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REVIEW ARTICLE

Current and Future Therapeutic Options in Pain Management: Multi-mechanistic Opioids Involving Both MOR and NOP Receptor Activation

Flaminia Coluzzi[1,2] · Laura Rullo[3] · Maria Sole Scerpa[2] · Loredana Maria Losapio[3] · Monica Rocco[4] · Domenico Billeci[5] · Sanzio Candeletti[3] · Patrizia Romualdi[3]

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Abstract

Opioids are widely used in chronic pain management, despite major concerns about their risk of adverse events, particularly abuse, misuse, and respiratory depression from overdose. Multi-mechanistic opioids, such as tapentadol and buprenorphine, have been widely studied as a valid alternative to traditional opioids for their safer profile. Special interest was focused on the role of the nociceptin opioid peptide (NOP) receptor in terms of analgesia and improved tolerability. Nociceptin opioid peptide receptor agonists were shown to reinforce the antinociceptive effect of mu opioid receptor (MOR) agonists and modulate some of their adverse effects. Therefore, multi-mechanistic opioids involving both MOR and NOP receptor activation became a major field of pharmaceutical and clinical investigations. Buprenorphine was re-discovered in a new perspective, as an atypical analgesic and as a substitution therapy for opioid use disorders; and buprenorphine derivatives have been tested in animal models of nociceptive and neuropathic pain. Similarly, cebranopadol, a full MOR/NOP receptor agonist, has been clinically evaluated for its potent analgesic efficacy and better tolerability profile, compared with traditional opioids. This review overviews pharmacological mechanisms of the NOP receptor system, including its role in pain management and in the development of opioid tolerance. Clinical data on buprenorphine suggest its role as a safer alternative to traditional opioids, particularly in patients with non-cancer pain; while data on cebranopadol still require phase III study results to approve its introduction on the market. Other bifunctional MOR/NOP receptor ligands, such as BU08028, BU10038, and AT-121, are currently under pharmacological investigations and could represent promising analgesic agents for the future.

Flaminia Coluzzi and Laura Rullo have contributed equally to this work.

✉ Sanzio Candeletti
sanzio.candeletti@unibo.it

1 Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, Latina, Italy

2 Unit Anesthesia, Intensive Care and Pain Medicine, Sant'Andrea University Hospital, Rome, Italy

3 Department of Pharmacy and Biotechnology, Alma Mater Studiorum – University of Bologna, Irnerio 48, Bologna 40126, Italy

4 Department of Surgical and Medical Science and Translational Medicine, Sapienza University of Rome, Rome, Italy

5 Ismerian Pain Clinic, Treviso, Italy

1 Introduction

Chronic pain is defined as pain that lasts or recurs for longer than 3 months and that persists beyond normal healing time, hence lacks the acute warning function of physiological nociception [1]. This pathological condition affects about 30% of people worldwide [2] and although mortality rates are highest for other pathologies, it represents one of the main sources of human suffering and disability that profoundly impacts patients' quality of life.

Even though therapeutic schemes should be mechanism based and tailored for each patient, opioids still represent one of the main choices for moderate-to-severe pain, in both patients with cancer [3] and non-cancer patients [4]. However, chronic opioid use is often linked to a series of adverse effects, of which the most common is opioid-induced bowel

Key Points

Multi-mechanistic opioids involving both mu opioid receptor (MOR) and nociceptin opioid peptide (NOP) receptor activation currently represent a major field of pharmaceutical and clinical investigations because the activity on the NOP receptor may reinforce the antinociceptive effect of MOR agonists and modulate some of their adverse effects.

Buprenorphine has been recently rediscovered as an "atypical analgesic" for its activity on all the opioid receptors (MOR, delta opioid receptor, kappa opioid receptor, and NOP) and as an alternative to methadone for the treatment of opioid use disorders, in many different innovative formulations.

Cebranopadol and other bifunctional MOR/NOP receptor ligands, such as BU08028, BU10038, and AT-121, are currently under investigations as promising analgesic agents for the management of acute and chronic pain syndromes.

dysfunction, which comprises a wide range of signs and symptoms, for example, nausea, vomiting, and opioid-induced constipation [5]. In the last few years, major concerns emerged from other emerging opioid-related side effects, particularly the risk of dependence, abuse, and misuse. The current opioid epidemic, faced by the US, represents a limiting factor, which strongly impacts opioid prescriptions even in other countries [6]. Several causes are responsible for the opioid crisis outcome including their misuse and/or abuse, as well as social and economic conditions [7].

Moreover, continuous activation of opioid receptors, owing to the prolonged opioid administration, results in the paradoxical enhancement of pain sensitivity and induces a series of molecular adaptive changes, which seem to be responsible of the decrease of the drug's effects over time (tolerance). Opioid-induced hyperalgesia and tolerance to the analgesic effect may impair the clinical effect of long-term opioid therapy, leading to the reduction/cessation of opioid administration or to an increase in the opioid dosage in order to maintain adequate analgesia [8].

These dose-limiting adverse effects of traditional opioids are mainly related to μ-opioid receptor (MOR) activation (respiratory depression, itching, gastrointestinal side effects, physical dependence, and abuse liability), which is also the main mechanism by which opioids provide analgesia. Therefore, the pharmaceutical research has been focused in the last few years in the identification of innovative analgesics, characterized by similar potency and efficacy compared to the common opioid agonists (i.e., morphine, oxycodone, fentanyl), but with a better tolerability profile (fewer side effects and abuse liability).

Current therapeutic strategies include the use of multi-mechanistic opioids, which are a class of molecules acting through distinct mechanisms. Tapentadol represents one of these drugs, as the first in class of a family of analgesics, named the MOR agonist and norepinephrine reuptake inhibitors, known as the MOR/norepinephrine reuptake inhibitors. Given its dual mechanism of action, tapentadol showed a good safety and tolerability profile compared to "classical" MOR agonists, especially for gastrointestinal side effects [9], providing better clinical outcomes at lower costs [10]. The norepinephrine reuptake inhibitor activity is responsible for enhancing inhibitory descending pathways, which play a key role in the maladaptive neuronal plasticity [11]. In addition, the lack of activity on the serotonin pathway ensures a safer profile, reducing the risk of nausea, vomiting, hypoglycemia, and serotonin syndrome, when compared with other drugs acting on both inhibitory descending neurotransmitters, such as tramadol [12]. Tapentadol has been considered an "atypical" opioid because of its ability as a strong analgesic, without being a strong opioid. Its activity on MOR is, indeed, 50-fold lower than morphine; however, in clinical trials, its effect was comparable to that of oxycodone [13]. This evidence led to the hypothesis that dual mechanistic opioids, through a lower activity on MOR, could be also evaluated for their potential in combating opioid misuse [14].

Methadone has also a unique multi-mechanistic pharmacological profile, as it is a potent agonist at the MOR and delta opioid receptor (DOR), but it has also been assumed to be a potent inhibitor of the N-methyl-D-aspartate (NMDA) receptor. This dual mechanism of action makes this drug interesting for treating severe chronic pain syndromes characterized by hyperalgesic states, such as in patients with cancer pain, in the context of opioid rotation, when other drugs lose their efficacy [15]. However, recent evidence showed that, at therapeutic doses, and by analyzing in vitro activities on different receptors, methadone is unlikely to have interactions with the NMDA receptors, which could play a role in analgesia. Its profile seems, indeed, to be closer to that of tramadol, in terms of serotonin reuptake inhibition. Based on these observations, ketamine could be considered a good adjuvant during methadone treatment, while antidepressants should be avoided for reducing the risk of serotonin syndrome [16]. The good oral bioavailability, the long half-life, the lack of active metabolites, and the low tolerance potential makes methadone suitable for the treatment of heroin and other opioid dependencies [17]. However, because of

its long half-life and the potential risk of respiratory depression, closer medical monitoring is needed compared with other drugs, such as buprenorphine. Moreover, because of the inhibitory activity on the cardiac ion channel KCNH2, methadone may induce prolongation of the QT interval and torsades de pointes; therefore, it requires routine electrocardiogram monitoring [18].

Similarly, levorphanol displays multiple mechanisms of action: it shows strong affinity for the opioid receptors, acts as a noncompetitive NMDA antagonist, and, finally, inhibits serotonin and noradrenaline reuptake. Similarly to methadone, plasma concentrations needed for obtaining serotonin reuptake inhibition are significantly lower compared with that required for NMDA antagonism [16]. However, probably because of the poor clinical experience on this drug, serotonin syndrome has been never described with levorphanol. This molecule displays a number of advantages over other opioids, such as the reduced risk of tolerance, the lack of interaction with the cytochrome P450 system and, conversely to methadone, it does not induce QTc prolongation [19].

Recently, the simultaneous multiple opioid receptor (MOR, DOR or δ, kappa opioid receptor [KOR] or κ, and nociceptin-opioid receptor [NOP]) activation has been proposed to reduce the excessive MOR overstimulation and its related side effects. This strategy led to the development of several mixed opioid receptor agonist and mixed agonist–antagonist ligands capable of carrying out MOR–KOR agonism, MOR–NOP receptor agonism, MOP–DOR dual agonism, MOR agonism–DOR antagonism, and KOR–DOR agonism [20].

In this frame, particular attention has been once again addressed to buprenorphine because of its unique pharmacological properties, mainly owing to its ability to interact with all four opioid receptors. Indeed, as reported by several studies, this atypical opioid compound appears able to induce a potent analgesia and to reduce the intensity of several classical opioid-related side effects, such as respiratory depression and abuse liability [21].

As there is a growing evidence that NOP receptor agonists could reinforce the antinociceptive effect of MOR agonists and modulate some of their adverse effects [22], the aim of this review was to elucidate how current and future multi-mechanistic approaches, involving both MOR and NOP receptor activation, could be useful to ensure effective and safe pain management.

2 Endogenous Opioid System

The endogenous opioid system consists of four main families of opioid ligands represented by β-endorphins, enkephalins, dynorphins, and nociceptin/orphanin FQ (N/OFQ) and comprises four seven-transmembrane G protein-coupled receptors, which are MOR, DOR, KOR, and NOP [23–25]. These opioid neuropeptides and their corresponding receptors are widely distributed across the neuraxis, and, in particular, in pain pathways [23]. Additionally, evidence showed that they also participate in the control of many different functions, such as stress responses, depression, anxiety, reward/aversion behavioral response, gastrointestinal transit, and the neuroendocrine and immune functions [26–28]. Upon agonist activation, either endogenous or exogenous, the inhibitory G proteins (Gαi–Gαo) dissociate and subsequently engage a variety of effectors that induce neuronal depression [24], through the inhibition of adenylate cyclase and ion channel modulation [29, 30]. The opioid receptor activation leads to a reduction in neurotransmitter release and membrane hyperpolarization [31, 32]. In addition, the G-protein-mediated signal, opioid receptor agonists also result in arrestin effector recruitment, which might play a key role in the balance between therapeutic and adverse effects of opioids [33, 34].

2.1 N/OFQ-NOP Receptor System

In 1994, after the discovery of MOR, KOR, and DOR opioid receptors, a fourth receptor has been identified [35], and it has been called opioid receptor-like 1 until its endogenous ligand, the heptadecapeptide N/OFQ was identified in 1995 ("FQ" refers to its first and last amino acid residues, F [Phe] and Q [Gln]) [36, 37]. Thereafter, opioid receptor-like 1 has been renamed NOP receptor. Despite the fact that NOP owns a 63–65% structural homology with MOR, classical opioid ligands seem to be unable to bind or activate this orphan receptor at a low concentration [38].

Via Gi/o protein coupling, NOP receptor inhibits adenylate cyclase, hence reducing cAMP accumulation, increases inwardly rectifying K+ channel conductance, and, via coupling to *Pertussis* toxin-sensitive Gi/o proteins, it closes Cav2.2 N-type channels, thus blocking calcium ions entrance in the presynaptic neuron. The effects on K^+ and Ca^{2+} conductance may depend on signal transducer and activator of transcription 3 pathway modulation. After coupling to Gi proteins, the βγ-subunit is free to regulate phosphatidylinositol 3-kinase and Src-kinase pathways. Moreover, NOP receptor is able to activate PLC, PLA2, PKC, ERK1/2, JNK (c-Jun N-terminal kinase), p38 MAPK, and NF-Kb pathways. When phosphorylated by G protein-coupled receptor kinase 3, NOP receptor participates in receptor desensitization, arrestin recruitment, internalization, and arrestin-dependent JNK-ROCK (Rho-associated coiled-coil-containing protein kinase) signaling (Fig. 1). Unlike MOR, this receptor can also couple to *Pertussis* toxin-insensitive G-proteins, Gz, Gs, and G16. All these pathways eventually

lead to reduced neuronal excitability and neurotransmitter release, especially dopamine, noradrenaline, serotonin, acetylcholine, and glutamate [39, 40].

The N/OFQ and NOP receptors are widely expressed both in the central and peripheral nervous systems, as well as in peripheral organs (e.g., heart, intestines) and the immune system (e.g., macrophages, lymphocytes) of rodents, non-human primates (NHPs), and humans. Given their distribution, N/OFQ and NOP receptors contribute to the regulation of different functions such as memory, emotion, reward, motor function, and sensory processing [22]. Moreover, this system seems to be also able to regulate respiratory functions and cough reflex, urinary bladder function, and micturition reflex, in addition to renal and cardiovascular functions, with special regard to sympathetic and parasympathetic regulation [40–42].

2.1.1 Role of N/OFQ-NOP Receptor System in Pain

Considering that NOP receptors are highly distributed in the brain, spinal cord, and dorsal root ganglia, there is growing evidence that suggests the involvement of this system in pain modulation [43]. However, NOP receptor agonist effects can be different according to the dose, the site of action, the animal species, and the experimental pain modalities [41, 43, 44]. Furthermore, these drugs showed different effects in nociceptive pain and in neuropathic pain, where they seem to be more effective than traditional opioids [41].

Spinal NOP receptor activation produces anti-hyperalgesic and anti-allodynic effects in different animal models of chronic pain [43]. Indeed, the intrathecal N/OFQ administration inhibited thermal hyperalgesia in rat models of inflammatory chronic pain induced by carrageenan or complete Freund's adjuvant [46, 47] and similar effects were observed in neuropathic pain models caused by chronic constriction injury (CCI) or spinal nerve ligation [47].

As studies in different chronic pain models reported either an increase or a decrease of NOP receptor at spinal cord and dorsal root ganglia levels [48, 49], the mechanism of NOP receptor agonist efficacy in chronic pain is somehow difficult to explain and may be dependent on specific cellular alterations involved in the development of this pathological condition [38]. Alterations of the N/OFQ-NOP receptor system caused by painful conditions have been also reported at the supraspinal level [42, 50] and, results about NOP receptor agonist effects at the supraspinal level appear to depend on the pain modalities. In fact, pronociceptive effects have been reported after N/OFQ-NOP receptor system activation in rodent inflammatory pain models [38, 51], while, in CCI-lesioned rats, both agonists (GRT-TA2210, Ro65-6570) and antagonists (UFP-101) of NOP receptor appear able to attenuate tactile allodynia [52, 53]. The effects of systemic administration of NOP receptor agonists could rely on the relative activation of peripheral, spinal, and supraspinal receptors. For instance, Ro64-6198 (NOP receptor agonist) does not increase tail flick latencies in rodent models of acute pain [40, 54]. On the contrary, systemic administration of GRT-TA2210 and Ro65-6570 decreases chronic inflammatory pain in rats [55], thus supporting the potential analgesic effects of systemic NOP receptor agonists in chronic

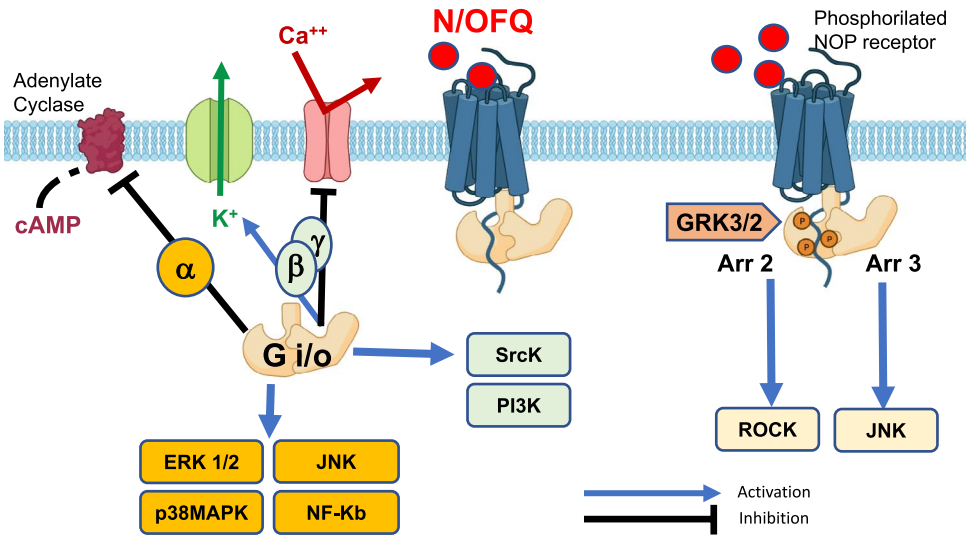

Fig. 1 Via Gi/o proteins coupling, NOP receptor inhibits adenylate cyclase, hence reducing intracellular cAMP, increases inwardly rectifying K+ channels conductance, and closes Cav2.2 N-type channels. The β-γ-subunit regulates phosphatidylinositol 3-Kinase (PI3K) and Src-kinase pathways. Moreover, NOP receptor activates ERK1/2, JNK (c-Jun N-terminal kinase), p38 MAPK, and NF-Kb pathways. When phosphorylated by G protein-coupled receptor kinase 3 (GRK3), NOP receptor participates in arrestin-dependent JNK-ROCK (Rho-associated coiled-coil-containing protein kinase) signaling

pain. The potential usefulness of these molecules is supported by findings in monkeys indicating that NOP receptor agonists generally produce analgesic effects across different non-human primate models, comprising acute, inflammatory, and capsaicin-induced pain. Interestingly, and differently from what observed in rodents, the analgesic effect of NOP agonists is independent of the route of administration [43, 56] in NHPs.

2.1.2 Role of N/OFQ-NOP Receptor System in Opioid Tolerance

In addition to the above-mentioned function of N/OFQ-NOP receptor system in chronic pain, a role of this system has been also proposed in the development of opioid-induced tolerance. Indeed, it has been demonstrated that tolerance to morphine was reduced in NOP receptor knockout mice [57]. In addition, the upregulation of NOP receptor mRNA in the spinal cord reported after long-term morphine treatment seems to be reduced by a subcutaneous or intrathecal administration of the NOP receptor antagonists, such as SB-612111 or J-113397. These results suggest that the appearance of morphine-induced tolerance could be related to an upregulation of the NOP system [57, 58]. Moreover, there is evidence that the intracerebroventricular administration of N/OFQ after daily systemic morphine treatment counteracts the development of tolerance [59]. However, the presence of conflicting data highlights the need for better clarification of the effects of NOP receptor agonists or antagonists in attenuating opioid tolerance.

3 Current Multi-mechanistic (MOR/NOP) Opioids

3.1 Buprenorphine

Buprenorphine is an oripavine derivative mainly used in clinical practice for pain management. However, in the last 20 years, this analgesic drug has also been used for the treatment of opioid dependence.

Buprenorphine is an atypical opioid generally classified as a partial agonist. The therapeutic effects of this molecule are mediated through the interaction with all the opioid receptors (MOR, DOR, KOR, and NOP). In particular, buprenorphine mainly acts as a MOR partial agonist endowed with a very high binding affinity but low efficacy. Unlike classical opioids, it shows a multi-mechanistic effect on the other receptors, as it also acts as an antagonist with a high binding affinity at the DOR and KOR and as an agonist with lower binding affinity for NOP receptor [21, 60]. Furthermore, the involvement of the truncated 6 transmembrane MOR-1 variant activation has been shown for buprenorphine actions [61]. Even though this molecule induces a lower total G-protein signaling activation, when compared to full MOR agonists, it has been demonstrated that it is able to provide a sufficient analgesic efficacy and, at the same time, to reduce opioid-related side effects (i.e., respiratory depression, euphoria, and abuse liability) [62]. Indeed, in moderate-to-severe post-operative pain and cancer pain, this molecule has been shown to have an analgesic efficacy comparable to that of morphine, oxycodone, and fentanyl [63]. While the pharmacological effects result from partial MOR agonism, the reduced side effects associated with buprenorphine treatment could be related to its ability to interact with DOR, KOR, and NOP receptors [64]. However, it is also interesting to point out that recent studies conducted by a rich panel of in vitro assays highlighted that the buprenorphine profile is closer to recently developed Gi-biased drugs (e.g., TRV 130 and PZM21) than morphine or fentanyl [65]. The partial MOR agonism, the slow dissociation from receptors, and the low potential for physical dependence made buprenorphine much more interesting as a potential candidate for the management of opioid use disorder (OUD), for which it received indication, in 2002, by the US Food and Drug Administration [66].

Buprenorphine is a highly lipophilic molecule, making it suited for sublingual (SL), transdermal (TD), and buccal formulations. Currently, two different formulations are available for the treatment of chronic pain: TD patches and buccal films. Transdermal and buccal formulations overcome the hepatic "first-pass" effect, hence increasing bioavailability and maintaining stable steady-state plasma concentrations. These two formulations have been approved for around-the-clock management of severe chronic pain requiring up to 160 mg/day of morphine milligram equivalents [64, 67].

Transdermal patches are available in two formulations: 5–20 mcg/h with a 1-week duration of effect and 35–70 mcg/h with up to 4 days duration of effect. These formulations have been approved for the treatment of chronic pain, but their availability may vary among different countries. Transdermal buprenorphine is applied on the deltoid region or the upper chest, with sites of application to be rotated in order to avoid cutaneous reactions, for example, rash, erythema, and pruritus [64, 67]

Buccal films of buprenorphine (Belbuca®) have been approved in the US for the treatment of severe chronic pain, and are available as 75–900 mcg per film. Starting doses range from 75 mcg to 300 mcg in a daily/12-h application. Treatment should be individualized by titration up to 1800 mcg daily. In clinical trials, doses were titrated every 4–8 days**,** reaching a mean effective dose between 450 and 900 mcg in an average of 24.5 days. Buccal films have a higher bioavailability than the SL formulations, as their back layer enhances the release of the drug into the buccal mucosa in a unidirectional manner, with less medication lost in the buccal cavity [68].

Higher dosages of buprenorphine are recommended when treating patients with OUD with a range from 2 mg up to 24 mg [69]. Innovative formulations have been specifically studied for the treatment of OUD. Sublingual tablets are available containing either buprenorphine alone (Subutex®) or combining buprenorphine and naloxone at the 4:1 ratio (Zubsolv® and generics). Naloxone is incorporated in transmucosal buprenorphine products, in order to decrease misuse of these formulations. Combinations of buprenorphine and naloxone are also available as sublingual films (ratio 4:1 buprenorphine and naloxone) [Suboxone®] and buccal films (Bunavail®). Novel buprenorphine products with unique delivery systems have been recently introduced in the market. Two long-acting formulations are currently available: a subdermal implant of buprenorphine with a 6-month duration of action (Probuphine®, Sixmo®), and a monthly subcutaneous injectable formulation (Sublocade®) [70].

The bioavailability of buprenorphine, after sublingual tablet absorption, is nearly 50%, while naloxone has extremely poor bioavailability. Therefore, the net effect of buprenorphine/naloxone association is given by buprenorphine, whereas naloxone is mainly not active. However, in the case of misuse, if the product is crushed and then injected, both buprenorphine and naloxone become active. Intravenous naloxone will displace buprenorphine, leading to an uncomfortable mild-to-moderate withdrawal reaction lasting from 60 to 90 min (Fig. 2). This mechanism makes this association unappealing for misuse. Therefore, the current recommendations suggest using combination tablets for most of the patients.

Considering the safety profile of this molecule and its analgesic properties, buprenorphine could be considered a valid option for the treatment of chronic pain. Transdermal buprenorphine has been found to be effective in chronic painful conditions, such as osteoarthritis, musculoskeletal, and chronic low back pain [67, 68], where it can be considered as a first choice, in particular at the lower available doses. In patients with non-opioid-naïve cancer, TD buprenorphine was shown to be superior to placebo and not significantly inferior in pain reduction and quality-of-life improvement, when compared to oral oxycodone, oral morphine, and TD fentanyl [71]. Guidelines on cancer-related pain, indeed, recognize a role for buprenorphine among TD formulations, only as an alternative option to oral opioids, for patients unable to swallow or when oral administration is not possible, for instance, in the case of nausea and vomiting, or for head, neck, and gastrointestinal cancer [3, 72].

Nonetheless, buprenorphine is overall well tolerated and safe when compared to classical MOR agonists, given its peculiar pharmacodynamics. Its slow dissociation from opioid receptors allows longer analgesia when compared with other MOR agonists, with reduced opioid-induced hyperalgesia [64, 73]. Pharmacodynamics of buprenorphine may also be accountable for its potential role in drug-resistant depression [74] and neuropathic pain, both in patients with cancer [71] and non-cancer patients [67].

Chronic pain management may be complicated by concomitant OUD. Stigma on this condition is still present among physicians and the level of knowledge on therapeutic options, including buprenorphine, may be inadequate, at least among "first prescribers", with the consequent reluctance in prescribing buprenorphine [73, 75]. Buprenorphine, particularly in its TD formulation, may represent a valid option for patients with OUD with chronic pain, even

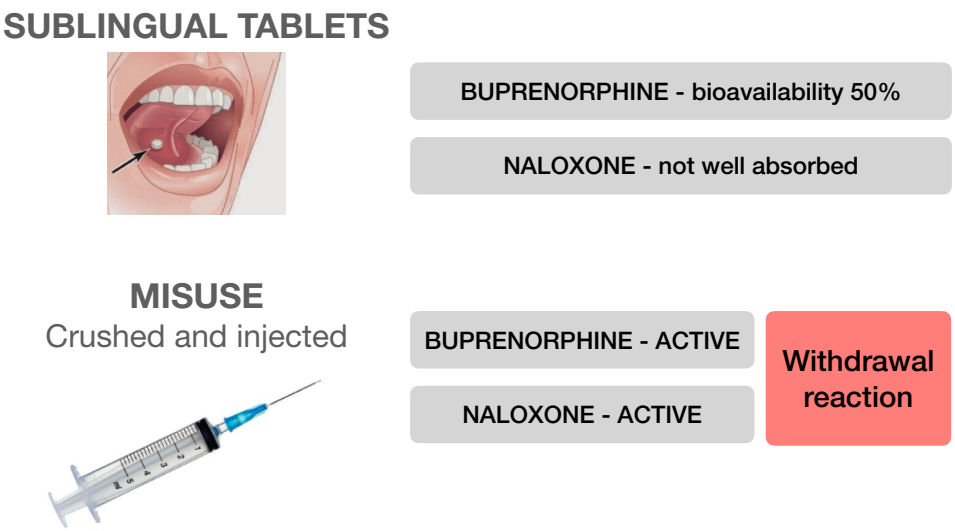

Fig. 2 Bioavailability of buprenorphine, after sublingual tablet absorption, is nearly 50%, while the naloxone has extremely poor bioavailability. However, in the case of misuse, if the product is crushed and then injected, both buprenorphine and naloxone become active, leading to an uncomfortable mild-to-moderate withdrawal reaction

though evidence on its long-term efficacy and safety is still poor and higher doses may be required. In this regard, preclinical studies pointed out both positive and negative long-term consequences, depending on buprenorphine dose and route of administration [76]. Randomized controlled trials in patients with OUD receiving buprenorphine treatment for chronic pain are warranted [77].

The hormonal and immunological impact of buprenorphine is scant when compared to classical MOR agonists [78]. Buprenorphine does not affect testosterone levels in rats; however, the long-term effects on the hypothalamic–pituitary–gonadal axis is still poorly investigated in the clinical setting [79]. Opioid-induced androgen deficiency can negatively affect quality of life, in terms of pain relief, sexual function, and mood. Tapentadol and buprenorphine, because of their lower activity on MOR, when compared with traditional opioids showed a lower effect on the development of hypogonadotropic hypogonadism [80].

Buprenorphine is mainly metabolized by the liver, therefore it is safe in patients with renal impairment [81], even when the glomerular filtration rate is lower than 30 mL/min and in patients with end-stage renal disease, undergoing hemodialysis, where pain is very common and often under-treated [82]. Buprenorphine is particularly suitable for elderly patients [83], as its metabolism remains quite stable with age and the possibility of drug–drug interactions with other drugs prescribed for comorbidities is lower than classical opioids [84]. In the case of severe hepatic failure, bioavailability of buprenorphine may be higher [67]. Cautions about buprenorphine may concern QT prolongation; however, the risk of arrhythmias is dose dependent (especially at therapeutic doses of 40–80 mcg/h), significantly lower than that of methadone, and probably reliable on concomitant use of other QT-prolonging drugs, such as macrolides, fluoroquinolones, tricyclic antidepressants, selective serotonin receptor antagonists, and antipsychotics. In this regard, it has been highlighted that, differently from methadone, the mechanism of QT prolongation by buprenorphine cannot be explained by a direct hERG channel block [85]. The safety of buprenorphine has been also reported in pregnant women, for OUD management [84]. However, some caution is suggested by either clinical [86] and preclinical studies [87, 88], indicating the development of neurological deficits after perinatal exposure to buprenorphine.

Buprenorphine is also suitable for acute and perioperative pain management, where opioids continue to be the cornerstone of severe acute pain, particularly in combined analgesic regimens [89, 90]. In buprenorphine users, anesthesiologists may decide to continue TD buprenorphine supply. However, they should be aware that in patients taking high buprenorphine doses (> 24 mg day) the administration of full MOR agonists may be ineffective. If possible, as in the case of elective surgery, buprenorphine dosage should be gradually reduced in order to use "rescue" full MOR agonists with full effectiveness [8, 91, 92].

Sublingual buprenorphine was also assessed in the perioperative setting [93]. Sublingual buprenorphine has a 60-min time to reach the maximum plasma concentration, a 11.2 h half-life, and a 35% bioavailability, and is actually approved for opioid withdrawal, but not for chronic pain management [84]. Nonetheless, it was found to be effective in chronic painful conditions [64]. In addition to the currently available SL tablets, a new SL buprenorphine wafer was recently developed and showed an higher bioavailability of about 45.4% and a reduced time to reach the maximum plasma concentration compared with other SL formulations [94].

In conclusion, buprenorphine, as an atypical opioid, shows many advantages in clinical practice, and the potential for non-medical use is relatively low compared with other opioid agents, which places buprenorphine in a unique role in the global chronic pain epidemic. However, surprisingly, its use is still limited by the lack of reimbursement by many payers, driving physicians to prescribe generic versions of the riskier Schedule II oral opioids, such as oxycodone and morphine [62].

3.2 Cebranopadol

Cebranopadol was discovered in 2014 and it represents a novel mixed NOP and opioid receptor agonist. More precisely, the order of potency NOP ≈ MOR > DOR ≥ KOR has been reported by calcium mobilization studies [95]. In vitro studies revealed that this molecule shows high affinities for MOR and NOP receptors and partial agonist efficacy for KOR [96].

As reported by several studies, cebranopadol is able to produce potent and efficacious antinociceptive, antihyperalgesic, and antiallodynic effects after local/peripheral, spinal, and supraspinal administration, in different models of chronic pain in rodents [97]. In contrast to traditional opioids, cebranopadol showed a potent analgesia even in neuropathic pain models, such as in streptozotocin-treated diabetic rats and in the CCI model [98]. Cebranopadol-induced analgesia was reversed by both selective MOR and NOP receptor antagonists, naloxone and J-113397, respectively, thus demonstrating that the activity of this molecule is strongly related to the coactivation of MOR and NOP receptors [41, 99, 100]. In addition to being 100-fold more potent and longer lasting when compared with morphine [101], cebranopadol also shows a more tolerable profile in terms of opioid-induced side effects. Indeed, in healthy volunteers, the potency of oral cebranopadol for respiratory

depression was shown to be three times that for analgesia, and the blood-effect-site equilibration half-life for respiratory depression was 1.2 h, compared with 8.1 h for analgesia [102]. These results confirmed the hypothesis that NOP receptor activation may reduce MOR-induced respiratory depression, and bifunctional combined NOP/MOR agonists may represent a valid and safer alternative for the future of analgesia.

Cebranopadol was also associated with delayed tolerance development (26 days) when compared with an equianalgesic dose of morphine (11 days), in the CCI model, and negligible motor impairment [103]. Cebranopadol has a relatively low oral bioavailability (13–23%) and reaches maximum plasma concentrations after 4–6 h, with a long half-value duration of 14–15 h, which made the development of an extended-release formulation unnecessary, as the current formulation has already the required pharmacokinetic characteristics. The pharmacokinetics of cebranopadol after repeated doses is predictable from a single dose [104].

In clinical trials, cebranopadol has been administered at a dosing interval of 24 h, which allowed it to achieve a steady-state plasma concentration within 2 weeks. Several phase II clinical trials have been completed and phase III trials are ongoing. Results of published studies on cebranopadol are summarized in Tables 1 and 2.

In subjects with chronic low back pain, cebranopadol, as well as tapentadol, showed statistically significant analgesic effects, with adverse effects (mainly constipation dizziness, fatigue, hyperhidrosis, nausea, vomiting, and somnolence) only occurring in < 10% of patients [105]. In patients with cancer with severe chronic pain, cebranopadol from 200 to 1000 mcg daily was shown to be non-inferior to controlled-release morphine, with a similar incidence of treatment-emergent adverse events (TEAEs) [106]. In an open-label study on long-term treatment (26 weeks) of patients with cancer, cebranopadol was shown to be a safe analgesic drug. The incidence of TEAEs was relatively high (84.2%), but most of them were mild to moderate in intensity and the percentage of patients who discontinued treatment because of TEAEs was negligible. Peripheral edema was the only unexpected TEAE [107]. Cebranopadol was also investigated in post-operative pain after buniectomy. Its effect was larger than that of controlled-release morphine in the first 10 h and better tolerated. The efficacy and the incidence of TEAEs increased with increasing cebranopadol doses (400–600 mcg) [108]. Finally, when evaluated for its abuse potential in non-dependent recreational opioid users, cebranopadol at doses up to 400 mcg was not different from placebo, while at the dose of 800 mcg its abuse potential was similar to that of hydromorphone 8 mg [109]. Therefore, clinical data confirm the hypothesis that cebranopadol, as MOR/NOP receptor agonists, could have a better pharmacological profile than other traditional opioid analgesics and provide safer pain relief with a lower risk of drug liking.

4 Future Multi-mechanistic Dual MOR/NOP Receptor Agonists

Considering the beneficial pharmacological efficacy and the reduced side effects showed by buprenorphine and cebranopadol and taking also into account the role of N/OFQ-NOP receptor system in pain management, the pharmacological research is currently focusing on dual MOR/NOP molecules. BU08028 is a buprenorphine-derived novel orvinol analog, with a buprenorphine-like binding profile to MOR, DOR, and KOR, but with higher binding affinity and efficacy for the NOP receptor [110, 111]. This molecule provides long-lasting antinociceptive effects in a tail-flick nociceptive pain assay, but also produces conditioned place preference in mice, thus suggesting its potential abuse liability in the clinic [111, 112]. However, data obtained in NHPs, which represent a better translational model compared to rodents, demonstrate that BU08028 is able to induce dose-dependent antinociception in the warm water tail withdrawal assay, and to reduce the capsaicin-induced thermal allodynia in monkeys [113]. Moreover, BU08028 did not show reinforcing effects when compared to remifentanil, buprenorphine, or cocaine. Furthermore, unlike morphine, BU08028 does not cause acute physical dependence after repeated treatment [113]. Beyond its role in analgesia, this drug has been also proposed for the treatment of alcohol use disorders. Some data suggest that the ability of buprenorphine to decrease ethanol drinking is shared by the bifunctional MOR/NOP receptor agonist BU08028. Indeed, after short-term and long-term administration, BU08028 was shown to be more potent and, in long-term treatment, more effective than buprenorphine in NHPs [114].

BU10038, a naltrexone-derived analog, is another MOR/NOP receptor partial agonist. As reported by Kiguchi et al. [115], it produces potent dose-dependent and long-lasting antinociception and antihypersensitive effects in monkeys. BU10038 did not compromise respiratory and cardiovascular functions at antinociceptive doses, or ten times above (0.01–0.1 mg kg^{-1}). The intrathecal administration of BU10038 (3 mcg) was able to produce a morphine-comparable antinociception and antihypersensitivity, without itching. In addition, like BU08028, it seems to be associated

Table 1 Clinical trials on cebranopadol: focus on efficacy

Trial (author, year)	Type of study	Type of patients	No. of patients	Study design	Primary outcome	Secondary outcome	Main results
Christoph, 2017 [105]	Phase II, randomized, double-blind, placebo- and active-controlled (14 weeks) NCT01725087	Chronic LBP	637	Cebranopadol 200/400/600 mcg OD vs tapentadol 200 mg BID vs placebo	Pain intensity (change from baseline pain to the average 24-h pain during the entire 12 weeks of the maintenance phase)	TEAEs Withdrawal (COWS) Risk for suicidal ideation (C-SSRS) Vital signs	A relevant improvement of analgesia over placebo was demonstrated for all cebranopadol doses. Higher efficacy was noted with increasing doses of cebranopadol; however, higher doses led to higher treatment discontinuation rates because of TEAEs during the titration phase The incidence rate of most frequently reported TEAEs during the maintenance phase was ≤ 10% Cebranopadol showed positive results even in other recommended key domains in chronic LBP such as physical functioning and sleep disturbance
Eerdekens, 2019 [106]	Phase III, randomized, double-blind, parallel-group, multiple-dose noninferiority NCT01964378	Cancer	127 (524 planned[a])	Cebranopadol from 200 to 1000 mcg vs morphine CR	Amount of daily rescue medication (morphine IR)	Average pain intensity; pain intensity reduction by ≥ 30%; pain intensity reduction by ≥ 2 points; TEAEs	Noninferiority of cebranopadol and superiority over morphine CR were demonstrated Most patients (≥ 75%) had clinically relevant pain reduction, at doses ≤ 800 mcg for cebranopadol and ≤ 120 mg for morphine CR daily Similar incidence of TEAEs was recorded for cebranopadol (83.1%) and morphine (82.0%)

Table 1 (continued)

Trial (author, year)	Type of study	Type of patients	No. of patients	Study design	Primary outcome	Secondary outcome	Main results
Scholz, 2018 [108]	Phase IIa, randomized, multi-center, double-blind, double-dummy, placebo- and active-controlled, parallel-group NCT00872885	Postoperative acute pain (primary bunionectomy)	258	Cebranopadol 200/400/600 mcg single dose vs morphine CR 60 mg vs placebo	Sum of pain intensity 2–10 h	Time and amount of rescue analgesic dose; TEAEs	Cebranopadol doses of 400 mcg and 600 mcg (not 200 mcg) were more effective than placebo The effect of morphine CR 60 mg was smaller than that of cebranopadol 400 mcg and 600 mcg in the first 10 h, but emerged later Cebranopadol 400 mcg was better tolerated than morphine CR 60 mg The frequency of TEAEs increased with increasing cebranopadol doses

BID twice daily, *COWS* Clinical Opiate Withdrawal Scale, *CR* controlled release, *C-SSRS* Columbia-Suicide Severity Rating Scale, *IR* immediate release, *LBP* low back pain, *OD* once daily, *TEAEs* treatment-emergent adverse events

[a]The trial was stopped early for business reasons

to a lesser degree with physical dependence or tolerance after long-term administration. Unlike oxycodone, BU10038 lacked reinforcing effects [115].

The potential value of these new analgesics with dual activity on the MOP/NOP receptor is also confirmed by studies on a new developed molecule, named AT-121. In contrast to cebranopadol, which is a full agonist at the MOR/NOP receptor, AT-121 is a bifunctional MOR/NOP partial agonist. Following repeated administration, AT-121 produced a potent analgesic effect (100-fold more potent than morphine), without inducing opioid-associated hyperalgesia or physical dependence, and attenuated the reinforcing effects induced by oxycodone in NHPs [116]. Moreover, AT-121 did not compromise respiratory and cardiovascular activity, did not affect body temperature, and did not induce sedation or motor impairment [116]. These results suggest a possible role of this molecule as a potential innovative safer analgesic.

These data confirm that the NOP receptor agonists synergistically enhance MOR agonist-induced analgesia and do not demonstrate the non-desirable adverse effects of traditional opioids in NHPs. Therefore, ligands with dual MOR and NOP receptor agonist activities could be useful to ensure adequate and safe pain relief across different pain modalities. However, additional studies are needed to evaluate the future development and potential application in humans. In particular, future studies are warranted, in patients with chronic pain, to investigate whether bifunctional MOR/NOP receptor agonists might cause tolerance or dependance to develop more slowly compared with traditionally used opioid agonists.

5 Future Perspectives

In this review, authors focused their attention mainly on the N/OFQ-NOP receptor system and for this reason, the current and future multi-mechanistic approaches that are involved in the modulation of this system have been discussed. Nevertheless, as other systems participate in the development and maintenance of chronic pain, many other therapeutic strategies might be promising analgesics of the future. Among these, valuable options could be represented by the utilization of biased agonists (i.e., oliceridine, PMZ21, and SR17018), monoclonal antibodies, molecules targeting G protein-coupled receptor heterodimers (i.e., MCC22, NNTA), dual molecules such as MOR/KOR, KOR/DOR agonists, and MOR agonists/DOR antagonists [117], as well as proteasome inhibitors [23, 118] for their potential role in pain treatment and opioid tolerance.

Table 2 Clinical trials on cebranopadol: focus on safety

Trial (author, year)	Type of study	Type of patients	No. of patients	Study design	Primary outcome	Secondary outcome	Main results
Dahan, 2017 [102]	Phase I	Healthy volunteers	12	Cebranopadol 600 mcg single dose	Respiratory depression	Pain threshold tolerance	Cebranopadol displayed typical opioid-like effects including miosis, analgesia, and respiratory depression The potency of cebranopadol for respiratory depression was three times that for analgesia measured by an experimental electrical pain model The blood-effect-site equilibration half-life for respiratory depression and analgesia were respectively, 1.2 h and 8.1 h
Koch, 2019 [107]	Phase III, open-label (26 weeks), single-arm NCT02031432	Cancer	76	Cebranopadol 200–1000 mcg	Incidence of TEAEs	Intensity of TEAEs	84.2% experienced at least one TEAE, the most common being asthenia (27.6%), malignant neoplasm progression (26.3%), and decreased appetite (22.4%) Most TEAEs were mild (36.6%) or moderate (45.4%) in intensity. Only two patients discontinued because of TEAEs in the titration phase The only unexpected TEAE was peripheral edema (11.8%)
Göhler, 2019 [109]	Single-dose, nested-randomized, double-blind crossover	Nondependent recreational opioid users	42	Cebranopadol 200, 400, and 800 mcg vs hydromorphone 8 and 16 mg vs 2 placebos	Peak effect of drug liking (at this moment) VAS Emax	Various secondary measures of drug liking; psychomotor and cognitive effects; pupillometry	Cebranopadol 200 and 400 mcg did not differentiate from placebo on the abuse potential assessments Cebranopadol 800 mcg resulted in a similar effect to hydromorphone 8 mg and smaller than hydromorphone 16 mg Cebranopadol administration was safe; no serious adverse events occurred

Emax peak effect, TEAEs treatment-emergent adverse events, *VAS* visual analogue scale

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