

RESEARCH MONOGRAPH . COMPOUND PROFILE

Low-Dose Naltrexone (LDN)

A mu-opioid antagonist used at low doses (1.5 to 4.5 mg) for autoimmune and chronic pain conditions; mechanism via transient opioid blockade and TLR4 modulation.

DOCUMENT	KDC-MN-351
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AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Mu-opioid antagonist (low-dose immunomodulatory use)

RESEARCH USE ONLY

ABSTRACT

Naltrexone ((5 α)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one; CAS 16590-41-3; molecular formula C₂₀H₂₃NO₄; molecular weight 341.40) is a long-acting mu-opioid antagonist approved by the FDA in 1984 (ReVia, Vivitrol) for opioid and alcohol use disorders at standard doses (50 mg/day or 380 mg monthly depot). The low-dose application (LDN, 1.5 to 4.5 mg/day) was developed by Bernard Bihari in the 1980s and has been adopted in immunology and chronic pain communities. Mechanism is multifactorial and incompletely characterized: brief, transient mu-opioid antagonism (only 4 to 6 hours per dose) triggers compensatory upregulation of endogenous opioid synthesis and receptor expression, producing a paradoxical increase in opioid-mediated tone over baseline; secondary TLR4 antagonism on microglia attenuates neuroinflammation. Approved indications: opioid and alcohol use disorders (standard dose). Off-label LDN use in multiple sclerosis, Crohn disease, fibromyalgia, complex regional pain syndrome, and Hashimoto thyroiditis is supported by small clinical trials with mixed methodology. Plasma half-life is approximately 4 hours. Used as a research compound for paradoxical opioid pharmacology and neuroimmune modulation.

1. Compound Identification

Low-Dose Naltrexone (LDN) is described as mu-opioid antagonist (low-dose immunomodulatory use). A mu-opioid antagonist used at low doses (1.5 to 4.5 mg) for autoimmune and chronic pain conditions; mechanism via transient opioid blockade and TLR4 modulation.

1.1 Class summary

Mu-opioid antagonist (low-dose immunomodulatory use)

1.2 Subtitle

A mu-opioid antagonist used at low doses (1.5 to 4.5 mg) for autoimmune and chronic pain conditions; mechanism via transient opioid blockade and TLR4 modulation.

2. Abstract

Naltrexone ((5 α)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one; CAS 16590-41-3; molecular formula C₂₀H₂₃NO₄; molecular weight 341.40) is a long-acting mu-opioid antagonist approved by the FDA in 1984 (ReVia, Vivitrol) for opioid and alcohol use disorders at standard doses (50 mg/day or 380 mg monthly depot). The low-dose application (LDN, 1.5 to 4.5 mg/day) was developed by Bernard Bihari in the 1980s and has been adopted in immunology and chronic pain communities. Mechanism is multifactorial and incompletely characterized: brief, transient mu-opioid antagonism (only 4 to 6 hours per dose) triggers compensatory upregulation of endogenous opioid synthesis and receptor expression, producing a paradoxical increase in opioid-mediated tone over baseline; secondary TLR4 antagonism on microglia attenuates neuroinflammation. Approved indications: opioid and alcohol use disorders (standard dose). Off-label LDN use in multiple sclerosis, Crohn disease, fibromyalgia, complex regional pain syndrome, and Hashimoto thyroiditis is supported by small clinical trials with mixed methodology. Plasma half-life is approximately 4 hours. Used as a research compound for paradoxical opioid pharmacology and neuroimmune modulation.

3. Mechanism of Action

Brief mu-opioid antagonism producing compensatory endogenous opioid upregulation; TLR4 antagonism on microglia. Distinct from standard-dose naltrexone in OUD/AUD.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Off-label LDN 1.5 to 4.5 mg per oral administration nightly. Standard naltrexone OUD 50 mg/day.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Younger J, et al. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol 2014.
2. Smith JP, et al. Low-dose naltrexone therapy improves active Crohn's disease. Am J Gastroenterol 2007.
3. Bihari B. Low-dose naltrexone for normalizing immune system function. Altern Ther Health Med 2013.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.