Opioid-type Respiratory Depressant Side Effects of Cebranopadol in Rats Are Limited by Its Nociceptin/Orphanin FQ Peptide Receptor Agonist Activity

Klaus Linz, Ph.D., Wolfgang Schröder, Ph.D., Stefanie Frosch, Ph.D., Thomas Christoph, Ph.D.

ABSTRACT

Background: Cebranopadol is a first-in-class analgesic with agonist activity at classic opioid peptide receptors and the nociceptin/orphanin FQ (NOP) peptide receptor. The authors compared the antinociceptive and respiratory depressant effects of cebranopadol and the classic opioid fentanyl and used selective antagonists to provide the first mechanistic evidence of the contributions of the nociceptin/orphanin FQ peptide and μ-opioid peptide receptors to cebranopadol’s respiratory side-effect profile.

Methods: Antinociception was assessed in male Sprague–Dawley rats using the low-intensity tail-flick model (n = 10 per group). Arterial blood gas tensions (PaCO₂ and PaO₂) were measured over time in samples from unrestrained, conscious rats after intravenous administration of cebranopadol or fentanyl (n = 6 per group).

Results: The ED₅₀ for peak antinociceptive effect in the tail-flick model was 7.4 μg/kg for cebranopadol (95% CI, 6.6 to 8.2 μg/kg) and 10.7 μg/kg for fentanyl citrate (9 to 12.7 μg/kg). Fentanyl citrate increased PaCO₂ levels to 45 mmHg (upper limit of normal range) at 17.6 μg/kg (95% CI, 7.6 to 40.8 μg/kg) and to greater than 50 mmHg at doses producing maximal antinociception. In contrast, with cebranopadol, PaCO₂ levels remained less than 35 mmHg up to doses producing maximal antinociception. The nociceptin/orphanin FQ peptide receptor antagonist J-113397 potentiated the respiratory depressant effects of cebranopadol; these changes in PaCO₂ and PaO₂ were fully reversible with the μ-opioid peptide receptor antagonist naloxone.

Conclusions: The therapeutic window between antinociception and respiratory depression in rats is larger for cebranopadol than that for fentanyl because the nociceptin/orphanin FQ peptide receptor agonist action of cebranopadol counteracts side effects resulting from its μ-opioid peptide receptor agonist action. (Anesthesiology 2017; 126:708-15)

What We Already Know about This Topic

- The nociceptin/orphanin FQ peptide (NOP) receptor represents a subcategory of the opioid receptor family with atypical low affinity for classic opioids
- Cebranopadol is a first-in-class analgesic that combines NOP receptor agonism with μ-opioid receptor agonism
- Antinociceptive doses of cebranopadol did not induce significant changes in respiratory parameters assessed using plethysmography in freely moving rats

What This Article Tells Us That Is New

- A selective nociceptin/orphanin FQ (NOP) receptor antagonist (J-113397) exaggerated the respiratory depressant effect of cebranopadol, providing the first evidence that the NOP receptor agonist activity of cebranopadol is responsible for limiting the respiratory depressant effect of its μ-opioid receptor agonist activity in rats

PAIN is the most common reason for people to seek medical attention.1 For patients with moderate to severe acute or chronic pain, opioid analgesics are the most effective treatments, but their use is limited by side effects such as respiratory depression, constipation, sedation, and nausea or vomiting. Respiratory depression is potentially life-threatening and is the main cause of opioid-related deaths.2 Prescription opioids were involved in more drug overdose deaths than heroin and cocaine combined in the United States in 2010,3 and mortality is rising as their use for chronic pain conditions becomes more common.4 Thus, safer and more effective analgesics for chronic pain are urgently needed.5

Classic opioids such as morphine and fentanyl are μ-opioid peptide (MOP) receptor agonists. Their MOP receptor agonist activity is responsible for their analgesic efficacy, as well as their peripheral and central nervous system side effects. The nociceptin/orphanin FQ peptide (NOP) receptor has emerged as a novel target for analgesic drugs since its identification by reverse pharmacology in the 1990s and is now considered to represent a subcategory of the opioid peptide receptor family with atypical low affinity for classic opioids.6 NOP receptor agonists may produce antinociceptive or pronociceptive effects and may potentiate or counteract the activity of classic opioids, depending on species and neuroanatomic site of administration.7 This modulatory activity results from intracellular molecular interactions between NOP and MOP receptors and interactions between neuronal circuits.8 Systemic coadministration of a NOP receptor agonist has been reported to potentiate the antinociceptive effects of morphine in rodents9 and nonhuman primates,10 without inducing opioid-like side effects.10–12 However, in rodents, NOP receptor activation has also been reported to attenuate the antinociceptive...
activity of MOP receptor activation.\textsuperscript{13} Combining a classic opioid receptor agonist with a NOP receptor antagonist, ideally in the form of a single small molecule, may therefore offer the potential to enhance analgesia and reduce side effects compared with classic opioids.\textsuperscript{14}

Cebranopadol is a first-in-class analgesic with agonist activity at the NOP receptor and the classic MOP, κ-opioid peptide, and δ-opioid peptide receptors.\textsuperscript{15,16} It has subnanomolar affinity for the human and rat NOP and MOP receptors and low nanomolar affinity for the κ-opioid peptide and δ-opioid peptide receptors.\textsuperscript{16} Cebranopadol was discovered in a program of rational optimization focusing on a family of novel spirocyclic indoleamines and is currently in clinical development.\textsuperscript{17,18}

In previous in vivo studies,\textsuperscript{16} the analgesic potency of cebranopadol ranged from more than 100- to more than 1,000-fold higher than that of morphine in rat pain models. The activity of cebranopadol in a rat model of pain hypersensitivity was inhibited by pretreatment with selective NOP or MOP receptor antagonists (J-113397\textsuperscript{19} or naloxone,\textsuperscript{20} respectively), indicating the involvement of both receptors.\textsuperscript{16} Unlike morphine, cebranopadol was about 10-fold more potent in rat models of chronic neuropathic pain than in models of nociceptive pain, inflammatory pain, and cancer-induced pain hypersensitivity. Compared with morphine, the duration of action of cebranopadol was extended and tolerance to its antiallodynic activity was delayed. Furthermore, cebranopadol did not induce the characteristic opioid side effects of motor discoordination and respiratory depression in rats.\textsuperscript{16}

In the current study, we used rat models of antinociception and respiratory depression to compare the therapeutic window of cebranopadol with that of the MOP receptor agonist fentanyl. In addition, we used selective antagonists of the NOP receptor (J-113397) and MOP receptor (naloxone) to provide the first mechanistic evidence of their contributions to the respiratory side-effect profile of cebranopadol.

**Materials and Methods**

**Animals**

Animal experiments were conducted at Grünenthal GmbH (Aachen, Germany) in accordance with the policies of the International Association for the Study of Pain\textsuperscript{21} and the German Animal Welfare Act.\textsuperscript{22} All study protocols were approved by the local government committee for animal research (Bezirksregierung Köln, Germany), which is advised by an independent ethics committee.

Male Sprague–Dawley rats weighing 200 to 550 g (Janvier, France) were delivered at least 4 days before procedures commenced and were housed in groups of five or six in polycarbonate cages (Ebeco, Germany) under standard conditions (12-h:12-h light:dark; 20° to 24°C; 35 to 70% relative humidity; 15 air changes per hour with air movement less than 0.2 m/s; water and standard rodent diet \textit{ad libitum}).

**Drugs and Doses**

Cebranopadol (trans-6′-fluoro-4′,9′-dihydro-4′-phenyl-spiro-[cyclohexane-1,1′(3′H)-pyrano[3,4-b]indol]-4-amine) hemicitrate (Grünenthal GmbH) was dissolved in a vehicle of polyethoxylated castor oil, 5% (Cremophor; Sigma-Aldrich, Germany), and dimethyl sulfoxide, 10%, in a glucose 5% (w/v) solution. Fentanyl citrate (Synopharm, Germany), J-113397 (1-[(3R,4R)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one; Grünenthal GmbH), and naloxone hydrochloride (Sigma-Aldrich) were dissolved in a vehicle of NaCl, 0.9% (Fresenius, Germany).

All test drugs were administered into the femoral vein in a volume of 1- to 5-ml/kg body weight. Adverse effects were monitored by technicians. Cebranopadol doses are expressed as free base, and fentanyl doses are expressed as the citrate salt throughout this article.

**Low-intensity Tail-flick Tests**

The latency of tail withdrawal ($t_t$) from a radiant heat beam focused on the dorsal surface of a rat’s tail about 20 to 40 mm from the root was measured using an analgesia meter-type 602001/b tail-flick device (RHEMA Labotechnik, Germany). To avoid tissue damage, the beam was switched off after 30 s ($t_{OFF}$) if the tail was not withdrawn. The heat intensity was set to 40% of maximum to produce a mean withdrawal latency of around 7 s ($t_t$) in untreated rats; only animals with pretreatment latencies of 15 s or less were used for further testing. These parameters allowed detection of changes in withdrawal latency resulting from drug modulation of the acute nocifensive reflex. Rats were tested before (baseline; 0 min) and 10, 20, 30, 60, 90, and 120 min after drug administration ($n = 10$ per group).

Maximum possible antinociceptive effect was calculated as ($t_{t} - t_{L})/(t_{OFF} - t_{L}) \times 100$ and expressed as mean percentage and SD.

**Blood Gas Measurements**

One week before testing, catheters were implanted into the femoral vein and femoral artery of rats and tunneled to the neck under general anesthesia (fentanyl, midazolam, and dexmedetomidine). Rats were housed individually after catheter implantation.

Unrestrained, conscious rats ($n = 6$ per group) were placed in polycarbonate cages, and they breathed room air at ambient pressure. Arterial blood samples (80 μl) were taken before (baseline; 0 min) and 2, 5, 20, 40, 60, 120, and 180 min after drug administration via the intravenous catheters. Arterial blood carbon dioxide and oxygen tensions were measured with an ABL 5 blood gas analyzer (Radiometer, Denmark) according to the manufacturer’s instructions. Rats were tested with multiple dose regimens during a period of about 3 to 4 weeks, with a washout period of at least 1 week between regimens. Changes in the rats’ body muscle tone were assessed subjectively during drug administration using the method of Irwin.\textsuperscript{25}
In cebranopadol antagonism experiments, rats received 2.15 mg/kg J-113397 or vehicle at \( t = -5\) min and 17.1 \( \mu g/kg \) cebranopadol or vehicle at \( t = 0\) min; one additional group treated with J-113397 and cebranopadol received 1 mg/kg naloxone at \( t = +20\) min. In fentanyl antagonism experiments, rats received vehicle, 30 \( \mu g/kg \) fentanyl, 1 mg/ kg naloxone, 2.15 mg/kg J-113397, 30 \( \mu g/kg \) fentanyl plus 1 mg/kg naloxone, or 30 \( \mu g/kg \) fentanyl plus 2.15 mg/kg J-113397 at \( t = 0\) min.

**Statistical Analyses**

Differences in maximum possible effect (%) in tail-flick tests were evaluated for statistical significance using a two-way repeated-measures ANOVA (\( \alpha = 0.05 \)) and post hoc Bonferroni tests to compare treatment groups with the vehicle control group. Differences in blood gas tensions (mmHg) were tested for statistical significance using a two-way repeated-measures ANOVA (\( \alpha = 0.05 \)) and post hoc Bonferroni tests to compare treatment groups with vehicle control group or with one another. When necessary, up to one animal per group with missing data at an individual time point was excluded from statistical analyses. Half-maximal ED\(_{50}\) and 95% CI were calculated for each drug by nonlinear regression at the peak time point of maximum possible antinociceptive effect or PaCO\(_2\) depression after administration, using the formula \( y = a + b \times \log(x) \). Statistical analyses were performed using Prism 4.00 (GraphPad Software Inc., USA).

**Results**

**Time-courses of Acute Antinociceptive Effects of Cebranopadol and Fentanyl**

In the low-intensity rat tail-flick model of acute nociceptive pain, intravenous cebranopadol (3.7 to 17.1 \( \mu g/kg \)) and fentanyl citrate (10 to 68.1 \( \mu g/kg \)) each elicited dose-dependent antinociceptive effects. Cebranopadol administration resulted in antinociception of at least 80% of the maximum possible effect at doses of 11.7 \( \mu g/kg \) from 10 to 60 min after administration and 17.1 \( \mu g/kg \) from 10 to 90 min after administration (fig. 1A). The effects of cebranopadol declined slowly over time and were still evident 120 min after administration at doses of 8 \( \mu g/kg \) or higher (\( P < 0.05 \) vs. vehicle). Fentanyl citrate administration resulted in antinociception of at least 80% of the maximum possible effect at doses of 21.5 \( \mu g/kg \) at 10 min after administration, 46.4 \( \mu g/kg \) from 10 to 20 min after administration, and 68.1 \( \mu g/kg \) from 10 to 60 min after administration. The effects of fentanyl declined rapidly compared with cebranopadol and returned to baseline by 30 to 120 min after administration, depending on the dose (fig. 1B).

**Time-courses of the Effects of Cebranopadol and Fentanyl on Blood Gas Tensions**

We assessed the effects of intravenous cebranopadol (2.5, 8, and 17.1 \( \mu g/kg \)) and fentanyl citrate 10, 30, and 100 \( \mu g/kg \) on arterial blood gas tensions in rats (fig. 2). Cebranopadol had no statistically significant effects on arterial blood gas tensions, with only modest dose-dependent decreases in arterial oxygen tension (PaO\(_2\)) and increases in arterial carbon dioxide tension (PaCO\(_2\)) from 10 to 180 min after administration (fig. 2, A and C). At the highest dose tested (17.1 \( \mu g/kg \)), mean PaO\(_2\) remained greater than about 70 mmHg from a baseline of about 90 mmHg, and PaCO\(_2\) remained less than about 35 mmHg from a baseline of about 30 mmHg. In contrast, fentanyl produced rapid and pronounced changes in blood gas tensions, with statistically significant decreases in mean PaO\(_2\) to less than 60 mmHg and increases in mean PaCO\(_2\) to greater than 50 mmHg at a dose of 30 \( \mu g/kg \) (fig. 2, B and D). These effects were even more pronounced at a higher dose (100 \( \mu g/kg \)) and were statistically significant from 2 to 20 min postadministration.

Cebranopadol (8 \( \mu g/kg \)) and fentanyl citrate (10 \( \mu g/kg \)) each produced approximately half-maximal levels of antinociception in the tail-flick assay. From a baseline of 32 mmHg, mean PaO\(_2\) remained less than 35 mmHg from 2 to 180 min...
postadministration with 8 μg/kg cebranopadol but exceeded 40 mmHg at 20 min postadministration with 10 μg/kg fentanyl citrate.

To verify that the effect of high doses of a MOP receptor agonist on respiration was not due to changes in body tone, muscle tone was assessed subjectively by an observer during the blood gas analysis experiments (table 1). These assessments did not indicate any differences in muscle tone at approximately equieffective doses of cebranopadol and fentanyl citrate (e.g., 8 and 10 μg/kg, respectively).

**Comparative Potencies of Cebranopadol and Fentanyl for Antinociception and Respiratory Depression**

To compare cebranopadol with fentanyl, we performed dose-response analyses (fig. 3) of the effects of each drug on antinociception in the tail-flick model and on PaCO₂ using the time points at which peak effects were observed in the time-course experiments presented in figures 1 and 2. The ED₅₀ for antinociception in the rat tail-flick model was 7.4 μg/kg for cebranopadol (95% CI, 6.6 to 8.2 μg/kg) and 10.7 μg/kg for fentanyl citrate (9 to 12.7 μg/kg). Because we did not demonstrate that a maximal effect was reached in the blood gas experiments, we calculated the dose required to increase PaCO₂ to 45 mmHg (the upper limit of the generally accepted normal range). This value was 17.6 μg/kg for fentanyl citrate (95% CI, 7.6 to 40.8 μg/kg) and could not be calculated for cebranopadol at the doses tested because PaCO₂ levels did not reach this threshold. At doses of cebranopadol that produced near-maximal antinociception (about 12 μg/kg), PaCO₂ levels

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**Table 1. Effect of Cebranopadol and Fentanyl on Muscle Tone**

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Muscle tone was assessed subjectively by an observer during blood gas analysis experiments (fig. 2). n = number of animals.
both the reduction in PaO2 and the increase in PaCO2, which
with J-113397 in a separate experiment. Naloxone reversed
receptor antagonism were MOP receptor-dependent, 1 mg/kg
gas tensions elicited by cebranopadol in the presence of NOP
arterial blood gas tensions when given alone (fig. 5). (data not shown). Neither J-113397 nor naloxone affected
from baseline were observed, either with or without J-113397
naloxone was given 20 min after cebranopadol to rats treated

dol dose of 8
fentanyl was given 20 min after cebranopadol to rats treated

Low-intensity tail-flick test antinociception data are from the following time points shown in figure 1 (n = 10 per group): cebrano-
padol, 20 min (A); fentanyl, 10 min (B). Arterial carbon dioxide tension (PaCO2) respiratory depression data are from the following
time points shown in figure 2 (n = 6 per group): cebranopadol, 40 min (A); fentanyl, 5 min (B). Dashed line indicates no effect in
tail-flick tests (0%). Error bars show SD (positive, negative, or both). *P < 0.05, drug versus vehicle (two-way ANOVA with post
hoc Bonferroni test).

remained at or less than 35 mmHg, compared with a baseline
of 32 mmHg. In contrast, doses of fentanyl citrate that
produced near-maximal antinociception (about 25 μg/kg)
would increase PaCO2 to more than 50 mmHg (fig. 3).

Effect of Selective NOP and MOP Receptor Antagonists on
Respiratory Depression

We used the selective NOP receptor antagonist J-113397
and the MOP receptor antagonist naloxone to investigate
the involvement of these receptors in the respiratory effects
of cebranopadol and fentanyl in rats (fig. 4). Treatment with
2.15 mg/kg J-113397 markedly potentiated the effects of 17.1
μg/kg cebranopadol on arterial blood gas tensions, with PaO2
decreasing to less than 60 mmHg and PaCO2 exceeding 50
mmHg (fig. 4, A and C). The differences between cebrano-
padol plus J-113397 and cebranopadol alone were statistically
significant at 20 min postdose for PaO2, and at 20 and 40 min
postdose for PaCO2 (fig. 4, A and C). At the lower cebranopa-
dol dose of 8 μg/kg, no changes in arterial blood gas tensions
from baseline were observed, either with or without J-113397
(data not shown). Neither J-113397 nor naloxone affected
arterial blood gas tensions when given alone (fig. 5).

To test whether the potentiation of changes in arterial blood
gas tensions elicited by cebranopadol in the presence of NOP
receptor antagonism were MOP receptor-dependent, 1 mg/kg
naloxone was given 20 min after cebranopadol to rats treated
with J-113397 in a separate experiment. Naloxone reversed
both the reduction in PaO2 and the increase in PaCO2, which
returned to baseline levels within 20 min (fig. 4, B and D).

The effects of 30 μg/kg fentanyl citrate on arterial blood
gas tensions were blocked by coadministration of 1 mg/kg
naloxone (fig. 5, B and D). Coadministration of 2.15 mg/
kg J-113397 with 30 μg/kg fentanyl citrate resulted in even
more pronounced changes in PaCO2 and PaO2 than fentanyl
citrate alone (fig. 5, A and C).

Discussion

Respiratory depression is a potentially life-threatening side
effect of classic opioid pain medications. Cebranopadol is a
novel spirocyclic indoleamine that combines NOP receptor
agonism with classic opioid receptor agonism. In this study
in rats, cebranopadol did not induce respiratory depression
doses that were highly effective in the low-intensity tail-
flick model of acute nociceptive pain. In marked contrast,
respiratory depression was evident at the antinociceptive
ED50 of fentanyl and was severe at higher doses. These results
are consistent with our previous study, in which antinoci-
ceptive doses of cebranopadol, but not morphine, did not
induce statistically significant changes in respiratory param-
eters assessed using plethysmography in freely moving rats.16
These findings suggest that cebranopadol may be more likely
to produce clinically useful levels of analgesia without potentially dangerous levels of respiratory depression. The potency of cebranopadol in
rodent models of chronic neuropathic pain is higher than that
in the acute nociceptive pain model,16 suggesting that the
potential therapeutic window between efficacy and side
effects may be even wider in some pain conditions than that
observed in the current study of acute pain.

The current study provides the first evidence that the
NOP receptor agonist activity of cebranopadol is responsi-
ble for limiting the respiratory depressant effect of its MOP
receptor agonist activity in rats. A selective NOP receptor
agonist (J-113397) exaggerated the respiratory depressant
effect of cebranopadol, with changes in arterial blood
gas tensions reaching levels similar to those observed with
fentanyl. These effects were fully reversible with a MOP
receptor agonist (naloxone). We also observed that the
NOP receptor antagonist J-113397 slightly worsened fen-
tanyl-induced respiratory depression in rats, even though
fentanyl is inactive at the NOP receptor.24 and speculate

Fig. 3. Dose-response curves for (A) cebranopadol and (B) fentanyl in models of nociceptive pain and respiratory depression. Low-intensity tail-flick test antinociception data are from the following time points shown in figure 1 (n = 10 per group): cebranopadol, 20 min (A); fentanyl, 10 min (B). Arterial carbon dioxide tension (PaCO2) respiratory depression data are from the following
time points shown in figure 2 (n = 6 per group): cebranopadol, 40 min (A); fentanyl, 5 min (B). Dashed line indicates no effect in
tail-flick tests (0%). Error bars show SD (positive, negative, or both). *P < 0.05, drug versus vehicle (two-way ANOVA with post
hoc Bonferroni test).
that endogenous nociceptin acting at NOP receptors may mildly attenuate respiratory depression with classic MOP receptor agonists. We have not investigated whether coadministration of a separate, exogenous NOP receptor agonist reduces the respiratory depressant effects of a MOP receptor agonist, because differences in the pharmacokinetic properties of the two drugs may influence the time course of their pharmacodynamic effects. Nevertheless, we conclude that simultaneous activation of the NOP receptor by cebranopadol protects against MOP receptor-dependent respiratory depression in rats.

Activation of NOP receptors by endogenous or synthetic ligands can positively or negatively modulate signaling through MOP receptors in response to opioid agonists. Activation of NOP receptors by endogenous nociceptin acting at NOP receptors may mildly attenuate respiratory depression with classic MOP receptor agonists. We have not investigated whether coadministration of a separate, exogenous NOP receptor agonist reduces the respiratory depressant effects of a MOP receptor agonist, because differences in the pharmacokinetic properties of the two drugs may influence the time course of their pharmacodynamic effects. Nevertheless, we conclude that simultaneous activation of the NOP receptor by cebranopadol protects against MOP receptor-dependent respiratory depression in rats.

Activation of NOP receptors by endogenous or synthetic ligands can positively or negatively modulate signaling through MOP receptors in response to opioid agonists.

The NOP receptor and its endogenous ligand (nociceptin/orphanin FQ) are widely distributed in the nervous system and regulate the cardiovascular and immune systems as well as nociceptive and reward processing. Coexpression and heterodimerization of NOP receptors with opioid receptors, interaction of NOP receptors with calcium channels, receptor internalization, trafficking, and splice isoform variation are factors that may be involved in determining the functional interactions between NOP and opioid receptors in different tissues and cell types and at different neuroanatomic locations. The current observation that the activity of cebranopadol at the NOP receptor attenuates the respiratory effects of its activity at the MOP receptor in rats is consistent with documented reversal of the effects of exogenous opioids by NOP receptor agonists when given locally at specific supraspinal sites. Conversely, both the NOP and MOP receptor agonist activities of cebranopadol were reported to contribute to antihypersensitivity in the spinal nerve ligation model of neuropathic pain in rats. This is consistent with documented antinociceptive effects of NOP receptor agonists given systemically or locally within the spine and with synergistic antihypersensitive and antinociceptive effects of coadministration of NOP and MOP receptor agonists in rodent and nonhuman primate models of pain, respectively.

The results of a phase 1 pharmacokinetic–pharmacodynamic study in healthy human volunteers are consistent with our findings in rats. This human study modeled a minimum ventilation value (Emin) of about 5 l/min for...
oral cebranopadol (from a baseline Emax of 20 l/min) under carbon dioxide clamp. No such ceiling for respiratory depression exists for classic opioids, including fentanyl and morphine, which have an Emin statistically indistinguishable from zero (no respiration).29,30 Although further studies at higher doses are needed, these findings suggest that cebranopadol may offer an advantage beyond opioid analgesics by reducing the potential for life-threatening levels of respiratory depression.

In conclusion, as an agonist of both NOP and MOP receptors, cebranopadol has an improved therapeutic window compared with classic opioids that do not activate the NOP receptor. The NOP receptor activity of cebranopadol appears to work in synergy with its MOP receptor activity in providing antihypersensitivity,16 but at the same time in opposition to its MOP receptor activity in controlling respiratory depressant side effects. Whether these intrinsic and complementary functional interactions will provide patients with a safer, more tolerable, and more effective pain medication remains to be established in ongoing clinical trials.

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Competing Interests
All authors are employees of Grünenthal GmbH (Aachen, Germany).

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References