# Ketamine for neuropathic: a systematic review and meta-analysis of animals studies
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## Citation

## Review question
Does administration of ketamine produce relief of neuropathic pain symptoms in animals with neuropathic pain, with special focus on timing of administration and time of measurement.

## Context and rationale

Ketamine is a dissociatie anesthetic that at low dose is able to relief acute pain. The drug is used increasing frequent for treatment of chronic and particularly chronic neuropathic pain in humans. However, the majority of randomized controlled trials is unable to show efficacy in neuropathic pain patients. In fact, ketamine seems only efficacious in an acute pain setting (eg preoperatively) for short periods of time. The question that we have is how ketamine behaves in animal models of neuropathic pain. Are the results generally positive, with positive ketamine effects lasting beyond the acute setting (eg > 24 h)? Or is ketamine, similarly to humans, only active at peak plasma concentration and consequently continuous or repetitive administrations are required to produce long-term (> 24h) plain relief. In fact, we contend that this is a study that examines the translation of animals studies in neuropathic pain to human studies.

## Searches
PubMed and Embase, no language restrictions.

## Study designs to be included

### Inclusion criteria:

Controlled, parallel design, irrespective of randomization or concealment (blinding)

### Exclusion criteria:

Non controlled studies or repetitive use of the same animals for multiple interventions.

## Human disease modelled
Neuropathic pain as defined by the International Association for the Study of Pain (IASP) as 'pain caused by a lesion or disease of the somatosensory nervous system'.

## Animals/population

### Inclusion criteria:

Animals with an accepted model of neuropathic pain, such as chronic nerve constriction injury (eg spinal nerve ligation), spared nerve injury. spinal cord injury, central pain, chemotherapy-induced neuropathic pain, diabetic neuropathic pain (induced by streptozotocin) or post-herpetic neuralgia.

### Exclusion criteria:

Animals with acute nociceptive pain (eg plantar incision or surgical pain), inflammatory pain, thermal pain or other pain models not related to peripheral or central neuropathic pain. Additionally CRPS models induced by tibia fracture will be excluded. Single cases or case series, human studies will be excluded as well.

## Intervention(s), exposure(s)

### Inclusion criteria:

Inclusion criteria were: (1) original non-human studies; (2) available full-text articles; (3) disease model (neuropathic pain) induced by one of the following methods: spared nerve injury, (full or partial) ligation of peripheral nerves (chronic constriction injury), spinal nerve ligation, spinal cord injury, plexus ablation, viral infections (post-herpetic neuralgia), chemotherapeutics, streptozotocin administration, or central lesions; (4) systemic (intravenous, subcutaneous, intraperitoneal, oral) or intrathecal administration of ketamine, either the racemic formulation or the S-enantiomer, to relief mechanical or heat/cold allodynia as measured by withdrawal responses to tactile or thermal stimuli; (5) ketamine is tested against control conditions (e.g. saline, vehicle); (6) ketamine treatment was initiated after the neuropathic disease model was fully established; and (7) mechanical allodynia or pain scores were quantitatively reported either in a table or in a graph.

## Exclusion criteria:

Exclusion criteria included case reports, case series, review papers, conference abstracts, studies that tested preemptive ketamine, the combined administration of ketamine with another drug, ketamine as positive or negative control (e.g., when administered at sub-effective low-dose or excessively high dose as stated in the text), ketamine administered directly into the brain, or ketamine tested as an anesthetic or analgesic for nerve damage surgery.

## Comparator(s)/control

### Inclusion criteria:

A saline administration via the identical route as the ketamine administration in a parallel design or a control group (without any treatment)

### Exclusion criteria:

Use of alternative control data (eg historical, or data from another study), use of ketamine as positive or negative control.

## Outcome measure(s)

### Inclusion criteria:

The following endpoint is our single and primary endpoint: mechanical or thermal allodynia induced by nerve damage.

### Exclusion criteria:

None

## Study selection and data extraction

### Procedure for study selection

Step 1. Screening of titles/abstracts

Step 2. Full reading of the paper

This process will be performed by 2 members of the team and discrepancies will be resolved by consensus. If no consensus can be obtained a third member will be consulted.

### Prioritise the exclusion criteria

STEP 1/2

1. Not an animal study (ie, human studies)
2. Other drugs than ketamine studied

3. Non pain-related outcomes

4. Non neuropathic pain related outcome (eg acute nociceptive pain (eg plantar incision or surgical pain),

inflammatory pain, thermal pain or other pain models not related to peripheral or central neuropathic pain; CRPS pain models not involving nerve damage).

STEP 2/1

5. No or insufficient quantitative data on ketamine effect

6. Absent control groups

7. Ketamine used as negative/positive control

8. Pre-emptive ketamine treatment

9. Drug interaction study and ketamine not studied separately

10. Single cases or case series.

## Methods for data extraction

The data will be extracted by two reviewers either from the text or from the graphs using precise calculation of effect and SD. In case of missing information, the authors may be contacted by email.

Discrepancies will be resolved by consensus or by involvement of a third reviewer.

### Data to be extracted: study design

Study designs will be interventional, controlled, parallel design with at least two groups available in each study, a ketamine group and a control (control, saline or vehicle treated) group.

### Data to be extracted: animal model

We will extract species (mice/rats/gerbil/other), gender, age, weight, randomization yes/no, concealment yes/no, pain model, outcome measure (eg mechanical allodynia, pain score)

### Data to be extracted: intervention of interest

Treatment (RS-ketamine, R-ketamine or S-ketamine), dose, route of administration, number of doses, time of dosing, time of measurement of relief of neuropathic pain, response to relief of allodynia ( with units -mechanical allodynia: gram, thermal allodynia: temp, cold allodynia: temp, hotplate paw response: sec, objective pain scores: numerical score, or other relevant units), species (mice, rats or other species).

### Data to be extracted: primary outcome(s)

Relief of neuropathic pain will be measured (a single primary outcome measure) by either (1) withdrawal response to von Frey elements (in grams), or withdrawal response frequency (in %) or delay to withdrawal response (in secs), or numerical pain score in response to von Frey probing.

All data are assumed to be continuous except the numerical pain score which is categorical.

### Data to be extracted: secondary outcome(s)

None planned

### Data to be extracted: other

Author, year published, number of animals in control and intervention groups, treatment (eg S-ketamine, R-ketamine or RS-ketamine), time point of endpoint measurement, number of ketamine administrations, route of administration, animal species, animal weight, ketamine dose.

## Risk of bias and/or quality assessment
By use of SYRCLE's risk of bias tool.

Two (or three) group members will perform the risk of bias assessment according g to SYRCLE criteria. If no consensus can be obtained a third member will be consulted..

## Strategy for data synthesis

### Planned approach

1. a narrative overview of the data will be given, followed by

2. a quantitative synthesis (if the data allows such a synthesis)

Re 1: The narrative review will put the animal work in perspective of clinical need. We will focus on the effect of single ketamine injections vs. multiple injections on the ability to relief neuropathic pain with emphasis on the duration of effect (ie the duration of relief of neuropathic pain). We plan to first describe each study in detail, and then group results in terms of acute effects (ketamine relief of neuropathic pain within 3 hours of administration), chronic effects (ketamine relief of neuropathic pain at 24 h or later following ketamine administration) and finally, effect of repetitive of continuous ketamine administration. Following the systematic review we intend to perform a quantitative (meta) analysis.

Re 2: The metanalysis will be performed with Comprehensive Metanalysis v3. A meta-analysis will be performed for three conditions: ketamine effect on neuropathic within 3 hours after ketamine administration; ketamine relief of neuropathic pain at 24 h or later following ketamine administration; and finally, the effect of repetitive or continuous infusion on ketamine induced relief of neuropathic pain. Our threshold for meta-analysis is 5 studies. Since we assume that most if not all studies that we will include have the same outcome measure (response to von Frey elements), we will pool the results using a random-effects meta-analysis, with standardized mean differences for continuous outcomes. Heterogeneity between the studies in effect measures will be assessed using both the ?2 test and the I² statistic. We will consider an I² value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses based on study quality. We will use stratified meta-analyses to explore heterogeneity in effect estimates according to: study quality; study populations; the logistics of intervention provision; and intervention content. We will also assess evidence of publication bias; because standardized mean differences may cause funnel plot distortion we plotted the standardized mean differences against a sample size-based precision estimate $1/\sqrt{n}$.

### Effect measure

standardized mean difference: Hedges 'g

### Effect models

Random effects model

### Heterogeneity

I^2 and Q

### Other

Whenever a control group serves more than one experimental group, we will correct the total number of control animals in the meta-analysis by dividing the number of animals in the control group by the number of treatment groups served. Where applicable, Holm-Bonferroni correction for testing multiple subgroup analyses will be performed. If one or more subgroup analyses cannot be performed due to insufficient data, the p-value will be adjusted accordingly.

## Analysis of subgroups or subsets

### Subgroup analyses

Subgroups will be analyzed (subgroup comparisons are restricted to subgroups with at least 3 studies):

- Intraperitoneal vs intrathecal administration

- dose effect (by meta-regression analysis)

- mice vs rats

- rats vs rats (background differences)

- SNI vs CCI (vs other models if possible)

- early measurement vs late measurement (by meta-regression analysis)

- single vs repetitive/continuopus administration of ketamine

- animal age effects (if possible)

- any other possible comparison that might come up.

## Sensitivity

A sensitivity analysis will be performed with the meta-analysis software

## Publication bias

Publication bias will be assessed

## Contact details for further information

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## Organisational affiliation of the review

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## Review team members and their organisational affiliations

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## Review type

Pre-clinical animal intervention review

## Anticipated or actual start date

27 July 2020

## Anticipated completion date

30 November 2020

## Funding sources/sponsors

No fundings

## Grant number(s)

None

## Conflicts of interest

None known

## Language

English

## Country

Netherlands

## Stage of review
Review Completed not published

## Details of final report/publication(s) or preprints if available
TBD

## Subject index terms status
Subject indexing assigned by CRD

## Subject index terms
Animals; Ketamine; Research

## Date of registration in PROSPERO
19 August 2020

## Date of first submission
27 July 2020

## Details of any existing review of the same topic by the same authors
We did publish several reviews/editorials on this topic in humans:

Dahan A, van Velzen M, Niesters M. Ketamine for neuropathic pain – a tiger that won't bite? Br J Anaesth 2020 (Epub ahead of print]

Kamp J, van Velzen M, Olofsen E, Boon M, Dahan A, Niesters M. Pharmacokinetic and pharmacodynamic considerations for NMDA-receptor antagonist ketamine in the treatment of chronic neuropathic pain: an update of the most recent literature. Exp Oinion Drug Metab Toxicol 2019; 15: 1033-1041

Jonkman K, Dahan A, van de Donk T, Aarts L, Niesters M, van Velzen M. Ketamine for pain. F1000Research 2017; 6: 1711.

Jonkman K, van de Donk T, van Velzen M, van Kleef M, Bhatia A, Dahan A, Niesters M. Ketamine for chronic pain: a systematic review of randomized controlled trials published between 2010 and 2016. NTvA 2017; 30: 43-49

Jonkman K, van de Donk T, Dahan A. Ketamine for cancer pain: what is the evidence? Review. Current Opinion in Supportive & Palliative Care. 2017; 11: 88-92

Niesters M, Martini C, Dahan A. Ketamine for chronic pain: Risks and Benefits. Br J Clin Pharmacol 2014; 77: 357-67.

## Stage of review at time of this submission

| Stage | Started | Completed |
| --- | --- | --- |
| Preliminary searches | No | Yes |
| Piloting of the study selection process | No | Yes |
| Formal screening of search results against eligibility criteria | No | Yes |
| Data extraction | No | Yes |
| Risk of bias (quality) assessment | No | Yes |
| Data analysis | No | Yes |

## Revision note

The changes are related to some minor adaptations that were made during the analyses process to enlarge the number of possible included studies and optimize the data analysis. The study is currently finalized and submitted for publication

*The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.*

*The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.*

## Versions

19 August 2020
19 August 2020
13 November 2020

# Supplemental file 1. Search strategy

**PubMed:**
"Ketamine"[Mesh] OR "Ketamine"[tw] OR "Ketamin*"[tw] OR "norketamin*"[tw] OR "hydroxynorketamin*"[tw] OR "2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone"[tw] OR "CI-581"[tw] OR "CI 581"[tw] OR "CI581"[tw] OR "Ketalar"[tw] OR "Ketaset"[tw] OR "Ketanest"[tw] OR "Calipsol"[tw] OR "Kalipsol"[tw] OR "Calypso"[tw] OR "Dehydronorketamin*"[tw]) AND "nerve injuries"[tw] OR "nerve injury"[tw] OR "nerve damage"[tw] OR "nerve trauma"[tw] OR "nerve traumas"[tw] OR "Cranial Nerve Injuries"[Mesh] OR "Peripheral Nerve Injuries"[Mesh] OR "Nervous System/injuries"[Mesh] OR (("nerve"[tw] OR "nerves"[tw]) AND ("injur*"[tw] OR "damag*"[tw] OR "trauma*"[tw] OR "lesion*"[tw])) OR "Neuralgia"[Mesh] OR "Neuralgia*"[tw] OR "neuropathic pain*"[tw] OR "nerve pain*"[tw] OR "Neurodynia*"[tw] OR "neuropathy"[tw] OR "neuropathies"[tw] OR "allodynia*"[tw] OR "Hyperalgesia"[Mesh] OR "hyperalgesia*"[tw] OR "Chronic Pain"[Mesh] OR "chronic pain*"[tw] OR Polyneuropathies[Mesh] OR Polyneuropathies [tiab] OR Polyneuropathy [tiab] OR Polyradiculoneuropathies [tiab] OR Polyradiculoneuropathy [tiab]OR Polyradiculoneuritis [tiab] OR Polyradiculoneuritides [tiab] OR Peripheral Autoimmune Demyelinating Disease [tiab] OR neurodynia [tiab] OR Peripheral Nerve atrophy [tiab] OR axonopathy [tiab] OR axonopathies [tiab] OR myelinopathy [tiab] OR myelinopathies [tiab] OR neuralgic pain [tiab] OR neuralgic pains [tiab]

The PubMed search was performed using the search filter for animals studies developped by Syrcle (Radboud MC, Nijmegen, the Netherlands) and avialable at: https://www.radboudumc.nl/getmedia/2c58b60d-e449-4be1-8b90-460b90815e27/animal-search-filter-pubmed-1-page-for-website.aspx). See also Ref. Hooijmans CR, Tillema A, Leenaars M, Ritskes-Hoitinga M. Enhancing search efficacy by means of a search filter for finding all studies on animal experimentation in PubMed. Lab Anim 2010; 44: 170-5.


**EMBASE:**
((((*"Ketamine"/ OR "Ketamine".ti,ab OR "Ketamin*".ti,ab OR "norketamin*".ti,ab OR "hydroxynorketamin*".ti,ab OR "2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone".ti,ab OR "CI-581".ti,ab OR "CI 581".ti,ab OR "CI581".ti,ab OR "Ketalar".ti,ab OR "Ketaset".ti,ab OR "Ketanest".ti,ab OR "Calipsol".ti,ab OR "Kalipsol".ti,ab OR "Calypso".ti,ab OR "Dehydronorketamin*".ti,ab) AND ("nerve injuries".ti,ab OR "nerve injury".ti,ab OR "nerve damage".ti,ab OR "nerve trauma".ti,ab OR "nerve traumas".ti,ab OR exp *"Nerve Injury"/ OR (("nerve".ti,ab OR "nerves".ti,ab) AND ("injur*".ti,ab OR "damag*".ti,ab OR "trauma*".ti,ab OR "lesion*".ti,ab)) OR exp *"Neuralgia"/ OR "Neuralgia*".ti,ab OR "neuropathic pain"/ OR "neuropathic pain*".ti,ab OR "nerve pain*".ti,ab OR "Neurodynia*".ti,ab OR exp *"Neuropathy"/ OR "neuropathy".ti,ab OR "neuropathies".ti,ab OR "allodynia*".ti,ab OR exp *"Hyperalgesia"/ OR "hyperalgesia*".ti,ab OR *"Chronic Pain"/ OR "chronic pain*".ti,ab) AND (exp "Animals"/ NOT exp "Humans"/)) **OR** ((exp *"Ketamine"/ OR "Ketamine".ti,ab OR "Ketamin*".ti,ab OR "norketamin*".ti,ab OR "hydroxynorketamin*".ti,ab OR "2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone".ti,ab OR "CI-581".ti,ab OR "CI 581".ti,ab OR "CI581".ti,ab OR "Ketalar".ti,ab OR "Ketaset".ti,ab OR "Ketanest".ti,ab OR "Calipsol".ti,ab OR "Kalipsol".ti,ab OR "Calypso".ti,ab OR "Dehydronorketamin*".ti,ab) AND ("nerve injuries".ti,ab OR "nerve injury".ti,ab OR "nerve damage".ti,ab OR "nerve trauma".ti,ab OR "nerve traumas".ti,ab OR exp *"Nerve Injury"/ OR (("nerve".ti,ab OR "nerves".ti,ab) AND ("injur*".ti,ab OR "damag*".ti,ab OR "trauma*".ti,ab OR "lesion*".ti,ab)) OR exp *"Neuralgia"/ OR "Neuralgia*".ti,ab OR "neuropathic pain"/ OR "neuropathic pain*".ti,ab OR "nerve pain*".ti,ab OR "Neurodynia*".ti,ab OR exp *"Neuropathy"/ OR "neuropathy".ti,ab OR "neuropathies".ti,ab OR "allodynia*".ti,ab OR exp *"Hyperalgesia"/ OR "hyperalgesia*".ti,ab OR *"Chronic Pain"/ OR "chronic pain*".ti,ab) AND (exp "Humans"/ AND "Animals"/)))