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Evidence of opioid-induced hyperalgesia in clinical populations following chronic opioid exposure: A systematic review and meta-analysis

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FULL TITLE: Evidence of opioid-induced hyperalgesia in clinical populations following chronic opioid exposure: A systematic review and meta-analysis

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Abstract

Background: Opioid-induced hyperalgesia (OIH) is well-documented in preclinical studies but findings of clinical studies are less consistent. The objective was to undertake a systematic review and meta-analysis of studies examining evidence for OIH in humans following opioid exposure.

Methods: Systematic electronic searches utilised six research databases (Embase, Medline, PubMed, Cinahl Plus, Web of Science and OpenGrey). Manual 'grey' literature searches were also undertaken. The PICOS framework was used to develop search strategies and findings are reported in accordance the PRISMA Statement. Data synthesis and subgroup analyses were undertaken using a random effects model (DerSimonian-Laird method).

Results: A total of 6167 articles were identified. Following abstract and full text reviews, 26 articles (involving 2706 participants) were included in the review. There was evidence of OIH, assessed by pain tolerance, in response to noxious thermal (hot and cold) stimuli but not electrical stimuli. There was no evidence of OIH when assessing pain detection thresholds. OIH was more evident in patients with opioid use disorder, than in patients with pain, and in patient groups treated with NMDA receptor antagonists (primarily evidenced in methadone-maintained populations).

Conclusions: OIH was evident in patients following chronic opioid exposure but findings were dependent upon pain modality and assessment measures. Further studies should consider evaluating both pain threshold and pain tolerance across a range of modalities to ensure assessment validity. Significant subgroup findings suggest that potential confounders of pain judgements – such as illicit substance use, affective characteristics or coping styles – should be rigorously controlled in future studies.

Keywords: Hyperalgesia; Pain Threshold; Pain; Analgesics, Opioid; Opioid-related disorders.

Introduction

Rationale

Prolonged use of opioids is associated with a number of debilitating side effects, including the potential for the development of tolerance, dependence and abuse. The development of opioid-induced hyperalgesia (OIH) may represent substantial additional challenges in the effective treatment of pain. Whilst OIH has been well-documented in preclinical studies, evidence in clinical populations is relatively sparse and inconsistent; therefore, elucidation of this phenomenon is of key importance to anaesthetists and other pain specialists. Whilst the apparent clinical effects of increasing opioid tolerance, opioid withdrawal and OIH may be the same (i.e. increased experience of pain), the physiological aetiologies likely differ and, therefore, effective management may require different approaches. Development of effective policy and practice necessitates synthesis of existing clinical evidence and to provide recommendations for future work in this area of study.

Several studies have documented hyperalgesia in response to systemic or intrathecal morphine at high doses and reported that pain is further potentiated following dose increases^{1 2 3 4}. Furthermore, hyperalgesia has been shown to be positively associated with baseline morphine-equivalent dose, even after adjusting for pain diagnosis, pain duration, pain severity and opioid withdrawal symptoms⁵. Furthermore, this study demonstrated that opioid tapering was associated with decreased hyperalgesia; however, it should be noted that the mean morphine-equivalent dose was relatively low. In a more recent study⁶, hyperalgesia was reported to be significantly associated with high-dose intra-operative remifentanil treatment compared with remifentanil with naloxone (an opioid antagonist) and low-dose remifentanil.

Whilst there are several proposed central and peripheral mechanisms, such as alpha-2 adrenoceptors and the endocannabinoid system, the most prominent of these is considered to be the potential role of the central glutaminergic system⁷, suggesting that opioid exposure increases N-methyl-D-aspartate (NMDA) activity. Indeed, several studies have reported down-regulation of spinal glutamate receptors following prolonged opioid exposure, resulting in spinal neuron sensitisation^{8 9 10 11}. This further substantiates the hypothesised role of NMDA receptors in hyperalgesic states.

The method of pain assessment is an important consideration when examining OIH. The two prominent methods are patient rating scales and quantitative sensory testing (QST). There are a number of potential limitations associated with the use of rating scales. First, in order to distinguish between tolerance and hyperalgesia, it may be considered wise to test experimental pain models at non-painful sites – rather than to obtain an overall rating of pain – which is difficult to achieve using rating scales but can be achieved using QST. Secondly, in the presence of persistent and debilitating pain, a ‘ceiling effect’ may arise when participants initially report their pain severity as the worst possible pain imaginable (i.e. a rating of ‘10/10’). QST enables testing at non-painful sites, thereby ensuring a baseline pain score of zero. **Indeed, all studies included in the present review conducted pain assessments using QST at non-painful sites.** This method has been used in the assessment of most experimental pain modalities, including thermal and electrical pain, and has been shown to be effective in predicting responses to treatment¹².

Objectives

The core objective of this study was to undertake a systematic review and meta-analysis of studies examining evidence for OIH in humans following opioid exposure. The secondary objectives were to examine subgroups and to attempt to explain any heterogeneity found in study effects. Three subgroup variables were used to examine three further hypotheses based on the above suggested mechanisms: evidence of OIH will differ by treatment group (pain or opioid use disorder); OIH will be negatively associated with opioids with NMDA receptor antagonist properties; and OIH will be positively associated with increasing opioid treatment dose.

Methods

The established PICOS framework (**P**opulation, **I**nterventions, **C**omparators, **O**utcomes and **S**tudy design) was used to design the current review and to develop an appropriate search strategy. The findings are reported in accordance with the recommendations set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹³. The structure of the current paper is based on the PRISMA 27-item checklist. The PRISMA four-phase flow diagram was used to show eligibility screening procedures (**Figure 1**).

Protocol and registration

The review protocol was registered on PROSPERO, the international database of prospectively registered systematic reviews in health and other related domains of study.

The protocol registration number is CRD42017058513 and it can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017058513.

Eligibility criteria

Populations were included if they were human and in receipt of opioid therapy for the treatment of either opioid use disorder or pain. Animal models and *in vitro* models were excluded.

Interventions took the form of opioid therapy. Data were extracted from all studies where participants were exposed to opioids for 1 month or more. Studies were excluded if they focused on acute opioid exposure (<1 month) – i.e. primarily the delivery of opioids during the perioperative period and exposure in healthy volunteers.

Comparator populations were included from several clinical settings and study designs. Healthy volunteers were included as were patients in receipt of non-opioid analgesics when compared with opioid exposure in patients with pain. Single-sample repeated measures designs were also included if patients initiated opioid treatment.

Outcomes were extracted for three experimental pain modalities: thermal (cold and heat); electrical; and mechanical pressure. They were confined to findings from quantitative sensory testing (QST) techniques. Studies were excluded if they relied upon patient-reported pain, such as visual analogue scales (VAS) or numerical rating scales (NRS) assessing pain intensity. Regarding mechanical stimuli, articles provided different metrics (e.g. kPa, Newtons, oz, etc.). An attempt was made to convert means and standard deviations to one consistent metric (kPa); however, the converted values differed, implausibly, by two orders of magnitude and were not deemed to be reliable. In consequence, data for mechanical stimuli were not pooled. This discrepancy may have resulted from insufficient data reported in original articles – e.g. a measure of force, but not area, was reported in these articles; for example, ‘Newtons’ rather than ‘Newtons per m²’ or ‘Newtons per cm²’. The appropriate authors were contacted for clarification; however, no responses were received. Computations were attempted using the appropriate SI unit (Newtons per m² in this particular example); however, in the absence of definitive information, this may not have accurately reflected the force applied in studies. Data from the remaining modalities were pooled.

Study designs that were excluded were secondary data (to avoid duplication of articles presenting primary data) and case reports (due to the absence of control data).

Information sources

Electronic searches were undertaken using: Embase; Medline; PubMed; Cinahl Plus; Web of Science and OpenGrey. Searches were run on 1 April 2017, and no language or date restrictions were applied. In an attempt to avoid publication bias, a broad manual grey literature search was undertaken; this included examination of conference proceedings, technical reports, organisation websites and dissertations. At a later stage, once included articles had been identified, a manual reference search was undertaken of these included articles.

Search

The search term was constructed using the PICOS principles, shown below, and was run in each of the electronic databases. The participants filter (human only) was applied where available (Embase, Medline and PubMed).

Population: opi*

Intervention: Not included in search strategy

Comparators: Not included in search strategy

Outcomes: hyperalg* OR OIH OR "pain sensit*" OR "pain toler*" OR PTO OR "pain thresh*" OR PTR

Study design: Not included in search strategy

Study selection

Initially, articles underwent title and abstract review. Where articles clearly did not meet inclusion criteria, they were excluded, and the reason for exclusion was recorded. Remaining articles underwent full text eligibility review, in light of careful consideration of

the inclusion and exclusion criteria, and the reason for each article excluded at this stage was recorded. A random selection of 25% of included articles was assessed by a second reviewer who was blind to title, author, journal and year of publication.

Data collection process

A data extraction proforma was designed and piloted with 5 of the included articles. Whilst it was evident that there would not be a full complement of data available for subgroup analyses, all items were retained in the proforma for assessment following the extraction of available data from all included articles. Where required, authors were contacted in an effort to seek clarification of the data presented in articles. A number of issues were encountered and, in the interests of transparency, they are discussed in this section. First, several studies reported findings visually and, therefore, the data extracted from these articles were obtained from graphs rather than precise numerical reports. Secondly, where studies reported data at individual patient level, means and standard deviations were calculated. Thirdly, where data were reported at subgroup level only (e.g. ‘buprenorphine group’ and ‘methadone group’), the overall means and standard deviation were calculated to facilitate the Cochrane-recommended single pairwise comparison¹⁴. An exception was made for the paper by Hay and colleagues¹⁵, in order to facilitate two pairwise comparisons (pain versus controls and opioid use disorder versus controls). In this case, the Cochrane recommendation to half the control group¹⁴ was used.

Data items

The data items that were extracted for each study (where available) were: author(s); article title; date of publication; study design; number recruited and final number included in sample; treatment group (opioid use disorder or pain); demographic characteristics (gender

composition, mean age and ethnic composition); psychiatric characteristics (depression and anxiety scores); duration of pain (where applicable); prescription drug information (name of drug, length of exposure to drug and mean morphine-equivalent daily dose); core outcomes (pain threshold and tolerance values); pain modality; evidence of attempts to control for tolerance; evidence of use of opioids with NMDA receptor antagonist properties (e.g. pethidine, levorphanol, methadone, dextropropoxyphene, and ketobemidone); and additional notes (free text box in which explanatory notes or issues for consideration were recorded). It should be noted, however, that adjusted effect values were not reported for many of these variables, including demographic characteristics and psychiatric morbidity. In consequence, several of the planned subgroup analyses were not undertaken.

Risk of bias in individual studies

Assessment of risk of bias in individual studies was undertaken at study level. Study design was identified using Agency for Healthcare Research and Quality AHRQ (US DoH) criteria¹⁶. Risk of bias assessment was achieved using instruments designed by the National Institutes of Health (NIH)^{17 18}. These instruments are not intended to be summed to provide a total score, since assigning scores may be considered to be misleading¹⁹. Instead, these instruments are designed to prompt consideration of the key concepts relating to internal validity and potential risk of bias in individual study designs. As such, study quality was rated as: 'poor'; 'fair'; or 'good'.

Summary measures

The principal measure used in the primary meta-analysis and in subgroup analyses was standardised mean difference (SMD) between exposed and control groups. This was

entered into the software as mean group pain threshold and pain tolerance values, standard deviations around the mean and number of participants in each group.

Synthesis of results

Pooled study effect estimates were generated using the random effects model (DerSimonian-Laird method). Individual studies were weighted in accordance with the principle of inverse variance and, since a random effects model was applied, this included between-study variance in addition to within-study variance. The preferred I^2 statistic²⁰ was used to classify heterogeneity. Definitive heterogeneity thresholds can be misleading; however, as per guidance in the Cochrane Handbook¹⁴ (section 9.5.2), we accepted that $\geq 50\%$ may represent substantial heterogeneity.

Risk of bias across studies

Publication bias was assessed using the Egger regression intercept bias detection test rather than the Begg-Mazumdar rank correlation test since, comparatively, it is more sensitive to a range of bias types and does not lose power to the same degree when assessing a smaller number of studies. The use of imputational strategies in meta-analyses remains controversial and, furthermore, is unlikely to alter the conclusions in over 90% of secondary data analyses²¹. In consequence, imputational strategies were not used in the current review.

Additional analyses

Subgroup analyses were undertaken in an effort to examine secondary hypotheses and meta-regression (DerSimonian-Laird method) was performed in an attempt to explain

substantial heterogeneity. Subgroup analyses were undertaken based on treatment characteristics: treatment for opioid use disorder or pain; whether or not the opioid had NMDA receptor antagonist properties; and opioid dose used in treatment. Morphine-equivalent doses were established using an online equianalgesic calculator based on the American Pain Society guidelines and critical review papers focusing on the issue of equianalgesic dosing (<http://clincalc.com/opioids/>). Buprenorphine was not available for conversion in the equianalgesic calculator so the Monthly Index of Medical Specialities (MIMS) conversion ratio (x80) was applied. Further subgroup analyses were planned for a range of demographic and clinical characteristics but, due to insufficient data, were not undertaken. Within the scope of the current review there were insufficient studies to undertake meta-regression with more than one subgroup variable in each analysis.

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Results

Study selection

Electronic searches identified 6121 articles and a further 46 were identified through manual searches. A total of 1831 duplicates were identified resulting in a total of 4336 articles retained for eligibility review. **Figure 1** shows the number of articles excluded during both abstract and full text review and reasons for exclusion. Data were extracted from 26 articles, involving a total of 2706 participants. An independent review was undertaken with a random 25% sample of included articles and there were no discrepancies between reviewers.

[Insert Figure 1 around here]

Several articles addressed more than one assessment metric and/or pain modality. The number of samples drawn from these 26 articles, by research question, is shown in **Figure 2**.

[Insert Figure 2 around here]

Study characteristics

The characteristics of included studies are shown in **Table 1**, and further information concerning the group breakdown and group characteristics can be found in the supplementary material (Table 2). Where the outcome measures for the current review were not a primary objective or were not the only primary objective, the study design was

reported for the method used to obtain the relevant data rather than the method used in the overall study.

[Insert Table 1 around here]

Risk of bias within studies

All studies were identified as being of either 'good' or 'fair' quality; none were excluded due to being of 'poor' quality.

Synthesis of results

Pain threshold

Pain threshold (PTR) in response to noxious thermal (cold) stimuli (k=13), measured in seconds of exposure to pain detection, was slightly lower in exposed patients compared with controls (SMD = -0.61; 95% CI = -1.553 to 0.331) but the difference was not statistically significant. PTR in response to noxious thermal (cold) stimuli (k=5), measured in degrees Celsius to pain detection, was slightly higher in exposed patients compared with controls (SMD = 0.79; 95% CI = -0.444 to 2.026) but the difference was not statistically significant. One study reported PTR in response to noxious thermal (heat) stimuli, measured in seconds of exposure to pain detection³¹. Findings were very similar for exposed patients and controls whereby the noxious heat stimulus was tolerated for 42 seconds and 41 seconds, respectively. PTR in response to noxious thermal (heat) stimuli (k=5), measured in degrees Celsius to pain detection, was slightly lower in exposed patients compared with controls (SMD = -1.43; 95% CI = -2.936 to 0.075) but the difference was not statistically significant.

PTR in response to noxious electrical stimuli (k=6), measured in volts to pain detection, was significantly higher in exposed patients compared with controls (SMD = 1.28; 95% CI = 0.471 to 2.090; p<0.001). Substantial heterogeneity was identified in study effects ($I^2=81.87$). Five of the six study samples that underwent PTR assessment in response to noxious electrical stimuli also underwent PTR assessment in response to noxious thermal (cold) stimuli measured in seconds of exposure to pain detection. Contrary to the findings of electrical experimental pain, the findings relating to thermal (cold) pain, in the same samples, lay in the opposite direction. The weighted standardised mean difference between exposed patients and controls was shown to be -0.772 (95% CI = -1.414 to -0.130), indicating significantly lower PTR in exposed patients compared with controls (p=0.018).

Pain tolerance

Pain tolerance (PTO) was evaluated in response to noxious thermal (cold and heat) and noxious electrical stimuli. Findings are reported in **Figure 3**.

[Insert Figure 3 around here]

Figure 3 shows that PTO in response to noxious thermal (cold) stimuli (k=19), measured in seconds tolerated, was significantly lower in exposed patients compared with controls (SMD = -1.83; 95% CI = -2.458 to -1.208; p<0.001). Substantial heterogeneity was identified in study effects ($I^2=96.09$).

Two studies reported PTO in response to noxious thermal (cold) stimuli, measured in degrees Celsius tolerated^{21 44}, and, in both studies, exposed patients were associated with lower tolerance levels than were controls. Exposed patients tolerated temperatures of 3.30

and 3.88 degrees Celsius, respectively, as compared with 0.50 and 0.56 degrees Celsius, respectively, in the control groups.

One study reported PTO in response to noxious thermal (heat) stimuli, measured in seconds tolerated³¹. Findings were identical for exposed patients and controls whereby the noxious heat stimulus was tolerated for 45 seconds in both groups.

[Insert Figure 4 around here]

Figure 4 shows that PTO in response to noxious thermal (heat) stimuli (k=3), measured in degrees Celsius tolerated, was significantly lower in exposed patients compared with controls (SMD = -4.17; 95% CI = -8.258 to -0.079; p=0.046). Substantial heterogeneity was identified in study effects ($I^2=99.19$).

PTO in response to noxious electrical stimuli (k=7), measured in volts tolerated, was slightly lower in exposed patients compared with controls (SMD = -0.30; 95% CI = -0.996 to 0.405) but the difference was not statistically significant. Six of the seven study samples that underwent PTO assessment in response to noxious electrical stimuli also underwent PTO assessment in response to noxious thermal (cold) stimuli, measured in seconds tolerated. Contrary to the PTO findings in response to noxious electrical stimuli, the findings relating to thermal (cold) stimuli in the same samples were associated with significant group differences. The weighted standardised mean difference between exposed patients and controls was shown to be -4.571 (95% CI = -6.568 to -2.574), indicating significantly lower PTO in exposed patients compared with controls (p<0.001).

Risk of bias across studies

Assessment of risk of publication bias was undertaken for articles in significant pain modalities and showed fairly symmetrical distributions suggesting no significant publication bias. This was confirmed by the Egger regression intercept: pain threshold in response to electrical stimuli ($t=2.44$; $df=4$; $p=0.071$); pain tolerance in response to cold stimuli measured in seconds ($t=1.95$; $df=17$; $p=0.068$); and pain tolerance in response to heat stimuli measured in degrees Celsius ($t=0.97$; $df=1$; $p=0.510$).

Additional analyses

Subgroup analyses were undertaken in an effort to further examine significant differences between exposed patients and controls. Subgroup analyses were performed, using meta-regression, for pain modalities and assessment measures associated with significant standardised mean differences between exposed patients and controls in the overall findings (PTR in response to noxious electrical stimuli; PTO in response to noxious thermal (cold) stimuli measured in seconds tolerated; and PTO in response to noxious thermal (heat) stimuli measured in degrees Celsius tolerated). Subgroup analyses were run separately for three variables (treatment group, NMDA receptor antagonism and opioid dose). Substantial heterogeneity had been anticipated, hence the *a priori* decision to employ the use of a random effects model. Additionally, where significant subgroup differences were identified, appropriate variables were entered into meta-regression models in an effort to explain the overall variance in study effects.

Subgroup analyses and examination of heterogeneity of study effects: Pain threshold (PTR) in response to noxious electrical stimuli, measured in volts tolerated

Pooled effect estimates of PTR in response to noxious electrical stimuli differed significantly by treatment group ($p < 0.001$). There was a significantly greater difference between exposed patients and controls in studies assessing patients with opioid use disorder (SMD = 1.54; 95% CI = 0.575 to 2.499; $k = 5$) compared with studies assessing patients with pain (SMD = 0.22; 95% CI = -0.537 to 0.985; $k = 1$), indicating elevated pain sensitivity in patients with opioid use disorder compared to patients with pain. Meta-regression generated a non-significant model.

Pooled effect estimates of PTR in response to noxious electrical stimuli differed significantly by NMDA receptor antagonist treatment ($p = 0.006$). There was a significantly greater difference between exposed patients and controls in studies where NMDA receptor antagonists were used (SMD = 1.29; 95% CI = 0.175 to 2.398; $k = 5$) compared with opioids with no NMDA receptor antagonist properties (SMD = 0.71; 95% CI = -0.096 to 1.507; $k = 3$), indicating elevated pain sensitivity in patients treated with NMDA receptor antagonists. Meta-regression generated a non-significant model.

Pooled effect estimates of PTR in response to noxious electrical stimuli did not differ significantly as a function of prescribed opioid dose and, in consequence, did not account for variance in overall study effects.

Subgroup analyses and examination of heterogeneity of study effects: Pain tolerance (PTO) in response to noxious thermal (cold) stimuli, measured in seconds tolerated

Pooled effect estimates of PTO in response to noxious thermal (cold) stimuli, measured by seconds tolerated, differed significantly by treatment group ($p<0.001$). There was a significantly greater difference between exposed patients and controls in studies assessing patients with opioid use disorder (SMD = -2.78; 95% CI = -3.748 to -1.811; $k = 12$) compared with studies assessing patients with pain (SMD = -0.84; 95% CI = -1.810 to 0.123; $k = 6$), indicating elevated pain sensitivity in patients with opioid use disorder compared to patients with pain. The meta-regression model was statistically significant ($Q=5.26$; $df=1$; $p=0.022$). Patients with opioid use disorder were associated with almost twice the difference between exposed patients and controls compared with patients treated for pain (coefficient = -1.829; 95% CI = -3.392 to -0.266). The coefficient was negative, indicating that patients with opioid use disorder were significantly associated with lower PTO (i.e. greater pain sensitivity) than patients with pain. The meta-regression showed that the inclusion of this subgroup variable in the regression model explained 6% of the overall variance in study effects ($R^2=0.06$).

Pooled effect estimates of PTO in response to noxious thermal (cold) stimuli, measured in seconds tolerated, differed significantly by NMDA receptor antagonist treatment ($p<0.001$). There was a significantly greater difference between exposed patients and controls in studies where NMDA receptor antagonists were used (SMD = -2.96; 95% CI = -4.073 to -1.854; $k = 10$) compared with opioids with no NMDA receptor antagonist properties (SMD = -1.21; 95% CI = -2.223 to -0.202; $k = 8$), indicating elevated pain sensitivity in patients treated with NMDA receptor antagonists. The meta-regression model was statistically significant ($Q=4.69$; $df=1$; $p=0.030$). Treatment with **opioids with NMDA receptor antagonist activity** was associated with almost twice the difference between exposed patients and controls

1 compared with the use of non-NMDA receptor antagonists (coefficient = -0.701; 95% CI = -
2 3.239 to -0.162). The coefficient was negative, indicating that patients in receipt of NMDA
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compared with the use of non-NMDA receptor antagonists (coefficient = -0.701; 95% CI = -3.239 to -0.162). The coefficient was negative, indicating that patients in receipt of NMDA receptor antagonists were significantly associated with lower PTO (i.e. greater pain sensitivity) than patients treated with non-NMDA receptor antagonists. The meta-regression showed that the inclusion of this subgroup variable in the regression model explained less than 1% of the overall variance in study effects ($R^2 < 0.01$).

Meta-regression of the standardised difference in means on mean morphine-equivalent opioid dose was significant ($Q=6.25$; $df=1$; $p=0.012$); the regression line is shown in **Figure 5**.

[Insert Figure 5 around here]

The standardised differences in mean PTO between exposed patients and controls decreased significantly as a function of increasing mean morphine-equivalent opioid dose (coefficient = -0.0014; 95% CI = -0.0025 to 0.0003), indicating that increasing doses were associated with increased PTO (i.e. less pain sensitivity). The meta-regression showed that the inclusion of this subgroup variable in the regression model explained 9% of the overall variance in study effects ($R^2=0.09$).

Subgroup analyses and examination of heterogeneity of study effects: Pain tolerance (PTO) in response to noxious thermal (heat) stimuli, measured in degrees Celsius tolerated

All studies included only patients treated for pain and none used opioids with NMDA receptor antagonist properties. Mean opioid dose was reported in two of the three studies but there were insufficient data to generate a meta-regression model.

Discussion

Summary of evidence

The primary objective of the current review was to undertake a systematic review and meta-analysis of studies examining evidence for OIH in humans following chronic opioid exposure. Electronic and manual searches generated a total of 6167 articles, 26 of which (involving 2706 participants) were retained for synthesis is the present review. Pooled summary effect estimates were generated using the random effects (DerSimonian-Laird method) model, and individual studies were weighted in accordance with the principle of inverse variance.

Findings suggested that there was evidence of OIH following chronic opioid exposure in response to noxious thermal stimuli assessed by pain tolerance. There was, however, little evidence to suggest that OIH can be identified using assessments of pain detection threshold. There was no significant group difference associated with noxious electrical stimuli; however, all but one of these studies also assessed pain threshold and tolerance in response to the cold pressor test, and participants taking opioids were found to have significantly lower threshold and tolerance values than those who were not. There was no significant publication bias but substantial heterogeneity in study effects was identified.

Subgroup analyses were computed where there were significant differences between exposed patients and controls and there were sufficient data to undertake subgroup analyses: pain threshold in response to noxious electrical stimuli; and pain tolerance in response to noxious thermal (cold) stimuli (measured in seconds tolerated). OIH was significantly more evident in patients with opioid use disorder than in patients treated for

1 pain in both modalities. However, this finding accounted for just 6% of variance in study effects in
2 the thermal (cold) pain modality, most of the remaining variance being explained by other factors
3 not amenable to meta-analysis. OIH was significantly more evident in samples treated with
4 NMDA receptor antagonists but this group difference accounted for less than 1% of variance
5 in study effects in both modalities. There was no effect of opioid treatment dose on OIH in
6 response to noxious electrical stimuli but higher doses were significantly associated with
7 decreased pain sensitivity in response to thermal (cold) stimuli. This finding did not account
8 for any variance in study effects.

Findings in context

21 The findings of the current meta-analysis suggest that OIH plays a role in the relative lack of
22 long-term effectiveness of opioid analgesics that has been reported recently⁴⁹. Given that
23 opioids leads to increased pain sensitivity despite the objective of achieving effective
24 analgesia, an individual's overall pain experience may be worse than before treatment, or at
25 least not as good as it might be with non-opioid analgesia. OIH is characterised by
26 aggravated pain compared with pain experienced prior to opioid use, or with the *de novo*
27 development of pain in the absence of pathology. In consequence, it may also contribute to
28 the high prevalence of chronic pain reported in patients in receipt of opioid replacement
29 therapy for the treatment of opioid dependence⁵⁰, whereby chronic opioid administration
30 contributes to exacerbation of pain or the development of pain in these patients.

31 Whilst evidence of OIH was fairly consistent across thermal experimental pain models
32 assessed by pain tolerance, elevated pain sensitivity was not observed in patients in
33 response to noxious electrical stimulation; however, in these same patients OIH was
34 demonstrated in response to cold pressor testing. This finding replicates previous findings

reported in the literature⁵¹. It is not clear why the findings of these tests differed; however, there could be several potential reasons for this disparity. First, short bursts of electrical stimulation are likely to elicit phasic pain whilst the relatively longer-term exposure in thermal pain models is likely to elicit tonic pain, relatively more similar to clinical pain⁵². It is proposed that each model is associated with different pain qualities⁵³ and different neurophysiological pathways and pharmacological modes of action⁵⁴. Indeed, in a factor analysis of responses to different pain modalities⁵⁵, five factors were identified, including thermal and electrical noxious stimuli, and there was shown to be little correlation between these factors. In conclusion, the authors recommended that a multi-modal experimental pain approach be used in assessing responses to noxious stimuli. Secondly, pain has crucial adaptive functions in daily life which serve as a warning mechanism in the presence of harmful stimuli⁵⁶. The role of pain is of clear value in the presence of thermal or mechanical stimulation, which are relatively common in daily life, but its value in response to electrical stimulation is less obvious, since air is a poor conductor of electricity and, in consequence, humans have not developed electroreception. Whilst the authors are not aware of any work in this specific area, it may be possible that, in evolutionary terms, central and peripheral nociceptive responses to thermal stimuli are ‘hardwired’ in human physiology but that responses to relatively uncommon stimuli, such as electricity, function differently. Further comparison of nociceptive responses in different experimental pain modalities is required to ensure the validity of assessment methods.

The psychometric properties of QST techniques using electrical experimental pain models are not as well-established as those of thermally-induced pain, and, since there are no objective, clinically-observable effects of central sensitisation, only face validity can be examined and construct validity, therefore, has not been established. Whilst the face

validity and reliability of thermally-induced pain have been well-examined⁵⁷, further assessment of other experimental pain modalities is required. In the meantime, future research studies should consider using a battery of tests conducted in different experimental pain modalities to verify findings. QST techniques are not currently used in clinical practice⁵⁸ but, following robust validation of these methods, they could prove valuable in helping to distinguish between opioid tolerance and OIH by facilitating testing specifically at non-painful sites.

Whilst it is generally assumed that the presence of OIH impacts on both pain detection threshold and pain tolerance, the findings of this review suggest assessment of pain tolerance is more effective in identifying hyperalgesic states. These findings are difficult to interpret without further empirical examination; however, they may reflect the findings of Harris and Rollman⁵⁹. Using the Campbell and Fiske⁶⁰ multitrait-multimethod matrix, they established a correlation matrix using pain modalities (i.e. multitrait) and measures of pain threshold and pain tolerance (i.e. multimethod) to evaluate convergent and discriminant validity. They concluded that pain threshold and pain tolerance indicate different components of the pain experience, since correlations were higher for threshold (and for tolerance) across pain modalities than they were for threshold and tolerance within each modality. It is, therefore, important that future studies assess both indices in the evaluation of responses to experimental pain.

Hyperalgesic states were more evident in patients with opioid use disorder than in patients with pain. Compared with many other clinical populations, patients with opioid use disorders are likely to experience greater life stress⁶¹ and to have higher prevalence of chronic illness, multimorbidity and attendance at emergency departments⁶². It is, therefore,

important that health assessments of these individuals control for a range of factors, including affective characteristics and coping styles, which may impact on judgements of the pain experience. Patients in receipt of ORT are likely to be in receipt of higher average equivalent opioid doses than patients with pain¹⁵ and this significant group difference may substantiate the dose-dependent relationship between opioids and hyperalgesia reported in a number of studies^{1 2 3 4}. The present review, however, found that elevated opioid doses were significantly associated with lower pain sensitivity. This finding requires further replication but may suggest that, in a proportion of patients at least, suspected hyperalgesia actually reflects inadequate analgesic treatment. Indeed, in an evidence-based, structured review of the literature on OIH, Fishbain and colleagues⁶³ reported having excluded articles due suspected OIH being identified as inadequate analgesic treatment.

The hypothesised lower pain sensitivity associated with NMDA receptor antagonist treatments was not evidenced; however, there may have been a confounding effect of group since most patients in receipt of NMDA receptor antagonists were treated with methadone-maintenance therapy for the treatment of opioid use disorders. Furthermore, this finding may be related to evidence suggesting that methadone has low NMDA receptor affinity⁶⁴, whereby one might anticipate no effect of methadone, and heightened pain sensitivity may be an effect of continued illicit opioid use in these patients (i.e. higher dose consumption than is recorded for these individuals). Further empirical examination of the role of NMDA receptor antagonism in OIH, and indeed in opioid tolerance, is required; this may involve the use of opioids with NMDA receptor antagonism properties or adjunctive NMDA antagonists to treat chronic pain, whilst ensuring rigorous control of substance misuse in study participants.

Limitations

A substantial limitation was that, due to the nature of observational studies, pooled studies were not identical regarding comparator group characteristics or study designs. Randomised controlled trials would be unethical in this field of study; however, the limitations associated with pooling observational studies should be borne in mind and findings should be interpreted with caution. One further limitation was that only 25% of included articles were assessed by an independent reviewer. Whilst this is an approach sometimes used^{47 48}, reviews could be strengthened further by independent review of all included articles, as recommended by most methods and reporting guidelines for systematic reviews.

Conclusions

Whilst there is some evidence to suggest that tolerance and dependence should be a concern⁶⁵ when administering opioids, OIH should also be of concern to anaesthetists and other pain specialists. The present review provides evidence for OIH in humans but this evidence is dependent upon the assessment metric and the nature of the noxious stimulus. Hyperalgesic states were more evident in patients with opioid use disorder and in treatment populations receiving opioids with NMDA receptor antagonist properties, but this primarily involved methadone-maintained, opioid-dependent patients. Further studies must include evaluation of both pain threshold and pain tolerance across several pain modalities and must ensure more rigorous control of relevant characteristics within treatment groups – such as substance misuse, affective components or coping styles – and may consider using adjunctive NMDA receptor antagonists in attempting to identify effective treatment strategies whilst reducing the potential impact of opioid-induced hyperalgesia.

Details of authors’ contributions

Conception and design was undertaken by all three authors (CH, BHS, KM). Data acquisition and analyses were undertaken by CH. All three authors (CH, BHS, KM) contributed to interpretation of data, critical evaluation of intellectual content and final approval of the published version.

For Peer Review

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For Peer Review

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Declaration of interests

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Figure legends

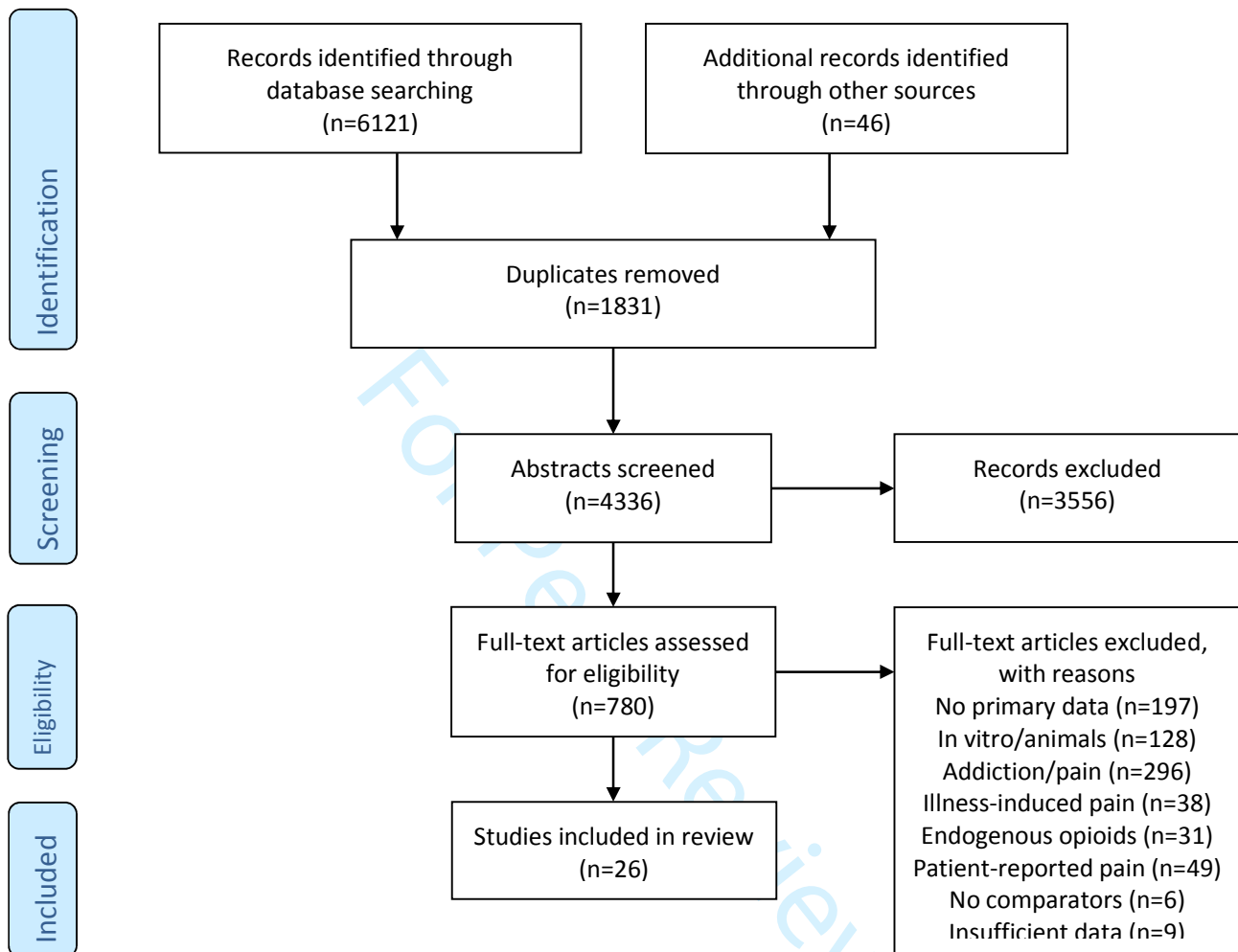
Figure 1: Eligibility screening procedures and the total number of articles included in the review, shown on the PRISMA four-phase flow diagram

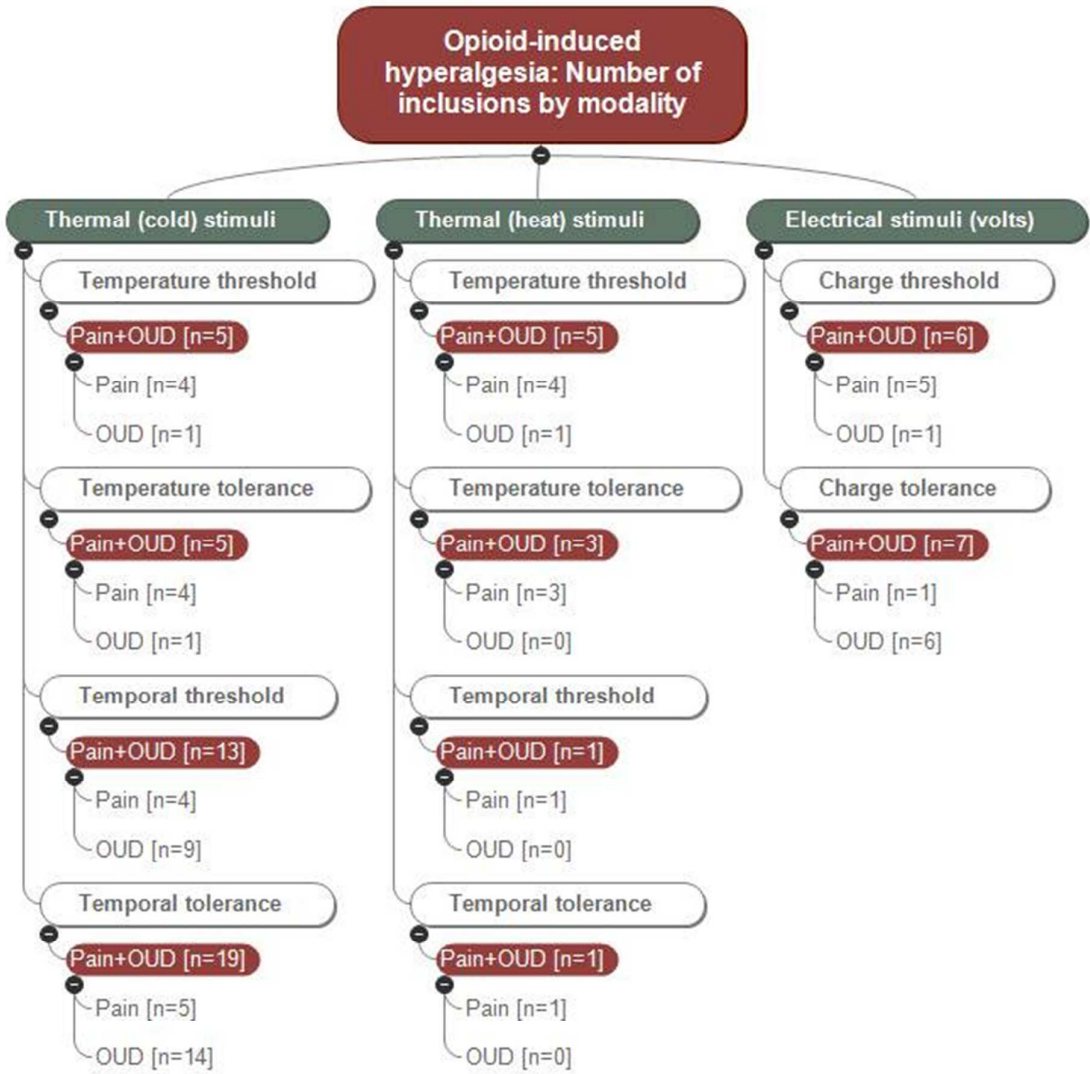
Figure 2: Number of samples (k=65) included in the review, by research question. Where meta-analyses or qualitative syntheses were undertaken, these numbers are shaded in dark red. Beneath that are the numbers included in each treatment group. Meta-analyses were undertaken where data were available from three or more studies. [OUD=opioid use disorder.]

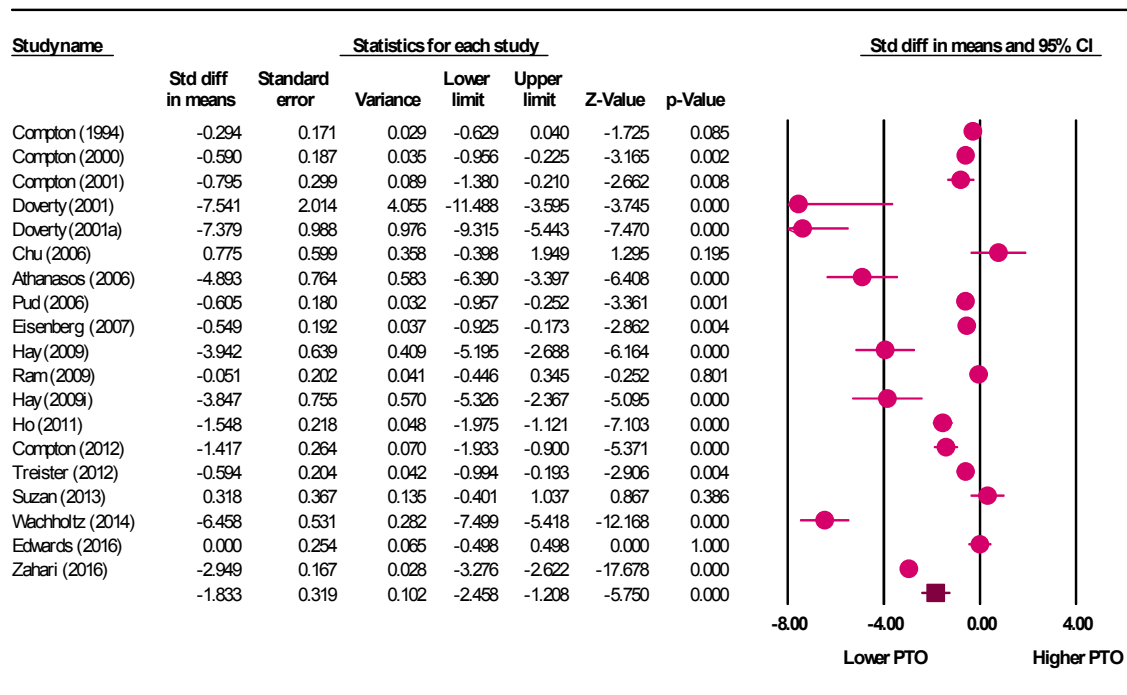
Figure 3: Meta-analysis (random effects model) – pooled study findings of pain tolerance (PTO) in response to thermal (cold) experimental pain, measured in seconds tolerated, at a non-painful site in patients in receipt of opioid therapy.

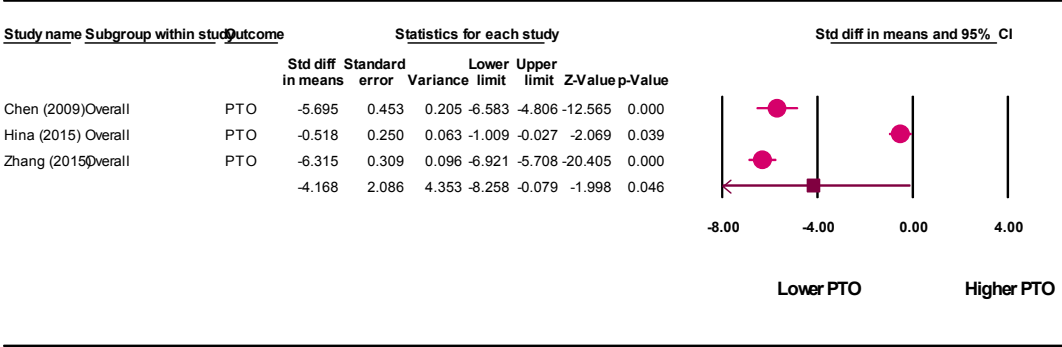
Figure 4: Meta-analysis (random effects model) – pooled study findings of pain tolerance (PTO) in response to thermal (heat) experimental pain, measured in degrees Celsius tolerated, at a non-painful site in patients in receipt of opioid therapy.

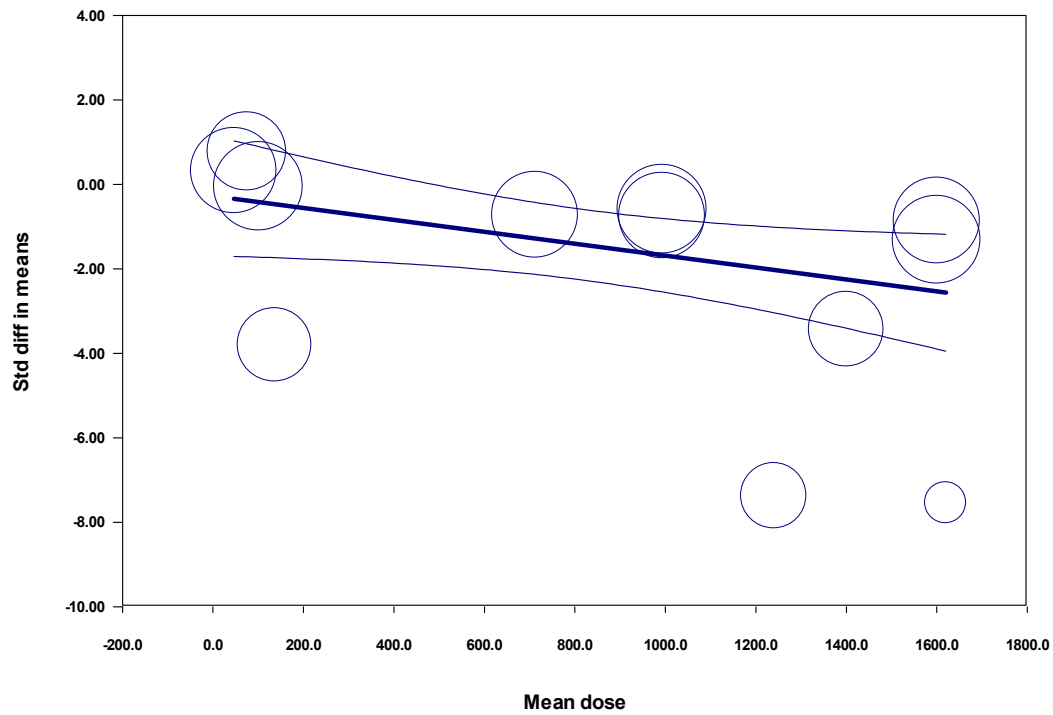
Figure 5: Regression of standardised difference in means on mean oral morphine-equivalent opioid dose per day (mg)











Author (year)	N	Study design	Study effect			
			Pain threshold		Pain tolerance	
			Exp.	Control	Exp.	Control
Athanasos (2006)²² – opioid use disorder treatment group						
Cold (seconds)	28	Cross-sectional	----	----	15	34
Electrical (volts)	28	Cross-sectional	----	----	54	65
Chen (2009)²³ –pain treatment group						
Cold (Celsius)	99	Cross-sectional	10.9	8.4	3.3	0.5
Heat (Celsius)	99	Cross-sectional	43.8	45.3	48.6	50.1
Chu (2006)²⁴ –pain treatment group						
Cold (seconds)	6	Pre-post	12.1	10.1	28.0	19.8
Compton (1994)²⁵ – opioid use disorder treatment group						
Cold (seconds)	220	Cross-sectional	----	----	62	86.1
Compton (2000)²⁶ – opioid use disorder treatment group						
Cold (seconds)	120	Cross-sectional			43.7	93.9
Compton (2001)²⁷ – opioid use disorder treatment group						
Cold (seconds)	54	Cross-sectional			60.4	138
Compton (2012)²⁸ – opioid use disorder treatment group						
Cold	103	Cross-sectional	9.38	11.79	18.26	41.54
Electrical (volts)	103	Cross-sectional	41.54	38.00	56.07	63.55
Doverty (2001)²⁹ – opioid use disorder treatment group						
Cold (seconds)	8	Cross-sectional	7.3	7.4	25	57
Electrical (volts)	8	Cross-sectional	37	28	63	52
Doverty (2001a)³⁰ – opioid use disorder treatment group						
Cold (seconds)	32	Cross-sectional	4	5	21	63
Electrical (volts)	32	Cross-sectional	34	28	54	63
Edwards (2011)³¹ –pain treatment group						
Cold (seconds)	276	Cross-sectional	15	18.32	----	45
Heat (seconds)	276	Cross-sectional	42	41	----	45
Edwards (2016)³² –pain treatment group						

Cold (seconds)	31	Pre-post	----	----	40	40
Eisenberg (2007)³³ – opioid use disorder treatment group						
Cold (seconds)	113	Cross-sectional	10.5	7.1	30.5	55.2
Hay (2009)¹⁵ –pain treatment group						
Electrical (volts)	25	Cross-sectional	35.6	34.8	48.1	52.6
Cold (seconds)	25	Cross-sectional	10.75	12.2	18.9	30.7
Hay (2009)¹⁵ – opioid use disorder treatment group						
Electrical (volts)	15	Cross-sectional	38.8	34.8	52.4	52.6
Cold (seconds)	15	Cross-sectional	8.9	12.2	18.9	30.7
Hina (2015)³⁴ –pain treatment group						
Heat (Celsius)	68	Cross-sectional	43	43.5	47.1	48.4
Ho (2011)³⁵ – opioid use disorder treatment group						
Cold (seconds)	111	Cross-sectional	11	9	24	34
Krishnan (2012)³⁶ – opioid use disorder treatment group						
Electrical (volts)	32	Cross-sectional	63.5	37	65.5	59
Peles (2010)³⁷ – opioid use disorder treatment group						
Cold (Celsius)	48	Cross-sectional	19.5	17.5	----	----
Heat (Celsius)	48	Cross-sectional	44	43	----	----
Pud (2006)³⁸ – opioid use disorder treatment group						
Cold (seconds)	130	Cross-sectional	10.6	6.6	29.1	56.4
Ram (2009)³⁹ –pain treatment group						
Cold (seconds)	110	Cross-sectional	9.9	10.1	22.8	24.1
Reznikov (2005)⁴⁰ –pain treatment group						
Heat (Celsius)	224	Cross-sectional	45.4	45.7	----	----
Suzan (2013)⁴¹ –pain treatment group						
Cold (seconds)	40	Cross-sectional	----	----	43.9	30.0
Treister (2012)⁴² – opioid use disorder treatment group						
Cold (seconds)	100	Cross-sectional	10.8	6.8	30.0	56.4
Wachholtz (2014)⁴³ –pain treatment group						
Cold (seconds)	90	Cross-sectional	24.22	54.4	53.3	137.1
Wang (2012)⁴⁴ –pain treatment group						

Cold (Celsius)	63	Cross-sectional	11	9	----	----
Heat (Celsius)	63	Cross-sectional	42	47	----	----
Zahari (2016)⁴⁵ – opioid use disorder treatment group						
Cold (seconds)	300	Cross-sectional	----	----	34.17	61.36
Zhang (2015)⁴⁶ –pain treatment group						
Heat (Celsius)	250	Cross-sectional	43.7	44.7	48.8	49.9
Cold (Celsius)	250	Cross-sectional	11.2	9.4	3.88	0.56

Note: Exp. = exposed

For Peer Review