Review of the Performance of Quantitative Sensory Testing Methods to Detect Hyperalgesia in Chronic Pain Patients on Long-term Opioids

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ABSTRACT

Background: Opioid-induced hyperalgesia is a clinical syndrome whereby patients on long-term opioids become more sensitive to pain while taking opioids. Opioid-induced hyperalgesia is characterized by increased pain intensity over time, spreading of pain to other locations, and increased pain sensation to external stimuli. To characterize opioid-induced hyperalgesia, laboratory methods to measure hyperalgesia have been developed. To determine the performance of these methods, the authors conducted a systematic review of clinical studies that incorporate measures of hyperalgesia in chronic pain patients on long-term opioids.

Methods: PubMed and Cochrane databases were searched (terms: opioid induced hyperalgesia, study or trial, and long-term or chronic). Studies published in English were selected if they were conducted in chronic pain patients on long-term opioids and incorporated measures of hyperalgesia; acute/single-dose studies and/or conducted in healthy volunteers were excluded.

Results: Fourteen articles made the final selection (11 were selected from the search and 3 others were found from additional sources); there was one randomized controlled trial, one prospective controlled study, three prospective uncontrolled studies, and nine cross-sectional observation studies. Hyperalgesia measurement paradigms used included cold pain, heat pain, pressure pain, electrical pain, ischemic pain, and injection pain. Although none of the stimuli were capable of detecting patients' hyperalgesia, heat pain sensitivity showed some promising results.

Conclusions: None of the measures reviewed herein met the criteria of a definitive standard for the measurement of hyperalgesia. Additional studies that use improved study design should be conducted. **(Anesthesiology 2015; 122:677-85)**

FOR many decades, physicians have expressed concerns about the manifestation of tolerance to opioids with long-term use. Tolerance to opioid analgesia can manifest either as loss of pain relief while receiving fixed doses of opioids or as the need for dose escalation to maintain the same degree of pain relief. Clinically, such patients end up on high doses of opioid therapy, with persistent high pain intensity, and poor physical and psychosocial function. There are a variety of reasons why relief from pain might be lost (or opioid doses escalated) in these patients, including worsening in pain intensity over time, worsening of underlying disease, a desire for hedonistic effects, the emergence of tolerance, or the emergence of opioid-induced hyperalgesia (OIH). OIH is defined as a clinical syndrome in which patients on long-term opioids become more sensitive to pain as a result of taking opioids. Clinically, OIH is characterized by a triad of symptoms: (1) an increase in pain intensity over time, (2) the spreading of pain to other location than the initial painful site, and (3) an increase in pain sensation to external stimuli. Whether clinical OIH truly exists is controversial. OIH has been reliably demonstrated in animal models and there is some clinical evidence to support its occurrence in humans.[1,2] Although opioid tolerance and OIH can be measured in behavioral models in rodents and human experimental pain models, the relevance of these models to patients on long-term opioid therapy for chronic pain is unclear.[1,3] Recent reviews and meta-analyses have documented remifentanil-associated increases in pain, postoperative opioid requirements, and hyperalgesia at or near the surgical site.[4] Although the effects of short-acting intraoperative opioids on acute postoperative outcomes is interesting, this topic is

What We Already Know about This Topic

- Opioid-induced hyperalgesia is a clinical concept associated with increased pain sensitivity and decreased efficacy at the same dose of opioids with ongoing opioid use
- The most appropriate sensory testing for opioid-induced hyperalgesia is not clear

What This Article Tells Us That Is New

- In a systematic review of 14 studies of opioid-induced hyperalgesia, most sensory modalities tested failed to demonstrate hypersensitivity to test stimuli, and additional work with stronger study designs is needed

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beyond the scope of this review which focuses on patients who are maintained on *long-term* opioid therapy.

To determine whether clinical OIH exists and to characterize it, researchers have aimed at developing *laboratory methods to measure hyperalgesia* (*i.e.*, the increase in pain sensitivity, as a proxy to clinical OIH) in chronic pain patients on long-term opioids, outside of the patient's primary clinical pain syndrome. To this end, laboratory methods have been developed that consist of evaluating patients' pain threshold and tolerance to external experimental stimuli such as mechanical (pressure, touch, or injection), thermal (cold/heat), electrical, or other stimuli (*e.g.*, ischemia). Two possible study designs have been typically used (1) patients with chronic pain on long-term opioids are cross-sectionally compared with patients with the same chronic pain syndrome not taking opioids, or (2) patients with chronic pain on long-term opioids are evaluated before and after an intervention such as discontinuing opioid therapy. However, none of these experimental approaches have been validated or is considered the definitive standard for measuring hyperalgesia in clinical trials of pain patients on chronic opioids. A suitable method for evaluating hyperalgesia would be reliable and responsive, that is, able to discriminate groups of patients known to have different levels of pain sensitivity that may be associated with opioid therapy. Therefore, we conducted a systematic review of clinical studies that incorporated measures of hyperalgesia in chronic pain patients on long-term opioids to determine and compare the performance of each method to measure hyperalgesia. Because responsiveness requires reliability, we have focused on responsiveness as the key performance characteristic for this review. Finding adequate experimental methods to measure hyperalgesia in chronic pain patients will help determine whether clinical OIH exist, to characterize it, and to prevent or treat it.

Materials and Methods

Literature Search

To find human studies that measure hyperalgesia in patients on long-term opioids for chronic pain, a search in PubMed and Cochrane databases was performed using terms ("all terms" search) such as "opioid induced hyperalgesia," "study or trial," and "long-term or chronic," and rejecting the terms "mice or rodent." A first screening of the retrieved articles was performed based on the title and abstract; the screened articles were then retrieved in their full version and carefully read to be included in the final selection. In order for an article to be selected, the study had to meet the following criteria: (1) be a randomized controlled trial, a prospective study, or a cross-sectional comparative study; (2) be conducted in patients on long-term opioids for chronic pain (single-dose/acute studies and studies conducted only in healthy volunteers were excluded); (3) include assessments or measures of hyperalgesia as part of the study; and (4) be published in English. The search included articles up to May 2014 (no date limit was used).

The methods used to measure hyperalgesia in the articles retrieved from the main search were compiled. To ensure that all possible original articles were found, a secondary literature search was conducted using the terms "opioid induced hyperalgesia" and the name of the test used to measure hyperalgesia (*e.g.*, cold pressor test, thermal sensory analyzer, lidocaine injection, electrical stimulation, *etc.*).

Data Analysis

Data extracted from the articles included the type of study (studies were categorized into randomized controlled trials, prospective controlled studies, prospective uncontrolled studies, and cross-sectional comparative studies), the patient population, the measure(s)/test(s) used to assess hyperalgesia, available results (difference between pre- and posttreatment, difference between groups, dose-related data, and any other relevant data), and *P* values (when available).

Results

Search Results

The article screening and selection process is illustrated in figure 1. The PubMed Library search retrieved 62 articles and the Cochrane database search retrieved 22; a search of our personal records retrieved 1 article. After elimination of duplicates, 68 articles were screened for relevance. A total of 11 articles made the final selection (from most to least recent): Suzan *et al.*,[5] Chu *et al.*,[6] Krishnan *et al.*,[7] Edwards *et al.*,[8] Wang *et al.*,[9] Hooten *et al.*,[10] Chen *et al.*,[11] Ram *et al.*[12] Hay *et al.*,[13] Cohen *et al.*,[14] and Chu *et al.*[15] Searching the references of these articles retrieved two other articles (Reznikov *et al.*[16] [cited in Suzan *et al.*[5]]; Doverty *et al.*[17] [cited in Chu *et al.*[6]]). Another original article was found *via* the secondary search for OIH and lidocaine injection (Kim *et al.*[18]). Thus, a total of 14 original studies that measured hyperalgesia in patients on long-term opioids for chronic pain were found.

Description of Studies

Of the 14 selected studies, 1 was a randomized controlled trial,[6] 1 was a prospective controlled study,[5] 3 were prospective uncontrolled studies,[9,10,15] and 9 were cross-sectional observation studies.[7,8,11–14,16–18] Six hyperalgesia measurement paradigms were used in these studies: cold pain, heat pain, pressure pain, electrical pain, ischemic pain, and injection pain; these methods are described in table 1. The design, patient population, and results of each study are summarized in table 2.

Summary of Findings

The ideal measure would be able to differentiate pain sensitivity in patients randomly exposed prospectively to opioids compared with a cohort randomly assigned to a control condition. Only one study[6] used such a design (randomized controlled trial), and the two experimental methods used in that study (cold pain threshold and tolerance using ice water

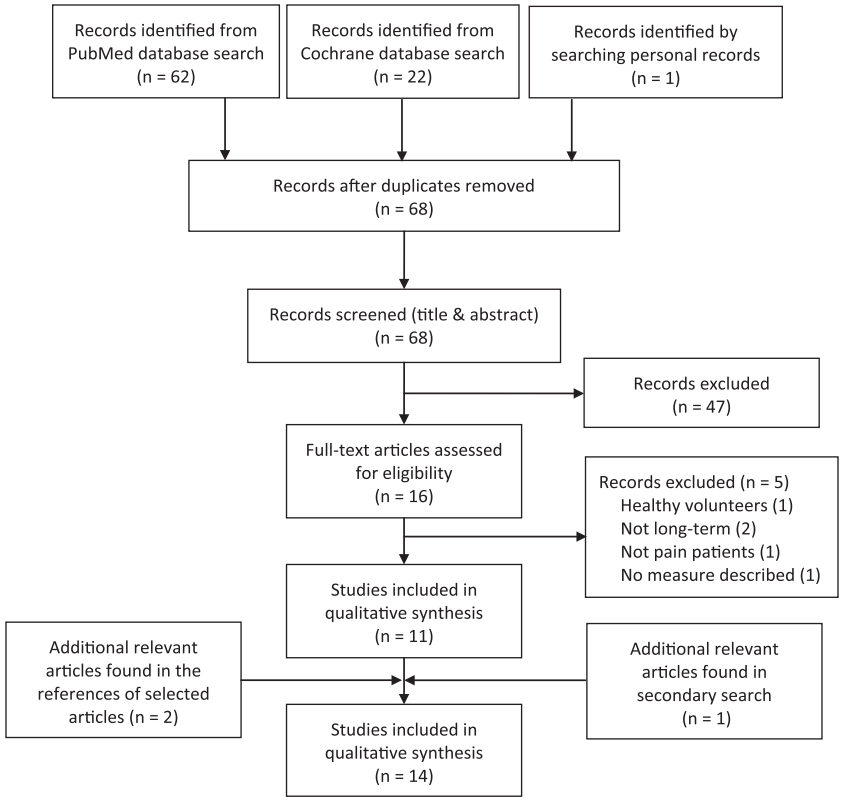

Fig. 1. Search result flow diagram.

Table 1. Summary of the Methods Used to Measure OIH

Type of Stimulation	Test Name	Methodology and Measurements	References
Cold pain	Cold pressor test	The subject's hand is submerged up to the wrist in a 0.5°–1°C ice water bath continuously recirculated by a pump (up to 120 s). Measures are time to pain detection (threshold) and to intolerable pain (withdrawal of the hand; tolerance); continuous pain scores. Painful cold water immersion was used as the conditioning stimulus in a CPM paradigm.	Chu *et al.*,[15] Chu *et al.*,[6] Hay *et al.*,[13] Suzan *et al.*[5]
Heat pain	Medoc TSA (Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel)	Quantitative pain threshold is determined with the method of limits with the Medoc TSA. A thermode is applied to the skin and heat is applied at various temperatures. Measures are pain threshold and pain tolerance (in °C); pain scores at various temperatures; temporal summation of suprathreshold heat stimuli (in a few studies); ratings of heat pain intensity used as the test stimulus in a CPM paradigm.	Reznikov *et al.*,[16] Chu *et al.*,[15] Chu *et al.*,[6] Suzan *et al.*,[5] Chen *et al.*,[11] Edwards *et al.*[8]
Pressure pain	Pressure algometer	A manual pressure algometer (*e.g.*, a 3-mm diameter paddle algometer; Medical-Hako, Hamburg, Germany) is pressed perpendicularly to the skin at selected points and increasing pressure is applied. Measures are time to perception of a painful sensation (threshold); the measurement is shown on an algometer scale.	Reznikov *et al.*[16]
Electrical pain	Electrical stimulation of ear lobe	Voltage is applied to ear lobe starting at 0 V and increasing at a constant rate of 2 V every 1.4 s, up to a maximum of 100 V. Measures are pain threshold and pain tolerance (in volts).	Doverty *et al.*,[17] Krishnan *et al.*,[7] Hay *et al.*[13]
Ischemic pain	Blood pressure cuff test with handgrip exercise	A blood pressure cuff is placed around the nondominant arm of the subject and the pressure is increased to 20 mmHg above the subject's systolic pressure. With the pressure maintained, subjects perform a handgrip exercise on an elastic ball, in accordance with the rhythm of a metronome (subject's eyes are covered to minimize distraction and time cues). Measures are time to feeling of pain (pain threshold); time to untolerable pain (to a maximum of 5 min) (pain tolerance).	Krishnan *et al.*,[7] Ram *et al.*[12]
Injection pain	Subcutaneous local anesthetic injection	A local anesthetic (generally lidocaine) is administered subcutaneously (before a full dose of anesthetic for a procedure). Measures are subject's ratings of pain and unpleasantness of the lidocaine injection.	Cohen *et al.*[14]

CPM = conditioned pain modulation; OIH = opioid-induced hyperalgesia; TSA = thermal sensory analyzer.

Table 2. Summary of Studies on OIH in Patients Taking Long-term Opioids

Experimental Pain Paradigm	Test Name*	Patient Population	Results	Reference
RCTs				
Cold pain Heat pain	Cold pressor test Thermal Sensory analyzer (Medoc Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel)	Patients with LBP treated with sustained-release morphine (n = 69) or placebo (n = 70) for 1 mo. Patients subjected to a target-controlled infusion with the opioid agonist remifentanil or saline.	Cold pain: Patients in the morphine group had significant changes in pain threshold from baseline ($P = 0.005$). There were no significant changes from baseline in tolerance in both groups. There were no significant differences in the changes for threshold and tolerance between the two groups. Heat pain: Patients in each treatment group had significant changes in pain threshold from baseline ($P = 0.05$ for morphine group; $P = 0.006$ for placebo group). There were no significant changes from baseline in tolerance in both groups. There were no significant differences in the changes in pain threshold and tolerance between groups.	Chu *et al.*[6]
Prospective controlled (nonrandomized) studies				
Heat pain intensity Cold pain	Thermal Sensory Analyzer (Medoc) Cold pressor test	Patients (n = 30) with chronic neuropathic (radicular) pain assessed before and after 4 wk of an individually titrated dose of oral HM (4–20 mg/d). Healthy volunteers (n = 10) used as control (receive no opioids).	Heat pain: HM treatment resulted in a significant rise for the entire group, on average, in the intensity of the phasic heat pain response (VAS at baseline = 48.2 ± 33.1; at wk 4 = 60.8 ± 29; $P < 0.05$). No significant differences for controls in the intensity of the phasic heat pain response between baseline and wk 4 (32.9 ± 27 *vs.* 33.9 ± 28, respectively; $P = 0.65$). Cold pain: No significant differences in cold pain tolerance between baseline and wk 4 for HM patients (40.1 ± 41.6 *vs.* 43.9 ± 48.8; $P = 0.38$) or controls (27.9 ± 15.8 *vs.* 30 ± 19.5; $P = 0.44$).	Suzan *et al.*[5]
Prospective uncontrolled studies (from most to less recent)				
Heat/cold pain	Thermal Sensory Analyzer (Medoc)	Patients with LBP taking opioids (n = 35) being tapered off; patients with LBP not taking opioids (n = 35); healthy controls (n = 28)	Parameters measured: cold and heat pain threshold in low back and nondominant hand before (T1), and 3 wk (T2) and 6 mo postopioid tapering (T3). Opioid patients were off opioids by T2 and remained off at T3. Heat pain thresholds: Opioid patients had lower heat pain thresholds than controls at all time points (T1, $P = 0.007$; T2, $P = 0.007$; T3, $P = 0.017$). Nonopioid patients had lower heat pain threshold than controls at T1 ($P = 0.001$) and T2 (0.002). At T3, heat pain thresholds of nonopioid patients normalized. There was no difference between opioid and nonopioid patients at any time point. Cold pain thresholds: Opioid patients had lower threshold to cold stimuli than nonopioid patients ($P = 0.004$ for hand) and controls ($P = 0.001$ for hand, $P = 0.021$ for left low back). Nonopioid patients had a cold pain threshold similar to controls.	Wang *et al.*[9]
Heat pain	Standardized QST: automated Computer Aided Sensory Evaluator IV	Patients (n = 109) taking opioids admitted to a multidisciplinary pain rehabilitation program which includes opioid tapering over 3 wk. (QST performed before and after taper).	Greater baseline morphine dose was associated with lower or more hyperalgesic values of HP 5-0.5† ($P = 0.040$). Tapering of greater morphine doses was associated with lower values of HP 5-0.5† ($P = 0.001$).	Hooten *et al.*[10]
Cold pain Heat pain	Cold pressor test Thermal Sensory Analyzer (Medoc)	Patients (n = 6) with LBP taking morphine assessed before and 1 mo after treatment.	Cold pain: Patients developed significant hyperalgesia to cold pressor pain after 1 mo of oral morphine therapy ($P < 0.01$). Pain threshold dropped by approximately 16% (from 12.1 ± 4.1 to 10.1 ± 3.7 s), and pain tolerance dropped by approximately 24% (from 28.0 ± 13.7 to 19.8 ± 6.0 s). Heat pain: Heat pain threshold did not change significantly between sessions (–0.2° ± 0.6°C).	Chu *et al.*[15]

(*Continued*)

Table 2. Continued

Experimental Pain Paradigm	Test Name*	Patient Population	Results	Reference
Cross-sectional comparative studies (from most to less recent)				
Injection	Subcutaneous injection of LA	Patients taking opioids (n = 62); patients not taking opioids (n = 20).	LA injection-specific pain score, unpleasantness, and behavior pain score are higher in opioid patients (at any dose) *vs.* nonopioid patients ($P < 0.01$). In nonopioid patients, postinjection pain scores, unpleasanteness, and behavioral pain score were higher in patients taking high dose (≥200 mg) than those taking low doses (1–59 mg) ($P < 0.05$).	Kim *et al.*[18]
Cold pain Electrical pain Mechanical pain Ischemic pain	Cold pressor test Electrical stimulation of ear lobe Pressure algometer Blood pressure cuff and handgrip exercise	Opioid-dependent subjects (n = 16) on Meth or Bup (n = 8 each); healthy controls (n = 16).	Cold pain: There were significant treatment group differences in cold pain threshold and tolerance, with the opioid groups being more sensitive than controls. Hazard ratio for pain threshold was 6.8 (95% CI, 2.2–20.6) in Bup group and 4.1 (95% CI, 1.4–11.7) in Meth group *vs.* controls. Hazard ratio for tolerance was 7.7 (95% CI, 2.6–23.3) in Bup group and 4.5 (95% CI, 1.7–15.6) in Meth group *vs.* controls. Electric pain: There were significant treatment group differences in electrical threshold but not tolerance, with higher thresholds in the opioid groups. For threshold, geometric mean was 1.5-fold (95% CI, 1.1–1.9) than that of control in the Bup group and 1.3-fold (95% CI, 1.04–1.7) that that of control in Meth group. Ischemic and pressure pain: No significant differences between treatment groups for either threshold or tolerance for ischemic and pressure pain tests.	Krishnan *et al.*[7]
Mechanical pain Pressure pain Heat pain	Punctate mechanical probes—mechanical temporal summation Pressure probe Thermal Sensory Analyzer (Medoc)	Chronic pain patients with spinal pain taking low-dose opioids (n = 88); high-dose opioids (n = 91); or no opioids (n = 97).	Mechanical pain: No significant differences between groups in mechanical pain sensitivity. Pressure pain: No significant differences between groups in pressure pain sensitivity. Heat pain: No significant differences between groups in (cold/warm) thermal sensitivity.	Edwards *et al.*[8]
Heat pain Mechanical pain	Thermal Sensory Analyzer (Medoc) Von Frey filaments Pinprick	Chronic pain patients taking opioids (n = 58); chronic pain patients not taking opioids (n = 41); controls: healthy volunteers not taking opioids (n = 41).	Heat pain: Statistically significant differences were detected among three groups in heat pain threshold ($P = 0.02$), cold pain tolerance ($P = 0.01$), heat pain tolerance ($P = 0.01$), and duration of tolerance to the suprathreshold heat stimulation ($P = 0.02$). *Post hoc* analysis showed significant differences in these four parameters between opioid patients and controls ($P < 0.05$) but not between nonopioid patients and controls. The degree of temporal summation of the second pain was significantly exacerbated in opioid patients *vs. nonopioid* patients and controls ($P < 0.05$) (no differences between nonopioid patients and controls). Opioid dose correlated (morphine equivalent ≥75 mg) with the decreased heat pain threshold and exacerbated temporal summation of the second pain in opioid patients ($P < 0.05$). Mechanical pain: No differences between groups in mechanical pain threshold from von Frey filaments and pinprick.	Chen *et al.*[11]
Cold pain CPM	Cold pressor test Heat stimulation (Medoc) + cold stimulation (cold pressor test)	Chronic pain patients on opioids (n = 73); chronic pain patients not on opioids (n = 37).	Cold pain: No significant differences between groups. CPM: The magnitude of CPM was significantly larger in the nonopioid group than in the opioid group ($P = 0.003$).	Ram *et al.*[12]

(*Continued*)

Table 2. Continued

Experimental Pain Paradigm	Test Name*	Patient Population	Results	Reference
Mechanical pain Cold pain Electrical pain	Von Frey filaments Cold pressor test Electrical stimulation	Chronic pain patients taking morphine or methadone more than once daily for ≥1 mo; Meth-maintained patients recruited from a methadone maintenance program; controls: opioid-naive subjects. N = 10 in each group.	Mechanical pain: There were no significant differences in Kaplan–Meier curves for each of the group for von Frey hair pain threshold ($P = 0.33$) or tolerance (P = 0.99). Cold pain: Tolerance values (mean ± SEM) were 18.1 ± 2.6 s in morphine patients, 19.7 ± 2.3 s in Meth patients, and 18.9 ± 1.9 s in Meth-maintained patients; all values are significantly ($P < 0.05$) lower than opioid-naive subjects (30.7 ± 3.9 s). Threshold values were not different between groups. Electrical pain: Electrical threshold and tolerance values were not significantly different between groups.	Hay *et al.*[13]
Injection	Subcutaneous injection of local anesthetic	Patients (n = 355) on steady regimen of opioids (doses 1 to >300 mg) and scheduled for an interventional procedure. Controls: healthy volunteers (n = 27) not taking opioids.	Opioid dose positively correlated with pain intensity ($P < 0.05$ at all doses [which start at 1 mg] *vs.* no opioids) and unpleasanteness score ($P < 0.05$ for doses ≥30 mg only *vs.* no opioids). Duration of opioid treatment was positively correlated with both pain and unpleasantness scores ($P = 0.001$ *vs.* duration = 0).	Cohen *et al.*[14]
Mechanical pain Pressure pain Heat pain	Von Frey filaments Manual algometer Thermal Sensory Analyzer (Medoc)	Opioid-treated patients (n = 142); nonopioid-treated group (n = 82)	Mechanical pain: No significant differences between groups were found for mechanical pain (difference = 17.0 g [95% CI, 8.8–42.8], $P = 0.19$). Pressure pain: No difference between groups were found for pressure pain (2.2 mmHg [28.7–33.2], $P = 0.89$) Heat pain: No difference between groups were found for heat pain threshold (–0.3°C [–1.5 to 0.9], $P = 0.70$) or suprathreshold heat pain intensity (difference between maximal pain intensities = –0.4 NPS units [1.2, 0.4], $P = 0.31$).	Reznikov *et al.*[16]
Cold pain Electric pain	Cold pressor test Electrical stimulation of ear lobe	Patients (n = 16) on stable, once-daily doses of methadone and matched control subjects (n = 16).	Cold pain: Meth patients detected pain significantly earlier than controls at 0 h and were also much less pain tolerant than controls at 0 and 3 h. No significant differences in pain detection values between groups at 3 h. Pain tolerance/pain detection ratios for Meth patients were significantly lower than controls at 0 and 3 h. Electrical pain: Meth patients' pain tolerance values were lower than controls at 0 h, but higher than controls at 3 h; no significant differences in pain detection values were found. Pain tolerance/pain detection ratios for Meth patients were significantly lower than controls at 0 h only.	Doverty *et al.*[17]

* Refer to table 1 for test description. † Measurements are based on the method of levels. Heat pain perception (HP 5, HP 0.5, and HP 5-0.5) are calculated. HP 0.5 is the midpoint between a nonpainful stimulus and the least stimulus magnitude necessary to elicit pain; thus, HP 0.5 is a measure of HP threshold. HP 5 is the stimulus magnitude necessary to elicit a pain rating of 5 from the subject; thus, HP 5 is considered to be a measure of intermediately intense pain. HP 5-0.5 is a measure of the slope of the line connecting these two points, and this HP parameter has been termed the pain-stimulus response slope.

Bup = buprenorphine; CPM = conditioned pain modulation; HM = hydromorphone; HP = heat pain perception; LA = local anesthetic; LBP = low back pain; Meth = methadone; NPS = numerical pain scale; OIH = opioid-induced hyperalgesia; QST = quantitative sensory testing; RCT = randomized controlled trial; VAS = visual analog scale.

Table 3. Summary of Results* from the Selected Studies

	Differences Measured*	Cold Pressor Tolerance	Cold Pressor Threshold	Heat Pain Tolerance	Heat Pain Threshold (and Suprathreshold)	Heat Pain Intensity	Heat Pain CPM	Electrical Pain	Injection Pain	Mechanical†	Ischemic or Other Pressure Pain
RCTs											
Chu *et al.* [6]	Between group	–	–	–	–						
	Pre–post	–	+	–	+						
Prospective controlled studies (nonrandomized)											
Suzan *et al.*[5]	Between group	–				+					
	Pre–post	–				+					
Prospective uncontrolled studies											
Wang *et al.*[9]	Between group				–						
	Pre–post				–						
Hooten *et al.*[10]	Pre–post					+					
Chu *et al.*[15]	Pre–post	+	+		–						
Cross-sectional comparative studies											
Kim *et al.*[18]	Between group								+		
Krishnan *et al.* [7]	Between group	+	+					±		–	–
Hay *et al.*[13]	Between group	+	–					–		–	
Edwards *et al.*[8]	Between group				–	–				–	–
Chen *et al.*[11]	Between group			+	+					–	
Ram *et al.*[12]	Between group	–	–				+				
Cohen *et al.*[14]	Between group								+		
Reznikov *et al.*[16]	Between group				–	–				–	
Doverty *et al.*[17]	Between group	±	±					–			
Number of positive studies		3	3	1	2	3	1	0	2	0	0
Number of negative studies		5	3	2	6	2	0	2	0	5	2

* + indicates a positive finding; – indicates a negative finding. ± indicates an equivocal finding (studies with ± findings are not taken into account in the total of negative and positive studies). For pre–post comparisons, a "+" indicates that patients on opioids are more sensitive to pain after long-term opioid treatment, as assessed by the test (or that tapering of opioid significantly decreases pain sensitivity). For group comparisons, a "+" indicates that patients on opioids are more sensitive to pain than patients not on opioids, as assessed by the test. † Von Frey filaments, pinprick, or algometry.

CPM = conditioned pain modulation; RCT = randomized controlled trial.

immersion and heat pain threshold and tolerance using the Medoc TSA; Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel) both failed to differentiate the two groups. It is unclear whether these approaches failed because of the measures, because the patients did not in fact develop hyperalgesia, or because treatment was short term and used relatively low doses. Thus, no measure of hyperalgesia can claim definitive standard status.

Table 3 summarizes the test results by indicating which measures were used in each study, and whether the *P* value for the between-group difference tested was greater than 0.05 (–) or less than 0.05 (+). The major methods that have been used are (1) cold pain threshold and tolerance using ice water immersion, and (2) heat pain threshold, tolerance, or intensity at suprathreshold stimulus levels using computer-controlled thermode devices. The summary results in table 3 suggest that, on average, none of the stimuli were capable of detecting hyperalgesia in chronic pain patients on long-term opioids. However, some specific findings merit attention. For instance, two controlled prospective studies[5,6] and one uncontrolled prospective study[10] found a significant difference in heat pain sensitivity between pre- and postopioid treatment.

Discussion

This systematic review was conducted to determine and compare the responsiveness of methods to measure hyperalgesia in clinical studies of chronic pain patients on long-term opioids. Fourteen articles reporting original studies measuring hyperalgesia in those patients were retrieved. Because clinical OIH has not yet been definitively demonstrated, it is not possible to directly determine the responsiveness of measures of this phenomenon. Furthermore, the studies performed in this area tend to have small sample sizes, different experimental designs, and different testing protocols, thereby precluding formal meta-analytic methods. The summary results in table 3 suggest that, on average, none of the stimuli have sufficient power to detect hyperalgesia in chronic pain patients on long-term opioids. However, some specific findings merit attention. For instance, it is notable that three prospective studies that assessed heat pain ratings reported heat hyperalgesia when patients were on opioid therapy (compared with when they were off opioids).[5,6,10] Although a larger number of studies have been performed with ice water immersion, a substantial proportion of these studies failed to discriminate "known" groups, and the aversive nature of the test should be considered. Mechanical testing approaches (algometry or von Frey filaments) have been used several times, never successfully.[7,8,11,13,16] Other approaches (conditioned pain modulation, ischemia, injection pain) have been unsuccessful, inconsistent, or have been used too rarely to conclude.[7,8,12,14,18]

Thus, this review failed to identify a definitive standard for hyperalgesia measures. This is mainly due to the fact that the measurements failed to detect a change because the measures are not sensitive enough, the sample is too small for the measure to detect change, the studies use suboptimal study designs (most being cross-sectional), and/or the timing of opioid dosing was not controlled for. Moreover, all these studies provide averages of hyperalgesia variables over the entire group of opioid-treated patients, which may obliterate the phenomenon if the development of hyperalgesia is a rare occurrence in patients on opioids. Therefore, clinicians who wish to conduct a clinical trial to measure hyperalgesia in opioid-treated patients should choose a randomized controlled trial design and report the proportion of patients on opioids who develop hyperalgesia during the treatment. Finally, although most studies focused on measure responsiveness, assessing reliability and other forms of validity would also be informative. This review identified heat stimuli (using the Medoc TSA; Medoc Ltd. Advanced Medical Systems) as a potentially good candidate for further testing in future studies. More data should also be generated with injection pain to determine whether this method holds true potential.

Importantly, clinicians should be cautious not to take the increase in pain sensitivity (hyperalgesia) to experimental stimuli as a proof of OIH in opioid-treated patients. Indeed, clinical OIH is a syndrome that has three main symptoms: one of them being an increase in pain sensitivity to external stimuli and the other two being an increase in pain intensity over time and the spreading of pain to other locations. To conclude that a patient experiences OIH should rely on additional evaluation of the patient's clinical data and medical history to determine whether all characteristics of clinical OIH are present. To this end, Chen *et al.*[11] provides a list of clinical factors that should be taken into account in the diagnosis of clinical OIH.

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Competing Interests

The authors declare no competing interests.

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