Received Date : 01-Nov-2015

Revised Date : 09-Feb-2016

Accepted Date : 22-Feb-2016

Article type : Original Article

Title: Placebo-controlled pilot trial testing dose-titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression.

Short title: Ketamine in depression: dosage titration and treatment route

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/acps.12572](https://doi.org/10.1111/acps.12572)

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Abstract

Objective: This pilot study assessed the feasibility, efficacy and safety of an individual dose-titration approach, and of the intravenous (IV), intramuscular (IM) and subcutaneous (SC) routes for treating depression with ketamine.

Method: Fifteen treatment-refractory depressed participants received ketamine or midazolam (control treatment) in a multiple crossover, double-blind study. Ketamine was administered by IV (n=4), IM (n=5) or SC (n=6) injection. Dose- titration commenced at 0.1 mg/kg, increasing by 0.1 mg/kg up to 0.5 mg/kg, given in separate treatment sessions separated by $\geq$ one week, with one placebo control treatment randomly inserted. Mood, psychotomimetic and hemodynamic effects were assessed, and plasma ketamine concentrations assayed.

Results: Twelve participants achieved response and remission criteria, achieved at doses as low as 0.1 mg/kg. All three routes of administration resulted in comparable antidepressant effects. Fewest adverse effects were noted with the SC route. Antidepressant response, adverse effects and ketamine concentrations were dose-related.

Conclusion: Antidepressant response occurred at a range of doses and at < 0.5 mg/kg. The dose titration approach is a practical method for optimizing the efficacy - side effects trade off on an individual patient basis. This pilot study provides preliminary evidence for SC injection as a practical, feasible and efficacious treatment approach.

Clinical trial registration: [clinicaltrials.gov: NCT01441505](https://clinicaltrials.gov/ct2/show/study/NCT01441505), registered 16.9.2011

Keywords: Ketamine, Dose titration, intravenous, intramuscular, intranasal.

Significant Outcomes:

- This is the first placebo-controlled study to demonstrate that antidepressant response (and psychotomimetic effects) of ketamine are related to dosage and plasma ketamine concentrations.
- Titrating ketamine dose can be a useful clinical treatment approach, as the dose needed for efficacy is identified on an individual patient basis, minimizing associated side effects.
- The subcutaneous route of administration is a promising method for ketamine treatment in depression, as it results in plasma levels comparable to intravenous administration, is easy

to administer, and had the most favourable efficacy – side effect profile of the three routes tested.

Limitations:

- This was a small pilot study in fifteen participants.
- Treatment assignment to ketamine route was by sequential cohorts rather than randomised.
- The effect of different doses was tested with an ascending dose design, rather than randomised dose design.

Introduction

Placebo-controlled trials of ketamine at sub-anesthetic doses have reported rapid, substantial antidepressant effects after a single 0.5 mg/kg dose (1-8). The magnitude and rapidity of antidepressant effect exceed those reported for regulatory approved antidepressant medications and even electroconvulsive therapy (ECT) (9, 10).

However, important gaps remain in the literature. Firstly, the dose-response relationship and minimum dosage required for effective antidepressant response are unclear. Most placebo-controlled, blinded studies have given ketamine at a fixed dose (0.5 mg/kg), based on earlier work modelling dissociative and psychotic states in healthy volunteers (11). Preliminary results (12, 13), including a small double-blind study in which ketamine at a range of doses (0.1 to 0.5 mg/kg) was tested against saline placebo (7), and case series (14), report clinically meaningful antidepressant response at doses < 0.5 mg/kg.

Secondly, the optimal route of treatment administration is unclear. All but one of the above placebo-controlled studies administered ketamine as an intravenous (IV) infusion of 0.5 mg/kg over 30-40 minutes, an approach requiring an infusion pump and extended medical supervision. Only one study (6) reported an alternative more convenient route, administering 50 mg ketamine intranasally, though with a lower response rate (44%) than other placebo-controlled studies. Antidepressant

efficacy has also been reported for ketamine given via intramuscular (IM) (12, 15, 16), sublingual (14) and subcutaneous (SC) routes (13), though only the latter (a preliminary case report from the full study reported here) was assessed within a placebo-controlled, double-blind study. The study reporting the most promising antidepressant outcomes with improvement sustained for ten days, gave ketamine 0.2 mg/kg by IV over two minutes, though this technique was assessed within an open label rather than controlled study design (17). Route of administration and dosage determine pharmacokinetics (e.g. peak plasma concentrations, duration for which plasma concentration exceeds a set threshold, etc.) and it is likely that these factors affect antidepressant efficacy and side effects. Thus, route of administration and dosage are important factors in determining treatment outcomes but it is not clear how these should be manipulated for maximum efficacy and tolerability.

Finally, the evidence base is limited by the use of saline as the placebo control in all prior controlled studies apart from Murrough *et al.* who used midazolam as an active placebo control, reporting similar subjective effects with ketamine and midazolam (5). Given the marked and characteristic psychotomimetic effects that typically occur when ketamine is given IV at 0.5 mg/kg, blinding is likely to have been inadequate in trials using saline as the placebo comparator.

Aims of the study

Within a double-blind, placebo-controlled design, the study piloted a practical, dose-titration approach, examining mood and safety outcomes on an intra-individual participant basis. Secondly, the study aimed to provide pilot data on the feasibility, safety, pharmacokinetics and mood effects of ketamine given by three routes of drug administration, tested in small numbers of participants sequentially assigned to intravenous, intramuscular or subcutaneous routes.

Materials and Methods

The study was approved by University of New South Wales Human Research Ethics Committee (Study 10409) and was conducted at Wesley Hospital (Sydney, Kogarah, Australia).

Participants

Participants were recruited through advertisement to the general public and to health professionals (newspapers, Black Dog Institute website and professional newsletters). Fifteen participants, aged ≥ 18 years, with a DSM-IV diagnosis of Major Depressive Disorder and a depressive episode of duration ≥ 4 weeks - confirmed with the Structured Clinical Interview for DSM-IV-TR (research version) and a face-to-face psychiatric interview with a clinician - were included in the study.

Exclusion criteria were: pregnancy, schizophrenia, bipolar disorder, current psychotic symptoms and drug abuse or dependence in the last six months. Participants were required to have a Montgomery-Asberg Depression Rating Scale (MADRS) (18) score ≥ 20 , and insufficient therapeutic response to ≥ 1 adequate trial of an antidepressant medication during the current depressive episode. Treatment resistance was measured using the Maudsley Staging of Treatment Resistance (19). Participants were allowed to remain on stable doses of psychotropic medications which had failed to produce antidepressant response despite trials of adequate dose and duration, but which the participants' treating psychiatrists judged on clinical grounds should be continued. No changes in medication dosage were permitted for 4 weeks prior to trial entry and throughout the trial. For participants who had received ECT, a minimum of 4 weeks from the last ECT treatment was required prior to trial entry. After complete description of the study to the participants, written informed consent was obtained.

Study Design & Drug Administration

The safety and efficacy of ketamine HCL (Ketalar®, Hospira, Australia) at five doses (0.1, 0.2, 0.3, 0.4, 0.5 mg/kg) were tested in an ascending dose design with random insertion of a placebo comparator treatment. Midazolam (Hypnovel®, Roche Products, Australia) - the active 'placebo' comparator - was given at 0.01 mg/kg (20). Sequential cohorts of participants were assigned to receive ketamine by the IV (n=4), IM (n=5) or SC (n=6) route; i.e. route of administration was not randomly assigned. For the IV route, the bolus IV injection method reported by Larkin and Beautrais (17) was used, in light of positive results and minimal adverse effects.

Intravenous (IV) injection was given through an IV cannula inserted in the forearm, slowly injected over 5 minutes (as detailed in(7)); IM injection was given into the deltoid muscle; and SC injection into the abdominal wall. Doses were given at least 1 week apart. Participants only proceeded to the next treatment if at Day 7 after the prior treatment they did not meet the criterion for response and the MADRS score was ≥ 20 . Response was defined as $\geq 50\%$ improvement in MADRS score, compared to the baseline score rated just before treatment at that session, and remission was defined as MADRS score < 10 . Participants who met the criterion for response on Day 7 after any treatment were deemed to have completed the treatment phase of the trial and were followed-up weekly for one month, then monthly for six months, until relapse (defined as MADRS score ≥ 20). The midazolam active control condition was randomly inserted within the first three treatment sessions to increase the chance that most participants received the placebo treatment (prior to completing

the treatment phase due to meeting the response criterion at Day 7). Each participant received at least two treatments, so that at least one active treatment was received.

The randomization list (position of placebo treatment) was allocated according to a computer-generated random number sequence. Participants were assigned sequentially to this list by the study coordinator. To ensure accurate dosing for each individual at a range of mg/kg doses, the study drug was drawn up by a study anesthetist who had access to the randomization list but had no involvement in outcome assessments. The randomization list was kept in a folder in a locked room and the anesthetists were instructed to keep treatment allocation concealed. Participants and raters were aware that one treatment was a control, but were blinded to its position, including that it was placed within the first three sessions. Participants were aware that a range of ketamine doses were to be given, but were blinded to the ascending dose design. Participants and raters were not blinded to the route of administration. All participants attended the hospital on the days of treatment sessions, and were monitored for 4 hours after each treatment. Each treatment was given under medical supervision.

Assessments – Mood and Side Effects

The primary outcome measure was change in MADRS scores over time. At each session, mood outcomes were assessed by a trained rater using the MADRS, after inter rater reliability was established with investigators CL and PM. MADRS assessments were performed at baseline in the hour prior to ketamine treatment (day 1) and at 4 hours, days 2, 4 and 7 after each treatment.

Secondary outcomes were psychotomimetic effects, assessed using positive symptom items (hallucinations, grandiosity, suspiciousness, unusual thought content, conceptual disorganization) from the Brief Psychiatric Rating Scale (BPRS) (21), item 1 (Elevated mood) of the Young Mania Rating Scale (YMRS) (22), and the Clinician Administered Dissociative Symptoms Scale (CADSS) (23), measured at baseline, 40 minutes after each injection (assessing symptoms experienced over the 40 minutes), and at 4 hours. Heart rate and blood pressure were measured before each treatment and 5, 10, 30, 60 and 240 minutes after treatment. Physical adverse effects were formally assessed using a modified version of the SAFTEE scale (24), at baseline and 4 hours after dosing. Orientation and simple and complex reaction times were assessed at study baseline and 4 hours after treatment.

Ketamine blood concentrations

Blood samples were collected before and after each treatment for pharmacokinetic analyses. Blood

was drawn at baseline, and at 5 minutes after the end of IV injection, and 15 minutes after IM and SC injection, then at 30 minutes, at 2 hours and up to 4 hours after injection for all routes. The plasma samples were assayed for ketamine by liquid-liquid extraction and LC-MS. Quality control samples provided accuracy data of > 90% and precision of < 5% (coefficient of variation) for intra-day (n=6) and inter-day (n=11) assays. The lower limit of quantification was 0.25 ng/ml. The highest plasma ketamine concentrations recorded over the first 30 minutes after injection are reported here.

Statistical Analyses

Clinical and demographic details of participants in each of the three routes of administration groups were compared using ANOVA or chi-squared tests. The number of responders at each dose level and each route of administration were determined. Further, to examine the efficacy of ketamine compared to placebo, a number of mixed effects models analyzed MADRS scores using PROC MIXED in SAS 9.4. Time of measurement (time points 0, 4 and 24 hours) was entered as coefficients of linear and quadratic orthogonal polynomials with adjustment for the unequal time intervals. Similar analyses (0, 4, 24, 72, 144 hour time points) examined effects over the 7 days after treatment. While there were two repeated factors (dose magnitude crossed with time of measurement) only the correlations between measurement occasions within dose magnitude were modelled (using a spatial power covariance matrix for the unequal intervals) and not across doses. Route of administration was entered as a fixed factor. Random intercepts were included at the patient level. The value from time point 0 was also included as a baseline measure. All tests of significance were two-tailed.

A further analysis examined adverse effects. As CADSS scores were measured twice (40 and 240 minutes), simpler models were fitted, one for 40 minutes and one for 240 minutes with 40 minutes as a covariate. For both outcomes, models were examined with and without interactions. For mood and CADSS outcomes, data were analyzed for the placebo (midazolam), 0.1 mg/kg and 0.2 mg/kg conditions, as not all participants received doses of 0.3 mg/kg and above, as per the study design. Data from all 15 participants were used in the analyses.

Results

Participants

Participants were highly treatment resistant, with 4.2 antidepressant medications failed on average during the current episode. One third of participants had also failed to respond to ECT and one

participant (IM group) had failed both ECT and Deep Brain Stimulation. There were no significant between-group differences in these characteristics prior to treatment (see Table 1).

Table 1 about here

All participants received ketamine treatment and fourteen received a midazolam placebo treatment in the trial. Six participants withdrew from the study prior to receiving all treatments for which they were eligible (see Consort diagram -Supplementary Figure 1). The number of participants who received ketamine at different doses and with different routes is shown in Figure 1. Note that the response to higher doses appears poor where participant numbers are particularly small (n=1) as this represents the most treatment resistant participants who had not responded to all lower doses.

Figure 1 about here

Mood outcomes

Twelve of fifteen participants met the criteria for both response and remission at least at one time point during the trial (across all dose levels and time points), corresponding to overall acute response/remission rates of 75% (IV), 60% (IM) and 100% (SC). The proportion of the whole sample who met response and remission criteria increased as ketamine dose was increased from 0 mg/kg (placebo) to 0.4 mg/kg (see Figure 2). Ten of the twelve responders were followed up until relapse. The mean time to relapse was 23.2 days (all routes, range 4-150 days; IV group, mean 9 days; IM group, mean 11.7 days; SC group, mean 34.5 days (16.4 days excluding outlier who remained well for 150 days). Mean changes in MADRS scores for different doses and routes are shown in Figure 1. Two participants (IV, SC) attained response and remission after midazolam treatment.

Figure 2 about here

Given the multiple crossover study design, a set of preliminary mixed effects model analyses of MADRS scores were first performed to examine for any order effects or carryover effects and revealed no evidence for either of these. In terms of significant effects of time, across the first 24 hours after each treatment (measured at 0 (pre), 4 and 24 hours) there was a linear trend for change over time (improvement in symptoms), and significant effects of dose (both 0.1 mg/kg and 0.2 mg/kg more effective than 0.0 mg/kg). There was a significant dose by time interaction, with greater

improvement over the 24 hours with 0.2 mg/kg than 0.0 mg/kg. There were no significant differences in MADRS scores between routes of administration. Plots of the residuals showed them to be highly normal.

When the analysis was conducted across the 7 days after each treatment (0, 4, 24, 72, and 144 hours for each treatment session), there was no linear trend (reflecting the return to essentially time-0 levels by day 7) but the quadratic trend was significant (reflecting improvement followed by attenuation of improvement). In terms of main effects of dose, MADRS scores were significantly lower after 0.2 mg/kg than 0.0 mg/kg (placebo) ($p=0.001$) and non-significantly lower for 0.2 mg/kg versus 0.1 mg/kg ($p = .095$), and for 0.1 mg/kg versus 0.0 mg/kg ($p = .066$). Dose by time interactions were not significant.

Adverse Effects and Safety Outcomes

A dose-response relationship was observed between dissociative psychotomimetic effects and ketamine treatment for all routes, with higher peak scores in the IV group (see Figure 3).

Figure 3 about here

Analysis of CADSS scores showed no significant main effect for route at either 40 minutes or 240 minutes after injection. There was a main effect of dose at 40 minutes, in which the comparison between 0.2 mg and 0.0 mg was significant ($p = 0.043$), demonstrating increased side-effects at the higher dose. In the model with dose-by-route interaction terms, a number of significant effects emerged, however, inspection of the data and residuals suggested that these were unreliable findings related to a small number of non-zero ratings for placebo. Symptoms typically reported included mild depersonalization, derealization, altered body perception and altered time perception. Peak effects occurred 10-15 minutes after injection, resolving without intervention by 40 minutes post-injection for all participants, all doses and all routes of administration. Items rated from the Brief Psychiatric Rating Scale and Item 1 of the YMRS (Elevated Mood) revealed no evidence of treatment emergent mania at any time point, across routes of administration and doses. No clinically significant change in BPRS or CADSS was observed in the midazolam condition, across all routes of administration (see Figure 3).

Transient increases in heart rate, systolic and diastolic blood pressure were observed with peak incidence 5-10 minutes after ketamine injection in the IV group, and 10-15 minutes after ketamine injection in the IM and SC groups. Across groups, increases in heart rate did not exceed 120% of baseline, except in three participants (one each in IV, IM and SC groups). Likewise, increases in mean arterial pressure (MAP) did not exceed 120% of baseline, with the exception of four participants (n=2, IV; n=2, IM). Adverse effects evaluated using the SAFTEE scale showed a range of symptoms. The most common adverse effects after ketamine were fatigue, light headedness, dizziness, blurred vision and emotional lability. The most common side effects after midazolam were light headedness, dizziness, blurred vision, fatigue, dry mouth and emotional lability. Hemodynamic and other effects resolved spontaneously, within thirty minutes and one hour respectively, without the need for medical intervention. All participants were oriented at 4 hours post-treatment, with no significant differences compared with pre-treatment orientation. Likewise, for all participants simple and complex reaction times performance was within one standard deviation of baseline means (data not shown).

Ketamine Plasma Concentrations

Blood was drawn from 14 participants (IV group, N=4; IM group, N=4, SC group, N=6). Results show that plasma concentrations recorded after IV injection were approximately double those recorded after IM and SC injection, and that increases in plasma concentrations were linearly related to mg/kg dosage (IV, $r=0.88$, $p<0.001$; IM, $r=0.92$, $p<0.001$; SC, $r=0.86$, $p<0.001$). Ketamine concentrations were also correlated to CADSS scores at 40 minutes post-injection ($r=0.44$, $p=0.001$) (see Figure 4).

Figure 4 about here

Discussion

This study provides the only detailed examination to date of the relationship between ketamine dose (mg/kg), antidepressant response and side effects, building on our earlier pilot work (7, 15). Results confirmed our earlier findings, demonstrating that both antidepressant response and psychotomimetic effects increased with higher mg/kg ketamine doses. The greater antidepressant response at higher dosage is shown in the larger proportion of participants attaining response and remission as dose was increased, and in the formal analyses comparing outcomes after 0.1 mg/kg and 0.2 mg/kg compared with placebo.

The study design also allowed careful examination of the dose-response relationship on an intra-individual basis. An important finding is that participants differed in their response to ketamine at specific mg/kg doses, with some attaining response and remission (including lasting improvement, up to five months) at doses lower than 0.5 mg/kg. This is consistent with findings from Chilukuri et al. (12) which demonstrated clinically significant antidepressant response with IM ketamine at 0.25 mg/kg and 0.5 mg/kg doses. Our results suggest that a dose titration method, such as used in this study, may be clinically useful, allowing individualization of dosage, optimizing efficacy and side effect outcomes for each patient. Once the optimal dose is determined, this dose can then be used in repeated treatment sessions if required, as described by Gálvez *et al.* (13).

This study also compared the IV slow 5 min, IM and SC injection routes for ketamine treatment in depression and is the first investigation to test the SC route of ketamine administration for individuals with major depression. Overall, high response and remission rates were seen with all modes of administration, with peak effects occurring 24 hours after treatment, consistent with the reports of earlier studies (2-6). No significant difference in efficacy was found between the three routes studied. Another study which compared antidepressant effects of ketamine given by IV infusion or IM injection also found no difference in efficacy (12). In the present study, the SC and IM routes resulted in less psychotomimetic effects than the IV injection method. This study did not find that the IV slow injection method led to antidepressant response lasting 10 days, in contrast to an earlier report (17). The SC route had the least cardiovascular effects and was the simplest to administer. Thus, SC injection of ketamine appeared the most advantageous of the three treatment routes studied.

Measurement of plasma ketamine concentrations after injection showed that substantially higher concentrations were attained after IV injection than in previous studies which infused ketamine intravenously over 40 minutes (25), as would be expected. Our results suggest the IM route leads to similar plasma concentrations as those reported after IV infusion, when given at doses in the range of 0.4-0.5 mg/kg. SC ketamine was also well absorbed and had comparable concentrations to IM ketamine. These results suggest that IM and SC injection lead to plasma ketamine concentrations that are comparable to the 40-minute IV infusion method, and that IM and SC routes may be a simpler and more feasible alternative to IV infusion.

Study limitations include the small number of participants and lack of randomization of participants to the three treatment groups (IV, IM, SC). This study was designed as an initial examination of effects of ketamine given by these routes, rather than a definitive randomized trial comparing these routes of administration. Due to the sample size, the study was not adequately powered for examination of potentially important confounding factors such as treatment resistance. Further, the study did not include a group treated with the 40-minute intravenous infusion method, limiting direct comparison with this commonly used method. Theoretically, with the ascending dose design, effects of higher doses may have been affected by prior treatments at lower doses, due to carryover or cumulative effects. However, the analyses tested for such carryover or order effects on mood outcomes and found no evidence of this.

In conclusion, several important findings emerged from this study. A relationship between dosage and response was evident for both antidepressant response and adverse effects for all routes of administration. The dose required for antidepressant response differed between individuals, suggesting that dose titration on an individual basis should be used rather than a fixed mg/kg dose for all patients. SC injection could be used as an equally effective and simpler-to-administer alternative to the IV infusion method.

Acknowledgements: This trial was supported in part by a NSW Institute of Psychiatry Research Fellowship Grant and Pfizer Neuroscience Research grant for investigator initiated research, awarded to Dr Lai. Dr Gálvez received a research scholarship from Fundacio Pedro i Pons (University

of Barcelona). Prof Cynthia Shannon Weickert was supported by Schizophrenia Research Institute (utilising infrastructure funding from the NSW Ministry of Health and the Macquarie Group Foundation), the University of New South Wales, and Neuroscience Research Australia. Prof Cynthia Shannon Weickert is a recipient of a National Health and Medical Research Council (Australia) Senior Research Fellowship (#1021970). Wesley Hospital supplied the cost of ketamine used in the study. The authors would like to thank Natalie Katalinic, Dr Laura Cotiga, Dr Harry Wark, Dr Brett Simpson, Dr Jenny McGoldrick, Wesley Hospital nursing staff and The Wesley Hospital, Sydney, for their support for this study.

Declaration of interest:

Professor Colleen K. Loo has received travel support and honoraria from Lundbeck and Astra-Zeneca to speak at hospital grand rounds and academic conferences which were sponsored by these companies. Dr. Verónica Gálvez reports no competing interests. Emily O’Keefe reports no competing interests. Professor Philip B. Mitchell reports no competing interests. Dr. Dusan Hadzi-Pavlovic reports no competing interests. Dr. John Leyden reports no competing interests. Dr. Simon Harper reports no competing interests. Andrew A Somogyi reports no competing interests. Dr Rosalyn Lai received a peer reviewed, competitive Pfizer Neuroscience Research grant to support early career researchers, for this investigator initiated study, and is a PI for a Takeda sponsored clinical trial. Professor Cynthia Shannon Weickert is on an advisory board for Lundbeck, Australia. Dr. Paul Glue is a consultant for Kinex Pharma, PI for clinical trials sponsored by Demerx Inc. The statistical analysis was done by Dusan Hadzi-Pavlovic of the University of New South Wales, email: d.hadzi-pavlovic@unsw.edu.au.

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Table 1. Demographic and clinical characteristics of the overall sample and by route of administration.

Characteristic / Group	All routes (N=15)		IV (n=4)		IM (n=5)		SC (n=6)		F/ χ^2	p
	N / mean	% / SD	N / mean	% / SD	N / mean	% / SD	N / mean	% / SD		
Demographic variables										
Age (years)	48.5	11	52.8	9.5	45.6	13.3	48.2	11	0.4	0.66
Gender male	4	26.7	2	50	4	80	5	83.3	1.5	0.46
Weight (kg)	88.7	17.9	82.5	20.2	81.8	15.8	98.5	16.2	1.6	0.23
BMI (kg/m2)	27.9	5	28.1	6.1	25.8	4.1	30	4.5	0.9	0.45
Clinical variables										
Age of Onset (yrs)	28.7	14.3	26.3	12.3	31	16.7	28.3	15.7	0.1	0.9
Melancholic Features (Y/N)	9	60	3	75	3	60	3	50	0.6	0.73
Baseline MADRS Score	29.1	6.5	31.3	8.9	31.6	6.9	25.5	2.7	1.7	0.23
Current Episode duration (weeks)	375.7	556.4	904.3	918.1	133.6	165	225	172.7	3.3	0.07
Lifetime duration of illness (weeks)	631.2	791.8	1321.8	1328	317	134	380.3	159.1	2.7	0.11
Treatment related variables										
Antidepressants Failed Current Episode	4.2	4.2	7	5	3.4	4.9	3	2.44	1.3	0.31
Antidepressants Failed Lifetime	6	3.9	7.8	4.3	5.8	5.2	5	2.6	0.6	0.58
Failed ECT current episode (Yes)	5	33.3	2	50	1	20	2	16.7	0.9	0.64

(IV) intravenous; (IM) intramuscular; (SC) subcutaneous; BMI (body mass index), kg (kilogram), m (meter); MADRS (Montgomery-Asberg Depression Rating Scale); ECT (Electroconvulsive Therapy).

Figure 1. Mean percentage change in Montgomery-Asberg Depression Rating Scale (MADRS) scores across all dose levels. Measured across time for: A) intravenous group (IV), B) intramuscular group (IM), and C) subcutaneous group (SC). N refers to the number of participants treated at that dose level.

Figure 2. Percentage (%) of responders/remitters at any time point across doses and route of administration. IV (intravenous), IM (intramuscular), SC (subcutaneous).

Figure 3. Mean increases in Clinician Administered Dissociative States Scale (CADSS; maximum score 108) and Brief Psychiatric Rating Scale (BPRS; maximum score 30) in the intravenous group (IV), intramuscular group (IM), and subcutaneous group (SC). Note decreases from baseline are shown as returns to baseline.

Figure 4. Correlations between maximum measured plasma ketamine concentrations for IV (intravenous), IM (intramuscular), SC (subcutaneous) routes of administration and **A)** treatment dose; **B)** Clinician Administered Dissociative Symptoms Scale total scores at 40 minutes.

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Title:

Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression

Date:

2016-07-01

Citation:

Loo, C. K., Galvez, V., O'Keefe, E., Mitchell, P. B., Hadzi-Pavlovic, D., Leyden, J., Harper, S., Somogyi, A. A., Lai, R., Weickert, C. S. & Glue, P. (2016). Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *ACTA PSYCHIATRICA SCANDINAVICA*, 134 (1), pp.48-56. <https://doi.org/10.1111/acps.12572>.

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