Do Opioids Induce Hyperalgesia in Humans? An Evidence-Based Structured Review

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ABSTRACT

Design/Objectives. Consistent rodent evidence indicates that opioid exposure will decrease the rodent’s pain threshold (ptr). This is termed opioids-induced hyperalgesia (OIH). Currently, the consistency of the evidence for the occurrence of OIH in humans is unclear. This is a structured evidence-based review for all levels of evidence (all studies and case reports) on OIH in humans in order to determine the consistency of this evidence.

Methods. Computer and manual literature searches yielded 504 OIH references (human and animal). Of these, 48 remained after application of inclusion/exclusion criteria. These references addressed 10 hypotheses that the OIH literature has utilized to test for the possibility of OIH in humans. These are the following: opioid addicts maintained on opioids will have decreased ptr and/or tolerance; detoxifying opioid addicts from opioids will increase their ptr and/or tolerance; stopping, decreasing, or rotating to a different opioid or detoxifying from an opioid will improve pain and/or allodynia; chronic pain patients (CPPs) placed on opioids will develop decreased ptr and/or tolerance; CPPs on opioids will have decreased ptr and/or tolerance vs CPPs not on opioids; opioid infusion in normal volunteers or CPPs will decrease ptr and/or tolerance; opioid infusion in normal volunteers or CPPs will decrease ptr and/or tolerance; former opioid addicts exposed to opioids will demonstrate a decrease in ptr and/or tolerance; opioid infusion in normal volunteers will increase secondary hyperalgesia as measured by allodynia or hyperalgesia; perioperative opioids will increase postoperative pain and/or opioid requirements; and placement on opioids postsurgery leads to progressive increased intake (acute tolerance). Each report was characterized by the type of study it represented according to the Agency for Health Care Policy and Research (AHCPR) guidelines and independently rated by two raters according to 14 quality criteria with a quality score calculated. For studies under each hypothesis, an average quality score and the percentage of studies supporting the hypothesis was calculated. Finally, for studies under each hypothesis, utilizing AHCPR criteria, a consistency rating was derived based on the percentage score of studies supporting the hypothesis.

Results. Two studies had quality scores below 65% and were not utilized. Overall, the strongest evidence (consistent, A) came from opioid infusion studies in normal volunteers as measured by secondary hyperalgesia. This evidence was supported by inconsistent evidence (C) from: studies addressing opioid infusions in normal volunteers or CPPs for decreasing ptr and/or tolerance; and studies addressing increases in postop opioid requirements or pain if peri-opioids were utilized. For the other seven hypotheses, there were too few studies to draw a conclusion or the evidence for the hypothesis were case reports or the results of the studies within the hypothesis were not interpretable.

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Conclusions. There is not sufficient evidence to support or refute the existence of OIH in humans except in the case of normal volunteers receiving opioid infusions. Prospective CPP clinical studies measuring ptrs and tolerances pre- and post-opioid placement with CPP non-opioid control groups are required.

Key Words. Pain; Opioids; Hyperalgesia; Allodynia; Humans; Opioid-Induced Hyperalgesia; Evidence-Based Structured Review

Introduction

Hyperalgesia is defined as exacerbated painful response to noxious stimulation. Allodynia occurs when normal stimulation, such as touch, is perceived as painful. Both hyperalgesia and allodynia are indications of a hypersensitivity state in nociceptive processing described in animal studies of chronic opioid intake. These studies are the following: Rats receiving repeated intrathecal morphine administration over a 7-day period will demonstrate a progressive reduction of baseline nociceptive thresholds (pain threshold [ptr]) in the paw withdrawal test [1–3]. A similar reduction in baseline nociceptive thresholds is also observed after a subcutaneous fentanyl bolus in the Randall–Sellito test (constantly increasing pressure is applied to a rat's hind paw) [4,5]. The decreased baseline nociceptive thresholds last as long as 5 days after cessation of four fentanyl bolus injections [4,5]. Similar results with rats have also been observed with repeated heroin administration [6]. This phenomenon is not related to subliminal opioid withdrawal because a progressive reduction of baseline nociceptive thresholds (thermal hyperalgesia and tactile allodynia) has also been demonstrated in animals receiving a course of continuous intrathecal opioid infusion via osmotic pumps [2,3,7]. In addition, high doses of spinally administered morphine elicit scratching, biting, and licking in mice and vocalizations and agitation in rats, all indicative of spontaneous nociceptive behavioral responses [8]. Finally, rats administered with morphine for 6 days via subcutaneous osmotic mini pumps demonstrated thermal hyperalgesia and mechanical allodynia for several days after cessation of morphine administration [9]. The consistency of this collective data has led researchers in this area to conclude that prolonged opioid treatment not only results in a loss of opioid antinociceptive efficacy (tolerance) but also leads to activation of a pronociceptive system manifesting as a reduction of nociceptive thresholds (sensitization) or opioid-induced hyperalgesia (OIH) [10–12].

Although there is strong evidence for the concept of OIH in rodents (above), human studies have led to conflicting results [13]. This in turn has led researchers in this area to conclude that animal opioid hyperalgesia models have limitations for accurately predicting human opioid pharmacology [13].

Whether OIH occurs in humans on opioid exposure is not a trivial issue. Recently, chronic opioid analgesic therapy (COAT) has gained acceptance as a potential treatment option for chronic pain patients (CPPs) who have failed other treatment options [14]. As such, if CPPs placed on COAT are at risk for OIH development then physicians should be aware of this risk and begin to monitor COAT CPPs for development of OIH.

It is the purpose of this evidence-based structured review to identify all human studies and case reports relevant to OIH and to address the quality of this research through the Agency for Health Care Policy and Research (AHCPR) criteria (Table 1) [15]. Although there have been numerous reviews [8,10,16–21] on OIH, these have generally been in reference to rodents and have been narrative rather than evidence based. One recent review [13] did address human studies and was evidence based but did not determine quality scores for the reviewed studies or did not look at the consistency of the evidence for OIH in humans. It is the intention of this evidence-based structured review to also accomplish this utilizing AHCPR criterion.

Methods

Relevant references were located by the following procedure. MEDLINE, Psychological Abstracts, Science Citation Index, and the National Library of Medicine Physician Data Query databases were reviewed utilizing the following subject headings: hyperalgesia, increased pain, induced pain,
increased antinociception, increased antinociceptive tolerance, chemically induced pain, allodynia, hypesthesia, drug tolerance, drug withdrawal, increased pain sensitivity, ptr, pain tolerance (pto). Each of these was sequentially exploded with the medical subject headings (MESH) opioids or opiates or analgesics. Each term was exploded for subheadings in MESH and all retrieved references were reviewed. The searches were not restricted to the English language, and conducted back to 1966, except for Science Citation Index, which was conducted back to 1974. The upper limit of each search was 2007. A manual search was also performed using key pain journals, pain meeting abstracts, and textbooks. For the following years: International Association for the Study of Pain 1981, 1984, 1987, 1990, 1993, 1996, 1999, 2002, and 2005, and the American Pain Society Meetings, 1982–2007. Three pain textbooks were reviewed for possible references. These were Evaluation and Treatment of Chronic Pain, Third Edition, G. Arnoff (ed.), 1999; Handbook of Pain Management, Second Edition, C.D. Collison, J.R. Satterthwaite, J.W. Collison (eds.), 1994; and Textbook of Pain, Third Edition, P. Wall, R. Melzack (eds.), 1993. In addition, previous reviews [8,10–13,16–21] were reviewed for any missed references. Five hundred four references were found in this manner and were subjected to a cursory review. Studies were then chosen for detailed review if they demonstrated problems that could confound the results of this evidence-based structured review. These problems were the following: no acceptable measure of hyperalgesia [22]; not clear within the study [23] if opioid addicts were being dealt with; studies that addressed rebound headaches [24]; the opioid in the study was an antagonist [25]; if the patients within the study were on opioids presurgery as this created a problem of making a distinction between hyperalgesia and tolerance/withdrawal [26]; studies where the mu agonist was utilized, which had been shown to be an inadequate analgesic in postoperative pain [27,28]; and studies where withdrawal hyperalgesia could have been an issue [29]. Through the use of these inclusion/exclusion criteria of the original 504 references, 48 references [30–77] remained for detailed review and were sorted according to 10 hypotheses (some developed from clinical observation) which the current OIH literature indicated may be reflective of evidence for OIH in humans. These are the following: opioid addicts maintained on opioids will have decreased ptr or pto (Table S1); opioid addicts when detoxified from opioids will increase their ptr/pto (Table S2); former opioid addicts will have decreased ptr/pto (Table S7); decreasing, stopping, detoxifying from an opioid or rotating to a different opioid will improve pain or allodynia (Table S3); CPPs placed on opioids will develop decreased ptr/pto (Table S4); CPPs on opioids will have decreased ptr/pto vs CPPs not on opioids; opioid infusion in normal volunteers or CPPs will decrease their ptr/pto (Table S6); opioid infusion in normal volunteers will increase secondary hyperalgesia as measured by allodynia or hyperalgesia (Table S8); perioperative opioids will increase postoperative pain or opioid requirements (Table S9); and placement on opioids postsurgery will lead to increased opioid intake (Table S10). It is to be noted that some studies

<table>
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<tr>
<th>Type of Evidence Guidelines</th>
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<tbody>
<tr>
<td>I. Meta-analysis of multiple well-designed controlled studies.</td>
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<tr>
<td>II. At least one well-designed experimental study.</td>
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<tr>
<td>III. Well-designed, quasi-experimental studies such as nonrandomized controlled, single group pre-post, cohorts, time series, or matched case-controlled studies.</td>
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<tr>
<td>IV. Well-designed non-experimental studies, e.g., comparative, correlational, descriptive, case control.</td>
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<tr>
<td>V. Case reports and clinical examples.</td>
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Strength and Consistency of Evidence Guidelines
A) There is evidence of Type I or consistent findings from multiple studies of Type II, III, or IV.
B) There is evidence of Type II, III, or IV, and findings are generally consistent.
C) There is evidence of Type II, III, or IV, but findings are inconsistent.
D) There is little or no evidence, or there is Type V evidence only.
E) Panel consensus: Practice recommended on the basis of opinion of experts in pain management.

Table 1 Type of evidence and strength/consistency of the evidence guidelines according to the AHCPR [15]
fitted into more than one hypothesis. These studies were utilized more than once, and when this was done, they are delineated by an asterisk in the tables in Supporting Information.

Research information from these studies was abstracted into tabular form. Tables S1 to S10 were organized according to the above hypotheses. These tables were arranged to present reference number, author, year, study question, design, type of study, sample size, type of pain, pain measure used, statistical analysis utilized, results, hyperalgesia measure utilized, quality score, type of evidence, and comment.

The quality of the studies was categorized according to the systems developed and reported by Hoogendoorn et al. [78] and Verhagen et al. [79]. These researchers developed and tested a list of criteria to be used to assess methodological quality of prospective, historical cohort, and case control studies. Of 23 criteria, 12 were selected as being appropriate to the studies utilized. In addition, two criteria were added: whether there was an acceptable control group and whether the study was prospective in nature for a total of 14 criteria (Table S10). For each included study, each criterion was rated as either present/fulfilled (+), not present/unfulfilled (−), or not applicable (NA). There were four types of studies analyzed for quality: case control, cohort, correlational, and case series. NA was used if the criterion in question pertained to another type of study other than the one being reviewed. When information was not available or not described [79] or did not meet a preselected criteria, negative was assigned [79]. Each study was rated independently for each criterion by the senior author (D.F.) and another author (B.C.). The assigned categorizations were then compared in a meeting. Discrepancies were resolved by mutual agreement. A quality score was obtained by counting the number of positives obtained, dividing by 14 (the total number of criteria) minus the number of NAs and multiplied by 100. This gave the percentage quality score. A number of the reports (Table S3) were case reports or case series and, consequently, no quality scores could be generated here.

Studies scoring less than 50% historically have been rated as “low quality” [80] and are usually not utilized to arrive at conclusions. For this review, we arbitrarily set the acceptable quality score at 65%. Studies scoring less than 65% were not utilized for arriving at a conclusion about the strength and consistency of the reviewed evidence.

D.F. abstracted the data into Tables S1–S9 but data abstraction and study categorization were checked independently by B.C. Discrepancies were resolved by mutual agreement. The categorization of the type of evidence the study represented was based on the guidelines developed by the AHCPR for categorizing the levels of evidence represented by reviewed studies (Table 1 Evidence Guidelines) [15]. Studies were categorized I through V according to this scheme. Here, I represent a meta-analysis of well-designed, controlled studies and V represents a case report or clinical example.

The consistency of the research evidence for each hypothesis (Tables S1–S10) was then categorized according to the AHCPR consistency of evidence guidelines [15] developed for this purpose (Table 1). These categorize the evidence as being consistent, generally consistent, inconsistent, or demonstrating little or no evidence for supporting the hypothesis under study. Categorizations were performed independently by D.F. and reviewed by B.C. Discrepancies were resolved by mutual agreement.

Finally, data from Appendix Tables S1–S10 were formatted into a summary table (Table 2). This table summarizes the overall finding of this structured evidence-based review by listing the following for each hypothesis: number of reports; type of evidence in percent; studies’ average quality score; percentage of studies supporting the hypothesis; and consistency of the evidence supporting the hypothesis according to the AHCPR guidelines (Table 1).

Results

Of the 48 reports, 30 were studies and 18 were case reports or case series. Of the 30 studies, two [57,59] had quality scores below 65 (Table S3). Nine studies [30–38] (Table S1) addressed the hypothesis that opioid addicts will have decreased ptr/pto. One hundred percent of these studies were Type 2 with a 96% average quality score (Table 2). In five studies [30–32,34,38], (20%) ptr were decreased vs controls. Of eight studies [30–33,35–38], 87.5% found pto to be decreased vs control on the cold pressure test. The consistency of this evidence was rated as B (there is evidence, but findings are inconsistent) for supporting the hypothesis utilizing pto and B for not supporting the hypothesis utilizing ptr. Overall, for reasons presented in the discussion, the evidence for this hypothesis was judged to be not interpretable.
Table 2  Type of evidence, quality scores, findings for studies within each hypothesis, and strength/consistency of the evidence for each hypothesis: Appendix  
Tables S1–S10

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Grouping of Studies According to the Hypothesis the Study Addresses in Reference to OIH</th>
<th>No. of Reports in Grouping</th>
<th>Type of Evidence Studies in Grouping Represent in %</th>
<th>Average Quality Score of Studies in Grouping</th>
<th>Overall Finding of All the Studies in the Grouping</th>
<th>Strength/Consistency of the Findings According to the AHCPR Guidelines in Table 1</th>
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<tbody>
<tr>
<td>Hypothesis #1: Opioid addicts maintained on opioids will have decreased pain threshold or pain tolerance. (Table S1)</td>
<td></td>
<td>9</td>
<td>100% Type 2</td>
<td>96.0%</td>
<td>20% of five studies found pain threshold to be decreased vs controls, but 87.5% of 8 studies found pain tolerance to be decreased vs controls.</td>
<td>B for supporting hypothesis utilizing pain tolerance, but B for not supporting hypothesis utilizing pain threshold. Overall findings not interpretable because of issues presented in discussion</td>
</tr>
<tr>
<td>Hypothesis #2: Detoxing opioid addicts from opioids will increase their pain threshold or pain tolerance. (Table S2)</td>
<td></td>
<td>2</td>
<td>100% Type 2</td>
<td>100%</td>
<td>100% of two studies found no change in pain threshold or pain tolerance as compared with controls with opioid detoxification.</td>
<td>(Too few studies to draw firm conclusion)</td>
</tr>
<tr>
<td>Hypothesis #3: Stopping or decreasing an opioid or rotating to a different opioid will improve pain and/or allodynia. (Table S3)</td>
<td></td>
<td>21, but 2 reports [58,60] not utilized because of low quality scores leaving 19 reports</td>
<td>94.7% Type 5 and 5.2% Type 4. For 18 reports no quality score as case reports For 1 study quality score of 92.8%.</td>
<td>Overall 123 pts. reported on. In 21 pts., allodynia reported on and improved in all cases (100%). In 114 pts., pain reported on and improved in all cases (100%).</td>
<td>D for supporting hypothesis.</td>
<td></td>
</tr>
<tr>
<td>Hypothesis #4: CPPs placed on opioids will develop decreased pain threshold and tolerance. (Table S4)</td>
<td></td>
<td>1</td>
<td>Type 3</td>
<td>81.8%</td>
<td>100% of one study demonstrated decreased pain threshold and tolerance.</td>
<td>(Too few studies to draw firm conclusion)</td>
</tr>
<tr>
<td>Hypothesis #5: CPPs on opioids will have decreased pain threshold and tolerance vs chronic pain patients not on opioids. (Table S5)</td>
<td></td>
<td>1</td>
<td>Type 2</td>
<td>100%</td>
<td>100% of one study demonstrated no difference for PTRE</td>
<td>(Too few studies to draw firm conclusion)</td>
</tr>
<tr>
<td>Hypothesis #6: Opioid infusion in normal volunteers or chronic pain patients will decrease pain threshold or tolerance. (Table S6)</td>
<td></td>
<td>5</td>
<td>60% Type 2 and 40% Type 3</td>
<td>88.4%</td>
<td>33.3% of 3 studies found pain threshold to decrease while 75% of 4 studies found pain tolerance to decrease</td>
<td>C for supporting hypothesis.</td>
</tr>
<tr>
<td>Hypothesis #7: Former opioid addicts exposed to an opioid will demonstrate a decrease in pain threshold and tolerance. (Table S7)</td>
<td></td>
<td>1</td>
<td>Type 3</td>
<td>81.8%</td>
<td>12.2% of pts in study showed decrease in pain threshold</td>
<td>(Too few studies to draw firm conclusion)</td>
</tr>
<tr>
<td>Hypothesis #8: Opioid infusion in normal volunteers will increase secondary hyperalgesia as measured by allodynia or hyperalgesia. (Table S8)</td>
<td></td>
<td>5</td>
<td>80% Type 2 and 20% Type 3</td>
<td>90.6%</td>
<td>100% of the five studies found either an increase in secondary hyperalgesia or allodynia after infusion</td>
<td>A for supporting the hypothesis.</td>
</tr>
<tr>
<td>Hypothesis #9: Perioperative opioids will increase postoperative pain and/or opioid requirements. (Table S9)</td>
<td></td>
<td>4</td>
<td>75% Type 2 and 25% Type 3</td>
<td>87.3%</td>
<td>75% of the four studies found an increase in postoperative pain and/or opioid requirements.</td>
<td>C for supporting the hypothesis.</td>
</tr>
<tr>
<td>Hypothesis #10: Placement on opioid postsurgery leads to progression increased intake (acute tolerance). (Table S10)</td>
<td></td>
<td>1</td>
<td>Type 3</td>
<td>90.9%</td>
<td>100% of one study did not find a progressive increase.</td>
<td>(Too few studies to draw firm conclusion)</td>
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pt. = patient; OIH = opioid-induced hyperalgesia; PTRE = Pain THRESHOLD; CPPs = chronic pain patients.
Twenty-one reports [39–59] (Table S3) addressed the hypothesis that stopping or decreasing an opioid or rotating to a different opioid will improve pain and/or allodynia (Table 2). Here, two reports had poor quality scores [57,59], leaving 19 reports. Of these, 94.7% were Type 5 (case reports) and 5.2% were Type 4 (one prospective study) [58]. The quality score for the study [58] was 92.8%. For this hypothesis including one study [58], there were 123 patients. In 21 patients, alldynia was reported on and improved in 100% of the cases. In 114 patients, pain was reported on and improved in 100%. The consistency of this evidence was rated as D (there is little or no evidence or Type 5 evidence only).

Five reports [62–66] (Table S6) addressed the hypothesis that opioid infusion in normal volunteers or CPPs will decrease ptp/pto. Here, 60% of the studies were type 2 and 40% were type 3 with an overall quality score of 88.4% (Table 2). Of three studies, 33.3% found ptp to decrease with opioid infusion while four studies (75%) found pto to decrease with opioid infusion. The consistency of this evidence was rated as C (there is evidence, but it is inconsistent) (Table 1).

Five reports [68–72] (Table S8) addressed the hypothesis: opioid infusion in normal volunteers will increase secondary hyperalgesia as measured by alldynia or hyperalgesia. Here, 80% of the studies were type 2 and 20% were type 3 with an overall quality score of 90.6% (Table 2). Of the five studies, 100% found either an increase in secondary hyperalgesia or alldynia after opioid infusion. The consistency of this evidence was rated as A (consistent findings from multiple studies) (Table 1).

Four reports [73–76] (Table S9) addressed the hypothesis: perioperative opioids will increase postoperative pain or postoperative opioid requirements. Here, 75% of the studies were type 2 and 25% were type 1 with an average quality score of 87.3% (Table 2). Here, 75% of the studies found an increase in postoperative pain or opioid requirements. The consistency of this evidence was rated as C (there is evidence, but findings are inconsistent) (Table 1).

For hypotheses 2, 4, 5, 7, and 10 (Table 10), there were too few studies to draw conclusions about consistency.

Discussion
The results of this evidence-based structured review indicate that the strongest evidence (con-
define OIH (Table S1). Here, conflicting results were obtained in opioid addicts maintained on opioids: ptr results did not support the concept of OIH, while pto results did (Table 2, under Hypothesis #1). Thus, the lack of agreement as to whether pto operationally defines OIH in humans leads to potential confounding for the “opioids addicts on opioids will have decreased ptr/pto” hypothesis. In addition, the difference between ptr and pto results under this hypothesis may not be inconsistent but could be related to statistical issues. Signal-to-noise ratio is better for measuring pto than for measuring ptr. Also, some studies within this hypothesis utilized the cold presser test as a pain stimulus, while others utilized electrical or phasic heat pain stimulation. Some of these studies arrived at inconsistent results. Different findings with different pain modalities do not necessarily imply inconsistency but may point to inherent differences in how opioid exposure modulates different nociceptive systems. These are the reasons why the results of the studies within this hypothesis were designated as not interpretable in terms of consistency.

The fourth potential confounder relates to the possibility that for patients on maintenance opioid doses, that ptr/pto is determined by plasma opioid levels [30]. Therefore, studies utilizing patients on opioid maintenance and measuring ptr/pto should control for variability in opioid plasma levels. This confounder applies to studies where maintenance opioid blood levels had the opportunity to fluctuate as under the following hypotheses: opioid addicts on opioids have decrease ptr/pto; CPPs placed on opioids will develop decreased ptr/pto; and CPPs on opioids will have decreased ptr/pto vs CPPs not on opioids.

The fifth potential confounder relates to a toxic metabolite of morphine-3-glucoronomide (M-3-G), which is associated with hyperalgesia, allodynia, and myoclonus occurring with high morphine [43] doses. Here, it is impossible to make a distinction between OIH and M-3-G toxicity. This issue applies to studies under the following hypotheses: opioids addicts on opioids will have decreased ptr/pto; CPPs placed on opioids will develop decreased ptr/pto; CPPs on opioids will have decreased ptr/pto vs CPPs not on opioids; opioids infusions in non-CPPs or CPPs will decrease ptr/pto; former opioid addicts exposed to opioids will decrease ptr/pto; and especially to a number of case reports under the “stopping/decreasing/rotating an opioids will decrease pain/allodynia” hypothesis.

The sixth potential confounder relates to the question of what opioid dose range leads to OIH, as this has not been derived in animals or humans [12]. The reviewed studies and case reports utilized different opioid dosages, making comparisons for this issue impossible.

The seventh potential confounder relates to the possibility that an opioid’s ability to cause OIH varies according to the route (intrathecal vs systemic) and the duration of opioid administration [12]. Studies not demonstrating OIH may have been affected by this potential confounder.

The eighth potential confounder relates to whether CPPs are hyperalgesic pre-opioid exposure and if so, should such a group be utilized in OIH studies? Some groups of CPPs are hyperalgesic [80,81]. In addition, we have recently compared chronic low back pain (lbp) patients with and without a current diagnosis of opioid dependence to normal pain-free controls for pressure pain threshold/tolerance. Both the chronic lbp groups had significantly lower ptr/tol vs the control group but were no different from each other [82]. Thus in CPPs, hyperalgesia may be associated with chronic pain or other undetermined issues. Chronic pain is extremely common in opioid addicts. As such, OIH studies in these should control for this problem. Thus, studies under the following hypotheses could have been confounded by this problem: opioid addicts on opioids will have decreased ptr/pto; detoxifying opioids addicts will increase ptr/pto; stopping/decreasing/rotating an opioids will improve pain/allodynia; former opioids addicts exposed to an opioids will have decreased ptr/pto; and placement on opioids post-surgery will lead to acute tolerance. This issue also leads to the possibility of another hypothesis. If CPPs are already hyperalgesic, perhaps opioid exposure will not lead to greater hyperalgesia. This question is important for COAT. To answer this question, prospective controlled studies are indicated.

The ninth potential confounder relates to the AHCPR evidence guidelines (Table 1). These guidelines give greater weight to experimental studies (Type 2) vs single group pre-/post-studies (Type 3) vs correlational (Type 4), etc. As such, for each hypothesis, the percentages of each type of study were reported. However, in the consistency part of these guidelines (Table 1), the hierarchical distinction between types of studies is not utilized except for category A. Yet, the distinction between study designs is critical to some hypotheses as some require a specific study design e.g., con-
trolled prospective which is superior to other designs. This makes it difficult to arrive at an overall impression of the status of OIH research in humans. That is why the status of this research is reported according to each hypothesis.

The 10th potential confounder relates to hypothesis #3 [stopping/decreasing/rotating an opioid will improve pain/allodynia]. Most reports that relate to this hypothesis are case reports/case series (Type 5 evidence). As such, these data were not utilized in the consistency ratings but were presented for the sake of completeness. Some clinicians would argue that this hypothesis should not be presented in the same context as the other hypotheses because most of the reports deal with the development of tactile allodynia on exposure to high doses of morphine. The mechanism of this type of OIH (intoxication) is distinctly different from OIH discussed in the other hypotheses and has been discussed under confounder #5. However, some of the reports within this hypothesis [41,44–46,53] relate to improvement in pain on rotation from one opioid to another and are therefore very important to COAT. Here, it is less clear that the mechanism of OIH is intoxication.

The final potential confounder relates to the use of “increase in pain” on opioid exposure or the “improvement in pain” on opioid lowering/withdrawal as proof of OIH. This is utilized in studies under the following hypotheses: stopping/decreasing/rotating opioids will improve pain/allodynia; perioperative opioids will increase postoperative pain or opioids requirements; and placement on opioids postsurgery will lead to acute tolerance. The studies here do not conform to the operational definition of OIH. In addition, increases in pain on opioid exposure may not be a manifestation of OIH but simply reduced efficacy of an opioid secondary to progressive induction of hepatic metabolism of the drug.

The final issue relates to how studies within each hypothesis can be improved. First, the above discussion has outlined a lengthy list of potential confounders for studies within each hypothesis. The organization of this research according to hypothesis and the list of confounders under each hypothesis could be useful in future design of OIH studies. Second, most of the reviewed studies were cross sectional. This design for demonstration of OIH is not satisfactory; as here, it is difficult to make a distinction between acute tolerance/withdrawal and OIH. Thus, prospective studies are needed where ptr/pto is measured pre- and post-opioid placement, such as the study by Chu et al. [60]. Ideally, such a study should also have a non-opioid CPP control group. This type of design is especially needed where CPPs are utilized where hyperalgesia pre-opioid placement could confound the results. Ideally, such a study would utilize as many types of pain modalities as possible. Such a study should also pay careful attention to and report the opioid utilized, prior opioid exposure, length of opioid exposure, speed of opioid dose escalation, opioid blood levels, and the opioid doses utilized.

Conclusions

The results of this evidence-based structured review indicate that there is limited evidence for the development of OIH in humans on opioid exposure. The strongest most consistent evidence comes from studies of normal volunteers exposed to opioid infusions. Unfortunately, many of the studies under the various hypotheses could have been confounded by issues presented. Should OIH then be an important consideration in the treatment of patients with chronic pain? This question will only be answered after prospective clinical studies are performed on CPPs with ptr/pto measurements pre- and post-opioid placement and utilizing a CPP non-opioid control group.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Opioid addicts maintained on opioids will have decreased pain threshold or pain tolerance
Table S2 Do opioid addicts when detoxed from opioids increase their pain threshold or pain tolerance?
Table S3 Do decreasing, stopping, detoxifying from an opioid or rotating to a different opioid improve pain or allodynia?
Table S4 Do chronic pain patients placed on opioids develop decreased pain threshold and pain tolerance?
Table S5 Do chronic pain patients on opioids have decreased pain threshold and pain tolerance vs chronic pain patients not on opioids?
Table S6 Does opioid infusion in normal volunteers or chronic pain patients decrease pain threshold or pain tolerance?
Table S7 Do former opioid addicts demonstrate decreased pain threshold on exposure to opioids?
Table S8 Does opioid infusion in normal volunteers increase secondary hyperalgesia as measured by allodynia or hyperalgesia?
Table S9 Do perioperative opioids increase postoperation pain or opioid requirements?
Table S10 Does placement on opioids postsurgery lead to progressive increased intake (acute tolerance)?
Table S11 Quality ratings and % quality scores for studies in Tables S1–10

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