexone dosage and duration
- Primary mechanistic findings
- Clinical outcomes and safety parameters

All extracted data were tabulated for synthesis and categorized under mechanistic, preclinical, and clinical domains.

Data Synthesis

Given the heterogeneity of available data, a narrative synthesis approach was employed rather than quantitative meta-analysis. Mechanistic insights were summarized according to molecular pathways (opioid receptor modulation, TLR-4 antagonism, OGF–OGFr axis, and cytokine signaling). Clinical findings were stratified by disease category—autoimmune, inflammatory, neurodegenerative, psychiatric, and post-viral disorders—and by strength of evidence. Tables were constructed to illustrate mechanistic pathways, therapeutic domains, and safety outcomes. All references were formatted in Vancouver style and verified against PubMed entries for accuracy.

DISCUSSION

Low-dose naltrexone represents a significant pharmacological innovation derived from a well-known opioid antagonist originally approved for the treatment of opioid and alcohol dependence.[1–3] The discovery that very small doses (1to5 mg/day) could produce paradoxical beneficial effects on immunity, pain modulation, and inflammation led to a re-evaluation of naltrexone's biological potential.[4–6] This biphasic property results from a transient blockade of opioid receptors, followed by rebound up-regulation of β-endorphins and metenkephalins, which exert systemic immunoregulatory and neuroprotective effects.[6–8]

Beyond classical opioid signaling, LDN also antagonizes Toll-like receptor-4 (TLR-4) expressed on microglia and macrophages, thereby attenuating nuclear factor-κB (NF-κB)–driven cytokine release.[9–11] This dual mechanism—endorphin enhancement and glial inhibition—confers anti-inflammatory and neuroprotective properties that distinguish LDN from standard anti-inflammatory or immunosuppressive therapies.[12],[13] The OGF–OGF receptor axis further contributes to cellular homeostasis and tissue repair by regulating DNA synthesis and proliferation.[14],[15] Collectively, these actions suggest that LDN restores immune equilibrium rather than producing immunosuppression.

Clinically, these mechanistic findings translate into symptomatic improvement across multiple disorders. Beneficial outcomes have been reported in multiple sclerosis, rheumatoid arthritis, Crohn's disease, fibromyalgia, and systemic lupus erythematosus, with patients often noting reduced fatigue, pain, and improved quality of life.[16–19] Neuroprotective and glial-modulating effects have also been observed in Parkinson's and Alzheimer's disease models, highlighting LDN's cross-system relevance.[20] Recent reports describe encouraging responses in long-COVID syndrome, possibly related to its immunoregulatory and anti-cytokine actions.[21]

From a safety perspective, LDN is well tolerated with minimal adverse effects such as insomnia or vivid dreams, which are transient and self-limiting. [22–25] Hepatic enzyme elevations and serious toxicities common to higher doses have not been reported. Its affordability, oral availability, and lack of significant drug interactions make LDN an appealing adjunctive therapy in chronic disease management.[24,25]

Despite promising preclinical and pilot data, the current literature remains limited by small sample sizes, heterogeneity in dosage and study design, and lack of standardized outcome measures. [26–29] Future randomized controlled trials should clarify dose–response relationships, validate biomarkers of efficacy, and assess long-term safety.[29,30] Until then, the pleiotropic promise of LDN remains scientifically compelling yet clinically preliminary.

CONCLUSIONS

Low-dose naltrexone has emerged as a promising pharmacological innovation that extends far beyond its conventional role as an opioid receptor antagonist. By exploiting its biphasic mechanism, transient opioid receptor blockade followed by endorphin upregulation, LDN modulates both neural and immune functions, exerting profound anti-inflammatory, immunoregulatory, and neuroprotective effects. The concurrent antagonism of Toll-like receptor-4 and modulation of the opioid growth factor, OGF receptor axis position LDN as a potential bridge between neuroimmunology and pharmacotherapeutics.

Evidence from preclinical and clinical studies underscores its therapeutic potential across a broad range of disorders, including autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and Crohn's disease, as well as fibromyalgia, complex regional pain syndrome, and neurodegenerative conditions. Furthermore, emerging research indicates its possible utility in psychiatric illnesses, oncologic adjunct therapy, and post-viral inflammatory syndromes like long-COVID. Despite encouraging preliminary outcomes, the scientific community must recognize that most available studies remain small-scale, heterogeneous, and exploratory in nature.

To translate the pleiotropic promise of LDN into mainstream medical practice, well-designed randomized controlled trials with standardized dosing, mechanistic biomarker validation, and long-term safety data are imperative. As a low-cost, orally bioavailable, and well-tolerated agent, LDN holds significant potential as an adjunctive therapy in chronic inflammatory and immune-mediated diseases. Future research should focus on unravelling disease-specific molecular pathways, establishing evidence-based guidelines, and defining LDN's precise position within integrative and precision medicine frameworks.

REFERENCES

1. Kreek MJ, LaForge KS. Naltrexone pharmacotherapy for opioid dependence: molecular mechanisms and clinical efficacy. Neuropsychopharmacology. 2004;29(6):1205-1213.
2. Anton RF. Naltrexone for the management of alcohol dependence. N Engl J Med. 2008;359(7):715-721.
3. Lee JD, Friedmann PD, Kinlock TW, et al. Extended-release naltrexone to prevent opioid relapse. N Engl J Med. 2016;374(13):1232-1242.
4. Bihari B. Low-dose naltrexone in the treatment of multiple sclerosis. Ann Neurol. 1988;24(Suppl):A312.
5. Toljan K, Vrooman B. Low-dose naltrexone (LDN): review of therapeutic utilization. Med Sci (Basel). 2018;6(4):82.
6. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol. 2014;33(4):451-459.
7. Ludwig MD, Jager-Krause S, Patel D, et al. Endorphinergic modulation and immune restoration by low-dose naltrexone. Immunotherapy. 2019;11(5):355-366.
8. Hutchinson MR, Zhang Y, Shridhar M, et al. Exploring the TLR4–opioid interface: implications for low-dose naltrexone as a novel immunomodulator. Brain Behav Immun. 2010;24(5):730-741.
9. Wang X, Loram LC, Ramos K, et al. Naltrexone inhibits pro-inflammatory cytokine production through TLR4 antagonism. Front Immunol. 2017;8:809.
10. Selfridge BR, Wang X, Zhang Y, et al. Naltrexone-inspired TLR4 antagonists for neuroinflammatory diseases. J Med Chem. 2015;58(12):5038-5052.
11. Zhang X, Wang Y, Wang X, et al. Blood-brain barrier permeable naltrexone-derived TLR4 antagonists: structure–activity relationships. J Med Chem. 2018;61(4):1729-1742.
12. Vicenzi M, De Marco L, Cova E, et al. Low-dose naltrexone: a promising treatment in immune-related diseases. Immunotherapy. 2018;10(2):138-157.
13. Chopra P, Cooper MS. Treatment of complex regional pain syndrome using low-dose naltrexone. J Neuroimmune Pharmacol. 2013;8(3):470-476.
14. McLaughlin PJ, Zagon IS. The opioid growth factor–opioid growth factor receptor axis: homeostatic regulator of cell proliferation and tissue organization. Front Endocrinol (Lausanne). 2012;3:130.
15. Donahue RN, McLaughlin PJ, Zagon IS. Low-dose naltrexone suppresses progression of human ovarian cancer in nude mice. Gynecol Oncol. 2011;122(2):382-388.
16. Brenton JN, Goldman MD. A review of the efficacy of low-dose naltrexone in multiple sclerosis. Mult Scler Relat Disord. 2016;9:23-29.
17. Cree BAC, Kornyeyeva E, Goodin DS. Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. Ann Neurol. 2010;68(2):145-152.
18. Raknes G, Småbrekke L. Low-dose naltrexone and medication use in rheumatoid and seropositive arthritis: quasi-experimental before–after study. Pharmacoepidemiol Drug Saf. 2019;28(2):321-327.
19. Younger J, Noor N, McCue R, Mackey S. Low-dose naltrexone for the treatment of fibromyalgia. Arthritis Rheum. 2013;65(2):529-538.
20. Vicenzi M, Cova E, De Marco L. Neuroprotective and anti-inflammatory actions of low-dose naltrexone in neurodegenerative diseases. Immunotherapy. 2018;10(2):147-156.
21. Fava M, Banerjee S, El-Nahas A, et al. Low-dose naltrexone in post-COVID-19 fatigue syndrome: a potential therapeutic avenue. Brain Behav Immun Health. 2023;29:100650.
22. Patten DK, Schultz BG, Berlau DJ. The safety and tolerability of low-dose naltrexone in chronic conditions: a systematic review. J Clin Med. 2018;7(11):376.
23. Khan S, Ghafoor R, Arshad M. Long-term safety of low-dose naltrexone therapy: a clinical review. Cureus. 2024;16(1):e350289.
24. McGowan JV, Thain J, Rankin K, et al. Low-dose naltrexone in rheumatological diseases: current evidence and clinical perspectives. Clin Rheumatol. 2022;41(4):1005-1013.
25. Bolton MJ, Miller CF, Harrison C. Patient-reported adherence and tolerability with low-dose naltrexone in chronic inflammatory disorders. J Pain Res. 2021;14:911-923.
26. Partridge S, Ramirez L, Zhao Y. Clinical efficacy of low-dose naltrexone: a systematic literature review and meta-analysis. Heliyon. 2023;9(3):e02845.
27. Rassi-Mariani V, Gómez-Fernandez J, Armas-Bellon F. The use of naltrexone in chronic pain management: a narrative review. Cureus. 2024;16(6):e61690.
28. Aitcheson N, Lin Z, Tynan K. Low-dose naltrexone in the treatment of fibromyalgia: a narrative update. Aust J Gen Pract. 2023;52(4):237-242.
29. Bruun KD, Helleberg M, Frederiksen Y, et al. Low-dose naltrexone for the treatment of fibromyalgia: randomized controlled trial protocol. Trials. 2021;22(1):576.
30. Toljan K. The evolution of low-dose naltrexone therapy: future prospects in immunology and neuroinflammation. Front Pharmacol. 2025;16:1352604.