**Supplementary files**

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# Supplementary file 1: PRISMA Checklist

| **Section and Topic** | **Item #** | **Checklist item** | **Location where item is reported** |
| --- | --- | --- | --- |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review. | Page 1 |
| **ABSTRACT** | | |  |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. |  |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Page 1 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Pages 2 & 3 |
| **METHODS** | | |  |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Pages 2 & 3 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 3 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Page 3 and supplementary file 3 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 4 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 4 & 5 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Page 4 & 5 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Page 4 & 5 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 4 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Page 5 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Page 5 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Page 5 |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | — |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Page 5 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Pages 5 & 6 |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Pages 5 & 6 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | — |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Pages 5 & 6 |
| **RESULTS** | | |  |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Page 6 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | A PRISMA flow diagram (Fig 1) |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Pages 6 & 7, and Table 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Pages 7 & 8, and Tables 3 & 4 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Pages 9 – 15 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Pages 9 – 15 |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Pages 9 – 15 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Pages 9 – 15 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Pages 9 – 15 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Pages 7 & 8, and Tables 3 & 4 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Supplementary files 7 & 8 |
| **DISCUSSION** | | |  |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Page 16 |
| 23b | Discuss any limitations of the evidence included in the review. | Page 17 |
| 23c | Discuss any limitations of the review processes used. | Page 17 |
| 23d | Discuss implications of the results for practice, policy, and future research. | Page 18 |
| **OTHER INFORMATION** | | |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 2 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 2 |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Supplementary file 2 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 20 |
| Competing interests | 26 | Declare any competing interests of review authors. | Pages 20 & 21 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Page 2 |

# Supplementary file 2: Protocol deviations

|  |  |  |
| --- | --- | --- |
| **Protocol deviation number** | **Section of manuscript** | **Details of protocol deviation** |
| 1 | Types of studies eligible for inclusion. | Our protocol stipulated that studies must have assessed SH within 120 minutes after induction (to avoid missing the expected peak of SH after experimental induction); however, induction models such as ultraviolet burn injuries have a delayed induction of SH of approximately 24 hours[4]. Therefore, we waived this requirement and included studies regardless of assessment timing (protocol deviation 1 of 5). |
| 2 | Screening other sources for eligible studies. | In anticipation of a paucity of literature, the protocol had planned to request unpublished data from laboratories that have published extensively on these techniques. Given the abundance of published studies available, this step was not followed. However, we did request data directly from authors where published records did not provide enough information. |
| 3 | Data management | Originally, the protocol specified the use of the online Systematic Review Facility (http://syrf.org.uk/) to manage the review process. However, given this platform is generally *not* used for human studies, it proved difficult for use in this review, so we switched to the Covidence (<https://covidence.org/>) online software and Microsoft Excel to manage the review process. |
| 4 | Risk of bias analysis | After the protocol had been published, we added sampling determination in the risk of bias assessment tool. |
| 5 | Pooling of data and measures of manipulation effect. | The protocol had anticipated subgrouping of studies into manipulations with localised effects, systemic effects, and time-limited effects to determine the potency of the manipulation methods. However, given the records retrieved and to maximise clarity, we opted to subgroup by the physiological mechanism(s) of action of the manipulation (i.e. drug class)(protocol deviation 5 of 5). We found this approach to better clarify the effects of different physiological processes that may influence SH. |

# Supplementary file 3: Electronic database search strategy

The search strategy was: ((“human\*” OR “women” OR “woman” OR “man” OR “men” OR “participant\*” OR “volunteer\* OR individual\*”) OR “normal skin” OR “healthy skin”) AND (“secondary hyperalgesia” OR “punctate hyperalgesia” OR “pinprick pain” OR “pinprick hyperalgesia” OR “mechanical hyperalgesia” OR “mechanical pain” OR “heat hyperalgesia” OR “neurogenic hyperalgesia”)). All terms were searched for in the title, keywords, or abstract.

# Supplementary file 4: Customised eligibility form

|  |  |  |
| --- | --- | --- |
|  | **Inclusion** | **Exclusion** |
| Participants | Pain-free, healthy humans | Animals OR people with pain |
| Study design | Used an experimental procedure with the aim of inducing secondary hyperalgesia AND manipulation secondary hyperalgesia  (identifiable goal AND site AND induction procedure AND manipulation procedure) | Review (*set aside for cross-checking)*  OR  Not an experimental procedure  OR  No identifiable manipulation procedure |
| Outcomes | Pain or sensitivity to provocation assessed subsequent to induction AND manipulation  Acceptable: pain yes or no, self-report of intensity, quality, pain threshold | Subjective ratings not provided  Unacceptable: facial expression, physical behaviour measurement, or psychophysiology in absence of self-report |
| Include (yes/no) | Tick in *every* box above: include | Tick in *any* box above: exclude | Review (reference lists of reviews were screened for studies that may have been missed by the electronic search. Reviews were not eligible for inclusion in this systematic review.) |

# Supplementary file 5: Risk of bias assessment tool and guide

|  |  |  |
| --- | --- | --- |
| Article ID: Reviewer: | | |
| **Selection bias** | | |
|  | Decision | Justification |
| Was the sampling/recruitment strategy appropriate to minimise bias? | € Yes € No € Unclear |  |
| Was it clearly and appropriately determined that participants were pain-free? | € Yes € No € Unclear |  |
| [B-G only] Similar baseline demographics among participants (age/sex/medical/psychological state)? | € Yes € No € Unclear |  |
| [Psych manip] Neutral psych status? | € Yes € No € Unclear |  |
| [B-G only] Random allocation  [B-site] Random allocation | € Yes € No € Unclear |  |
| **Risk of selection bias summary** | € High (failure to include any of the above probably influenced results FOR THE QUESTION OF THIS REVIEW)  € Low (results unlikely to have been influenced)  € Unclear (not enough information) | |

|  |  |  |
| --- | --- | --- |
| **Performance bias** | | |
| Blinding | Decision | Justification |
| Were participants blinded to the research question and paradigm and [if relevant] group allocation? | € Yes € No € Unclear |  |
| **Risk of performance bias summary** | € High  € Low  € Unclear | |
| **Detection bias** | | |
| Were outcome assessors blinded to the research question and paradigm? | € Yes € No € Unclear |  |
| Were analysing researchers blinded to the group allocation of participants and/or to site allocation? | € Yes € No € Unclear |  |
| **Risk of detection bias summary** | € High  € Low  € Unclear | |
| **Manipulation veracity** | | |
| [Psych] Did a manipulation check confirm the effectiveness of the manipulation? | € Yes € No € Unclear |  |
| **Risk of manipulation veracity problem** | € High € Low € Unclear |  |
| **Attrition bias** | | |
| Incomplete outcome data | Decision | Justification |
| Have attrition/exclusions/ withdrawals been reported and appropriately dealt with in analysis? | € Yes € No € Unclear |  |
| **Risk of attrition bias summary** | € High  € Low  € Unclear | |
| **Measurement bias** | | |
|  | Decision | Justification |
| Were valid and reliable outcome measurements used to assess severity & SA of secondary hyperalgesia? | 2H: € Yes € No € Unclear  SA: € Yes € No € Unclear |  |
| Were identical equipment items used for measurements between groups/sites/time points? | 2H: € Yes € No € Unclear  SA: € Yes € No € Unclear |  |
| Did the same assessor conduct assessments between groups/sites/time points? | 2H: € Yes € No € Unclear  SA: € Yes € No € Unclear |  |
| **Risk of measurement bias summary** | 2H: € High € Low € Unclear  SA: € High € Low€ Unclear | |
| **Reporting bias** | | |
| Selective reporting | Decision | Justification |
| Were all outcomes for experimental and control groups reported on? | € Yes € No |  |
| Were conflicts of interest and funding sources declared? | € Yes € No |  |
| **Risk of reporting bias summary** | € High  € Low  € Unclear | |

|  |  |  |
| --- | --- | --- |
| Article ID: Reviewer: | | |
| **Selection bias** | | |
|  | Decision | Justification |
| Was the sampling/recruitment strategy appropriate to minimise bias? | € Yes  € No  € Unclear | Yes: general population or subgroup. Convenience sampling is acceptable as long as eligibility criteria do not restrict to a certain group that could plausibly respond differently to the induction.  No: group selected on basis of particular feature (e.g. high catastrophising positive affect / athletes in training) |
| Was it clearly and appropriately determined that participants were pain-free? | € Yes  € No  € Unclear | Yes: participant self-report of no pain at time of testing AND no history of chronic pain (pain on most days for > 3 months) in preceding 2 years.  No: reports failure to ask BOTH questions.  Unclear: does not report asking both questions. |
| [B-G only] Similar baseline demographics among participants (age/sex/medical/psychological state)? | € Yes  € No  € Unclear | Yes: Psych (trauma Hx, stress status, general affect, sex, age, medication variables accounted for and similar)  No: Psychiatric diagnoses or medication use (esp. analgesics/anti-inflammatories/SNRI, etc) amongst participants.  Unclear: not reported  \*Consider design features, e.g. within-subject control or pre-post design |
| [Psych manip] Neutral psych status? | € Yes  € No € Unclear | Yes: Psych variables accounted for and normal  No: selected for responses on psych assessment |
| [B-G only] Random allocation  [B-site] Random allocation | € Yes  € No  € Unclear | Yes: random sequence generation / roll of die / other truly random procedure named  No: counterbalancing of group size (i.e. pseudo-randomisation) [but consider ROB in context] / sequential allocation  Unclear: not reported in enough detail to allow decision |
| **Risk of selection bias summary** | € High (failure to include any of the above probably influenced results FOR THE QUESTION OF THIS REVIEW)  € Low (results unlikely to have been influenced)  € Unclear (not enough information) | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Performance bias** | | | | |
| Blinding | Decision | | Justification | |
| Were participants blinded to the research question and paradigm and [if relevant] group allocation? | € Yes  € No  € Unclear | | Yes: evidence provided - blinding strategy AND blinding check AND results reported AND analysis done accordingly  No: Blinding reported broken  Unclear: not enough information / failure to report) | |
| **Risk of performance bias summary** | € High  € Low  € Unclear | | High: Plausible doubt that participant blinding was applied and maintained throughout  Low: Confident that participant blinding was applied and maintained throughout  Unclear: not enough information to make informed judgement (e.g. blinding strategy AND blinding check AND results mentioned BUT not fully reported) | |
| **Detection bias** | | | | |
| Were outcome assessors blinded to the research question and paradigm? | € Yes  € No  € Unclear | | Yes: evidence provided - blinding strategy AND blinding check AND results reported AND analysis done accordingly  No: Blinding reported broken  Unclear: not enough information / failure to report) | |
| Were analysing researchers blinded to the group allocation of participants and/or to site allocation? | € Yes  € No  € Unclear | | Yes: evidence provided - blinding strategy AND blinding check AND results reported AND analysis done accordingly  No: Blinding reported broken  Unclear: not enough information / failure to report) | |
| **Risk of detection bias summary** | € High  € Low  € Unclear | | High: Plausible doubt that participant blinding was applied and maintained throughout  Low: Confident that participant blinding was applied and maintained throughout  Unclear: not enough information to make informed judgement (e.g. blinding strategy AND blinding check AND results mentioned BUT not fully reported) | |
| **Risk of manipulation veracity problem** | | | | |
| [Psych] Did a manipulation check confirm the effectiveness of the manipulation? | € Yes € No € Unclear | | | Yes: manipulation check done and results reported and confirmed effectiveness  No: no manipulation check done OR manipulation check done but results not reported.  Unclear: manipulation check done and results confirmed ineffectiveness or were inconclusive |
| **Risk of manipulation veracity problem** | € High € Low € Unclear | | |  |
| **Attrition bias** | | | | |
| Incomplete outcome data | Decision | | | Justification |
| Have attrition/exclusions/ withdrawals been reported and appropriately dealt with in analysis? | € Yes € No € Unclear | | | Yes: no attrition/withdrawals OR stats handled withdrawals appropriately AND relevant adverse events reported |
| **Risk of attrition bias summary** | € High  € Low  € Unclear | | | |
| **Measurement bias** | | | | |
|  | Decision | | | Justification |
| Were valid and reliable outcome measurements used to assess severity & SA of secondary hyperalgesia? | 2H: € Yes € No € Unclear  SA: € Yes € No € Unclear | | | Yes:  Self-report: VAS / NRS / validated scale  Surface area: independently duplicated measurements or validated approach  Consider test-retest reliability if relevant  No: single measurement of distance/SA; un-validated self-report scale |
| Were identical equipment items used for measurements between groups/sites/time points? | 2H: € Yes € No € Unclear  SA: € Yes € No € Unclear | | |  |
| Did the same assessor conduct assessments between groups/sites/time points? | 2H: € Yes € No € Unclear  SA: € Yes € No € Unclear | | |  |
| **Risk of measurement bias summary** | 2H: € Yes € No € Unclear  SA: € Yes € No € Unclear | | | |
| **Reporting bias** | | | | |
| Selective reporting | | Decision | | Justification |
| Were all outcomes for experimental and control groups reported on? | | € Yes € No | | Check each outcome (compare methods vs results) |
| Were conflicts of interest and funding sources declared? | | € Yes € No | | Consider relevant conflicts |
| **Risk of reporting bias summary** | | € High  € Low  € Unclear | | |

# Supplementary file 6: Data extraction form

**Study identification**

|  |  |
| --- | --- |
| First author |  |
| Year of publication |  |
| First word of title |  |
| Sponsorship source |  |
| Country |  |
| Location/setting |  |
| Comments |  |

**Author’s contact details**

|  |  |
| --- | --- |
| Author’s name |  |
| Institution |  |
| Email |  |
| Address |  |

**Methods**

|  |  |
| --- | --- |
| Author’s name |  |
| Study design | (RCT / case-control / cross-over / pre-post experimental W-S / pre-post experimental B-G) |
| Primary aim |  |
| Sample size |  |

**Participants**

|  |  |
| --- | --- |
| Inclusion criteria |  |
| Exclusion criteria |  |
| Sample size calculation |  |

**Baseline characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Induction (experimental) | Control | Overall |
| Age |  |  |  |
| Sex (n male; n female) |  |  |  |
| Co-morbid diagnoses |  |  |  |
| Psychological variables |  |  |  |

**Interventions**

|  |  |  |
| --- | --- | --- |
|  | Induction (experimental) | Control |
| Method/modality: |  |  |
| Timing |  |  |
| Duration |  |  |
| Dosage |  |  |
| Method of administration |  |  |
| Equipment required |  |  |
| Ease of application score |  |  |

**Outcomes**

|  |  |  |
| --- | --- | --- |
|  | **Secondary hypersensitivity** | |
|  | **intensity (cont)** | **surf area (cont)** |
| Test stimulus modality/ies: |  |  |
| Report scale used |  |  |
| Time point(s) |  |  |
| Level reported | indiv/ grp | indiv/ grp |

**Results**

Note: for point estimate, specify mean/median/mode; for variance, specify SD/SE/SEM/CI.

**Secondary hypersensitivity magnitude**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline | | | | Time point 1: | | | |
|  | Point est | Variance | Sample size | p-value | Point est | Variance | Sample size | p-value |
| Measure used |  |  |  |  |  |  |  |  |
| Experimental 1 |  |  |  |  |  |  |  |  |
| Experimental 2 |  |  |  |  |  |  |  |  |
| Control |  |  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Time point: | | | | Time point: | | | |
|  | Point est | Variance | Sample size | p-value | Point est | Variance | Sample size | p-value |
| Measure used |  |  |  |  |  |  |  |  |
| Experimental 1 |  |  |  |  |  |  |  |  |
| Experimental 2 |  |  |  |  |  |  |  |  |
| Control |  |  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Time point: | | | | Time point: | | | |
|  | Point est | Variance | Sample size | p-value | Point est | Variance | Sample size | p-value |
| Measure used |  |  |  |  |  |  |  |  |
| Experimental 1 |  |  |  |  |  |  |  |  |
| Experimental 2 |  |  |  |  |  |  |  |  |
| Control |  |  |  |  |  |  |  |  |

**Secondary hypersensitivity surface area**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline | | | | Time point 1: | | | |
|  | Point est | Variance | Sample size | p-value | Point est | Variance | Sample size | p-value |
| Measure used |  |  |  |  |  |  |  |  |
| Experimental 1 |  |  |  |  |  |  |  |  |
| Experimental 2 |  |  |  |  |  |  |  |  |
| Control |  |  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Time point: | | | | Time point: | | | |
|  | Point est | Variance | Sample size | p-value | Point est | Variance | Sample size | p-value |
| Measure used |  |  |  |  |  |  |  |  |
| Experimental 1 |  |  |  |  |  |  |  |  |
| Experimental 2 |  |  |  |  |  |  |  |  |
| Control |  |  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Time point: | | | | Time point: | | | |
|  | Point est | Variance | Sample size | p-value | Point est | Variance | Sample size | p-value |
| Measure used |  |  |  |  |  |  |  |  |
| Experimental 1 |  |  |  |  |  |  |  |  |
| Experimental 2 |  |  |  |  |  |  |  |  |
| Control |  |  |  |  |  |  |  |  |

**Adverse events**

|  |  |
| --- | --- |
| Nature(s) |  |
| Number of events |  |
| n affected |  |

# Supplementary file 7: Primary outcome – magnitude of secondary hypersensitivity

## 7.1. Do cyclooxygenase-1 and/or -2 enzymes inhibitors decrease the magnitude of secondary hypersensitivity? (n = 3)

Three datasets used a cyclooxygenase-1 and -2 enzyme inhibitor anticipated to decrease the magnitude of SH: ibuprofen (n = 2) and acetylsalicylic acid (n = 1). Two (of 3) datasets induced SH using topical capsaicin[50, 64 dataset 2] and one used UV burn injury [3 dataset 1]. Two (of 3) datasets administered a single dose of either oral ibuprofen [64] or an “injection” of acetylsalicylic acid[50]. The remaining dataset administered multiple oral doses of ibuprofen[3 dataset 1]. Of the three datasets that used a cyclooxygenase-1 and -2 enzyme inhibitor, one dataset found that multiple doses of ibuprofen decreased the magnitude of experimentally induced SH[3 dataset 1]; two found that a single dose of either ibuprofen or acetylsalicylic acid had no effect.

## 7.2 Do adenosine receptor A2a, A2b, A3, and A1 agonists decrease the magnitude of secondary hypersensitivity? (n = 3)

Three datasets used an adenosine receptor A2a, A2b, A3, and A1 agonist anticipated to decrease the magnitude of SH: adenosine (n = 3). Each of these three datasets used a different method to induce secondary hypersensitivity: topical mustard oil[55, dataset 1], contact burn injury[55, dataset 2], or intradermal capsaicin injection[16]. Two (of 3) administered a single intravenous dose of adenosine[55 datasets 1 & 2]; one administered a single intrathecal dose of adenosine[16]. All three datasets found that adenosine had no effect on the magnitude of experimentally induced SH.

## 7.3 Does cannabinoid receptor agonists (n = 2), serotonin receptor agonists (n = 2), H1-receptor antagonist (n = 1), serotonin and norepinephrine inhibitor (n = 1), transient receptor potential vanilloid 1 receptor (n = 1), or glucocorticoid (n = 1) decrease the magnitude of secondary hypersensitivity?

The remaining eight (of 47) datasets that assessed the effect of a manipulation on the magnitude of experimentally induced SH had only one or two datasets per manipulation category. A glucocorticoid (n = 1)[37] and a transient receptor potential vanilloid 1 receptor agonist (n = 1)[19] both decreased the magnitude of experimentally induced SH. Cannabinoid receptor agonists (n = 2)[51 dataset 1 & 2], an H1 receptor agonist (n = 1)[63 dataset 3], and a serotonin and norepinephrine inhibitor (n = 1)[62] found no effect. Serotonin receptor agonists (n = 2)[43 datasets 1 & 2] had conflicting effects: one dataset found a decrease and one found no effect.

## 7.4 Publication bias and assessment of the quality of evidence (GRADE)

### 7.4.1 NMDA receptor antagonists

For datasets using NMDA receptor antagonists, publication bias could not be assessed due to the low number of datasets. For the GRADE assessment (Table 1), we downgraded the risk of bias by two, indicating that there is a very serious limitation in the risk of bias in this evidence base. This was because all five datasets had unclear risk of performance and detection bias for inadequate reporting of blinding. Further, two datasets had either a high risk of measurement bias for using an unvalidated scale [41 dataset 1] or an unclear risk of measurement bias for not reporting what scale they used to assess magnitude of SH [48]. There was not indirectness, nor was there imprecision, and results were consistent across datasets. Therefore, there were no downgrades for these domains. Overall, the certainty of evidence that NMDA receptor antagonists can decrease the magnitude of experimentally induced SH was scored as “moderate”, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Table 1: Assessment of the quality of the body of evidence on the effect of NMDA receptor antagonists on the magnitude of secondary hypersensitivity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Population:** adult (≥18 years old) humans without clinical pain conditions  **Setting:** experimental laboratory  **Intervention (manipulation):** NMDA receptor antagonists  **Comparison (control):** sham | | | | | | |
| Outcome measure: magnitude of secondary hypersensitivity | | | | | | Certainty of evidence |
| Number of datasets (number of participants in experimental group: control group) | Study design | Factors that may decrease certainty of evidence | | | |
| Risk of bias | Indirectness | Inconsistency | Imprecision |
| 5 (63:63) | Crossover | Very serious limitations | No | No | No | Moderate |

### 7.4.2 Alpha-2-delta subunit of voltage-gated calcium channel ligands

For datasets using alpha-2-delta subunit of VGCC ligands, publication bias could not be assessed due to the low number of datasets. For the GRADE assessment (Table 2), we downgraded the risk of bias by one indicating that there is a serious limitation in the risk of bias in this evidence base. This was because all five datasets had unclear risk of performance and detection bias for inadequate reporting of blinding. There was not indirectness, nor was there imprecision, and results were consistent across datasets. Therefore, there were no downgrades for these domains. Overall, the certainty of evidence that alpha-2-delta subunit of VGCC ligands can decrease the magnitude of experimentally induced SH was scored as “moderate”, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Table 2: Assessment of the quality of the body of evidence on the effect of alpha-2-delta subunit of voltage-gated calcium channel ligands on the magnitude of secondary hypersensitivity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Population:** adult (≥18 years old) humans without clinical pain conditions  **Setting:** experimental laboratory  **Intervention (manipulation):** alpha-2-delta subunit of voltage-gated calcium channel ligands  **Comparison (control):** sham | | | | | | |
| Outcome measure: magnitude of secondary hypersensitivity | | | | | | Certainty of evidence |
| Number of datasets (number of participants in experimental group: control group) | Study design | Factors that may decrease certainty of evidence | | | |
| Risk of bias | Indirectness | Inconsistency | Imprecision |
| 5 (74:74) | Crossover | Serious limitations | No | No | No | Moderate |

### 7.4.3 Voltage-gated sodium channel blockers

For the datasets using VGSC blockers, publication bias could not be assessed due to the low number of datasets. For the GRADE assessment (Table 3), we downgraded the risk of bias by one, indicating a serious limitation in the risk of bias in this evidence base. This was because all four datasets had unclear risk of performance and detection bias for inadequate reporting of blinding. There was not indirectness, nor was there imprecision, and results were consistent across datasets. Therefore, there were no downgrades for these domains. Overall, the certainty of evidence that VGSC blockers can decrease the magnitude of experimentally induced SH was scored as “moderate”, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Table 3: Assessment of the quality of the body of evidence on the effect of voltage-gated sodium channel blockers on the magnitude of secondary hypersensitivity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Population:** adult (≥18 years old) humans without clinical pain conditions  **Setting:** experimental laboratory  **Intervention (manipulation):** voltage-gated sodium channel blockers  **Comparison (control):** sham | | | | | | |
| Outcome measure: magnitude of secondary hypersensitivity | | | | | | Certainty of evidence |
| Number of datasets (number of participants in experimental group: control group) | Study design | Factors that may decrease certainty of evidence | | | |
| Risk of bias | Indirectness | Inconsistency | Imprecision |
| 4 (56:56) | Crossover | Serious limitations | No | No | No | Moderate |

### 7.4.4 Opioid receptor agonists

For opioid receptor agonists, data were unavailable for pooling and therefore neither publication bias nor GRADE was assessed.

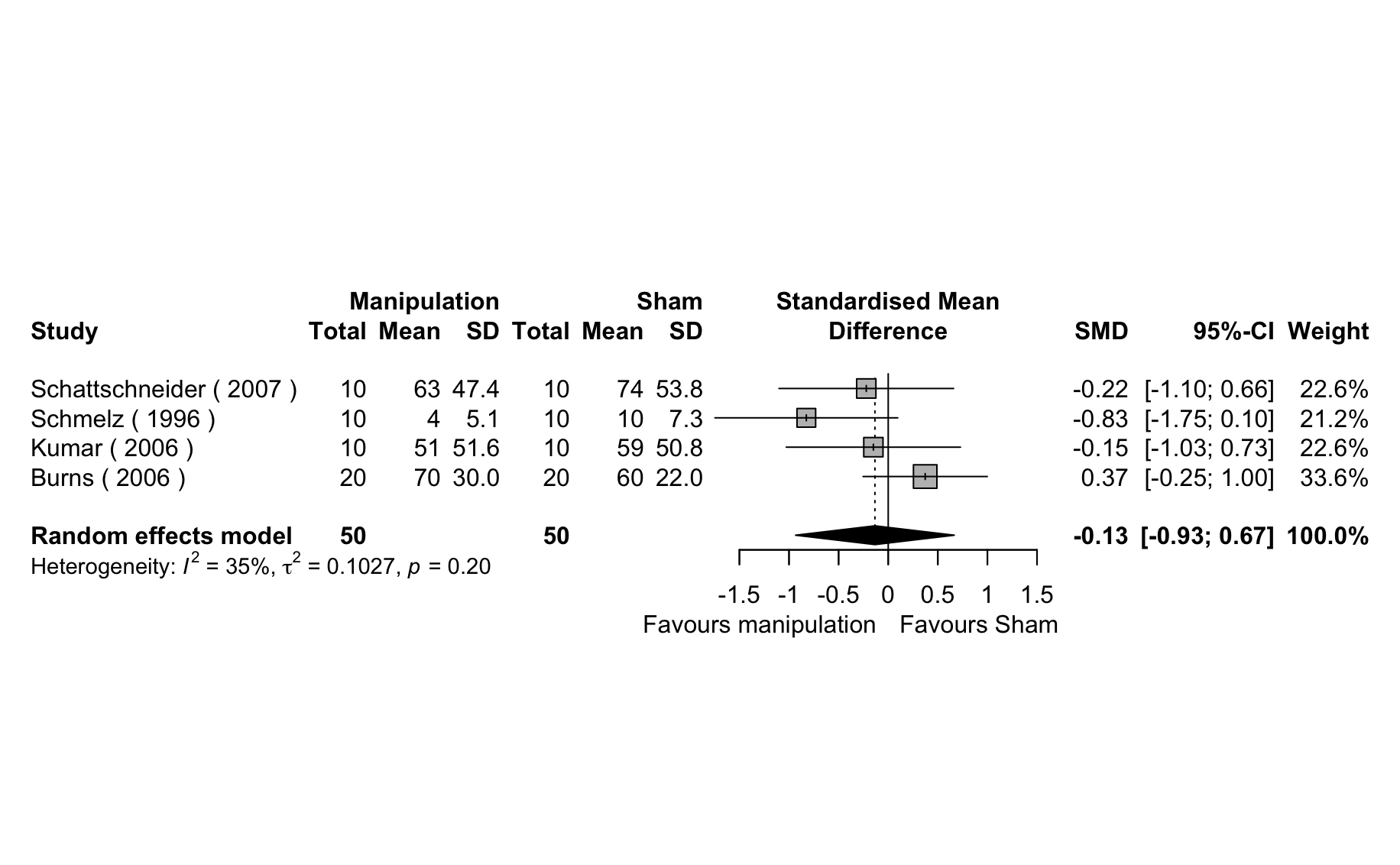
# Supplementary file 8: Secondary outcome – surface area of secondary hypersensitivity

## 8.1 Do the cyclooxygenase-1 and/or -2 enzyme inhibitors decrease the surface area of secondary hypersensitivity? (n = 16)

Sixteen datasets used a cyclooxygenase-1 and/or -2 enzymes inhibitor anticipated to decrease the surface area of secondary hypersensitivity: ibuprofen (n = 5), ketorolac (n = 4), rofecoxib (n = 3), acetylsalicylic acid (n = 2), parecoxib (n = 1), valdecoxib (n = 1). Of these 16 datasets, five induced SH using contact burn injury [39, 46, 57, 65 datasets 1 & 2], four used ultraviolet burn injury[3 dataset 1, 58 datasets 1, 2 & 3], two used a contact freeze injury[9 datasets 1 & 3], two used topical capsaicin[50, 52], one used intradermal capsaicin injection[31], and one used topical capsaicin and thermal contact[8]. Of the 16 datasets, five administered a single dose of ibuprofen (n = 2 oral[9 dataset 1, 46, 65 dataset 2]; n = 2 topical[9 dataset 3, 65 dataset 1]), three administered a single intravenous dose of ketorolac[31, 35 dataset 3, 57 dataset 2], three administered a single oral dose of rofecoxib[58 datasets 1, 2 & 3], two administered a single dose of acetylsalicylic acid (n = 1 topical[52]; n = 1 “injection”[50]), one administered a single oral dose of valdecoxib[8], and two administered multiple doses of oral ibuprofen[3 dataset 1] or topical ketorolac[39]. Of the 16 datasets that used cyclooxygenase-1 and/or -2 enzyme inhibitors, 7 found a decrease, 8 found no effect and data were missing for 1 dataset[22 dataset 3].

Of the 15 datasets that used an inhibitor of cyclooxygenase-1 and/or -2 enzyme, four datasets reported data that were available for pooling. All four reported surface area data as between-condition comparisons. The SMD pooled effect point estimate [95% CI] was -0.13 [-0.93; 0.67]; *I2* = 35% (Fig 1), the 95% CI therefore includes the null hypothesis of no difference in effect between inhibitor of cyclooxygenase-1 and/or -2 enzymes and the sham manipulations.

Figure 1: Forest plot of the pooled effect estimated of an inhibitor of cyclooxygenase-1 and -2 enzyme on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons. Green = acetylsalicylic acid, blue = ketorolac, orange = valdecoxib.



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## 8.2 Do opioid receptor antagonists increase the surface area of secondary hypersensitivity (n = 9)

Nine datasets used an opioid receptor antagonist anticipated to increase the surface area of secondary hypersensitivity: naloxone (n = 9). Of these nine, five induced SH using contact burn injury[6 datasets 1 & 2, 44 dataset 1, 45 dataset 1, 56], two used intradermal electrical stimulation[24 dataset 3, 26], and two used brief thermal stimulation[44 dataset 2, 45 dataset 2]. Of these nine, five administered a single intravenous dose[24 dataset 3, 44 datasets 1 & 2, 45 datasets 1 & 2] and four administered multiple intravenous doses of naloxone. Two (of 9) datasets found an increase in the surface area of SH; seven found no effect.

Of the nine datasets that used an inhibitor of opioid receptor antagonist, five datasets reported data that were available for pooling. All five reported surface area data as between-condition comparisons. The SMD pooled effect point estimate [95% CI] was 0.83 [-0.18; 1.85]; *I2* = 74% (Fig 2), the 95% CI therefore includes the null hypothesis of no difference in effect between naloxone and the sham manipulations.

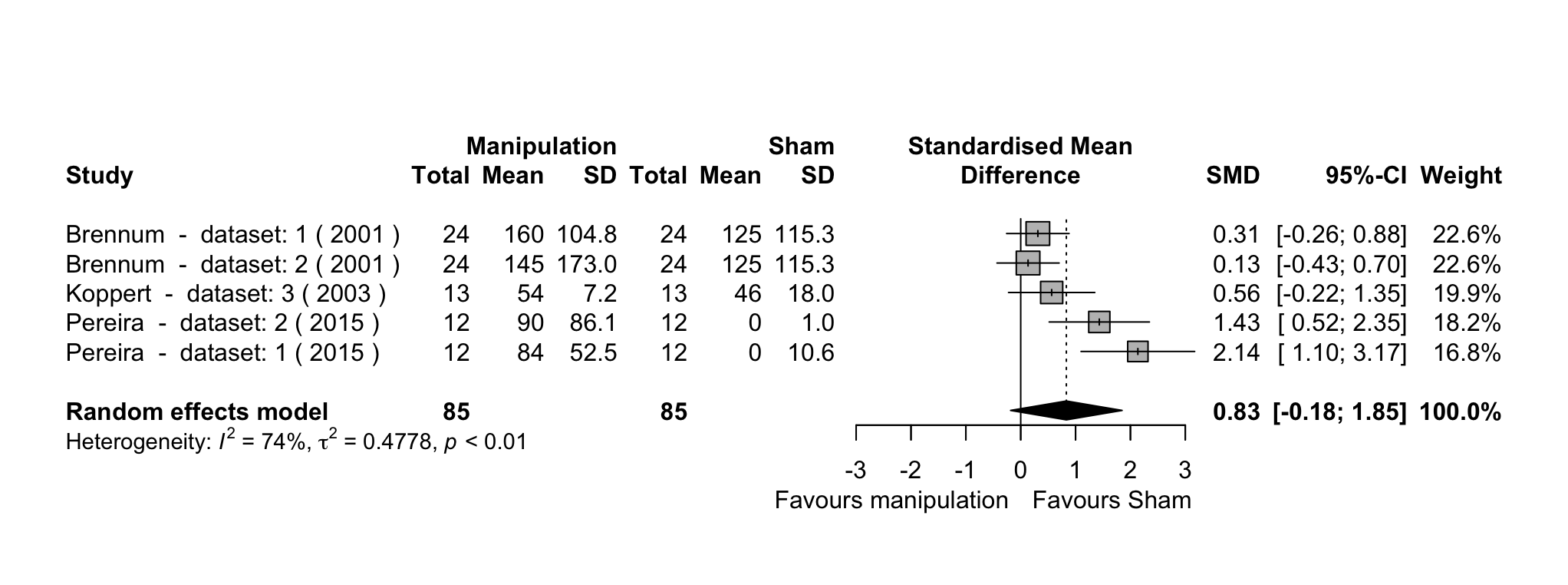


Figure 2: Forest plot of the pooled effect estimated of an opioid receptor antagonist – naloxone – on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons.

## 8.3 Do presynaptic acetylcholine inhibitors release decrease the surface area of secondary hypersensitivity? (n = 6)

Six datasets used an inhibitor of presynaptic acetylcholine release anticipated to decrease the surface area of secondary hypersensitivity: Botulinum-neurotoxin A (n = 6). Three (of 8) datasets induced SH using intradermal capsaicin injection[13 dataset 1, 20, 21], two used intradermal electrical stimulation[13 dataset 2, 30], and one used ultraviolet burn injury[59]. Of these six datasets, two administered a single intracutaneous dose of botulinum-neurotoxin A [13 datasets 1 & 2], and fouradministered multiple doses of botulinum-neurotoxin A (subcutaneous n = 2[20, 21]; intracutaneous n = 2[30, 59])*.* Two (of 6) datasets[20, 21] found a decrease the surface area of SH induced at the forehead; four found no effect at the thigh (n = 3)[13 datasets 1 & 2, 59] or forearm (n = 1)[30].

Of the six datasets that used an inhibitor of presynaptic acetylcholine release, all six datasets reported data that were available for pooling. All six reported surface area data as between-condition comparisons. The SMD pooled effect point estimate [95% CI] was -0.24 [-0.80; 0.32]; *I2* = 32% (Fig 3), the 95% CI therefore includes the null hypothesis of no difference in effect between botulinum-neurotoxin-A and the sham manipulations.

A diagram of a number of objects

Description automatically generated with medium confidence

Figure 3: Forest plot of the pooled effect estimated of an inhibitor of presynaptic acetylcholine – botulinum-neurotoxin A – release on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons.

## 8.4 Do adenosine receptor A2a, A2b, A3, and A1 agonists decrease the surface area of secondary hypersensitivity? (n = 5)

Five datasets used an adenosine receptor A2a, A2b, A3, and A1 agonist anticipated to decrease the surface area of SH: adenosine (n = 5). Each of these five used a different method to induce secondary hypersensitivity: mustard oil [55, dataset 1], burn injury[55, dataset 2], intradermal capsaicin injection[16], topical capsaicin and heat[14], or intradermal electrical stimulation[10]. All five administered a single dose of adenosine (intravenous n = 4; intrathecal n = 1[16]). Four (of 5) datasets found a decrease in the surface area of SH; one[14] found no effect.

Of the five datasets that used an adenosine receptor A2a, A2b, A3, and A1 agonist, three datasets reported data that were available for pooling. All three reported surface area data as between-condition comparisons. The SMD pooled effect point estimate [95% CI] was -0.67 [-1.88; 0.55]; *I2* = 32% (Fig 4), the 95% CI therefore includes the null hypothesis of no difference in effect between adenosine and the sham manipulations.

A diagram of a number of objects

Description automatically generated with medium confidence

Figure 4: Forest plot of the pooled effect estimated of an adenosine receptor A2a, A2b, A3, and A1 agonist – adenosine – on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons.

## 8.5 Do GABA-A receptor agonists decrease the surface area of secondary hypersensitivity? (n = 4)

Four datasets used a GABA-A receptor agonist anticipated to decrease the surface area of SH: N-desmethyl-clobazam (n = 2), clonazepam (n = 1), or propofol (n = 1). Three (of 4) datasets induced SH using ultraviolet burn injury[36 datasets 1, 2 & 3] and one used intradermal electrical stimulation[40 dataset 1]. Three (of 4) administered a single oral dose[36 datasets 1, 2 & 3] and one administered a single intravenous dose[40 dataset 1] of a GABA-A receptor agonist. All four datasets found that GABA-A receptor agonists had no effect on the surface area of experimentally induced SH.

## 8.6 Do cannabinoid receptor agonists decrease the surface area of secondary hypersensitivity? (n = 4)

Four datasets used a cannabinoid receptor agonist anticipated to decrease the surface area of SH: delta-9-tetrahydrocannabinol (THC) (n = 2), cannabidiol (n = 1), or HU210 (n = 1). Two (of 4) datasets induced SH using intradermal capsaicin injection[51 datasets 1 & 2], one used topical capsaicin[49], and one used intradermal electrical stimulation[53]. All four datasets administered a single dose of a cannabinoid receptor agonist (intravenous: n = 2[51 datasets 1 & 2], oral: n = 1[53], topical: n = 1[49]). All four datasets found that cannabinoid receptor agonists had no effect on the surface area of experimentally induced SH.

Of the four datasets that used a cannabinoid receptor agonist, all four datasets reported data that were available for pooling. All four reported surface area data as between-condition comparisons. The SMD pooled effect point estimate [95% CI] was 0.02 [-0.45; 0.49]; *I2* = 0% (Fig 5), the 95% CI therefore includes the null hypothesis of no difference in effect between cannabinoid receptor agonists and the sham manipulations.

A diagram of a number of individuals

Description automatically generated with medium confidence

Figure 5: Forest plot of the pooled effect estimated of a cannabinoid receptor agonist on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons.

## 8.7 Do paracetamol/acetaminophen decrease the surface area of secondary hypersensitivity? (n = 4)

Four datasets used paracetamol/acetaminophen anticipated to decrease the surface area of SH. Two (of 40) datasets induced SH using intradermal electrical stimulation[18 dataset 1, 29 dataset 2], one used contact freeze injury[9 dataset 2] and the remaining one used ultraviolet burn injury[35 dataset 2]. All four administered a single dose of paracetamol/acetaminophen (intravenous n = 3; oral n = 1[9 dataset 2]). Three (of 4) datasets found a decrease in the surface area of SH; data were missing for the remaining dataset[22 dataset 2]. Data were unavailable for pooling from two (of 4) datasets.

## 8.8 Do glucocorticoids decrease the surface area of secondary hypersensitivity? (n = 3)

Three datasets used a glucocorticoid anticipated to decrease the surface area of SH: clobetasol propionate (n = 1)[42], dexamethasone (n = 1)[68], or methylprednisolone (n = 1)[57 dataset 1]. All three datasets induced SH using a contact burn injury. Two (of 3) datasets administered a single intravenous[57 dataset 1, 68] dose and one multiple topical doses[42] of a glucocorticoid. One dataset found that methylprednisolone[57] decreased the surface area of experimentally induced SH; two datasets (administering dexamethasone or clobetasol propionate) found no effect. Two datasets reported data as between-group comparisons and one as change-from-baseline; therefore, there were not enough datasets for pooling.

## 8.9 Do glutamate receptor 5 antagonists decrease the surface area of secondary hypersensitivity? (n = 2)

Two datasets used a glutamate receptor 5 antagonist anticipated to decrease in the surface area of SH: ionotropic glutamate receptor 5 antagonist LY545694 (n = 1)[47], or mGluR5-antagonist AZD9272 (n = 1)[23]. One dataset induced SH using brief thermal stimulation[47], and the other used intradermal electrical stimulation[23]. One dataset found that multiple doses of LY545694[47] decreased the surface area of SH; one dataset found that a single dose of mGluR5-antagonist AZD9272[23] had no effect.

## 8.10 Do serotonin receptor agonists (n = 2), melatonin (n = 2), transient receptor potential vanilloid 1 receptor agonists (n = 2), selective IF channel inhibitors (n = 2) decrease the surface area of secondary hypersensitivity?

Eight datasets used either serotonin receptor agonists (n = 2), melatonin (n = 2), transient receptor potential vanilloid 1 receptor agonists (n = 2), or selective IF channel inhibitors (n = 2) anticipated to decrease the surface area of SH. Transient receptor potential vanilloid 1 receptor agonists had conflicting effects: one dataset found a decrease[12] and one found no effect[19]. Serotonin receptor agonists [43 datasets 1 & 2], melatonin[2 dataset 1 & 2], and selective IF channel inhibitors[33, 60] all had no effect.

## 8.11 Do acetylcholinesterase enzyme inhibitor (n = 1), H1 receptor agonist (n = 1), serotonin and norepinephrine inhibitor (n = 1), neurokinin-1 antagonist (n = 1), transient receptor potential melastatin-8 activator (n = 1), or histamine (n = 1) decrease the surface area of secondary hypersensitivity?

Six datasets used either an acetylcholinesterase enzyme inhibitor (n = 1), H1 receptor agonist (n = 1), serotonin and norepinephrine inhibitor (n = 1), neurokinin-1 antagonist (n = 1), transient receptor potential melastatin-8 activator (n = 1), or histamine (n = 1) anticipated to decrease the surface area of SH. Only transient receptor potential melastatin-8 activator[1] found a decrease the surface area.

Acetylcholinesterase enzyme inhibitor[67 dataset 1], H1 receptor agonist[63 dataset 3], serotonin and norepinephrine inhibitor[62], neurokinin-1 antagonist[11], and histamine[7] all had no effect.

## 8.12 Does the combination of an opioid receptor agonist and a cyclooxygenase-1 and/or -2 inhibitor decrease the surface area of secondary hypersensitivity? (n = 8)

Eight datasets used a combination of an opioid receptor agonist with a cyclooxygenase-1 and/or -2 inhibitor anticipated to decrease in the surface area of secondary hypersensitivity: diclofenac and methadone (n = 4), remifentanil and parecoxib (n = 3), remifentanil and ketorolac (n = 1). Four (of 8) datasets induced SH using used intradermal electrical stimulation[34 datasets 2 & 3, 61 datasets 2 & 3], two used intradermal capsaicin injection[32 datasets 3 & 4], and two used Intradermal nerve growth factor injection[32 datasets 1 & 2]. Four (of 8) datasets administered a single topical dose of diclofenac and methadone and four administered a single intravenous dose of remifentanil and parecoxib/ketorolac. Four datasets found that of remifentanil and parecoxib/ketorolac decreased the surface area of SH; four found that diclofenac and methadone had no effect.

## 8.13 Does the combination of different manipulations decrease the surface area of secondary hypersensitivity?

One dataset[18 dataset 3] using a combination of paracetamol/acetaminophen and opioid receptor agonist found a decrease in the surface area of SH. The following manipulation combinations had no effect on the surface area of SH: acetylcholinesterase enzyme inhibitor and opioid receptor agonist (n = 1)[67 dataset 3], GABA-A receptor agonist and opioid receptor agonist (n = 1)[40 dataset 2], GABA-A receptor agonist, opioid receptor agonist and NMDA receptor antagonist (n = 1)[40 dataset 3], NMDA receptor antagonist and opioid receptor antagonist (n = 1)[38 dataset 2], alpha 2-delta subunit of voltage-gated calcium channel blocker and opioid receptor agonist (n = 1)[28 dataset 5], alpha 2-delta subunit of voltage-gated calcium channel blocker and acetylcholinesterase enzyme inhibitor (n = 1)[5 dataset 2]. A combination of opioid receptor agonist and an NMDA receptor antagonist had conflicting effects: one dataset found a decrease[28 dataset 2] and one found no effect[54 dataset 3]. Data were not reported for one dataset that used a combination of cyclooxygenase-1 and/or -2 enzyme inhibitor and paracetamol/acetaminophen[35 dataset 1].

## 8.14 Publication bias and assessment of the quality of evidence (GRADE)

### 8.14.1 NMDA receptor antagonists

Publication bias was seen, by an asymmetrical funnel plot as seen by one outlier on the left-hand-side of the funnel plot (Fig 6), and confirmed by a statistically significant Begg’s test (*p* = 0.01).

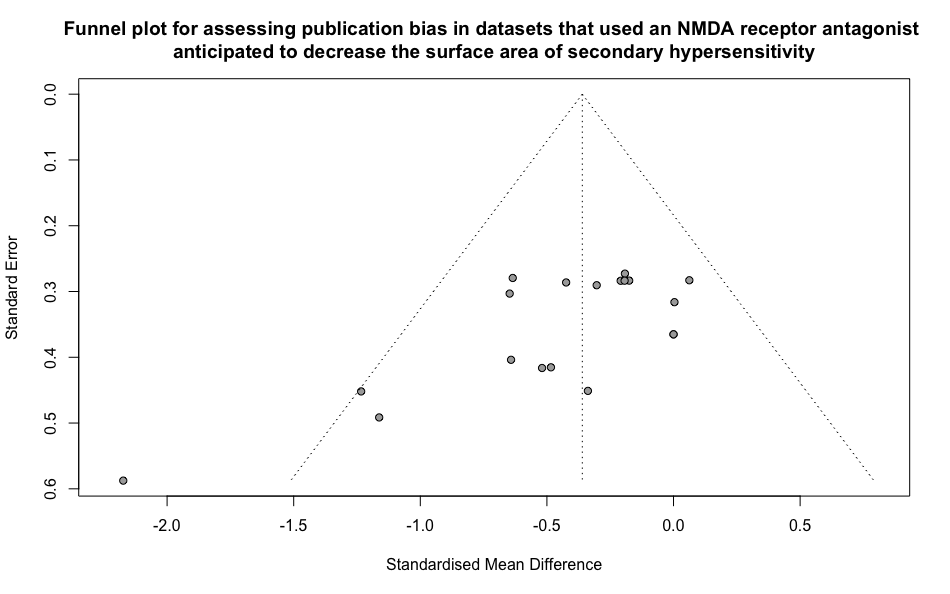


Figure 6: Funnel plot for assessing publication bias in datasets that used an NMDA receptor antagonist anticipated to decrease the surface area of secondary hypersensitivity.

For the GRADE assessment (Table 4), we downgraded the risk of bias by two, indicating “very serious limitations” in the risk of bias in this evidence base. This was because 23 (of 26) datasets had unclear risk of performance and detection bias for inadequate reporting of blinding; the remaining three had high risk of performance and detection bias[15 datasets 1 & 2, 25 dataset 1]. Further, two datasets had an unclear risk of measurement bias for not reporting instructions given to participants[38 dataset 1] or the force of the von Frey filament used[66 dataset 1] to measure the surface area of SH. There was not indirectness, nor was there imprecision. There were some inconsistent results across datasets, but there were no downgrades for these domains. Overall, the certainty of evidence that NMDA receptor antagonist can decrease the surface area of experimentally induced SH was scored as “moderate”, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Table 4: Assessment of the quality of the body of evidence on the effect of NMDA receptor antagonists on the surface area of secondary hypersensitivity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Population:** adult (≥18 years old) humans without clinical pain conditions  **Setting:** experimental laboratory  **Intervention (manipulation):** NMDA receptor antagonists  **Comparison (control):** sham | | | | | | |
| Outcome measure: surface area of secondary hypersensitivity | | | | | | Certainty of evidence |
| Number of datasets (number of participants in experimental group: control group) | Study design | Factors that may decrease certainty of evidence | | | |
| Risk of bias | Indirectness | Inconsistency | Imprecision |
| 26 (481:481) | Crossover | Very serious limitations | No | Yes | No | Moderate |

### 8.14.2 Alpha-2-delta subunit of voltage-gated calcium channel ligands

Publication bias was notobserved, as seen by a symmetrical funnel plot (Fig 7), and confirmed by Begg’s test (*p* = 0.70).

A diagram of a funnel plot

Description automatically generated

Figure 7: Funnel plot for assessing publication bias in datasets that used an alpha-2-delta subunit of voltage-gated calcium channel ligand anticipated to decrease the surface area of secondary hypersensitivity.

For the GRADE assessment (Table 5), we downgraded the risk of bias by two, indicating “very serious limitations” in the risk of bias in this evidence base. This was because all 11 datasets had unclear risk of performance and detection bias for inadequate reporting of blinding, and five datasets had an unclear risk of measurement bias for not reporting instructions given to participants to measure the surface area of SH[17 datasets 1, 2, 3 & 4, 69]. There was not indirectness, nor was there imprecision, and results were consistent across datasets. Therefore, there were no downgrades for these domains. Overall, the certainty of evidence that alpha-2-delta subunit of VGCC ligands can decrease the surface area of experimentally induced SH was scored as “moderate”, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Table 5: Assessment of the quality of the body of evidence on the effect of alpha-2-delta subunit of voltage-gated calcium channel ligands on the surface area of secondary hypersensitivity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Population:** adult (≥18 years old) humans without clinical pain conditions  **Setting:** experimental laboratory  **Intervention (manipulation):** alpha-2-delta subunit ofvoltage-gated calcium channel ligands  **Comparison (control):** sham | | | | | | |
| Outcome measure: surface area of secondary hypersensitivity | | | | | | Certainty of evidence |
| Number of datasets (number of participants in experimental group: control group) | Study design | Factors that may decrease certainty of evidence | | | |
| Risk of bias | Indirectness | Inconsistency | Imprecision |
| 11 (212:172) | Crossover; within-subject | Very serious limitations | No | No | No | Moderate |

### 8.14.3 Voltage-gated sodium channel blockers

Publication bias was observed by an asymmetrical funnel plot as seen by four outliers on the left-hand-side of the funnel plot (Fig 8) and confirmed by a statistically significant Begg’s test for VGSC blockers (*p* = 0.01).

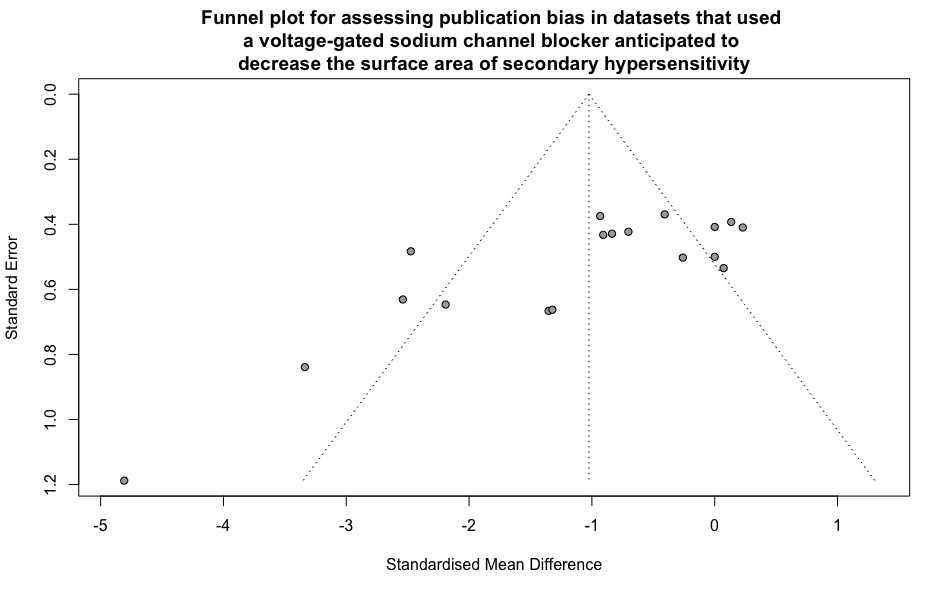


Figure 8: Funnel plot for assessing publication bias in datasets that used a voltage-gated sodium channel blocker anticipated to decrease the surface area of secondary hypersensitivity.

For the GRADE assessment (Table 6), we downgraded the risk of bias by one, indicating “serious limitations” in the risk of bias in this evidence base. This was because 16 of 18 datasets had unclear risk of performance and detection bias for inadequate reporting of blinding, and two had a low risk of performance bias[27 datasets 1 & 2]. Additionally, one dataset had an unclear risk of measurement bias for not reporting for force of the von Frey filament used to measure the surface area of SH[66 dataset 2]. There was not indirectness, nor was there imprecision, and results were consistent across datasets. Therefore, there were no downgrades for these domains. Overall, the certainty of evidence that voltage-gated calcium sodium blocker can decrease the surface area of experimentally induced SH was scored as “moderate”, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Table 6: Assessment of the quality of the body of evidence on the effect of voltage-gated sodium channel blockers on the surface area of secondary hypersensitivity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Population:** adult (≥18 years old) humans without clinical pain conditions  **Setting:** experimental laboratory  **Intervention (manipulation):** voltage-gated sodium channel blockers  **Comparison (control):** sham | | | | | | |
| Outcome measure: surface area of secondary hypersensitivity | | | | | | Certainty of evidence |
| Number of datasets (number of participants in experimental group: control group) | Study design | Factors that may decrease certainty of evidence | | | |
| Risk of bias | Indirectness | Inconsistency | Imprecision |
| 11 (184:196) | Crossover; within-subject | Serious limitations | No | No | No | Moderate |

### 8.14.4 Opioid receptor agonists

Publication bias was observed by an asymmetrical funnel plot (Fig 9), and confirmed by a statistically significant Begg’s test (*p* = 0.02).

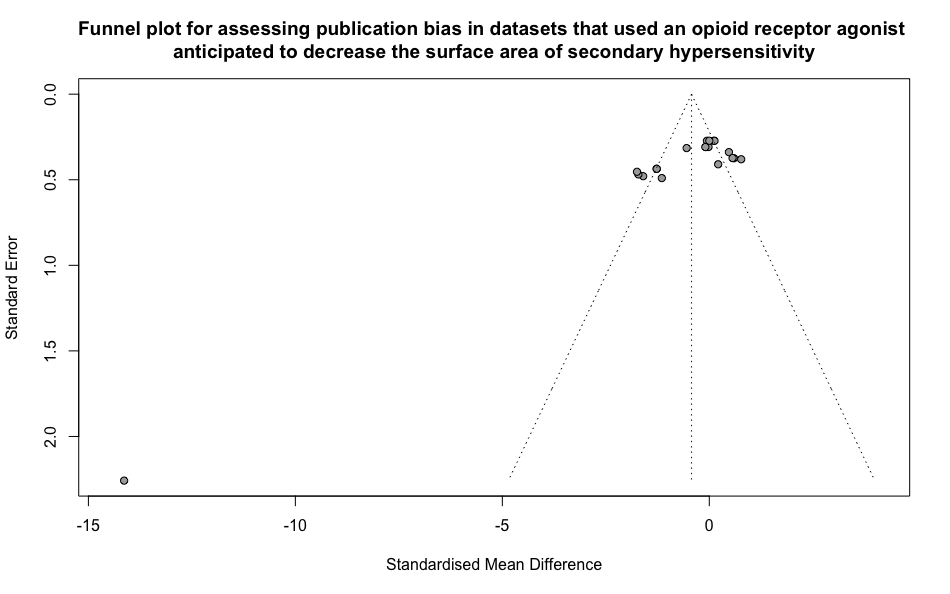


Figure 9: Funnel plot for assessing publication bias in datasets that used an opioid receptor agonist anticipated to decrease the surface area of secondary hypersensitivity.

For the GRADE assessment (Table 7), we downgraded the risk of bias by one, indicating a serious limitation in the risk of bias in this evidence base. This was because 27 (of 28) datasets had unclear risk of performance and detection bias for inadequate reporting of blinding; the remaining dataset had a high risk of performance and detection bias[25 dataset 2]. There was not indirectness, nor was there imprecision, and results were consistent across datasets. Therefore, there were no downgrades for these domains. Overall, the certainty of evidence that voltage-gated calcium sodium blockers can decrease the surface area of experimentally induced SH was scored as “moderate”, meaning that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Table 7: Assessment of the quality of the body of evidence on the effect of opioid receptor agonists on the surface area of secondary hypersensitivity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Population:** adult (≥18 years old) humans without clinical pain conditions  **Setting:** experimental laboratory  **Intervention (manipulation):** opioid receptor agonists  **Comparison (control):** sham | | | | | | |
| Outcome measure: surface area of secondary hypersensitivity | | | | | | Certainty of evidence |
| Number of datasets (number of participants in experimental group: control group) | Study design | Factors that may decrease certainty of evidence | | | |
| Risk of bias | Indirectness | Inconsistency | Imprecision |
| 28 (468:468) | Crossover | Serious limitations | No | No | No | Moderate |

# Supplementary file 9: adverse effects

Table 8: Adverse effects associated with the following manipulations: NMDA receptor antagonists, alpha-2-delta subunit of voltage-gated calcium channel ligands, voltage-gated sodium channel blocker, and opioid receptor agonists.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Dataset** | **Number of participants who received the active drug and sham placebo**  **(active drug; sham placebo)** | **Manipulation drug** | **Adverse effects** | |
| **Active drug**  **(adverse effect: number or percentage of participants who experienced adverse effect)** | **Sham placebo**  **(adverse effect: number or percentage of participants who experienced adverse effect)** |
| Opioid receptor agonist (n = 38) | | | | |
| Brennum, Dahl et al. (1994) datasets 1, 2, 3 & 4 | 10; 10 in each dataset | Morphine | * Itch: 10 * Burning sensation: 7 * Nausea: 8 * Sedation: 5 * Headache: 5 | Not reported |
| Lilleso, Hammer et al. (2000) datasets 1 & 2 | 18; 18 | Morphine | * Euphoria * Nausea * Bluntness * Headache * Dizziness * Confusion * Feeling of being drunk * Itching * Restlessness   Number of participants experiencing adverse event was not reported. | None observed |
| Ravn, Secher et al. (2013) dataset 1 | 27; 28 | Morphine | * Nausea and/or vomiting: 2 * Itch: 4 * Sedation: 3 * Desaturation: 1; Impairment in hearing: 1 * Dizziness: 2 * Headache: 1 | * Itch: 1 * Sedation: 1 |
| Ravn, Secher et al. (2013) dataset 2 | 28; 28 | Morphine | * Nausea and/or vomiting: 11 * Itch: 13 * Sedation: 11 * Desaturation: 5; Impairment in hearing: 2 * Visual disturbance: 1 * Dizziness: 2 * Headache: 1 | * Itch: 1 * Sedation: 1 |
| Schulte, Sollevi et al. (2004) dataset 1 | 11; 11 | Morphine | * Nausea and/or vomiting: 3 * Flush: 2 * Chest oppression: 2 * Tiredness: 5 * Dizziness: 1 * Anxiety: 1 * Out-of-body sensation: 1 | None observed |
| Wang, Bolongnese et al (2008) dataset 2 | 19; 20 | Morphine | Adverse events were assessed but not reported | Not reported |
| Warncke, Stubhaug et al. (1997) dataset 1 | 12; 12 | Morphine | * Fatigue: 6 * Dizziness: 3 * Discomfort: 1 * Nausea: 3 * Pleasant feeling: 1 * Feeling of muscular stiffness: 2 * Sleepy: 6 | Not reported |
| Warncke, Stubhaug et al. (1997) dataset 2 | 12; 12 | Morphine | * Fatigue: 9 * Dizziness: 5 * Visual disturbance: 1 * Discomfort: 4 * Nausea: 6 * Pleasant feeling: 1 * Feeling of muscular stiffness: 4 * Sleepy: 4 | Not reported |
| Angst, Koppert et al. (2003) dataset 2 | 10; 10 | Remifentanil | * Sedation: 10 * Nausea: 2 * Pruritus: 5 * Euphoric: 1 | Not reported |
| Chu, Cun et al. (2012) | 9; 9 | Remifentanil | * Nausea: 4   Pruritus: 5 | * Sedation: 10 |
| Chu, Dairmont et al. (2011) |  | Remifentanil | None observed | Not reported |
| Hood, Curry et al. (2003) | 10; 10 | Remifentanil | Adverse events were assessed but not reported | Not reported |
| Koppert, Sittl et al. (2003) dataset 3 | 13; 13 | Remifentanil | * Sedation   Number of participants experiencing adverse event was not reported. | Not reported |
| Koppert, Angst et al. (2003) dataset 1 | 13; 13 | Remifentanil | * Sedation: 13 | Not reported |
| Koppert, Angst et al. (2003) dataset 2 | 13; 13 | Remifentanil | * Sedation: 13 | Not reported |
| Lenz, Raeder et al. (2011) dataset 1 | 16; 16 | Remifentanil | * Sedation: 14 * Pruritus: 10 * Nausea:1 * Dizziness: 6 | None observed |
| Petersen, Jones et al. (2001) | 14; 14 | Remifentanil | * Nausea * Itching * Dry mouth * Sleepy * Light headedness * Spacey   Number of participants experiencing adverse event was not reported. | * Nausea   Number of participants experiencing adverse event was not reported. |
| Petersen, Maloney et al. (2003) dataset 4 | 13; 13 | Remifentanil | * Nausea: 1 * Vasovagal episode:1 | Not reported |
| Troster, Sittl et al. (2006) dataset 1 | 15; 15 | Remifentanil | * Pruritus: 2 * Hypoacusis/hyperacusis: 2 * Dizziness: 5 * Sedation: 11 | * Hypoacusis/hyperacusis: 1 * Dizziness: 2 * Nausea: 1 * Sedation: 3 |
| Andresen, Staahl et al. (2011) dataset 1 & 3 | 21; 21 in each dataset | Buprenorphine | At 24 hours:   * Local irritation at the buprenorphine patch site: 6 * Nausea: 16 * Pruritus: 6 * Dizziness: 18 * Drowsiness: 15 * Fatigue: 1 * Insomnia: 2 * Vomiting: 6 * Dysuria: 4 * Constipation: 5 * ‘Other’: 2 (specifics not reported)   At 48 hours:   * Local irritation at the buprenorphine patch site: 16 * Nausea: 13 * Pruritus: 10 * Dizziness: 18 * Drowsiness: 15 * Fatigue: 1 * Vomiting: 3 * Dysuria: 5 * Constipation: 4 * Headache: 1 * ‘Other’: 2 (specifics not reported)   At 72 hours:   * Local irritation at the buprenorphine patch site: 15 * Nausea: 10 * Pruritus: 9 * Dizziness: 18 * Drowsiness: 14 * Vomiting: 1 * Dysuria: 5 * Constipation: 3 * Headache: 3   At 144 hours:   * Local irritation at the buprenorphine patch site: 13 * Nausea: 3 * Pruritus: 2 * Dizziness: 8 * Drowsiness: 11 * Vomiting: 1 * Dysuria: 3 * Constipation: 3 * ‘Other’: 2 (specifics not reported) | Not reported |
| Koppert, Ihmsen et al. (2005) dataset 1 | 15; 15 | Buprenorphine | * Nausea and vomiting: 4 | * Nausea and vomiting: 1 |
| Koppert, Ihmsen et al. (2005) dataset 2 | 15; 15 | Buprenorphine | * Nausea and vomiting: 2 | * Nausea and vomiting: 1 |
| Ravn, Secher et al. dataset 3 | 28; 28 | Buprenorphine | * Nausea and vomiting: 14 * Itch: 11 * Sedation: 15 * Desaturation: 3 * Urinary retention 2: * Impairment in hearing: 2 * Visual disturbance: 1 * Dizziness: 6 | * Itch: 1 * Sedation: 1 |
| Ravn, Secher et al. dataset 4 | 28; 28 | Buprenorphine | * Nausea and vomiting: 19 * Itch: 18 * Sedation: 24 * Desaturation: 10 * Urinary retention 2: * Impairment in hearing: 1 * Visual disturbance: 1 * Dizziness: 8 | * Itch: 1 * Sedation: 1 |
| Troster, Ihmsen et al. (2012) dataset 2 | 15; 15 | Buprenorphine | Adverse events were assessed but not reported | Not reported |
| Koppert, Dern et al. (2001) dataset 2 | 12; 12 | Alfentanil | * Pruritus: 3 * Perioral numbness: 1 * Dizziness: 4 * Nausea: 3 * Sedation: 8 | * Dizziness: 1 * Sedation: 2 |
| Park, Max et al (1995) dataset 3 | 12; 12 | Alfentanil | * Sedation: 12 * Emesis: 3 * Nausea: 3 * Pruritus: 9 | None observed |
| Park, Max et al (1995) dataset 4 | 12; 12 | Alfentanil | * Pruritus: 9 * Nausea: 3 * Emesis: 2 * Sedation: 12 | * Sedation: 1 |
| Schifftner, Schulteis et al. (2017) | 18; 18 | Alfentanil | * Sedation: 15 * Light headedness: 10 * Nausea: 4 * 'Other': 3 (specifics not reported) | * Sedation: 2 * Light headedness: 1 |
| Andresen, Staahl et al. (2011) dataset 2 & 4 | 21; 21 in each dataset | Fentanyl | At 24 hours:   * Local irritation at the fentanyl patch site: 13 * Nausea: 12 * Pruritus: 10 * Dizziness: 19 * Drowsiness: 15 * Fatigue: 2 * Vomiting: 4 * Dysuria: 2 * Constipation: 1 * ‘Other’: 1 (specifics not reported)   At 48 hours:   * Local irritation at the fentanyl patch site: 14 * Nausea: 2 * Pruritus: 6 * Dizziness: 11 * Drowsiness: 10 * Dysuria: 2 * Constipation: 5 * Headache: 2   At 72 hours:   * Local irritation at the fentanyl patch site: 14 * Nausea: 5 * Pruritus: 2 * Dizziness: 7 * Drowsiness: 8 * Dysuria: 1 * Headache: 2 |  |
| Troster, Ihmsen et al. (2012) dataset 1 | 15; 15 | Fentanyl | Adverse events were assessed but not reported | Not reported |
| Worrich, Schuler et al. (2007) | 12; 12 | Fentanyl | None observed | Not reported |
| Filitz, Ihmsen et al. (2008) dataset 2 | 17; 17 | Tramadol | Nauseas and vomiting: 1 | Not reported |
| Petersen, Maloney et al. (2003) dataset 3 | 13; 13 | Hydromorphone | Adverse events were assessed but not reported | Not reported |
| Troster, Ihmsen et al. (2012) dataset 3 | 15; 15 | Fentanyl and buprenorphine | Adverse events were assessed but not reported | Not reported |
| NMDA receptor antagonist (n = 37) | | | | |
| Andersen, Felsby et al. (1996) | 17; 17 | Ketamine | * Pleasant feeling of detachment and occasional recall phenomena.   Number of participants experiencing adverse event was not reported. | Not reported |
| Angst, Koppert et al. (2003) dataset 1 | 10; 10 | Ketamine | * Sedation: 10 * Nausea: 1 * Dysphoric: 1 * Blurred vision: 2 * General numbness: 1 | Not reported |
| Gottrup, Hansen et al (2000) dataset 1 | 12; 12 | Ketamine | * Paraesthesia: 2 * Dizziness: 4 * Sleepiness: 1 * Relaxed: 5 * Euphoria: 1 * Unreality: 3 * Drunkenness: 3 * ‘Flying’: 2 | None observed |
| Gottrup, Bach et al (2004) dataset 1 | 12; 12 | Ketamine | * Paraesthesia: 6 * Dizziness: 6 * Sleepiness: 6 | None observed |
| Gottrup, Bach et al (2000) dataset 2 | 10; 10 | Ketamine | * Paraesthesia: 6 * Dizziness: 6 * Sleepiness: 6 | None observed |
| Ilkjaer, Petersen et al. (1996) datasets 1 & 3 | 19; 19 in each dataset | Ketamine | * Drowsiness: 19 * Discomfort: 5 * Feeling drunk or dizzy: not reported | Not reported |
| Ilkjaer, Petersen et al. (1996) datasets 2 & 4 | 19; 19 in each dataset | Ketamine | * Drowsiness: 19 * Discomfort: 3 * Feeling drunk or dizzy: not reported | Not reported |
| Koppert, Dern et al. (2001) dataset 1 | 12; 12 | Ketamine | * Perioral numbness: 4 * Hypoacusis/hyperacusis: 10 * Dizziness: 3 * Sedation: 11 * Dissociative effects: 8 | * Dizziness: 1 * Sedation: 2 |
| Koppert, Sittl et al. (2003) dataset 1 | 13; 13 | Ketamine | * Primary hyperacusis and sedation: 8 | Not reported |
| Mikkelsen, Jorgensen et al. (2000) datasets 1, 2, 3 & 4 | 24; 24 in each dataset | Ketamine | * Sedation   Number of participants experiencing adverse event was not reported. | None observed |
| Mikkelsen, Ilkjaer et al. (1999) dataset 1 | 23; 23 | Ketamine | * Changed perceptions of body parts * Sedation   Number of participants experiencing adverse event was not reported. | Not reported |
| Park, Max et al (1995) dataset 1 | 12; 12 | Ketamine | * Sedation: 12 | None observed |
| Park, Max et al (1995) dataset 2 | 12; 12 | Ketamine | * Nausea: 1 * Emesis: 1 * Dissociative effect: 2 * Sedation: 12 | * Sedation: 1 |
| Pedersen, Galle et al (1998) dataset 1 | 15; 15 | Ketamine | * Drowsiness: 5 * Dizziness: 5 * Nausea: 1 * Vertigo: 5 * Anxiety: 4 * Feeling drunk: 5 * Paraesthesia: 1 | * Drowsiness: 1 * Dizziness: 1 * Nausea: 1 |
| Pedersen, Galle et al (1998) dataset 2 | 15; 15 | Ketamine | * Drowsiness: 4 * Dizziness: 5 * Nausea: 2 * Vertigo: 5 * Anxiety: 1 * Feeling drunk: 7 * Paraesthesia: 1 | * Drowsiness: 1 * Dizziness: 1 * Nausea: 1 |
| Pöyhiä and Vainio (2006) | 9; 9 | Ketamine | None observed |  |
| Schulte, Sollevi et al. (2004) dataset 2 | 11; 11 | Ketamine | * Nausea and/or vomiting: 2 * Flush: 1 * Chest oppression: 1 * Tiredness: 3 * Dizziness: 10 * Anxiety: 1 * Out-of-body sensation: 10 | None observed |
| Warncke, Stubhaug et al. (1997) dataset 2 | 12; 12 | Ketamine | * Fatigue: 2 * Dizziness: 8 * Visual disturbance: 5 * Discomfort: 3 * Pleasant feeling: 4 * Paraesthesia: 4 * Feeling of ‘unreality’: 2 * Sleepy: 3 | Not reported |
| Warncke, Jorum et al. (1997) dataset 1 | 10; 10 | Ketamine | None observed | Not reported |
| Warncke, Stubhaug et al. (2000) dataset 1 | 12; 12 | Ketamine | * Fatigue: 4 * Dizziness: 4 * Visual disturbance: 7 * Pleasant feeling: 3 * Paraesthesia: 4 * Feeling of ‘unreality’: 4 * Sleepy: 3 | Not reported |
| Duedahl, Dirks et al. (2005) datasets 1 & 2 | 22; 22 in dataset 1 and 20; 20 in dataset 2 | dextromethorphan | * Drowsiness: 13 * Dizziness: 10 * Redness at the site of infusion: 11 * Itching/burning at the site of infusion: 14 | * Drowsiness: 2 * Light headedness: 1 |
| Ilkjaer, Dirks et al. (1997) datasets 1, 2, 3 & 4 | 25; 25 in each dataset | dextromethorphan | * Dizziness * Nausea * Drowsiness * Discomfort   Number of participants experiencing adverse event was not reported. | * Dizziness * Nausea * Drowsiness * Discomfort   Number of participants experiencing adverse event was not reported. |
| Martin, Narjoz et al. (2019) | 20; 20 | dextromethorphan | * Dry mouth: 3 * Fatigue: 3 | * Fatigue: 3 * Stomach ache: 3 |
| Mathiesen, Imbimbo et al. (2006) datasets 1 & 2 | 17; 17 in each dataset | CHF3381 | * Fatigue: 12 * Dizziness: 19 * Somnolence: 4 * Paraesthesia: 6 * Nausea: 3 * Blurred vision: 2 * Feeling drunk: 2 * Feeling abnormal: 1 * Headache: 2 * Increased salivation: 1 * Hot flush: 1 | * Fatigue: 7 * Dizziness: 2 * Somnolence: 1 * Feeling drunk: 2 * Depression: 1 * Increased alanine transaminase: 2 * Increased bilirubin: 1 |
| Klein, Magerl et al (2008) dataset 2 | 18; 19 | Flupirtine | * Dizziness: 4 * Vertigo: 1 * Fatigue: 3 * Headache: 1 * Hepatic enzyme increased: 2 | * Dizziness: 2 * Fatigue: 2 * Euphoric mood: 1 * Hepatic enzyme increase: 1 * Nausea: 1 * Photophobia: 2 |
| Mikkelsen, Dirks et al. (2001) | 15; 15 | Magnesium sulphate | * Light headedness * Drowsiness   Number of participants experiencing adverse event was not reported. | None observed |
| Klein, Magerl et al (2008) dataset 1 | 18; 19 | Neramexane | * Dizziness: 8 * Vertigo: 9 * Euphoric mood: 3 * Headache: 2 * Nausea: 2 * Gait disturbance: 2 | * Dizziness: 2 * Fatigue: 2 * Euphoric mood: 1 * Hepatic enzyme increase: 1 * Nausea: 1 * Photophobia: 2 |
| Alpha-2-delta subunit of voltage-gated calcium channel blocker (n = 16) | | | | |
| Boyle, Fernando et al. (2014) dataset 1 | 30; 14 | Gabapentin | * Headache: 6 * Fatigue: 4 * Feeling abnormal: 1 * Dizziness: 1 * Feeling of relaxation: 1 * Lethargy: 1 | * Headache: 2 |
| Dirks, Petersen et al. (2002) datasets 1 & 2 | 25; 25 in each dataset | Gabapentin | * Light headedness: 7 | * Light headedness: 2 |
| Gottrup, Juhl et al. (2004) | 20; 20 | Gabapentin | * Fatigue: 11 * Dizziness: 7 * Headache: 7 * Somnolence: 2 * Concentration impaired: 2 * Rash: 1 * Nervousness: 1 * Unpleasant dreams: 1 | * Fatigue: 8 * Dizziness: 3 * Headache: 5 * Somnolence: 2 * Concentration impaired: 1 |
| Mathiesen, Imbimbo et al. (2006) datasets 3 & 4 | 27; 27 | Gabapentin | * Fatigue: 20 * Dizziness: 3 * Somnolence: 7 * Feeling drunk: 1 * Euphoric mood: 2 * Feeling abnormal:1 * Headache: 2 * Hangover: 1 * Sedation: 1 * Increased alertness: 1 * Increased bilirubin:2 * Increased platelets: 1 | * Fatigue: 7 * Dizziness: 2 * Somnolence: 1 * Feeling drunk: 2 * Depression: 1 * Increased ALAT: 2 * Increased bilirubin: 1 |
| Petersen, Iyengar et al. (2014) dataset 2 | 25; 25 | Gabapentin | * Headache: 2 * Dizziness: 1 * Abdominal pain: 1 * Diarrhoea: 1 * Dizziness postural: 1 * Hypoesthesia: 1 * Petechiae: 1 * Somnolence: 1 | * Headache: 1 |
| Wallace, Schulteis (2008) | 10; 10 | Gabapentin | * Dry mouth: 10 * Fatigue: 10 * Sedated: 29 * Dizziness: 22 * Nausea: 1 * Diarrhoea: 1 * Headache: 2 | * Dry mouth: 1 * Fatigue: 2 * Sedated: 9 * Diarrhoea: 3 |
| Werner, Perkins et al. (2001) | 22; 22 | Gabapentin | * Drowsiness * Postural instability   Number of participants experiencing adverse event was not reported. |  |
| Chizh, Gohring et al. (2007) dataset 1 | 16; 32 | Pregabalin | * Fatigue: 4 * Dizziness: 9 * Dry mouth: 4 * Drowsiness: 6 * Muscle weakness: 1 * Feeling energetic: 2 * Heavy tongue: 1 | * Fatigue: 3 * Taste change: 1 * Diarrhoea: 2 * Drowsiness: 1 * Headache: 1 |
| Di Lionardo, Di Stefano et al. (2021) | 10; 10 | Pregabalin | * Somnolence: 3 | Not reported |
| Lötsch, Walter et al. (2020) | 16; 16 | Pregabalin | * Tiredness * Drowsiness   Number of participants experiencing adverse event was not reported. | Not reported |
| Wang, Bolognese et al. (2008) dataset 1 | 20; 20 | Pregabalin | Adverse events were assessed but not reported | Not reported |
| Wong and Wallace (2014) | 13; 13 | Pregabalin | * Drowsiness: 6 * Euphoria: 4 * Dizziness: 1 | None observed |
| Eisenach, Hood et al. (2000) | 24; 24 | Clonidine | * Blood pressure decrease * Heart rate decrease (after epidural injection but not after intrathecal injection) * Sedation   Number of participants experiencing adverse event was not reported. | Not reported |
| Koppert, Sittl et al. (2003) dataset 4 | 13; 13 | Clonidine | * Blood pressure decrease * Desaturation Sedation   Number of participants experiencing adverse event was not reported. | Not reported |
| Voltage-gated sodium channel blocker (n = 21) | | | | |
| Dirks, Fabricius et al. (2000) | 25; 15 | Lidocaine | After bolus lidocaine:   * Light headedness: 88% Drowsiness: 67% * Perioral numbness: 29% * Metal taste: 17% * Dry mouth: 42% * Nausea: 17% * Muscular twitch: 4% * Tinnitus: 17% * Visual disturbances: 35%   After infusion lidocaine:   * Light headedness 50% * Drowsiness: 46% * Perioral numbness: 4% * Metal taste:13% * Dry mouth: 21% * Nausea: 13% * Muscular twitch: 4% * Tinnitus: 4% * Visual disturbances:13% | After bolus saline:   * Light headedness: 4% Drowsiness: 13% * Metal taste: 4%   After infusion with saline:   * Light headedness: 4% * Drowsiness: 17% * Dry mouth: 4% |
| Gottrup, Hansen et al. (2000) dataset 2 | 12; 12 | Lidocaine | * Paraesthesia: 6 * Dizziness: 3 * Sleepiness: 2 * Nausea: 1 * Dry mouth: 3 * Blurred vision: 2 * Light headedness: 2 * Relaxed: 1 * Unreality: 2 * Drunkenness: 4 * Palpitations: 2 | None observed |
| Gottrup, Bach et al. (2004) dataset 2 | 12; 12 | Lidocaine | None observed | Not reported |
| Gottrup, Bach et al. (2000) dataset 1 | 12; 12 | Lidocaine | None observed | Not reported |
| Holthusen, Irsfeld et al. (2000) datasets1 & 2 | 6; 6 in each dataset | Lidocaine | * Hyperacusis * Light headedness or dizziness   Number of participants experiencing adverse event was not reported. | * Fatigue   Number of participants experiencing adverse event was not reported. |
| Kawamata, Takahashi et al. (2002) dataset 1 | 8; 8 | Lidocaine | * Nausea: 1 * Visual disturbance 38% * Light headedness: 63% * Perioral Numbness: 88% * Tinnitus: 63%. | None observed |
| Kawamata, Takahashi et al. (2002) dataset 2 | 8; 8 | Lidocaine | * Light headedness: 88% * Perioral numbness: 50% * Tinnitus: 50% | * Light headedness: 13% |
| Kawamata, Watanabe et al. (2002) dataset 1, 2, 3 & 4 | 6; 12 in datasets 1 &2  7;7 in datasets 3&4 | Lidocaine | None observed | * Nausea: 1 |
| Koppert, Dern et al. (2001) dataset 3 | 12; 12 | Lidocaine | * Perioral numbness: 8 Hypoacusis/hyperacusis: 7 * Dizziness: 4 * Nausea: 1 * Sedation: 4 | * Dizziness: 1 * Sedation: 2 |
| Koppert, Ostermeier et al. (2000) dataset 1 | 12; 12 | Lidocaine | None observed | Not reported |
| Koppert, Ostermeier et al. (2000) dataset 2 | 12; 12 | Lidocaine | None observed | Not reported |
| Lam, Wallace et al. (2011) | 13; 13 | Lidocaine | None observed | Not reported |
| Wallace, Laitin et al. (1997) | 15; 15 | Lidocaine | * Light headedness Sedation * Oral numbness * Metal taste * Muscle twitch   Number of participants experiencing adverse event was not reported. | Not reported |
| Warncke, Jorum et al. (1997) dataset 2 | 10; 10 | Lidocaine | None observed | Not reported |
| Petersen, Maloney et al. (2003) datasets 1 & 2 | 13; 13 in each dataset | Lamotrigine | * Sleepiness: 1 * Light headedness: 1 * Dizziness: 1 * Poor coordination: 1 * Shortness of breath: 1   All seen in a single participant | Not reported |
| Ando, Wallace et al. (2000) | 12; 12 | Mexiletine | * Nausea: 10 * Dizziness: 9 * Tremors: 4 * Muscle twitching: 3 * Headache: 2 * Visual disturbance: 2 * Pruritis: 2 * Difficulty concentrating: 2 * Muscle weakness: 1 * Dysphoria: 1 * Sedation: 1 * Rash: 1 * Dry mouth: 1 * Nervousness: 1 * Chest pressure: 1 | Not reported |
| Haller, Gantenbein et al. (2014) | 19; 19 | Ropivacaine | * Dizziness and/or tingling around the mouth: 9 | None observed |

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