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# Opioid Antagonists for Hedonic Liberation—Not All Is Over

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**Abstract**

Recent Phase 3 clinical trials of selective kappa-opioid (KOP) receptor antagonists aticaprant and navacaprant failed to demonstrate sufficient clinical efficacy in treatment-resistant depression (TRD). This highlights a critical gap in current strategies that target opioid-mediated hedonic suppression. We propose two hypotheses to explain these setbacks: (1) neutral antagonists are inherently ineffective in blocking constitutively active KOP receptor hyperactivation and (2) the nociceptin opioid (NOP) receptor provides functional redundancy that compensates for KOP receptor blockade. Gaining insights from paralogous compensation in drug-resistant tumors, we argue for shifting from selective opioid antagonists to dual KOP/NOP receptor blockers to meaningfully improve reward function. This concept provides a theoretical framework for overcoming clinical resistance where selective KOP targeting with neutral antagonists has failed. Thus, we advocate for the development of opioid inverse agonists (such as nor-BNI, CAS: 105618-26-6), pan-antagonists (such as AT-076, CAS: 1657028-64-2), and combinations of selective blockers.

**Keywords:** anhedonia; dynorphin; nociceptin; kappa-opioid receptor; KOP; NOP; treatment-resistant depression

## 1. Introduction

Anhedonia, or hedonic deficit, defined as a diminished capacity to experience pleasure, interest, and satisfaction from activities, is one of the most significant challenges in modern psychiatry and psychopharmacology. This phenomenon is central to the pathophysiology of depression, post-traumatic stress disorder, substance use disorders, and other conditions such as schizophrenia and Parkinson's disease, which are characterized by impaired motivational functioning [1,2]. Anhedonia is considered a key suicide risk factor [3]. Despite advances in the development of antidepressants, antipsychotics, and other psychopharmacological agents, a significant proportion of patients continue to experience persistent symptoms of hedonic deficit, highlighting the need for novel therapeutic strategies [4].

A substantial body of research indicates that activity of the brain's reward system, particularly the mesolimbic and mesocortical dopaminergic pathways, determines hedonic tone at a given moment. Accordingly, in a simplified model, increased synaptic dopamine levels or release are perceived as pleasure, whereas a decrease leads to dysphoria, depressed mood, apathy, or anhedonia [5]. The opioid system is one of the most potent regulators of the dopaminergic reward system. The hedomimetic effect is typical of mu- (μ) opioid

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(MOP) receptor agonists and, to a lesser extent, delta- (δ) opioid (DOP) receptor agonists. These receptors increase dopamine levels in the nucleus accumbens (NAc), a key center of the brain's reward system. In contrast, stimulation of kappa- (κ) opioid (KOP) and nociceptin opioid (NOP, previously ORL1) receptors exerts a hedolytic (anti-hedonic) effect, reducing dopaminergic neurotransmission in the NAc [6–9]. KOP agonists seemed promising for pain treatment because of their anti-nociceptive effects, reduced respiratory depression, and lack of abuse potential. However, their clinical use is limited because of their depressogenic, prodysphoric, proanhedonic, and psychotomimetic effects [10]. Thus, based on their influence on hedonic status, opioid receptors can be divided into two functionally opposing groups. The "anti-hedonic" pole of the opioid system is referred to as part of the brain's "anti-reward" system [11].

Traditionally, pharmacological strategies for treating depression have focused on enhancing monoaminergic transmission. Although most standard treatments prioritize targeting serotonergic neurotransmission, there is a growing awareness that noradrenergic and, crucially, dopaminergic pathways are the main drivers of motivation and hedonic tone [12,13]. Anhedonia, a core depression symptom, frequently remains resistant to purely serotonergic agents and often requires enhancing these catecholamines [4]. Recently, the therapeutic landscape has expanded to include rapid-acting glutamatergic modulators such as ketamine and esketamine, as well as novel GABAergic agents such as zuranolone [14]. However, these approaches often prove insufficient for patients with treatment-resistant depression (TRD), which is defined as the failure to achieve remission despite at least two adequate trials of different antidepressant classes [15,16]. In TRD, persistent hedonic deficit is one of the most difficult symptoms to resolve [16,17]. Thus, the brain's "anti-reward" system seems to be a promising target for developing innovative antidepressants [18,19]. Preclinical studies suggest that KOP and/or NOP receptor blockers would increase dopaminergic neurotransmission in cases where reduced reward system activity is accompanied by increased kappa-opioid and/or nociceptin system tone. Therefore, traditional antidepressants may not work as long as the dopamine system is under kappa-opioid suppression. Accordingly, three selective KOP receptor antagonists (aticaprant, navacaprant, and icalcaprant) and one selective NOP receptor antagonist (LY2940094 or BTRX-246040) have undergone clinical trials for treating TRD, an insufficient response to first-line antidepressants, and depression with anhedonia [20]. Notably, despite high expectations and significant industrial investment, their clinical efficacy has proven surprisingly limited. This suggests that the selective blockade strategy may be fundamentally flawed.

This review evaluates potential reasons for the insufficient clinical efficacy of selective antagonists of either KOP or NOP receptors. As KOP and NOP coding genes are evolutionary paralogs [21], we hypothesize that they retain a degree of functional homology that enables them to compensate for each other's blockade. Consequently, we propose that the simultaneous blockade of both receptors, particularly via dual inverse agonists, is necessary to overcome hedonic suppression. Our work establishes a theoretical basis for a novel pharmacological class of antagonists of the hyperactive opioidergic negative feedback loop within the endogenous reward system.

## 2. Literature Search Strategy

To support the proposed hypotheses, we conducted a comprehensive literature search of the PubMed/MEDLINE, Google Scholar, and eLibrary databases. The search focused on the outcomes of clinical trials for selective KOP antagonists, NOP receptor signaling and the molecular mechanisms of paralogous compensation. Selection criteria included direct relevance to the neurobiology of reward and treatment-resistant depression. Both foundational studies on opioid receptor genetics and the most recent clinical updates (up

to 2026) were included. Studies that strictly focused on non-depressive opioid disorders were generally excluded, unless they provided critical mechanistic insights.

## 3. Hedonic Capacity as an Independent Clinical Dimension

Hedonic tone or hedonic potential is a person's capacity to experience positive emotions and pleasure from various life events and social interactions [22]. Anhedonia is the inability to experience pleasure from stimuli that were previously enjoyable or meaningful to an individual. Within the dimensional approach, anhedonia is a transdiagnostic phenomenon (observed in many mental disorders) and can be quantitatively assessed on a spectrum ranging from "mild" to "severe" or complete loss of pleasure. This dimension can intersect with others, such as low mood, anxiety, dysphoria, and apathy [2,4,23,24].

Dopaminergic system dysfunction, particularly in pathways from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and prefrontal cortex (PFC), plays a central role in anhedonia pathogenesis. Impaired dopaminergic transmission in these brain regions reduces motivation and the ability to anticipate pleasure [25]. Anhedonia is commonly observed in depressive syndrome, dissociative disorders following psychological trauma, and substance use disorders [23,26].

Currently, anhedonia lacks specific therapy and low hedonic tone is a strong predictor of poor treatment response, independent of depression severity and the type of antidepressant used [22,24,27–29]. Anhedonia may also be a clinical predictor of unsuccessful treatment outcome and a potential target for pharmacological intervention in addiction [30]. Patients with substance use disorders exhibit reduced sensitivity to pleasurable non-drug-related stimuli [31]. The emergence of anhedonia marks the transition from recreational drug use to drug dependence. A strong correlation exists between anhedonia and craving, which is associated with vulnerability to relapse [26,30,32].

Dissociative symptoms are also linked to devitalization and hedonic deficit. This state is accompanied by a subjective feeling of inner emptiness, lifelessness of the surrounding world, and lack of emotional coloring of experience. Individuals with devitalization may describe their state as feeling "emotionally frozen," "emotionally numb," as if they have "stopped living," "exist on autopilot," or as "death with open eyes" [33–36].

In the Russian psychiatric literature, the term "devitalization" is often used synonymously with anhedonia, as this state is characterized by a reduced capacity to experience not only negative but also positive emotions [33,34]. However, the term "anesthesia psychica dolorosa" is more commonly used. Patients often describe it as an inability to love, feel joy, or grieve. Although this condition is most frequently observed in the context of depressive disorders, PTSD, and schizophrenia, the feeling of detachment from oneself or the surrounding world in its pure form is a characteristic of depersonalization-derealization disorder [35,36]. According to the ICD-11 (code 6B66) and DSM-5 (code 300.6), depersonalization-derealization disorder is characterized by persistent or recurrent episodes of derealization and/or depersonalization. Similar to anhedonia, dissociation is a significant predictor of treatment resistance, affecting therapeutic outcomes in patients with anxiety, depression, PTSD, and personality disorders [37–39].

## 4. Functional Polarization of the Opioid System During Evolution

The evolution of opioid receptors is closely linked to two rounds of whole-genome duplication that occurred early in vertebrates [40,41]. The common ancestor of vertebrates possessed a single prototype gene that encoded an ancient opioid receptor. The first round of duplication (R1) occurred approximately 500–550 million years ago in the common ancestor of vertebrates, leading to the formation of two opioid receptor genes: (1) a MOP/DOP-precursor and (2) a KOP/NOP-precursor. These two receptors evolved

independently, specializing in interactions with diverging peptide ligands. The second round (R2) occurred approximately 450 million years ago in the early Paleozoic era and gave rise to the four modern types of opioid receptors: MOP, DOP, KOP and NOP [21,41,42]. Thus, the closest evolutionary and genetic relationship was observed between the gene pairs encoding the KOP/NOP and MOP/DOP receptors. This explains the observed functional polarization in the regulation of dopaminergic neurotransmission within the mesocorticolimbic pathways, that is, suppression and facilitation.

MOP and DOP receptors are located on GABAergic neurons that provide tonic inhibitory control over the activity of dopaminergic neurons in the reward system. Under physiological conditions, these GABAergic neurons exert a baseline inhibitory control over the firing rate of dopaminergic neurons in the VTA. Since all opioid receptors are inhibitory (coupled to the inhibitory Gi protein), activation of MOP and DOP receptors decreases the excitation of these GABAergic neurons. Deprived of GABAergic inhibition, the dopaminergic neurons increase their spontaneous firing rate, thus elevating dopamine levels in the nucleus accumbens to supraphysiological levels. This mechanism is associated with the euphoria induced by mu-opioid analgesics [43,44].

KOP receptors are localized in the somatodendritic regions of dopaminergic neurons [43]. Notably, blockade of KOP receptors does not increase the firing rate of dopaminergic neurons in the reward system [45,46]. This indicates that dynorphinergic neurotransmission is "silent"—dynorphin is not tonically released and does not inhibit dopaminergic transmission under baseline conditions.

NOP receptors are similarly expressed on the cell bodies of VTA dopaminergic neurons (Figure 1) [47–49].

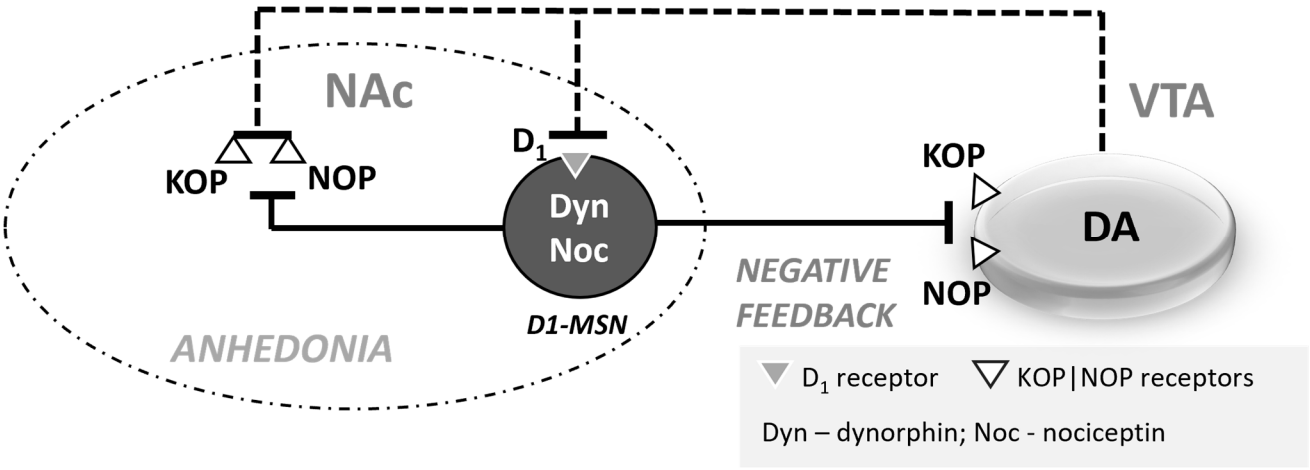



**Figure 1.** Hypothetical negative feedback in the reward system (anti-reward system). D1 dopamine receptor is excitatory. Its activation also increases preprodynorphin and prepronociceptin gene expression in a striatal medium-sized spiny neuron (MSN). These GABAergic neurons synapse on the dopamine (DA) cell bodies, thus providing a feedback inhibitory input to VTA. Activation of somatodendritic KOP and NOP receptors decreases DA cells' firing rate. Presynaptic KOP and NOP receptors, expressed on the dopaminergic nerve terminals, function to inhibit synaptic release of dopamine. Stimulation of KOP and NOP receptors in animals cancels the antidepressant-like and positive reinforcing effects of opioids, stimulants, and alcohol. Thus, the KOP/NOP system functions as a powerful negative feedback mechanism within the dopaminergic reward system. Dashed line represents inhibition of neuronal activity; solid line represents enhancement of neuronal activity. NAc, nucleus accumbens; VTA, ventral tegmental area; D1-MSN, medium-sized spiny neurons expressing D1 receptors; DA, dopamine. Based on animal studies, see references [43–57].

In the midbrain, 50–60% of neurons expressing prepronociceptin mRNA co-express the key GABA-synthesizing enzyme glutamate decarboxylase, a marker of GABAergic neurons, and are co-localized with neurons expressing tyrosine hydroxylase (TH) [47]. NOP receptor mRNA is expressed predominantly in dopaminergic neurons, whereas prepronociceptin mRNA is expressed predominantly in local GABAergic neurons, indicating that nociceptin, along with dynorphin, suppresses the bioelectrical activity of VTA and substantia nigra pars compacta (SNc) dopaminergic neurons [50]. Olianas et al. [51] (2008) demonstrated the inhibitory effect of nociceptin on the activity of the dopamine-synthesizing enzyme TH in the presynaptic terminals of striatal dopaminergic projections. Studies have shown that blockade of NOP receptors enhances dopaminergic neurotransmission [52], showing promise in Parkinson's disease [53].

Duplicated genes have contributed to the evolution of the mammalian brain [58]. Many paralogs perform similar functions, and if one is lost, the other can partially take over its functions to maintain homeostasis [59–61]. Regarding neurotransmitter systems, genes encoding $\beta_1$- and $\beta_2$-adrenergic receptors, cyclooxygenases (COX) types 1 and 2, and alcohol dehydrogenases represent classic examples of paralogs that diverged after the duplication of a single ancestral gene [62–64].

Previous findings suggest similar changes between the kappa-opioid and nociceptin systems in a rodent two-bottle choice alcohol-drinking test [65,66]. An increase in alcohol preference was associated with lower mRNA expression of both KOP and NOP receptors, as well as their endogenous ligands—dynorphin and nociceptin—in the ventral striatum and amygdala. Hyperfunction of the kappa-opioid system typically emerges only after the establishment of substance dependence. Prior to that, its tone may have been reduced, predisposing individuals to experience more intense positive reinforcement during initial exposure to psychoactive substances, which may increase the risk of developing addiction [67].

## 5. Dynorphin and Nociceptin Opioid Systems as Negative Regulators of Hedonic Homeostasis

Opioid systems play a key role in modulating pain perception. While mu-opioid activation by endorphins appears most effective in suppressing nociceptive physical pain, kappa-opioid and nociceptin receptor activation seem to play a key role in 'emotional anesthesia.' *Salvia divinorum*, a hallucinogenic plant containing the most potent and selective KOP agonist salvinorin A, induces strong dissociative effects. These include a sense of time stopping, intense derealization, depersonalization, loss of physical body sensation, and hallucinatory experiences [68–70]. In animal models, anhedonic states are accompanied by an increased intracranial self-stimulation (ICSS) threshold [71]. KOP receptor agonists, such as salvinorin A, increase the ICSS threshold, indicating suppression of the reward system and producing effects similar to the signs of depression in humans [72,73]. Importantly, systemic administration of KOP receptor agonists to intact animals increases the ICSS threshold [72,74], whereas administration of KOP receptor antagonists does not change it. This suggests that the "reward" system is not under tonic inhibitory influence from the kappa-opioid system under normal conditions. That is, in a baseline (euthymic) physiological state, KOP receptors are "silent." In healthy volunteers, administration of KOP receptor agonists (ketazocine, spiradoline, enadoline, etc.) causes dysphoria, depression, dissociation, hallucinogenic effects, and increased prolactin and cortisol levels [75–79].

In rats, KOP receptor agonists induce conditioned place aversion (CPA) mediated by KOP localized on dopaminergic neurons [80,81]. Activation of these receptors reduces dopamine release in the nucleus accumbens and cerebral cortex [19]. Presynaptic KOP receptors in the striatum may be directly associated with DAT, positively modulating its

activity and enhancing dopamine reuptake [82,83]. Direct microinfusion of a KOP blocker into the nucleus accumbens has been shown to produce an antidepressant effect [19,57,74]. Thus, the kappa-opioid system acts as a negative feedback mechanism to suppress excessive dopaminergic neurotransmission in the ventral striatum [54] (Figure 1). GABAergic medium-sized spiny neurons (MSNs) of the direct pathway express both dynorphin and D1 receptor (D1-MSNs) [55]. These neurons send projections to the VTA [56,57], where KOP receptors are localized on the cell bodies and dendrites of dopaminergic neurons of the mesocortical, but not mesolimbic, pathway [84–86]. This partly sheds light on the possible mechanism of reciprocal relations in activity between the mesolimbic and mesocortical systems: hyperactivation of dopaminergic neurotransmission in the mesolimbic system activates D1-MSNs, leading to increased dynorphin levels in the VTA. This causes selective inhibition of mesocortical dopaminergic neurons and decreases dopamine levels in the prefrontal cortex.

The influence of nociceptin on the brain's reward system is suppressive and similar to that of dynorphins [87]. Similar to dynorphin, nociceptin and its agonists reduce or even abolish the positive reinforcing properties of alcohol and drugs of abuse (morphine, cocaine, and amphetamines), preventing the development of conditioned place preference [88–91] and locomotor sensitization [92]. Exogenous administration of nociceptin has been shown to reduce both basal and evoked dopamine release in the NAc, as well as to abolish the positive reinforcing effects of drugs and alcohol [93–95]. Phylogenetic proximity likely underlies the functional similarity between the dynorphin and nociceptin opioid systems observed in the cortical and limbic regions of the brain. Interestingly, unlike dynorphin, nociceptin does not induce conditioned place preference or conditioned place aversion [96].

Activation of nociceptinergic neurons innervating VTA suppresses reward motivation, while a single dose of a NOP receptor antagonist enhanced electrophysiological markers of reward learning [97,98].

Pizzagalli et al. [99] (2025) demonstrated that a single dose of NOP antagonist BTRX-246040 significantly enhanced reward-based behavioral modulation in rats. Specifically, the treated animals exhibited a more pronounced bias toward stimuli associated with a higher reward frequency.

## 6. Dynorphin and Nociceptin Opioid Systems and Stress

KOP receptors play an important role in mediating the effects of stress, which is a risk factor for the development of several mental disorders, including depression [100]. Acute and subchronic stress in rodents induces immobility, which is prevented by KOP receptor blockers and is absent in animals with knockout of the genes encoding dynorphin or the KOP receptor [101,102]. The aversive effect of stress (stress-induced conditioned place aversion, CPA) is absent in prodynorphin gene knockout animals. Stressful events are major risk factors for the onset of addictive disorders [103]. Stress enhances cocaine-induced conditioned place preference (CPP), and this effect is mimicked by the intravenous administration of a KOP receptor agonist [104]. Pretreatment with a non-peptide KOP receptor antagonist JDTic or nor-BNI (norbinaltorphimine) significantly reduced stress-induced (foot-shock) reinstatement of extinguished cocaine self-administration [105,106]. Furthermore, exposure to acute or repeated stress reinstated cocaine CPP in wild-type mice but not in mice with a knockout of the gene encoding the KOP receptor or prodynorphin or after pharmacological blockade of KOP receptors [106].

Activation of the NOP receptor, as well as social defeat stress, induces neuroinflammatory effects in the hippocampus and is associated with depressive-like behaviors in mice [107]. NOP receptor antagonists prevented the development of helplessness in mice exposed to inescapable stress [108].

Prolonged blockade of NOP receptors reversed the stress-induced reduction in sucrose consumption caused by chronic stress. A 21-day administration of a selective peptide NOP receptor antagonist UFP-101 abolished the behavioral, neurochemical, and endocrine changes induced by chronic mild stress [109]. Thus, nociceptin not only shares structural similarities with dynorphin but also exerts a functionally similar influence on hedonic tone under baseline conditions [99].

## 7. Dynorphin and Nociceptin Opioid Systems and Addiction

KOP receptor agonists reduce the reinforcing effects of alcohol and drugs of abuse [110,111] by suppressing mesolimbic dopaminergic neurotransmission [112]. For instance, systemic administration of KOP receptor agonists dose-dependently reduces self-administration of cocaine and morphine in intact (non-dependent) rats [113,114]. Investigation of the reinforcing properties of cocaine in intact monkeys revealed that the KOP receptor agonist U50,488 administered prior to cocaine self-administration significantly suppressed the motivation to obtain cocaine [115]. These results provide robust evidence for the inhibitory effect of KOP receptor stimulation on the rewarding effects of drugs of abuse in non-dependent rats. However, in dependent animals, after the resolution of withdrawal syndrome, the administration of KOP receptor agonists increases drug consumption, which can be interpreted as an attempt to overcome the anhedonia induced by KOP receptor stimulation [116,117]. In animals with established dependence, a reduction in substance consumption can be achieved through the administration of KOP receptor blockers. This indicates hyperactivation of the kappa-opioid system, reflecting the mechanism of drug tolerance and establishment of the anhedonic component of withdrawal syndrome [118].

Increased stress sensitivity and anxiety in ethanol-dependent subjects during protracted abstinence from alcohol may be partly associated with the dysregulation of the nociceptin system. In particular, central nucleus of the amygdala (CeA) prepronociceptin gene expression in ethanol-dependent animals was markedly higher three weeks post-withdrawal compared with both nondependent controls and experimentally naïve rats [119].

In a free-choice task combined with RT-PCR analysis, prepronociceptin and NOP receptor mRNA levels were measured in the mesolimbic areas of rats with different alcohol drinking behaviors [120]. Alcohol-preferring rats showed lower levels of prepronociceptin mRNA in the striatum and NOP receptor mRNA in the amygdala, suggesting that nociceptin, along with dynorphin, may play a key role in addiction [120].

## 8. Clinical Trials of KOP Receptor Antagonists

According to the WHO, 300 million people worldwide suffer from depressive disorders, and 1 million people die by suicide annually. One-third of patients with depression are resistant to treatment with two or more types of antidepressants. Approximately 30% of patients with TRD do not respond to any further treatment [16]. Table 1 summarizes the results of clinical trials and ClinicalTrials.gov IDs of KOP receptor antagonists.

The Phase 2a proof-of-mechanism study of aticaprant for anhedonia in patients with mood disorders employed functional magnetic resonance imaging (fMRI)-indexed mesolimbic activation as the primary outcome measure, on the premise that ventral striatal responses to reward-predicting cues would provide a more sensitive readout of KOP antagonist-mediated dopaminergic disinhibition than clinician-rated symptom instruments [121]. Patients receiving aticaprant had a significant increase in ventral striatal activation during reward anticipation in a monetary incentive delay task, compared with the placebo group. The observed effect of aticaprant on brain regions involved in reward

was associated with a reduction in anhedonia, as assessed by the Snaith–Hamilton Pleasure Scale (SHAPS), indicating its potential as a therapy for anhedonia [121].

The efficacy and safety of aticaprant as an adjunct to antidepressants in major depressive disorder (MDD) were studied in a Phase 2 placebo-controlled trial [122]. This study involved 184 patients with MDD experiencing an ongoing moderate-to-severe episode despite an adequate course of SSRI/SNRI antidepressants for ≥6 weeks. The primary endpoint was the improvement in the MADRS (Montgomery–Åsberg Depression Rating Scale) score after 6 weeks in those who did not respond to placebo during a 3-week lead-in phase. Although the overall difference in the MADRS score was only 2.1 points (a clinically insignificant difference) in favor of aticaprant, the difference was statistically significant. The greatest effect was observed in patients with high baseline anhedonia; however, no statistically significant improvement was observed in the SHAPS (anhedonia), CGI-S (severity), or HAM-A (Hamilton Anxiety Rating Scale) scores [122,123].

According to an official corporate statement, in March 2025, Johnson & Johnson announced the discontinuation of its Phase 3 (VENTURA) program because the drug did not demonstrate sufficient efficacy as an adjunctive therapy in patients with MDD despite having a good safety profile [124]. By the end of 2023, J&J had forecasted the annual peak sales of aticaprant to be between $1 and $5 billion [125].

It was officially stated that in January 2025, Neumora Therapeutics reported that its selective kappa-opioid antagonist, navacaprant, did not demonstrate sufficient efficacy in KOASTAL-1—the first of three Phase 3 trials [126]. By week 6, the reduction in the total MADRS score from baseline was equivalent in both the navacaprant and placebo groups. The data revealed a sex-based divergence in the efficacy of navacaprant, with results favoring the drug among the 105 female patients based on the SHAPS scores. The proportion of female participants in the KOASTAL-1 trial was lower than that in Neumora's earlier Phase 2 study.

In a Phase 2 study of navacaprant, the primary endpoint was not met in the efficacy population, which included participants with moderate depression without treatment resistance [127]. At week 8, the difference in the Hamilton Depression Rating Scale (HAMD-17) score for navacaprant compared with placebo was not statistically significant. However, navacaprant significantly improved depressive symptoms, including anhedonia, in a subgroup of patients with severe MDD. In a predefined subgroup with severe MDD, navacaprant significantly improved the HAMD-17 score at both time points and the SHAPS score at week 8. The safety profile was favorable [127].

Previously, the combined opioid antagonist ALKS-5461 from Alkermes did not receive FDA approval [128]. ALKS-5461 is a combination of buprenorphine (a partial MOP agonist and neutral KOP antagonist) with samidorphan (a MOP antagonist). Before the clinical development stage of selective KOP receptor blockers, the kappa-opioid antagonism of buprenorphine was utilized by adding an MOP receptor antagonist to neutralize the abuse potential associated with stimulation of the latter [129,130]. A Phase 2 study enrolled patients with MDD who had an inadequate response to 1 or 2 courses of antidepressant treatment. At 4 weeks, ALKS-5461 outperformed the placebo on all three efficacy measures [131]. Despite the positive Phase 2 data, ALKS-5461 encountered significant challenges in Phase 3.

In the Phase 3 FORWARD-3 trial, ALKS-5461 failed to show superiority over placebo after 6 weeks [132]. Two other multicenter Phase 3 RCTs (FORWARD-4 and FORWARD-5) also evaluated the safety and efficacy of ALKS-5461 for the same indication [133]. The primary endpoint of FORWARD-4 was not met. However, FORWARD-5 met its primary endpoint. A pooled analysis of the FORWARD-4 and FORWARD-5 trials also demonstrated superiority over placebo [133]. Nevertheless, in 2018, the FDA refused to approve ALKS

5461 for the treatment of treatment-resistant depression due to "insufficient evidence of effectiveness for the pursued indication" [128].

Excessive and unpredictable placebo effects "dilute" the therapeutic response, thereby negating statistical significance [134]. One approach to reduce the placebo response is to include a several-week lead-in period in the RCT design, during which all enrolled participants receive a placebo, and their initial response is tracked before randomization into active and control groups. It is assumed that participants who respond to a placebo during the lead-in period are more likely to respond to a placebo during the dosing period. Excluding this placebo-responsive group from the final analysis is thought to potentially benefit drug efficacy signal detection [134].

A placebo lead-in period was used as one of the optimization procedures in the aforementioned Phase 2 study of aticaprant [122]. The authors defined two intent-to-treat (ITT) populations: the first, enriched with participants who did not respond to the placebo lead-in (eITT), and the second, full ITT (fITT), including all participants regardless of their response during the lead-in period. However, the results were the opposite of what was predicted. The aticaprant-induced improvement in MADRS was greater in the fITT population than in the eITT population [122]. It is hypothesized that effects associated with the placebo/nocebo are driven by an interaction between the reward system and interconnected systems of aversive emotions, which are also regulated by dynorphin [135,136]. This can be seen as an enhancement of reward/aversion dynamics, which should be particularly noticeable in subjects who maintained an active placebo response during the lead-in phase. This phenomenon will be discussed in detail below in the context of agonist-independent (constitutive) KOP receptor activation [136].

**Table 1.** Selected clinical trials of KOP receptor antagonists.

| Study | Indication | Study Design | Number of Participants (*n*) | Groups and Daily Doses | Efficacy Results |
|---|---|---|---|---|---|
| Aticaprant Phase 2a FAST-MAS Proof-of-Mechanism Study [121] NCT02218736 | Anhedonia (MDD/anxiety disorders) | RCT, double-blind, 8 weeks | 89 | 10 mg | Aticaprant significantly increased fMRI ventral striatum activation during reward anticipation (primary outcome) compared with placebo. |
| Aticaprant Phase 2 [122] NCT03559192 | Major depressive disorder | RCT, double-blind, 6 weeks, placebo lead-in | 166 (fITT); 121 (eITT) | 10 mg (adjunctive to SSRI/SNRI) | MADRS: ↓ vs. placebo (eITT & fITT; $p \leq 0.044$; ES 0.23–0.36), stronger in high SHAPS subgroup; Responders: 36.4% (aticaprant) vs. 24.0% (PBO); QIDS: $p = 0.029$; CGI-I: $p = 0.046$ |
| Aticaprant Phase 3 VENTURA Program (2025) [124] NCT05455684 NCT05550532 NCT05518149 NCT06635135 NCT06514742 | MDD with moderate-to-severe anhedonia | RCT, double-blind, 42 days | Not disclosed | 10 mg (adjunctive to SSRI/SNRI) | Insufficient efficacy; primary endpoint (change in MADRS) not achieved; Safety confirmed; secondary efficacies not disclosed |
| Navacaprant Phase 2a [127] NCT04221230 | MDD with anhedonia and anxiety | RCT, double-blind, 8 weeks | 204 | 80 mg | HAMD-17 (primary): not achieved; significant in moderate-to-severe subgroup ($n = 100$) at weeks 4, 8; SHAPS significant at week 8. |

**Table 1.** *Cont.*

| Study | Indication | Study Design | Number of Participants (*n*) | Groups and Daily Doses | Efficacy Results |
|---|---|---|---|---|---|
| Navacaprant Phase 3 KOASTAL-1 [126] NCT06029426 | Moderate-to-severe MDD | RCT, double-blind, 6 weeks | 383 | 80 mg | Primary endpoint not achieved; SHAPS & MADRS: no between-group difference; SHAPS significant vs. placebo in female subgroup. |
| ALKS-5461 Phase 2 [131] NCT01500200 | MDD with inadequate antidepressant response | RCT, double-blind, two-stage sequential parallel comparison design, 4 weeks | 142 | 2 mg/2 mg 8 mg/8 mg Placebo (adjunctive to antidepressant) | 2 mg/2 mg: improvement vs. placebo across HAM-D, MADRS, CGI-S; 8 mg/8 mg: trend, NS. HAM-D response: 60% (2 mg/2 mg) vs. 20% (PBO) |
| ALKS-5461 Phase 3 FORWARD-3 [132] NCT02158546 | MDD with inadequate antidepressant response | Double-blind, placebo run-in, 10 weeks | 295 | 2 mg/2 mg Placebo (adjunctive to antidepressant) | MADRS-10: NS. Response: 16.9% vs. 14.4% (NS); Remission: 14.1% vs. 12.3% (NS). |
| ALKS-5461 Phase 3 FORWARD-4 FORWARD-5 [133] NCT02158533 NCT02218008 | MDD with inadequate antidepressant response | Two phase 3 RCT, double-blind, studies that utilized the same sequential parallel-comparison design, 2 stages, 11 weeks | Not formally reported | 2 mg/2 mg 1 mg/1 mg 0.5 mg/0.5 mg Placebo (adjunctive to antidepressant) | FORWARD-5: primary endpoint achieved (MADRS-10, 2 mg/2 mg). FORWARD-4: not achieved (MADRS-10 at week 5; $p = 0.109$). Pooled: consistently greater MADRS-10 reduction for 2 mg/2 mg at multiple timepoints. |

NCT-numbers: ClinicalTrials.gov Identifier; eITT, fITT—see text; CGI-I—Clinical Global Impressions—Improvement scale; CGI-S—Clinical Global Impressions—Severity scale; fMRI—functional magnetic resonance imaging; HAM-D—Hamilton Depression Rating Scale; MADRS—Montgomery–Åsberg Depression Rating Scale; MDD—major depressive disorder; NS—non-significant; PBO—placebo; QIDS—Quick Inventory of Depressive Symptomatology; RCT—randomized controlled trial; SHAPS—Snaith–Hamilton Pleasure Scale; SNRI—serotonin–norepinephrine reuptake inhibitors; SSRI—selective serotonin reuptake inhibitors; ↓—decreased versus placebo.

## 9. Clinical Trials of NOP Receptor Antagonists

According to data from small-scale studies, plasma nociceptin levels are elevated in depressive states and negatively correlate with severity in manic states [137]. Gu et al. [138] (2003) measured plasma levels of nociceptin and 5-HT in patients with postpartum depression and compared them with healthy controls. Plasma nociceptin levels were significantly elevated in the postpartum depression group. Conversely, serotonin levels were lower than those in the control group. This study found a negative correlation between nociceptin and 5-HT levels.

A single nucleotide polymorphism (rs6010719) in the NOP receptor gene is more frequent in individuals who develop PTSD symptoms following moderate or severe childhood abuse [139]. The study also reported that subjects with the NOP rs6010719 variant process fear-related images differently and exhibit increased amygdala reactivity and specific fMRI markers [139]. Furthermore, a genome-wide association study conducted as part of a dedicated program (>200,000 participants) revealed a positive association between the NOP variant rs6090040 and anxiety-related personality traits [140].

PET imaging in humans has demonstrated that the NOP receptor is activated in healthy individuals under stress conditions [141]. The acute rise in glucocorticoids during stress increases the density of NOP receptors in various brain regions [141]. In women who have experienced sexual abuse, a positive correlation was identified between NOP receptor density in the midbrain and the severity of PTSD symptoms, particularly those related to intrusive memories and avoidance behavior. The findings indicate that a lower number of NOP receptors in the midbrain is associated with less severe PTSD symptoms [142]. Table 2

summarizes the results of clinical trials and their ClinicalTrials.gov IDs of NOP receptor antagonists.

BTRX-246040 (also known as LY2940094) is a selective NOP antagonist [143,144]. In Phase 2 clinical trials involving patients with depression [145] and alcohol dependence [146], BTRX-246040 was safe and well tolerated. The first double-blind placebo-controlled study involved 184 patients with MDD who received BTRX-246040 for 8 weeks [145]. The primary endpoint of the study, the probability of LY2940094 being better than placebo on the GRID-HAMD-17 depression scale, was not met in the full analysis set (intent-to-treat population) but was met in the per-protocol population [145].

Patients with depression exhibit a bias towards interpreting emotionally neutral information as negative. The Oxford Emotional Test Battery (ETB) is used to assess cognitive function and emotional processing in humans [147]. The ETB can detect early effects of antidepressants, such as improved recognition of emotions from facial expressions, which often precedes mood improvement [148]. The ETB assesses the ability to accurately identify emotions from facial expressions displaying varying levels of anger, disgust, fear, happiness, sadness, and surprise, as well as ten neutral expressions [147,148]. This battery was used to determine whether BTRX-246040 affects the processing of information contained in facial expressions. Emotional processing improved after 1 week of treatment in the BTRX-246040 group in terms of accuracy in identifying emotionally positive facial expressions compared with placebo. The BTRX-246040 group showed worsening sleep-related items, primarily early and middle insomnia, compared with placebo, which likely reflects the stimulant properties of the drug [145].

Another double-blind, placebo-controlled study involved patients with alcohol dependence who received BTRX-246040 for 8 weeks [146]. The reduction in the mean number of drinking days (NDD) did not differ between the BTRX-246040 and placebo groups [146]. However, the BTRX-246040 group showed a more pronounced reduction in the mean percentage of heavy drinking days (HDD) per month compared with the placebo group. An increase in the mean percentage of abstinence days per month relative to placebo was also observed. Patients receiving BTRX-246040 exhibited reduced plasma gamma-glutamyl transferase levels at multiple time points. The most common adverse events in the BTRX-246040 group included insomnia, vomiting, and anxiety [146].

BlackThorn Therapeutics has discontinued development of BTRX-246040 after it failed to meet its primary endpoints in its next Phase 2a clinical trial for MDD [149]. Neumora Therapeutics, which acquired BlackThorn [150], has not announced plans to resume studies of the drug.

Pizzagalli et al. [99] (2025) present a landmark series of four complementary studies that elegantly bridge preclinical mechanisms to human clinical outcomes. The investigation establishes the NOP receptor system as a stress-sensitive modulator of reward learning and motivation across species. The study systematically progresses from molecular underpinnings (Studies 1–2) to behavioral pharmacology (Study 3) and culminates in a Phase 2a clinical trial reanalysis (Study 4).

Most compellingly, 8-week BTRX-246040 treatment significantly increased the Effort Expenditure for Rewards Task (EEfRT) inverse temperature parameter (t) in MDD patients versus placebo, reflecting restored decision confidence known to be abnormally lowered in MDD patients [151]. This demonstrates that NOP antagonism increases incentive motivation with significantly higher willingness to exert efforts to pursue high rewards among individuals with MDD. Despite this, primary (MADRS) and various secondary (SHAPS, DARS) endpoints demonstrated nonsignificant differences [99].

**Table 2.** Clinical trials of NOP receptor antagonist BTRX-246040 (LY2940094).

| Study | Indication | Study Design | Number of Participants (N) | Groups and Daily Doses | Efficacy Results |
|---|---|---|---|---|---|
| BTRX-246040 Phase 2 [145] NCT01724112 | MDD | RCT, double-blind, 8 weeks | 136 | 40 mg | Primary endpoint (GRID-HAMD-17, week 8): not met in FAS (82.9%), met in PP (88.6%); weeks 9–10: 97.4%. Secondary endpoint (positive emotional recognition): achieved (92.4%). |
| BTRX-246040 Phase 2 [146] NCT01798303 | Alcohol dependence | RCT, double-blind, 8 weeks | 88 | 40 mg | NDD: no difference vs. placebo. HDD: ↓ drinking (−24.5 vs. −15.7%; 93% better than PBO); abstinent days ↑ (9.1 vs. 1.9%; 91% better than PBO). |
| BTRX-246040 Phase 2 [99] NCT03193398 | MDD | RCT, double-blind, 8 weeks | 102 | 40–80 mg | MADRS & secondary endpoints (DARS, SHAPS): not achieved. EEfRT (t): significant group × time interaction (b = 0.84, $p = 0.015$); ↑ in BTRX-246040 group (b = 0.88, $p < 0.001$). |

NCT number: ClinicalTrials.gov Identifier; DARS—Dimensional Anhedonia Rating Scale; EEfRT—Effort-expenditure for Rewards Task; FAS—full analysis set; HDD—heavy drinking days; MADRS—Montgomery–Åsberg Depression Rating Scale; MDD—major depressive disorder; NDD—number of drinking days; PBO—placebo; PP—per protocol (population); RCT—randomized controlled trial; SHAPS—Snaith–Hamilton Pleasure Scale; ↓ or ↑—decreased or increased versus placebo.

## 10. Novel Drug Development Prospects

### *10.1. Ligand-Receptor Interactions*

Clinically significant characteristics of ligand-receptor interactions extend beyond the simple continuum of a ligand intrinsic activity, ranging from –100% to +100%, where 100% represents the maximum level of activation of secondary messengers caused by the corresponding endogenous (or reference) agonist (e.g., a neurotransmitter) at its maximum concentration [152,153].

G protein-coupled receptors (GPCRs) can adopt multiple active conformations spontaneously, even in the absence of an agonist. Each conformation is associated with the activation of a specific intracellular signaling pathway and its corresponding biological response [153].

At any given time, a certain proportion of receptors in a population exists in one active conformation or another, determining the basal level of activation of the respective secondary messenger system. This agonist-independent receptor activation is called constitutive activity. An endogenous neurotransmitter is considered a full agonist, and its maximal agonist efficacy ($E_{max}$—the magnitude of maximum activation of the secondary messenger system by an agonist at its maximum concentration) is conventionally set at +100%. An inverse agonist decreases the basal level of activation of secondary messenger systems, conventionally taken as "0". Accordingly, $E_{max}$ for an inverse agonist is a negative value. A ligand that competes with the neurotransmitter for receptor binding but does not shift the equilibrium in the percentage of active receptors is called a neutral antagonist. Thus, it does not decrease biological response in the absence of an agonist and creates an effect equivalent to the absence of an agonist (a "silent" antagonist). Thus, an inverse agonist produces a biological effect opposite to that of an agonist. Therefore, inverse agonists can exert more pronounced clinical effects (therapeutic or adverse) than neutral antagonists [152,154,155].

In most preclinical studies on KOP receptors, selective antagonists such as norbinaltorphimine (nor-BNI) or JDTic have been used. They possess unusual properties

of delayed onset and very long duration of action in vivo. For example, a single injection of nor-BNI in mammals can block KOP receptors for several weeks [156–158].

Several naltrindole derivatives can also induce prolonged blockade of KOP receptors. 5′-AMN [5′-(2-aminomethyl)naltrindole] and 5′-MABN [N-((naltrindol-5-yl)methyl)pentanimidamide] produce continued anxiolytic and antidepressant effects in rats after a single injection, with KOP receptor blockade lasting up to 28 days [159–162].The mechanisms underlying such a prolonged receptor blockade have remained unclear for a long time. Neither nor-BNI nor JDTic was found to be a classical antagonist. Rather, they are functionally selective agonists of the KOP receptor that activate c-Jun N-terminal kinase (JNK) [163,164]. JNK recruits peroxiredoxin 6 (PRDX6) to the plasma membrane, which binds to the KOP receptor and stimulates NADPH oxidase to generate reactive oxygen species that oxidize sulfhydryl groups in exposed cysteine residues and depalmitoylates the Gαi protein. This hypothetically alters the orientation of the receptor-G protein binding interface and irreversibly blocks guanine nucleotide exchange, preventing receptor activation [165–167].

Pharmacological inhibition of JNK or PRDX6 components in this signaling pathway, or genetic deletion of JNK-1, prevented the long duration of action of nor-BNI, converting it into a short-acting competitive antagonist [163–165]. In this context, ligands such as nor-BNI are better described as “inactivating” or “desensitizing” antagonists. Classical kappa-opioid agonists, including endogenous dynorphin peptides, activate both heterotrimeric G proteins and β-arrestin-dependent signaling cascades. β-arrestin, in turn, triggers the mitogen-activated protein kinase p38α MAPK. Because p38α MAPK inhibits JNK, classical KOP receptor agonists do not cause long-term inactivation [165].

Constitutive receptor activity can exert a tonic influence on the basal level of neuronal activity even in the absence of a neurotransmitter [152]. The degree of constitutive activity in a receptor population is influenced by several factors. Chronic GPCR stimulation can lead to an “accumulation” of constitutive activity, although the mechanism remains poorly understood [168]. For instance, chronic morphine administration significantly increases the level of constitutive MOP receptor activity in the rat brain [169]. This may be relevant to the development of withdrawal syndrome induced by naloxone and naltrexone, which, in this case, behave as inverse agonists of MOP receptors [154,168]. Moreover, chronic exposure to mu-opioid agonists causes constitutive activation of MOP receptors in direct proportion to their $E_{max}$ magnitude—the more efficacious mu-agonist DAMGO causes a more pronounced increase in constitutive receptor activity than morphine [169]. An increase in the level of an endogenous agonist (neurotransmitter) also likely increases the level of constitutive receptor activity. Polter et al. [170] (2017) showed that acute stress increases the constitutive activity of KOP receptors in inhibitory synapses of the VTA. They demonstrated that in GABAergic synapses on VTA dopamine neurons, a single exposure to brief cold-water swim stress induced constitutive activation of KOP receptors, which triggered a relapse to cocaine seeking behavior. Administration of the neutral KOP receptor antagonist 6β-naltrexol does not prevent such relapse, whereas the KOP receptor inactivator (inverse agonist) nor-BNI does. This study suggests that new KOP receptor antagonists (such as aticaprant), which likely lack negative agonistic efficacy, may not be ideal candidates for treating cocaine addiction. Previously, Graziane et al. [171] (2013) showed that blocking KOP receptors with nor-BNI within the VTA prior to forced swim stress prevents the reinstatement of cocaine seeking behavior. Unfortunately, there are currently no data on the comparative efficacy of neutral and inactivating KOP receptor antagonists in other animal models (depression, anxiety, anhedonia). The chronicity and therapeutic resistance of depressive disorders may be largely related to a transition from elevated dynorphin levels at the onset of the disease to increased KOP receptor constitutive activity once the process becomes chronic. This could partially explain the paradoxical results published

by Merlo Pich [136] (2024), where aticaprant was most effective in participants who still retained an active response to placebo during the lead-in phase.

The response to a placebo in RCTs is believed to be determined by various factors, mainly related to participants' expectations based on the informational context surrounding treatment delivery. These expectations are common to all RCT participants, and this effect is often defined as the intrinsic placebo response. The response to placebo (mood improvement) likely reflects the corresponding increase in the activity of the dopaminergic system. If the assumption by Merlo Pich [136] (2024) is correct and the dynorphin/kappa-opioid system plays a role in the development of the placebo effect, then a placebo response can likely be expected in those patients whose reward system activity may still be increased by reducing dynorphin levels. However, presumed patients whose dopaminergic neurotransmission is reduced due to high constitutive KOP receptor activity (rather than elevated dynorphin) would likely not demonstrate rapid restoration of dopaminergic neurotransmission. Reducing constitutive receptor activity may take much longer than reducing synaptic neurotransmitter levels, as perhaps illustrated by the time dynamics of resolving opioid withdrawal syndrome [154,168].

According to the data presented above, kappa-opioid neurotransmission is "silent," meaning that under normal physiological conditions, dynorphin is not tonically released to suppress dopaminergic transmission. A homeostatically more ergonomic mechanism of long-term maintenance of the status quo in neural circuits would be one that does not require constant synthesis and release of a neurotransmitter. Such a mechanism could involve an increase in receptor expression or receptor constitutive activity.

No published data on the $E_{max}$ value of aticaprant were identified. However, the assumption that it is a neutral antagonist (rather than an inverse agonist) could explain its particular efficacy in hypothetical patients whose depression is specifically associated with an excess of dynorphin peptide. Conversely, it may have lower efficacy in hypothetical patients resistant to the placebo effect due to high constitutive KOP receptor activity.

Furthermore, as the placebo response was assumed to be associated with a decrease in dynorphin levels, nocebo reactions might be associated with an increase in dynorphin levels. This could explain an interesting phenomenon: in the navacaprant group, adverse events leading to study discontinuation were observed 12 times less often than in the placebo group [172].

Promising efficacy results of JDTic observed in animal studies of cocaine abuse and acceptable preclinical safety led this compound to Phase 1 clinical trials in 12 healthy volunteers (six received JDTic 1 mg, six received placebo) [173]. 11–13 h after administration of JDTic, two out of six subjects (and 0 out of six in the placebo group) experienced a single, few-second-long, asymptomatic episode of non-sustained ventricular tachycardia (NSVT). The prevalence of asymptomatic NSVT among healthy men ranges from 2 to 3.2% [173]. Therefore, these events led to the cessation of the clinical study. No differences were observed between the placebo and JDTic groups in terms of laboratory or other ECG parameters. The plasma levels of JDTic were below the lower limit of quantification (below 0.1 nM) in all subjects [173]. Although the evidence is indirect, it suggests that NSVT may represent a cardiotoxic potential of JDTic in humans.

Previous studies in macaques showed that 11 h after an oral dose of JDTic, one out of six cynomolgus monkeys (17%) experienced an NSVT event. However, the JDTic dose was 200 mg/kg, which corresponds to an equivalent adult human dose of 4500 mg. Spontaneous NSVT episodes are observed in 13% of the cynomolgus monkeys [173].

Advancement to Phase 1 clinical trials indicates acceptable safety of JDTic in preclinical studies. No evidence of the arrhythmogenic potential of clinically relevant doses of inactivating KOP receptor antagonists in animals has been reported [174]. Given the

presence of KOP receptors in the myocardium, it has been suggested that NSVT might be a consequence of JNK activation in human cardiomyocytes, since neutral KOP receptor antagonists (buprenorphine, aticaprant) lack arrhythmogenic potential [175].

Despite the lack of conclusive evidence that NSVT is a class side effect of inactivating KOP receptor antagonists, attention in subsequent years has been focused only on the development of short-acting kappa-opioid antagonists. Given the disappointment in the clinical efficacy of aticaprant and navacaprant, and the potentially higher clinical efficacy of inactivating antagonists, further research is needed to determine whether the NSVT events in the JDTic group indeed represent a class pharmacological effect unique to humans (but not other primates), caused by JNK activation, and what the associated risks are. However, some attention to inactivating KOP receptor antagonists reemerges [176,177].

### *10.2. Receptor Profile*

Given the paralogous relationship between the kappa-opioid and nociceptin systems, a profound synergy at the level of simultaneous blockade of KOP and NOP receptors, even with neutral antagonists, is plausible.

The hypothesis of paralog compensation is supported by oncology experience, where selective blockade of only one paralogous receptor can lead to compensatory activation of another, leading to resistance when using selective BCL-2 or PARP1 inhibitors, as opposed to non-selective ones [178,179]. Tumor cells tolerate disruption of paralogs better than perturbations of singleton genes, a phenomenon known as "proteomic compensation by paralogs" [59] or "paralog-based synthetic lethality" [61]. Given that COX types 1 and 2 are paralogs [62], in some clinical situations, non-selective NSAIDs seem to be more effective analgesics than selective COX-2 inhibitors [180]. These examples highlight the need to consider the compensatory potential of paralogs in drug development.

Zaveri et al. [181] (2015) demonstrated that removing the methyl groups at the 3 and 4 positions of the JDTic molecule yields AT-076, a blocker of all four opioid receptors, a pan-opioid antagonist. AT-076 is a potent competitive antagonist of MOP and DOP receptors but has the profile of a non-competitive (insurmountable) antagonist at both NOP and KOP receptors. Rational modification of the AT-076 structure could lead to the creation of a dual KOP/NOP antagonist with an acceptable safety profile.

There are theoretical concerns that blockade of MOP receptors may cause (or worsen) depression and anhedonia, since endorphins and enkephalins increase the tone of the reward system. However, published data do not support this hypothesis. In a randomized double-blind placebo-controlled trial involving 306 patients with opioid dependence, Krupitsky et al. [182] (2016) compared the effects of oral naltrexone, long-acting naltrexone (implant), and placebo. Patients receiving naltrexone (both oral and implant) showed no statistically significant differences compared with placebo on depression, anxiety, and anhedonia. This indicates that neutral MOP antagonism does not cause negative affective states [182].

Data on the efficacy of the non-selective opioid antagonist ondelopran (LY2196044) in patients with alcohol dependence have been reported from a Phase 3 double-blind placebo-controlled study. Ondelopran is an equally effective competitive blocker of KOP, MOP, and DOP receptors. Here, too, no differences were observed in the frequency of adverse events such as depression and other affective symptoms, despite the additional blockade of DOP receptors [183].

The results of these studies do not support the hypothesis that blockade of MOP and/or DOP receptors can cause or worsen depression and weaken the "hedoliberating" action associated with antagonism at KOP and/or NOP receptors. Thus, even if new drug candidates block MOP and DOP receptors in addition to KOP and/or NOP receptors,

their therapeutic potential will not be reduced. This expands the opportunities for the development of effective antianhedonic drugs, up to the creation of pan-opioid antagonists.

## 11. Discussion

Despite significant interest in the kappa-opioid system, driven by extensive and consistent preclinical data, large-scale trials of selective KOP or NOP receptor antagonists have demonstrated insufficient clinical efficacy in treatment-resistant or anhedonic depression. Preclinical data suggested potentially high efficacy of KOP blockers for a wide range of conditions associated with hedonic deficit.

One potential reason for this may be that in humans with resistant or anhedonic depression, the increase in kappa-opioidergic tone occurs to a greater extent through an increase in the proportion of spontaneously active (constitutively active) KOP receptors, rather than through elevated dynorphin levels, as appeared in animal models. In such cases, neutral antagonists would be unable to exert significant inhibitory effects on agonist-independent receptor signaling. Inverse agonists or inactivating antagonists of the KOP receptor may be significantly more clinically effective. However, a safety signal related to the potential risk of non-sustained ventricular tachycardia (NSVT), observed in two healthy volunteers after JDTic administration, has impeded the development of this approach.

Another possible reason for the insufficient clinical efficacy of selective antagonists of either KOP or NOP receptors is the mutual functional complementation of these two evolutionarily related receptor systems. Almost all biological systems possess multiple complementary negative feedback loops. These loops can be represented by neurotransmitter systems that emerged during evolution as a result of genome duplications. The resulting duplicate genes (paralogs) seem to retain core functional properties throughout subsequent evolution. Therefore, overcoming system resistance to change by blocking only one paralog (either KOP or NOP receptor), especially with a neutral antagonist, may prove challenging, thus suggesting the promise of developing dual blockers.

This review demonstrates the existence of a large number of research teams studying either the kappa-opioid or nociceptin system separately. However, few, if any, studies have drawn analogies between them or investigated their functional commonalities. The question of their paralogous compensation upon the loss of function of one of them remains unexplored. The pharmacophore structure of a dual KOP/NOP antagonist has been described in the literature; therefore, we believe that clinically effective and safe dual antagonists will eventually be found.

Should this KOP/NOP dual blockade approach prove synergistic at least in animal models, a dual paralog targeting approach would justify research into other families of G protein-coupled receptors.

## 12. Conclusions

The integration of evolutionary genetics concepts into opioid neuropharmacology offers potentially valuable insights, revealing how evolutionarily closely related receptors can compensate for one another's loss of function, rendering selective antagonism of either target alone insufficient. Targeting both paralogous receptors, KOP and NOP, thus represents a rational path forward for drug development. Analogous to the emergence of dopamine receptor blockers (antipsychotics) and monoamine reuptake inhibitors (antidepressants), this strategy may herald a new psychopharmacological class aimed at treating transdiagnostic states of hedonic deficit across depression, PTSD, addictions, and other neuropsychiatric disorders. Should this approach prove effective, the novelty of its target profile and clinical-dimensional scope invites consideration of a psychopharmacological class name. One candidate may be "hedoliberants"—from Greek hēdonē (ἡδονή, plea-

sure) and Latin liberatio (release), highlighting the alleviation of excessive reward system suppression and, potentially, a low or absent addictive potential.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| 5-HT | serotonin (5-hydroxytryptamine) |
| cAMP | cyclic adenosine monophosphate |
| CeA | central nucleus of the amygdala |
| CGI-I | Clinical Global Impression-Improvement |
| CGI-S | Clinical Global Impression-Severity |
| COX | cyclooxygenase |
| CPA | conditioned place aversion |
| CPP | conditioned place preference |
| D1-MSN | medium-sized spiny neurons expressing D1 receptors |
| DA | dopamine |
| DAT | dopamine transporter |
| DARS | Dimensional Anhedonia Rating Scale |
| DOP | delta-opioid peptide (receptor) |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, 5th edition |
| Dyn | dynorphin |
| ECG | electrocardiogram |
| EEfRT | Effort Expenditure for Rewards Task |
| eITT | enriched intent-to-treat (population) |
| ES | effect size |
| ETB | Emotional Test Battery |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| fITT | full intent-to-treat (population) |
| fMRI | functional magnetic resonance imaging |
| GABA | gamma-aminobutyric acid |
| GPCR | G protein-coupled receptor |
| GRID-HAMD-17 | GRID-Hamilton Depression Rating Scale, 17-item version |
| HAM-A | Hamilton Anxiety Rating Scale |
| HAM-D/HAMD-17 | Hamilton Depression Rating Scale (17-item) |
| HDD | heavy drinking days |
| ICD-11 | International Classification of Diseases, 11th revision |
| JNK | c-Jun N-terminal kinase |

| | |
|---|---|
| KOP | kappa-opioid peptide (receptor) |
| MADRS | Montgomery–Åsberg Depression Rating Scale |
| MAPK | mitogen-activated protein kinase |
| MDD | major depressive disorder |
| MOP | mu-opioid peptide (receptor) |
| mRNA | messenger ribonucleic acid |
| MSN | medium-sized spiny neuron |
| NA | noradrenaline (norepinephrine) |
| NAc | nucleus accumbens |
| NADPH | nicotinamide adenine dinucleotide phosphate |
| NDD | number of drinking days |
| NOP | nociceptin opioid peptide (receptor) |
| norBNI | nor-binaltorphimine |
| NSAID | non-steroidal anti-inflammatory drug |
| NSVT | non-sustained ventricular tachycardia |
| ORL1 | opioid receptor-like 1 (receptor) |
| PARP | poly(ADP-ribose) polymerase |
| PET | positron emission tomography |
| PFC | prefrontal cortex |
| PRDX6 | peroxiredoxin 6 |
| PTSD | post-traumatic stress disorder |
| QIDS | Quick Inventory of Depressive Symptomatology |
| R1 | first round of genome duplication |
| R2 | second round of genome duplication |
| RCT | randomized controlled trial |
| ROS | reactive oxygen species |
| RT-PCR | real-time polymerase chain reaction |
| SHAPS | Snaith–Hamilton Pleasure Scale |
| SNc | substantia nigra pars compacta |
| SNRI | serotonin–norepinephrine reuptake inhibitor |
| SSRI | selective serotonin reuptake inhibitor |
| TH | tyrosine hydroxylase |
| TRD | treatment-resistant depression |
| VTA | ventral tegmental area |
| WHO | World Health Organization |

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