

# Naltrexone and Transdiagnostic Modulation of Reward Salience in “Instinctopathies”: A Narrative Review and Clinical Hypothesis

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## Abstract

**Introduction:** Naltrexone is an opioid antagonist with established indications for alcohol dependence and opioid blockade and has been investigated in behaviors characterized by craving and repetitive reward seeking. Objective: To examine whether the literature supports a transdiagnostic reward-salience hypothesis and to define the clinical limits of the proposed “instinctopathy” construct.

**Methods:** A narrative review of PubMed/MEDLINE, Scopus, and Google Scholar was conducted through September 20, 2026, including regulatory, mechanistic, preclinical, and clinical studies.

**Synthesis:** Evidence is strongest for approved indications. Gambling disorder and kleptomania show signals of benefit with limited certainty, whereas findings in compulsive sexual behavior disorder are mixed. Animal studies, experiments in healthy volunteers, case reports, and combination treatments do not demonstrate broad transdiagnostic efficacy or establish effects of naltrexone monotherapy.

**Conclusion:** “Instinctopathy,” “motivational depotentiation,” and “anti-drive” are heuristic constructs. Their validity and intermittent-dosing hypotheses require prospective testing and do not constitute clinical indications or dosing recommendations.

**Keywords:** Naltrexone, Substance-Related Disorders, Compulsive Behavior, Reward Salience, Opioid System, Narrative Review

## 1. Introduction

Psychiatry classifies substance-related disorders, gambling disorder, compulsive sexual behavior disorder (CSBD), kleptomania, and other repetitive reward-directed behaviors separately. These conditions may share functional components, such as craving, elevated motivational salience, and difficulty interrupting the approach-and-consumption sequence; however, this does not imply a single mechanism or a uniform pharmacological response [1-4].

In this article, we provisionally use the term “instinctopathy” as a heuristic, non-nosological construct to organize hypotheses about

the dysregulation of appetitive drives. The construct does not replace recognized diagnoses and does not presuppose that alcohol, other drugs, sex, gambling, or food are clinically equivalent. The question under investigation is narrower: could measurable components of motivational salience and reward seeking represent partially shared pharmacological targets?

Naltrexone is a plausible candidate for investigating this question, not an established transdiagnostic treatment. Recent reviews, dimensional models, and unifying nosographic frameworks propose transdiagnostic lenses for addictions [5-8]. In a large population sample, Oka et al. identified self-reported dimensions of reward

and punishment sensitivity that cut across psychopathological categories [9]. A critical appraisal of the general psychopathology dimension similarly concluded that it functions as a replicable descriptive summary of vulnerability and impairment, not as a demonstrated unitary syndrome [7]. These works support models, dimensional associations, and nosographic frameworks, but they did not measure response to naltrexone nor demonstrate a common neurobiological mechanism or pharmacological efficacy across diagnoses.

The literature on response phenotypes in alcohol use disorder is promising but inconsistent. A recent secondary analysis of a randomized pilot trial did not replicate a preferential benefit of naltrexone among reward-motivated drinkers; in that profile, the placebo group showed lower consumption per day [10]. A 2025 review found signals that the sweet-liking phenotype might modulate this response, but noted heterogeneity, confounding, and the need for replication [11]. Thus, there is a hypothesis of phenotypic moderation restricted to alcohol use disorder; there is no demonstration that it crosses diagnoses. Taken together, these findings justify investigating naltrexone as a possible modulator of specific reward components. The aim of this narrative review is to distinguish established regulatory evidence, preliminary clinical findings, mechanistic plausibility, and the authors' hypotheses, outlining a testable proposal for modulation of motivational salience in "instinctopathies."

## 2. Methods

This article constitutes a narrative, hypothesis-generating review, not a systematic review. Its aim is to gather mechanistic, preclinical, and clinical evidence to discuss a heuristic construct proposed by the authors — "instinctopathy" — and the hypothesis of pharmacological modulation of motivational salience. These terms do not represent validated diagnostic categories or psychopharmacological classes.

The literature search was conducted in PubMed/MEDLINE, Scopus, and Google Scholar through September 20, 2026. Search terms, combined in Portuguese and English, included naltrexone, opioid antagonist, reward, wanting, liking, behavioral addiction, compulsive sexual behavior, pathological gambling, kleptomania, bipolar disorder, autism spectrum disorder, self-injurious behavior, binge eating, and motivation/anhedonia. Publications from 2021 to 2026 were prioritized, without excluding classic mechanistic studies, founding pharmacokinetic trials, or regulatory information still in effect.

Randomized clinical trials, systematic reviews and meta-analyses, observational studies, case series and case reports, studies in healthy volunteers, and animal models were considered. The synthesis distinguishes these levels of evidence and separates naltrexone alone from pharmacological combinations or concomitant treatments. Selection was non-systematic, without a pre-registered protocol, duplicate screening, formal risk-of-bias assessment, or quantitative synthesis; therefore, the conclusions do not allow estimation of combined efficacy.

Clinical observations that were not systematically recorded were used only to formulate research questions. They are not presented as pharmacokinetic, efficacy, safety, or dosing-recommendation data.

Reading principle: throughout the text, mechanistic plausibility is not treated as proof of efficacy; results of combined treatments are not attributed to naltrexone monotherapy; and the alternative regimens described in the package insert do not validate extended intervals for unapproved indications. The caveats below follow this principle and are repeated only when they add a new limitation.

## 3. Synthesis of Evidence

### 3.1. Pharmacological Basis and Mechanistic Evidence

Naltrexone is an opioid antagonist with affinity for  $\mu$  receptors and interaction also with  $\kappa$  and  $\delta$  receptors. Its regulatory indications cover the treatment of alcohol dependence and the blockade of the effects of exogenous opioids [12]. In animal models, the opioid system modulates dopaminergic circuits that include the ventral tegmental area and the nucleus accumbens. Microdialysis studies in rats show receptor- and region-dependent effects and naltrexone-induced attenuation of the ethanol-induced increase in dopamine in the nucleus accumbens [13,14]. These results offer mechanistic plausibility but do not demonstrate global suppression of mesolimbic dopamine or transdiagnostic clinical efficacy in humans.

In healthy volunteers, Soutschek et al. (2021) observed, after an acute 50 mg dose, a reduction in wanting ratings, with no significant effect on liking, along with altered frontostriatal connectivity [15]. The study used an experimental paradigm and did not assess craving or compulsive behavior in patients. In rats, Malikowska-Racia et al. (2025) found a dose-selective, non-linear pattern: 0.01 mg/kg transiently increased vigor, 0.1 mg/kg impaired effort-based choices, and 1 mg/kg did not reproduce the same effect [16]. These findings do not define a therapeutic dose or window in humans.

In a positron emission tomography study of five volunteers, cerebral blockade of  $\mu$  receptors persisted for 72 to 108 hours [17]. This finding allows one to distinguish the duration of receptor blockade from plasma half-life, but does not demonstrate clinical persistence of hypomotivation, anhedonia, or reduced drive during that period, nor does it support therapeutic intervals for unapproved indications.

### 3.2. Clinical Evidence in Behavioral Addictions and Related Conditions

A meta-analysis of six randomized trials in behavioral addictions found a small overall effect of naltrexone, with heterogeneity and no inclusion of compulsive sexual behavior disorder [2]. Reviews indicate signals of benefit in gambling disorder and kleptomania, but sample sizes are small and do not support a pharmacological recommendation for all impulse-control disorders [3,4]. In a 2025 network meta-analysis on gambling disorder, the estimate for severity favored naltrexone, but the confidence interval included

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no effect; there was improvement in quality of life and greater discontinuation due to adverse events [18].

In alcohol use disorder, Kady, Grodin, and Ray (2024) did not confirm a preferential benefit of naltrexone in the “reward drinker” profile [10]. The secondary analysis was small, brief, and used different outcomes than earlier trials. The result weakens claims of an already validated clinical phenotype but leaves open the hypothesis that motivational variables may moderate response in larger, pre-specified, replicated studies.

Compulsive sexual behavior disorder is classified in ICD-11 among impulse-control disorders [19]. In an open-label study of twenty men, naltrexone was feasible and tolerable and was associated with symptom reduction during treatment, without allowing causal inference [20]. In a double-blind trial with 73 men, naltrexone and paroxetine did not differ from placebo on self-reported questionnaires or on the frequency or duration of pornography use; clinical interviews showed some favorable secondary signals that require confirmation [21]. The World Federation of Societies of Biological Psychiatry guidelines prioritize psychoeducation and psychotherapy and present naltrexone as an off-label option in selected cases, not as an approved treatment [22]. The CESAR study, which compared naltrexone and fluoxetine, is listed as completed in the trial registry; a 2026 abstract described 80 participants and feasibility aspects, without disclosing complete comparative efficacy results [23-25].

Smoking cessation constitutes an important boundary for any generalization. A Cochrane review found no consistent benefit of naltrexone, alone or combined with nicotine replacement, for smoking cessation [26]. Partially shared reward mechanisms do not imply a shared pharmacological response across conditions.

### 3.3. Evidence in Specific Populations and Conditions

In patients with bipolar disorder and alcohol dependence, a small randomized trial of adjunctive naltrexone found no significant difference in depressive or manic symptoms compared with placebo [27]. An earlier open-label study by the same group also evaluated naltrexone as an adjunct [28]. These results do not authorize the use of naltrexone to treat mania or bipolar depression. Mechanistic reviews and commentaries on individual differences support further investigation, not a validated pharmacogenetic or affective phenotype [29,30]. In a cross-sectional observational study, patients receiving depot naltrexone or opioid agonists showed more anhedonia and depressive symptoms than healthy controls, but there was no significant difference between the two treatments [31].

In autism spectrum disorder, older, small pediatric studies suggested reduced hyperactivity or restlessness on some measures, with null or inconsistent results for sociability, stereotypies, and core features [32-34]. A case report described temporary improvement in self-injurious behavior after adding naltrexone, but the child continued oxcarbazepine and received environmental and behavioral interventions; causality or a monotherapy effect cannot be attributed [35]. These data justify, at most, a research hypothesis about target symptoms in subgroups, not treatment of autism or a routine clinical recommendation.

In eating disorders, the 2024 review evaluated the naltrexone-bupropion combination, not naltrexone alone, and pooled heterogeneous populations and designs [36]. Pre-post designs without a control group are not equivalent to superiority over placebo, and weight changes, Binge Eating Scale scores, and episode frequency are not interchangeable outcomes. A 2025 meta-analysis of three randomized trials with 177 participants found no significant benefit of the combination over placebo for binge frequency, body mass index, or depression [37]. These results do not support naltrexone alone as an appetite suppressant or an established treatment for binge eating disorder. Nausea and reduced appetite should be interpreted as adverse events or potential mediators, not as demonstration of motivational depotentiation [12,38].

### 3.4. Safety, Pharmacokinetics, and Limits of Alternative Regimens

Naltrexone is contraindicated in individuals receiving opioid analgesics, with current opioid dependence, in acute withdrawal, or with a positive naloxone challenge test or a urine test positive for opioids, including tramadol [9,12]. Inappropriate initiation can precipitate severe withdrawal syndrome. A minimum interval of 7 to 10 days without short-acting opioids before initiation is generally recommended; transition after methadone or buprenorphine may require up to two weeks and individual assessment. Blockade can hinder opioid analgesia, and attempts to overcome it with high doses increase the risk of intoxication. After blockade reduction or discontinuation, lower tolerance can increase vulnerability to potentially fatal overdose. Hepatitis, liver dysfunction, and transaminase elevations have also been reported; hepatic and renal assessment should be guided by the clinical situation, symptoms, and risk factors. The package insert describes, for supervised administration in approved indications, 100 mg on alternate days or 150 mg every three days, but warns that extended intervals may reduce blockade and that single doses above 50 mg may increase the risk of hepatocellular injury [12]. These regimens do not validate intermittent treatment of “instinctopathies.”

| Domain                | Main source                                                           | Synthesis                                                                                | Limit for the model                                                          |
|-----------------------|-----------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Alcohol and opioids   | Regulatory package insert [12]                                        | Established indications.                                                                 | Does not demonstrate efficacy in other diagnoses.                            |
| Gambling disorder     | Network meta-analysis; 16 RCTs, n=977 [18]                            | Favorable estimate for quality of life; severity estimate with CI including null effect. | Greater discontinuation due to adverse events; not a transdiagnostic effect. |
| Kleptomania           | Small RCTs and reviews [2-4]                                          | Preliminary clinical signal.                                                             | Small samples and little replication.                                        |
| CSBD                  | Open-label study n=20; RCT n=73 [20,21]                               | Feasibility and secondary signals; self-reports show no superiority over placebo.        | Off-label use; psychotherapy remains the priority [22].                      |
| Bipolar disorder      | Adjunctive trials in bipolar patients with alcohol dependence [27,28] | No significant difference in mood in small samples.                                      | Does not treat mania or bipolar depression.                                  |
| Autism/self-injury    | Older pediatric studies and case report [33-36]                       | Inconsistent symptomatic signals.                                                        | Does not demonstrate treatment of autism or monotherapy effect.              |
| Binge eating disorder | Naltrexone-bupropion combination; meta-analysis n=177 [32,37]         | No significant benefit over placebo for binge frequency.                                 | Cannot be attributed to naltrexone alone.                                    |

**Table 1. Summary of the Level of Evidence and Interpretive Limits**

#### 4. Discussion: Building and Limiting the Hypothesis

The findings allow formulation of an integrative hypothesis about motivational salience and seeking behavior. They do not demonstrate that naltrexone treats a transdiagnostic dimension independent of diagnosis, nor that heterogeneous conditions share pharmacological efficacy. The discussion below separates what is established, what constitutes a preliminary clinical signal, and what remains an authors' proposition.

##### 4.1. Motivational Depotentiation Hypothesis

We term “motivational depotentiation” the hypothesis of a pharmacological reduction in the capacity of an appetitive stimulus to organize and mobilize behavior. The construct distinguishes consummatory pleasure, desire or craving, motivational salience, and seeking effort. The reduction in wanting without significant change in liking observed by Soutschek et al. offers an experimental bridge to this distinction [15], but does not prove a therapeutic effect in patients. Clinical signals in alcohol use, gambling disorder, kleptomania, and compulsive sexual behavior disorder are specific to each condition and vary in quality [1,2,4,5,12,13,34,35]. The transdiagnostic hypothesis will only be supported if prospective studies demonstrate convergent change in comparable motivational outcomes across diagnoses.

Naltrexone is not an antipsychotic or “neuroleptic-like” drug: its primary mechanism is not D2 dopaminergic antagonism, and no trial has demonstrated it as an alternative to antipsychotics. Psychosis, mania, and other syndromes with an established indication for antipsychotics or mood stabilizers must receive specific treatment. Indirect modulation of dopaminergic circuits by the opioid system constitutes mechanistic plausibility, not pharmacological, clinical, or safety equivalence [9,10,15].

We use “anti-drive” only as a heuristic label for a research question, not as an established psychopharmacological category. Operationally, the hypothesis predicts a reduction in craving, salience, or seeking effort beyond non-specific changes in sedation, fatigue, nausea, mood, or cognition. It should be tested

with validated scales, behavioral measures, and appropriate comparators.

##### 4.2. Persistent Patterns and Mood Episodes: Implications for Bipolar Disorder

A persistent increase in craving or reward seeking must be differentiated from episodic changes related to mania or hypomania. The expression “constitutional instinctopathy” is used here only as a descriptive hypothesis for a persistent pattern, not as a diagnosis. When increased sexuality, spending, substance use, impulsive eating, or risk seeking occurs during a mood episode, the priority remains treatment of bipolar disorder with recommended interventions. Naltrexone does not replace mood stabilizers or antipsychotics when indicated [6,7].

Response to naltrexone may vary, but individual predictors are not yet validated [28,30,31]. The Kady study did not confirm a preferential response in the reward-motivated profile, while the sweet-liking review found promising but heterogeneous signals limited mainly to alcohol use disorder [33]. It is unknown whether these markers apply to other conditions. Hypomotivation, loss of initiative, reduced appetite, or devitalization, when observed, require clinical reassessment, taking into account adverse events, depressive symptoms, medical illness, and concomitant treatments, and should not automatically be interpreted as a therapeutic “drive-blocking” effect. We propose investigating a possible balance between reduction of pathological motivation and preservation of adaptive motivation. The literature on effort, vigor, and anhedonia helps define outcomes but does not demonstrate that naltrexone systematically produces hypomotivation or depression [29]. The hypothesis of a subgroup more sensitive to opioid antagonism should be tested with baseline measures, placebo comparison, prospective follow-up, and explicit stopping criteria.

##### 4.3. Research Hypothesis on Pharmacodynamic Duration and Dosing Intervals

The persistence of receptor blockade beyond plasma half-life suggests a pharmacodynamic question, not an already-

demonstrated explanation for prolonged clinical effects [25]. Future studies could relate receptor occupancy, naltrexone and 6 $\beta$ -naltrexol concentrations, craving, effort, general motivation, anhedonia, and adverse events. Non-systematically recorded clinical reports of persistent effects do not allow estimation of duration, causality, or therapeutic window.

As a research hypothesis, prospective trials could compare daily administration with pre-specified intervals of two, three, four, or five days, accompanied by pharmacokinetics, pharmacodynamics, efficacy, and safety assessments. These intervals are not recommended for clinical practice and cannot be inferred from the package insert's alternative regimens, which were described in a different context and include warnings about reduced blockade and increased hepatic risk with single doses above 50 mg [9]. Any study must have ethical approval, eligibility criteria, a fixed dose, monitoring of opioids and liver function, pre-registered outcomes, and stopping rules. Until such data exist, it is not possible to propose a temporal titration scheme for "instinctopathies."

#### 4.4. Proposed Integrative Model

From the perspective of Cognitive Psychiatry, the proposed construct describes a hypothetical alteration in the relationship between representation, value, and action. A reinforcer may acquire excessive anticipatory value and organize repetitive seeking behavior. Naltrexone could modify components of this process through opioid antagonism; however, the literature does not demonstrate that it acts selectively at a single stage or that it necessarily preserves all other components of pleasure, cognition, and motivation. The model should be treated as a framework for generating measurable predictions.

The most cautious mechanistic formulation is as follows: the endogenous opioid system participates in the modulation of reward circuits, and opioid antagonism can alter motivational measures in experimental contexts [3,10,15]. It cannot be concluded that naltrexone "interrupts" a global dopaminergic cascade or functions as a neuroleptic. The term "drive modulator" designates, in this article, only a hypothesis about changes in salience and seeking behavior, to be distinguished from sedation, anhedonia, nausea, reduced appetite, spontaneous improvement, and placebo effect.

The central hypothesis, therefore, is that a yet-unidentified subgroup of patients with craving and repetitive reward seeking may show a measurable reduction in motivational salience during opioid antagonism. Current evidence demonstrates efficacy in approved indications and heterogeneous signals in some specific conditions; it does not demonstrate independence from diagnosis nor a general class of responsive "instinctopathies" [1,2,4,5,12,13,23,32-35].

#### 4.5. Research Agenda

The hypothesis can be tested in a prospective protocol with defined diagnoses and pre-registered common outcomes. Before and after randomization to naltrexone, placebo, or an active comparator, craving, frequency of the target behavior, wanting, liking, effort, impulsivity, appetite, general motivation, anhedonia, and manic or depressive symptoms should be measured separately. Analyses

should test interaction between treatment and diagnosis, as well as pre-specified moderators, to determine whether there is a shared dimensional effect or only condition-specific responses. Dose-interval studies should constitute independent pharmacokinetic and safety protocols, not empirical extensions of clinical practice. For neurodevelopmental and eating conditions, outcomes should be symptom-specific and predefined: in autism spectrum disorder, frequency and severity of self-injury and of target symptoms such as hyperactivity, with systematic recording of concomitant behavioral, environmental, and pharmacological interventions; in eating conditions, food craving, hunger, consummatory pleasure, binge episode frequency, and weight should be separated, with gastrointestinal events and reduced appetite monitored as possible mediators rather than as demonstration of motivational depotentiation. In both cases, studies should compare naltrexone with placebo or standard treatment, without replacing psychosocial interventions or medications with established efficacy.

As a limitation, this review did not specifically test the motivational depotentiation hypothesis, the distinction between persistent patterns and mood episodes, or intermittent administration — all remain propositions to be evaluated in the proposed protocols.

#### 5. Conclusion

Naltrexone has established indications for alcohol dependence and opioid blockade and shows pharmacological plausibility for modifying components of reward. There are exploratory clinical signals in gambling disorder and kleptomania, while evidence in compulsive sexual behavior disorder is limited and mixed.

"Instinctopathy," "motivational depotentiation," and "anti-drive" are heuristic constructs proposed by the authors, not diagnoses, validated mechanisms, or therapeutic classes; their usefulness depends on operational definitions and falsifiable predictions. In summary, the evidence supports the approved indications and heterogeneous signals in specific conditions; it does not support transdiagnostic efficacy, attribution of combined-treatment effects to naltrexone monotherapy, or intermittent intervals for clinical practice, and changes in salience, craving, or effort must be distinguishable from sedation, nausea, fatigue, anhedonia, or non-specific improvement.

Naltrexone should not be presented as an alternative to indicated antipsychotics, mood stabilizers, or psychosocial interventions. Safety assessment must include evaluation of opioid use, risk of precipitated withdrawal, difficulty with analgesia, reduced tolerance and overdose, as well as hepatic and renal function [9].

The potential contribution of this model is to guide stratified studies capable of distinguishing diagnosis-specific responses from a possible shared motivational component. This position converges with the critical appraisal of transdiagnostic frameworks, in which clinical signals and dimensional associations do not equate to a demonstrated unitary syndrome or mechanism [39]. Until such studies are carried out, the formulation must remain explicitly exploratory [40].

## Conflicts of Interest

The authors declare no conflicts of interest related to this article.

## Funding

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

## Ethical Aspects

As this is a narrative review with no collection of individual data, intervention in participants, or use of medical records, ethics committee approval does not apply. Non-systematized clinical observations were used only to formulate research questions and are not presented as data.

## Data Availability

No original datasets were generated or analyzed. The sources used are identified in the references.

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