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Effects of opioid rotation to buprenorphine/naloxone on pain, pain thresholds, pain tolerance, and quality of life in patients with chronic pain and opioid use disorder

Stijn Veldman\textsuperscript{a,}* , Maria van Beek\textsuperscript{a,b} , Steffie van Rijsijk\textsuperscript{a} , Hannah Ellerbroek\textsuperscript{a} , Hans Timmerman\textsuperscript{c,d} , Selina van der Wal\textsuperscript{d} , Monique Steegers\textsuperscript{d,e} , Arnt Schellekens\textsuperscript{a,b,f}

Abstract
Long-term opioid use in patients with chronic noncancer pain (CNCP) can lead to opioid use disorder (OUD) and has been associated with hyperalgesia and reduced quality of life (QoL). Studies suggest antihyperalgesic properties of buprenorphine, and buprenorphine or naloxone (BuNa) has shown beneficial effects on QoL in patients with OUD without CNCP. This study investigated the added value of BuNa in patients with CNCP with OUD on self-reported pain, pain thresholds, and QoL. In the current study, 43 outpatients with CNCP and OUD were included for inpatient conversion from full \( \mu \)-receptor agonist opioids to BuNa. Self-reported pain, pain thresholds, and QoL were determined at baseline and after 2 months of follow-up, using respectively, a Visual Analogue Scale (VAS-pain and VAS-QoL), quantitative sensory testing, and EuroQol-5 dimensions. In total, 37 participants completed the protocol, and their data were analyzed. The mean VAS-pain score decreased from 51.3 to 37.2 (27.5\%, \( F = 3.3; P = 0.044 \)), whereas the pressure pain threshold and electric pain threshold or tolerance increased after substitution (\( F = 7.8; P = 0.005 \) and \( F = 44.5; P < 0.001 \), respectively), as well as QoL (EuroQol-5 dimensions questionnaire: \( F = 10.4; P = 0.003 \) and VAS-QoL: \( F = 4.4; P = 0.043 \)). We found that conversion of full \( \mu \)-receptor agonists to BuNa, in patients with CNCP with OUD, was accompanied with lower self-reported pain, higher pain thresholds, higher pain tolerance, and improved QoL. Despite several study limitations, these data suggest that BuNa might be of value in patients with CNCP with OUD. Future studies should investigate long-term effects of BuNa in randomized trials.

Keywords: Buprenorphine/naloxone, Suboxone, Chronic pain, Opioid induced hyperalgesia, Pain threshold, Pain tolerance, Quality of life, Opioid use disorder, Pain

1. Background
Chronic noncancer pain (CNCP) is commonly defined as any chronic pain syndrome not related to cancer that persists for over 3 to 6 months.\textsuperscript{107} CNCP has an estimated prevalence of 16\% to 21\% in the general population\textsuperscript{7,25,58,96} and is a major health issue worldwide, with a significant impact on the quality of life (QoL) of individual patients and major consequences for the society.\textsuperscript{7,22} Although opioids administration is a common treatment strategy for CNCP, the long-term analgesic effects are modest.\textsuperscript{15,31,36,66,71} In addition, long-term opioid use is associated with several adverse effects, including constipation, tolerance, hyperalgesia, respiratory depression, sedation, and addiction.\textsuperscript{3,20,24,83,86,104}

Despite their limitations, the prevalence of long-term use of prescription opioids has risen in recent years.\textsuperscript{95} A review of current literature shows a prevalence of opioid use disorder (OUD) among patients with CNCP ranging between 8\% and 12\%.\textsuperscript{110} Opioid use disorder has additional negative impact on QoL on top of CNCP.\textsuperscript{44}

Treatment of patients with CNCP and comorbid OUD is a complex clinical challenge because tapering of opioids is likely to increase pain, whereas further increasing the opioid dose will aggravate the addiction, tolerance, and pain sensitivity.\textsuperscript{18} Currently available evidence-based treatment for OUD in the Netherlands mainly consists of detoxification, psychological treatment to enhance motivation and promote abstinence, and opioid substitution treatment (OST). Opioid substitution treatment consists of the long-acting full \( \mu \)-opioid receptor agonist methadone or the partial \( \mu \)-opioid receptor agonist buprenorphine, frequently combined with naloxone (BuNa).\textsuperscript{2,4,13,32,38,40,46,49,63,65,66,73,84,90,99,100}

In the context of CNCP, OST with buprenorphine (or BuNa) is of particular interest, given its pharmacological profile. Besides being a partial agonist at \( \mu \)-opioid receptors, which is particularly relevant for analgesia\textsuperscript{29} and the hedonic aspects of OUD,\textsuperscript{26} buprenorphine is...
also an antagonist at the k-opioid receptor, which is involved in stress-related aspects of both pain and OUD. Indeed, several randomized controlled trials have shown not only the analgesic ability of buprenorphine in patients with CNCP but also antidepressant properties. The potential beneficial effect of BuNa on pain, stress, and depression may contribute to a better QoL in patients with combined CNCP and OUD. Furthermore, buprenorphine is associated with a slower onset of tolerance. Unfortunately, only few studies investigated effectiveness of buprenorphine as OST in patients with CNCP and OUD. Although these studies did suggest improvement in self-reported pain, they were hampered by retrospective designs, small sample sizes (i.e., less than 10 participants finished the trial), additional self-administration of oxycodone, and OUD was not an inclusion criterion in all studies.

In addition, long-term use of full μ-opioid receptor agonists has been suggested to cause so-called opioid-induced hyperalgesia (OIH). Hyperalgesia is an increased central nervous system sensitivity to pain and has been associated with increased pain, expansion of pain to other locations, decreased pain thresholds, and decreased pain tolerance. However, the evidence for the OIH concept is still limited, especially concerning decreased pain thresholds. It has been hypothesized that buprenorphine causes less OIH compared with full agonist opioids, which is mainly based on animal studies. However, other studies show that buprenorphine causes hyperalgesia as well.

The aim of this study was to investigate the effect of opioid rotation of full μ-opioid receptor agonists to BuNa in patients with CNCP and OUD. Specifically, we tested the hypotheses that rotation to BuNa in these patients would lead to (1) improved perceived pain, (2) increased pain thresholds and tolerance (indicative of reduced hyperalgesia), and (3) increased QoL.

### 2. Methods

#### 2.1. Design

In an open-label, observational study, patients with CNCP and OUD were rotated to BuNa. The local institutional ethical review board approved this study (NL 2015-1551), and all participants gave written informed consent.

#### 2.2. Study population

Patients with CNCP and OUD (n = 43) were referred to the Department of Psychiatry of Radboud University Medical Center by their general practitioner or pain practitioner. Patients were included between 2017 and 2019. Inclusion criteria were (1) age between 18 and 65 years, (2) meeting criteria for chronic pain (i.e., >6 months), (3) OUD according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), and (4) using a morphine equivalent dose of over 90 mg per day, for at least a year. Patients with a contraindication for the use of BuNa (severe respiratory insufficiency, severe liver insufficiency, alcohol use disorder, or with psychiatric emergencies, eg, acute psychosis or suicidality) were excluded from this study.

#### 2.3. Intervention

The rotation of full μ-opioid receptor agonists to BuNa took place in an inpatient facility of the Department of Psychiatry of Radboud University Medical Center. First, if long-acting opioids were used, these were substituted for a short-acting opioid (oxycodone) based on morphine equivalent doses, withdrawal severity, and self-reported pain. Second, short-acting opioids were rotated to the partial agonist BuNa, under continuous measurement of opioid withdrawal severity in line with the Dutch detoxification guideline and pain monitoring using a Visual Analogue Scale (VAS). Withdrawal symptoms were determined up to 6 times a day during the rotation period, using the subjective withdrawal scale and the objective withdrawal scale, based on the subjective opioid withdrawal scale and clinical opioid withdrawal scale, respectively.

Participants started with a dose of 4/1 mg BuNa at least 4 hours after the last opioid intake and after opioid withdrawal set in (ie, scoring ≥12 on the subjective withdrawal scale). Buprenorphine or naloxone was subsequently titrated with 2/0.5 mg every 4 hours based on pain scores and severity of withdrawal symptoms, to a maximum of 24/6 mg on day one. The subsequent days participants started in the morning with the total dosage of the previous day and similar titration procedure with an ultimate maximum dosage of 36/9 mg per day. After 7 days, a BuNa dosing regimen was set for the subsequent 2 months, until follow-up. During the rotation, participants were offered supportive medication per protocol, including paracetamol and nonsteroidal anti-inflammatory drugs for pain and clonidine and benzodiazepines for withdrawal symptoms. Hereafter, no other opioids and no changes were allowed with respect to other pain treatments.

### 2.4. Measurements

The following participant characteristics were determined at baseline from medical records: demographics, years of opioid use, kind of opioids used, calculation of the oral morphine equivalent (OME), use of nonopioid analgesics and other comedication, use of other psychoactive substances, and pain type.

Self-reported pain was assessed using a VAS. The VAS-pain consisted of a line of 100 mm, with zero as no pain at all and 100 as the most severe pain imaginable. Participants drew their pain score on this scale. The VAS-pain has been validated for patients with CNCP, showing similar sensitivity compared with the commonly used Numerical Rating Scale. In addition, the VAS-pain is the pain measurement that is influenced the least by non-pain-related factors. The VAS-pain is also commonly used to monitor pain severity over time in clinical practice.

Pain thresholds and tolerance were assessed using quantitative sensory testing (QST), based on the Nijmegen–Aalborg Screening QST protocol. Patients were examined by only one researcher. A total of 3 trained and experienced examiners took the tests for this study. Instructions to the patient were standardized and read from the instruction sheet. Tests were performed in a standard test order according to the Nijmegen–Aalborg Screening QST protocol. Quantitative sensory testing consisted of 3 measurements: (1) pressure stimulus, (2) electric stimulus, and (3) testing of the participant’s capacity to modulate pain using the conditioned pain modulation (CPM). For the pressure pain threshold (PPT), the Wagner Pain Allogometer FPX50 (Wagner Instruments, Greenwich, CT) was used. The amount of applied ndewton at which the participants started feeling pain, assessed at 8 different locations across the body (musculus abductor hallucis, musculus trapezius, thenar, and musculus rectus femoris), was measured. All locations were tested on both the right and left side of the body. Pressure pain threshold scores ranged between zero and the maximum value detectible by the device (250 N) or the maximum force the researcher was able to produce. No ceiling
effects were observed, as all participants felt pain before the maximum was reached.

For the electric stimulus, the QST-IV electrical stimulator (Embedded Control BV, Ruurlo, the Netherlands) was used. We measured the electric stimulus strength at which the stimulus (1) was felt, electric sensitivity threshold, (2) started to be painful, electric pain threshold (EPT), and (3) could not be tolerated any longer, electric pain tolerance (EPTol). This was assessed at 4 different locations across the body (dermatome C5,6 left and right and dermatome L2-4 left and right). The current was a tetanic stimulation at 100 Hz, 2-ms square waves applied to the skin by self-adhesive electrodes 4 cm apart from each other. The electrical stimulus was expressed in milliamperes, on a scale of zero to a maximum of 50 mA to prevent tissue damage. For the EPT measurements, a ceiling effect occurred in some patients, both at baseline and follow-up. The electrical stimulus test was repeated 3 times in a sequence.

For the CPM, the participant’s dominant hand was put into ice water. The participants had to withdraw their hand if the cold could no longer be sustained, with a cutoff point of 180 seconds to prevent tissue damage. Hereafter, the PPT and EPTol were remeasured on the contralateral musculus femoris (L2-4). For this EPTol measurement, a ceiling effect occurred in some patients as well. These values were converted into percentual difference of the PPT/EPTol after CPM and the previous PPT/EPTol.

Standardized QST, performed by skilled examiners, has proven to be an instrument with good interobserver and test–retest reliability.9,39,78,87 Quantitative sensory testing has repeatedly been used to assess pain thresholds or tolerance, including in patients with CNCP on long-term opioid treatment.52,112

Quality of life was determined through the EuroQol-5 dimensions (EQ-5D) and consisted of 2 values: (1) a questionnaire with 5 questions (mobility, self-care, daily activities, pain, and mood), with 3 answer options, and (2) a VAS scale.34 The VAS-QoL is a scale from 0 to 100, with zero as the lowest QoL imaginable and 100 as best QoL imaginable. Both the questionnaire as well as the VAS-QoL measure QoL with a time window of one day. The EQ-5D is a widely used instrument and has been validated for patients with chronic pain.106 The EQ-5D scores were converted before analysis, using the time trade-off method, which has been validated for the Dutch population.59

2.5. Procedure

After informed consent, potential participants were screened for inclusion and exclusion criteria. Subsequently, baseline measurements were taken in eligible patients, including demographics, baseline VAS-pain, QST, VAS-QoL, EQ-5D, and opioid use measures. Participants were subsequently admitted for inpatient opioid rotation to BuNa. During opioid rotation, the VAS-pain was determined up to 6 times a day, of which the last measurement before discharge was used to investigate the immediate effect of rotation to BuNa on perceived pain, before discharge from the hospital. The VAS-pain, QST, VAS-QoL, and EQ-5D were repeated 2 months after the opioid rotation.

2.6. Data analysis

Descriptive analyses were performed to assess baseline characteristics of the study sample. The relation between the OME dose at baseline and the final BuNa dose at discharge was analyzed using Pearson correlation analyses. For the correlation analyses, 2 participants with a very high OME dose at baseline (1580 mg and 2270 mg, respectively) were not included, given the dose cap of BuNa at 36/9. However, these participants were included in all further analyses.

An analysis of completed subjects was used to investigate the effect of BuNa rotation. The effect of BuNa rotation on self-reported pain was analyzed using a linear mixed model approach, with time as the fixed factor and VAS-pain score as the dependent variable. The factor time had 3 levels: baseline, last measurement before discharge, and at 2 months follow-up. Post hoc analyses were performed to explore the effect per time point compared with baseline.

To analyze the effect of BuNa rotation on pain thresholds and pain tolerance, separate linear mixed model analyses were performed per type of stimulus. For the electrical stimuli, the EPT and the EPTol were analyzed together in a multivariate design, with time (2 levels), location, and type of measure as fixed factors and amount of electricity administered as the dependent variable. For the PPT, a separate mixed model was built, with time (2 levels) and location as fixed factors and amount of pressure administered as the dependent variable. Furthermore, the CPM and the electric sensitivity threshold could not be analyzed because of technical issues.

Finally, 2 separate linear mixed models were performed to analyze the effect of BuNa rotation on perceived QoL. In the first model, the total EQ-5D score was used as the dependent variable and time as the fixed factor (2 levels). In the second model, the VAS-QoL score was used as the dependent variable and time as the fixed factor (2 levels). For all mixed models, compound symmetry was used as the covariance type. All statistical analyses were performed in SPSS Statistics for Windows version 25 (IBM Corp, Armonk, NY). A P-value of <0.05 was considered statistically significant.

3. Results

Thirty-seven of the 43 included participants (86%) finished the trial; see Table 1 for detailed description of analyzed participants. Twenty-three participants (62.2%) were male, and the mean age was 47.5 years (±10.9). The mean VAS-pain at baseline was 51.3 (±25.8). Furthermore, the mean OME at baseline was 328.3 mg (±411.0), the mean duration of opioid usage was 5.6 years (±3.8), the mean daily dose of buprenorphine at discharge was 19.6 mg (±8.2; BuNa compound contains 2 mg buprenorphine and 0.5 mg naloxone), and the mean daily dose of buprenorphine at follow-up was 18.3 mg (±9.9). The morphine equivalent dose at baseline correlated moderately with the BuNa dose after the rotation (R = 0.36 [P = 0.032]), see Figure 1.

Of the 6 participants who dropped out of the study, 4 participants could not complete the follow-up because of inadequate pain control and were rotated back to their original opioids. One participant was converted to buprenorphine (instead of BuNa) because of unbearable taste of BuNa. One participant was lost to follow-up. As can be seen in Table 2, the dropouts significantly had a higher baseline OME in comparison with the analyzed participants (593.3 ± 381.2 and 328.3 ± 411.0; P = 0.015). No other significant differences were found between the groups, see Table 2.

For the QST analysis, 2 participants were excluded because one participant refused the QST measurement and one participant could not participate in the QST measurements because of paraplegia (Fig. 2).

The main results of the statistical analysis and the descriptive statistics are listed in Table 3. Self-reported pain levels reduced from 51.3 ± 25.8 to 37.2 ± 25.1 (decrease of 27.5%; F[2,70.1] =
Table 1
Patient characteristics.

<table>
<thead>
<tr>
<th>No. of participants (%)*</th>
<th>Employment†</th>
<th>Domestic situation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 (27.0)</td>
<td>Single 8 (21.6), Cohabitating 29 (78.4)</td>
</tr>
</tbody>
</table>

| Education level§ | Low 3 (8.1), Middle 25 (67.6), High 9 (24.3) |

| Opioid at baseline‖ | Oxycodone 28 (75.7), Methadone 6 (15.8), Fentanyl 10 (27.0), Others 9 (24.3), Polypopioid 14 (37.8) |

| Intoxications‖ | Smoking 14 (37.8), Alcohol 15 (40.5), Drugs 10 (27.0) |

| Pain type# | Neuropathic pain 13 (35.1), Nociceptive pain 20 (54.1), Idiopathic pain 4 (10.8) |

| Other analgesics‖ | Paracetamol 21 (56.8), Nonsteroidal anti-inflammatory drugs 4 (10.8), Antidepressant 10 (27.0), Gamma-aminobutyric acid 15 (40.5) |

| Other medications‖ | Sedatives 10 (27.0), Psychotropic 12 (32.4), Gastrointestinal 21 (56.8), Laxatives 14 (37.8), Cardiology 9 (24.3), Pulmonary 6 (16.2) |

* Participants who did complete the trial.
† Percentage employed.
‡ Living with a partner.
§ Highest achieved degree of education.
‖ Amount of participants taking these types of medication.
¶ Amount of participants answering “yes.”
# Main cause of the chronic pain.

Table 2
Differences in mean between analyzed participants and dropouts on baseline parameters.

<table>
<thead>
<tr>
<th>Analyzed*, mean ± SD</th>
<th>Dropouts, mean ± SD</th>
<th>Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.5 ± 10.9</td>
<td>39.3 ± 12.8</td>
</tr>
<tr>
<td>OME†</td>
<td>328.3 ± 411.0</td>
<td>593.3 ± 381.2</td>
</tr>
<tr>
<td>VAS-pain‖</td>
<td>52.1 ± 25.3</td>
<td>61.3 ± 7.4</td>
</tr>
</tbody>
</table>

* Participants who finished the trial.
† Analyzed using the Mann–Whitney U test.
‡ OME at baseline.
§ P-value considered statistically significant (P < 0.05).
‖ VAS-pain at baseline.

Figure 1. Correlation between the suboxone dose at discharge and the morphine equivalent at baseline.

4. Discussion
This study investigated the effect of rotation from full agonist opioids to BuNa on (1) perceived pain, (2) pain thresholds or tolerance, and (3) QoL in patients with CNCP and OUD. The dropout rate was 14% (n = 6), mostly because of inadequate analgesia (4 of 6 participants). As hypothesized, BuNa rotation was associated with reduced pain, increased pain thresholds, measured by electric stimulation and pressure stimulus, and increased pain tolerance measured by electric stimulation. Finally, an increase in QoL was observed. These findings suggest that BuNa rotation might be beneficial in a subset of patients with CNCP and OUD, both for analgesia and QoL.

Our findings are in line with previous studies, showing beneficial effects of rotation to either buprenorphine alone or BuNa on self-reported pain in patients with CNCP.11,26,72,74,88,89 However, these studies either lacked implementation of validated measurements,11 were retrospective in nature,26,72,74 or did not include patients with CNCP and OUD.17 The current work further supports the potentially beneficial role of BuNa in pain management of patients with CNCP and OUD. The reduction in pain severity levels observed here (VAS = 14.1 points on average; −27.5%) is in line with previous studies (pain reduction between −8 and −45 on the VAS).26,27,72,74,88 A possible explanation of the relatively mild decrease in VAS scores in the current study in comparison with the previous studies may be related to our prospective design,26,27,74,88,89 lower severity of baseline pain,26,72,74,88 or higher oral morphine equivalent at baseline.27,74,88,89 However, a decrease of 27.9% on a 0 to 10 scale is generally considered as “much-to-very-much improved.”35 Furthermore, it should be noted that our findings are likely an overestimation of the beneficial effects of BuNa rotation because only the completed participants were analyzed. Future larger randomized controlled trials should further explore the decrease in pain severity after rotation to BuNa, using an intention-to-treat analysis.
The decrease in VAS-pain after rotation from a full \( \mu \)-opioid agonist to a partial \( \mu \)-opioid agonist might be related to the predicted beneficial effects on opioid-induced hyperalgesia.\(^{53,56,85,105,113}\) Indeed, we observed increases in pain thresholds and tolerance after the rotation. Specifically, we observed increased thresholds for electric stimulus pain and pressure stimulus pain and increased tolerance for electric stimulus pain. This is consistent with previous research, which suggests that buprenorphine might cause less OIH compared with full-opioid agonists,\(^{53,56,85,105,113}\) and animal work showing buprenorphine to block OIH.\(^{97}\) Such beneficial effects on OIH might on the one hand be related to the partial agonism at the \( \mu \)-opioid receptor. On the other hand, OIH has been related to increased dynorphin levels during opioid use. OIH has been suggested to result from dynorphin binding to \( \kappa \)-opioid receptors. The \( \kappa \)-antagonist effect of buprenorphine may thus reduce dynorphin-induced OIH through blocking \( \kappa \)-opioid receptors.\(^{52,79}\) Furthermore, buprenorphine has also been shown to have some anti-NMDAR activity,\(^{67}\) which has been hypothesized to contribute to OIH as well.\(^{20,42}\) It remains to be studied whether the observed changes in pain threshold and tolerance are clinically relevant. Therefore, the beneficial effects on the other outcome measures do support clinically relevant improvements after BuNa rotation, both on the VAS-pain and QoL measures. Furthermore, several studies did not find evidence for OIH, especially in patients on short-term opioids and lower dosages than our participants.\(^{21,90}\) Future studies should further explore the potential mechanisms (\( \kappa \)-opioid or NMDAR antagonism) mediating OIH and the clinical relevance of the potentially beneficial profile of buprenorphine in OIH.

The observed increased QoL after rotation to BuNa is in line with several previous reports, particularly studies on effectiveness of BuNa as an opioid substitution therapy.\(^{40,41,68,70,80,87}\) However, the current study is the first to demonstrate the improvement of QoL in patients with CNCP with OUD. Furthermore, an increase of 0.20 on the EQ-5D scale is considered clinically relevant.\(^{116}\) It remains to be studied whether improved QoL is mediated by beneficial effects of BuNa rotation on perceived pain or might also be mediated by other effects of BuNa rotation, for

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* two participants were excluded for the QST analysis, due to refusal (n=1) and due to paraplegia (n=1)
instance on mood, a more beneficial side effect profile compared with full-opioid receptor agonists, or other mechanisms.

It is important to note that about 14% of participants dropped out of the study during rotation to BuNa. Furthermore, baseline OME of participants who dropped out during the study was higher than that of participants who finished the trial. This might indicate that participants with a very high OME are less likely to successfully undergo BuNa rotation. Future studies should further explore potential predictors of BuNa rotation failure.

The current findings should be seen in the light of several study limitations. First, the observational design without a control group and the limited number of participants prevent firm conclusions concerning the effectiveness of BuNa in patients with CNCP and OUD. Future studies using randomized designs, including a control condition, are needed to confirm the current findings. In addition, the current study included mainly men (62.2%), and the major pain type was nociceptive pain (54.1%). Future studies might explore potential sex differences or differences in effectiveness of BuNa rotation between patients with different types of pain.

In addition, it is unclear how the BuNa dose after rotation compares with the baseline dose of full receptor agonist opioids. Indeed, BuNa doses correlated only moderately with baseline OME doses (Fig. 1). Furthermore, the reliability of OME conversion rates for BuNa are limited, among others because of kinetic variation (differences in absorption because of sublingual administration) and the unique pharmacological profile of buprenorphine as partial agonist. As a result, currently available conversion rates show substantial ranges in the conversion factor (10-30). It can thus not be fully ruled out that the total OME might have increased after BuNa rotation. Future studies might provide more insight in OME of BuNa.

Another limitation is that we did not collect urine toxicology data on opioid use, either at baseline or after 2 months follow-up. Such data would have strengthened our conclusions, as the use of any nonprescribed opioids could then be ruled out. However, to evaluate opioid misuse, including the use of nonprescribed opioids, we did use systematic self-report (COMM), commonly used to monitor opioid misuse,55 at baseline and at follow-up. None of the participants reported using a nonprescribed opioid at follow-up. Furthermore, it should be noted that in the Netherlands the use of illegally manufactured opioids (eg, fentanyl) and nonprescribed opioids is relatively rare, particularly compared with the United States, Canada, and the United Kingdom.117 Furthermore, our study had a follow-up of 2 months. In patients with CNCP, it is likely that they will have analgesic requirements exceeding these 2 months. It is therefore important to have longer follow-up observations, to observe long-term effects of BuNa rotation. In addition, some studies suggest that gradual tapering of opioids might be beneficial in patients with CNCP with success rates up to about 28% in patients rotated to methadone.117 It is therefore highly relevant to explore potential for tapering BuNa in patients with CNCP.

Finally, it has to be acknowledged that nonpharmacological interventions play an important role in CNCP treatment. For instance, cognitive behavioral therapy and mindfulness–based interventions are potential beneficial in patients with CNCP.108 Adding such psychological interventions to a pharmacological intervention, such as BuNa rotation, might increase its effectiveness and facilitate tapering of opioids after rotation. This should be addressed in future studies.

In conclusion, this is the first prospective study in which the effect of BuNa rotation on pain, pain thresholds, pain tolerance, and QoL was assessed in patients with CNCP and OUD. Self-reported pain decreased after the rotation, pain thresholds increased, and pain tolerance increased, with subsequent improved QoL. These findings indicate a potentially beneficial effect of BuNa in a subset of patients with CNCP and OUD, although more research is needed to confirm effectiveness and identify patients who are most likely to benefit from BuNa rotation.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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