Supplementary files

Table of Contents

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	Page 5

Section and Topic	Item #	Checklist item	Location where item is reported
		the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	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	24a	Provide registration information for the review, including register name and registration number, or state that the review was not	Page 2

Section and Topic	Item #	Checklist item	Location where item is reported
and protocol		registered.	
	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	
<u>Attrition bias</u>		
<u>Incomplete outcome data</u>	<u>Decision</u>	<u>Justification</u>
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	
<u>Measurement bias</u>		
	<u>Decision</u>	<u>Justification</u>
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]; I^2 = 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.

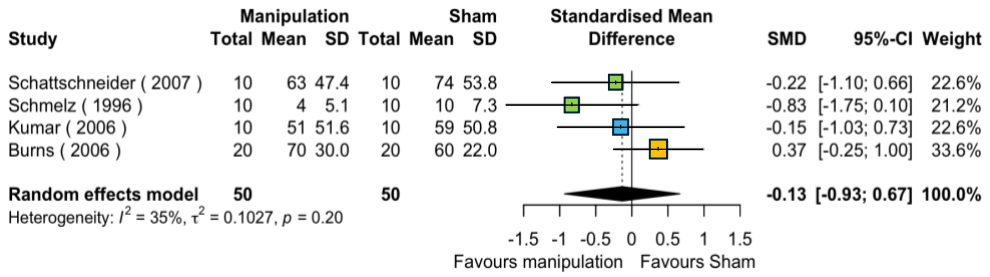

Figure 1: Forest plot of the pooled effect estimated of an inhibitor of cyclooxygenase-1 and -2 enzyme on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons. Green = acetylsalicylic acid, blue = ketorolac, orange = valdecoxib.

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]; I^2 = 74% (Fig 2), the 95% CI therefore includes the null hypothesis of no difference in effect between naloxone and the sham manipulations.

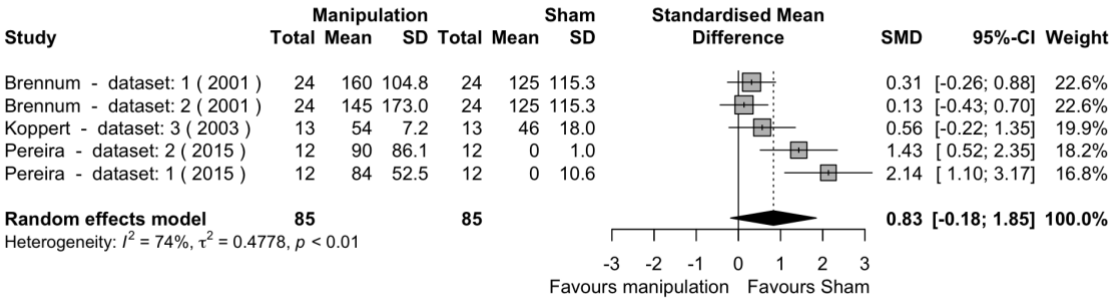

Figure 2: Forest plot of the pooled effect estimated of an opioid receptor antagonist – naloxone – on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons.

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 four administered 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]; I^2 = 32% (Fig 3), the 95% CI therefore includes the null hypothesis of no difference in effect between botulinum-neurotoxin-A and the sham manipulations.

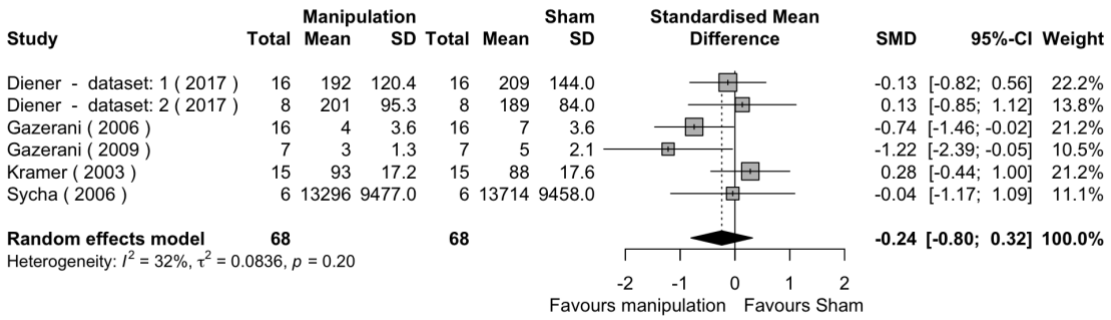

Figure 3: Forest plot of the pooled effect estimated of an inhibitor of presynaptic acetylcholine – botulinum-neurotoxin A – release on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons.

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]; I^2 = 32% (Fig 4), the 95% CI therefore includes the null hypothesis of no difference in effect between adenosine and the sham manipulations.

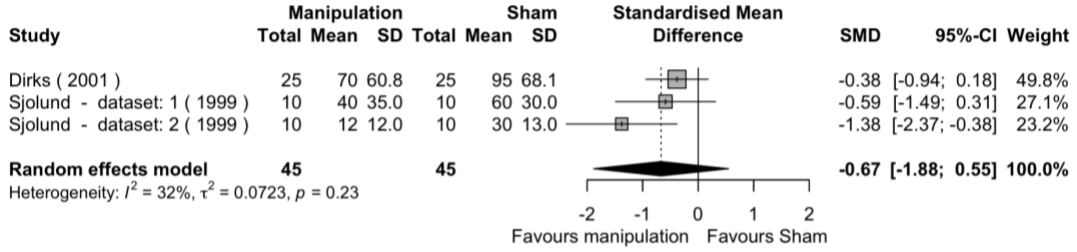

Figure 4: Forest plot of the pooled effect estimated of an adenosine receptor A2a, A2b, A3, and A1 agonist – adenosine – on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons.

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]; I^2 = 0% (Fig 5), the 95% CI therefore includes the null hypothesis of no difference in effect between cannabinoid receptor agonists and the sham manipulations.

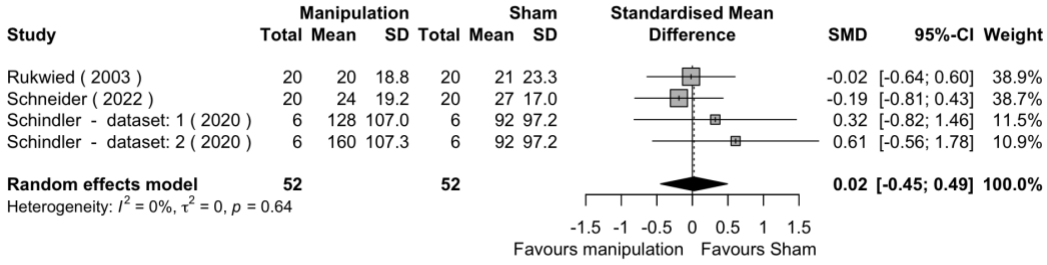

Figure 5: Forest plot of the pooled effect estimated of a cannabinoid receptor agonist on the surface area of secondary hypersensitivity from datasets that reported surface area data as between-group comparisons.

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).

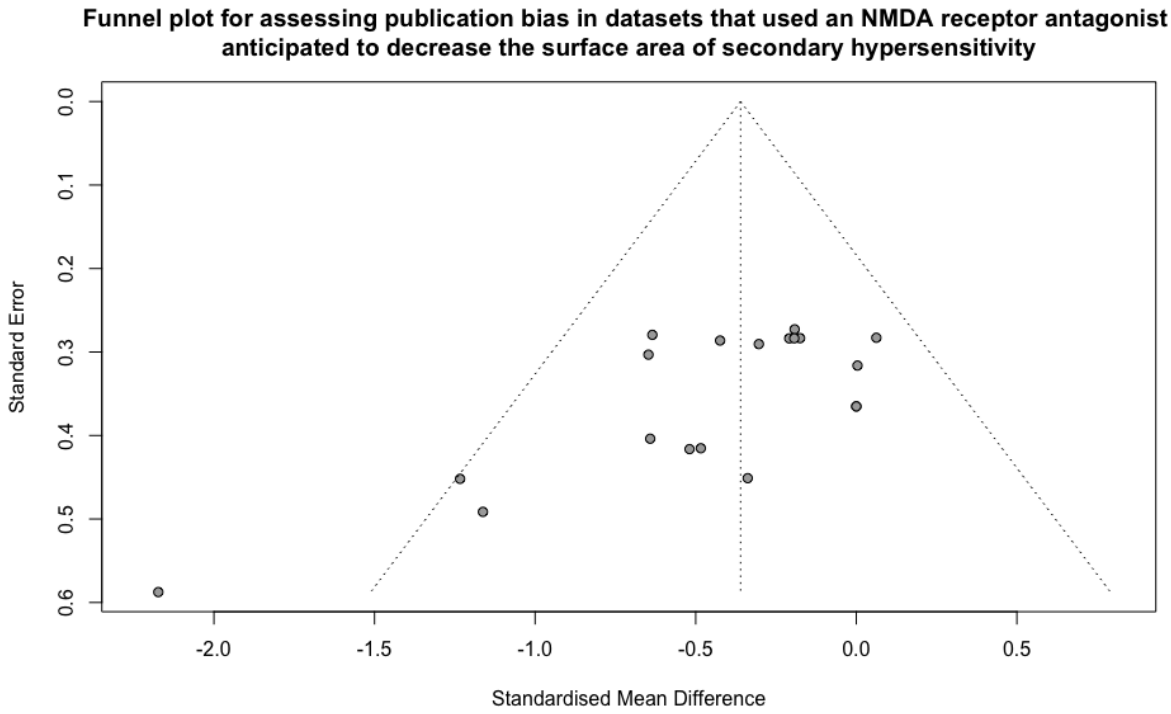

Figure 6: Funnel plot for assessing publication bias in datasets that used an NMDA receptor antagonist anticipated to decrease the surface area of secondary hypersensitivity.

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 not observed, as seen by a symmetrical funnel plot (Fig 7), and confirmed by Begg's test (p = 0.70).

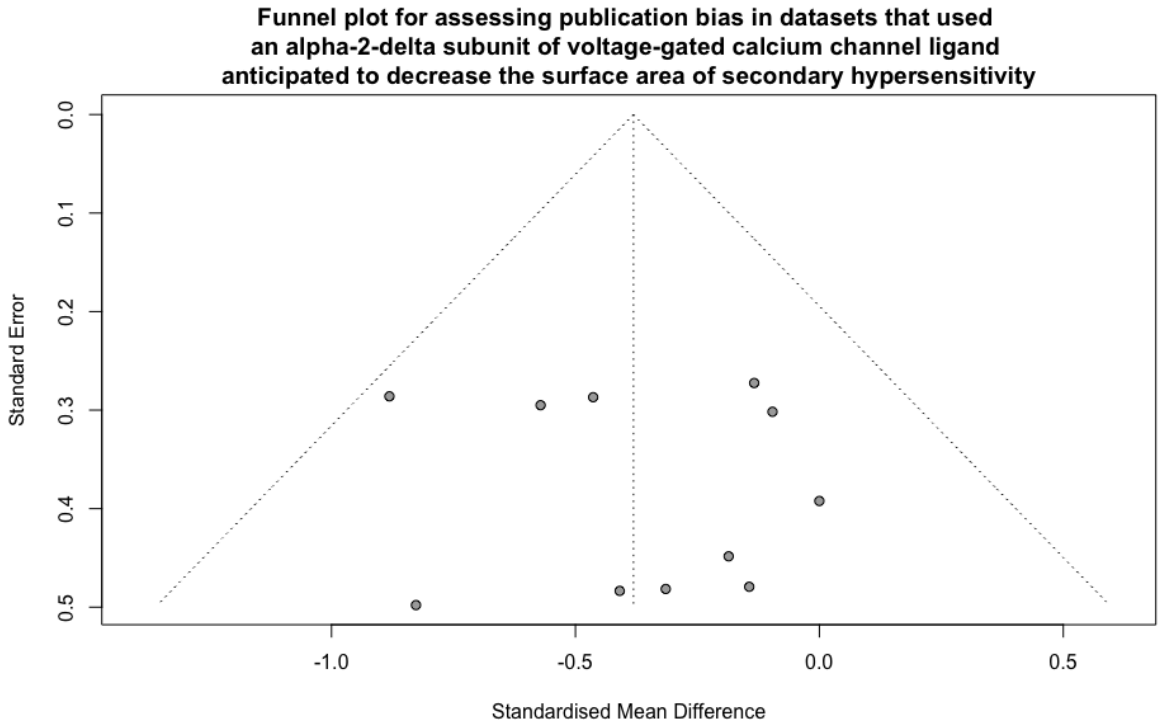

Figure 7: Funnel plot for assessing publication bias in datasets that used an alpha-2-delta subunit of voltage-gated calcium channel ligand anticipated to decrease the surface area of secondary hypersensitivity.

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 of voltage-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).

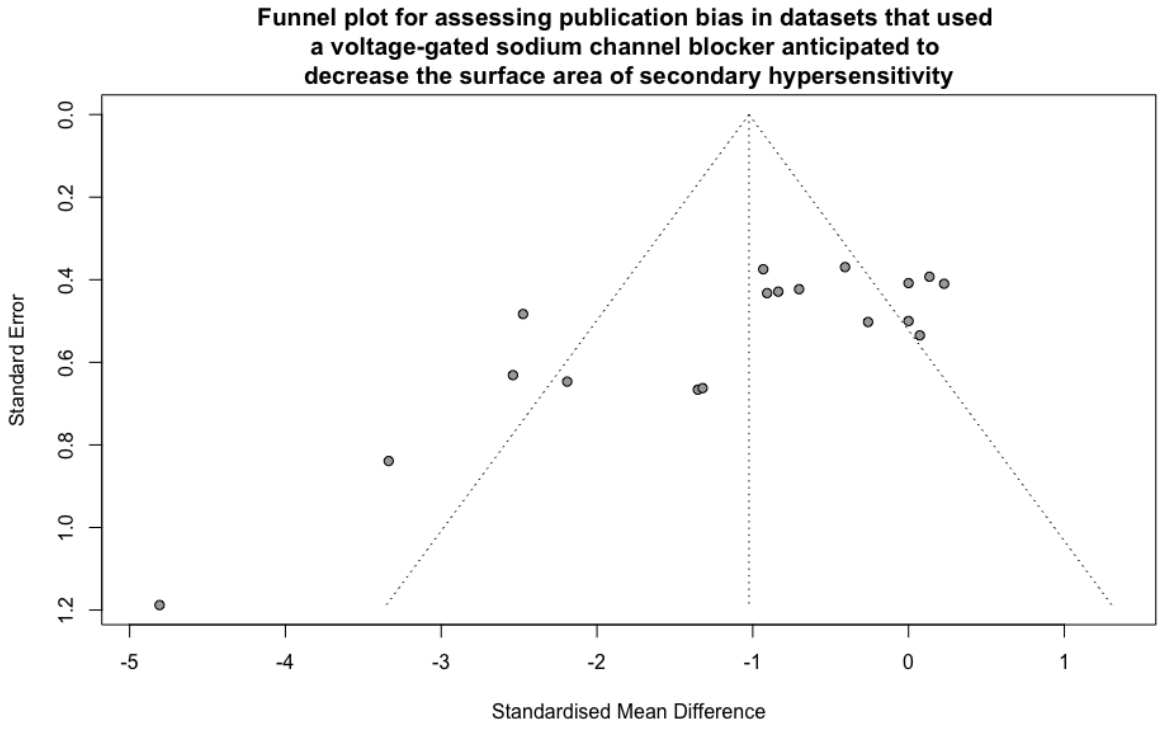

Figure 8: Funnel plot for assessing publication bias in datasets that used a voltage-gated sodium channel blocker anticipated to decrease the surface area of secondary hypersensitivity.

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 ($p = 0.02$).

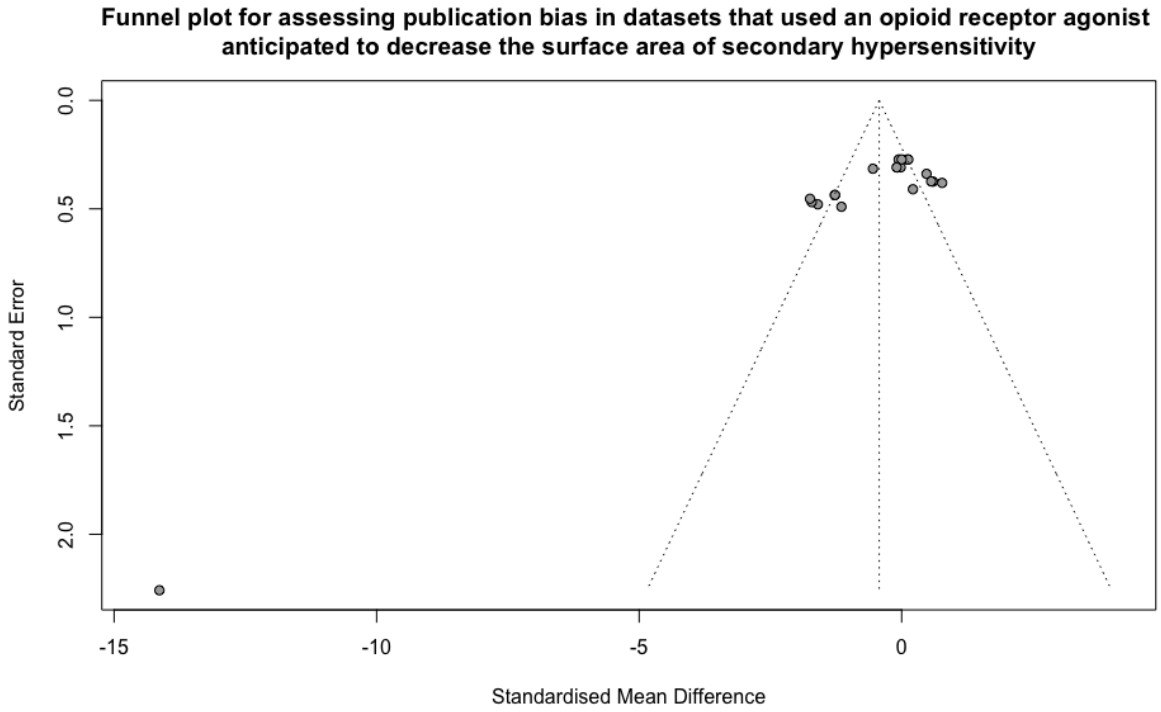

Figure 9: Funnel plot for assessing publication bias in datasets that used an opioid receptor agonist anticipated to decrease the surface area of secondary hypersensitivity.

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	Not reported

			- Feeling of muscular stiffness: 2 - Sleepy: 6	
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	<u>At 24 hours:</u> - 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) <u>At 48 hours:</u> - Local irritation at the buprenorphine patch site: 16 - Nausea: 13	Not reported

			- Pruritus: 10 - Dizziness: 18 - Drowsiness: 15 - Fatigue: 1 - Vomiting: 3 - Dysuria: 5 - Constipation: 4 - Headache: 1 - 'Other': 2 (specifics not reported) <u>At 72 hours:</u> - Local irritation at the buprenorphine patch site: 15 - Nausea: 10 - Pruritus: 9 - Dizziness: 18 - Drowsiness: 14 - Vomiting: 1 - Dysuria: 5 - Constipation: 3 - Headache: 3 <u>At 144 hours:</u> - 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)	
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	<u>At 24 hours:</u> - 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) <u>At 48 hours:</u> - Local irritation at the fentanyl patch site: 14 - Nausea: 2 - Pruritus: 6 - Dizziness: 11 - Drowsiness: 10 - Dysuria: 2 - Constipation: 5 - Headache: 2 <u>At 72 hours:</u> - 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	None observed

			- Euphoria: 1 - Unreality: 3 - Drunkenness: 3 - 'Flying': 2	
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	Not reported

			- Feeling of 'unreality': 2 - Sleepy: 3	
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	- Fatigue: 8 - Dizziness: 3 - Headache: 5 - Somnolence: 2

			- Concentration impaired: 2 - Rash: 1 - Nervousness: 1 - Unpleasant dreams: 1	- 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	<u>After bolus lidocaine:</u>	<u>After bolus saline:</u>

			- Light headedness: 88% Drowsiness: 67% - Perioral numbness: 29% - Metal taste: 17% - Dry mouth: 42% - Nausea: 17% - Muscular twitch: 4% - Tinnitus: 17% - Visual disturbances: 35% <u>After infusion lidocaine:</u> - Light headedness 50% - Drowsiness: 46% - Perioral numbness: 4% - Metal taste:13% - Dry mouth: 21% - Nausea: 13% - Muscular twitch: 4% - Tinnitus: 4% - Visual disturbances:13%	- Light headedness: 4% Drowsiness: 13% - Metal taste: 4% <u>After infusion with saline:</u> - 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

References for supplementary files

1. Andersen, H.H., P. Gazerani , L. Arendt-Nielsen, *High-concentration l-menthol exhibits counter-irritancy to neurogenic inflammation, thermal and mechanical hyperalgesia caused by trans-cinnamaldehyde.* The journal of pain : official journal of the American Pain Society, 2016. **17**(8): p. 919-29
2. Andersen, L.P., I. Gogenur, A.Q. Fenger, M.C. Petersen, J. Rosenberg , M.U. Werner, *Analgesic and antihyperalgesic effects of melatonin in a human inflammatory pain model: A randomized, double-blind, placebo-controlled, three-arm crossover study.* Pain, 2015. **156**(11): p. 2286-94
3. Bickel, A., S. Dorfs, M. Schmelz, C. Forster, W. Uhl , H. Handwerker, *Effects of antihyperalgesic drugs on experimentally induced hyperalgesia in man.* Pain, 1998. **76**(3): p. 317-325
4. Bishop, T., A. Ballard, H. Holmes, A.R. Young , S.B. McMahon, *Ultraviolet-b induced inflammation of human skin: Characterisation and comparison with traditional models of hyperlagesia.* European journal of pain, 2009. **13**(5): p. 524-532
5. Boyle, Y., D. Fernando, H. Kurz, S.R. Miller, M. Zucchetto , J. Storey, *The effect of a combination of gabapentin and donepezil in an experimental pain model in healthy volunteers: Results of a randomized controlled trial.* Pain, 2014. **155**(12): p. 2510-6
6. Brennum, J., F. Kaiser , J.B. Dahl, *Effect of naloxone on primary and secondary hyperalgesia induced by the human burn injury model.* Acta anaesthesiologica Scandinavica, 2001. **45**(8): p. 954-60
7. Brull, S.J., P.G. Atanassoff, D.G. Silverman, J.M. Zhang , R.H. LaMotte, *Attenuation of experimental pruritus and mechanically evoked dysesthesiae in an area of cutaneous allodynia.* Somatosensory and Motor Research, 1999. **16**(4): p. 299-303.<Go to ISI>://WOS:000084546000004
8. Burns, D., L. Hill, M. Essandoh, T.M. Jarzembowski, H.G. Schuler , P.K. Janicki, *Effect of valdecoxib pretreatment on pain and secondary hyperalgesia: A randomized controlled trial in healthy volunteers [isrctn05282752, nct00260325].* BMC anesthesiology, 2006. **6**: p. 3
9. Chassaing, C., J. Schmidt, A. Eschalier, J.M. Cardot , C. Dubray, *Hyperalgesia induced by cutaneous freeze injury for testing analgesics in healthy volunteers.* British journal of clinical pharmacology, 2006. **61**(4): p. 389-97
10. Chizh, B.A., M. Dusch, M. Puthawala, M. Schmelz, L.M. Cookson, R. Martina, J. Brown , W. Koppert, *The effect of intravenous infusion of adenosine on electrically evoked hyperalgesia in a healthy volunteer model of central sensitization.* Anesthesia and analgesia, 2004. **99**(3): p. 816-22
11. Chizh, B.A., M. Gohring, A. Troster, G.K. Quartey, M. Schmelz , W. Koppert, *Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers.* British journal of anaesthesia, 2007. **98**(2): p. 246-54
12. Davis, K.D., R.A. Meyer, J.L. Turnquist, T.G. Filloon, M. Pappagallo , J.N. Campbell, *Cutaneous pretreatment with the capsaicin analog ne-21610 prevents the pain to a burn and subsequent hyperalgesia.* Pain, 1995. **62**(3): p. 373-8
13. Diener, S.A., M. Breimhorst, T. Vogt, H.H. Krämer, P.D. Drummond, C. Geber , F. Birklein, *Differential effect of incobotulinumtoxin a on pain, neurogenic flare and hyperalgesia in human surrogate models of neurogenic pain.* European Journal of Pain, 2017. **21**(8): p. 1326-1335.http://ezproxy.uct.ac.za/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2017-18499-001&site=ehost-live frank.birklein@unimedizin-mainz.de
14. Dirks, J., K.L. Petersen, M.C. Rowbotham , J.B. Dahl, *Effect of systemic adenosine on pain and secondary hyperalgesia associated with the heat/capsaicin sensitization model in healthy volunteers.* Regional anesthesia and pain medicine, 2001. **26**(5): p. 414-9
15. Duedahl, T.H., J. Dirks, K.B. Petersen, J. Romsing, N.E. Larsen , J.B. Dahl, *Intravenous dextromethorphan to human volunteers: Relationship between pharmacokinetics and anti-hyperalgesic effect.* Pain, 2005. **113**(3): p. 360-8
16. Eisenach, J.C., D.D. Hood , R. Curry, *Preliminary efficacy assessment of intrathecal injection of an american formulation of adenosine in humans.* Anesthesiology, 2002. **96**(1): p. 29-34
17. Eisenach, J.C., D.D. Hood , R. Curry, *Intrathecal, but not intravenous, clonidine reduces experimental thermal or capsaicin-induced pain and hyperalgesia in normal volunteers.* Anesthesia and analgesia, 1998. **87**(3): p. 591-6

18. Filitz, J., H. Ihmsen, W. Gunther, A. Troster, H. Schwilden, J. Schuttler , W. Koppert, *Supra-additive effects of tramadol and acetaminophen in a human pain model.* Pain, 2008. **136**(3): p. 262-70
19. Fuchs, P.N., J.N. Campbell , R.A. Meyer, *Secondary hyperalgesia persists in capsaicin desensitized skin.* Pain, 2000. **84**(2-3): p. 141-9
20. Gazerani, P., N.S. Pedersen, C. Staahl, A.M. Drewes , L. Arendt-Nielsen, *Subcutaneous botulinum toxin type a reduces capsaicin-induced trigeminal pain and vasomotor reactions in human skin.* Pain, 2009. **141**(1-2): p. 60-9
21. Gazerani, P., C. Staahl, A.M. Drewes , L. Arendt-Nielsen, *The effects of botulinum toxin type a on capsaicin-evoked pain, flare, and secondary hyperalgesia in an experimental human model of trigeminal sensitization.* Pain, 2006. **122**(3): p. 315-25
22. Giuliani, A., L. Lorenzini, V.A. Baldassarro, M. Pannella, M. Cescatti, M. Fernandez, G. Alastra, A. Flagelli, G. Villetti, B.P. Imbimbo, L. Giardino , L. Calzà, *Effects of topical application of chf6467, a mutated form of human nerve growth factor, on skin wound healing in diabetic mice.* J Pharmacol Exp Ther, 2020. **375**(2): p. 317-331
23. Kalliomäki, J., K. Huizar, M. Kågedal, B. Hägglöf , M. Schmelz, *Evaluation of the effects of a metabotropic glutamate receptor 5-antagonist on electrically induced pain and central sensitization in healthy human volunteers.* European Journal of Pain, 2013. **17**(10): p. 1465-1471.http://ezproxy.uct.ac.za/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2013-36084-006&site=ehost-live jarkko.kalliomaki@ki.se
24. Koppert, W., M. Angst, M. Alsheimer, R. Sittl, S. Albrecht, J. Schuttler , M. Schmelz, *Naloxone provokes similar pain facilitation as observed after short-term infusion of remifentanil in humans.* Pain, 2003. **106**(1-2): p. 91-9
25. Koppert, W., S.K. Dern, R. Sittl, S. Albrecht, J. Schuttler , M. Schmelz, *A new model of electrically evoked pain and hyperalgesia in human skin: The effects of intravenous alfentanil, s(+)-ketamine, and lidocaine.* Anesthesiology, 2001. **95**(2): p. 395-402
26. Koppert, W., J. Filitz, A. Troster, H. Ihmsen, M. Angst, H. Flor, J. Schuttler , M. Schmelz, *Activation of naloxone-sensitive and -insensitive inhibitory systems in a human pain model.* The journal of pain : official journal of the American Pain Society, 2005. **6**(11): p. 757-64
27. Koppert, W., N. Ostermeier, R. Sittl, C. Weidner , M. Schmelz, *Low-dose lidocaine reduces secondary hyperalgesia by a central mode of action.* Pain, 2000. **85**(1-2): p. 217-24
28. Koppert, W., R. Sittl, K. Scheuber, M. Alsheimer, M. Schmelz , J. Schuttler, *Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by s-ketamine and clonidine in humans.* Anesthesiology, 2003. **99**(1): p. 152-9
29. Koppert, W., A. Wehrfritz, N. Korber, R. Sittl, S. Albrecht, J. Schuttler , M. Schmelz, *The cyclooxygenase isozyme inhibitors parecoxib and paracetamol reduce central hyperalgesia in humans.* Pain, 2004. **108**(1-2): p. 148-53
30. Kramer, H.H., C. Angerer, F. Erbguth, M. Schmelz , F. Birklein, *Botulinum toxin a reduces neurogenic flare but has almost no effect on pain and hyperalgesia in human skin.* Journal of neurology, 2003. **250**(2): p. 188-93
31. Kumar, K., G.R. Polston , M.S. Wallace, *The effect of intravenous ketorolac on capsaicin-induced deep tissue hyperalgesia.* Anesthesia & Analgesia, 2006. **103**(3): p. 696-702.<Go to ISI>://BIOABS:BACD200600410267
32. Larsen, I.M., A.M. Drewes , A.E. Olesen, *The effect of a combination of diclofenac and methadone applied as gel in a human experimental pain model – a randomized, placebo-controlled trial.* Basic and Clinical Pharmacology and Toxicology, 2018. **123**(2): p. 188-194.https://www.scopus.com/inward/record.uri?eid=2-s2.0-85045273888&doi=10.1111%2fbcpt.12993&partnerID=40&md5=a5e4b0c96b69dc3246b2f1902379265d
33. Lee, M.C., S. Bond, D. Wheeler, I. Scholtes, G. Armstrong, P. McNaughton , D. Menon, *A randomised, double blind, placebo-controlled crossover trial of the influence of the hcn channel blocker ivabradine in a healthy volunteer pain model: An enriched population trial.* Pain, 2019
34. Lenz, H., J. Raeder, T. Draegni, F. Heyerdahl, M. Schmelz , A. Stubhaug, *Effects of cox inhibition on experimental pain and hyperalgesia during and after remifentanil infusion in humans.* Pain, 2011. **152**(6): p. 1289-97
35. Lorenzini, K., M. Besson, Y. Daali, D. Salomon, P. Dayer , J. Desmeules, *Validation of the simplified uvb model to assess the pharmacodynamics of analgesics in healthy human volunteers.* Chimia, 2012. **66**(5): p. 296-9

36. Matthey, A., Y. Daali, F. Curtin, A. Poncet, J. Desmeules , M. Besson, *Gabaergic modulation of secondary hyperalgesia: A randomized controlled 4-way crossover trial with the α2-subunit preferring gaba positive allosteric modulator, n-desmethyl-clobazam in healthy volunteers.* Eur J Pain, 2020. **24**(6): p. 1094-1106
37. Michaux, G.P., W. Magerl, F. Anton , R.D. Treede, *Experimental characterization of the effects of acute stresslike doses of hydrocortisone in human neurogenic hyperalgesia models.* Pain, 2012. **153**(2): p. 420-8
38. Mikkelsen, S., S. Ilkjaer, J. Brennum, F.M. Borgbjerg , J.B. Dahl, *The effect of naloxone on ketamine-induced effects on hyperalgesia and ketamine-induced side effects in humans.* Anesthesiology, 1999. **90**(6): p. 1539-45
39. Moiniche, S., J.L. Pedersen , H. Kehlet, *Topical ketorolac has no antinociceptive or anti-inflammatory effect in thermal injury.* Burns : journal of the International Society for Burn Injuries, 1994. **20**(6): p. 483-6
40. Nickel, F.T., S. Ott, S. Mohringer, T. Munster, S. Riess, J. Filitz, W. Koppert , C. Maihofner, *Effects of different anesthetics on pain processing in an experimental human pain model.* Pain practice : the official journal of World Institute of Pain, 2016. **16**(7): p. 820-30
41. Park, K.M., M.B. Max, E. Robinovitz, R.H. Gracely , G.J. Bennett, *Effects of intravenous ketamine, alfentanil, or placebo on pain, pinprick hyperalgesia, and allodynia produced by intradermal capsaicin in human subjects.* Pain, 1995. **63**(2): p. 163-72
42. Pedersen, J.L., S. Moiniche , H. Kehlet, *Topical glucocorticoid has no antinociceptive or anti-inflammatory effect in thermal injury.* British journal of anaesthesia, 1994. **72**(4): p. 379-82
43. Peng, K.P., T. Jürgens, H. Basedau, L. Ortlieb , A. May, *Sumatriptan prevents central sensitization specifically in the trigeminal dermatome in humans.* Eur J Pain, 2022
44. Pereira, M.P., R.R. Donahue, J.B. Dahl, M. Werner, B.K. Taylor , M.U. Werner, *Endogenous opioid-masked latent pain sensitization: Studies from mouse to human.* PloS one, 2015. **10**(8): p. e0134441
45. Pereira, M.P., M.U. Werner, T.K. Ringsted, M.C. Rowbotham, B.K. Taylor , J.B. Dahl, *Does naloxone reinstate secondary hyperalgesia in humans after resolution of a burn injury? A placebo-controlled, double-blind, randomized, cross-over study.* PloS one, 2013. **8**(5): p. e64608
46. Petersen, K.L., J. Brennum , J.B. Dahl, *Experimental evaluation of the analgesic effect of ibuprofen on primary and secondary hyperalgesia.* Pain, 1997. **70**(2-3): p. 167-74
47. Petersen, K.L., S. Iyengar, A.S. Chappell, E.D. Lobo, H. Reda, W.R. Prucka , S.J. Verfaille, *Safety, tolerability, pharmacokinetics, and effects on human experimental pain of the selective ionotropic glutamate receptor 5 (iglur5) antagonist ly545694 in healthy volunteers.* Pain, 2014. **155**(5): p. 929-36
48. Poyhia, R. , A. Vainio, *Topically administered ketamine reduces capsaicin-evoked mechanical hyperalgesia.* The Clinical journal of pain, 2006. **22**(1): p. 32-6
49. Rukwied, R., A. Watkinson, F. McGlone , M. Dvorak, *Cannabinoid agonists attenuate capsaicin-induced responses in human skin.* Pain, 2003. **102**(3): p. 283-8
50. Schattschneider, J., I. Zum Buttel, A. Binder, G. Wasner, J. Hedderich , R. Baron, *Mechanisms of adrenosensitivity in capsaicin induced hyperalgesia.* European journal of pain (London, England), 2007. **11**(7): p. 756-63
51. Schindler, E.A.D., A.M. Schnakenberg Martin, R.A. Sewell, M. Ranganathan, A. DeForest, B.P. Pittman, A. Perrino, Jr. , D.C. D'Souza, *In an exploratory randomized, double-blind, placebo-controlled, cross-over study, psychoactive doses of intravenous delta-9-tetrahydrocannabinol fail to produce antinociceptive effects in healthy human volunteers.* Psychopharmacology (Berl), 2020. **237**(10): p. 3097-3107
52. Schmelz, M. , M. Kress, *Topical acetylsalicylate attenuates capsaicin induced pain, flare and allodynia but not thermal hyperalgesia.* Neuroscience letters, 1996. **214**(1): p. 72-4
53. Schneider, T., L. Zurbriggen, M. Dieterle, E. Mauermann, P. Frei, K. Mercer-Chalmers-Bender , W. Ruppen, *Pain response to cannabidiol in induced acute nociceptive pain, allodynia, and hyperalgesia by using a model mimicking acute pain in healthy adults in a randomized trial (canab i).* Pain, 2022. **163**(1): p. e62-e71
54. Schulte, H., A. Sollevi , M. Segerdahl, *The synergistic effect of combined treatment with systemic ketamine and morphine on experimentally induced windup-like pain in humans.* Anesthesia and analgesia, 2004. **98**(6): p. 1574-80
55. Sjolund, K.F., M. Segerdahl , A. Sollevi, *Adenosine reduces secondary hyperalgesia in two human models of cutaneous inflammatory pain.* Anesthesia and analgesia, 1999. **88**(3): p. 605-10

56. Springborg, A.D., E.K. Jensen, M. Kreilgaard, M.A. Petersen, T. Papathanasiou, T.M. Lund, B.K. Taylor , M.U. Werner, *High-dose naloxone: Effects by late administration on pain and hyperalgesia following a human heat injury model. A randomized, double-blind, placebo-controlled, crossover trial with an enriched enrollment design.* PLoS One, 2020. **15**(11): p. e0242169
57. Stubhaug, A., L. Romundstad, T. Kaasa , H. Breivik, *Methylprednisolone and ketorolac rapidly reduce hyperalgesia around a skin burn injury and increase pressure pain thresholds.* Acta anaesthesiologica Scandinavica, 2007. **51**(9): p. 1138-46
58. Sycha, T., S. Anzenhofer, S. Lehr, L. Schmetterer, B. Chizh, H.G. Eichler , B. Gustorff, *Rofecoxib attenuates both primary and secondary inflammatory hyperalgesia: A randomized, double blinded, placebo controlled crossover trial in the uv-b pain model.* Pain, 2005. **113**(3): p. 316-22
59. Sycha, T., D. Samal, B. Chizh, S. Lehr, B. Gustorff, P. Schnider , E. Auff, *A lack of antinociceptive or antiinflammatory effect of botulinum toxin a in an inflammatory human pain model.* Anesthesia and analgesia, 2006. **102**(2): p. 509-16
60. Tanaka, S., T. Ishida, K. Ishida, S. Fuseya, M. Ito, A. Sakamoto , M. Kawamata, *A randomized, double-blinded, placebo-controlled, crossover study of the hcn channel blocker ivabradine in a capsaicin-induced pain model in healthy volunteers.* Sci Rep, 2022. **12**(1): p. 17246
61. Troster, A., R. Sittl, B. Singler, M. Schmelz, J. Schuttler , W. Koppert, *Modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by parecoxib in humans.* Anesthesiology, 2006. **105**(5): p. 1016-23
62. Wallace, M.S., D. Barger , G. Schulteis, *The effect of chronic oral desipramine on capsaicin-induced allodynia and hyperalgesia: A double-blinded, placebo-controlled, crossover study.* Anesthesia and analgesia, 2002. **95**(4): p. 973-8, table of contents
63. Wang, H., J. Bolognese, N. Calder, J. Baxendale, A. Kehler, C. Cummings, J. Connell , G. Herman, *Effect of morphine and pregabalin compared with diphenhydramine hydrochloride and placebo on hyperalgesia and allodynia induced by intradermal capsaicin in healthy male subjects.* The Journal of Pain, 2008. **9**(12): p. 1088-95
64. Wanigasekera, V., M. Mezue, J. Andersson, Y. Kong , I. Tracey, *Disambiguating pharmacodynamic efficacy from behavior with neuroimaging: Implications for analgesic drug development.* Anesthesiology, 2016. **124**(1): p. 159-68
65. Warncke, T., J. Brennum, L. Arendt-Nielsen , P.-E. Branebjerg, *Effects of local and systemic ibuprofen on primary and secondary hyperalgesia in man.* Current Therapeutic Research, 1996. **57**(12): p. 937-949.<Go to ISI>://BIOABS:BACD199799384187
66. Warncke, T., E. Jorum , A. Stubhaug, *Local treatment with the n-methyl-d-aspartate receptor antagonist ketamine, inhibit development of secondary hyperalgesia in man by a peripheral action.* Neuroscience letters, 1997. **227**(1): p. 1-4
67. Wehrfritz, A.P., H. Ihmsen, S. Schmidt, C. Muller, J. Filitz, J. Schuttler , W. Koppert, *Interaction of physostigmine and alfentanil in a human pain model.* British journal of anaesthesia, 2010. **104**(3): p. 359-68
68. Werner, M.U., B. Lassen , H. Kehlet, *Analgesic effects of dexamethasone in burn injury.* Regional anesthesia and pain medicine, 2002. **27**(3): p. 254-60
69. Werner, M.U., F.M. Perkins, K. Holte, J.L. Pedersen , H. Kehlet, *Effects of gabapentin in acute inflammatory pain in humans.* Regional Anesthesia and Pain Medicine, 2001. **26**(4): p. 322-8