Systematic Review and Meta-Analysis

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# A systematic review and meta-analysis of pharmacological methods to manipulate experimentally induced secondary hypersensitivity

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**Abstract**

Understanding the physiology of specific clinical features of persistent pain, such as secondary hypersensitivity, is crucial for developing effective treatments. This systematic review and meta-analysis investigated the effects of pharmacological manipulations on the magnitude (primary outcome) and surface area (secondary outcome) of experimentally induced secondary hypersensitivity. Following Cochrane Collaboration guidelines and a published and registered protocol, we conducted an electronic search on February 7, 2024. After screening articles in duplicate, we included 117 articles, consisting of 222 datasets. Risk of bias assessments identified potential flaws in methodological quality. Datasets were pooled by the mechanism of action of the manipulation and by outcome. Effect sizes were estimated using standardised mean difference (SMD). Most datasets (207 of 222) had an unclear risk of performance and detection bias for inadequate reporting of blinding procedures. Thirteen different methods were used to induce, and 23 different drug classes were used to manipulate secondary hypersensitivity. The pooled SMDs [95% CI] suggested that alpha-2-delta subunit of voltage-gated calcium channel ligands reduced both the magnitude (−0.24 [−0.39; −0.08]) and surface area (−0.38 [−0.59; −0.18]) of secondary hypersensitivity, and that both N-methyl-D-aspartate receptor antagonists (−0.36 [−0.55; −0.17]) and voltage-gated sodium channel blockers (−1.02 [−1.63; −0.42]) reduced only the surface area of secondary hypersensitivity. These results suggest a need to understand and compare the physiological underpinnings of magnitude and area of secondary hypersensitivity, and to clarify the relative importance of magnitude vs anatomical spread (ie, surface area) of secondary hypersensitivity to people living with pain.

**Keywords:** Secondary hyperalgesia, Hypersensitivity, Central senitization, Pain, Pinprick pain, Pharmacotherapy

## 1. Introduction

Persistent pain is surprisingly common and is a prominent cause of disability worldwide. Low back pain alone is estimated to affect more than half a billion people worldwide and is the leading cause of years lived with disability.[24] Persistent pain often responds poorly to pharmacotherapy, possibly because most medications target symptoms rather than mechanisms. Medication-driven relief of symptoms may, therefore, be short-lived because the medication has not changed the physiological mechanisms underpinning the persistence of the pain. This recognition has driven a large body of work on mechanisms-based approaches to understanding and managing persistent pain.[6,112,132,133]

Experimental manipulations can clarify the role of different mechanisms underlying clinical features of persistent pain, particularly if the manipulations are known to target specific physiological processes. The clinical feature of interest is measured with and without the manipulation, to determine the contribution that the manipulated process makes to the clinical feature. One such clinical feature that is common across several pain types is secondary hyperalgesia. Clinically, secondary hyperalgesia is common in patients with acute (eg, postsurgical pain)[129] or persistent pain (eg, fibromyalgia,[105] and complex regional pain syndrome).[104]

The physiological mechanisms underlying secondary hyperalgesia are thought to operate primarily at the spinal level.[7,103] Tissue injury prompts a barrage of afferent signalling, leading to upregulation of excitatory neurotransmitters and receptors, enhanced binding affinity of neurotransmitters to receptors, increased neuronal membrane excitability, and structural reorganisation such as sprouting of afferent neurons and death of inhibitory interneurons.[96–98,107] The overall effect is an increased efficiency in dorsal horn synapses. Immune signalling, including

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from astrocytes and microglia, is also implicated in this enhancement of synaptic efficiency at the dorsal horn of the spinal cord.[91] Recent revisions to IASP pain classifications[53,54,75] have drawn attention to the likely importance of these changes for what is now called "nociplastic" pain, although some version of this increase in efficiency is also a normal feature of pain with tissue injury.[115]

Human surrogate models of secondary hyperalgesia provide an opportunity to investigate, in vivo, the processes that underpin this enhancement of synaptic efficiency. Methods to safely induce short-lived secondary hyperalgesia in humans include intradermal injection or topical application of capsaicin,[58,65] burn injury,[82] and electrical stimulation.[87,110] To test mechanistic hypotheses, manipulations are used before, during, or after the induction, and the magnitude or surface area of secondary hyperalgesia is assessed. For example, the N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, has been tested for its ability to decrease the surface area of capsaicin-induced secondary hyperalgesia,[4] thus clarifying the role of the NMDA receptor in secondary hyperalgesia.

There is some discussion of the most appropriate term to use for this experimental analogue of clinical secondary hyperalgesia. The pinprick probes and von Frey filaments that are commonly used in this paradigm are not consistently perceived as painful in normal skin, which renders the term "hyperalgesia" technically inaccurate.[69] Therefore, for clarity's sake, we proceed with the term secondary *hypersensitivity* in this paper.

To synthesise the current state of knowledge about the mechanisms underlying secondary hypersensitivity, this systematic review and meta-analysis aimed to identify, collate, and describe all the published studies that have administered pharmacological manipulations intended to influence experimentally induced secondary hypersensitivity in human participants without clinical pain. Together with its sibling review of non-pharmacological manipulations,[8] this thorough examination of the literature is anticipated to yield a resource that summarises the current body of evidence, provides pooled effect size estimates (where possible), and identifies gaps in knowledge and opportunities for further inquiry. A thorough understanding of the physiological mechanisms that underlie the clinical features of persistent pain is anticipated to support the development of mechanism-based therapies, thus increasing the likelihood of clinically meaningful improvements.

## 2. Methods

This systematic review and meta-analysis was planned and conducted according to Cochrane Collaboration[36] guidelines and a published[63] and registered protocol (PROSPERO CRD42020146486), and reported according to the reporting guidelines for Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[76] (Supplementary file, http://links.lww.com/PAIN/C239). All extracted data and code for the meta-analyses are publicly available at https://osf.io/y6xsv/?view_only=74f05a33d6d54df084528b507140356d. The protocol was for a review of studies that used either non-pharmacological or pharmacological manipulations of experimentally induced secondary hypersensitivity (SH). The review of nonpharmacological manipulations was published separately.[8] Here, we focus on the studies that tested pharmacological manipulations only, including manipulations involving administration of a chemical substance via ingestion, injection, or topical route. All protocol deviations are reported in Supplementary file: Section 2, http://links.lww.com/PAIN/C239.

### 2.1. Types of studies

Prospective experimental studies were eligible—ie, studies of the effects of a manipulation on experimentally induced SH (ie, not naturally occurring clinical SH). Published, in-press, or accepted records for which title, abstract, and full-text versions were available in English were eligible for inclusion.

### 2.2. Types of participants

Data from human participants without clinical pain conditions were included. No restrictions were placed on the ages of participants, but data from adults were to be treated separately from data from children (<18 year old). Data from non-human studies were excluded.

### 2.3. Types of interventions

Data were included from experimental studies that aimed to manipulate SH. Studies that manipulated SH as 1 step in a larger study were considered eligible only if suitable baseline/control data were available to estimate the effect of the manipulation. Studies comparing manipulations to active placebos (rather than true shams) were excluded.

### 2.4. Types of outcome measures

#### 2.4.1. Primary outcome

As designated in the locked study protocol, the primary outcome was the magnitude of mechanical SH—specifically, a change in rating to mechanical punctate stimulation inside the area of SH surrounding the induction site from pre-manipulation levels. Secondary hypersensitivity assessed by other modalities was outside the scope of this review. Studies had to have provided a control for the manipulation. For example, ratings of mechanical punctate stimulation before and after manipulation (within-subject comparison) or ratings of mechanical punctate stimulation after 1 group received the manipulation and the other a sham (between-group comparison).

#### 2.4.2. Secondary outcome

We also extracted data on 3 other outcomes. These were (1) surface area of SH, as measured using reproducible methods (such as a radial lines approach)[1,34,136]; (2) time course of SH; and (3) adverse effects of the manipulation.

### 2.5. Screening

#### 2.5.1. Electronic searches

The following electronic databases were searched (on June 24, 2019, updated on February 7, 2024) with a strategy that spanned the time from their inception to the date of the search: Biosis (via Web of Science), PubMed (includes MEDLINE), Scopus, PsycARTICLES, PsycINFO, Cochrane library, Web of Science Core (search strategy in Supplementary file, http://links.lww.com/PAIN/C239).

#### 2.5.2. Other sources

Reference lists of eligible studies were screened for eligible studies that may have been missed by the electronic searches. Experts in the field and the corresponding authors of the most

recent narrative reviews on experimental induction and manipulation of SH were contacted to identify any missed studies.

### 2.6. Data collection and analysis

#### 2.6.1. Data management

Covidence (https://covidence.org/) online software and Microsoft Excel were used to manage the review process. Data were pooled and forest plots were generated using R (version 4.2.1), packages: tidyverse,[126] dplyr,[128] magrittr,[73] readxl,[127] meta,[5] metafor,[113] and estmeansd[68] in RStudio.[94]

#### 2.6.2. Study selection

Identified records were independently screened for eligibility by 2 of 3 reviewers (G.J.B., P.C.C., and L.M.) in 2 sequential stages: screening of title and abstracts (stage 1) and screening of full texts (stage 2). A customised eligibility form (Supplementary file, http://links.lww.com/PAIN/C239) was used in stage 2. Any disagreements about study inclusion were resolved by discussion or by adjudication from a fourth reviewer (V.J.M.).

#### 2.6.3. Risk of bias analysis

Risk of bias assessments were independently conducted by 2 of 3 reviewers (G.J.B., L.M., and P.M.) to assess the quality of the methods and identify potential flaws in the study design or reporting that might render the results unreliable to answer the question of the current review.[62] The assessment considered the risks of selection, determining sample size, performance, detection, attrition, measurement, and reporting bias. The criteria used to estimate the risk of bias were based on recommendations from the Cochrane collaboration,[35] known quality instruments (eg, the CONSORT[74] and STROBE[111] statements as relevant), and known areas of bias relevant to the study designs used[95] and were specified in the risk of bias assessment tool and guide (Supplementary file, http://links.lww.com/PAIN/C239). The reviewers piloted the risk of bias assessment form on 3 studies and adapted it before formal application to all included studies. The appraisals of the 3 reviewers were compared, and any disagreements were resolved through discussion or by adjudication from a fourth reviewer (V.J.M.).

#### 2.6.4. Data extraction

Data were extracted independently from each included study by 2 reviewers (G.J.B. and L.M.) using a standardised form (Supplementary file, http://links.lww.com/PAIN/C239). The reviewers piloted the data extraction on 5 studies and adapted it before extracting data from all included studies. Study authors were contacted to obtain data that were unavailable or unclear from the published texts. If no relevant data were received within 6 weeks, the data were considered unavailable. Any published data that seemed implausible were verified directly with the corresponding author where possible.

#### 2.6.5. Data analysis

Data were analysed to (1) determine the effect of each manipulation method on magnitude and surface area of SH, (2) pool and compare data where possible and sensible, (3) facilitate relative ranking of manipulations to compare the potency of the various manipulation procedures for influencing SH, and (4) detect publication bias. Data were grouped by outcome (magnitude vs surface area of SH) and then by manipulation drug class. We interpreted data for each outcome separately and did not weigh magnitude more heavily than area. If the quantity and quality of data allowed, the pooled effect size estimates were compared to rank the different manipulations in order of potency and risk. We generated and visually inspected funnel plots with random effects and conducted Begg test[9] to assess for publication bias in each manipulation drug class that had 10 or more datasets available for meta-analytical pooling[106] for each outcome: magnitude or surface area of SH.

#### 2.6.6. Rescaling of rating scales

To allow for descriptive comparison across ratings data, all ratings from 0 to 10 rating scales were rescaled to 0 to 100, by multiplying by 10. Ratings data from studies that used alternative scales were managed separately.

#### 2.6.7. Pooling of data and measures of manipulation effect

Across the eligible studies, magnitude and surface area of SH had been assessed at different times after the induction. It was not possible to determine the time of peak effect of each manipulation, but it was possible to use control data to determine the time point of peak effect of each induction. Therefore, we extracted data for the time point at which the control group/condition showed the highest ratings to mechanical punctate stimulation or greatest surface area of SH.

We used the mean, standard deviation (SD), and sample size to calculate the standardised mean difference (SMD), as recommended for continuous data where different scales have been used.[37] In anticipation of heterogeneity between studies, we used a random effects model, which weighs studies by variance and heterogeneity. When studies did not provide data as mean and SD, we converted alternative measures of central tendency and spread as per the guidelines in the Cochrane Handbook. Data from each manipulation drug class were pooled if there were 3 or more datasets with data available for pooling. We pooled studies that reported data as between-group comparisons separately from those that reported data as changes-from-baseline.[37] In accordance with the methodology proposed in the Cochrane Handbook,[102] we followed a three-step approach to interpret the pooled effect estimate (ie, SMD) and 95% CIs of the random effects models. First, to judge whether the pooled results suggested a difference in effect between the active and sham manipulations, we identified whether the 95% CI for the pooled effect estimate included zero. The 95% CI crossing zero would indicate that the distribution of the effects of the pooled studies is consistent with the null hypothesis of no difference in effect between active and sham manipulations. Second, in cases where the 95% CI did not include zero, we interpreted the size of the pooled effect point estimate using Cohen interpretation, where 0.2 represents a small effect, 0.5 represents a moderate effect, and 0.8 represents a large effect. Third, we used the width of the 95% CI to gauge the precision of the estimate. A wider 95% CI provided lower confidence in the precision of the effect estimate.

#### 2.6.8. Assessment of the quality of body of evidence

The quality of the body of evidence for each outcome was assessed using the GRADE criteria[32] and the GRADEpro GDT software (www.gradepro.org). The assessment judges (1) risk of bias, (2) directness, (3) consistency of results across studies, and (4) reporting precision into categories of the evidence having "no," "serious," or "very serious" limitations (for details see Schünemann, Higgins).[101]

## 3. Results

### 3.1. Results of search

The literature search included records up to February 7, 2024. A total of 3197 records investigating non-pharmacological *or* pharmacological manipulations were included in title/abstract screening. Thereafter, 270 articles went to full-text screening. Of these, 142 records were eligible for inclusion. Of the 142 records eligible for inclusion, 25 reported on nonpharmacological manipulations and, therefore, are reported elsewhere[8]; the remaining 117 records reported on pharmacological manipulations and are reviewed here.

Sixty-one of 117 records yielded more than 1 eligible dataset. Therefore, the total number of datasets included in this review was 222. A PRISMA flow diagram (**Fig. 1**) summarises the inclusion process.

#### 3.1.1. Types of studies

Table S1, http://links.lww.com/PAIN/C256 summarises the characteristics of the eligible datasets. The study designs included crossover (n = 183), within-subject (without crossover) (n = 25), and between-group comparisons (n = 14).

#### 3.1.2. Participants

The 222 eligible datasets included 4028 participants (3097 males, 821 females, 110 sex not reported), all of whom were adults (≥18 years old). Many of these participants were reused across datasets. It was not possible to accurately report the number of unique participants as many datasets did not report whether new or the same participants were used across multiple datasets. Participant ages are shown by dataset in Table S1, http://links.lww.com/PAIN/C256.

#### 3.1.3. Types of interventions

Table S2, http://links.lww.com/PAIN/C257 lists the induction and manipulation methods by dataset and the effects of the manipulations on magnitude and area of SH. Across the 222 datasets, 13 different methods were used to induce SH. The most commonly used inductions were contact burn injury (n = 52), intradermal capsaicin injection (n = 50), and intradermal electrical stimulation (n = 47).

Across the 222 datasets, 23 different drug classes were used to manipulate the magnitude and/or area of the experimentally induced SH. The most commonly used manipulations were opioid receptor agonist (n = 45 datasets), NMDA receptor antagonist (n = 40), voltage-gated sodium channel blocker (n = 28), alpha-2-delta subunit of voltage-gated calcium channel ligands (n = 21), cyclooxygenase-1 and/or -2 enzyme inhibitor (n = 18), and opioid receptor antagonist (n = 9). Eighteen (of 222 datasets) used a combination of drug classes (eg, opioid receptor agonist *and* NMDA receptor antagonist). Given the heterogeneity among the studies with respect to the dosages and mode of administration of the manipulations, we were unable to meaningfully rank manipulations by the potency of effect on induced SH.

#### 3.1.4. Outcome measures

Nine (of 222) datasets assessed only the magnitude of SH. One hundred seventy-five (of 222) datasets assessed only the surface area SH. Thirty-eight (of 222) datasets assessed *both* the

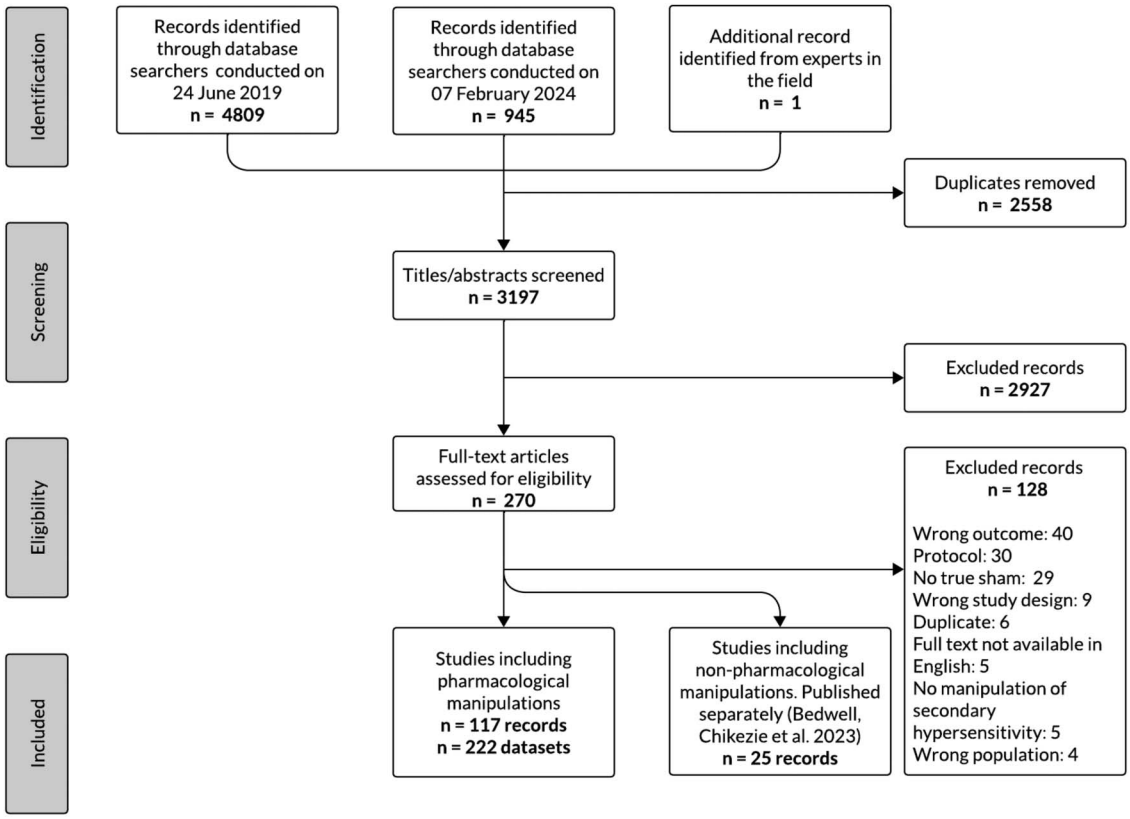


**Figure 1.** PRISMA flow diagram. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

magnitude and surface area of SH. Not 1 (of 222) dataset assessed the time course of induced SH. One hundred sixteen (of 222) datasets assessed adverse effects from the manipulations.

### 3.2. Risk of bias

Tables S3 and S4, http://links.lww.com/PAIN/C258, http://links.lww.com/PAIN/C259 summarise the risk of bias results. Overall, most studies were judged to have unclear risk of bias in 4 domains: selection, determining sample size, performance, and detection bias for not reporting sufficient information on (1) screening of participants; (2) methods used for determining sample size; (3) assessing the effectiveness of the blinding procedure for participants; and (4) assessing whether the outcome assessor was blinded to the research question and/or whether the data analyst was blinded to group/site allocation of participants. Most studies were judged to have a low risk of bias in the remaining 4 domains: veracity of manipulation, attrition, measurement, and reporting bias for reporting sufficient information on (1) the dosage of the pharmacological manipulation; (2) withdrawals, or clearly and appropriately managing withdrawals in their statistical analysis; (3) the method for valid measurements of magnitude and/or surface area of SH; and (4) all outcome measures, conflicts of interests, and funding sources.

### 3.3. Primary outcome

#### 3.3.1. The effects of manipulations on the magnitude of secondary hypersensitivity (n = 47)

Forty-seven of 222 datasets assessed the effect of a manipulation on the magnitude of experimentally induced SH, as indicated by ratings to mechanical punctate stimulation. All 47 datasets used manipulations with a single mechanism of action (eg, an opioid receptor agonist). All the manipulations were expected to decrease the magnitude of SH. The largest bodies of evidence grouped by manipulations were NMDA receptor antagonists (n = 13 datasets), alpha-2-delta subunit of voltage-gated calcium channel ligands (n = 8 datasets), voltage-gated sodium channel blockers (n = 6 datasets), and opioid receptor agonists (n = 6 datasets). The remaining manipulations with smaller bodies of evidence are reported in Supplementary file: Section 7, http://links.lww.com/PAIN/C239. **Figure 2** shows the narrative synthesis of the effect of manipulations on the magnitude of experimentally induced SH. Data were available for pooling from datasets using (1) NMDA receptor antagonists (5 of 13 datasets), (2) alpha-2-delta subunit of voltage-gated calcium channel ligands (5 of 8 datasets), and (3) voltage-gated sodium channel blockers (4 of 6 datasets). Data were not available for pooling for opioid receptor agonists. Publication bias and assessment of the quality of evidence (GRADE) are reported in Supplementary file: Section 7.4, http://links.lww.com/PAIN/C239.

#### 3.3.2. Do N-methyl-D-aspartate receptor antagonists decrease the magnitude of secondary hypersensitivity? (n = 13)

Thirteen datasets used an NMDA receptor antagonist anticipated to decrease the magnitude of SH: ketamine (n = 11), neramexane (n = 1), and flupirtine (n = 1). Of these 13 datasets, 10 induced SH using intradermal capsaicin injection[27] [dataset 2,[28] dataset 1,[29] dataset 1,[45] datasets 1 and 2,[52] datasets 1 and 2,[77] datasets 1 and 2[88]], 2 used contact burn injury[81] [datasets 1 and 2], and the remaining 1 used transcutaneous electrical stimulation.[46] Ten (of 13) datasets administered a single dose of ketamine (n = 4 subcutaneous[27] [dataset 2,[28] dataset 1,[81] datasets 1 and 2]; n = 2 intradermal[51] [datasets 1 and 2]; n = 1 intravenous[46]; and n = 1 topical[88]) or a single oral dose of either neramexane[45] [dataset 1] or flupirtine[45] [dataset 2]. The remaining 3 datasets administered multiple intravenous doses of ketamine[29] [dataset 1,[77] datasets 1 and 2]. Of the 13 datasets that used NMDA receptor antagonists, 3 found a decrease in the magnitude of experimentally induced SH; 10 found no effect (**Fig. 2**).

Five of the 13 datasets that used an NMDA receptor antagonist were available for pooling. All 5 datasets administered ketamine and reported magnitude data as between-condition comparisons. The pooled SMD point estimate [95% CI] was −0.42 [−1.23; 0.39]; $I^2$ = 50% (**Fig. 3**), the 95% CI, therefore, includes the null hypothesis of no difference in effect between ketamine and the sham manipulations.

#### 3.3.3. Do alpha-2-delta subunit of voltage-gated calcium channel ligands decrease the magnitude of secondary hypersensitivity? (n = 8)

Eight datasets used an alpha-2-delta subunit of voltage-gated calcium channel (VGCC) ligands anticipated to decrease the magnitude of SH: pregabalin (n = 4) or gabapentin (n = 4). Of these 8 datasets, 5 induced SH using intradermal capsaicin injection[30,61,117,118] [dataset 1[130]], 2 used topical capsaicin[18,119] [dataset 1], and 1 used a contact burn injury.[124] Six (of 8) datasets administered a single oral dose of either pregabalin[18,61,118] [dataset 1][130] or gabapentin[119,124]; the remaining 2 datasets administered multiple oral doses of

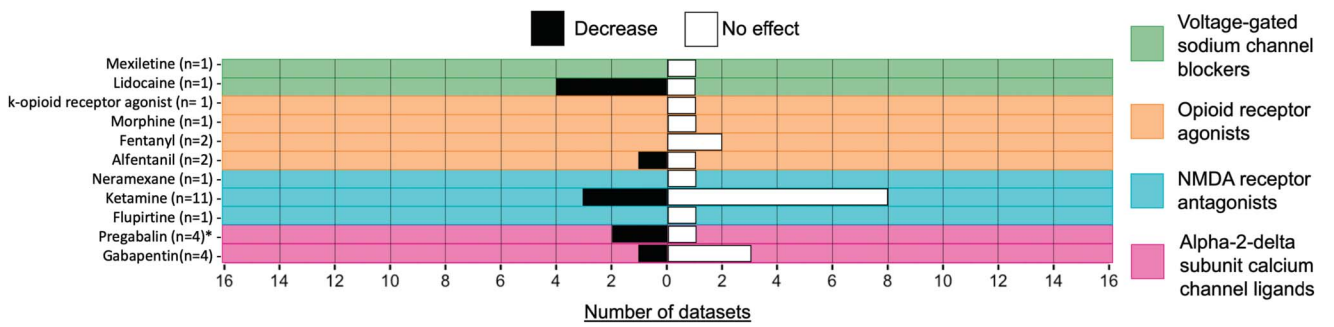


**Figure 2.** Narrative synthesis of the effect of manipulations on the magnitude of secondary hypersensitivity. Manipulations are grouped by mechanism of action. *One (Wong et al. 2014) dataset that used pregabalin did not report on the effect of the pregabalin on the magnitude of seconadary hypersensitivity.

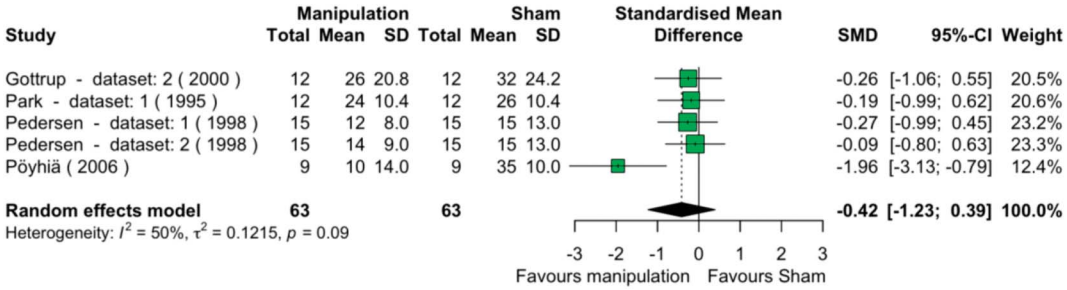


**Figure 3.** Forest plot of the pooled estimated effect size of an NMDA receptor antagonist—ketamine—on the magnitude of secondary hypersensitivity from datasets that reported magnitude data as between-condition comparisons. NMDA, N-methyl-D-aspartate.

gabapentin.[30,117] Of the 8 datasets that used an alpha-2-delta subunit of VGCC ligands, 3 found a decrease in the magnitude of experimentally induced SH; 4 found no effect (**Fig. 2**) and 1 did not report their results.[130]

Five of the 8 datasets that used an alpha-2-delta subunit of VGCC ligands were available for pooling. These 5 datasets administered pregabalin (n = 3) and gabapentin (n = 2) and reported magnitude data as between-condition comparisons. The pooled SMD point estimate [95% CI] was −0.24 [−0.39; −0.08]; $I^2$ = 0% (**Fig. 4**), the 95% CI, therefore, excludes the null hypothesis of no effect. The small, negative pooled effect point estimate, and the range of its plausible values, which range from a very small to a moderately sized effect, suggest that alpha-2-delta subunit of VGCC ligands reduced magnitude of SH relative to the sham manipulations.

### *3.3.4. Do voltage-gated sodium channel blockers decrease the magnitude of secondary hypersensitivity? (n = 6)*

Six datasets used a voltage-gated sodium channel (VGSC) blocker anticipated to decrease the magnitude of SH: lidocaine (n = 5) or mexiletine (n = 1). Five induced SH using intradermal capsaicin injection; 1 used ultraviolet burn injury[31] [dataset 2]. Three (of 6) datasets administered a single dose of either subcutaneous[27] [dataset 1],[28] [dataset 2] or intravenous lidocaine[29] [dataset 2]. Three datasets administered multiple doses of either topical lidocaine[31] [datasets 1 and 2] or oral mexiletine.[2] Of the 6 datasets that used a VGSC blocker, 4 (all lidocaine) found a decrease in the magnitude of SH, while 2 found no effect (**Fig. 2**).

Four of the 6 datasets that used a VGSC blocker were available for pooling. These 4 datasets administered lidocaine (n = 3) and mexiletine (n = 1) and reported magnitude data as between-condition comparisons. The pooled SMD point estimate [95% CI] was −0.39 [−0.88; 0.10]; $I^2$ = 0% (**Fig. 5**), the 95% CI, therefore, includes the null hypothesis of no difference in effect between VGSC blockers and the sham manipulations.

### *3.3.5. Do opioid receptor agonists decrease the magnitude of secondary hypersensitivity? (n = 6)*

Seven datasets used an opioid receptor agonist anticipated to decrease the magnitude of SH: fentanyl (n = 2), alfentanil (n = 2), a peripherally acting selective κ-opioid receptor agonist (n = 1), and morphine (n = 1). Of these 6 datasets, 5 induced SH using intradermal capsaicin injection[52] [datasets 3 and 4,[77] datasets 3 and 4,[118] dataset 2] and 1 used a burn injury[10] [dataset 2]. Three (of 6) datasets administered a single dose of either intradermal fentanyl[52] [datasets 3 and 4] or intravenous morphine[118] [dataset 2]. Three (of 6) datasets administered multiple doses of either intravenous alfentanil[77] [datasets 3 and 4] or oral peripherally acting κ-opioid receptor agonist[10] [dataset 2]. Of the 6 datasets that used opioid receptor agonists, only 1 found a decrease in the magnitude of experimentally induced SH; 5 found no effect (**Fig. 2**).

In summary, while the pooled point estimates provided evidence that NMDA receptor antagonists and VGSC blockers affect magnitude of SH more than the sham manipulations, the 95% CIs also indicated that the data were consistent with the null hypothesis of no difference in effect between the interventions and the sham manipulations. Alpha-2-delta subunit of VGCC ligands reduce magnitude of SH by a small amount relative to the sham manipulations. From the narrative analysis, the majority of datasets (5 of 6) using opioid receptor agonists indicated no effect; data were unavailable for pooling.

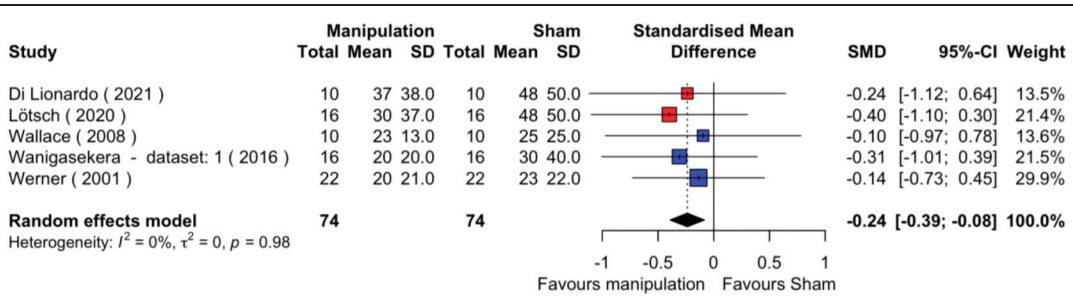


**Figure 4.** Forest plot of the pooled estimated effect size of alpha-2-delta subunit of voltage-gated calcium channel ligands on the magnitude of secondary hypersensitivity from datasets that reported magnitude data as between-condition comparisons. Gabapentin = blue; pregabalin = red.

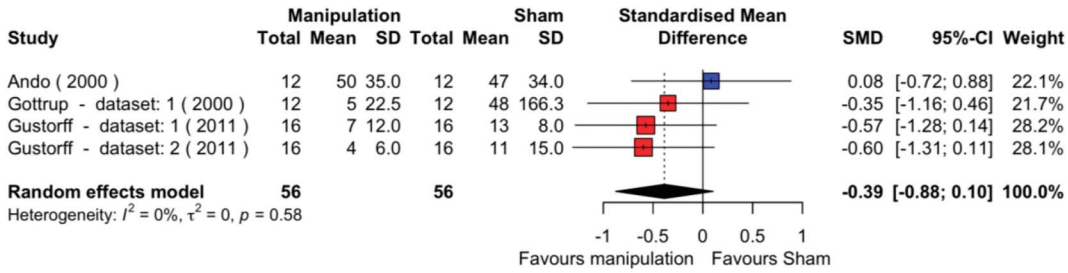


**Figure 5.** Forest plot of the pooled estimated effect size of voltage-gated sodium channel blockers on the magnitude of secondary hypersensitivity from datasets that reported magnitude data as between-condition comparisons. Mexiletine = blue; lidocaine = red.

### *3.4. Secondary outcome*

#### *3.4.1. The effects of manipulations on the surface area of secondary hypersensitivity (n = 213)*

Two hundred thirteen datasets assessed the effect of a manipulation on the surface area of experimentally induced SH. One hundred ninety-five (of 213) datasets used manipulations with a single mechanism of action (eg, opioid receptor agonist). Most (186 of 195) manipulations were expected to decrease the surface area of SH. The remaining 9 were expected to *increase* the surface area of SH. The largest bodies of evidence grouped by manipulations were NMDA receptor antagonists (n = 37 datasets), alpha-2-delta subunit of VGCC ligands (n = 19 datasets), VGSC (n = 28 datasets), and opioid receptor agonists (n = 44 datasets). The remaining manipulations with smaller bodies of evidence are reported in Supplementary file: Section 8, http://links.lww.com/PAIN/C239. The 9 datasets with manipulations expected to increase the surface area of SH were all opioid receptor antagonists (Supplementary file, http://links.lww.com/PAIN/C239).

Eighteen of 213 datasets used manipulations with a combination of mechanisms of action (eg, opioid receptor agonist *and* NMDA receptor antagonist). All these manipulations were expected to decrease the surface area of SH and are reported in Supplementary file: Section 8, http://links.lww.com/PAIN/C239.

**Figure 6** shows the narrative synthesis of the effect of manipulations on the surface area of experimentally induced SH. Data were available for pooling from datasets using (1) NMDA receptor antagonists (26 of 37 datasets), (2) alpha-2-delta subunit of VGCC ligands (11 of 19 datasets), (3) VGSC blockers (18 of 28 datasets), and (4) opioid receptor agonists (28 of 44 datasets). Publication bias and assessment of the quality of evidence (GRADE) are reported in Supplementary file: Section 8.14, http://links.lww.com/PAIN/C239.

#### *3.4.2. Do N-methyl-D-aspartate receptor antagonists decrease the surface area of secondary hypersensitivity? (n = 37)*

Thirty-eight datasets used a NMDA receptor antagonist anticipated to decrease the surface area of SH: ketamine (n = 27), dextromethorphan (n = 7), CHF3381 (n = 2), or magnesium sulphate (n = 1). Of these 37 datasets, 13 induced SH using a burn injury[40] [datasets 1 and 2,[41] datasets 1 and 2,[71] dataset 1,[72] datasets 1 and 2,[81] datasets 1 and 2,[100] dataset 2,[120] dataset 1,[121] dataset 1,[122] dataset 2], 8 used intradermal capsaicin injection[27] [dataset 2,[28] dataset 1,[29] dataset 1,[52] datasets 1 and 2,[77] datasets 1 and 2[88]], 8 used brief thermal stimulation[21] [dataset 2,[40] datasets 3 and 4,[41] datasets 3 and 4,[67] dataset 2,[72] datasets 3 and 4], 3 used intradermal electrical stimulation[4] [dataset 1,[48] dataset 1,[51] dataset 1], 3 used topical capsaicin and heat[21] [dataset 1,[67] dataset 1,[70]], 1 used topical capsaicin,[1] and 1 used a freeze injury.[66] Of the 37 datasets, 17 administered a single dose of ketamine (n = 5 intravenous[1,48] [dataset 1,[51] dataset 1,[100] dataset 2,[122] dataset 2]; n = 5 subcutaneous[27]

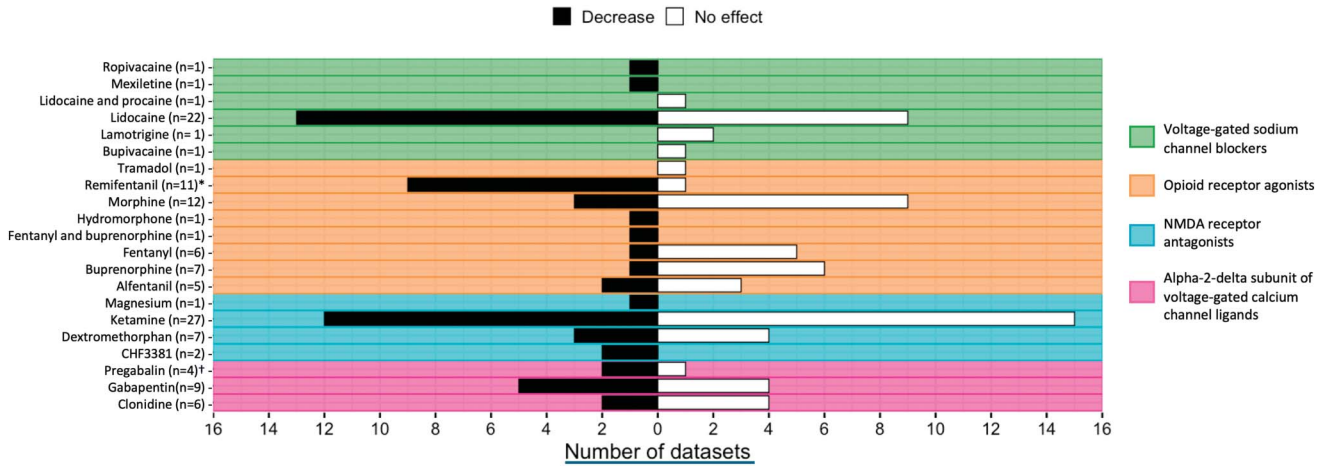


**Figure 6.** Narrative synthesis of the effect of manipulations on the surface area of secondary hypersensitivity. Manipulations are grouped by mechanisms of action. *One (Angst et al. 2003) dataset that used remifentanil found an *increase* in the surface area of secondary hyperalgesia. †One (Wong et al. 2014) dataset that used pregabalin did not report on the effect of the pregabalin on the surface area of seconadary hypersensitivity.

[dataset 2,[28] dataset 1,[81] datasets 1 and 2,[120] dataset 1]; n = 4 oral[72] [datasets 1, 2, 3, and 4]; n = 2 intradermal[52] [datasets 1 and 2]; and topical n = 1).[88] Ten (of 37) administered multiple doses of intravenous ketamine[4] [dataset 1,[29] dataset 1,[41] datasets 1, 2, 3, and 4,[71] dataset 1,[77] datasets 1 and 2,[121] dataset 1]. Six (of 37) administered a single dose of dextromethorphan (n = 4 oral[40] [datasets 1, 2, 3, and 4]; n = 2 intravenous[21] [datasets 1 and 2]), and 1 (of 37) administered multiple oral doses of dextromethorphan.[66] Two (of 37) administered a single oral dose of CHF3381[67] [datasets 1 and 2] and 1 (of 37) administered multiple intravenous doses of magnesium sulphate.[70] Of the 37 datasets that used NMDA receptor antagonists, 18 found a decrease in the surface area of experimentally induced SH; 19 found no effect (**Fig. 6**).

Twenty-six of the 37 datasets that used an NMDA receptor antagonist were available for pooling. Nineteen (of 26) reported surface area data as between-condition comparisons. The pooled SMD point estimate [95% CI] was −0.36 [−0.55; −0.17]; $I^2$ = 30% (**Fig. 7**), the 95% CI, therefore, excludes the null hypothesis of no effect. The small-to-moderate, negative pooled effect point estimate, and the range of its plausible values, which range from a small to a moderately sized effect, suggest that NMDA receptor antagonists reduced surface area of SH relative to the sham manipulations. Seven (of 29) reported surface area data as change-from-baseline comparisons. The pooled SMD point estimate [95% CI] was −0.90 [−1.60; −0.20]; $I^2$ = 73% (**Fig. 8**), the 95% CI, therefore, excludes the null hypothesis of no effect. The large, negative pooled effect point estimate, and the range of its plausible values, which range from a small to a very large effect, suggest that NMDA receptor antagonists reduced suface area of SH relative to the sham manipulations. However, the wide CI suggests imprecision of the effect estimate.

### *3.4.3. Do alpha-2-delta subunit of voltage-gated calcium channel ligands decrease the surface area of secondary hypersensitivity? (n = 19)*

Nineteen datasets used an alpha-2-delta subunit of VGCC ligands anticipated to decrease the surface area of SH: gabapentin (n = 9), or clonidine (n = 6), pregabalin (n = 4). Of these 19 datasets, 10 induced SH using intradermal capsaicin injection[22,23] [datasets 1, 2, 3, and 4,[30] dataset 1,[61,117,118] dataset 1[130]], 3 brief thermal stimulation[20] [dataset 2,[67] dataset 4,[84] dataset 2], 3 used intradermal electrical stimulation[11] [dataset 1,[15] dataset 1,[51] dataset 4], 2 used topical capsaicin and heat[20] [dataset 1,[67] dataset 3], and 1 used contact burn injury.[124] Of the 19 datasets, 5 administered a single oral dose[20] [datasets 1 and 2,[67] datasets 3 and 4,[124]] and 4 administered multiple oral doses[11] [dataset 1,[30,84] dataset 2,[117]] of gabapentin. Three (of 16) administered a single oral dose[61,118] [dataset 1[130]] and 1 administered multiple oral doses of pregabalin[14] [dataset 1].

Three administered a single intravenous dose of clonidine[23] [datasets 3 and 4,[51] dataset 4], 2 administered single intrathecal dose of clonidine[23] [datasets 1 and 2], and 1 administered a single intrathecal or epidural dose of clonidine.[22] Of the 19 datasets that used an alpha-2-delta subunit of VGCC ligands, 9 found a decrease in the surface area of experimentally induced SH; 9 found no effect (**Fig. 6**). One dataset did not report the effect.[130]

Eleven of the 19 datasets that used an alpha-2-delta subunit of VGCC ligands were available for pooling. All 11 reported surface area data as between-condition comparisons. The pooled SMD point estimate [95% CI] was −0.38 [−0.59; −0.18]; $I^2$ = 0% (**Fig. 9**), the 95% CI, therefore, excludes the null hypothesis of no effect. The small-to-moderate, negative pooled effect point estimate, and the range of its plausible values, which range from a small to a moderately sized effect, suggest that alpha-2-delta subunit of VGCC ligands reduced SH surface area relative to the sham manipulations.

### *3.4.4. Do voltage-gated sodium channel blockers decrease the surface area of secondary hypersensitivity? (n = 28)*

Twenty-eight datasets used a VGSC blocker anticipated to decrease the surface area of SH: lidocaine (n = 22), lamotrigine (n = 2), combination lidocaine and procaine (n = 1), bupivacaine (n = 1), mexiletine (n = 1), or ropivacaine (n = 1). Of these 28

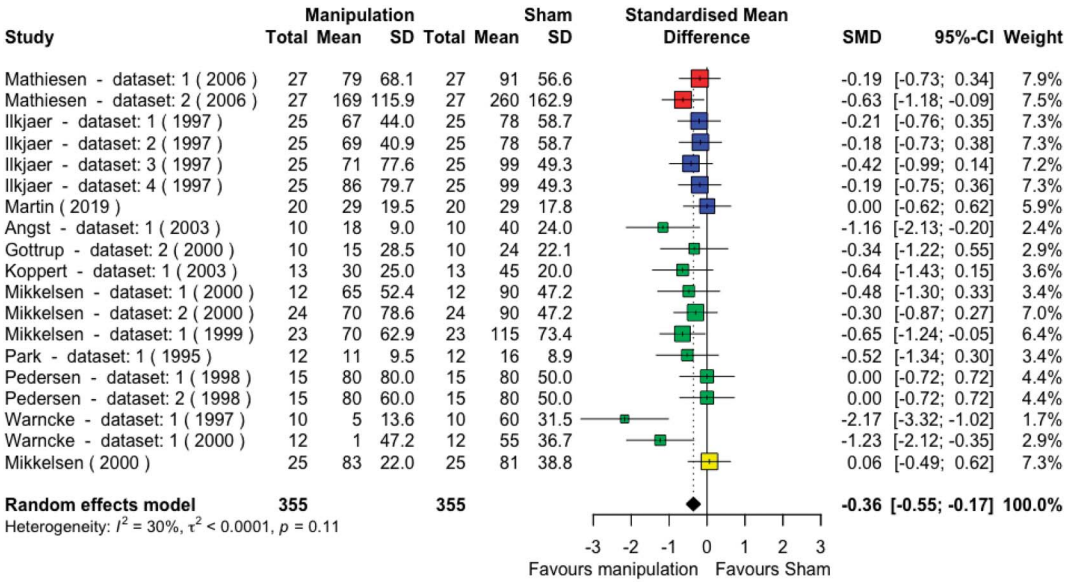


**Figure 7.** Forest plot of the pooled effect estimated of an NMDA receptor antagonist on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-condition comparisons. Red = CHF3381, blue = dextromethorphan, green = ketamine, yellow = magnesium sulphate. NMDA, N-methyl-D-aspartate.

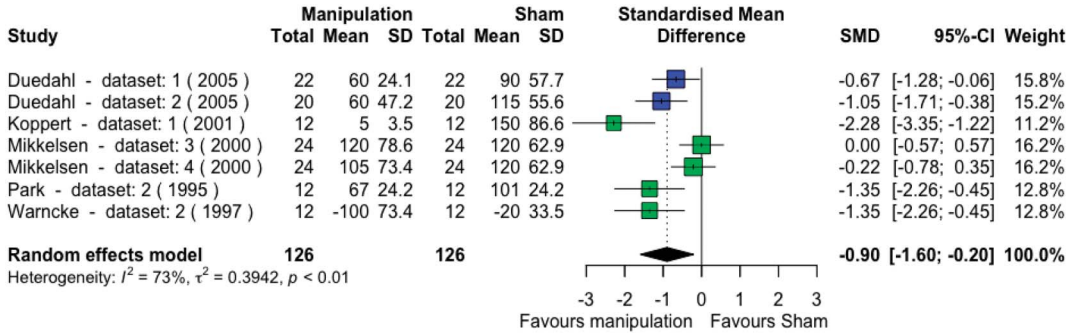


**Figure 8.** Forest plot of the pooled effect estimated of an NMDA receptor antagonist on the surface area of secondary hypersensitivity from datasets that reported surface area data as change-from-baseline comparisons. Blue = dextromethorphan, green = ketamine. NMDA, N-methyl-D-aspartate.

datasets, 9 induced SH using intradermal capsaicin injection[2,27] [dataset 1,[28] dataset 2,[29] dataset 2,[31] dataset 1,[50] datasets 1 and 2[57,116]], 6 used an incision injury[43] [datasets 1 and 2,[44] datasets 1, 2, 3, and 4], 6 used contact burn injury[38] [datasets 1 and 2,[79,80,83,120] dataset 2], 3 used topical capsaicin and heat[19,86] [datasets 1 and 2], 2 used ultraviolet burn injury[31] [dataset 2],[93] and 2 used intradermal electrical stimulation[33,48] [dataset 3].

Of these 28 datasets, 13 administered a single dose of lidocaine (n = 5 intravenous[29] [dataset 2,[38] datasets 1 and 2,[48] dataset 3,[50] dataset 2]; n = 5 subcutaneous[27] [dataset 1,[28] dataset 2,[44] datasets 1 and 2,[120] dataset 2]; n = 1 topical[57]; n = 1 intradermal[93]; n = 1 saphenous nerve block).[80] Nine administered multiple doses of lidocaine (n = 5 intravenous[19,43] [datasets 1 and 2,[50] dataset 1,[116]]; n = 2 topical[31] [datasets 1 and 2]; n = 2 subcutaneous[44] [datasets 3 and 4]) 5 (of 28) administered a single dose of lamotrigine (n = 2 oral[86] [datasets 1 and 2]), bupivacaine (n = 1 lumbar sympathetic nerve block[83]), ropivacaine (n =1 intravenous[33]), or a combination of lidocaine and procaine (n = 1 topical).[79] The remaining dataset (of 28) administered multiple oral doses of mexiletine.[2] Of the 28 datasets that used VGSC blockers, 15 found a decrease in the surface area of experimentally induced SH; 13 found no effect.

Eighteen of the 28 datasets that used a VGSC blocker were available for pooling. All 18 reported surface area data as between-condition comparisons. The pooled SMD point estimate [95% CI] was −1.02 [−1.63; −0.42]; $I^2$ = 76% (**Fig. 10**), the 95% CI, therefore, excludes the null hypothesis of no effect. The very large, negative pooled effect point estimate, and the range of its plausible values, which range from a moderate to a very large effect, suggest that VGSC blockers reduced surface area of SH relative to the sham manipulations. However, the wide CI suggests imprecision of the effect estimate.

### *3.4.5. Do opioid receptor agonists decrease the surface area of secondary hypersensitivity? (n = 44)*

Fifty datasets used an opioid receptor agonist anticipated to decrease the surface area of SH: morphine (n = 12), remifentanil (n = 11), buprenorphine (n = 7), fentanyl (n = 6), alfentanil (n = 5), hydromorphone (n = 1), tramadol (n = 1), or fentanyl and buprenorphine (n = 1). Of the 44 datasets, 16 seven induced SH using intradermal electrical stimulation[4] [dataset 2,[16,17,25] dataset 2,[47] datasets 1 and 2,[48] dataset 2,[49] datasets 1 and 2,[51] dataset 3,[59] dataset 1,[108] datasets 1, 2, and 3,[109] dataset 1,[123] dataset 2]; 13 used contact burn injury[12] [datasets 1 and 2,[60] datasets 1 and 2,[90] datasets 1, 2, 3, and 4,[99,100] dataset 1,[121] dataset 2,[122] dataset 1,[134]]; 7 used intradermal capsaicin injection[3] [datasets 3 and 4,[52] datasets 3 and 4,[77] datasets 3 and 4,[118] dataset 2]; 4 used topical capsaicin and heat[39,85,86] [datasets 3 and 4]; 2 used ultraviolet burn injury[3] [datasets 1 and 2]; and 2 used brief thermal stimulation[12] [datasets 3 and 4].

Of the 44 datasets, 11 administered a single dose of morphine (n = 5 intravenous[90] [datasets 1 and 2,[100] dataset 1,[118] dataset 2,[122] dataset 1]; n = 4 epidural[12] [datasets 1, 2, 3, and 4]; n = 2 subcutaneous[60] [datasets 1 and 2]) and 1 administered multiple intravenous doses of morphine[121] [dataset 2]. Ten datasets administered a single intravenous dose of remifentanil[16,17,39,47] [datasets 1 and 2,[51] dataset 3,[59] dataset 1,[85,86] dataset 4,[109]

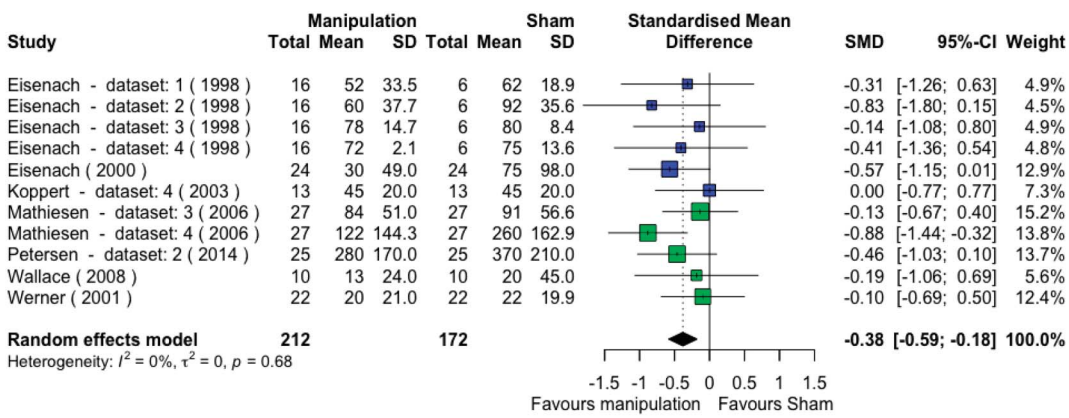


**Figure 9.** Forest plot of the pooled effect estimated of an alpha-2-delta subunit of voltage-gated calcium channel ligand on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons. Blue = clonidine, green = gabapentin.

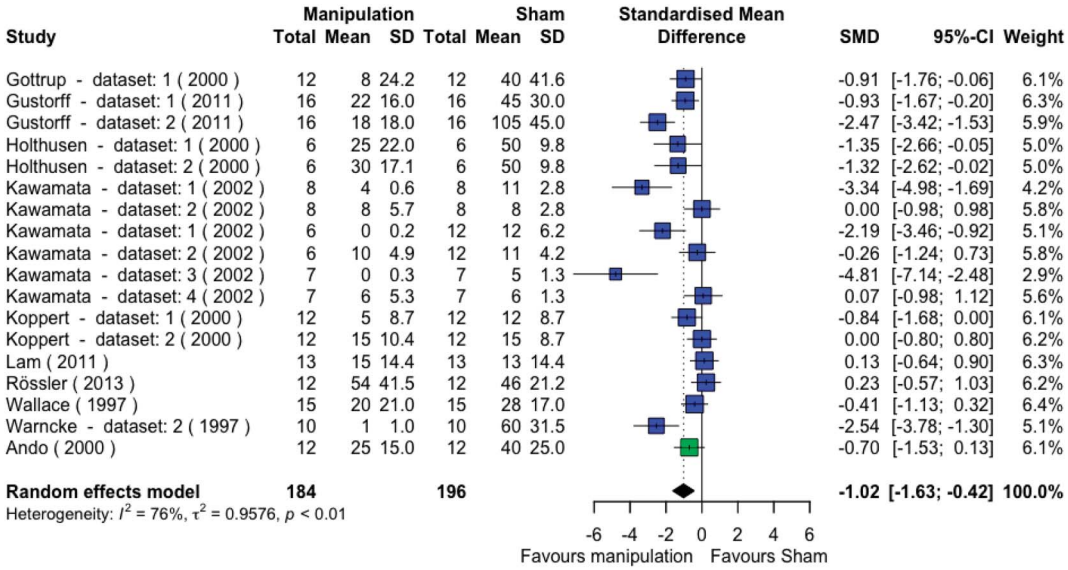


**Figure 10.** Forest plot of the pooled effect estimated of a voltage-gated sodium channel blocker on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons. Blue = lidocaine, green = mexiletine.

dataset 1] and 1 administered multiple intravenous doses of remifentanil[4] [dataset 2]. Seven datasets administered a single dose of buprenorphine (n = 4 intravenous[49] [dataset 1,[90] datasets 3 and 4,[108] dataset 2]; n = 2 topical[3] [datasets 1 and 3]; n = 1 sublingual[49] [dataset 2]). Six administered a single dose of fentanyl (n = 3 topical[3] [datasets 2 and 4,[134]]; n = 2 intradermal[52] [datasets 3 and 4]; and n = 1 intravenous[108] [dataset 1]). Three administered a single intravenous dose[48] [dataset 2,[99,123] dataset 2] of alfentanil and 2 administered multiple intravenous doses[77] [datasets 3 and 4] of alfentanil. The remaining 3 datasets administered a single intravenous dose of tramadol[25] [dataset 2] or a combination of fentanyl and buprenorphine[108] [dataset 3], or an oral dose of hydromorphone[86] [dataset 3]. Of the 44 datasets that used an opioid receptor agonist, 18 found a decrease in the surface area of experimentally induced SH; 25 found no effect and 1 found an unexpected increase.[16]

Twenty-eight of the 44 datasets that used an opioid receptor agonist were available for pooling. Twenty (of 28) reported surface area data as between-condition comparisons. The pooled SMD point estimate [95% CI] was −0.43 [−1.13; 0.27]; $I^2$ = 83% (**Fig. 11**), the 95% CI, therefore, includes the null hypothesis of no difference in effect between opioid receptor agonists and the sham manipulations. Eight (of 28) reported surface area data as change-from-baseline comparisons. The pooled SMD point estimate [95% CI] was −0.61 [−1.15; −0.06]; $I^2$ = 61% (**Fig. 12**), the 95% CI, therefore, excludes the null hypothesis of no effect. The moderate-to-large, negative pooled effect point estimate, and the range of its plausible values, which range from a very small to a very large effect, suggest that opioid receptor agonists reduced surface area of SH relative to the sham manipulations. However, the wide CI suggests imprecision of the effect estimate.

In summary, for NMDA receptor antagonists, the pooled effect estimate suggested that NMDA receptor antagonists reduced the surface area of SH relative to the sham manipulations. While pooling of the between-condition datasets indicated a small-to-moderately sized effect of NMDA receptor antagonists, a precise estimate of effect could not be confidently obtained from pooling of change-from-baseline datasets. For alpha-2-delta subunit of VGCC ligands, the pooled findings suggested alpha-2-delta subunit of VGCC ligands reduced the surface area of SH by a small-to-moderate amount relative to the sham manipulations. For VGSC blockers, the pooled effect estimate also suggested that VGSC blockers reduced the surface area of SH relative to the sham manipulations, but a precise estimate of effect could not be confidently obtained. For opioid receptor agonists, while the pooled effect point estimate for the between-condition comparisons provided evidence that opioid receptor agonists affect surface area of SH more than sham manipulations, the 95% CIs also indicated that the data were consistent with the null hypothesis of no difference in effect between the opioid receptor agonists and the sham manipulations. Conversely, the pooled effect estimate for the change-from-baseline comparisons suggested that opioid receptor agonists reduced the surface area of SH relative to the sham manipulations, but a precise estimate of effect could not be confidently obtained.

#### *3.4.6. Time course of secondary hypersensitivity*

None of the 222 datasets assessed the time course of SH after induction.

#### *3.4.7. Adverse effects associated with the manipulation*

Most datasets that used an NMDA receptor agonist (37 of 37), an alpha-2-delta subunit of VGCC ligand (16 of 16), a VGSC blocker (21 of 28), or an opioid receptor agonist (38 of 44) assessed and reported adverse effects associated with the manipulation (Supplementary file: Table 8, http://links.lww.com/PAIN/C239).

## 4. Discussion

This systematic review and meta-analysis included 117 published reports, with 222 datasets, that administered pharmacological manipulations to influence experimentally induced SH in human participants without clinical pain. The 222 datasets represent data from 4028 participants. We collated and reported the results for magnitude (primary review outcome) and surface area (secondary review outcome) of SH separately.

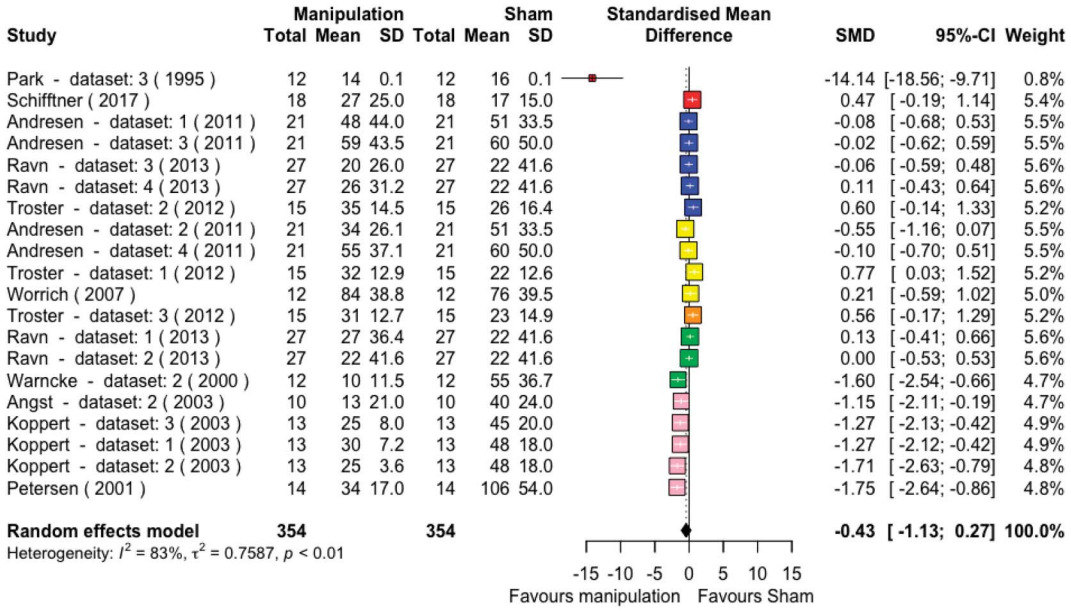


**Figure 11.** Forest plot of the pooled effect estimated of an opioid receptor agonist on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons. Red = alfentanil, blue = buprenorphine, yellow = fentanyl, orange = fentanyl and buprenorphine, green = morphine, pink = remifentanil.

With respect to the magnitude of SH, for alpha-2-delta subunit of VGCC ligands, there were conflicting results between the narrative and meta-analytical syntheses. Specifically, alpha-2-delta subunit of VGCC ligands decreased magnitude in only 3 of 8 datasets, yet the pooled effect estimate of −0.24 [95% CI −0.39; −0.08] from 5 datasets indicated alpha-2-delta subunit of VGCC ligands reduced magnitude of SH by a small amount relative to the sham manipulations. Conversely, there was agreement between the syntheses for NMDA receptor antagonists and VGSC blockers: neither drug class definitively outperformed the sham manipulations. For opioid receptor agonists, the narrative analysis found 5 of 6 datasets showed no effect and data were unavailable for pooling.

With respect to the surface area of SH, for all 3 classes of NMDA receptor antagonists, alpha-2-delta subunit of VGCC ligands, and VGSC blockers, the results of the narrative analysis were conflicting, but meta-analytical synthesis suggested that each of these 3 drug classes reduced the surface area of SH relative to the sham manipulations. For opioid receptor agonists, the pooled effect estimate for the between-condition datasets was consistent with the null hypothesis of no difference in effect between opioid receptor agonists and the sham manipulations, whereas the pooled effect estimate for the change-from-baseline datasets suggested that opioid receptor agonists reduced the surface area of SH relative to the sham manipulations.

In general, the results of this review suggest that surface area of SH may be more responsive to pharmacological manipulation than magnitude of SH. This may reflect different test–retest reliability between the 2 outcomes. The reliability of the surface area outcome is well established as good—including by meta-analysis and across 2 induction methods (meta-analysis intra-class correlation coefficients of 0.69 and 0.74),[125] whereas the reliability of the magnitude outcome seems to be poor (intraclass correlation coefficient = 0.53), although this estimate comes from a single study.[13] The reliability of magnitude may be compromised by relying on scale-based ratings of stimulation events, which are known to have large within-subject variability, even in highly controlled environments.[64,89,92] In contrast, surface area is assessed by participants indicating the point of transition in stimulus percept—effectively, a 2-alternative forced choice. High degrees of freedom, large within-subject variability, and corresponding low reliability may limit power to detect a potential effect of a manipulation on magnitude of SH. Future studies that select magnitude as the most appropriate outcome

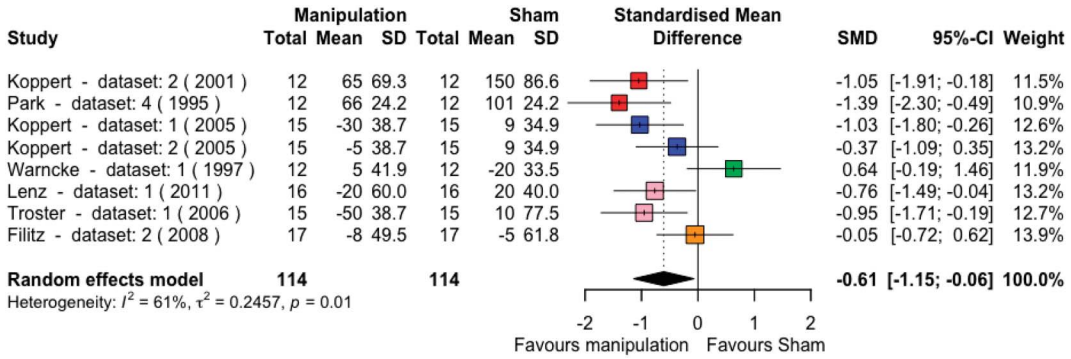


**Figure 12.** Forest plot of the pooled effect estimated of an opioid receptor agonist on the surface area of secondary hypersensitivity from datasets that reported surface area data as change from baseline. Red = alfentanil, blue = buprenorphine, green = morphine, pink = remifentanil, orange = tramadol.

may need to test larger samples or alter other study aspects of design to account for these concerns with the magnitude outcome.

The physiological mechanisms by which NMDA receptor antagonists, alpha-2-delta subunit of VGCC ligands, and VGSC blockers may influence SH are varied and include both neural and immune processes. However, their general mechanistic effect is to reduce hyperexcitability at the dorsal horn of the spinal cord that is assumed to reflect "central sensitisation."[131] In the dorsal horn, NMDA receptor antagonists reduce synaptic hyperexcitability by inhibiting activation of NMDA receptors and the release of substance P at the presynaptic membrane, and inhibiting phosphorylation of NMDA receptors at the postsynaptic membrane. Alpha-2-delta subunit of VGCC ligands inhibit calcium channels and calcium signalling, thus reducing the release of excitatory neurotransmitters.[26,78] Alpha-2-delta subunit of VGCC ligands also act on glial cells to reduce the release of proinflammatory cytokines.[55] Voltage-gated sodium channel blockers are thought to act in both the periphery and the spinal cord. In the periphery, their inhibition of VGSC activity reduces ectopic firing,[26] thus decreasing the barrage of afferent signalling contributing to hyperexcitability at the dorsal horn of the spinal cord. At the spinal cord, they inhibit the release of the excitatory neurotransmitter glutamate,[56,135] thus reducing synaptic hyperexcitability.

The overarching goal of investigating the effects of manipulations on experimentally induced SH is to provide insight to the underlying mechanisms of clinical secondary hyperalgesia, thus informing the development of mechanism-focused treatments. However, 2 caveats are important. First, the different effects of manipulations on magnitude and surface area of SH prompts consideration of their relative clinical relevance, which has not yet been defined. Speculatively, magnitude could relate to the *intensity*, while surface area could relate to the *anatomical spread* of clinical secondary hyperalgesia—but this idea remains to be substantiated. Second, although data exist on the prevalence of secondary hyperalgesia in different pain conditions,[42] there is a lack of data on the *impact* or importance of secondary hyperalgesia in different pain conditions. Understanding patients' experiences with respect to the impact of the intensity and spread of clinical secondary hyperalgesia would direct the focus of future research towards the clinical feature that is the most problematic for patients.

### 4.1. Strengths and limitations of this review

This review used 4 recommended strategies to optimise rigour and clarity[37,76]: we followed a published protocol, reported all deviations from protocol, piloted and refined our risk of bias assessment tool and data extraction tool, and used best-practice duplicate reviewing. However, as in all reviews, the quality of the review findings depends on the quality of the primary data. The 222 datasets presented similar limitations in data quality. First, assessments of selection, performance, and detection bias were limited by poor reporting affecting most datasets (180 and 207 of 222, respectively). Diligent reporting of primary studies would support accurate assessment of risk of bias in future reviews. Second, not all datasets could be included in meta-analysis. Some reports had omitted raw or useable summary data; some manipulation groups included datasets with different and non-comparable control conditions. Across the 4 main classes of manipulations, 12 studies investigated doses–response relationships by including 2 datasets in which they used different dosages of the same manipulation (NMDA receptor antagonists: $n = 5$; opioid receptor agonists: $n = 4$; alpha-2-delta subunit of VGCC ligands: $n = 2$; and VGSC blockers: $n = 1$). Given the heterogeneity among the studies with respect to the dosages and mode of administration of the manipulations, we were unable to meaningfully pool data across studies to assess for a dose–response relationship, but we briefly summarise the conflicting results here. Three (of 12) studies ($n = 1$ for each alpha-2-delta subunit of VGCC ligand, VGSC blocker, and opioid receptor agonist) found that the higher dose of the drug decreased area, whereas the lower dose did not. Two (of 12) studies found that the *lower* dose of dextromethorphan decreased area, whereas the higher dose did not. The remaining seven (of 12) studies ($n = 3$ for NMDA receptor antagonists, $n = 3$ for opioid receptor agonist, and $n = 1$ for alpha-2-delta subunit of VGCC ligands) found no difference in effect between different doses of the same drug. Third, different induction methods were used across the included datasets. We assumed that all these induction models have face validity for modelling the mechanisms of SH, but this was not formally assessed as it was out of the scope of this review. Finally, the designation of magnitude as the primary review outcome (as specified in the protocol) is no longer in keeping with recent evidence that suggests that surface area is a more reliable measure of SH. Even with these limitations, the narrative, graphical, and statistical syntheses presented provide an informative overview of the diverse body of current evidence and provide clear direction for elevating the design and reporting of future studies on this topic. Experiment design and reporting guidelines (eg, STROBE[114] and CONSORT[74]) provide valuable resources for researchers looking to elevate the standard of their work, and diligent application of these documents would improve confidence in study findings.

## 5. Conclusion

Across all the datasets included in this review, the risk of bias assessments revealed problems with reporting that prevented thorough assessment of rigour. With that caveat, with respect to the magnitude of SH, this review found evidence that alpha-2-delta subunit of VGCC ligands can reduce the magnitude of SH by a small amount relative to sham manipulations, and no evidence that NMDA receptor antagonists or VGSC blockers can reduce the magnitude of SH. With respect to the surface area of SH, this review found that NMDA receptor antagonists, alpha-2-delta subunit of VGCC ligands, and VGSC blockers can reduce the surface area of SH relative to sham manipulations. While this effect is small to moderate for VGCC ligands, we are unable to confidently report the size of the effect for NMDA receptor antagonists and VGSC blockers.

Although this review found large bodies of evidence for 5 (of 23) classes of manipulations, 18 classes had been investigated by only 1 or 2 datasets each. Future attention could be directed towards testing the effects of those manipulations for which we have little data, rather than the manipulations for which we have ample data. Our results suggest a need to understand and compare the physiological underpinnings of the magnitude and area of SH. The focus and utility of future research would be supported by clarifying the relative importance of magnitude vs anatomical spread of SH to people living with pain and by improving methodological rigor and reporting. A growing body of high-quality evidence on the effects of manipulations on experimental SH would pave the way for mechanistically motivated and clinically relevant development and testing of treatments for pain that features secondary hyperalgesia.

## Conflict of interest statement

G.J.B. receives speakers' fees for talks on pain and rehabilitation. L.M. has no conflicts of interest relating to this work. R.P. receives speakers' fees for talks on pain and rehabilitation, is a director of the not-for-profit organisation, Train Pain Academy, and serves as a councillor for the International Association for the Study of Pain. P.C.C. has no conflicts of interest relating to this work. P.R.K. is the sole proprietor of Blueprint Analytics and is a consultant for Partners in Research. M.R.H. receives speakers' fees for talks on pain and science policy. A.S.C.R. interests occurring in last 24 months: (1) Officer (President-Elect) of International Association for the Study of Pain. (2) ASCR undertakes consultancy and advisory board work for Imperial College Consultants-in the last 24 months this has included remunerated work for: AstraZeneca, Pharmnovo, Confo and Combigene. (3) Member Joint Committee on Vaccine and Immunisation-varicella subcommittee. (4) Analgesic Clinical Trial Translation: Innovations, Opportunities, and Networks (ACTTION) steering committee member. (5) Medicines and Healthcare products Regulatory Agency (MHRA), Commission on Human Medicines—Neurology, Pain & Psychiatry Expert Advisory Group. (6) Grants and studentships—UKRI (Medical Research Council & BBSRC), Versus Arthritis, Alan and Sheila Diamond Trust, Royal British Legion, European Commission, Ministry of Defence, Dr Jennie Gwynn Bequests, The British Pain Society, Royal Society of Medicine. A.S.C.R. is named as an inventor on patents: (1) Rice A.S.C., Vandevoorde S. and Lambert D.M Methods using N-(2-propenyl) hexadecanamide and related amides to relieve pain. WO 2005/079771. (2) Okuse K. et al. Methods of treating pain by inhibition of vgf activity EP13702262.0/WO2013 110945. V.J.M. receives speakers' fees for talks on pain and rehabilitation and is an associate director of the not-for-profit organisation, Train Pain Academy.

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## Supplemental digital content

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