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Review Article

PAIN

Nociceptin/orphanin FQ receptor ligands and translational challenges: focus on cebranopadol as an innovative analgesic

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Abstract

Opioids are characterised as classical (mu, delta, and kappa) along with the non-classical nociceptin/orphanin FQ (N/OFQ) receptor or NOP. Targeting NOP has therapeutic indications in control of the cardiovascular and respiratory systems and micturition, and a profile as an antidepressant. For all of these indications, there are translational human data. Opioids such as morphine and fentanyl (activating the mu receptor) are the mainstay of pain treatment in the perioperative period, despite a challenging side-effect profile. Opioids in general have poor efficacy in neuropathic pain. Moreover, longer term use is associated with tolerance. There is good evidence interactions between opioid receptors, and receptor co-activation can reduce side-effects without compromising analgesia; this is particularly true for mu and NOP co-activation. Recent pharmaceutical development has produced a mixed opioid/NOP agonist, cebranopadol. This new chemical entity is effective in animal models of nociceptive and neuropathic pain with greater efficacy in the latter. In animal models, there is little evidence for respiratory depression, and tolerance (compared with morphine) only develops after long treatment periods. There is now early phase clinical development in diabetic neuropathy, cancer pain, and low back pain where cebranopadol displays significant efficacy. In 1996, N/OFQ was formally identified with an innovative analgesic profile. Approximately 20 yr later, cebranopadol as a clinical ligand is advancing through the human trials process.

Keywords: analgesia; biased agonist; cebranopadol; NOP receptor ligands; opioids; pain; respiratory depression; tolerance; opioid receptors

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Editor's key points

- There is potential for novel analgesic effectiveness and side-effect reduction using mu and NOP receptor co-activation.
- The novel agent cebranopadol has analgesic effectiveness (particularly in neuropathic pain), with reduced propensity for respiratory depression and tolerance.

The neuropeptide nociceptin/orphanin FQ (N/OFQ)[1,2] has been identified as the endogenous ligand of the opioid receptor-like 1 receptor, now referred to as N/OFQ peptide receptor (NOP). N/OFQ and the NOP receptor display high structural homology with peptides and receptors of the opioid family. In addition, the NOP receptor is a seven transmembrane domain (7TM) receptor coupled with G_i proteins; thus, its transduction mechanisms are similar to those of classical opioid receptors [e.g. reduction of cyclic adenosine monosphosphate (cAMP) levels, stimulation of outward potassium currents and inhibition of inward calcium conductance].[3] Despite these similarities, the pharmacological profile of the NOP receptor is completely distinct from that of classical opioid receptors; for instance the action of N/OFQ (and those of selective NOP agonists) are resistant to naloxone the universal opioid receptor antagonist (for a detailed analysis of the NOP pharmacological profile, see Toll and colleagues[4]).

The NOP receptor and the N/OFQ prepropeptide (ppN/OFQ) are widely expressed in the central and peripheral nervous systems. N/OFQ, via selective stimulation of the NOP receptor, controls several biological functions including pain transmission, locomotor activity, stress and anxiety, emotional states, learning and memory, food intake, drug reward, gastrointestinal, cardiovascular and immune functions, and the cough and micturition reflexes.[3] This broad spectrum of actions stimulated the interest of academic and industrial researchers and generated a large panel of NOP receptor ligands useful for target validation studies (Table 1). Among NOP peptide ligands, the partial agonist SER100 (alias ZP120),[5] the full agonist Rec 0438 (alias UFP-112),[6] and the antagonist UFP-101[7] are worthy of mention. As far as NOP non-peptide ligands are concerned, the most well used compounds are the agonists Ro 65-6570,[8] Ro 64-6198,[9] MCOPPB,[10] and AT-403[11] and the antagonists J-113397,[12] SB-612111,[13] and C-24.[14] Moreover, the crystal structures of the NOP receptor in complex with the two latter compounds have been recently solved.[15,16] The availability of these structures may be used in the future for the rational structure-based design of innovative NOP ligands. In parallel, genetic models have been developed for investigating the biology of the N/OFQ-NOP receptor system including mouse[17] and rat[18,19] knockouts of the NOP receptor gene (NOP(−/−)), a mouse knockout of the ppN/OFQ gene,[20] and more recently a mouse knock-in of the NOP-eGFP fusoprotein in place of the native NOP.[21] Based on a large body of evidence coming from preclinical studies performed using the above tools, NOP receptor agonists have been proposed as innovative drugs for treating anxiety, drug abuse, cough, and urinary incontinence,[3,22,23] whereas NOP selective antagonists have been suggested as novel treatments for Parkinson's disease[24] and depression[25] (Table 2). For some of these indications of NOP ligands, preclinical findings were confirmed by clinical studies that are briefly described in the following sections.

NOP receptor ligands and potential therapeutic indications (non-pain studies)

Cardiovascular dysfunction

The NOP partial agonist SER100 has been designed and tested in preclinical studies as an aquaretic.[26,27] The compound also elicits hypotensive and vasorelaxant actions that are more pronounced in spontaneously hypertensive rats.[28] SER100 displayed an acceptable safety profile in patients with isolated systolic hypertension and produced significant lowering of systolic blood pressure.[29] This proof of concept study generated encouraging results for the further development of NOP receptor (partial) agonists for the treatment of hypertension.

Micturition

A series of preclinical studies reviewed by Lecci and colleagues[30] demonstrated that N/OFQ elicits profound inhibitory effects on the micturition reflex in rats. Based on this evidence the effects of N/OFQ were evaluated in patients suffering from overactive bladder. A first proof of concept study,[31] a second randomised, placebo-controlled, double-blind study,[32] and a third study in which 1 mg N/OFQ for 10 days was given intravesically once a day for 10 days[33] demonstrated a large increase in mean bladder capacity and volume threshold for the appearance of detrusor hyperreflexia only in patients assigned to the N/OFQ group. Interestingly, recent findings demonstrated that NOP receptor expression in nerve fibres within the

Table 1 Nociceptin/orphanin FQ (NOP) receptor ligands

Compound name	Chemical nature	Pharmacological activity	References
N/OFQ	Peptide	Endogenous agonist	1,2
Rec 0438	Peptide	Full agonist	6
Ro 65-6570	Non-peptide	Full agonist	8
Ro 64-6198	Non-peptide	Full agonist	9
MCOPPB	Non-peptide	Full agonist	10
AT-403	Non-peptide	Full agonist	11
SER 100	Peptide	Partial agonist	5
UFP-101	Peptide	Antagonist	7
J-113397	Non-peptide	Antagonist	12
SB-612111	Non-peptide	Antagonist	13
C-24	Non-peptide	Antagonist	14
LY2940094	Non-peptide	Antagonist	48

Table 2 Therapeutic indications for nociceptin/orphanin (NOP) ligands

Therapeutic indication	NOP ligand	Pivotal study/ review	Clinical evidence
Anxiety	Agonists	101	No
Drug abuse	Agonists	102,103	No
Cough	Agonists	104	Yes[44]
Overactive bladder	Agonists	30	Yes[31–33]
Hypertension	Partial agonists	28	Yes[29]
Depression	Antagonists	25,45	Yes[50]
Parkinson disease	Antagonists	105	No
Memory deficits	Antagonists	106	No
Pain	Mixed NOP/opioid agonists	69	Yes[100]

bladder sub-urothelium is increased by several fold in detrusor overactivity patient specimens.[34] Thus, these findings strongly support the use of NOP receptor agonists as a therapeutic approach for controlling detrusor overactivity incontinence.

With the aim of increasing N/OFQ potency and duration of action, different chemical modifications were combined in the same molecule generating Rec 0438.[6] Rodent studies reviewed by Calo and colleagues[35] demonstrated that Rec 0438 behaves as a potent and selective NOP agonist and is able to mimic *in vivo* N/OFQ actions producing longer lasting effects. This has been confirmed in a series of experiments performed in Recordati laboratories (P. Angelico, personal communication) in rats where Rec 0438 produced a dose-dependent and SB-612111-sensitive increase of the volume of saline infused into the bladder necessary to induce detrusor contraction followed by micturition. A phase I clinical study with Rec 0438 was recently completed in normal subjects and in patients with an overactive bladder, demonstrating that intravesical infusion of Rec 0438 is well tolerated, and there is no leakage to the systemic circulation. A phase II study is now ongoing; if the encouraging results obtained with N/OFQ are confirmed with Rec 0438, a novel possibly well tolerated and highly effective option will be soon available for treating these patients.

Respiratory system and cough

N/OFQ has a potential role to play in the aetiopathogenesis of asthma where its immunomodulatory and bronchodilatory actions in an animal model of asthma offer advantages over beta-adrenergic agonist and steroid combinations. The animal data perfectly match observational studies in *ex vivo* human tissue and tissues samples.[36,37] Use of nebulised N/OFQ is an interesting possible indication. N/OFQ demonstrated antitussive effects in experimental cough models in guinea pigs and cats via selective stimulation of the NOP receptor.[38] With the aim of identifying a drug-like molecule for this indication, Schering–Plough researchers developed a large series of non-peptide NOP agonists[39–42] and SCH 486757 was selected for further development. After oral administration, SCH 486757 dose-dependently suppressed cough in guinea pigs and cats.[43] SCH 486757 was also evaluated in patients with sub-acute cough in comparison with placebo and codeine. However, there were no significant changes in average cough severity scores from baseline to treatment either between SCH 486757 and placebo or between codeine and placebo. There were several hints of possible limited antitussive efficacy with SCH 486757, but the dose used was limited by its tendency to produce somnolence.[44] Development of NOP receptor agonists as antitussive agents can only advance after finding molecules with a therapeutic window larger than SCH 486757. It is worthy of mention at this regard that are now several non-peptide NOP agonists (such as MCOPPB and AT-403) available that are more potent and much more selective than SCH 486757 (see Ferrari and colleagues[11] for a direct comparison of the basic pharmacological profile of these molecules).

Antidepressant actions

In the mouse forced swimming test, NOP receptor antagonists produced antidepressant-like effects.[45] This initial finding was later confirmed using different antagonists, animal species, and behavioural assays. Converging evidence has been obtained in genetic studies as NOP(−/−) mice and rats displayed an antidepressant-like phenotype.[25] More recent studies investigating lipopolysaccharide-induced depression[46] and learned helplessness[47] in mice confirmed previous findings and further corroborated the antidepressant-like activity of NOP antagonists. Researchers at Eli Lilly discovered the potent and selective NOP receptor antagonist, LY2940094,[48] which displayed antidepressant-like behavioural effects in the forced-swimming test in mice, an effect absent in NOP(−/−) animals.[49] This compound was used in a proof of concept, double-blind, placebo-controlled trial that evaluated its therapeutic potential as a novel oral medication for the treatment of patients with major depressive disorder. Once daily oral dosing of LY2940094 at 40 mg for 8 weeks *vs* placebo provided evidence for an antidepressant effect based on the change from baseline to Week 8 in the GRID-Hamilton Depression Rating Scale-17 item total score. LY2940094 was safe and well tolerated.[50] Preclinical findings were confirmed by this first human data providing evidence that blockade of NOP receptor signalling represents a promising strategy for the treatment of depression.

NOP receptor ligands and pain

As far as pain transmission is concerned, the effects of N/OFQ and NOP selective agonists are complex depending on multiple factors including: (i) dose—at very low doses (pmol range) intrathecal N/OFQ facilitates pain transmission in the spinal cord while at higher doses (nmol range) robust antinociceptive effects have been consistently reported; (ii) site of action—in rodents N/OFQ elicits antinociceptive effects both after local and spinal injection whereas intracerebroventricular N/OFQ promotes a pronociceptive action and is able to counteract the analgesic effect of opioid drugs such as morphine; (iii) animal species—as mentioned before at supraspinal level N/OFQ has a pronociceptive action in mice and rats; however, recent evidence[51] has demonstrated that in non-human primates an antinociceptive effect is measured in response to supraspinal N/OFQ; (iv) pain modality—non-peptide NOP agonists (e.g. Ro 65-6570) given systemically do not affect nociceptive pain, but they display antinociceptive effects in models of inflammatory and neuropathic pain (for related studies, see Toll and colleagues,[4] Zeilhofer and Calo,[52] Schroder and colleagues[53]). This complex picture clearly made the development of selective NOP agonists as analgesics difficult. However, consistent results have been reported in the literature regarding the analgesic potential associated with the simultaneous activation of NOP and opioid (particularly mu) receptors. In rodents, spinal N/OFQ increased systemic and spinal morphine analgesia.[54,55] Moreover, isobolographic analysis demonstrates a supra-additive interaction between NOP and mu activation at the spinal level in the rat chronic constriction injury model,[55] and subthreshold doses of morphine and Ro 64-6198 elicited robust analgesic effects in the mouse hot plate test when given together.[56] These rodent findings were confirmed and corroborated by studies performed in non-human primates where spinal N/OFQ[57] or Rec 0438[58] strongly potentiated morphine analgesia and systemic NOP and opioid receptor agonists produced supra-additive analgesic effects.[59] Collectively, this evidence strongly suggests that mixed NOP/opioid receptor agonists may have therapeutic potential as novel analgesics. Some compounds with the above pharmacological profile have been reported in the literature including the peptides [Dmt^1]N/OFQ(1–13)-NH_2[60] and its tetrameric derivative PWT-[Dmt^1]N/OFQ(1–13),[61] DeNo (a dermorphin-N/OFQ chimeric peptide),[62] and some non-peptide compounds

SR16435, SR16507, and SR14150 (reviewed by Toll and colleagues[4]) that display variable potency and efficacy at NOP and mu receptors. Moreover, BU08028 is a buprenorphine derivative that displayed high affinity for NOP and opioid receptors.[63] After spinal administration in mice BU08028 was more potent than morphine in attenuating nerve injury-induced tactile allodynia and inflammation-induced thermal hyperalgesia; meanwhile, antagonist experiments demonstrated the involvement of NOP and opioid receptors in the action of BU08028.[64] BU08028 has also been evaluated in non-human primates where after systemic administration it produced a dose-dependent and long-lasting antinociceptive and antiallodynic effects. These effects were blocked by both mu and NOP receptor antagonists. Importantly, BU08028 at antinociceptive doses did not cause respiratory depression and did not promote physical dependence.[65] Collectively, these findings provide a strong rationale for mixed NOP/opioid receptor agonists as analgesic drugs.

Cebranopadol preclinical studies

In order to identify and optimise novel compounds acting as mixed NOP/opioid selective agonists, a large series of structure–activity studies were performed by Schunk and colleagues.[66,67] These efforts led to the identification of cebranopadol (*trans*-6′-fluoro-4′-9′-dihydro-*N*,*N*-dimethyl-4-phenyl-spiro[ciclohexane-1,1′(3′*H*)-pyrano[3,4-*b*]indol]-4-amine; see chemical structure in Fig. 1). An alternative, robust, and easy method for the synthesis of cebranopadol has also been recently reported in the literature.[68]

In receptor binding studies, cebranopadol displayed high affinity for NOP (0.9 nM) and opioid (0.7, 2.6, and 18 nM for mu, kappa and delta, respectively) receptors. In agonist stimulated [^{35}S]GTPγS binding experiments cebranopadol displayed high potency and efficacy at NOP and mu receptor, whereas it showed reduced potency at the delta and reduced potency and efficacy at the kappa receptors.[69] This basic pharmacological profile has been confirmed in an independent study performed measuring calcium mobilisation in cells co-expressing NOP or classical opioid receptors and chimeric G proteins.[70] The same study also evaluated the ability of cebranopadol to promote NOP and mu receptor interaction with G protein and β-arrestin2. This study demonstrated that cebranopadol behaves as a biased agonist towards G protein; the degree of the bias was modest for the mu receptor, whereas it was very large for the NOP receptor.[70] G protein biased agonism (see Box 1) is clearly an advantageous feature for a mu receptor ligand; in studies performed in β-arrestin2 knockout mice, the analgesic properties of morphine are strongly associated with G protein-dependent signalling,[71] whereas tolerance liability,[72] respiratory depression, and constipation[73] are more dependent on β-arrestin2. This suggests that mu receptor agonists biased towards G protein may be developed as safer analgesics.[74] Preclinical[75] and clinical findings[76–78] recently obtained with the G protein biased agonist oliceridine (alias TRV130) seem to confirm this proposal. In contrast, the possible biological implications of the large G protein bias displayed by cebranopadol at NOP receptors are at present unknown. Indeed, functional selectivity studies in the NOP receptor field are still in their infancy[11,79–81]; thus, further investigations—for example, evaluation of the actions of N/OFQ and NOP selective ligands in mice knockout for β-arrestin2 and discovery and testing of NOP ligands with large bias towards G protein and towards β-arrestin2—are needed to understand the possible role of functional selectivity in the development of NOP agonists as analgesics.

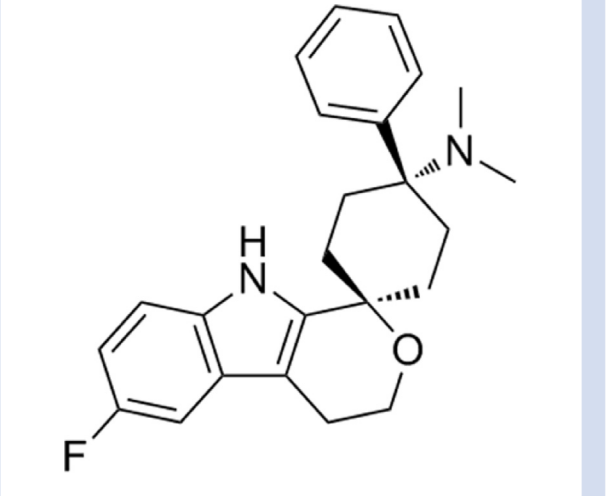


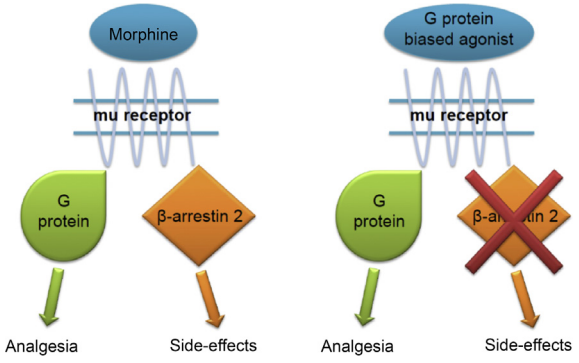
Fig 1. Chemical structure of cebranopadol.

The pharmacokinetic parameters of cebranopadol in rats have been investigated in detail (see table 3 of Linz and colleagues[69]). Cebranopadol was extensively distributed with a half-life of 4.5 h; its oral bioavailability was 13–23%. Cebranopadol displayed dose-dependent and potent antinociceptive effects both when given orally and intravenously in models of nociceptive, inflammatory, and neuropathic pain in mice and rats.[67,69] Compared with morphine, cebranopadol was more than 100-fold more potent and produced longer-lasting effects.[67,69] These results were confirmed in other laboratories[70] and extended to chemotherapy-induced neuropathic pain,[82] Freund's adjuvant induced arthritic pain,[83] and to painful conditions of the trigeminal territory.[84] Importantly, the antinociceptive actions of cebranopadol are attributable to the simultaneous activation of NOP and opioid receptors as consistently demonstrated in antagonist studies. Both naloxone and NOP selective antagonists (J-113397[69,83] or SB-612111[70]) were able to counteract the effects of cebranopadol.

Interestingly, when compared with morphine, which displayed similar potency in various assays, cebranopadol was more potent in models of chronic neuropathic than acute nociceptive pain.[69] This has been confirmed by Rizzi and colleagues,[70] who noted that fentanyl displayed similar potency in the tail withdrawal and formalin test; they also observed that the NOP selective agonist Ro 65-6570 was active in the latter but not in the former assay, and cebranopadol was active in both assays but was approximately 10-fold more potent in the formalin test. Collectively, these findings are in line with previous results briefly discussed in the Introduction, suggesting that NOP receptor agonists are much more efficacious in models of inflammatory and neuropathic pain than nociceptive pain (also reviewed by Toll and colleagues[4] and Schroder and colleagues[53]). This may be explained, at least in part, by an upregulation of NOP receptors in dorsal root ganglia[85,86] and nerve fibres,[34] which has been reported during neuropathic and inflammatory conditions.

Box 1
Functional selectivity or biased agonism

Receptor selectivity is particularly important in drug design and as a concept simply describes the propensity of a ligand to bind exclusively to the desired target; a ligand with 100-fold selectivity will produce off target effects at 100× the dose required for its therapeutic indication. In other words, receptor selectivity indicates the ability of a synthetic ligand to discriminate some of the biological actions of a receptor family based on the receptor type involved. In the past, more effective drugs, better tolerated drugs, or both, have been generated by identifying highly selective receptor ligands, that is, β_1 selective antagonists, β_2 selective agonists, H_2 selective antagonists, and so on. Recent findings indicated that receptors may signal via activation of different effectors, that is, G proteins and arrestins, and that synthetic agonists for a given receptor may display different ability to stimulate one effector pathway (e.g. G protein) *vs* the other (e.g. arrestin). Functional selectivity also known as biased agonism describes the propensity of an agonist to promote signalling via selective activation of one signalling pathway. Thus, in the future, more effective drugs, better tolerated drugs, or both, can be generated not only based on the receptor type involved (receptor selectivity) but also by selecting only some specific pathways among those associated with activation of that specific receptor type (functional selectivity). To give a practical example, as mentioned in the text, there is a large and elegant set of experimental evidence to indicate that the analgesic response to opioids depends on mu receptor/G protein signalling, whereas some important side-effects of these drugs (respiratory depression, constipation, tolerance) mainly depend on mu receptor/arrestin signalling (see the scheme below). Thus, mu receptor agonists biased towards G protein might maintain the analgesic effects of opioids but display reduced respiratory depression, constipation, and tolerance liability therefore acting as safer analgesics.



A separate study investigated the site of action of cebranopadol; experiments performed in different models of chronic neuropathic pain demonstrated that cebranopadol exerts potent and efficacious antihyperalgesic, antiallodynic, and antinociceptive effects after local/peripheral, spinal, and supraspinal administration.[87]

These initial studies demonstrated that cebranopadol not only promoted highly potent and efficacious analgesic effects in various pain models but also displayed a favourable side-effect profile. Cebranopadol did not modify animal performance in the rotarod test, even at doses several fold higher than its maximal analgesic dose,[69,70] whereas a small but consistent reduction of animal performance on the rod was already measurable at maximal analgesic doses of morphine.[69] Disruption of motor behaviour is a typical feature of selective NOP agonists at full doses, and for this reason the dose–response curve to Ro 65-6570 in the formalin assay could not be completed.[70] Thus, in terms of ratio between disruption of motor activity and analgesic doses, cebranopadol is not only superior to NOP selective agonists but also to classical opioid drugs. Another dose-limiting and potentially life-threatening acute side-effect of opioids is respiratory depression. This has been investigated in detail in a recent study in which the antinociceptive and respiratory depressant effects of cebranopadol and fentanyl were compared in rats.[88] At maximally effective analgesic doses, cebranopadol did not produce significant effects on arterial carbon dioxide tension whereas the ratio of fentanyl potencies for increasing carbon dioxide tension and for analgesic effects were less than 3. Importantly, the NOP antagonist J-113397 potentiated the respiratory depressant effects of cebranopadol that were, as expected, fully sensitive to naloxone.[88] These findings suggest that NOP activation by cebranopadol counteracts mu receptor-dependent respiratory depression, making the therapeutic index (in terms of analgesia *vs* respiratory depression) larger for cebranopadol than for the mu selective agonist fentanyl.

Among the issues associated with the use of opioid drugs in chronic pain, analgesic tolerance and the development of physical dependence are perhaps the most important. As far as tolerance is concerned, it is worthy of note that 26 days were needed to obtain complete tolerance to the analgesic action of cebranopadol, whereas under the same experimental conditions an equi-effective dose of morphine became completely inactive after only 11 days of treatment.[69] The reasons underlying the reduced tolerance liability of cebranopadol are far from obvious. It can be speculated that, as tolerance is a function of the amount of receptor stimulation and as the analgesic action of cebranopadol derives from the activation of two different receptors (NOP and the mu), it is somewhat expected that the tolerance liability of

cebranopadol is lower than that of morphine, whose analgesic effects solely depends on mu receptor activation. However, it should be borne in mind that NOP receptor signalling may play a role in controlling the development of tolerance, expression of tolerance, or both, to the analgesic action of opioid drugs and at this regard conflicting results have been reported in the literature. A single study reported the beneficial effects of NOP receptor stimulation on morphine tolerance,[89] whereas several studies reported the beneficial effects of NOP receptor blockade.[13,90–93] Clearly, further studies are needed to understand the mechanism(s) responsible for the reduced tolerance liability of the analgesic action of cebranopadol. As far as physical dependence is concerned, this aspect has been specifically evaluated in a recent study.[94] In a naloxone-precipitated withdrawal assay, mice treated with morphine within the analgesic dose range displayed clear withdrawal symptoms whereas animals treated with cebranopadol (even exceeding the analgesic dose range) showed very little withdrawal symptoms. Similar results were obtained in rat studies investigating both spontaneous and naloxone-precipitated withdrawal.[94] These results suggest a lower potential of cebranopadol to produce physical dependence in rodents than morphine, and the authors of the study speculated that this may derive from the ability of cebranopadol to stimulate the NOP receptor. This is certainly an attractive hypothesis that should be validated experimentally by testing cebranopadol in similar experiments in the absence and presence of selective NOP receptor antagonists, in wild type, NOP(−/−) mice or rats, or both.

Finally, very recent studies[95,96] demonstrated that cebranopadol is worthy of development as a treatment for drug addiction. Cebranopadol prevented cocaine self-administration, escalation of intake, and reinstatement in rats. Importantly, this action of cebranopadol derives from its ability to simultaneously activate NOP and mu receptors being prevented only by the co-administration of SB-612111 (NOP antagonist) and naltrexone (opioid antagonist).

Cebranopadol clinical studies

As previously discussed in an editorial in this journal,[97] cebranopadol is now in clinical development for analgesic indications. According to a clinicaltrial.org search performed at the end of 2017, nine studies on cebranopadol have been completed in patients suffering from different painful conditions including diabetic polyneuropathy (three); bunionectomy, chronic low back pain, osteoarthritis of the knee (two); and cancer (two) (some of these are outlined in Table 3). The following section summarises the published information relative to these trials.

The basic pharmacokinetic properties of cebranopadol were assessed in phase I and phase II clinical trials.[98] After oral administration, cebranopadol displayed a late time to reach maximum plasma concentration (4–6 h), a long half-life (14–15 h), and a terminal phase half-life in the range of 62–96 h. After multiple once-daily dosing in patients, an operational half-life of 24 h was calculated. In summary, cebranopadol displayed basic pharmacokinetic features compatible with a once-daily regimen that is a convenient treatment option for patients with chronic pain[98]; this is an advantage over the commonly used analgesics in this patient population.

A phase 1 clinical trial was performed aimed at the quantification of cebranopadol respiratory effects in healthy subjects.[99] A dose of 0.6 mg cebranopadol orally induced typical opioid-like effects including miosis, analgesia, and respiratory depression. However, compared with its analgesic effects, the respiratory depression induced by cebranopadol was moderate and short lasting. This is in line with preclinical studies that demonstrated in receptor antagonist experiments a protective role of NOP receptor stimulation on mu receptor induced respiratory depression.[88] Thus these findings suggest that, compared with classical opioid drugs, cebranopadol has lower propensity to depress respiratory function.

Christoph and colleagues[100] conducted the first phase II, randomised, double-blind, placebo- and active-controlled trial,

Table 3 Significant clinical trial information. *Diabetes trial—opioid typical AE. Cebranopadol 600/Placebo group 6.5/3.2% and 84/69% incidence serious and non-serious AE, respectively. †Cancer trial—tumour progression and opioid typical AE. Cebranopadol/Morph group 21.5/18.0% and 80/79% incidence serious and non-serious AE, respectively. ‡Cancer trial—death, tumour progression and opioid typical AE. ¶Back pain trial—opioid typical AE. Cebranopadol 600/Placebo group 1.6/1.6% and 90/63.5% incidence serious and non-serious AE, respectively. AE, adverse events; TEAE, treatment emergent adverse events

Trial	Started; CTR entry	Pain type	No. of patients	Primary end point	Secondary end point
KF6005/08	27/9/13; 27/4/16	Neuropathic diabetes	314	Pain Int *vs* placebo Cebranopadol 600 μg* **Significant**	None
KF6005/07	29/10/13; 30/9/16	Cancer	200	Morphine rescue Cebranopadol 200–1000 μg by patient titration† **Significant**	No. of patients with relevant pain reduction Similar number to Morphine group (no stats)
KF6005/09	18/12/13; 29/1/17	Cancer—26 week safety patients completed 6005/07	76	Incidence TEAE 64/76 (no stats)	(i) Intensity TEAE 42%, serious; 83%, non-serious‡ (ii) Change baseline pain NRS 0.8 (0=no pain; no stats)
KF6005/06	30/11/12; 25/2/16	Chronic low back	637	(i) Change baseline pain NRS Cebranopadol 200/400/600 μg *vs* placebo¶ **All significant**	None

evaluating the analgesic efficacy, safety, and tolerability of cebranopadol in patients with low back pain. This is a common pain phenotype with both nociceptive and neuropathic components fitting well with the pre-clinical profile described above. Patients were treated for 14 weeks with cebranopadol (0.2, 0.4, or 0.6 mg) once daily, tapentadol (200 mg) twice daily, or placebo. Cebranopadol and tapentadol demonstrated analgesic efficacy, with statistically significant and clinically relevant improvements over placebo. Beneficial effects of cebranopadol were also reported regarding physical functioning and sleep disturbance. Cebranopadol treatment was safe, with higher doses leading to higher treatment discontinuations mostly during the 2 week titration phase. The incidence rate of the most frequently reported adverse events (constipation, dizziness, fatigue, hyperhidrosis, nausea, vomiting, and somnolence) during maintenance phase was $\leq$10%. Interestingly and in line with preclinical findings,[94] discontinuation of cebranopadol after 14 weeks of treatment was not followed by clear withdrawal symptoms, and only a few cases of mild to moderate withdrawal symptoms were reported. Therefore, slow tapering off of the cebranopadol treatment seems not to be required. This study demonstrated that cebranopadol is a new drug candidate for the treatment of patients with low back pain. Moreover, further studies aimed at optimising the titration scheme to find the optimal dose for each patient may probably contribute to increase cebranopadol tolerability.

From the clinical trials register it is possible to extract some highlight data in: (i) diabetic neuropathy, and (ii) cancer pain. In patients with diabetic neuropathy, 0.6 mg cebranopadol produced significant analgesia when compared with placebo. In cancer pain, 0.2–1 mg cebranopadol (by patient titration) produced significant analgesia (CORAL trial). This study was extended to 26 week safety (CORAL XT); the side-effect profile of a typical opioid was reported.

Conclusions

Current opioid-based analgesic options are effectively limited to activation of mu receptors with drugs such as morphine, fentanyl or with pharmacokinetic advantage (remifentanil). Despite their utility, there are a wide range of side-effects including respiratory depression and the induction of tolerance. Tolerance can lead to a vicious circle of dose escalation and increasing side-effects. In the ~20 yr period since the formal identification of N/OFQ as the endogenous ligand for the NOP receptor and a role in pain processing, data confirming interaction with mu are emerging. Indeed, activation of NOP and mu receptors produces analgesia at the expense of reduced side-effects. This evidence coming from animal experiments has been confirmed in the first-generation clinical studies with cebranopadol. Clearly further clinical investigation is necessary to firmly establish the place in therapy of mixed NOP/opioid agonists as innovative analgesics. It is, however, worthy of mention that in just two decades the research work in the field of N/OFQ–NOP receptor system has been translated into significant clinical development, with cebranopadol, and important indications in particularly challenging pains such as those of neuropathic origin.

Authors' contributions

Writing of the first draft of the article: G.C.
Critical revision of the manuscript: D.G.L.
Approved the final version of the article: both authors.

Declaration of interest

G.C. and D.G.L. have both received in the past small research grants from Grunenthal, the company that is developing cebranopadol. G. Calo' is one of the inventors of the patents covering Rec 0438 and PWT-N/OFQ and derivatives and one of the founders of the University of Ferrara spin-off company, UFPeptides s.r.l., the assignee of such patents.

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