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Farid Shagiakhmetov * , Inna Shamakina , Viktor Kokhan , Evgeny Krupitsky

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Review

Opioid Antagonists for Hedonic Liberation—Not All Is Over

Farid Shagiakhmetov [1,*], Inna Shamakina [1], Viktor Kokhan [1] and Evgeny Krupitsky [2,3]

[1] Federal State Budgetary Institution "V.P. Serbsky National Medical Research Center of Psychiatry and Narcology" of the Ministry of Health of the Russian Federation

[2] Federal State Budgetary Institution "V. M. Bekhterev National Medical Research Center for Psychiatry and Neurology" of the Ministry of Health of the Russian Federation

[3] A.V. Valdman Institute of Pharmacology, Pavlov First Saint Petersburg State Medical University of the Ministry of Health of the Russian Federation

* Correspondence: shagiakhmetov.f@serbsky.ru; Tel.: +79660931117

Abstract

Recent Phase 3 clinical trials of selective kappa-opioid peptide (KOP) receptor antagonists – aticaprant (Johnson & Johnson, VENTURA trial, 2025) and navacaprant (Neumora, KOASTAL-1 trial, 2025) – failed to demonstrate sufficient clinical efficacy in treatment-resistant depression (TRD). We propose two hypotheses that could explain these setbacks: (1) neutral antagonists may be poorly effective in patients with TRD due to constitutive KOP receptor hyperactivation and (2) the KOP receptor paralog – nociceptin opioid peptide (NOP) receptor – can effectively compensate for KOP receptor blockade decreasing the magnitude of clinical efficacy. We hypothesize that functional redundancy provided by NOP receptor signaling requires dual KOP/NOP blockade to achieve clinically meaningful improvement in reward function. Recent insights gained from paralogous compensation in drug-resistant tumors underscore the need for dual-target approaches. We propose that future studies, if successful, may yield a novel pharmacological class targeting opioid-mediated hedonic suppression, advocating for the development of opioid inverse agonists (such as norBNI), pan-antagonists (such as AT-076), and combinations of selective blockers.

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

1. Introduction

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, posttraumatic 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-opioid peptide (MOP) receptor agonists and, to a lesser extent, delta-opioid peptide (DOP) receptor agonists. These receptors increase dopamine

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levels in the nucleus accumbens (NAc), a key center of the brain's reward system. In contrast, stimulation of KOP and NOP receptors exerts a hedolytic 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, the action of antidepressants has been targeted to enhance monoaminergic transmission in the limbic system and cortex [12,13]. The brain's "anti-reward" system seems to be a promising target for the development of innovative antidepressants [14,15]. 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 tone of the kappa-opioid and/or nociceptin systems. Thus, as long as the dopamine system is under kappa-opioid suppression, antidepressants will not work. Three selective KOP receptor antagonists (aticaprant, navacaprant, and icalcaprant) and one selective NOP receptor antagonist (LY2940094 or BTRX-246040) have undergone clinical trials for the treatment of resistant depression (TRD), insufficient response to a first-line antidepressant, and depression with anhedonia [16]. However, their efficacy has been lower than anticipated.

Here we discuss the potential reasons for insufficient clinical efficacy of selective neutral antagonists of KOP or NOP receptors. KOP and NOP coding genes are evolutionary paralogs formed by the duplication of a single ancestor gene [17]. They diverged during evolution but retained some degree of functional homology, and can potentially compensate for each other's loss of function. Simultaneous blockade of both KOP and NOP receptors could increase clinical efficacy. The development of dual inverse agonists for both KOP and NOP receptors may prove to be the most promising approach. This review represents a theoretical basis for the emergence of a new psychopharmacological class: antagonists of the hyperactive opioidergic negative feedback loop within the endogenous reward system. We also propose a name for this class at the end of this article.

2. 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 [18]. 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 [2,4,19,20].

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 [21]. Anhedonia is commonly observed in depressive syndrome, dissociative disorders following psychological trauma, and substance use disorders (SUD) [19,22].

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 [18,20,23–25]. Anhedonia may also be a clinical predictor of unsuccessful treatment outcome and a potential target for pharmacological intervention in addiction [26]. Patients with substance use disorders exhibit reduced sensitivity to pleasurable non-drug-related stimuli [27]. The emergence of anhedonia marks the transition from recreational drug use to drug dependence. A strong

 doi:10.20944/preprints202603.1698.v1

correlation exists between anhedonia and craving, which is associated with vulnerability to relapse [22,26,28].

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" [29,30].

In the psychological 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. In psychiatric literature, "devitalization" is rarely used as a clinical term; instead, 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 [29,30]. According to the ICD-11 (code 7B36) 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 [31–33].

3. 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 [34,35]. 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 μ/δ precursor and (2) a κ/ORL1 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: μ- (MOP), δ- (DOP), κ- (KOP), and ORL1- (NOP) [17,35,36]. 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.

KOP receptors are localized in the somatodendritic regions of dopaminergic neurons [37]. Notably, blockade of KOP receptors does not increase the firing rate of dopaminergic neurons in the reward system [38,39]. 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) [40–42].

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 [40]. 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 [43]. Olianas et al. (2008) demonstrated the inhibitory effect of nociceptin on the activity of the dopamine-synthesizing enzyme TH in the presynaptic terminals of striatal dopaminergic projections [44]. Studies have shown that blockade of NOP receptors enhances dopaminergic neurotransmission [45] showing promise in Parkinson's disease [46].

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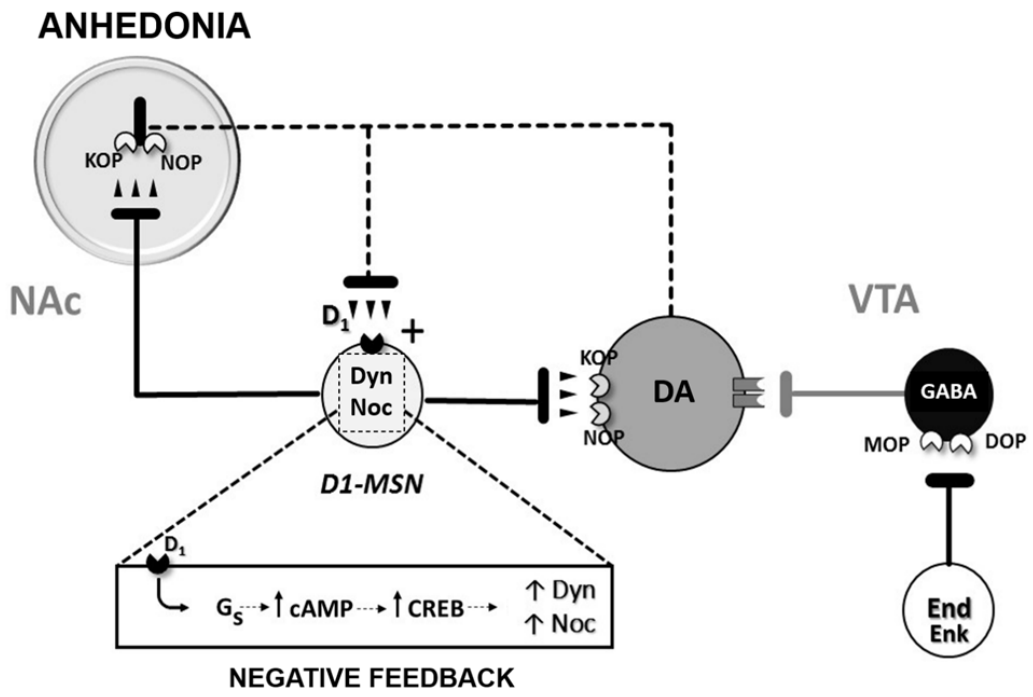

Figure 1. Negative feedback in the reward system (anti-reward system). Activation of MOP and DOP receptors disinhibits dopamine neurons and significantly increases dopamine levels in the nucleus accumbens of the ventral striatum. In contrast, the activation of KOP and NOP receptors suppresses the release of dopamine, producing depression, dysphoria, and anhedonia. Stimulation of KOP and NOP receptors in animals cancels the antidepressant-like and positive reinforcing effects of opioids, cocaine, and alcohol. Thus, the KOP/NOP system functions as a powerful negative feedback mechanism within the dopaminergic reward system. NAc, nucleus accumbens; VTA, ventral tegmental area; D1-MSN, medium-sized spiny neurons expressing D1 receptors; Dyn, dynorphin; Noc, nociceptin; End, endorphin; Enk, enkephaline; DA, dopamine; GABA, gamma-aminobutyric acid; cAMP, cyclic adenosine monophosphate; CREB, transcription factor.

Duplicated genes likely contributed to the evolution of the mammalian brain [47]. Many paralogs perform similar functions, and if one is lost, the other can partially take over its functions to maintain homeostasis [48–50]. Regarding neurotransmitter systems, genes encoding β_1- and β_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 [51–53].

Our data suggest similar changes between the kappa-opioid and nociceptin systems in a rodent two-bottle choice alcohol-drinking test [54,55]. 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 nociception – 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 [54,55].

4. 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,

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depersonalization, loss of physical body sensation, and hallucinatory experiences [56–58]. In animal models, anhedonic states are accompanied by an increased intracranial self-stimulation (ICSS) threshold [59]. 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 [60,61]. Importantly, systemic administration of KOP receptor agonists to intact animals increases the ICSS threshold [60,62], 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 [63–67].

In rats, KOP receptor agonists induce conditioned place aversion (CPA) mediated by KOP localized on dopaminergic neurons [68,69]. Activation of these receptors reduces dopamine release in the nucleus accumbens and cerebral cortex [15]. Presynaptic KOP receptors in the striatum may be directly associated with DAT, positively modulating its activity and enhancing dopamine reuptake [70,71]. Direct microinfusion of a KOP blocker into the nucleus accumbens has been shown to produce an antidepressant effect [15,62,72]. Thus, the kappa-opioid system acts as a negative feedback mechanism to suppress excessive dopaminergic neurotransmission in the ventral striatum [73]. GABAergic medium-sized spiny neurons (MSNs) of the direct pathway express both dynorphin and D1 receptor (D1-MSNs) [74]. These neurons send projections to the VTA [72,75], where KOP receptors are localized on the cell bodies and dendrites of dopaminergic neurons of the mesocortical, but not mesolimbic, pathway [76–78]. 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 [79]. 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 [80–83] and locomotor sensitization [84]. 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 [85–87]. 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 [88].

Activation of nociceptinergic neurons innervating VTA suppresses reward motivation, while a single dose of a NOP receptor antagonist enhanced electrophysiological markers of reward learning [89,90].

Pizzagalli et al. (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 [91].

5. 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 [92]. 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 [93,94]. 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 [95].

 doi:10.20944/preprints202603.1698.v1

Stress enhances cocaine-induced conditioned place preference (CPP), and this effect is mimicked by the intravenous administration of a KOP receptor agonist [96]. Pretreatment with a KOP receptor antagonist (JDTic or nor-BNI) significantly reduced stress-induced (foot-shock) reinstatement of extinguished cocaine self-administration [97,98]. 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 [98].

Activation of NOP receptor as well as social defeat stress induce neuroinflammatory effects in the hippocampus and are associated with depressive-like behaviors in mice [99]. NOP receptor antagonists prevented the development of helplessness in mice exposed to inescapable stress [100]

Prolonged blockade of NOP receptors reversed the stress-induced reduction in sucrose consumption caused by chronic stress. A 21-day administration of UFP-101 abolished the behavioral, neurochemical, and endocrine changes induced by chronic mild stress [101]. Thus, nociceptin not only shares structural similarities with dynorphin but also exerts a functionally similar influence on hedonic tone under baseline conditions [91].

6. Dynorphin and Nociceptin Opioid Systems and Addiction

KOP receptor agonists reduce the reinforcing effects of alcohol and drugs of abuse [102,103] by suppressing mesolimbic dopaminergic neurotransmission [104]. For instance, systemic administration of KOP agonists dose-dependently reduces self-administration of cocaine and morphine in intact (non-dependent) rats [105,106]. Investigation of the reinforcing properties of cocaine in intact monkeys revealed that the KOP agonist U50,488 administered prior to cocaine self-administration significantly suppressed the motivation to obtain cocaine [107]. These results provide robust evidence for the inhibitory effect of KOP 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 agonists increases drug consumption, which can be interpreted as an attempt to overcome the anhedonia induced by KOP stimulation [108,109]. In animals with established dependence, a reduction in substance consumption can be achieved through the administration of KOP blockers. This indicates hyperactivation of the kappa-opioid system and reflecting the mechanism of drug tolerance and establishment of the anhedonic component of withdrawal syndrome [110].

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, CeA prepronociceptin gene expression in ethanol-dependent animals was markedly higher three weeks post-withdrawal compared with both nondependent controls and experimentally naïve rats [111].

Using a free-choice task combined with RT-PCR analysis, we measured prepronociceptin and NOP receptor mRNA levels in the mesolimbic areas of rats with different alcohol drinking behaviors. We found that alcohol rats have lower levels of prepronociceptin mRNA in the striatum and NOP receptor mRNA in the amygdala, suggesting that the nociceptin, along with dynorphin, may play a key role in addiction [112].

7. Clinical Trials of Kappa Opioid 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 [113].

Table 1 summarizes the results of clinical trials of κ-opioid antagonists. A key clinical trial of selective KOP blockers was the aticaprant trial, which used the NIMH Fast-Fail methodology. This methodology assumes that biomarkers (brain activity) are more sensitive and allow for early confirmation of effects on target neural circuits using smaller sample sizes [114].

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This randomized, double-blind, placebo-controlled Phase 2a proof-of-mechanism study investigated the use of aticaprant for treating anhedonia in patients with mood or anxiety disorders. Patients receiving aticaprant had a significant increase in ventral striatal activation during reward anticipation in a monetary incentive delay task, measured using functional magnetic resonance imaging (fMRI), compared with the placebo group. The observed effect of aticaprant on brain regions involved in pleasure was associated with a reduction in anhedonia, as assessed by the Snaith-Hamilton Pleasure Scale (SHAPS), indicating its potential as a therapy for anhedonia [114].

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. 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 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 (anxiety) scores [115,116].

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[1]. By the end of 2023, J&J had forecasted the annual peak sales of aticaprant to be between $1 and $5 billion [2].

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 [3]. 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 [4].

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. At week 8, the difference in the 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 [117].

Previously, the combined opioid antagonist ALKS-5461 from Alkermes did not receive FDA approval. ALKS-5461 is a combination of buprenorphine (a partial MOP agonist and neutral KOP

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[1] Johnson & Johnson. (2025, 6 Mar). Johnson & Johnson statement on Ventura program [Press release]. https://www.jnj.com/media-center/press-releases/johnson-johnson-statement-on-ventura-program [Accessed 22.07.2025]

[2] Fierce Biotech (2025, 7 Mar). J&J fails an Ace Ventura, stopping phase 3 depression program over insufficient efficacy. Fierce Biotech. https://www.fiercebiotech.com/biotech/jj-fails-ace-ventura-stopping-phase-3-depression-program-over-insufficient-efficacy [Accessed 22.07.2025]

[3] Fierce Biotech (2025, 2 Jan). Neumora stumbles at start of phase 3 depression readout run, sending stock down 80%. Fierce Biotech. https://www.fiercebiotech.com/biotech/neumora-stumbles-start-phase-3-depression-readout-run-sending-stock-down-80 [Accessed 22.07.2025]

[4] https://ir.neumoratx.com/news-releases/news-release-details/neumora-therapeutics-reports-data-koastal-1-study-navacaprant

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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 [118,119]. 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 [120]. 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 [121]. Two other multicenter Phase 3 RCTs (FORWARD-4 and FORWARD-5) also evaluated the safety and efficacy of ALKS-5461 for the same indication [122]. 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 [122]. 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" [5].

Excessive and unpredictable placebo effects "dilute" the therapeutic response, thereby negating statistical significance. 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 placebo and their initial response is tracked before randomization into active and control groups. It is assumed that participants who respond to placebo during the lead-in period are more likely to respond to placebo during the dosing period. Excluding this placebo-responsive group from the final analysis is thought to potentially benefit drug efficacy signal detection [123].

A placebo lead-in period was used as one of the optimization procedures in the aforementioned Phase 2 study of aticaprant. The authors defined two populations: the first, enriched with participants who did not respond to the placebo lead-in (eITT), and the second, including all participants regardless of their response during the lead-in period (fITT). However, the results were the opposite of what was predicted. The aticaprant-induced improvement in MADRS was stronger in the fITT population than in the eITT population [115]. 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 [124,125]. 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 [125].

Table 1. Selected clinical trials of kappa-opioid 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 [114]	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 [115]	Major depressive disorder	RCT, double-blind, 6 weeks, placebo lead-in	166 (fITT); 121 (eITT)	10 mg (adjunctive to SSRI/SNRI)	Improvement in MADRS total score for aticaprant was significant versus placebo (eITT: −2.1 [−1.09], 1-sided p = 0.044; effect size (ES) 0.23; fITT −3.1 [2.21], 1-sided p = 0.002; ES 0.36). The between-group difference was larger among participants with SHAPS score greater/equal to versus less than baseline median SHAPS. Responders: 36.4% (JNJ) vs 24.0% (PBO)

[5] FDA Advisors Overwhelmingly Reject Alkermes Depression Drug. BioSpace, 2 Nov. 2018 [cited 2025 Jan 10]. Available from: www.biospace.com/article/fda-advisors-overwhelmingly-reject-alkermes-depression-drug

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					fITT, p<0.05; QIDS: p=0.029; CGI-I: p=0.046
Aticaprant Phase 3 VENTURA Program (2025) [J&J Press Release][6]	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 efficacy not disclosed
Navacaprant Phase 2a [117]	MDD with anhedonia and anxiety	RCT, double-blind, 8 weeks	204	80 mg	Primary endpoint (change in HAMD-17) not achieved; but was statistically significant in moderate-to-severe subgroup (n=100) at weeks 4 and 8 as well as SHAPS score at week 8
Navacaprant Phase 3 KOASTAL-1 [Neumora Therapeutics press release][7]	Moderate-to-severe MDD	RCT, double-blind, 6 weeks	383	80 mg	Primary endpoint not achieved; change in SHAPS and MADRS was identical for both groups; change in SHAPS was statistically significant in favor of navacaprant in female subset of patients https://ir.neumoratx.com/news-releases/news-release-details/neumora-therapeutics-reports-data-koastal-1-study-navacaprant
ALKS-5461 Phase 2 [120]	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)	Greater improvement over placebo was observed in the 2 mg /2 mg group across all three depression outcome measures (HAM-D; MADRS; CGI-S). There was also evidence of improvement in the 8 mg /8 mg dosage group, although it did not achieve statistical significance. HAM-D response rates: 60% (2 mg /2 mg dose) vs 20% (PBO);
ALKS-5461 Phase 3 FORWARD-3 [121]	MDD with inadequate antidepressant response	Double-blind, placebo run-in, 10 weeks	295	2 mg/2 mg Placebo (adjunctive to antidepressant)	Change in MADRS-10 did not achieve statistical significance. Response rate 16.9% (ALKS-5461) vs 14.4% (placebo), non-significant; Remission 14.1% vs 12.3%, non-significant.
ALKS-5461 Phase 3 FORWARD-4 FORWARD-5 [122]	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 achieved the primary endpoint (change from baseline through end of treatment (EOT) in MADRS-6 and -10) in 2 mg/2 mg group. FORWARD-4 did not achieve the primary endpoint (change from baseline in MADRS-10 at week 5 versus placebo, P = 0.109). The pooled analysis of the two studies demonstrated consistently greater reduction in MADRS-10 scores from baseline for 2 mg/2 mg group at multiple timepoints including primary endpoint.

8. Clinical Trials of Nociceptin Opioid 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 [126]. Gu et al. (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 [127].

[6] Johnson & Johnson. (2024). Johnson & Johnson statement on Ventura program. [cited 2025 Jan 10]. Available from: https://www.jnj.com/media-center/press-releases/johnson-johnson-statement-on-ventura-program

[7] Neumora Therapeutics. (2025). Neumora Therapeutics reports data from KOASTAL-1 study of navacaprant. [cited 2026 Jan 10]. Available from:https://ir.neumoratx.com/news-releases/news-release-details/neumora-therapeutics-reports-data-koastal-1-study-navacaprant

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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 [128]. 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. 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 [129].

PET imaging in humans has demonstrated that the NOP receptor is activated in healthy individuals under stress conditions. The acute rise in glucocorticoids during stress increases the density of NOP receptors in various brain regions [130]. 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 [131].

BTRX-246040 (also known as LY2940094) is a selective NOP antagonist [132,133]. In Phase 2 clinical trials involving patients with depression [134] and alcohol dependence [135], BTRX-246040 was safe and well tolerated. Table 2 summarizes the data on the results of clinical trials of BTRX-246040.

The first double-blind placebo-controlled study involved 184 patients with MDD who received BTRX-246040 for 8 weeks. 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 [134].

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. The ETB can detect early effects of antidepressants, such as improved recognition of emotions from facial expressions, which often precedes mood improvement. 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 [136,137]. 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 [134].

Another double-blind, placebo-controlled study involved patients with alcohol dependence who received BTRX-246040 for 8 weeks. The reduction in the mean number of drinking days (NDD) did not differ between the BTRX-246040 and placebo groups. 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 [135].

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. Neumora Therapeutics, which acquired BlackThorn, has not announced plans to resume studies of the drug[8].

Pizzagalli et al. (2025) present a landmark series of four complementary studies that elegantly bridge preclinical mechanisms to human clinical outcomes. The investigation establishes the NOP

[8] BioCentury. (2019, 11 Jan). BlackThorn deprioritizing MDD compound after Phase IIa miss. https://www.biocentury.com/article/300266/blackthorn-deprioritizing-mdd-compound-after-phase-iia-miss [Accessed 22.07.2025]

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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) [91].

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 [138]. This demonstrates 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 [91].

Table 2. Clinical trials of nociceptin opioid receptor antagonist BTRX-246040 (LY2940094).

Study	Indication	Study Design	Number of Participants (N)	Groups and daily doses	Efficacy Results
BTRX-246040 Phase 2 [134]	Major Depressive Disorder	RCT, double-blind, 8 weeks	136	40 mg	The primary endpoint (probability of BTRX-246040 being better than placebo⩾88% on the GRID-HAMD-17 depression scale) in the full analysis set was not met (the actual value was 82,9%), but was met in per protocol population (88,6%). When the analysis in the full analysis set was extended to include a follow-up visit (weeks 9-10), the probability of BTRX-246040 being better than placebo reached 97,4%. The probability of BTRX-246040 being better than placebo in improving the ability to recognize positive emotional expressions was 92.4%
BTRX-246040 Phase 2 [135]	Alcohol dependence	RCT, double-blind, 8 weeks	88	40 mg	NDD did not differ versus placebo; HDD showed improvement versus placebo (-24.5 vs. -15.7%; 93% better than placebo); mean percentage of abstinent days was higher compared to placebo (9.1 vs. 1.9%; 91% better than placebo)
BTRX-246040 Phase 2 [91]	Major Depressive Disorder	RCT, double-blind, 8 weeks	102	40-80 mg	BTRX-246040 did not significantly separate from placebo on the primary MADRS or on secondary endpoints (DARS, SHAPS). EEfRT (t) parametr showed significant group×time interaction (b=0.84, p=0.015); was significantly increasing for the BRTX 246060 group (b = 0.88, p <0.001).

9. Novel Drugs Development Prospects

9.1. 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 [139,140].

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 [140].

At any given time, a certain proportion of receptors in a population exist 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

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endogenous neurotransmitter is considered a full agonist, and its maximal agonist efficacy (E_{max}) [9] is conventionally set at +100%. Agonists have the highest affinity for one or more active receptor conformations, whereas inverse agonists have the highest affinity for the inactive conformation. By binding to the receptor, they increase the duration for which the receptor remains in a specific spatial configuration. Thus, an inverse agonist decreases the basal level of activation of secondary messenger systems, conventionally taken as "0". Accordingly, E_{max} for inverse agonists 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 [139,141,142].

In most preclinical studies on kappa-opioid receptors, selective antagonists such as nor-binaltorphimine (norBNI) 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 norBNI in mammals can block KOP receptors for several weeks [143–145].

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)pentanamideamide] produce continued anxiolytic and antidepressant effects in rats after a single injection, with KOP receptor blockade lasting up to 28 days [146–149].

The mechanisms underlying such a prolonged receptor blockade have remained unclear for a long time. Neither norBNI nor JDTic were found to be classical antagonists. Rather, they are functionally selective agonists of the KOP receptor that activate c-Jun N-terminal kinase (JNK) [150,151]. 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 [152–154].

Pharmacological inhibition of JNK or PRDX6 components in this signaling pathway, or genetic deletion of JNK-1, prevented the long duration of action of norBNI, converting it into a short-acting competitive antagonist [150–152]. In this context, ligands such as norBNI 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 [152].

Constitutive receptor activity can exert a tonic influence on the basal level of neuronal activity even in the absence of a neurotransmitter [139]. 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. For instance, chronic morphine administration significantly increases the level of constitutive MOP receptor activity in the rat brain. 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 [141,155]. 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 [156]. An increase in the level of an endogenous agonist (neurotransmitter) also likely

[9] E_{max} [agonist efficacy] — the magnitude of the maximum activation of the secondary messenger system under the action of an agonist at its maximum concentration. Previously, the term intrinsic (agonistic) activity was used in the literature.

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increases the level of constitutive receptor activity. Polter et al. (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) norBNI 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 [157]. Previously, Graziane et al. (2013) showed that blocking KOP receptors with norBNI within the VTA prior to forced swim stress prevents the reinstatement of cocaine seeking behavior [158]. 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 (2024), where aticaprant was most effective in participants who still retained an active response to placebo during the lead-in phase [125].

The response to 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 (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 [125]. 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 [141,155].

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.

We were unable to find data on the E_{max} value of aticaprant. 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 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 [10].

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

[10] Neumora Therapeutics. Phase 2 results of NMRA-140 in major depressive disorder [poster presentation]. ACNP Annual Meeting; December 2023. https://neumoratx.com/wp-content/uploads/2024/08/ACNP23_Ph2_Poster_Final.pdf [Accessed 22.07.2025]

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JDTic 1 mg, six received placebo). 11-13 hours 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% [50]. 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. 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 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 [50].

Advancement to Phase 1 clinical trials indicates acceptable safety of JDTic in preclinical studies. We also could not find evidence of the arrhythmogenic potential of clinically relevant doses of inactivating KOP receptor antagonists in animals [159]. 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 [160].

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 [161,162].

9.2. 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 [163,164]. Tumor cells tolerate disruption of paralogs better than perturbations of singleton genes, a phenomenon known as “proteomic compensation by paralogs” [48] or “paralog-based synthetic lethality” [50]. Given COX types 1 and 2 are paralogs [51], in some clinical situations, non-selective NSAIDs seem to be more effective analgesics than selective COX-2 inhibitors [165]. These examples highlight the need to consider the compensatory potential of paralogs in drug development.

Zaveri et al. (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 [166]. 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, the results of our study refute this hypothesis. In a randomized double-blind placebo-controlled trial involving 306 patients with opioid dependence, the effects of oral naltrexone, long-acting naltrexone (implant), and placebo were compared. Patients receiving naltrexone (both oral and implant) showed no statistically significant differences compared with

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placebo on depression, anxiety, and anhedonia. This indicates that neutral MOP antagonism does not cause negative affective states [167].

We also present data on the efficacy of the novel non-selective opioid antagonist ondelopran (LY2196044) in patients with alcohol dependence, obtained 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 [11].

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.

10. Conclusions

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 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 both KOP and NOP receptors is the mutual functional complementation of these two evolutionarily related receptor systems. Almost all biological systems possess multiple complementing 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) 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 the kappa-opioid and nociceptin systems separately. However, few 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 inhibitors of these two opioid systems will eventually be found. Much like the emergence of dopamine receptor blockers (forming the class of antipsychotics) and monoamine reuptake inhibitors (forming the class of

[11] Shagiakhmetov F, Mukhametshina E, Samsonov M. Novel triple opioid receptor antagonist ondelopran (LY2196044) for the treatment of alcohol dependence. Phase III study: female subjects subset efficacy and safety analysis [poster]. Presented at: European Psychiatric Association Congress (EPA); 2019; Nice. Available from: https://doi.org/10.13140/RG.2.2.35480.96001.

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antidepressants), we are on the verge of a new psychopharmacological class for treating states of hedonic deficit caused by depression, PTSD, addictions, and other neuropsychiatric disorders.

The potential for the emergence of a novel psychopharmacological class in terms of receptor targets and clinical-dimensional profiles prompts consideration of a name for this class. One option could be the term "hedoliberants" – from Latin "hedon" (pleasure) and "liberatio" (liberation). This term emphasizes the nature of relieving excessive suppression of the reward system, likely reflecting a low or absent addictive potential for this class of positive regulators of hedonic tone.

Conflicts of Interest: The authors declare no conflicts of interest.

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