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SYSTEMATIC REVIEW

# A literature review on the pharmacological sensitivity of human evoked hyperalgesia pain models

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## AIMS

Human evoked pain models can be used to determine the efficacy of new and existing analgesics and to aid in the identification of new targets. Aspects of neuropathic pain can be simulated by inducing hyperalgesia resulting from provoked sensitization. The present literature review aimed to provide insight into the sensitivity of different hyperalgesia and allodynia models of pharmacological treatment.

## METHODS

A literature search was performed to identify randomized, double-blind, placebo-controlled studies that included human hyperalgesia pain models and investigated the pharmacodynamic effects of different classes of drugs.

## RESULTS

Three hyperalgesia models [ultraviolet B (UVB) irradiation, capsaicin and thermode burn] have been used extensively. Assessment of hyperalgesia/allodynia and pharmacological effect are measured using challenge tests, which generally comprise thermal (heat/cold) or mechanical stimulation (pin-prick, stroking or impact). The UVB model was sensitive to the antihyperalgesic effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. The capsaicin model was partially sensitive to opioids. The burn model did not detect any antihyperalgesic effects when NSAIDs or local anaesthetics were administered but responded to the effects of N-methyl D-aspartate (NMDA) receptor antagonists by moderately reducing mechanical hyperalgesia.

## CONCLUSIONS

Based on pharmacological sensitivity, the UVB model adequately reflects inflammatory pain and was sensitive to NSAIDs and opioids. Findings from the capsaicin and burn models raised questions about the translatability of these models to the treatment of neuropathic pain. There is a need for a reproducible and predictive model of neuropathic pain, either in healthy subjects or in patients.



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## Introduction

Chronic pain is highly prevalent, estimated to range between 20% and 30% in Europe and the USA [1, 2]. The nature of pain is complex as many different physiological and psychological mechanisms are at play. Commonly, pain is classified according to its supposed pathophysiology: nociceptive pain, neuropathic pain, psychogenic pain, or mixed or unspecified pain [3]. These differ in terms of onset and expression; in general, nociceptive pain is associated with acute pain, whereas neuropathic pain is more frequently chronic in nature. Underlying mechanisms differ greatly; nociceptive pain results from activation by a noxious stimulus of the nociceptive afferents distributed throughout the body. Neuropathic pain has been defined as 'Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system' [4], which results in sensitization of the somatosensory system. Central sensitization results from an increased responsiveness of the neurones in the dorsal horn and thalamus (including nociceptive responses to the A-β mechanoreceptors). Peripheral sensitization is the consequence of increased sensitivity of nociceptors, resulting from lower activation thresholds and increased responsiveness, often associated with inflammation [5–8]. Central or peripheral sensitization gives rise to the clinical presentation of neuropathic pain: allodynia (pain in response to a normally non-nociceptive stimulus) and/or hyperalgesia (more intense pain in response to a normally noxious stimulus). The treatment of neuropathic pain currently has a largely unmet medical need, as analgesics are often ineffective or limited by side effects. In the development of new (analgesic) drugs, biomarkers can be a useful tool in early phase research [9]. Evoked pain models using biomarkers cannot describe the complexity of pain in a single parameter, yet using pain models rather than patients to test the efficacy of analgesic drugs can be advantageous in terms of standardization, proof of concept and to provide insight into pharmacological background. Furthermore, the use of pain models excludes confounding due to coexisting fever, general malaise and psychological cognitive and social aspects of illness. Various human evoked hyperalgesia models have been developed that induce central and/or peripheral sensitization in healthy volunteers in a well-controlled manner. This level of sensitization is subsequently measured and quantified using a normally non-painful thermal or mechanical challenge. Use of this challenge enables assessment of the analgesic efficacy of novel drugs.

To be able to benchmark the effects of novel pharmacological compounds and provide guidance in the selection of an appropriate biomarker, the objective of the present study was to evaluate the capacity of each selected model to detect the antihyperalgesic effects of different pharmacological subclasses of drugs. The review also aimed to map the abundance of methods and degree of heterogeneity among the individual hyperalgesia models.

## Methods

### *Literature evaluation*

A literature study was performed using MEDLINE, Web of Science and EMBASE up to 21 March 2016. MeSH and free terms were used for the following search terms: 'hyperalgesia OR allodynia OR sensitization'. Searches were limited to healthy human adults and manuscripts written in English. There was no limit to the year of publication. To ensure clinical homogeneity, cutaneous hyperalgesia models were selected based on uniformity of methods, and thus comparability. Hyperalgesia models that had been used in fewer than 10 individual clinical trials or to investigate fewer than three different classes of analgesics were excluded. This resulted in the selection of three cutaneous hyperalgesia models: the ultraviolet B (UVB) model, the (thermode) burn model and the capsaicin model.

The UVB (or 'sunburn') model is regarded as a model for inflammatory pain; in this model, hyperalgesia is evoked by exposing an area of skin to an individualized dose of UVB on the leg, arm or back. Prior to the start of the study, the minimal erythemal dose (MED) for each subject is determined, and subsequently a one-, two- or threefold multiple of this dose is applied to the skin. Over the course of 2–96 h, a clearly discernible dose-related area of erythema becomes apparent, where a lowered activation threshold for painful and nonpainful stimuli (primary hyperalgesia) is observed [10].

The thermode burn model is generally considered as a model for heat injury and the associated inflammatory pain. Hyperalgesia evoked by inducing a first-degree burn by exposing the subject to a specific heat paradigm, ranging from 100 s to 7 min, using a contact thermode at the skin. This procedure induces primary hyperalgesia on the site of exposure, but also secondary hyperalgesia in adjacent tissue, resulting from central sensitization.

The capsaicin model is the most widely used model to mimic the symptoms of neurogenic hyperalgesia as observed in neuropathic pain. Capsaicin exerts its hyperalgesic effects via transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor activation. Capsaicin is applied either topically or as an intradermal or intramuscular injection. As TRPV1 receptors are also activated by heat (>43°C), the method is also used in combination with heat exposure in order to potentiate the hyperalgesic effects of capsaicin. Topical absorption of capsaicin can be variable, so the extent of hyperalgesia can vary. When capsaicin is applied intradermally, acute severe stinging or burning pain occurs, followed by primary and secondary hyperalgesia up to 24 h [10, 11].

A thermal or mechanical challenge was the predominant method used to determine the magnitude of hyperalgesia. Rarely, an electrical challenge was also used to quantify hyperalgesia or allodynia but findings from using this challenge were not included in the present review owing to the lack of standardization and the resulting difficulty in comparability. The efficacy of the investigated pharmacological compound was quantified according to its effect on pain induced by a mechanical or thermal challenge. Studies lacking adequate blinding or randomization were excluded from the review, as well as studies including fewer than six subjects. To address the temporal nature of evoked hyperalgesia, either as a result of the body's adaptation to (mild) tissue damage or resulting from the pharmacokinetics of a chemical hyperalgesic agent, only studies using adequate controls (active or inactive placebo) were included in the review. Studies solely reporting baseline controlled results were excluded. Finally, drugs that were still in the experimental phase of development were excluded as the pharmacology of such drugs had not yet been established completely.

The review categorized the selected randomized, double-blind, controlled trials investigating the efficacy of pharmacological compounds according to hyperalgesia model, corresponding challenge and class of pharmacological compound.

Other human evoked hyperalgesia models that were identified, but did not meet the entrance criterion regarding frequency of use for inclusion in the review, included freeze lesion [12–14], mustard oil [15–18], menthol [19–21] or substances including centrally acting opioids or local glutamate [22–27].

### *Individual studies*

All of the included studies yielded the following outcomes, according to challenge: the effect of a pharmacological compound on thermal and mechanical pain detection threshold (PDT), pain tolerance threshold (PTT) and pain ratings [visual analogue scales (VAS), numeric rating scales (NRS)] in the hyperalgesic area, and magnitude of area of hyperalgesia and allodynia. Besides provoked hyperalgesia, stimulus-independent hyperalgesia was also considered to be a relevant outcome, with outcomes including size and intensity of visual flare and spontaneous or ongoing pain.

For the present review, it was decided to use the term 'hyperalgesia' in accordance with commonly used terminology in the reviewed literature referring to both 'hyperalgesia' and 'allodynia', even if 'allodynia' would have been more appropriate based on definition. Pain responses to mild mechanical (punctate, brush) and thermal (heat/cold) challenge indicate a pain response to a normally non-noxious stimulus, and thus represent allodynia, rather than hyperalgesia.

Owing to an anticipated variation in effect sizes, the individual results were ranked as 'positive' (antihyperalgesic effect/(statistically) significant improvement compared with placebo) or 'no effect' (no significant difference compared with placebo) for each separate outcome, rather than quantifying the magnitude of effect of the pharmacological compound. Outcomes for different forms of administration were regarded as separate outcomes. Differential dose or time effects were noted, and scored as a positive effect, as the model in use was apparently able to detect an antihyperalgesic effect, given the appropriate execution of the test.

### *Grouping of test results*

The outcomes per challenge method were grouped according to type of outcome: thermal, mechanical and stimulus independent. The category 'thermal' was subdivided into the specific outcomes measured in the individual studies – e.g. heat/cold PDT or PTT. The category 'mechanical' consisted of static (pin-prick), dynamic (stroking with a brush, cotton gauze, etc.) and impact (using an algometer) stimuli, providing the aforementioned outcomes. Stimulus-independent outcomes were related to spontaneous pain resulting from hyperalgesia, and to intensity and size of flare. Results from the individual studies were subsequently grouped according to drug class to provide an insight into the pharmacological effect of each class of drug on a specific hyperalgesia–challenge combination. The responsiveness of each model to each particular class of drugs was defined here as the pharmacological sensitivity.

## Results

### *Study designs*

The literature study yielded 94 individual studies on the three selected hyperalgesia models: 16 used the UVB model to induce hyperalgesia, 48 studies explored the effects of various pharmacological compounds on capsaicin-induced hyperalgesia and 30 studies investigated thermode burn-induced hyperalgesia. Seven studies examined more than one hyperalgesia model. The general study characteristics are presented in Table 1. The participants were aged between 17 and 65 years.

Even though the UVB, capsaicin and thermode burn models were selected based on a high degree of standardization, there was considerable variation in the execution of the models, as shown in Table 2. All studies utilizing UVB to induce hyperalgesia administered a dose of one-, two- or three times the MED. The administration of one times the MED was shown to be inconsistent at producing hyperalgesia in one study [28]. Larger variation was found among the methods for inducing hyperalgesia with capsaicin. Capsaicin was either injected intradermally or applied topically.

## Table 1

Characteristics of randomized, double-blind, (active) placebo-controlled studies specified according to hyperalgesia model

| | Design | | Control | | Subjects | | |
|---|---|---|---|---|---|---|---|
| | Crossover (%) | Parallel (%) | Inactive placebo (%) | Active control (%) | *N* (Median/range) | Age in years (range) | Gender (%) Males/mixed sample/females/unknown |
| **UVB (*n* = 16)** | 93.7 | 6.3 | 81.3 | 18.7 | 16 (6–42) | 18–55 | 31.3/62.5/6.2/0 |
| **Capsaicin (*n* = 48)** | 97.9 | 2.1 | 89.6 | 12.5 | 16.5 (6–50) | 18–65 | 31.3/60.4/2.1/6.3 |
| **Burn (*n* = 30)** | 100 | 0 | 93.3 | 6.7 | 17 (6–29) | 17–52 | 50.0/46.7/0/3.3 |

UVB, ultraviolet B.

## Table 2

Frequency of use (%) of general methods for the induction of hyperalgesia specified according to hyperalgesia model

| Hyperalgesia model | Specific methods | | Frequency of use (%) |
|---|---|---|---|
| **UVB (*n* = 16)** | UVB dose | 1 × MED | 6.3 |
| | | 2 × MED | 18.8 |
| | | 3 × MED | 75.0 |
| | Location | Leg | 68.8 |
| | | Arm | 18.8 |
| | | Back | 6.3 |
| | Time between exposure and hyperalgesia assessment | 12 h | 6.3 |
| | | 20 h | 18.8 |
| | | 24 h | 62.5 |
| | | 20–26 h | 6.3 |
| | | Not specified | 6.3 |
| **Capsaicin (*n* = 48)** | Formulation and duration of application | Topical | 41.7 |
| | | 30 min | 65.0 |
| | | 40 min | 5.0 |
| | | 60 min | 15.0 |
| | | 90 min | 5.0 |
| | | Not specified | 10.0 |
| | | Intradermal injection | 58.3 |
| | Administration form and dose | Topical | 41.7 |
| | | 0.075% | 55.0 |
| | | 0.1% | 5.0 |
| | | 1% | 20.0 |
| | | Other/not specified | 20.0 |
| | | Intradermal injection | 59.6 |
| | | 10 μg | 3.6 |
| | | 20 μg | 14.3 |
| | | 40 μg | 7.1 |
| | | 100 μg | 67.9 |
| | | 250 μg | 7.1 |
| | Applying heat | No heat applied | 70.8 |
| | | Rekindling * | 25.0 |

(*continues*)

## Table 2

(Continued)

| Hyperalgesia model | Specific methods | | Frequency of use (%) |
|---|---|---|---|
| | | Constant temperature | 4.2 |
| | Location | Leg | 12.5 |
| | | Arm | 87.5 |
| | | Foot | 2.1 |
| | | Forehead | 2.1 |
| **Burn (*n* = 30)** | Application | 100 s at 50°C | 3.3 |
| | | 2 min at 48°C | 3.3 |
| | | 3 min at 45°C | 6.7 |
| | | 3–5 min at 45°C | 3.3 |
| | | 4 min at 49°C | 3.3 |
| | | 5 min at 47°C | 10 |
| | | 5 min at 49°C | 13.3 |
| | | 6 min at 47°C | 3.3 |
| | | 7 min at 46°C | 6.7 |
| | | 7 min at 47°C | 46.7 |
| | Surface area | 3.75 $cm^2$ | 10.0 |
| | | 4.5 $cm^2$ | 3.3 |
| | | 12.5 $cm^2$ | 73.3 |
| | | 22.8 $cm^2$ | 3.3 |
| | | Unknown | 6.7 |
| | Blistering in any subject | Yes | 20.0 |
| | | No | 47.0 |
| | | Unknown | 33.0 |
| | Location | Leg | 83.3 |
| | | Arm | 13.3 |
| | | Abdomen | 3.3 |

MED, minimal erythemal dose; UVB, ultraviolet B. *All studies that used rekindling also preheated before capsaicin application for 5 min at 45°C.

Ofthe 16 capsaicin studies that used heat further to exacerbate/prolong the hyperalgesia, two studies kept the skin at a constant temperature, while the remainder used the method of rekindling: 5 min at a set temperature (40°C or 45°C at fixed time points), with a thermode placed directly on the skin or using a radiant heat lamp. The largest variation was seen in the thermode burn model: 10 different heat administration regimens were identified, ranging from 100 s at 50°C ($n$ = 1) to 7 min at 47°C ($n$ = 14), causing blistering in one or more subjects in 20% of the studies. The thermode burn and UVB models were most often administered on one or both legs (68.8% and 83.3%, respectively), whereas for administration of capsaicin to induce hyperalgesia, one or both arms were selected most often (89.4%). The frequency of use of challenge methods among the different hyperalgesia models is shown in Table 3.

## *Sensitivity of the UVB model*

The use of the UVB model as a model for inflammation was relatively uncommon; 16 studies using this method were identified, in which eight classes of drugs were investigated. Studies that investigated the effects of a combination of drugs are listed in a separate category. Table 4 shows an overview of the pharmacological sensitivity of the UVB model for each separate challenge method (mechanical, thermal or stimulus independent), grouped according to drug class.

A total of four studies investigating nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen [28–30] and rofoxecib [31], showed a significant effect by reducing hyperalgesia to thermal and mechanical stimuli. Two studies investigating the effects of ketorolac alone and in combination with paracetamol found mixed results [32, 33]. Mixed results were also observed for the benzodiazepines

## Table 3

Frequency of use (%) of main challenge methods specified according to hyperalgesia model

| Challenge | Method | Frequency of use (%) * | | |
|---|---|---|---|---|
| | | UVB ($n$ = 16) | Capsaicin ($n$ = 48) | Burn ($n$ = 30) |
| **Thermal – heat** | Thermode | 68.8 | 50.0 | 76.7 |
| | Halogen bulb | 12.5 | 2.1 | 3.3 |
| **Thermal – cold** | Thermode | 25.0 | 8.3 | 3.3 |
| **Mechanical (static) – pin prick** | Von Frey | 56.3 | 77.1 | 80.0 |
| | Custom-made/other | 12.5 | 6.3 | 10.0 |
| **Mechanical (dynamic) – stroking** | Brush | 12.5 | 43.8 | 13.3 |
| | Cotton | 18.8 | 35.4 | 6.7 |
| | Fingertip | 0 | 0 | 6.7 |
| | Von Frey | 0 | 0 | 3.3 |
| **Mechanical – impact stimulus** | Algometer (static) | 6.3 | 0 | 0 |
| | Algometer (dynamic) | 18.8 | 2.1 | 3.3 |

UVB, ultraviolet B. *Frequencies of use exceed 100% because most studies make use of more than one method.

clobazam and clonazepam [34]. Systemically administered opioids reduced hyperalgesia to thermal and mechanical stimuli [35–38]. Transdermal administration of either buprenorphine or fentanyl did not attenuate hyperalgesia to heat or static mechanical stimuli, but buprenorphine did have a significant effect on the PTT to impact stimuli [38]. Furthermore, remifentanil in combination with gabapentin showed no greater reduction in hyperalgesia than remifentanil alone [36].

Lidocaine, a local anaesthetic, showed mixed results. One study found an attenuating effect on hyperalgesia to impact stimuli when lidocaine was injected intravenously [39]. Another study applied lidocaine topically and found a reduction in hyperalgesia to static and dynamic mechanical stimuli, but no attenuating effects on hyperalgesia to heat stimuli [40]. Studies investigating the voltage-gated calcium channel α2–δ-modulating anticonvulsant gabapentin [36], the neurotoxin botulinum toxin A [41] and paracetamol [33, 37] found no significant effects on hyperalgesia. Tetrahydrocannabinol (THC), a cannabinoid receptor agonist, also showed no significant positive effects on hyperalgesia to mechanical and thermal stimuli [42]. Of note, THC even showed significantly increased hyperalgesia at specific electrical stimulus intensities at specific time points [42].

## *Sensitivity of the capsaicin model*

The capsaicin model has been used extensively to test the efficacy of new and existing pharmacological compounds. The present literature study yielded 48 articles eligible for inclusion. A total of 14 classes of pharmacological compounds were identified, with only one study for analgesics and one for corticosteroids. Table 5 provides an overview of the findings of the individual studies using the capsaicin model, grouped by class of drug and type of challenge/hyperalgesia.

Opioids, anaesthetics, N-methyl D-aspartate (NMDA) receptor antagonists, and, to a lesser degree, calcium channel α2-δ ligands appear to have an attenuating effect on capsaicin-induced hyperalgesia to mechanical stimuli [43–46], although there were also a number of studies for each of these drug classes where no effect could be found (e.g. [47–49]). The α-2 adrenoreceptor agonist clonidine [50, 51] appeared to be effective in reducing hyperalgesia, particularly in response to mechanical stimuli, in two studies.

Although NMDA receptor antagonists appeared to be effective in reducing hyperalgesia, a number of the studies demonstrated a positive effect only at specific time points, mostly during infusion or measured immediately after infusion or bolus injection, particularly in relation to mechanical hyperalgesia (e.g. [52–54] for ketamine, [55] for dextromethorphan and [56] for neramexane) (see the corresponding footnotes in Table 5). The remaining drug classes investigated showed no, or very limited, efficacy in attenuating capsaicin-induced hyperalgesia: NSAIDs [32, 57], analgesics [56], cannabinoids [42, 58, 59], tricyclic antidepressants [60, 61] and antiarrhythmic agents [62–64].

## *Sensitivity of the thermode burn model*

The present review included 30 studies investigating the efficacy of pharmacological compounds to attenuate hyperalgesia induced by the thermode burn model. Ten classes of pharmacological compounds to reduce hyperalgesia were found. Of these classes, five involved a single compound. In addition, three studies investigating a combination of drugs were included. An overview of these results is shown in Table 6.

No class of drug showed clear efficacy in reversing thermode burn-induced hyperalgesia completely. However, NMDA

## Table 4

Schematic summary of results of randomized controlled trials investigating hyperalgesia induced by UVB, according to type of challenge

| Drug class | Drug (administration form/dose | Challenge type | Challenge/outcome | Overall effect | |
|---|---|---|---|---|---|
| | | | | Effective | No effect |
| **Opioids** | **Morphine** (IV/4 mg) [35]<br>**Remifentanil** (IV/0.8 μg $kg^{-1}$ $min^{-1}$) [36]A*<br>**Fentanyl** (transdermal/25 μg $h^{-1}$, 72 h) [38]A<br>**Buprenorphine** (Transdermal / 20μg/h, 144h) [38]B<br>**Tramadol** (IV / 0.3 mg/kg, 0.6 mg/kg, 1 mg/kg) [37]†<br>**Remifentanil** (IV infusion/0.8μg/kg/min) &<br>**Gabapentin** (Oral/ 600 mg) [36]B* | T | Heat/PDT | [35], [36]A, [36]B | [37] |
| | | | Heat/PTT | [36]A, [36]B | [38]B |
| | | | Cold/PDT | | [37] |
| | | M | Pin prick/area | [36]A, [36]B | [38]A, [38]B, [37] |
| | | | Pin prick/pain score | [37]† | |
| | | | Impact stimulus/pain score | | [35] |
| | | | Impact stimulus/PTT | [38]B‡ | [38]A |
| **Anaesthetics** | **Lidocaine** (topical patch/5% medicated plaster) [40],<br>(IV bolus/2 mg $kg^{-1}$ in 10 min,<br>then 2 mg $kg^{-1}$ $h^{-1}$ for 30 min) [39];<br>**Benzocaine** (topical/10% ointment) [95] | T | Heat/PDT | | [40] |
| | | | Heat/PTT | | [40] |
| | | | Cold/PDT | [40] | |
| | | | Cold/PTT | | [40] |
| | | M | Impact/pain score | [39] | |
| | | | Pin prick/area | [40] | |
| | | | Stroking/pain score | [40] | |
| | | S-I | Flare/intensity | [39] | |
| | | | Flare/area | | [40] |
| | | | Spontaneous pain | | [95] |
| **NSAIDs** | **Ibuprofen** (oral/400–800 mg) [28–30]<br>**Rofecoxib** (oral/50 mg, 250 mg, 500 mg) [31]<br>**Ketorolac** (oral/20 mg) [33]A;<br>(Intrathecal / 2 mg) [32]<br>**Ketorolac** (Oral / 20 mg) &<br>**Paracetamol** (Oral / 1 mg) [33]B | T | Heat/PDT | [28–31], [33]B | [33]A |
| | | | Heat/PTT | [30, 31] | |
| | | M | Impact stimulus/pain score | [28] | |
| | | | Pin prick/area | [31, 32] | [33]A, [33]B |
| | | | Pin prick/PDT | [29], [33]B | [33]A |
| | | | Stroking/area | | [32] |
| | | S-I | Flare/intensity | [28, 31] | |
| **Calcium channel α2-δ ligand** | **Gabapentin**<br>(oral/600 mg) [36]C* | T | Heat/PDT | | [36]C |
| | | | Heat/PTT | | [36]C |
| | | M | Pin prick/pain score | | |
| | | | Pin prick/area | | [36]C |
| **Cannabinoids** | **Δ-9-THC**<br>(oral/20 mg) [42]§,¶ | T | Heat/PDT | | [42] |
| | | | Heat/PTT | | [42] |
| | | M | Pin prick/area | | [42] |
| | | | Stroking/area | | [42] |
| **Benzodiazepines** | **Clobazam** (oral/20 mg) [34]**A<br>**Clonazepam** (oral/1 mg) [34]**B | T | Heat/PDT | [34]A | [34]B |
| | | | Heat/PTT | [34]B | [34]A |
| | | | Cold/PDT | | [34]A |
| | | M | Pin prick/area | [34]A, [34]B | |
| | | | Pin prick/PDT | [34]B | [34]A |

(*continues*)

## Table 4

(Continued)

| Drug class | Drug (administration form/dose | Challenge type | Challenge/outcome | Overall effect | |
|---|---|---|---|---|---|
| | | | | Effective | No effect |
| **Neurotoxins** | Botulinum toxin A (intracutaneous/100 mouse units) [41] | T | Heat/PDT | | [41] |
| | | | Cold/PDT | | [41] |
| | | M | Stroking/pain score | | [41] |
| | | | Pin prick/area | | [41] |
| | | | Pin prick/PDT | | [41] |
| **Analgesics** | Paracetamol (oral/1 g) [33]C; (IV/330 mg) [37] | M | Pin prick/PDT | | [33]C |
| | | | Pin prick/area | | [33]C, [37] |
| | | | Pin prick/pain score | | [37] |
| | | T | Heat/PDT | | [33]C, [37] |
| | | | Cold/PDT | | [37] |

IV, intravenous; M, mechanical; PDT, pain detection threshold; PTT, pain tolerance threshold; S-I, stimulus-independent; T, thermal; THC, tetrahydrocannabinol; UVB, ultraviolet B. *Effect compared with active placebo: diazepam (2 mg). †Significant effect found only at 1 mg $kg^{-1}$ dose of tramadol, not at 0.3 mg $kg^{-1}$ or 0.6 mg $kg^{-1}$ doses. ‡Significant effect found at 48 h and 72 h postdosing, but not at 24 h or 144 h postdosing: neither short- nor long-term effect. §Electrical stimuli also administered – results not shown here. ¶Compared with active placebo: diazepam (5 mg). **Compared with active placebo: tolterodine (1.37 mg). Numbers between brackets signify references. Studies that investigated more than one type of pharmacological intervention are denoted with a letter (A, B, C).

receptor antagonists were found to attenuate mechanical, but not thermal, hyperalgesia to a moderate extent [55, 65–71], although a number of studies did not demonstrate this effect e.g. [72, 73]. A similar reduction in mechanical hyperalgesia, but not on thermal hyperalgesia, was observed when ketamine was combined with the opioid receptor antagonist naloxone [67], indicating that coadministration of naloxone does not reduce the effects of ketamine.

Two studies were performed to investigate the presence of a synergistic effect of combined treatment with an opioid (morphine) and an NMDA receptor antagonist but the results were inconclusive [69, 72].

Opioids [69, 70, 74, 75], intracellular sodium channel blockers [76, 77], NSAIDs [78–82], corticosteroids [83, 84], the calcium channel α2-δ ligand gabapentin [85], the glutamate antagonist riluzole [86], the opioid receptor antagonist naloxone [87] and the purinergic P1 receptor activator adenosine [15] were inconsistent at attenuating heat, mechanical and unprovoked hyperalgesia.

## Discussion

The present literature review aimed to provide insight into the pharmacological sensitivity of three cutaneous hyperalgesia models (the UVB, capsaicin and thermode burn models), to determine the applicability of individual hyperalgesia models in early phase pharmacological pain research. The review of the identified randomized, double-blind, placebo-controlled trials investigating the efficacy of numerous pharmacological compounds generated an overview of the classes of drugs that are investigated in pain paradigms and their efficacy at reducing specific hyperalgesia–challenge combinations.

The summarized findings of the included trials reflect the pharmacological sensitivity of three hyperalgesia models in combination with specific challenges, which were selected on the basis of their standardized methodology and frequency of use.

The UVB model was responsive only to the pharmacological effects of NSAIDs and, to a lesser extent, opioids. The pharmacological sensitivity of the thermode burn model, used as a translational model for inflammatory pain as well as neuropathic pain, showed a different profile compared with the UVB model. First, NSAIDs and opioids did not seem to show antihyperalgesic effects when administered to reduce burn-induced hyperalgesia. The NMDA receptor antagonists were moderately effective at attenuating mechanical hyperalgesia but had little effect on thermal hyperalgesia. Some authors referred to the central mechanism involved in secondary mechanical hyperalgesia, in contrast to the peripheral sensitization in primary (thermal) hyperalgesia, as an explanation for the differential effect of NMDA receptor antagonists between heat and mechanical hyperalgesia [70, 71]. Although capsaicin has generally been regarded as a model for neuropathic pain, the model appeared to be insensitive to the classes of pharmacological compounds clinically prescribed in the first-line treatment of neuropathic pain [88]. Calcium channel α2-δ ligands (gabapentin and pregabalin), tricyclic antidepressants or topical lidocaine provided a limited, or no, attenuation of hyperalgesia in the majority of the studies investigating this model. Most of the studies investigating the effects of opioids on mechanical hyperalgesia yielded positive results.

## Table 5

Schematic summary of results of randomized controlled trials investigating hyperalgesia induced by capsaicin, according to type of challenge

| Drug class | Drug (administration form/dose) | Challenge Type | Challenge/ outcome | Overall effect | |
|---|---|---|---|---|---|
| | | | | Effective | No effect |
| **Opioids** | **Morphine** (oral/30 mg) [72]A; (IV infusion/10 mg) [96] **Morphine** (oral/30 mg) & **dextromethorphan** (Oral / 30 mg) [72]B **Alfentanil** (IV/plasma concentration 50 ng $ml^{-1}$ or 200 ng $ml^{-1}$) [60]A*; (IV/3.075 mg [54]; (IV infusion/1.9 ± 0.5 mg) [48]*; (IV infusion/3.33 ± 0.42 mg) [97] **Alfentanil** (IV/plasma concentration 50 ng $ml^{-1}$ or 200 ng $ml^{-1}$) & **Amitriptyline** (intramuscular injection/25 mg) [60]B* **Remifentanil** (IV / 0.05 μg/kg/min for 5 minutes, then 0.1 μg/kg/min for 35 minutes) [98]; (IV / 0.05 μg/kg/min for 10 minutes, then 0.1 μg/kg/min for 25 minutes) [99]A **Fentanyl** (Transdermal / 25μg/h, 72h) [38]A; (Intradermal injection / 1 μg, 10 μg) [53] **Buprenorphine** (Transdermal / 20μg/h, 144h) [38]B **Hydromorphone** (Oral / 8 mg) [99]B | T | Heat/PDT | | [48] |
| | | | Heat/rating | [98] | [48] |
| | | | Heat/area | | [48, 97] |
| | | | Cold/PDT | | [48] |
| | | | Cold/rating | | [48] |
| | | M | Pin prick/area | [96], [60]A, [60]B, [54, 97, 98], [99]A, [99]B | [72]A, [72]B, [48], [38]A, [38]B, [53] |
| | | | Pin prick/pain rating | [54, 96]† | [48, 53] |
| | | | Pin prick/PDT | [97] | [48] |
| | | | Stroking/area | [72]A, [60]A, [60]B, [97, 98], [99]A, [99]B, [54], [96]* | [72]B, [48], [38]A, [38]B, [53] |
| | | | Stroking/pain score | [96]* | [48, 53] |
| | | S-I | Flare/area | | [48, 96, 97] |
| | | | Flare/intensity | [53]‡ | |
| | | | Spontaneous pain | [60]A, [60]B, [54, 97] | [48, 53, 96] |
| **Anaesthetics** | **Lidocaine** (IV/bolus of 2 mg $kg^{-1}$ in 10 min, then infusion of 2 mg $kg^{-1}$ $h^{-1}$ for another 50 min) [100]A; (IV/2 mg $kg^{-1}$ $min^{-1}$ for 10 min, then 3 mg $kg^{-1}$ $h^{-1}$) [47]; (5 mg $kg^{-1}$ in 30 min) [52]; (IV infusion/1 μg $ml^{-1}$, 2 μg $ml^{-1}$, 3 μg $ml^{-1}$ [101]* (Intradermal injection/20 μg per 40 ml) [100]B; (Subcutaneous infiltration/20 mg per 2 ml) [102]; (Transdermal patch/dose unknown) [103]; (Topical patch/5% medicated plaster) [40] **EMLA** (Topical cream / 2 g of 2.5% Lignocaine and 2.5% Procaine) [104] | T | Heat/PDT | | [40, 47, 101, 103], [100]A, [100]B |
| | | | Heat/PTT | | [40, 52] |
| | | | Heat/rating | [104] | [47] |
| | | | Heat/area | [101] | |
| | | | Cold/PDT | | [101] |
| | | M | Pin prick/area | [52], [104]§, [40], [100]A, [102] | [47, 101, 103], [100]B |
| | | | Pin prick/pain rating | [102, 104] | [52] |
| | | | Pin prick/PDT | [102, 104] | [101, 103] |
| | | | Stroking/area | [40, 102, 104] | [47, 52, 101], [100]A, [100]B, [103] |
| | | | Stroking/pain score | | [52] |
| | | S-I | Flare/area | [101], [100]A, [100]B | [40, 103] |
| | | | Spontaneous pain | | [40, 101], [100]A, [100]B, [103] |
| **NSAIDs** | **Ibuprofen** (oral/1200 mg, 2400 mg) [105]; (oral/600 mg) [46]A; (topical cream/0.5 g in 100 mg of gel containing 5% ibuprofen) [106] **Valdecoxib** (oral/40 mg) [57] **Ketorolac** (intrathecal/2 mg per 2 ml) [32] | M | Pin prick/area | | [32, 57] |
| | | | Pin prick/pain rating | | [46]A |
| | | | Stroking/area | [106] | [32, 57, 105] |
| | | | Stroking/pin prick | | [46]A |
| | | S-I | Spontaneous pain | | [46]A |

(*continues*)

## Table 5

(Continued)

| Drug class | Drug (administration form/dose) | Challenge Type | Challenge/ outcome | Overall effect | |
|---|---|---|---|---|---|
| | | | | Effective | No effect |
| **Analgesics** | **Flupirtine** (oral/100 mg) [56] | M | Pin prick/pain rating | | [56] |
| | | | Stroking/pain rating | | [56] |
| | | S-I | Flare | | [56] |
| | | | Spontaneous pain | [56] | |
| **NMDA receptor antagonists** | **Ketamine** (IV infusion/20 μg $kg^{-1}$ $min^{-1}$ for 10 min, then 5 μg $kg^{-1}$ $min^{-1}$) [107]; (IV infusion/28 mg, 375 mg in 30 min) [52]; (IV/32 mg in 35 min) [54]; (IV infusion/15.8 ± 4.4 mg) [48]*; (IV infusion/35 mg i n 20 min) [97]; (subcutaneous infiltration/5 mg per 2 ml) [102]; intradermal injection/0.1 mg, 1 mg) [53]; (topical 50 mg $ml^{-1}$) [108] **Dextrometorphan** (IV/0.5 mg $kg^{-1}$) [55]; (oral/30 mg) [72]; (oral/100 mg, 200 mg) [109] **Neramexane** (oral/40 mg) [56] | T | Heat/PDT | [107] | [48, 55] |
| | | | Heat/rating | [108] | [48] |
| | | | Heat/PTT | | [52] |
| | | | Heat/area | | [48, 97] |
| | | | Cold/PDT | | [48] |
| | | | Cold/rating | | [48] |
| | | M | Pin prick/area | [52]¶, [54]**, [55]†† | [48, 53, 72, 97, 102] |
| | | | Pin prick/pain rating | [54], [53]‡‡, [56, 108] | [48, 52, 102] |
| | | | Pin prick/PDT | [97] | [48] |
| | | | Stroking/area | [52]§§ | [48, 53, 54, 72, 97, 102] |
| | | | Stroking/pain rating | [53]‡‡, [56]¶¶ | [48, 52, 102] |
| | | S-I | Flare/area | | [48, 97] |
| | | | Flare/intensity | | [53, 56] |
| | | | Spontaneous pain | [56]***, [54, 97] | [48, 53, 108, 109] |
| **Calcium channel α2-δ ligands** | **Gabapentin** (Oral / 1200 mg) [45]; (Oral / 1200 mg) [43]; (Oral – Chronic / 2400 mg per day on day 15) [44]; (Oral / 1800 mg per day on day 10) [49]; (Oral / 1200 mg) [46]B **Pregabalin** (Oral / 300 mg) [96] | T | Heat/PDT | [43] | [45] |
| | | | Heat/rating | | [43] |
| | | M | Pin prick/area | [43, 45, 96]† | [44, 49] |
| | | | Pin prick/pain rating | [96]*, [46]B | [44, 49] |
| | | | Stroking/area | [43, 44] | [49, 96] |
| | | | Stroking/pain rating | | [44, 49, 96], [46]B |
| | | S-I | Flare/area | | [49, 96] |
| | | | Spontaneous pain | [96]††† | [44, 46, 49] |
| **Benzodiazepines** | **Clobazam** (oral/20 mg) [110]A **Clonazepam** (oral/1 mg) [110]B | T | Heat/PDT | | |
| | | M | Pin prick/area Pin prick/pain rating | [110]A, [110]B | [110]A, [110]B |
| | | | Stroking/area | | [110]A, [110]B |
| | | S-I | Spontaneous pain | | [110]A, [110]B |
| **Anticonvulsants** | **Lamotrigine** (oral/400 mg) [99]; (oral/300 mg) [111]; **Magnesium sulfate** (IV infusion/0.2 mmol $kg^{-1}$ in 15 min, then 0.2 mmol $kg^{-1}$ $h^{-1}$ for 90 min) [112] | T | Heat/PDT | | [112] |
| | | | Heat/rating | | [111, 112] |
| | | | Heat/area | | [111] |
| | | M | Pin prick/area | | [99, 111, 112] |
| | | | Pin prick/pain rating | | [111] |
| | | | Stroking/area | | [99, 111, 112] |
| | | | Stroking/pain rating | | [111] |
| | | S-I | Spontaneous pain | | [111] |

(*continues*)

## Table 5

(Continued)

| Drug class | Drug (administration form/dose) | Challenge Type | Challenge/ outcome | Overall effect | |
|---|---|---|---|---|---|
| | | | | Effective | No effect |
| **Cannabinoids** | **Δ-9-THC** (inhalation/2%, 4%, 8%) [59]‡‡‡; (oral/1–3 mg) [58] **Δ-9-THC + cannabidiol** (oral/20 mg) [42]¶¶¶ | T | Heat/PDT | | [58, 59] |
| | | | Cold/PDT | | [59] |
| | | M | Pin prick/area | | [42, 59] |
| | | | Pin prick/PDT | | |
| | | | Pin prick/pain rating | | [59] |
| | | | Stroking/area | [59]§§§ | [58] |
| | | | Stroking/pain rating | | [59] |
| | | S-I | Flare/area | | [42, 59] |
| | | | Flare/intensity | | |
| | | | Spontaneous pain | [59]**** | [42, 58] |
| **Tricyclic antidepressants** | **Amitriptyline** (intramuscular injection/25 mg) [60] **Desipramine** (oral – chronic/300 mg $day^{-1}$ on day 14) [61] | T | Heat/rating | | [61] |
| | | | Heat/area | | [61] |
| | | M | Pin prick/area | | [60, 61] |
| | | | Pin prick/pain rating | | [61] |
| | | | Stroking/area | | [60, 61] |
| | | | Stroking/pain rating | | [61] |
| | | S-I | Spontaneous pain | | [60, 61] |
| **Neurotoxins** | **Botulinum toxin A** (intradermal/30 mouse units) [113]; (Intradermal / 100 mouse units) [114]; (Intramuscular / 150 mouse units) [115] | T | Heat/PDT | | [114] |
| | | | Cold/PDT | | [114] |
| | | M | Pin prick/area | [115]†††† | [113] |
| | | | Impact stimulus/area | [115] | |
| | | S-I | Flare/area | | [113, 114] |
| | | | Spontaneous pain | | [113] |
| **Antiarrhythmic agents** | **Adenosine** (IV bolus/5.1 mg $kg^{-1}$) [63]; (intrathecal/0.5 mg, 2 mg) [64] **Mexiletine** (oral – chronic/increasing dose: 1350 mg $day^{-1}$ on days 13–17) [62] | T | Heat/PDT | | [63] |
| | | | Heat/rating | [64]‡‡‡‡ | [62, 63] |
| | | | Heat/area | | [62] |
| | | M | Pin prick/area | [62] | [63, 64] |
| | | | Pin prick/pain rating | | [62] |
| | | | Stroking/area | [64] | [62, 63] |
| | | | Stroking/pain rating | | [62] |
| | | S-I | Flare/area | | [62] |
| | | | Spontaneous pain | | [62] |
| **Antihypertensive agents** | **Clonidine** (IV bolus/50 μg, 150 μg) [50]A; (intrathecal/50 μg, 150 μg) [50]B; (intrathecal/75 μg, 150 μg, 300 μg) [51]A; (epidural/150 μg, 300 μg, 600 μg) [51]B | T | Heat/rating | [50]B§§§§ | [50]A |
| | | M | Pin prick/pain rating | [51]A, [51]B | |
| | | | Stroking/pain rating | [51]A, [51]B | |
| | | | Pin prick/area | [50]B§§§§ | [50]A |

(*continues*)

## Table 5

(Continued)

| Drug class | Drug (administration form/dose) | Challenge Type | Challenge/ outcome | Overall effect | |
|---|---|---|---|---|---|
| | | | | Effective | No effect |
| **Corticosteroids** | **Hydrocortisone** (oral/40 mg) [116] | M | Stroking/pain score | | [116] |
| | | | Pin prick/pain score | [116] | |
| | | S-I | Spontaneous pain | [116] | |
| | | | Flare/area | | [116] |

IV, intravenous; M, mechanical; NMDA, N-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug; PDT, pain detection threshold; PTT, pain tolerance threshold; S-I, stimulus-independent; T, thermal; THC, tetrahydrocannabinol. *Compared with active placebo: diphenhydrate hydrochloride. †Only significant effect when compared with active placebo (diphenhydrate) group, not when compared with true placebo. ‡Only significant difference in flare intensity at high dose (10 μg/200 μl). §No effect shown in elderly subpopulation (mean age 74.9 ± 4.4 years). ¶Effect only seen during infusion; no significant differences from 15 min post-infusion onwards. **Effect only when dosed after capsaicin; no significant difference when dosed during capsaicin. ††Effect only after 135 min. ‡‡Effect only at high dose (1 mg); no significant difference at lower dose (0.1 mg). §§Effect only seen during infusion; no significant differences from 15 min post-infusion onwards. ¶¶Only significant when measured 30 min postcapsaicin, and not when measured up to 1.5 h. ***Only significant effect when measured 1 min postcapsaicin, not 2–5 min. †††Only significant effect when compared with placebo group, not when compared with active placebo (diphenhydrate). ‡‡‡A reverse effect was demonstrated at high dose (8% THC) at 65 min postdosing: increased spontaneous pain and medium dose (4% THC) at 65 min postdosing: reduction of PDT to impact stimuli. §§§Only short-term effect; significant difference up to 30 min postdosing. ¶¶¶Compared with active placebo: diazepam (2 mg/5 mg). ****Only significant difference in medium dose (4% THC), not at low (2%) or high (8%) dose, only at 65 min postdosing. ††††Only significant after 1 week and 4 weeks. ‡‡‡‡Only significant difference at 80 min and 120 min postdosing. §§§§Only significant effect at high dose (150 μg). Numbers between brackets signify references. Studies that investigated more than one type of pharmacological intervention are denoted with a letter (A,B,C).

However, only a few studies [48, 97, 98] investigated the effects of opioids on thermal hyperalgesia and therefore provided no conclusive evidence for the responsiveness, or lack thereof, of thermal hyperalgesia induced by capsaicin to opioids. The observed positive effects in the few studies investigating clonidine [50, 51] suggest that clonidine exerts its effects by reducing spinal hypersensitivity through α2-adrenergic agonism in the dorsal horn. NMDA receptor antagonists exert their antihyperalgesic effects through inhibition of the glutamatergic signalling pathways. A limited number of studies demonstrated that the capsaicin model is sensitive to NMDA receptor antagonists. The results showed a differential antihyperalgesic effect, in that mechanical hyperalgesia, but not thermal hyperalgesia, was attenuated in a small number of studies [52, 55, 97]. The capsaicin model appeared to be insensitive or inconclusive to the remainder of the pharmacological compounds that were investigated, including botulinum toxin A and cannabinoids.

For a several of the classes of drugs investigated, the present literature review included only one study and one compound per drug class. Therefore, for these drug classes, no strong recommendations can be made with respect to the suitability of the cutaneous hyperalgesia models, other than those based on face validity [15, 36, 42, 41, 56, 86, 120].

## *Limitations to this approach*

In the present review, characterization of the pharmacological sensitivity of the selected hyperalgesia models was based on the capacity of the model to detect an antihyperalgesic effect for each class of drug. Inherent to this approach was the assumption that the clinical trials had been executed appropriately. The included clinical trials had to meet the following criteria: randomized, double-blind and placebo- or active-controlled. Only 6.7–18.5% of the studies used an active control (alone or in combination with a true placebo). This may have introduced bias when investigating psychoactive pharmacological compounds compared with true placebo, as analgesia is known to be prone to a placebo response [89]. This can be avoided by using an active placebo with a known lack of analgesia but comparable psychoactive effects. Dosing regimens and the forms of administration are included in Tables 4–6, to provide insight into potential differences; however, for the studies that were included, clinically relevant dosing regimens were generally used.

Variability in the reporting of the results was observed on different levels. Owing to the bilateral nature of evoked hyperalgesia models, both induction and assessment of hyperalgesia potentially introduce variability. For example, some authors reported absolute pain thresholds, whereas others reported calculated hyperalgesia (compared with healthy control skin). Furthermore, to assess pharmacodynamic response, some groups compared a single postdose measurement with a baseline in a paired *t*-test analysis, whereas other groups included multiple measurements in the analysis of (co)variance. Consequently, a statistical meta-analysis of the results of the included clinical trials was not deemed feasible, and does not fall within the scope of the present review.

Hyperalgesia models that were not included in the present review, including the freeze lesion model, may eventually also prove to be useful tools for detecting the antihyperalgesic effects of novel compounds, given the reproducible and non-invasive methodology, but because of their limited use thus far, no conclusions on the pharmacological sensitivity of such models can be made.

For ethical reasons, evoked hyperalgesia models are temporal by nature; either physical adaptations to (mild) tissue damage or the pharmacokinetics of a chemical hyperalgesic agent result in hyperalgesia that attenuates over time without

## Table 6

Schematic summary of results of randomized controlled trials investigating hyperalgesia induced by thermode burn, according to type of challenge

| Drug class | Drug (administration form/dose) | Challenge type | Challenge/ outcome | Overall effect: Effective | Overall effect: No effect |
|---|---|---|---|---|---|
| **Opioids** | **Morphine** (IV injection/2 mg) [74]A; (IV infusion/0.14 mg $kg^{-1}$, 0.28 mg $kg^{-1}$) [117]A†; (IV infusion/0.1 mg $kg^{-1}$) [69]A; (IV infusion/0.15 mg $kg^{-1}$) [70]A; (IV infusion/0.205 mg $kg^{-1}$ in 80 min) [71]A; (Oral/30 mg) [72]A; (subcutaneous injection in burn/2 mg) [74]B; (subcutaneous injection in burn/2 mg) [118] **Morphine** (IV Infusion / 0.1 mg $kg^{-1}$) & **Ketamine** (IV Infusion / 0.405 mg $kg^{-1}$) [69]B; **Morphine** (Oral / 30 mg) & **Dextrometorphan** (Oral / 30 mg) [72]B **Fentanyl** (Local injection / 10 μg) [75] **Alfentanil** (IV infusion / 73 μg $kg^{-1}$) [117]B† | T | Heat/PDT | [75]*, [118] | [74]A, [74]B, [71]A, [70]A |
| | | | Cold/PDT | | [70]A |
| | | | Heat/rating | | [74]A, [74]B, [75] |
| | | M | Pin prick/area | [71]A, [72]B, [117]B‡ | [74]A, [74]B, [117]A, [69]A, [69]B, [70]A, [72]A |
| | | | Pin prick/pain rating | [69]B¶ | [74]A, [74]B, [69]A, [75] |
| | | | Pin prick/PDT | [69]B, [117]A§, [117]B‡ | [74]A, [74]B, [69]A, [71]A |
| | | | Stroking/area | [71]A | [72]A, [72]B, [70]A |
| | | | Impact stimulus/ PDT | | [118] |
| | | S-I | Spontaneous pain | | [74]A, [74]B |
| **Opioid antagonists** | **Naloxone** (IV bolus/0.4 mg) [87] | T | Heat/PDT | | [87] |
| | | | Heat/rating | | [87] |
| | | M | Pin prick/area | | [87] |
| | | | Stroking/area | | [87] |
| **Anaesthetics** | **Lidocaine** (IV infusion/317.5 mg) [76] **EMLA** (topical cream/2 g 2.5% Lignocaine and 2.5% Procaine) [77] | T | Heat/PDT | | [76, 77] |
| | | | Heat/pain rating | | |
| | | M | Pin prick/area | | [76, 77] |
| | | | Pin prick/PDT | | [76, 77] |
| | | S-I | Flare/area | | [76] |
| | | | Flare/intensity | | [77] |
| **NSAIDs** | **Ibuprofen** (oral/500 mg) [81]; (oral/600 mg) [82]A; (topical cream/3 g) [82]B **Ketorolac** (local injection/0.3 mg) [78]; (topical gel/0.075 g) [80]; (IV injection/60 mg) [119]; **Piroxicam** (topical gel/5 mg) [79] | T | Heat/PDT | | [82]A, [82]B, [79, 80] |
| | | | Heat/rating | | [78] |
| | | | Heat/PTT | | [82]A, [82]B, [79, 80] |
| | | M | Pin prick/area | [119] | [81], [82]A, [82]B, [79, 80] |
| | | | Pin prick/PDT | | [79, 80] |
| | | | Stroking/area | | [81] |
| | | | Stroking/pain rating | [81] | |
| | | S-I | Flare/intensity | | [79, 80] |
| | | | Spontaneous pain | | [81] |
| **Calcium channel α2-δ ligands** | **Gabapentin** (oral/1200 mg) [45, 85] | T | Heat/PDT | | [85] |
| | | M | Pin prick/area | [45] | [85] |
| | | | Pin prick/pain rating | | [85] |
| | | | Pin prick/PDT | [85] | |
| | | | Stroking/area | | [85] |

(*continues*)

## Table 6

(Continued)

| Drug class | Drug (administration form/dose) | Challenge type | Challenge/ outcome | Overall effect: Effective | Overall effect: No effect |
|---|---|---|---|---|---|
| | | S-I | Spontaneous pain | | [85] |
| **NMDA receptor antagonists** | **Ketamine** (IV infusion/0.49 mg kg$^{-1}$ in 150 min) [65]A; (IV infusion/0.98 mg kg$^{-1}$ in 150 min) [65]B; (IV infusion/0.405 mg kg$^{-1}$ in 45 min) [69]B; (IV infusion/0.15 mg kg$^{-1}$) [70]B; (IV Infusion/0.39 mg kg$^{-1}$ in 80 min) [71]B; (oral/0.5 mg kg$^{-1}$, 1.0 mg kg$^{-1}$) [73]; (IV infusion/0.3 mg kg$^{-1}$ in 15 min, then 0.3 mg kg$^{-1}$ h$^{-1}$ for 15 min) [67]A; (systemic subcutaneous injection/15 mg) [68]A; (local subcutaneous injection/7.5 mg) [68]B; **Naloxone** (IV infusion / 0.8 mg kg$^{-1}$ in 15 minutes) & **Ketamine** (IV Infusion / 0.375 mg kg$^{-1}$ per 30 minutes) [67]B **Dextrometorphan** (Oral / 60 mg, 120 mg) [66]; (IV infusion / 0.5 mg kg$^{-1}$) [55]; (Oral / 30 mg) [72] | T | Heat/PDT | [65]B | [65]A, [73], [71]B, [70]B, [68]A, [68]B, [67]A, [67]B, [66] |
| | | | Heat/rating | | [68]A, [68]B |
| | | | Cold/PDT | | [70]B |
| | | M | Pin prick/area | [65]B, [70]B††, [71]B, [67]A, [67]B**, [66]‡‡, [55]§§, [69]B¶¶ | [65]A, [73], [68]A, [68]B, [72] |
| | | | Pin prick/PDT | [71]B***, [68]B†††, [69]B | [68]A |
| | | | Pin prick/pain rating | | [68]A, [68]B, [69]B |
| | | | Stroking/area | [65]A***, [65]B, [70]B†††, [71]B¶¶¶, [67]A, [67]B** | [66, 72, 73], [68]A, [68]B |
| | | S-I | Spontaneous pain | [65]B, [68]B | [65]A, [73], [68]A, [66] |
| **Glutamate receptor antagonists** | **Riluzole** (oral/300 mg) [86] | T | Heat/PDT | | [86] |
| | | | Heat/rating | | [86] |
| | | M | Pin prick/area | | [86] |
| | | | Pin prick/PDT | | [86] |
| | | | Pin prick/pain rating | | [86] |
| | | S-I | Spontaneous pain | | [86] |
| **Corticosteroids** | **Clobetasol propionate** (topical cream/0.05 g) [83]; **Dexamethasone** (IV infusion/8 mg) [84]; **Methylprednisolone** (IV injection/125 mg) [119] | T | Heat/PDT | | [83, 84] |
| | | | Heat/PTT | | [83] |
| | | | Heat/pain rating | | [84] |
| | | M | Pin prick/area | [119] | [83, 84] |
| | | | Pin prick/PDT | | [83, 84] |
| | | | Pin prick/pain rating | | [84] |
| | | S-I | Flare/intensity | | [83, 84] |
| | | | Spontaneous pain | | [84] |
| **Hormones** | **Melatonin** (IV infusion/100 mg****) [120] | T | Heat/PDT | | [120] |
| | | M | Pin prick/area | | [120] |
| | | | Pin prick/PDT | | [120] |
| | | | Impact stimulus/ PDT | | [120] |
| | | | Impact stimulus/ PTT | | [120] |
| | | S-I | Flare/intensity | | [120] |

(*continues*)

## Table 6

(Continued)

| Drug class | Drug (administration form/dose) | Challenge type | Challenge/ outcome | Overall effect: Effective | Overall effect: No effect |
|---|---|---|---|---|---|
| | | | Spontaneous pain | | [120] |
| **Antiarrhythmic agents** | **Adenosine** (IV infusion/7.2 mg kg$^{-1}$) [15] | T | Heat/PDT | | [15] |
| | | | Heat/rating | | [15] |
| | | M | Pin prick/PDT | | [15] |
| | | | Pin prick/area | [15] | |
| | | | Pin prick/pain rating | | [15] |

IV, intravenous; EMLA, eutectic mixture of local anaesthetics; M, mechanical; NMDA, N-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug; PDT, pain detection threshold; PTT, pain tolerance threshold; S-I, stimulus-independent; T, thermal. *Concomitant treatment with naloxone (80 μg) reversed this statistically significant reduction in pain score. †Compared with saline or active placebo: midazolam (2 mg kg$^{-1}$ min$^{-1}$). ‡Only significant effect when measured during infusion 85 min postburn, and not 80 min post-infusion 205 min postburn. §Significant difference only seen at high dose (0.28 mg kg$^{-1}$) at late phase (80 min postdosing), not in earlier measurements. ¶Only significant difference up to 45 min postdosing. **Only effect at late phase (135 min postburn). ††Only short-term effect: no significant difference from 15 min postdosing onwards. ‡‡Only at specific time point (180 min postburn, not before or after) at high dose (120 mg). §§Significant difference from 90 min to 180 min postdosing, not earlier. ¶¶Only significant effect at 45 min postdosing, not at 75 min postdosing. ***Only short-term effect during infusion; no significant difference at 80 min or 120 min postdosing. †††Only significant effect at 0 min postburn; no significant difference at 60 min or 120 min postburn. ‡‡‡Only significant effect at 100 min postdosing, not at 60 min or 160 min postdosing. §§§Only short-term effect: no significant difference from 15 min postdosing onwards. ¶¶¶Only short-term effect during infusion; no significant difference at 80 min or 120 min postdosing. ****Administration of melatonin 10 mg IV infusion demonstrated equal lack of analgesic effect on all parameters. Numbers between brackets signify references. Studies that investigated more than one type of pharmacological intervention are denoted with a letter (A,B,C).

intervention. To overcome this, a protocol with an appropriate control needs to be designed. Nonetheless, this temporal aspect potentially interferes with the interpretation of the results of studies using analgesics or antihyperalgesics with a prolonged pharmacological effect.

### *Implications for pain research*

In early phase drug development, research in healthy subjects can form the bridge between animal models and clinical application, and provide the basis for proof-of-concept of new compounds or techniques. Furthermore, experiments can investigate basic pain mechanisms to characterize sensory dysfunction in patients [90]. The main concern in human pain research is to appraise the value of a model in terms of translation to clinical practice. In this respect, the UVB model is a highly satisfactory paradigm for inflammation as it is highly reproducible and responds well to NSAIDs. The thermode burn model responds well to NMDA receptor antagonists in the attenuation of mechanical hyperalgesia. This might reflect a specific component of neuropathic pain, so-called 'wind-up' pain, which is also reduced by NMDA receptor antagonists in clinical practice [91]. However, as the model does not respond well to the other medications that are efficacious in the treatment of neuropathic pain, this model appears to be solely capable of mimicking this specific element of neuropathic pain. As a model for inflammatory pain, the thermode burn model is unsuitable as it is insensitive to anti-inflammatory drugs. The capsaicin model shows most sensitivity to the antihyperalgesic effects of opioids compared with other drug classes. The established drugs for the treatment of neuropathic pain, such as the calcium channel α2-δ ligands only show antihyperalgesic effects on specific endpoints, indicating that fine tuning of the model in combination with the correct challenge could potentially provide a pharmacologically sensitive model for these classes of compounds. Although sensitization is present in the capsaicin challenge model, it is due to different mechanisms than those involved in the clinical presentation of neuropathic pain. Nonetheless, fine tuning of this model may render it a useful tool for early phase drug research as no single model can completely replicate the clinical presentation of neuropathic pain. However, the capsaicin model may only mimic the features of clinical (neuropathic) pain in certain healthy subjects [92], therefore subjects may have to be prescreened for 'responders', and the model individualized for each subject, as is commonly performed with the UVB model, this may be necessary for the capsaicin model. Prescreening for 'responders', as is occasionally carried out in studies performing pain models [93, 94], ensures homogeneity and thereby reduces variability. In early phase research for a compound with a novel mechanism of action for the indication of treating neuropathic pain, one needs to keep these limitations in mind. As such, the capsaicin model is not suitable for go/no-go decision making but can be a useful tool to aid the clinical development of novel analgesic treatments.

## Conclusions

The present literature review demonstrates the importance of carefully considering the appropriate design in early phase pharmacological research. Due to the abundance of possible

working mechanisms, no single human evoked pain model is capable of detecting the antihyperalgesic or analgesic effects of each class of drugs. Therefore, the appropriateness and translatability of the model has to be taken into account when designing an early phase proof-of-concept study. In this respect, the UVB model can be considered as a predictive model for inflammatory pain based on its capacity to detect the antihyperalgesic effects of NSAIDs. The thermode burn model is considered to reflect a specific aspect of neuropathic pain; however, as a whole, this model lacks sensitivity to serve as an overarching model for neuropathic pain. The capsaicin model in its current form also lacks pharmacological sensitivity to be used as a model for neuropathic pain. It may, however, provide an important insight into the mechanisms involved in hyperalgesia, including signal transduction and pain perception. In our opinion, further standardization and validation are needed before the capsaicin model can be used as a model to screen drugs for their effect on the symptoms of neuropathic pain.

While investigating the pharmacological sensitivity of hyperalgesia pain models, we revealed the lack of robust models for neuropathic pain. Current hyperalgesia models evidently do not reflect the clinical presentation of neuropathic pain. Asserting that a certain model is representative of neuropathic pain overstates the confidence in the models. Neuropathic pain is a heterogeneous entity and further research is needed to investigate the link between the evoked pain models and the different types of this pain modality. Carefully selecting appropriate biomarkers and understanding their merits and limitations for early phase drug research are essential for effective and efficient drug development.

## Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

## Contributors

GvA worked on the conception and design of the study, data acquisition and writing the manuscript. MWdB worked on data acquisition and writing the manuscript. GJG worked on the conception and design of the study, data acquisition and writing the manuscript. JLH worked on the conception and design of the study, data acquisition and writing the manuscript.

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