

# NMDA receptor antagonists and pain relief: A meta-analysis of experimental trials

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Table 1 (study characteristics)

Appendices 2 (search terms), 3 (validity criteria) and 4 (reference list of studies included in meta-analysis).

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**ABSTRACT**

**OBJECTIVES:** We conducted a meta-analysis of controlled trials that used experimental models of acute pain and hyperalgesia to examine the analgesic effects of *N*-methyl-D-aspartate receptor (NMDAR) antagonists. **METHODS:** Six major databases were systematically searched (to 03/2018) for studies using human evoked pain models to compare NMDAR antagonists with no-intervention controls. Pain outcome data were analyzed with random-effects meta-analysis. **RESULTS:** Searches identified 70 eligible trials (N=1069). Meta-analysis found that low-dose ketamine (<1 mg/kg) produced a decrease in the size of hyperalgesic area (Standardized Mean Difference=0.54, CI<sub>95</sub>[0.34, 0.74], *p*<.001), and a 1.2-point decrease (CI<sub>95</sub>[0.88, 1.44], *p*<.001) in pain ratings from 4.6 to 3.4 on a 0-10 scale (a 26% reduction). Similar analgesia was observed for acute and hyperalgesic models and was constant across the dosing range (0.03-1.00 mg/kg). Moderate-high variability in effect size was observed and mild side effects (e.g. sedation, sensory disturbance) were common. No effects of dextromethorphan were found. **CONCLUSIONS:** Findings provide robust evidence for analgesic and anti-hyperalgesic effects of ketamine, supporting its utility for acute and chronic pain management. However, pain relief was modest, suggesting ketamine may potentially be most useful when opioids are contraindicated, rapid analgesia is required or for pain resistant to conventional medication.

**Keywords:** pain, NMDA, ketamine, dextromethorphan, analgesia, review, meta-analysis

## INTRODUCTION

Unsatisfactory pain relief from traditional pain medication and the ongoing opioid crisis have created an urgent need for alternative analgesics<sup>19</sup>. *N*-methyl-D-aspartate receptor (NMDAR) antagonists such as ketamine have experienced a surge of renewed clinical and research interest in subanesthetic doses (<1mg/kg) for pain treatment, leading to recent consensus guidelines on the best usage of ketamine for pain<sup>6</sup>. Several analgesic mechanisms of NMDAR antagonists have been suggested<sup>25</sup>, with a key candidate the reversal of central sensitization believed to be a fundamental component of chronic pain. Clinical data are consistent with analgesic benefits of NMDAR antagonists for neuropathic pain<sup>1</sup>, CRPS<sup>1,8</sup>, acute pain in the emergency room<sup>15</sup>, and a reduced requirement for opioids<sup>4</sup>.

However, conclusions on efficacy of NMDAR antagonists are based on heterogeneous clinical data often of low-grade evidence<sup>6,17</sup>. To circumvent the methodological issues associated with clinical data, experimental pain models have also been employed. These replicate key pathological features of acute and chronic hyperalgesic pain states<sup>5</sup> in healthy people, and can provide insights into analgesic strength, dose-response effects and potential mechanisms. However, the use of small samples (typically 10-12 participants) and methodological (e.g. dosage) variation across experimental studies have prevented a clear overall picture of the analgesic benefits of NMDAR antagonists or a consensus on optimal dosages<sup>6</sup>.

We conducted a meta-analysis of controlled experimental pain trials of NMDAR antagonists in healthy participants to: (1) estimate the magnitude of pain relief; (2) estimate a dose-response relationship, to facilitate identification of the lowest meaningful analgesic dose;

(3) establish the most efficacious NMDAR antagonists; and (4) compare analgesic effects for acute and hyperalgesic states.

## **METHOD**

This meta-analysis was conducted following an *a priori* but unpublished protocol (available upon request), based on PRISMA-P 2015 guidelines<sup>18</sup>.

### *Eligibility Criteria*

Inclusion criteria were the use of: (1) an NMDAR antagonist; (2) a no-intervention control; (3) an experimental pain stimulus and quantitative pain assessment; (4) healthy participants free from chronic pain. Exclusion criteria were co-administration of other pain interventions, drugs with only secondary effects on NMDARs (e.g. methadone) or NMDAR antagonists not available as experimental drugs or approved clinical medications.

### *Search Strategy*

PubMed, Embase, CENTRAL, CINAHL, PsycINFO and Web of Science databases were independently searched (to 19-03-2018) by two reviewers (FW, KG). Search strings consisted of terms relating to NMDA AND pain AND noxious experimental stimuli (Appendix 2, available from Dryad: <https://doi.org/10.5061/dryad.sm4tj6tX>). No language restrictions were imposed, but animal studies were excluded. Searches were augmented through manual searching of reference lists of included articles.

### *Study selection*

Two reviewers (FW, KG) independently screened titles/abstracts, with the full-text of potentially eligible articles then examined to reach a final list of articles to be included in the meta-analysis. Any disagreements were resolved through discussion with a third reviewer (TT). Where necessary, corresponding authors were contacted for more information with an initial and, if needed, follow-up email request over a six-week period. Of 4 author groups contacted, 1 reply was received.

### *Outcomes*

Primary outcomes were: (1) pain ratings, (2) pain tolerance (the point of maximum endurance), and (3) size of hyperalgesic area. Secondary outcomes were side effect incidence and pain threshold. Threshold was designated as a secondary outcome, as it refers to minimum pain and is therefore of lesser clinical relevance.

### *Moderators*

Primary moderators were: (1) NMDAR antagonist type and dosage, and (2) hyperalgesic vs. acute pain (with no hyperalgesic induction) models. We included (1), as dosage and differing receptor affinities across antagonists<sup>16</sup> should influence pain response. We included (2), as this should provide insights into mechanisms of actions (e.g., whether analgesic mechanisms are primarily anti-hyperalgesic or also modulate acute pain).

Secondary moderators were examined to provide preliminary data on drug timing (before/during stimulation), noxious stimulus type, study biological sex composition,

testing site (upper/lower body), infusion period (for intravenous studies) and pain duration (brief phasic/longer-lasting tonic).

### *Quality of evidence*

Two reviewers (FW, TT) independently rated each study on 15-item scale used in our previous work<sup>28</sup> (Appendix 3, available from Dryad:

<https://doi.org/10.5061/dryad.sm4tj6tX>) assessing methodological rigor, selection and reporting bias. A third reviewer (BS) was consulted in the event of disagreement. This scale was based on items from Cochrane collaboration criteria, PRISMA recommendations and PEDro guidelines and adapted from our previous work<sup>28</sup> for the current review.

### *Standard protocol approvals, registrations, and patient consents*

No additional ethical approval was required for this meta-analysis.

### *Data Extraction*

Extraction and coding of study data was performed by two reviewers (FW, TT) on a standardized template<sup>28</sup>. Data extracted were: (1) age, sex and bodyweight; (2) NMDAR antagonist type, dosage, delivery method, delivery timing (pre-emptive vs. during pain stimulation); (3) study design and control condition (nothing vs. placebo); (4) pain outcome; (5) pain induction: method, body site and pain model (hyperalgesic vs. acute nociceptive testing). Hyperalgesic pain models were those where noxious stimuli were applied to primary (injured area) or secondary (surrounding area) sites following established protocols to induce hyperalgesia (e.g. topical capsaicin application for >15 minutes to produce

inflammation)<sup>12</sup>. Acute nociceptive models were those where noxious stimulation was applied in the absence of hyperalgesic induction.

When multiple effect sizes were available for a study (e.g. across time points or different dosages), all such data were extracted. The following data decisions were also made: (1) for intravenous ketamine studies, only pain outcome data collected during the infusion period were extracted, due to ketamine's rapid elimination from the bloodstream<sup>24</sup>; (2) When *M/SDs* were not reported, effect sizes were calculated from any other data that allowed their computation<sup>7</sup>; (3) for a few studies reporting use of multiple outcomes but only providing data for some outcomes, data were extracted for available outcomes, and; (4) while NMDA dosage in mg/kg bodyweight was extractable for most studies, (i) 16 studies reported total dose only, and (ii) 1 study reported blood plasma. For (i), mg/kg was calculated using mean body weight imputed from study sex composition and country<sup>35</sup>, and for (ii) we used published equivalency data for blood plasma<sup>2,34</sup>. The impact of decision 4 was assessed with sensitivity analysis.

### *Effect size*

The standardized mean difference (*SMD*) for NMDAR antagonists vs. control was computed using Hedges' *g* formula where .20, .50 and .80 represent small, medium and large effects<sup>7</sup>. When computing variance for crossover designs<sup>20</sup>, we used  $r=0.65$  as an estimated correlation amongst within-trial pain outcomes but assessed alternative correlations in sensitivity analysis. Effect size was coded so that positive values indicated drug analgesia.

### *Meta-analysis*

An overall effect size was estimated using a random-effects model based on anticipated heterogeneity due to methodological variation. We used the robust variance estimation (RVE) method<sup>13</sup> which allows for the inclusion of multiple, statistically-dependent effect sizes from within a study without requiring (rarely reported) information on correlations between outcomes. Instead, effect size dependency is based on a single estimated common correlation<sup>27</sup> and has shown to produce accurate parameter estimates provided adjusted RVE degrees of freedom ( $df$ ) $<4$  (which primarily results from low study numbers)<sup>27</sup>.

Because different NMDAR antagonists may have different effects on pain, we added medication type as a moderator in our initial meta-analysis. If effect size differed across medication types, we conduct separate analyses for each medication, as a single overall effect size based on pooled data may be misleading.

### *Meta-regression*

We computed  $I^2$  as a measure of effect size inconsistency across studies, and tau ( $\tau^2$ ) as a measure of heterogeneity (twice the value of tau above and below the summary estimate gives the estimated 95% range of effects in the population)<sup>7</sup>. If  $I^2 > 50\%$ <sup>7</sup>, RVE meta-regression was performed to identify potential effect modifiers. For moderators that were categorical, these were dummy-coded (omitting any categories with  $<5$  studies), with two different model parameterizations used to obtain comparisons of each category vs. no effect (no-intercept model) and each category vs. another category (intercept model).

### *Publication bias*

Funnel plots of effect sizes against standard errors for outcomes with >10 studies<sup>7</sup> were examined for asymmetry, with Egger's bias test<sup>10</sup> used as a corresponding statistical test with  $p < .10$  indicating asymmetry. If asymmetry is a result of a lack of small studies with small effects, this can indicate possible publication bias, and we computed a revised effect size estimate using the trim and fill method<sup>9</sup>.

Analyses were performed using the *metafor*<sup>30</sup> and *robumeta*<sup>11</sup> packages in R.

### *Data availability*

Data will be made available to qualified investigators upon request to the corresponding author.

## **RESULTS**

### *Study selection and data characteristics*

#### Study inclusion

4,903 unique hits were identified through database searches. Initial screening of titles/abstracts identified 131 potentially eligible articles, reduced to 70 eligible articles following full text review (Figure 1). Rater agreement for study selection was high (90% agreement).

### Participant characteristics

A total of  $N=1069$  participants comprised the aggregated data, with  $n=994$  receiving NMDA medication and  $n=971$  a control procedure. As crossover designs were primarily used, study biological sex composition (reported by  $k=65$  of 70 studies;  $M=72.3\%$  male) and age ( $k=45$ ;  $M= 28.2$  years,  $SD=6.2$ ) were closely equivalent for NMDA and control conditions. Twenty-one studies reported bodyweight ( $M=74.0\text{kg}$ ).

### Study characteristics

Study locations were Denmark ( $k=16$ ), Germany ( $k=8$ ), USA ( $k=9$ ), Sweden ( $k=7$ ), Netherlands ( $k=6$ ), Norway ( $k=4$ ), UK ( $k=4$ ), France ( $k=3$ ), Japan ( $k=3$ ), Canada ( $k=2$ ), Finland ( $k=2$ ), South Korea ( $k=2$ ), Switzerland ( $k=2$ ), Australia ( $k=1$ ) and Brazil/France ( $k=1$ ).

Medication/control was administered using a repeated-measures crossover ( $k=64$ ) or parallel independent-groups ( $k=6$ ) design, with most studies ( $k=54$ ) also recording baseline pain responses. All 70 articles were published in peer reviewed journals and are summarised in Table 1 (available from Dryad: <https://doi.org/10.5061/dryad.sm4tj6tX>).

### NMDAR antagonists

There were 54 ketamine (racemic  $k=41$ , S(+)-ketamine  $k=12$ , both=1) and 12 dextromethorphan studies with several other antagonists each examined by a single study. For acute noxious stimulation (without previous hyperalgesic induction), medication was administered pre-emptively ( $k=52$ ) and/or during ( $k=26$ ) noxious stimulation. For hyperalgesic inductions, medication was initiated pre-emptively ( $k=24$ ) and/or during ( $k=16$ ) hyperalgesia. For pre-emptive administration, oral compounds were administered so that pain assessment occurred before the drug's half-life period had been reached.

*Delivery methods and dosage.* Ketamine was delivered through IV ( $k=43$ ), intramuscular ( $k=4$ ), oral ( $k=3$ ) or subcutaneous ( $k=3$ ) routes or as a topical gel ( $k=1$ ). Mean ketamine dosage ( $k=49$ ) was 0.34 mg/kg (range=0.03 – 1.00), with similar mean dosages used for racemic ( $M=0.33$  mg/kg, range=0.06 - 1.00) and S(+)-ketamine ( $M=0.39$  mg/kg, range=0.03-0.95). IV infusions were delivered with ( $k=29$ ) or without ( $k=12$ ) an initial bolus dose or this could not be determined ( $k=3$ ), with a mean infusion time of 36 mins (range=1-150 mins). Dextromethorphan was administered in oral ( $k=11$ ) and IV ( $k=1$ ) form with a mean dosage of 0.92 mg/kg (range=0.17–2.71 mg/kg).

66 studies used a placebo and 4 studies used a baseline control. For the placebo, 64 studies used an inactive compound and 2 used diphenhydramine, which exhibits ketamine-like sedative effects without analgesia<sup>32</sup>.

#### Pain induction methods and outcomes

Noxious stimuli were applied to areas of primary ( $k=33$ ) or secondary ( $k=24$ ) hyperalgesia or unsensitized areas ( $k=66$ ). Hyperalgesia was most commonly induced with capsaicin applied for 15-60 mins ( $k=16$ ) or a 7-min heat burn ( $k=13$ ) in accordance with common protocols. Pain outcomes were intensity ( $k=56$ ), usually 0-10 ratings, threshold ( $k=35$ ), size of secondary hyperalgesic area ( $k=22$ ), tolerance ( $k=12$ ) and/or affective pain ratings ( $k=6$ ). Several experimental pain inductions were used across upper and lower body sites (see Table 1). Acute pain stimuli were typically brief (0-5 mins), with principal exceptions of ischemic ( $M=24$  mins) and capsaicin ( $M=29$  mins).

## Outliers

Large externally studentized residuals<sup>29</sup> (>3.0) suggested one possible outlier for hyperalgesic area (ref e-33 in Appendix 4, available from Dryad: <https://doi.org/10.5061/dryad.sm4tj6tX>) and two for pain intensity (ref e-33 and e-38 in Appendix 4). Scrutiny of the data and methodology from these studies did not reveal any identifiable study anomalies. Nevertheless, given the small number of outliers these cases were removed, with sensitivity analysis conducted to determine the effect of their removal.

## *Quality of evidence*

Good agreement (>90%) was found across raters for study validity items, with disagreement resolved after consultation with a third reviewer. Validity ratings (Appendix 3) and study characteristics described previously suggested common use of sound methodological practices. Most studies used randomization (86%), at least single (90%) or double (81%) blinding, and were placebo-controlled (94%), with 67% studies using randomized placebo-controlled double-blind designs. Crossover studies reported a washout period of  $\geq 1$  (typically 7) days (88%), with 10% not providing data and 2% reporting <1-day washout. Fewer than 50% of studies provided details on any pre-existing pain, analgesic use or the population from which participants were recruited. However, the predominant use of crossover designs (91%) may largely obviate the possibility that analgesic effects are attributable to differences in group characteristics.

## *Meta-analysis: Primary outcomes*

As racemic ketamine and S(+)-ketamine demonstrated consistently larger effect sizes than dextromethorphan (see 'Drug type, dosage and hyperalgesic state' subsection), analysis of

pooled data was not considered appropriate, and separate meta-analyses were conducted for each of these antagonists. Six different NMDAR antagonists were only assessed by a single study (see data in Table 1 available from Dryad: <https://doi.org/10.5061/dryad.sm4tj6tX>). As this is insufficient data for individual meta-analyses of these antagonists, they were not included in further analyses of pain outcomes. Pain affect was not examined as an outcome as initial analysis produced an adjusted  $df < 4^{27}$ .

### Pain intensity ratings

A forest plot of effect sizes for 54 studies of pain intensity is presented in Figure 2. Detailed results of meta-analyses are presented in Table 2 and show analgesic effects for racemic ketamine ( $SMD=0.57$ ,  $p < .001$ ) and S(+)-ketamine ( $SMD=0.69$ ,  $p = .001$ ) but not dextromethorphan ( $SMD=0.07$ ,  $p = .59$ ). Moderate-high variability in effect size for ketamine agents was observed ( $I^2=67-70\%$ ,  $\tau^2=0.15-0.19$ ) but direction of effects consistently indicated analgesia.

To obtain the magnitude of ketamine effects in the original 0-10 pain rating units, we repeated analyses using unstandardized pain ratings where available ( $k=42$ ). As a direct comparison of racemic ketamine and S(+)-ketamine found no differences in effect size ( $p=0.54$ ), we collapsed these into a single ketamine category to maximize power. Results indicated that average pain ratings were 1.2 points ( $CI_{95}[0.88, 1.44]$ ,  $p < .001$ ) lower for ketamine ( $M=3.4$ ) compared to control ( $M=4.6$ ), a reduction of 26%. The heterogeneity statistic  $\tau$  indicated that the average magnitude of different analgesic effects in the population was likely to vary between a -0.41 and 2.72 mean points reduction.

For remaining pain outcomes, ketamine and S(+)-ketamine data were collapsed into a single ketamine category as there were relatively few studies of S(+)-ketamine for these outcomes (hyperalgesia  $k=1$ , tolerance  $k=3$ ), and little difference in their mean effect sizes (maximum SMD difference=.12).

#### Area of hyperalgesia

Ketamine (racemic and S(+)-ketamine enantiomers combined) produced a moderate reduction in the size of the area of secondary hyperalgesia ( $k=15$ ;  $SMD=0.54$ ,  $CI_{95}[0.34, 0.74]$ ,  $p<.001$ ). Moderate variation in the magnitude of effect size was observed ( $I^2=46\%$ ,  $\tau^2=0.07$ ), but with all studies indicating a reduction in pain area. No effects of dextromethorphan were found ( $k=4$ ,  $SMD=0.21$ ,  $CI_{95}[-0.31, 0.73]$ ,  $p=.73$ ).

#### Pain tolerance

Ketamine resulted in moderately increased pain tolerance ( $k=9$ ;  $SMD=0.46$ ,  $CI_{95}[0.19, 0.72]$ ,  $p=.004$ ), with direction of effects in all studies consistent with analgesia but with moderate inconsistency in size of effect ( $I^2=60\%$ ,  $\tau^2=0.08$ ) observed. No meta-analysis was performed for dextromethorphan as only one study of pain tolerance was available.

#### *Meta-analysis: Secondary outcomes*

##### Pain threshold

A small increase in pain threshold was found following ketamine administration ( $k=30$ ;  $SMD=0.31$ ,  $CI_{95}[0.17, 0.45]$ ,  $p<.001$ ), with all studies indicating analgesia but with high

inconsistency in effect size ( $I^2=72\%$ ,  $\tau^2=0.13$ ). There were too few studies of dextromethorphan and pain threshold for reliable analysis (adjusted  $df<4$ ).

### Side effects

Side effects (SEs) of NMDAR antagonists were assessed by 48 studies, 37 of which reported incidence. Assessment method was often unreported, but some studies stated use of standard checklists or recording of spontaneously-reported effects. Incidence was computed for studies where SEs were reported by at least 5 studies and were: sedation ( $k=8$ ; 70% of participants), feeling of drunkenness ( $k=7$ ; 58%), dizziness ( $k=23$ ; 57%), drowsiness ( $k=5$ ; 56%), out-of-body sensations ( $k=5$ ; 54%), paresthesia ( $k=10$ ; 37%), and nausea ( $k=15$ ; 19%). Nearly all studies reported side effects were mild. SEs on the placebo arm were occasionally assessed with no SEs generally reported.

While these statistics provide an indication of common SEs, likely bias in incidence values should caution against their interpretation as representative of true incidences and prompted us not to conduct meta-analysis on SEs. Specifically, studies often did not report *a priori* which SEs were assessed and often stated that only commonly occurring symptoms were reported. This is likely to upwardly bias estimates, as omission of unreported low incidences would artificially increase average incidence.

### *Publication bias*

Funnel plots and Egger's test for ketamine (collapsed across enantiomers to maximize power) indicated asymmetry ( $p's<.01$ ) for pain intensity (Figure 3) and hyperalgesic area consistent with possible publication bias. Trim and fill estimates resulted in smaller

estimated effects for ketamine for both pain intensity ratings ( $SMD=0.48$  from  $0.58$ ) and hyperalgesic area ( $SMD=0.37$  from  $0.54$ ).

#### *Meta-regression: Primary moderators*

Meta-regression was performed for the pain intensity outcome only, as adjusted  $df$  was largely  $<4$  for other outcomes. Although previous analyses showed no effects of dextromethorphan, we included this in meta-regression to provide preliminary information on whether any effects might exist but be affected by potential moderators. When examining dose-response relationship, we included antagonist type in the same analysis to control for differences across antagonists in dosage. Only oral and IV routes were included in dose-response analysis so that a common, standardized mg/kg metric could be used.

#### Drug type, dosage and hyperalgesic state

Meta-regression results indicated larger effect sizes for racemic ketamine ( $k=31$ ; difference ( $\Delta$ ) in  $SMD = +.50$ ,  $p=.006$ ) and S(+)-ketamine ( $k=11$ ;  $\Delta SMD = +.62$ ,  $p=.008$ ) compared to dextromethorphan. No association of dosage with effect size was found ( $k=43$ ;  $p=.20$ ) as illustrated in Figure 4 (dose x drug interaction terms were also included to explore whether any dose-response relationship varied with drug type, but no statistically significant effects were found,  $p>.65$ ). For hyperalgesic state, slightly smaller analgesic effects were observed for secondary hyperalgesic ( $k=10$ ;  $\Delta SMD = -0.21$ ) and primary hyperalgesic ( $k=14$ ;  $\Delta SMD = -0.14$ ) inductions compared to acute testing (without hyperalgesia), but these differences were not statistically significant ( $p's = .24-.39$ ).

### *Meta-regression: Secondary moderators*

Meta-regression of pain intensity was performed separately for each secondary moderator of noxious stimulus type ( $k=51$ ), drug timing ( $k=51$ ), sex composition ( $k=49$ ), testing site ( $k=51$ ), IV infusion period and pain duration ( $k=51$ ) coded as tonic (typically 20-30 mins) and phasic (0-5 mins). No statistically significant effects were found for any secondary moderators ( $p$ 's=.22-.92).

### *Sensitivity analysis*

The effect of various data decisions on results were examined by repeating analyses (a) replacing the estimated value of  $r=0.65$  between outcomes with alternative correlations ( $r$ 's=0.40-0.90), (b) excluding studies where extraction decisions described in the Method section (Data Extraction subsection) were made, and (c) not removing outliers. We also reran all meta-analyses using only randomized double-blind placebo-controlled trials. Little change in effect size was found for all reanalysis, with a maximum *SMD* change of 0.12 observed (indicating an increased *SMD* for pain tolerance).

## **DISCUSSION**

Meta-analysis of 70 controlled experimental pain trials, totaling 1069 participants and consisting mostly of randomized double-blind designs, provided robust evidence for analgesic effects of low-dose ketamine. Key findings were: (1) ketamine produced a moderate decrease in pain, with estimated effects slightly diminished after accounting for possible publication bias; (2) racemic ketamine ( $SMD=0.57$ ) and S(+)-ketamine ( $SMD=0.69$ ) produced similar analgesia; (3) dextromethorphan did not reliably produce analgesia; (4)

pain relief was observed for both short-term acute pain and in hyperalgesic models; and (5) side effects (e.g. sedation, sensory disturbance) were common but mild at the relatively low doses used.

Low-dose ketamine (0.03–1.00 mg/kg) decreased mean pain intensity ratings from 4.6 to 3.4 on a 0-10 scale, a reduction of 1.2 points or 26%. This is broadly consistent with a recent meta-analysis of 9 trials of surgical patients that found a decrease of 1cm on a 10cm VAS for ketamine used as an adjunctive analgesic<sup>3</sup>. The mean 1.2-point pain reduction that we observed across 42 experimental ketamine trials approaches the median decrease of 1.4 points or 23% identified by a recent meta-analysis<sup>21</sup> as indicating minimum clinically important change. However, the same meta-analysis found that a median decrease of 3.2 points (a 57% reduction) was needed for substantial clinically important pain relief, and the reduction we found here for ketamine would seem unlikely to be recognized as offering major improvement in pain. Considerable heterogeneity in effect size was also observed, indicating that ketamine analgesia is likely to be inconsistent across individuals or conditions, although no reliable modifiers of effect were identified from the available data (but are likely to include differences in the ability to metabolize ketamine). Overall, while findings from a large number of trials strongly support the pain-relieving effects of subanesthetic doses of ketamine, these effects were modest. This suggests that ketamine could be most useful when opioids are contraindicated, when a very rapid onset of action is required, or as a molecular basis for the future development of more potent and refined NMDAR medications.

A comparison of the analgesic potency of racemic ketamine, S(+)-ketamine and dextromethorphan found that, despite the greater NMDA receptor affinity of S(+)-

ketamine<sup>6</sup>, there was limited evidence of a superior analgesic effect compared to racemic ketamine. Moreover, both types of ketamine exhibited analgesic effects where dextromethorphan did not. The apparently selective effects of ketamine could help guide the identification of key cellular properties fundamentally involved in analgesia, such as differing affinities for specific binding sites across different NMDAR antagonists<sup>26</sup>.

Alternatively, dextromethorphan may have been ineffective due to insufficient dosages for analgesia (although these were nearly 3 times higher than ketamine). Even if dosages were inadequate, however, the risk of exacerbating side effects at higher dosages might prove prohibitive in all but the most refractory cases and emphasizes the need for refinement of existing NMDAR antagonists if there is any hope of their routine use as pain medication.

One of the primary therapeutic mechanisms of ketamine is believed to be reversal of central sensitization, via the NMDAR-mediated suppression of neuronal hyperexcitability that occurs during persistent pain states and leads to hyperalgesia<sup>6</sup>. Interestingly, current findings identified ketamine as similarly effective for reducing both acute pain and hyperalgesia. As acute pain activates primary afferent C fibers and these fibers synapse onto the wide dynamic range neurons involved in central sensitization, this suggests that inhibition of NMDARs in this area also affects the processing of acute nociceptive signals. Alternatively, ketamine acts on numerous other pathways including muscarinic, monoaminergic and (at high dosages)  $\mu$ -opioid receptors, although these are generally believed to be less likely candidates for ketamine's analgesic effects<sup>23</sup>. While our current understanding of complex structures of NMDARs in humans is limited, these findings appear to provide reliable evidence of significant NMDAR involvement in both acute and hyperalgesic pain processes.

Evidence of ketamine analgesia in acute and hyperalgesic models (which mimic central sensitization in chronic pain), suggests a basis for the development of more refined NMDAR antagonists for management of both acute and chronic pain. If such antagonists can be sufficiently refined to isolate analgesic from adverse effects, this might lead to the development of a new class of routinely used pain medication as alternatives to existing treatments. As cellular mechanisms of action of NMDAR antagonists are different to opioids, they may provide potentially effective treatment for refractory pain resistant to conventional opioid treatment. In addition, there is little current consensus on optimal dosage within subanesthetic range (up to 1mg/kg)<sup>14</sup>. The current finding suggests that dosing at lower end of range may be preferable to higher doses in achieving similar analgesic effects while minimizing adverse reactions. The current findings also demonstrate that human experimental pain models are sensitive to the analgesic effects of NMDAR antagonists and thus provide a useful means of enquiry where stimulus parameters can be carefully manipulated to provide insights into underlying mechanisms.

The current meta-analysis has limitations. First, while experimental models of acute pain and hyperalgesia avoid many of the confounds present in clinical data and can reliably replicate key pathological features of acute and chronic pain, they do not capture the entire range of experience of a multifactorial pain condition. In addition, NMDAR antagonists may offer the potential for longer-term clinical pain reduction through gradual changes in neuroplasticity, that would not be captured by short-term testing. Second, although most study designs were double-blind RCTs, overt side effects may rule out true blinding. Although some control conditions included medications with ketamine-like side effects and found similar analgesia, active placebo effects cannot be dismissed.

Given the potential for abuse, hepatotoxicity and other side effects of ketamine at high doses<sup>23</sup>, there is an obvious need for the development of NMDAR antagonists that selectively target analgesia, which may involve activation of specific protein subunits<sup>22</sup>. Experimental selective NMDAR antagonists such as AV-101<sup>31</sup> and GV196771<sup>33</sup> have unfortunately met with limited success, but research is still at a preliminary stage. Given the considerable variation in the analgesic effects of ketamine across different studies, it is also important for research to identify for whom and under what conditions pain relief is likely to be optimal.

We found robust evidence that low-dose ketamine (up to 1mg/kg), but not dextromethorphan, reduces acute pain and hyperalgesia. Dose-response curves also suggests ketamine may be just as effective when administered at the lower end of the subanesthetic dose range. However, pain relief was only modest, and if this translates to similarly modest effects for clinical pain, the most useful application of ketamine for pain could be when opioids are contraindicated, rapid analgesia is required, or pain is resistant to conventional medication. Nevertheless, there is still much that is unknown on the mechanisms of NMDAR antagonists and future pharmacokinetic development may lead to a more refined and potent analgesic.

## Appendix 1. Author contributions.

Name	Location	Role	Contribution
Trevor Thompson, PhD	University of Greenwich, London, UK	Author	study design and conceptualization, data extraction, analysis and interpretation, drafting manuscript
Fiona Whiter, PhD	York Health Economics Consortium, York, UK	Author	study selection, data extraction, quality assessment
Katy Gallop, MSc	Acaster-Lloyd Health Outcomes Consulting, London, UK	Author	study selection, data extraction, quality assessment
Nicola Veronese, MD	National Research Council, Padova, Italy	Author	critical revision of manuscript for intellectual content
Marco Solmi, MD	University of Padova, Padova, Italy	Author	critical revision of manuscript for intellectual content
Paul Newton, PhD	University of Greenwich, London, UK	Author	critical revision of manuscript for intellectual content
Brendon Stubbs, PhD	Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK	Author	interpretation of data, critical revision of manuscript for intellectual content

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## LIST OF FIGURES

Figure 1. PRISMA flowchart.

Figure 2. Forest plot of Standardized Mean Differences (SMDs) for pain ratings across 54 studies, with summary SMDs for racemic ketamine, S(+)-ketamine and dextromethorphan based on random-effects meta-analysis (effect sizes from single studies of other medications shown for comparative purposes)

Figure 3. Funnel plot of standardized mean differences (*SMDs*) from 42 studies of ketamine and pain intensity (filled circles) and 7 estimated *SMDs* (empty circles) assumed to be missing due to publication bias.

Figure 4. No dose-response relationship for pain ratings for S(+)-ketamine, racemic ketamine or dextromethorphan.

## LIST OF TABLES

Table 1. Characteristics of studies included in meta-analysis (available from Dryad: <https://doi.org/10.5061/dryad.sm4tj6tX>).

Table 2. Meta-analysis of pain intensity ratings and aggregated study characteristics for three different NMDAR antagonists.

## APPENDICES

Appendix 1. Author contributions.

Appendix 2. Search strategy (available from Dryad: <https://doi.org/10.5061/dryad.sm4tj6tX>)

Appendix 3. Study validity criteria (available from Dryad: <https://doi.org/10.5061/dryad.sm4tj6tX>).

Appendix 4. References of studies included in meta-analysis (available from Dryad:

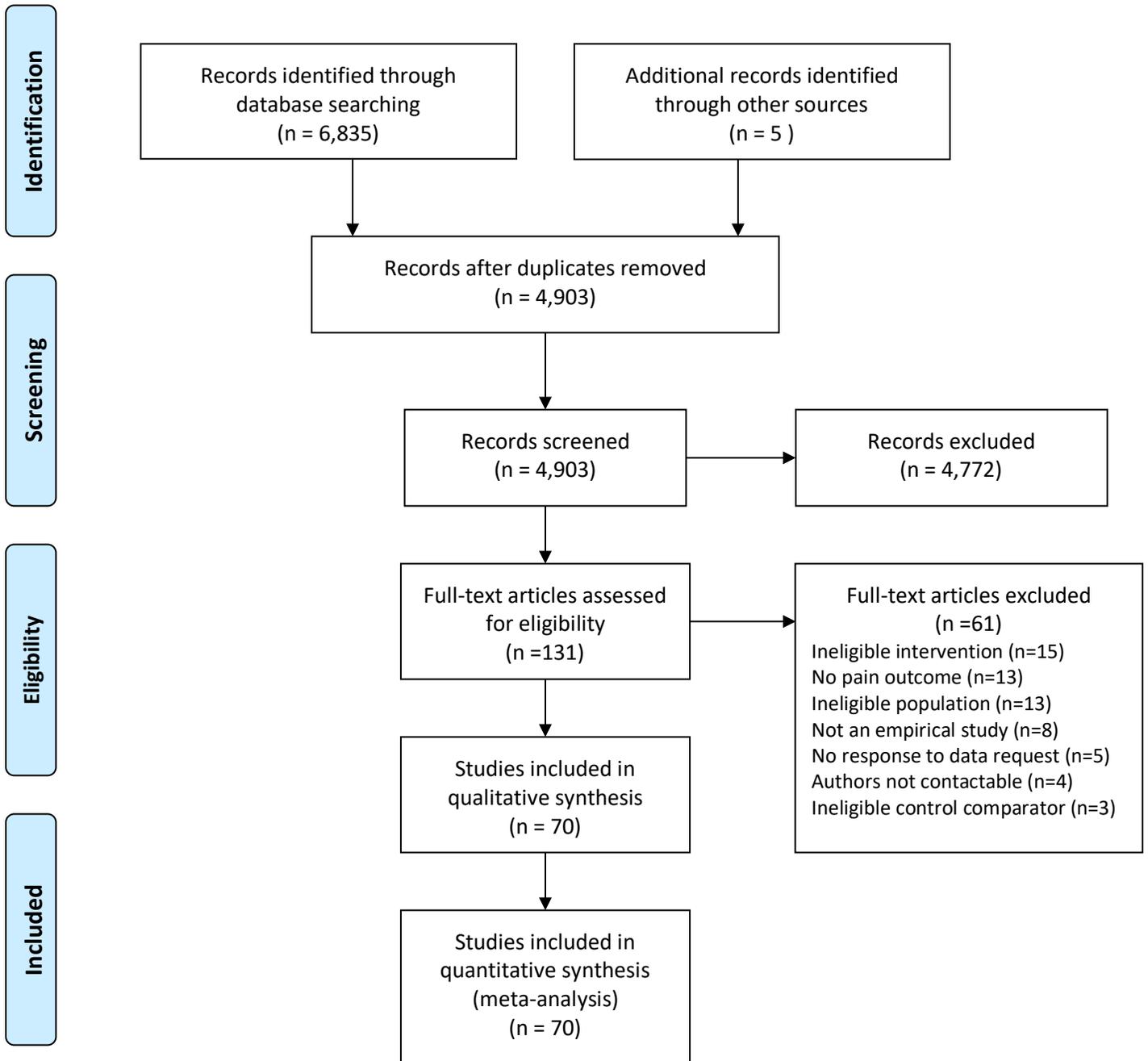
<https://doi.org/10.5061/dryad.sm4tj6tX>).

Table 2. Meta-analysis of pain intensity ratings and aggregated study characteristics for three different NMDAR antagonists.

	SMD	95% CI	<i>p</i>	Number of studies	Number of participants	<i>I</i> <sup>2</sup>	$\tau^2$	Mean dose mg/kg	Primary delivery route (number of studies)	Mean age / proportion of males
Racemic ketamine	0.57	0.40, 0.74	<.001	31	508	70	.15	0.39	Intravenous (23/31)	28 yrs / 70%
S(+)-Ketamine	0.69	0.35, 1.03	.001	11	123	67	.19	0.37	Intravenous (10/11)	27 yrs/ 74%
Dextromethorphan	0.07	-0.21, 0.34	.591	10	132	53	.09	0.95	Oral (10/10)	32 yrs / 74%

SMD=standardized mean difference; 95% CI=95% confidence interval

Figure 1



# Pain Intensity

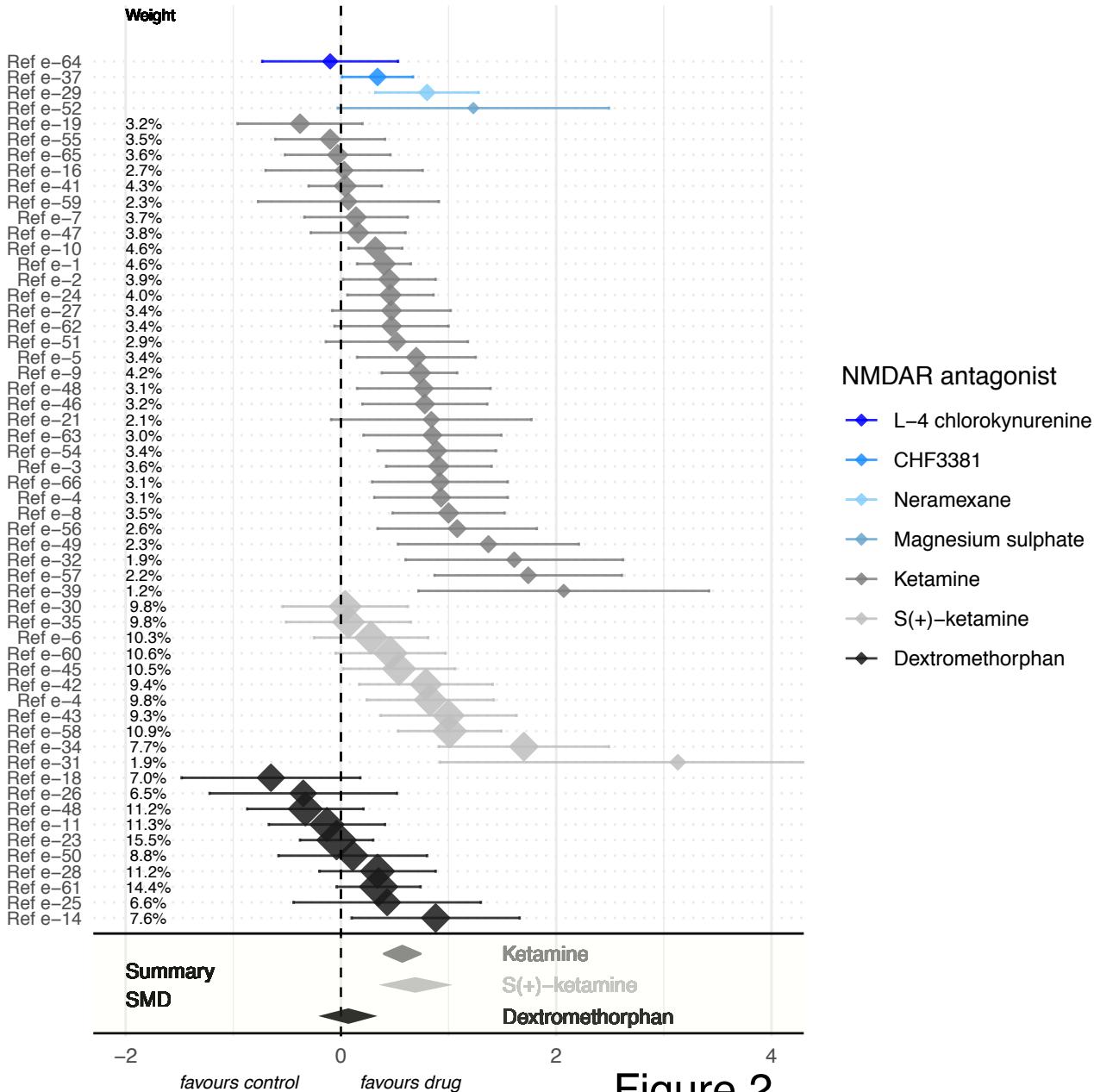


Figure 2

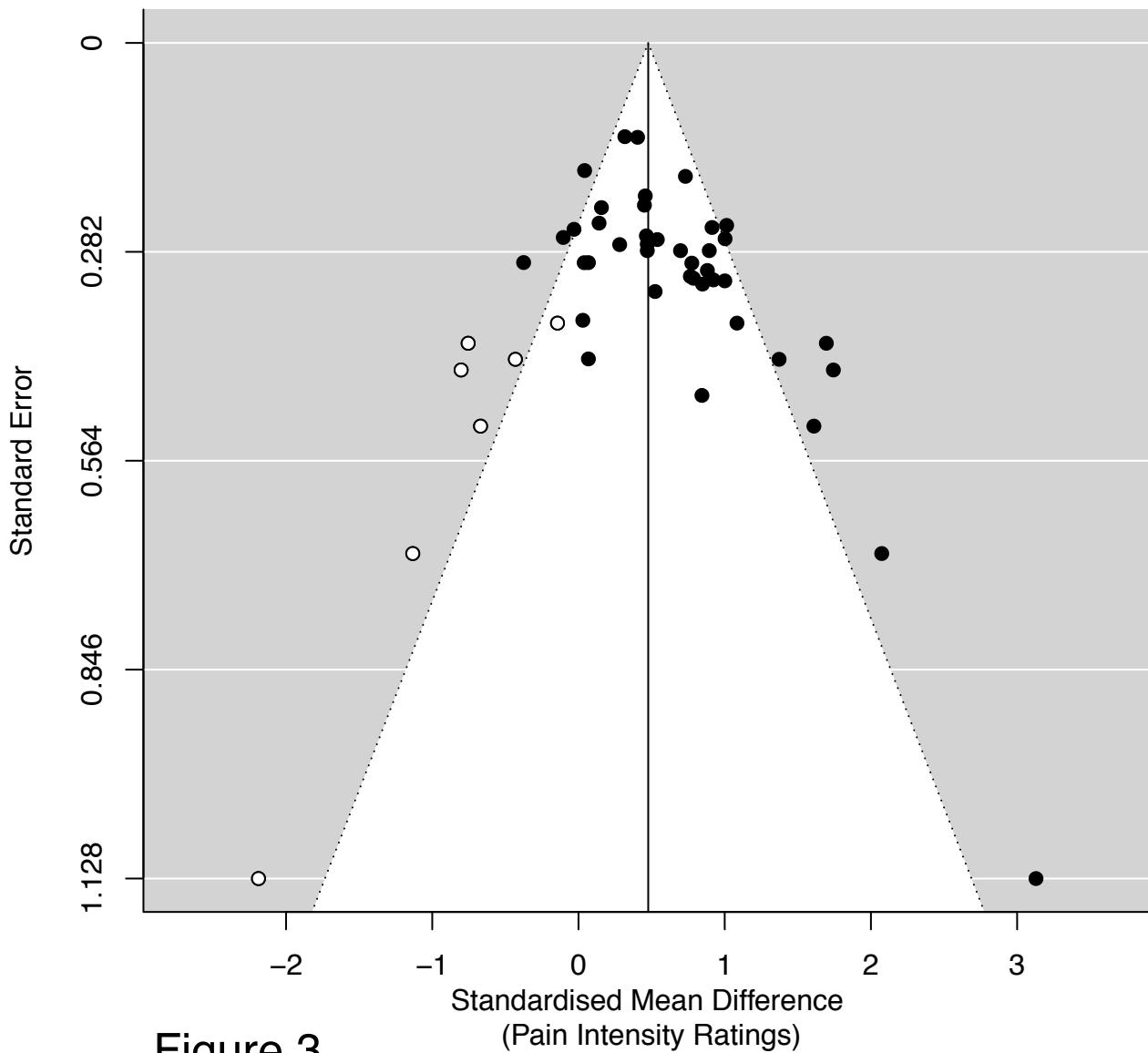
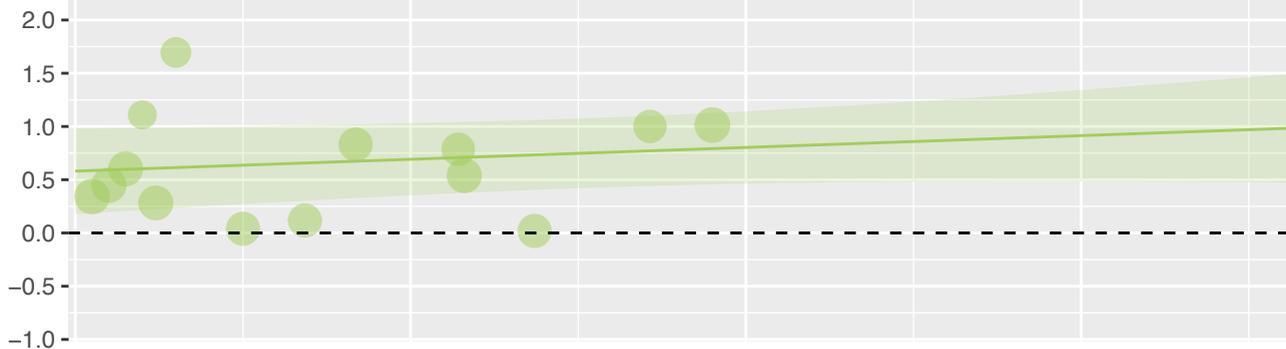
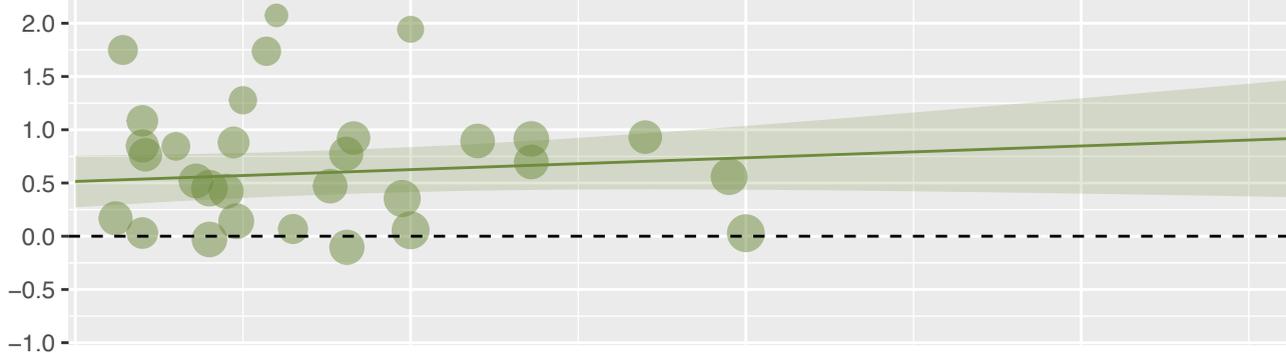


Figure 3

### S(+)-Ketamine



### Ketamine



### Dextromethorphan

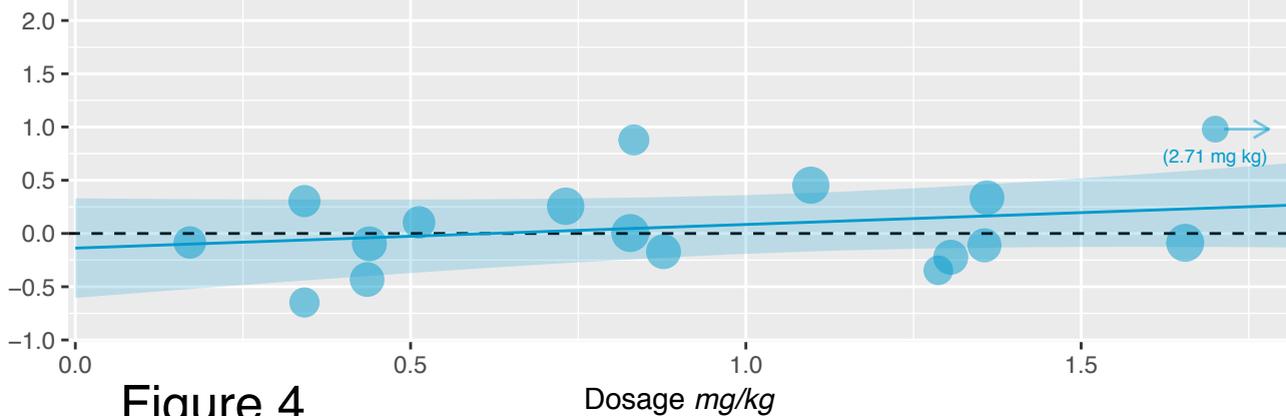


Figure 4

Dosage mg/kg