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Randomized trial of ketamine masked by surgical anesthesia in patients with depression

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Ketamine may have antidepressant properties, but its acute psychoactive effects complicate successful masking in placebo-controlled trials. Here we present a single-center, parallel-arm, triple-masked, randomized, placebo-controlled trial assessing the antidepressant efficacy of intravenous ketamine masked by surgical anesthesia (ClinicalTrials.gov, NCT03861988). Adult patients ($N = 40$) with major depressive disorder who were scheduled for routine surgery were randomized to a single infusion of ketamine (0.5 mg kg^{-1}) or placebo (saline) during usual anesthesia. All participants, investigators and direct-patient-care staff were masked to treatment allocation. The primary outcome was depression severity measured by the Montgomery–Åsberg Depression Rating Scale at 1, 2 and 3 days post-infusion. After all follow-up visits, participants were asked to guess which intervention they received. A mixed-effects model showed no evidence of effect of treatment assignment on the primary outcome (−5.82, 95% confidence interval −13.3 to 1.64, $P = 0.13$). Of all participants, 36.8% guessed their treatment assignment correctly; both groups allocated their guesses in similar proportions. In conclusion, a single dose of intravenous ketamine delivered during surgical anesthesia had no greater effect than placebo in acutely reducing the severity of depressive symptoms in adults with major depressive disorder. This trial successfully masked treatment allocation in patients with moderate-to-severe depression using surgical anesthesia. Although this masking strategy is impractical for most placebo-controlled trials, future studies of novel antidepressants with acute psychoactive effects should make efforts to fully mask treatment assignment to minimize participant-expectancy bias.

Ketamine, a dissociative anesthetic with multiple molecular targets[1,2], is associated with rapid-acting antidepressant effects in patients with major depressive disorder (MDD), including those with treatment-resistant depression (TRD)[3–5]. Across studies, an intravenous infusion of 0.5 mg kg^{-1} ketamine produces a clinical response in 41% and remission in 19% of patients with TRD at 24 h (ref. 6). Therapeutic effects appear within 2 h of a single ketamine infusion[5].

In most randomized controlled trials (RCTs) of ketamine for depression, participant masking has been nearly impossible given the drug's obvious acute psychological effects. Inadequate masking

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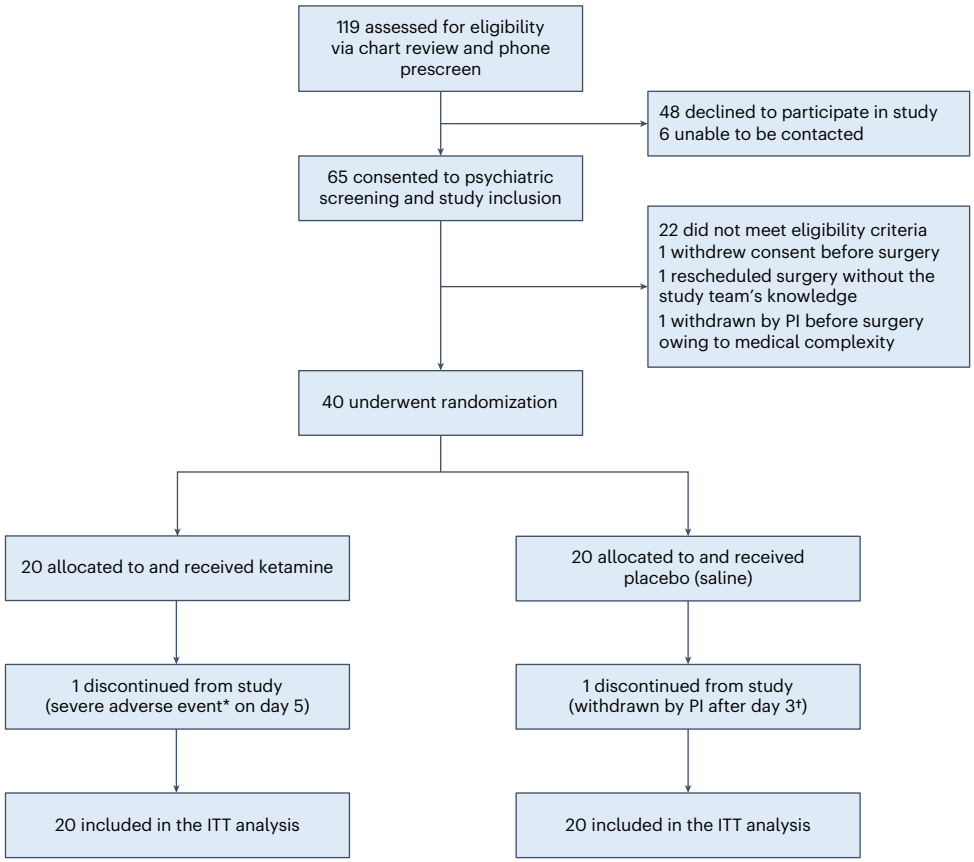

Fig. 1 | CONSORT flow diagram. Participants were randomized to a single intravenous dose of either ketamine or saline, given during surgical anesthesia. *Unexpected death that occurred 2 days after the patient was discharged home without complications on postoperative day 3; this patient experienced a witnessed cardiac arrest, attributed to the participant's medical factors and not resulting from study procedures. †One participant was withdrawn by the principal investigator (PI) owing to an unanticipated surgical revision of an implanted device, which took place on postoperative day 3 after study assessments were completed.

presents a major confounding in interpreting studies of ketamine, as well as other rapid-acting psychoactive therapeutics such as psilocybin and methylenedioxymethamphetamine (MDMA)[7–10], to the extent that most investigations do not report on the success of participant masking[10]. Incomplete masking may lead to participant-expectancy bias, which occurs when a research participant has an expectation for a given result that influences the reported outcome. Participant-expectancy bias may contribute to the overestimation of treatment effect sizes in antidepressant trials involving ketamine[11].

We utilized ketamine's established safety in surgical settings by conducting a randomized placebo-controlled trial in which the administration of ketamine was masked by other surgical anesthetics. The primary aim of this study was to determine whether ketamine, given at a dose of 0.5 mg kg^{-1} over 40 min during surgical anesthesia, produces a greater antidepressant effect than placebo. We recruited patients with depression severity comparable to that of previous studies and analyzed similar follow-up timepoints. We hypothesized that ketamine is superior to an inert placebo (0.9% sodium chloride, that is, normal saline) in reducing depression symptoms within the first 3 days post-infusion in a population of adults with moderate-to-severe levels of MDD. A supportive aim was to test whether a conscious dissociative reaction to ketamine is needed for an antidepressant response.

Results

Participants

Participant recruitment occurred between February 2020 and August 2022. The first patient was enrolled in the randomized trial on February 19, 2020, and the final patient was enrolled on August 18, 2022. The last day of follow-up was September 9, 2022. For participant flow through the clinical trial, see the Consolidated Standards of Reporting Trials (CONSORT) diagram (Fig. 1). The screening visit occurred between 27 days and 16 h before surgery (mean (s.d.), 5.1 (4.6) days). The mean age of trial participants was 51 years; they were mostly female (70%), white (65%), non-Hispanic (87.5%) and employed (62.5%), and never smoked (65%). At screening, both groups had moderate levels of depression as rated by the Montgomery–Åsberg Depression Rating Scale (MADRS; mean score for ketamine, 27.7, and placebo, 30.6) and moderate levels of treatment resistance as measured by the Maudsley staging method (MSM; mean score for ketamine, 8.3, and placebo, 7.5). The presence of symptomatic depression was also supported by the Hospital Anxiety and Depression Scale (HADS; mean score for ketamine, 24.6, and placebo, 24.7). Although current MDD episode durations were longer in the ketamine group, the difference did not reach statistical significance (ketamine, median = 38 months; placebo, 17 months). Both groups also scored similarly on the Brief Pain Inventory Short Form (BPI-SF) at screening, except for two questions in which participants in the ketamine group reported having more pain interference with sleep (mean 7.7 versus 5.5, $P = 0.02$) and enjoyment of life (mean 7.6 versus 5.7, $P = 0.04$). Other characteristics were similar between groups (Table 1).

Table 2 summarizes participants' surgical and anesthetic characteristics. Participants in both study arms had similar levels of disease burden, as measured by the American Society of Anesthesiologists (ASA) physical status classification[12] and the Charlson comorbidity index (CCI)[13]. Patients presented to a range of surgical departments which were distributed similarly between the two groups. With regard to anesthetic type, all except one patient underwent general anesthesia.

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Table 1 | Demographics and clinical characteristics of the participants at baseline

Characteristics	Ketamine (*N*=20)	Placebo (*N*=20)	Overall (*N*=40)
Demographic characteristics			
Age (years)	50.5±12	51.9±18.9	51.2±15.7
Female sex (*N* (%))	12 (60)	16 (80)	28 (70)
Male sex (*N* (%))	8 (40)	4(20)	12 (30)
Race (*N* (%))[a]			
White	13 (65)	13 (65)	26 (65)
Black	2 (10)	2 (10)	4 (10)
Asian	0 (0)	2 (10)	2 (5)
Native Hawaiian or other Pacific Islander	0 (0)	1 (5)	1 (2.5)
More than one race	2 (10)	0 (0)	2 (5)
Unknown or not reported	3 (15)	2 (10)	5 (12.5)
Ethnicity (*N* (%))[a]			
Hispanic	2 (10)	2 (10)	4 (10)
Non-Hispanic	18 (90)	17 (85)	35 (87.5)
Unknown or not reported	0 (0)	1 (5)	1 (2.5)
Married or life partnered (*N* (%))	9 (45)	9 (45)	18 (45)
Employed (*N* (%))	13 (65)	12 (60)	25 (62.5)
Never smoked (*N* (%))	14 (70)	12 (60)	26 (65)
Body mass index (kg m^{-2})	29.9±5	29.5±4.4	29.7±4.7
Previous ketamine exposure (*N* (%))			
None or did not know	15 (75)	19 (95)	34 (85)
Received in a medical setting	5 (25)	1 (5)	6 (15)
Used recreationally	0 (0)	0 (0)	0 (0)
Psychiatric history			
Age at first MDD onset (years)	31.0±14.3	21.8±15.0	26.5±15.2
Duration of current MDD episode (months)			
Mean	80.1	43.7	61.9
Median	38	17	24
Duration of current MDD episode (*N* (%))			
Acute (≤12 months)	6 (30)	10 (50)	16 (40)
Subacute (13–24 months)	1 (5)	7 (35)	8 (20)
Chronic (>24 months)	13 (65)	3 (15)	16 (40)
Recurrent MDD (*N* (%))	11 (55)	16 (80)	27 (67.5)
Number of antidepressants trialed (*N* (%))			
1–2	9 (45)	7 (35)	16 (40)
3–4	4 (20)	9 (45)	13 (32.5)
5–6	6 (30)	2 (10)	8 (20)
7–10	0 (0)	0 (0)	0 (0)
>10	1 (5)	0 (0)	1 (2.5)
Antidepressant augmentation trialed (*N* (%))	3 (15)	7 (35)	10 (25)
ECT trialed (*N* (%))	0 (0)	0 (0)	0 (0)
MSM score	8.3±2.3	7.5±1.7	7.9±2
MSM resistance category (*N* (%))			
Mild (<7)	4 (20)	5 (25)	9 (22.5)
Moderate (≥7 and <11)	13 (65)	14 (70)	27 (67.5)
Severe (≥11)	3 (15)	1 (5)	4 (10)
Depression scores			
PHQ-8 total score[b]	15.8±3.6	15.8±3.8	15.8±3.7
MADRS total score[c]	27.7±7.8	30.6±6.3	29.1±7.1
HADS[d]			
Total score	24.6±6.0	24.7±5.7	24.6±5.8
Depression subscore	12.0±3.2	10.5±3.6	11.2±3.5
Anxiety subscore	12.6±4.4	14.2±3.3	13.4±3.9

Plus–minus values represent means±s.d. Participants were randomized to a single intravenous dose of either ketamine or saline, given during surgical anesthesia. Percentages may not total 100 owing to rounding. [a]Race and ethnicity were reported by the participants. [b]Total scores on the PHQ-8 range from 0 to 27, with higher scores indicating greater severity of depression. [c]Total scores on the MADRS range from 0 to 60, with higher scores indicating greater severity of depression. [d]Total scores on the HADS range from 0 to 42, with higher scores indicating greater severity of anxiety and depression; subscales range from 0 to 21. Missing data: Ethnicity for one participant in the placebo group, marital status for two participants in the ketamine group and one participant in the placebo group, age of first MDD onset for one participant in the placebo group, recurrent MDD type for two participants in the ketamine group and number of antidepressants trialed for two participants in the placebo group.

One participant in the ketamine group had monitored anesthesia care with a neuraxial block; however, the depth of anesthesia was within study parameters. Two participants in the ketamine arm and one participant in the placebo arm received nitrous oxide (N_2O) at a concentration of ≥50% for ≥1 h. Use of preoperative and intraoperative opioids and length of surgery were similar between groups.

Outcomes

For the primary outcome on post-infusion days 1, 2 and 3, the mixed-effects model (Table 3) showed no evidence of effect of group assignment on MADRS scores (95% confidence interval (CI) −13.3 to 1.64, $P = 0.13$, $N = 20$ per arm). The MADRS rate of change also did not differ between groups (95% CI −1.54 to 4.93, $P = 0.30$). An alternative model using change from pre-infusion baseline MADRS scores on the day of surgery ('day 0') also showed no between-group difference in change scores (95% CI −6.25 to 7.89, $P = 0.82$). The rate of change for the MADRS change scores also did not differ between groups (95% CI −1.96 to 4.62, $P = 0.43$). Missing MADRS scores among enrolled participants did not exceed 5% at any visit; therefore, missing data were not imputed for the primary outcome.

Pre-infusion baseline MADRS scores on day 0 did not differ between trial groups (ketamine, 25.1 (s.d. 8.3); placebo, 29.9 (s.d. 7.0)). From day 0 to day 1, the average change in MADRS scores was −12.4 points (s.d. 9.2) in the ketamine group and −14.7 points (s.d. 9.0) in the placebo group, corresponding to a mean decrease of 46% and 48% on the MADRS, respectively. In both groups, MADRS scores increased slightly on day 2 relative to the nadir at day 1, but the decrease from baseline persisted through all follow-up timepoints up to day 14 (Fig. 2a). The HADS scores also followed a trajectory similar to the MADRS scores (Extended Data Table 1).

At the end of the follow-up period (day 14), participants were asked to guess which intervention they had received; 36.8% of all participants guessed correctly, and the distribution of guesses between groups was comparable, with Cohen's kappa = 0.33, indicating fair agreement between groups (Fig. 2b). We performed an exploratory analysis to determine whether patients' guesses regarding their treatment allocation were related to their final MADRS score (day 14).

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Table 2 | Surgical and anesthetic characteristics of the participants

Characteristic	Ketamine (*N*=20)	Placebo (*N*=20)	Overall (*N*=40)
ASA physical status classification (*N* (%))[a]			
I	0 (0)	1 (5)	1 (2.5)
II	12 (60)	15 (75)	27 (67.5)
III	8 (40)	4 (20)	12 (30)
CCI total score[b]			
Mean	2.1±2.7	2.7±2.6	2.4±2.7
Median	1	2.5	1.5
Surgery department (*N* (%))			
General surgery	6 (30)	3 (15)	9 (22.5)
Orthopedics, non-spine	5 (25)	4 (20)	9 (22.5)
Otolaryngology	2 (10)	2 (10)	4 (10)
Gynecology	2 (10)	3 (15)	5 (12.5)
Urology	2 (10)	0 (0)	2 (5)
Neurosurgery, non-intracranial	1 (5)	3 (15)	4 (10)
Orthopedics, spine	1 (5)	2 (10)	3 (7.5)
Thoracic	1 (5)	0 (0)	1 (2.5)
Plastics	0 (0)	3 (15)	3 (7.5)
Anesthesia type (*N* (%))			
General anesthesia	19 (95)	20 (100)	39 (97.5)
Neuraxial block with sedation	1 (5)	0 (0)	1 (2.5)
Maintenance anesthetics used (*N* (%))			
N_2O[c]	2 (10)	1 (5)	3 (7.5)
Propofol (*N* (%))	18 (90)	17 (85)	35 (87.5)
Sevoflurane (*N* (%))	17 (85)	14 (70)	31 (77.5)
Isoflurane (*N* (%))	1 (5)	3 (15)	4 (20)
Use of regional anesthesia (*N* (%))	1 (5)	3 (15)	4 (10)
Use of preoperative opioids (*N* (%))	9 (45)	7 (35)	16 (40)
Preoperative opioids (MME per day)[d]			
Mean	9.1±16.4	10.5±27.7	9.8±22.4
Median	0	0	0
Use of intraoperative opioid infusion (*N* (%))	5 (25)	7 (35)	12 (30)
Length of surgery (min)	244±121	269±109	256±114

Plus–minus values represent means ± s.d. [a]ASA physical status classification ranges from I to VI, with higher values indicating greater numbers and severity of pre-anesthesia medical comorbidities. [b]Total scores on the CCI range from 0 to 37, with higher scores indicating greater numbers and severity of pre-anesthesia medical comorbidities. [c]Inhaled N_2O concentration of at least 50% for at least one continuous hour. [d]MME represents potencies of opioids relative to those of oral morphine, with higher values indicating higher opioid doses.

Table 3 | Linear mixed model estimates for MADRS scores

	Coefficient	95% CI	*t* value	*P* value
MADRS scores from post-infusion days 1 to 3				
Intercept	16.6	11.3 to 21.9	6.15	<0.001
Group	−5.82	−13.3 to 1.64	−1.53	0.13
Time	0.24	−2.04 to 2.52	0.21	0.84
Group×time	1.70	−1.54 to 4.93	1.03	0.30
Change from pre-infusion baseline MADRS scores on post-infusion days 1 to 3				
Intercept	−15.0	−20.1 to −9.95	−5.79	<0.001
Group	0.82	−6.25 to 7.89	0.23	0.82
Time	0.58	−1.77 to 2.93	0.49	0.63
Group×time	1.33	−1.96 to 4.62	0.79	0.43

The effect of group on MADRS scores from post-infusion days 1 to 3 was not significant (P=0.13 using absolute scores and P=0.82 using change from baseline scores). Significance was evaluated using likelihood ratio tests and applying the normal approximation to Wald *t* values from the model output. No adjustments for multiple comparisons were made for the two models presented here.

We regrouped MADRS data according to patient guess ('ketamine', 'placebo' or 'I don't know'; Extended Data Fig. 1). At day 14, aggregating across actual treatment allocations, mean (s.d.) MADRS scores were, for patients guessing 'ketamine' (N = 16), 10.1 (7.2); guessing 'placebo' (N = 10), 19.2 (7.7); and replying 'I don't know' (N = 12), 23.0 (13.7). A simple logistic regression of day 14 MADRS score onto guessing either 'ketamine' (coded '1') or otherwise (coded '0') suggested a significant inverse relationship between these two variables (odds ratio = 0.89 (95% CI 0.81 to 0.96); P = 0.001). MADRS change scores relative to day 0 are visualized in Fig. 2c. A secondary outcome was clinical response, defined as ≥50% reduction in MADRS scores from screening baseline. On post-infusion day 1, 60% and 50% of participants in the ketamine and placebo group, respectively, met criteria for clinical response. Rates of clinical response in both trial groups remained similar to each other on post-infusion days 2 and 3 (Fig. 2d and Extended Data Table 1). We also analyzed remission, which we defined in our study as MADRS score of ≤12. Remission occurred in 50% and 35% of participants in the ketamine and placebo group, respectively, on post-infusion day 1; this difference closed on post-infusion day 3, when 40% of both groups remained in remission (Extended Data Table 1).

Cumulative opioid consumption and average daily inpatient opioid use did not differ between groups (Fig. 2e and Extended Data Table 2). On postoperative days 7 and 14, five participants in the ketamine group and two participants in the placebo group were still using opioids. Of note, no participants received either preoperative or postoperative methadone or buprenorphine, nor were any maintained on opioid antagonist therapy. Average pain intensity on the BPI-SF at 14 days post-infusion was not different between groups (ketamine, 4.8 (s.d. 1.5); placebo, 3.7 (s.d. 2.0)). Pain interference on the BPI-SF at day 14 post-infusion also did not differ between groups (ketamine, 6.2 (s.d. 2.2); placebo, 5.7 (s.d. 3.5)). Hospital length of stay was longer in the placebo group (mean 1.9 (s.d. 1.7) days versus 4.0 (s.d. 3.3) days, P = 0.02).

Protocol violations and safety

One participant in the ketamine group initially met inclusion criteria at screening but was retrospectively found not to have maintained her symptom severity on the morning of surgery (additive MADRS and HADS score of 30, below the minimum of 31). This participant was randomized and included in the intention-to-treat (ITT) analysis. No protocol deviations related to the administration of the study drug occurred in this trial.

Adverse events were evaluated at every visit. Notably, one death in the ketamine group occurred 5 days post-infusion, which triggered the unmasking of treatment assignment. The patient had been discharged from the hospital on postoperative day 3, with no surgical or anesthetic complications documented before discharge. Subsequently, the patient experienced a witnessed cardiac arrest at home; advanced cardiac life support was initiated by paramedics and continued in the emergency room until the patient expired. One patient in the placebo group experienced a surgical complication requiring reoperation on postoperative day 3.

Sensitivity analyses

We tested whether our results were sensitive to (1) a possible difference in pre-infusion baseline MADRS scores and (2) the exclusion

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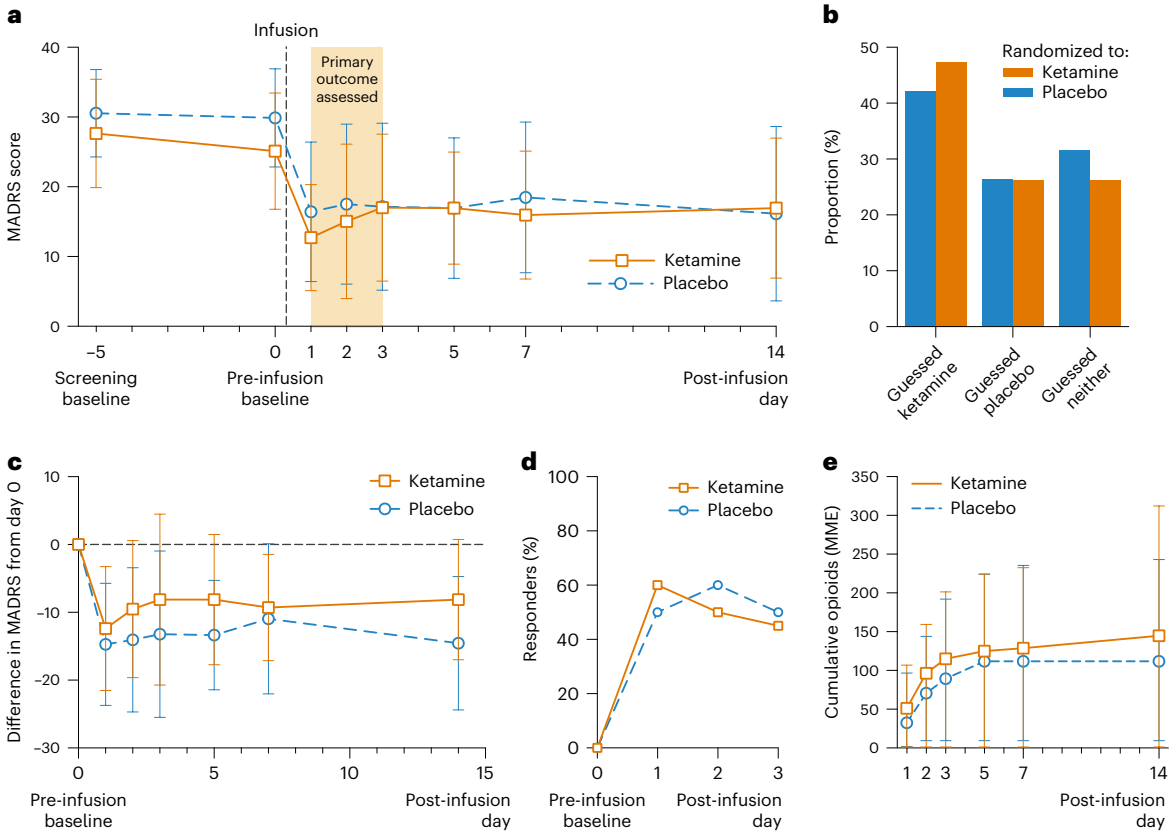

Fig. 2 | Depression severity, masking assessment and other outcomes. a, Mean and s.d. scores by group on the MADRS: scores range from 0 to 60, with higher scores indicating greater depression; the screening baseline visit occurred on average 5 days before infusion on day 0. Total $N = 39$ independent participant responses per day, on post-infusion days 1 to 3 (see Extended Data Table 1 for group-specific counts). **b**, Distribution of guesses as a percentage of each group ($N = 19$ per group) made by participants when asked to guess which treatment they received after the last follow-up visit. **c**, Difference in MADRS scores relative to pre-infusion baseline scores obtained on day 0 (same sample size as reflected in **a**). **d**, Proportions of clinical response as a percentage of each group ($N = 20$ per group), within the first 3 days. **e**, Cumulative opioid consumption in MME by group, represented as median and interquartile range; both inpatient and outpatient opioids were included in the total ($N = 20$ per group).

of participants who received N_2O, an anesthetic which may also have antidepressant qualities[14]. We adjusted for a possible difference in pre-infusion baseline MADRS scores by including it as a fixed covariate and specifying random effects only for slopes in our mixed-effects model; this showed no between-group difference in MADRS scores (95% CI −8.41 to 4.49). When we applied our original mixed-effects model for the primary outcome after excluding three participants who received N_2O at a concentration of 50% for at least 1 h, there was also no between-group difference in MADRS scores (95% CI −13.3 to 2.74, $P = 0.13$).

Discussion

This randomized, triple-masked trial compared the short-term antidepressant efficacy of ketamine with that of placebo in adults with moderate-to-severe depression. There was no effect of treatment on our primary outcome, MADRS scores on days 1, 2 and 3 post-infusion. Baseline MADRS scores obtained at screening and on the day of surgery did not meaningfully differ between groups. In both trial groups, the observed decrease in MADRS score at day 1 was similar to, or exceeded, the decreases observed in previous ketamine trials in awake patients[15–18]. The variance in MADRS change scores observed in our study is also comparable to those of previous studies in awake patients[19], supporting our a priori power calculation to detect a between-group difference. The HADS, an alternative patient-rated depression scale, yielded a similar score trajectory as the MADRS and strengthens our conclusion that ketamine and placebo did not differentially impact mood in this trial. Participant retention was excellent, with no loss to follow-up occurring within the primary outcome window. Notably, one participant death occurred in the ketamine group. However, this severe adverse event was attributed to underlying cardiovascular comorbidities rather than a direct result of trial procedures, consistent with previous analyses of cardiovascular safety outcomes after intravenous ketamine infusion[19].

Both the ketamine and placebo groups appeared to show a strong antidepressant response, although, counter to our hypothesis, the magnitude of this response did not differ between groups. We review the available evidence for several potential interpretations of this result, while noting that the relatively small sample size, the unusual background of surgical anesthesia on which treatments were delivered and our two-arm study design limit broadly generalizable conclusions about ketamine's efficacy or mechanism. To the extent that the treatment effect in the ketamine group is similar to that of other studies, our data raise the possibility that antidepressant effects of ketamine may be achieved in the absence of a typical ketamine-induced conscious dissociative experience. However, a conscious dissociative experience may yield an even more robust response, significantly greater than that seen with placebo, in a situation in which treatment-arm masking is maintained without the use of anesthesia. Furthermore, adjunctive psychotherapy may act synergistically with the acute subjective effects of ketamine treatment (for example, ketamine-assisted psychotherapy), potentially outperforming ketamine-only treatment[20], although controlled data on this form of ketamine therapy are still lacking[21]. Nonetheless, our successful masking of treatment allocation, and associated large apparent treatment effect across groups,

may have implications for interpreting results from studies of acutely psychoactive treatments in which trials are not designed for adequate treatment masking. In this study, patients' guess regarding group allocation was strongly related to their MADRS score at the end of the study (14 days post-infusion), potentially reflecting a previous belief about the efficacy of ketamine treatment for depression. Together, these data point to a major role for extra-pharmacological effects in the response to ketamine among patients with depression.

The surprisingly robust clinical response and remission rate observed in both arms of this trial raise the question of whether anesthetics besides ketamine may have antidepressant effects. N_2O has been shown to improve depression symptoms in patients with TRD[14,22]. However, only 3 out of 40 participants in our study were exposed to N_2O at a concentration of 50% for ≥1 h, making it unlikely to impact depression scores at the group level, as confirmed in our sensitivity analyses. Propofol infusions and inhaled isoflurane have also shown antidepressant properties when given at doses that suppress electroencephalography (EEG) activity ('burst suppression') for 15 min, over multiple administrations[23,24], although these findings are not consistent[25] and differ substantially in depth and timing from standard surgical anesthesia used in our study (the recommended patient state index (PSI) range of 25–50 avoids burst suppression). We also considered the possibility that surgery and general anesthesia without ketamine has an antidepressant effect. However, our review of previous studies measuring symptoms of depression in the perioperative period strongly suggests otherwise. In the control arms (surgery and anesthesia alone) from studies of populations of patients with[26–30] and without[31,32] depression, primary mood outcomes in the first days after surgery reflect either no significant change[26,29,31,33,34] or possibly worsened symptoms[27,32]. The anesthetic regimens used across these studies broadly resemble our own (most commonly propofol, sevoflurane and opioid based), although the anesthetic depth was rarely noted. Taken together, these data suggest that non-pharmacological factors can strongly influence reported depression outcomes.

The lack of separation between placebo and ketamine groups in our trial may indicate that anesthetic agents blocked the antidepressant effects of ketamine. This possibility is somewhat difficult to reconcile with our observed effect size (comparing pretreatment with posttreatment), which is within the range of most previously observed ketamine effect sizes[6]. However, anesthetic agents may have interfered with neural mechanisms required for the antidepressant effect of ketamine, leaving in place, for example, large expectancy-driven antidepressant effects. Among several potential molecular and neural-circuit-based mechanisms for the antidepressant effects of ketamine[35–37], a popular model is that ketamine, via antagonism of cortical *N*-methyl-D-aspartate receptors, enhances cortical glutamate release and triggers neuroplastic changes through activity-dependent release of neurotrophic factors. In this model, anesthetic agents could blunt ketamine effects by reducing the excitability of cortical neurons. GABAergic anesthetic agents do indeed reduce cortical activity[38]; however, emerging human data suggest that ketamine's mechanisms may be substantially more complex than once thought. Based on a glutamate modulation theory of ketamine antidepressant action, multiple compounds have been tested as antidepressants in clinical trials and have not separated from placebo[39–44], suggesting that other molecular targets may be involved. Furthermore, interactions between ketamine and anesthetic agents like propofol may have both antagonistic and additive effects in cortical and subcortical networks[45,46], possibly linked to biologically and clinically significant actions of ketamine at, among other targets[1], hyperpolarization-activated cyclic-nucleotide-gated potassium channel 1 (refs. 45–49), as well as opioid receptors[2,50–53]. Opioids are also routinely used during surgical anesthesia, and recent evidence shows that blocking opioid receptors attenuates the antidepressant effect of ketamine[50,54]. No patients were on opioid antagonist or partial agonist therapy, and the average daily milligram morphine equivalent (MME) use in both groups before surgery was relatively low. Our review of available data suggests that surgical anesthesia does not have substantial intrinsic antidepressant efficacy, and although we cannot exclude the possibility that anesthetic agents interfered with the antidepressant effect of ketamine, the antidepressant mechanism of ketamine in humans is not well enough characterized to make such a determination at this time. We hypothesize that a minimal dose of anesthetic agent may allow for adequate treatment masking and minimal interference with putative ketamine antidepressant mechanisms.

Baseline heterogeneity in psychiatric characteristics could potentially explain the smaller-than-anticipated difference in post-treatment depression scores. Although clinical and sociodemographic characteristics were largely similar between trial groups, there was a notable difference in current MDD episode length—with the ketamine group having a longer median episode duration (38 months) compared with the placebo group (17 months). A longer current MDD episode may predict more treatment resistance to traditional antidepressants[55]. However, studies comparing characteristics of responders and nonresponders to ketamine therapy have been mixed, with some studies showing that the current MDD episode length impacts treatment response[56] whereas other studies do not[57,58]. We also cannot rule out the effect of surgical heterogeneity between groups, which we did not control for in our recruitment design; however, between-group differences in case counts did not exceed three for any surgical department, and intraoperative factors, including length of surgery and types of anesthetic used, did not meaningfully differ between groups.

Contrary to our primary findings and other secondary findings, a between-group difference was observed in the hospital length of stay. Participants who received ketamine were discharged 2 days earlier on average than participants who received placebo. Although this difference reached statistical significance ($P = 0.02$), it is important to note that such a significance would not withstand corrections for multiplicity. Furthermore, previous randomized trials have failed to demonstrate reductions in postoperative length of stay with intraoperative ketamine administration[59–62]. Nevertheless, our findings suggest the potential for a unique response to perioperative ketamine administration among patients who were clinically depressed.

Other studies have also evaluated the effect of ketamine on mood ratings in surgical patients[30]; however, numerous methodological limitations prevent direct comparison with studies of intravenous ketamine for depression in the psychiatric literature. Frequently, these trials were not conducted in a population likely to meet criteria for moderate-to-severe MDD[31,32,63–65]. In the Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) study—the largest study to date comparing ketamine with saline in surgical patients—depression scores were analyzed as a secondary outcome from a study designed to evaluate the efficacy of ketamine for postoperative delirium in patients >60 years old. Notably, only 9.6% of participants met the eight-item Patient Health Questionnaire (PHQ-8) cutoff for moderate depression preoperatively, and no diagnostic data or clinician-rated scales were reported[27]. Among perioperative studies that recruited patients with at least mild–moderate symptoms of depression[26,27,29,33], comparison with psychiatric trials in conscious patients is complicated by the use of nonstandard ketamine doses and methods of administration[26,27,33], reliance on patient-reported scale versus clinician-administered scale outcome measures[26,27] and treatment masking that was neither described nor assessed. Two previous studies enrolled surgical patients with mild-to-moderate depression severity[26,28]. A 2021 RCT testing ketamine during surgical anesthesia required moderate-to-severe depression (MADRS ≥ 22) for eligibility; however, these participants underwent intracranial tumor resection[29], a population we excluded owing to the possibility of mood and personality changes associated with cortical lesions and resections of such lesions[66,67].

A key strength of our trial was the evaluation of participant masking. At their last follow-up visit, patients in both groups allocated their guesses in similar proportions and fewer than half guessed correctly. The intervention was effectively masked—an uncommon finding among antidepressant trials with ketamine. Assessment of masking is also rare among RCTs involving ketamine and electroconvulsive therapy (ECT), an important antidepressant treatment delivered to briefly anesthetized patients. Most RCTs evaluating the effect of adjunctive ketamine on ECT outcomes have found no benefit of ketamine given at doses of 0.5 mg kg^{-1} or higher[68]. Of the RCTs included in a previous review[68], only one reported on masking effectiveness[69].

Outcome expectancy related to the stated intent of the trial may drive apparent treatment effects. Previous studies of ketamine in surgical patients generally find that when patients are recruited to test ketamine's antidepressant effect as a primary outcome, depression scores decrease postoperatively. Conversely, among the patients in the Prevention of Delirium and Complications Associated with Surgical Treatments, who were recruited to participate in a trial focused on reducing postoperative delirium, depression symptoms (a secondary outcome) worsened slightly in the postoperative period.

One limitation of our study is that we did not assess the blind of the anesthesiologists who administered the study drug. Although it is possible that close inspection of the intraoperative processed EEG could reveal changes consistent with a 0.5 mg kg^{-1} subanesthetic ketamine infusion[70], we specifically instructed the anesthesiologists to avoid altering the patient's anesthetic in response to the processed EEG during drug infusion (barring large excursions in PSI that correlate with patient awareness). Nonetheless, we cannot exclude the possibility that anesthesiologists who guessed the patient's treatment allocation may have altered their anesthetic in a way that influenced postoperative mood.

Our results suggest that when differential participant-expectancy bias is minimized with successful masking, the treatment effect size of ketamine is reduced considerably. However, a major limitation of our study is that we did not measure treatment expectancies before randomization. Therefore, we cannot definitively conclude that participant-expectancy bias mediates the causal relationship between effective masking and smaller treatment effect sizes. Regardless of the intervention being tested, participant expectations of a positive outcome—also known as hope—may drive large decreases in depression symptoms seen in antidepressant trials[71]. Our trial design cannot distinguish between a null effect of ketamine for depression and an occlusion of ketamine's antidepressant effect through a placebo-like mechanism maintained in the absence of unmasking.

Conclusion

This trial utilized surgical anesthesia to successfully mask the allocation of a single antidepressant dose of ketamine or placebo in a sample of depressed patients and found that depression scores at 1, 2 and 3 days post-infusion did not differ between trial groups. Both groups improved similarly. With the exception of a shorter hospital length of stay of individuals who received ketamine, the secondary outcomes did not demonstrate an advantage of ketamine over placebo. Our primary findings differ from those of previous antidepressant trials with ketamine conducted without adequate masking, which find robust effects of ketamine. Confounding surgical and anesthetic factors in our study prevent a determination of whether ketamine, on its own, is an effective short-term treatment of MDD. However, our robust, masked placebo response suggests that previously reported large effect sizes for ketamine may reflect a degree of expectancy bias. Although it is impractical to use surgical anesthesia for most placebo-controlled trials, future studies of novel antidepressants with acute psychoactive effects should make stronger efforts to mask treatment assignment to minimize the effects of participant-expectancy bias.

Methods

Trial oversight

This was an investigator-initiated study sponsored by the university and the Society for Neuroscience in Anesthesiology and Critical Care. The trial protocol was approved by the institutional review board at Stanford University (protocol number 49114), and all participants gave written informed consent. The trial protocol can be viewed in the Supplementary Information of this paper. Participants were compensated US$50–100 for completing screening procedures and another US$50 after all follow-up visits were completed. None of their medical costs were covered by the study. A data safety monitoring board was not required as the primary study intervention did not deviate from the standard of care and posed no known incremental risk to participants. Randomization and drug compounding were handled by Stanford Health Care Investigational Drug Service.

Participants

Adults undergoing elective noncardiac, non-intracranial surgery were recruited from preoperative clinics at Stanford University Medical Center. The PHQ-8 was distributed to patients through a perioperative mental health screening service. To be eligible for the study, patients must score ≥12 on the PHQ-8, corresponding with at least moderate depression[72]. Research staff screened the electronic health records (EHRs) of patients scheduled for surgery who scored ≥12 points on the PHQ-8; those who did not meet the exclusion criteria were introduced to the study and consent was sought for an additional screening visit. Surgical clinics also referred patients with symptomatic depression who expressed interest in the trial. These patients were contacted by research staff for a telephone prescreen, and consent for an additional screening visit was obtained from qualifying patients. At this visit, research staff collected information on demographics and medical and psychiatric history, including level of antidepressant treatment resistance assessed by the MSM[73]. Inclusion and exclusion criteria were assessed via a hybrid approach of corroborating EHR data with patient self-report.

Inclusion criteria included English literacy, body mass index of 17–40 kg m^{-2}, a diagnosis of MDD (single or recurrent) and a major depressive episode of ≥4 weeks duration before screening. The diagnosis of MDD was confirmed by the Mini International Neuropsychiatric Interview Module A[74]. Participants must also have had a combined score of ≥31 from the MADRS[75] and the HADS[76]. These scales were administered in person or by secure videoconference or telephone, which has been validated for the PHQ[77], HADS[78] and MADRS[79,80].

Exclusion criteria included pregnancy, breastfeeding, moderate or severe substance use disorder, history of schizophrenia or schizoaffective disorder, history of psychotic symptoms in the current or previous depressive episodes, dementia or other amnestic cognitive disorder, history of surgery involving the brain or meninges, encephalitis, meningitis, degenerative central nervous system disorder, clinically significant thyroid dysfunction within the past 6 months, and chronic use of >90 MME per day. Patients at high risk of suicidal behavior on the Columbia-Suicide Severity Rating Scale[81] were also excluded. Concurrent psychotherapy and antidepressant therapy were allowed if therapy was stable for ≥4 weeks before screening. Participation in any clinical trial with an investigational drug or device within the past month or concurrent to study participation was not allowed.

Trial design and procedures

This was a triple-masked, randomized, placebo-controlled trial. Before randomization, five patients were recruited for an open-label study to evaluate study procedures. Data from these five patients are not included in this paper. For the randomized trial, 20 participants were allocated to a single dose of intravenous ketamine (0.5 mg kg^{-1} diluted into 40 ml of normal saline, infused over 40 min using a programmable pump). Another 20 participants were allocated to 40 ml of normal saline infused similarly over 40 min. Pharmacy staff randomized participants

using computerized block randomization with five blocks of eight. The participant, investigators and direct-care providers (for example, anesthesiologists) were masked. Unmasking occurred after all 40 participants progressed through all follow-up timepoints (that is, end of trial).

Processed EEG from a SedLine device (Masimo) was used to confirm anesthetic depth, measured by the device's PSI. To ensure participant masking, the infusion was initiated after anesthetic induction and surgical incision, during maintenance anesthesia (PSI of 25 to 50, consistent with the manufacturer recommendations for general anesthesia). The study drug was provided to the anesthesiologist in an unlabeled syringe.

Anesthesiologists, masked to patient group allocation, administered routine anesthesia tailored to the surgical procedure and patient comorbidities; they were asked to avoid altering the anesthetic in response to any perceived changes to the processed EEG during the study drug infusion (except excessively high PSI values indicating that the patient was at risk of intraoperative awareness). Anesthesiologists were asked to minimize use of N_2O, which has reported antidepressant effects[14]. Agents used for anesthetic maintenance included intravenous propofol and inhaled sevoflurane or isoflurane. A standard multimodal analgesic regimen was used, consisting of intravenous opioid and acetaminophen, with or without intravenous lidocaine. Owing to the heterogeneity of surgical cases represented in this study, we did not mandate specific anesthetic or analgesic regimens outside of the requested constraint on depth of anesthesia.

Outcome measures

The primary outcome was the MADRS score measured 1, 2 and 3 days post-infusion, as previous studies have found the greatest antidepressant effect occurs within the first 72 h of a single ketamine infusion[82]. The same sample was assessed at 1, 2 and 3 days post-infusion, as participant dropout occurred only after outcomes were assessed on day 3. Additional assessments were made 5, 7 and 14 days post-infusion and used for exploratory analyses. The MADRS is a clinical rating scale used widely in antidepressant trials; it consists of ten items that measure the severity of depression in individuals, with a total score ranging from 0 to 60 and higher scores indicating more severe depression[75]. Trained clinical research personnel administered the MADRS.

Secondary outcomes included clinical response, defined as ≥50% reduction in MADRS scores from screening baseline[83], and remission, defined as MADRS score ≤12 in our study[84]. Other secondary outcomes included the HADS score, postoperative pain intensity, cumulative opioid use, average daily inpatient opioid use and presence of opioid use at 7 and 14 days postoperatively. The HADS is a self-reported questionnaire used to assess the severity of anxiety and depression in hospital patients; it consists of 14 items (7 items measuring anxiety, 7 items measuring depression) with a total score ranging from 0 to 42, with higher scores indicating more severe symptoms[76]. Postoperative pain was assessed by the BPI-SF modified for postoperative use[85,86]. The BPI-SF measures the severity of pain and its impact on daily functioning; it consists of nine items, each using a numeric rating scale from 0 to 10. Inpatient postoperative opioid use, calculated as total daily MME[87], was abstracted from the EHR for each day of hospitalization. For discharged patients, outpatient postoperative opioid use, via pill counts, was obtained during remote scheduled assessment days (1, 2, 3, 5, 7 and 14 days post-infusion). At 14 days post-infusion, participants were asked to guess their treatment arm. Outcomes were assessed in person during postoperative hospitalization and by video or telephone after discharge. Participants who remained in the hospital for at least 24 h postoperatively provided blood samples for secondary immunological analyses (in progress).

Statistical methods

ITT analysis was performed for the primary outcome. A mixed-effects model for repeated measures was the analysis strategy preregistered before data unmasking to evaluate the antidepressant superiority of ketamine to placebo on postoperative days 1, 2 and 3. The following fixed effects were included in the model: group, time in days and the interaction between group and time. We included random effects for intercepts and slopes to account for variation in MADRS scores and differential treatment effects. An alternative, non-prespecified mixed-effects model using change from pre-infusion baseline scores on the day of surgery was also used to analyze the primary outcome. An unstructured covariance matrix was used in all mixed models described in this study. We calculated Cohen's kappa statistic, in a post hoc analysis, to assess the level of agreement between groups regarding their guesses on treatment allocation. We also performed a simple logistic regression to investigate the relationship between final MADRS score and patients' treatment group guess (coded as '1' for guessing 'ketamine' and '0' otherwise). Both variables were obtained at day 14 during the final assessment. Logistic regression results are reported as odds ratios. All analyses were performed using RStudio software (version 2022.07.1 for MacOS). The lme4 package was used for mixed-effects modeling. Prism GraphPad (version 9.5.0 for MacOS) was used to make figures.

Our sample size estimation was derived from an a priori power analysis for the primary outcome. In an RCT of ketamine versus active placebo, participants had a mean decrease of 10.9 points (s.d. 8.9) in MADRS total score relative to pre-infusion scores compared with a mean decrease of 2.8 points (s.d. 3.6) with midazolam[15]. For reference, the minimum clinically important difference on the MADRS is estimated to range from 3 to 9 points[88]. Using these results, we computed an estimated total sample size of 38 participants at a two-sided alpha level of 0.05 and 80% power to detect this difference if using parametric testing. An additional two participants were added to account for potential attrition, for a total of 40 participants. Interim analyses were not performed.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

De-identified participant data, data dictionaries, the study protocol and the statistical analysis plan are available at https://osf.io/zdkr8/ (https://doi.org/10.17605/OSF.IO/ZDKR8). All participants have consented to sharing de-identified data with outside entities for scientific research purposes.

Code availability

R code used for data analysis is publicly available at https://osf.io/zdkr8/ (https://doi.org/10.17605/OSF.IO/ZDKR8).

References

1. Sleigh, J., Harvey, M., Voss, L. & Denny, B. Ketamine—more mechanisms of action than just NMDA blockade. *Trends Anaesth. Crit. Care* **4**, 76–81 (2014).
2. Bonaventura, J. et al. Pharmacological and behavioral divergence of ketamine enantiomers: implications for abuse liability. *Mol. Psychiatry* **26**, 6704–6722 (2021).
3. Berman, R. M. et al. Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* **47**, 351–354 (2000).
4. McIntyre, R. S. et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am. J. Psychiatry* **178**, 383–399 (2021).
5. Zarate, C. A. et al. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psychiatry* **63**, 856–864 (2006).
6. Marcantoni, W. S. et al. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009–January 2019. *J. Affect. Disord.* **277**, 831–841 (2020).

7. Butler, M., Jelen, L. & Rucker, J. Expectancy in placebo-controlled trials of psychedelics: if so, so what? *Psychopharmacology* **239**, 3047–3055 (2022).
8. Hall, W. D. & Humphreys, K. Is good science leading the way in the therapeutic use of psychedelic drugs? *Psychol. Med.* **52**, 2849–2851 (2022).
9. Aday, J. S. et al. Great expectations: recommendations for improving the methodological rigor of psychedelic clinical trials. *Psychopharmacology* **239**, 1989–2010 (2022).
10. Muthukumaraswamy, S. D., Forsyth, A. & Lumley, T. Blinding and expectancy confounds in psychedelic randomized controlled trials. *Expert Rev. Clin. Pharmacol.* **14**, 1133–1152 (2021).
11. Price, R. B. et al. A novel, brief, fully automated intervention to extend the antidepressant effect of a single ketamine infusion: a randomized clinical trial. *Am. J. Psychiatry* **179**, 959–968 (2022).
12. Horvath, B., Kloesel, B., Todd, M. M., Cole, D. J. & Prielipp, R. C. The evolution, current value, and future of the American Society of Anesthesiologists physical status classification system. *Anesthesiology* **135**, 904–919 (2021).
13. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* **40**, 373–383 (1987).
14. Nagele, P. et al. A phase 2 trial of inhaled nitrous oxide for treatment-resistant major depression. *Sci. Transl. Med.* **13**, eabe1376 (2021).
15. Phillips, J. L. et al. Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. *Am. J. Psychiatry* **176**, 401–409 (2019).
16. Murrough, J. W. et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am. J. Psychiatry* **170**, 1134–1142 (2013).
17. Sos, P. et al. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. *Neuro Endocrinol. Lett.* **34**, 287–293. (2013).
18. Singh, J. B. et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *Am. J. Psychiatry* **173**, 816–826 (2016).
19. Sanacora, G. et al. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry* **74**, 399 (2017).
20. Dore, J. et al. Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J. Psychoactive Drugs* **51**, 189–198 (2019).
21. Joneborg, I. et al. Active mechanisms of ketamine-assisted psychotherapy: a systematic review. *J. Affect. Disord.* **315**, 105–112 (2022).
22. Nagele, P. et al. Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial. *Biol. Psychiatry* **78**, 10–18 (2015).
23. Mickey, B. J. et al. Propofol for treatment-resistant depression: a pilot study. *Int. J. Neuropsychopharmacol.* **21**, 1079–1089 (2018).
24. Weeks, H. R. et al. Antidepressant and neurocognitive effects of isoflurane anesthesia versus electroconvulsive therapy in refractory depression. *PLoS ONE* **8**, e69809 (2013).
25. García-Toro, M. et al. Inefficacy of burst-suppression anesthesia in medication-resistant major depression: a controlled trial. *J. ECT* **17**, 284–288 (2001).
26. Kudoh, A., Takahira, Y., Katagai, H. & Takazawa, T. Small-dose ketamine improves the postoperative state of depressed patients. *Anesth. Analg.* **95**, 114–118 (2002).
27. Mashour, G. A. et al. Intraoperative ketamine for prevention of depressive symptoms after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *Br. J. Anaesth.* **121**, 1075–1083 (2018).
28. Liu, P. et al. Effect of pretreatment of S-ketamine on postoperative depression for breast cancer patients. *J. Invest. Surg.* **34**, 883–888 (2021).
29. Zhou, Y. et al. Ketamine alleviates depressive symptoms in patients undergoing intracranial tumor resection: a randomized controlled trial. *Anesth. Analg.* **133**, 1588–1597 (2021).
30. Guo, J. et al. Efficacy and safety of perioperative application of ketamine on postoperative depression: a meta-analysis of randomized controlled studies. *Mol. Psychiatry* https://doi.org/10.1038/s41380-023-01945-z (2023).
31. Jiang, M. et al. Effect of intraoperative application of ketamine on postoperative depressed mood in patients undergoing elective orthopedic surgery. *J. Anesth.* **30**, 232–237 (2016).
32. Wang, J. et al. Effects of a single subanaesthetic dose of ketamine on pain and mood after laparoscopic bariatric surgery: a randomised double-blind placebo controlled study. *Eur. J. Anaesthesiol.* **36**, 16–24 (2019).
33. Liu, P. et al. Effect of pretreatment of S-ketamine on postoperative depression for breast cancer patients. *J. Invest. Surg.* https://doi.org/10.1080/08941939.2019.1710626 (2020).
34. Zhang, Z. et al. Intraoperative low-dose S-ketamine reduces depressive symptoms in patients with Crohn's disease undergoing bowel resection: a randomized controlled trial. *J. Clin. Med.* **12**, 1152 (2023).
35. Aleksandrova, L. R. & Phillips, A. G. Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. *Trends Pharmacol. Sci.* **42**, 929–942 (2021).
36. Hess, E. M., Riggs, L. M., Michaelides, M. & Gould, T. D. Mechanisms of ketamine and its metabolites as antidepressants. *Biochem. Pharmacol.* **197**, 114892 (2022).
37. Johnston, J. N., Henter, I. D. & Zarate, C. A. The antidepressant actions of ketamine and its enantiomers. *Pharmacol. Ther.* **246**, 108431 (2023).
38. Brown, E. N., Lydic, R. & Schiff, N. D. General anesthesia, sleep, and coma. *N. Engl. J. Med.* **363**, 2638–2650 (2010).
39. Heresco-Levy, U. et al. Controlled trial of D-cycloserine adjuvant therapy for treatment-resistant major depressive disorder. *J. Affect. Disord.* **93**, 239–243 (2006).
40. Zarate, C. A. et al. A double-blind, placebo-controlled study of memantine in the treatment of major depression. *Am. J. Psychiatry* **163**, 153–155 (2006).
41. Wilkinson, S. T. & Sanacora, G. A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems. *Drug Discov. Today* **24**, 606–615 (2019).
42. Sanacora, G. et al. Adjunctive lanicemine (AZD6765) in patients with major depressive disorder and history of inadequate response to antidepressants: a randomized, placebo-controlled study. *Neuropsychopharmacology* **42**, 844–853 (2017).
43. Ibrahim, L. et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology* **37**, 1526–1533 (2012).
44. Mathew, S. J., Gueorguieva, R., Brandt, C., Fava, M. & Sanacora, G. A randomized, double-blind, placebo-controlled, sequential parallel comparison design trial of adjunctive riluzole for treatment-resistant major depressive disorder. *Neuropsychopharmacology* **42**, 2567–2574 (2017).
45. Vesuna, S. et al. Deep posteromedial cortical rhythm in dissociation. *Nature* **586**, 87–94 (2020).
46. Tian, F. et al. Characterizing brain dynamics during ketamine-induced dissociation and subsequent interactions with propofol using human intracranial neurophysiology. *Nat. Commun.* **14**, 1748 (2023).

47. Chen, X., Shu, S. & Bayliss, D. A. HCN1 channel subunits are a molecular substrate for hypnotic actions of ketamine. *J. Neurosci.* **29**, 600–609 (2009).
48. Anand, A. et al. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of *N*-methyl-D-aspartate receptor antagonists. *Arch. Gen. Psychiatry* **57**, 270–276 (2000).
49. Cichon, J. et al. Ketamine triggers a switch in excitatory neuronal activity across neocortex. *Nat. Neurosci.* **26**, 39–52 (2023).
50. Williams, N. R. et al. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. *Am. J. Psychiatry* **175**, 1205–1215 (2018).
51. Hustveit, O., Maurset, A. & Oye, I. Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. *Pharmacol. Toxicol.* **77**, 355–359 (1995).
52. Klein, M. E., Chandra, J., Sheriff, S. & Malinow, R. Opioid system is necessary but not sufficient for antidepressive actions of ketamine in rodents. *Proc. Natl Acad. Sci. USA* **117**, 2656–2662 (2020).
53. Wulf, H. A., Browne, C. A., Zarate, C. A. & Lucki, I. Mediation of the behavioral effects of ketamine and (2*R*,6*R*)-hydroxynorketamine in mice by kappa opioid receptors. *Psychopharmacology* https://doi.org/10.1007/s00213-022-06118-4 (2022).
54. Marton, T., Barnes, D. E., Wallace, A. & Woolley, J. D. Concurrent use of buprenorphine, methadone, or naltrexone does not inhibit ketamine's antidepressant activity. *Biol. Psychiatry* **85**, e75–e76 (2019).
55. Trivedi, M. H. et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am. J. Psychiatry* **163**, 28–40 (2006).
56. Chen, M.-H. et al. Using classification and regression tree modelling to investigate treatment response to a single low-dose ketamine infusion: post hoc pooled analyses of randomized placebo-controlled and open-label trials. *J. Affect. Disord.* **281**, 865–871 (2021).
57. Pennybaker, S. J., Niciu, M. J., Luckenbaugh, D. A. & Zarate, C. A. Symptomatology and predictors of antidepressant efficacy in extended responders to a single ketamine infusion. *J. Affect. Disord.* **208**, 560–566 (2017).
58. Jesus-Nunes, A. P. et al. Clinical predictors of depressive symptom remission and response after racemic ketamine and esketamine infusion in treatment-resistant depression. *Hum. Psychopharmacol. Clin. Exp.* **37**, e2836 (2022).
59. Ustun, Y. B. et al. Comparison of ketamine, dexmedetomidine and lidocaine in multimodal analgesia management following sleeve gastrectomy surgery: a randomized double-blind trial. *J. Perianesth. Nurs.* **37**, 820–826 (2022).
60. Seman, M. T. et al. Low-dose ketamine infusion for perioperative pain management in patients undergoing laparoscopic gastric bypass: a prospective randomized controlled trial. *Anesthesiol. Res. Pract.* **2021**, e5520517 (2021).
61. Moro, E. T. et al. Ketamine does not enhance the quality of recovery following laparoscopic cholecystectomy: a randomized controlled trial. *Acta Anaesthesiol. Scand.* **61**, 740–748 (2017).
62. Ragazzoni, L. et al. Intra-operative low-dose ketamine does not reduce the cost of post-operative pain management after surgery: a randomized controlled trial in a low-income country. *Afr. Health Sci.* **19**, 3127–3135 (2019).
63. Mortero, R. F. et al. The effects of small-dose ketamine on propofol sedation: respiration, postoperative mood, perception, cognition, and pain. *Anesth. Analg.* **92**, 1465 (2001).
64. Aubrun, F. et al. Effect of a low-dose ketamine regimen on pain, mood, cognitive function and memory after major gynaecological surgery: a randomized, double-blind, placebo-controlled trial. *Eur. J. Anaesthesiol.* **25**, 97–105 (2008).
65. Lee, C. et al. The effects of a combination of intravenous dexamethasone and ketamine on postoperative mood in patients undergoing laparoscopically assisted-gynecologic surgery. *Psychopharmacology* **235**, 2417–2422 (2018).
66. Irle, E., Peper, M., Wowra, B. & Kunze, S. Mood changes after surgery for tumors of the cerebral cortex. *Arch. Neurol.* **51**, 164–174 (1994).
67. Jenkins, L. M., Drummond, K. J. & Andrewes, D. G. Emotional and personality changes following brain tumour resection. *J. Clin. Neurosci.* **29**, 128–132 (2016).
68. McGirr, A. et al. Adjunctive ketamine in electroconvulsive therapy: updated systematic review and meta-analysis. *Br. J. Psychiatry* **210**, 403–407 (2017).
69. Anderson, I. M. et al. Ketamine augmentation of electroconvulsive therapy to improve neuropsychological and clinical outcomes in depression (Ketamine–ECT): a multicentre, double-blind, randomised, parallel-group, superiority trial. *Lancet Psychiatry* **4**, 365–377 (2017).
70. Vlisides, P. E. et al. Neurophysiologic correlates of ketamine sedation and anesthesia: a high-density electroencephalography study in healthy volunteers. *Anesthesiology* **127**, 58–69 (2017).
71. Rutherford, B. R., Wall, M. M., Glass, A. & Stewart, J. W. The role of patient expectancy in placebo and nocebo effects in antidepressant trials. *J. Clin. Psychiatry* **75**, 1040–1046 (2014).
72. Kroenke, K. et al. The PHQ-8 as a measure of current depression in the general population. *J. Affect. Disord.* **114**, 163–173 (2009).
73. Fekadu, A., Donocik, J. G. & Cleare, A. J. Standardisation framework for the Maudsley staging method for treatment resistance in depression. *BMC Psychiatry* **18**, 100 (2018).
74. Sheehan, D. V. et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* **59**, 22–33 (1998). quiz 34-57.
75. Montgomery, S. A. & Åsberg, M. A new depression scale designed to be sensitive to change. *Br. J. Psychiatry* **134**, 382–389 (1979).
76. Zigmond, A. S. & Snaith, R. P. The Hospital Anxiety and Depression Scale. *Acta Psychiatr. Scand.* **67**, 361–370 (1983).
77. Pinto-Meza, A., Serrano-Blanco, A., Peñarrubia, M. T., Blanco, E. & Haro, J. M. Assessing depression in primary care with the PHQ-9: can it be carried out over the telephone? *J. Gen. Inter. Med.* **20**, 738–742 (2005).
78. Hedman, E. et al. Telephone versus internet administration of self-report measures of social anxiety, depressive symptoms, and insomnia: psychometric evaluation of a method to reduce the impact of missing data. *J. Med. Internet Res.* **15**, e229 (2013).
79. Hermens, M. L. et al. Administering the MADRS by telephone or face-to-face: a validity study. *Ann. Gen. Psychiatry* **5**, 3 (2006).
80. Kobak, K. A., Williams, J. B. W., Jeglic, E., Salvucci, D. & Sharp, I. R. Face-to-face versus remote administration of the Montgomery–Asberg Depression Rating Scale using videoconference and telephone. *Depress. Anxiety* **25**, 913–919 (2008).
81. Posner, K. et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am. J. Psychiatry* **168**, 1266–1277 (2011).
82. Kishimoto, T. et al. Single-dose infusion ketamine and non-ketamine *N*-methyl-D-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychol. Med.* **46**, 1459–1472 (2016).
83. Nierenberg, A. A. & DeCecco, L. M. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. *J. Clin. Psychiatry* **62**, 5–9 (2001).
84. Machado, M., Iskedjian, M., Ruiz, I. & Einarson, T. R. Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials. *Curr. Med. Res. Opin.* **22**, 1825–1837 (2006).

85. Keller, S. et al. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin. J. Pain* **20**, 309 (2004).
86. Mendoza, T. R. et al. The utility and validity of the modified brief pain inventory in a multiple-dose postoperative analgesic trial. *Clin. J. Pain* **20**, 357 (2004).
87. *Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors* (US Department of Health and Human Services; 2021); https://www.hhs.gov/guidance/document/opioid-oral-morphine-milligram-equivalent-mme-conversion-factors-0
88. Hengartner, M. P. & Plöderl, M. Estimates of the minimal important difference to evaluate the clinical significance of antidepressants in the acute treatment of moderate-to-severe depression. *BMJ Evid. Based Med.* **27**, 69–73 (2022).

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Author contributions

T.R.L. and B.D.H. designed the trial. T.R.L. analyzed the data and wrote the first draft of the paper. A.E.S., J.R.F., R.L.O., C.A.N. and L.J.C. performed the trial and collected the data. L.M.H. and A.F.S. provided content expertise and advice on trial design. The overall trial was overseen by B.D.H. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Competing interests

B.D.H. is on the scientific advisory boards of Osmind and Journey Clinical and is a consultant to Clairvoyant Therapeutics and Vine Ventures. A.F.S. has served as a consultant to Alto Neuroscience, ANeurotech, Compass, Magnus, NeuraWell, Parexal, Sage and Signant. He holds equity in Alto Neuroscience, Corcept, Delpor, Madrigal, Magnus, Seattle Genetics, Titan and Xhale. These interests had no role in the present trial. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s44220-023-00140-x.

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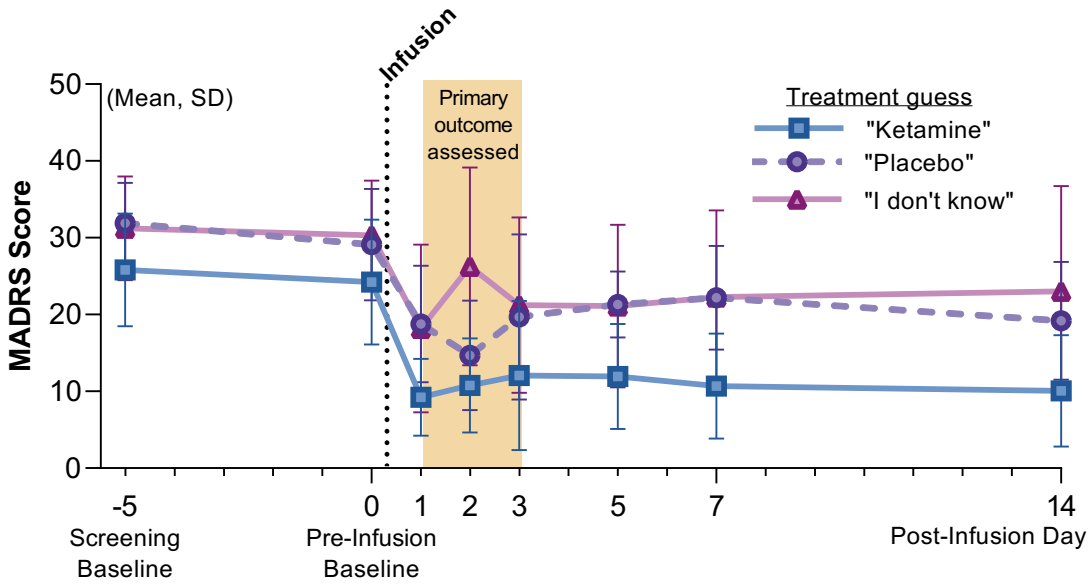

Extended Data Fig. 1 | Depression ratings reanalyzed according to patient guess. On day 14, the final day of patient assessments, patients were asked the following questions: "What treatment do you think you received?" MADRS scores were reanalyzed according to their guess, irrespective of their true group allocation. Mean and standard deviation (SD) MADRS scores are shown using the alternate grouping: "Ketamine", n = 17; "Placebo", n = 10; "I don't know", n = 11.

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Extended Data Table 1 | Depression Outcomes

Measure	Ketamine			Placebo		
	Mean	SD	N with data	Mean	SD	N with data
MADRS total score						
Day 0 (pre-infusion)	25.1	8.3	20	29.9	7.0	19
Day 1	12.7	7.6	20	16.4	10.0	19
Day 2	15.1	11.1	19	17.5	11.5	20
Day 3	17.0	10.5	19	17.2	12.0	20
Day 5	16.9	8.0	19	16.9	10.1	18
Day 7	15.9	9.2	18	18.5	10.8	19
Day 14	16.9	10.0	19	16.2	12.5	19
HADS total score						
Day 0 (pre-infusion)	22.9	4.2	20	24.6	5.6	19
Day 1	17.8	6.6	20	19.9	5.5	19
Day 2	18.8	7.5	18	21.2	5.9	20
Day 3	19.3	6.3	19	20.8	5.4	20
Day 5	18.3	4.8	19	18.9	7.3	19
Day 7	18.4	5.3	16	19.6	8.1	19
Day 14	16.4	7.2	19	17.2	8.5	19
	n/N in trial	%		n/N in trial	%	
Clinical response on MADRS						
Day 0 (pre-infusion)	0/20	0.0		0/20	0.0	
Day 1	12/20	60.0		10/20	50.0	
Day 2	10/20	50.0		12/20	60.0	
Day 3	9/20	45.0		10/20	50.0	
Day 5	7/19	36.8		8/19	42.1	
Day 7	6/19	31.6		7/19	36.8	
Day 14	8/19	42.1		11/19	57.9	
Remission on MADRS						
Day 0 (pre-infusion)	1/20	5.0		0/20	0.0	
Day 1	10/20	50.0		7/20	35.0	
Day 2	11/20	55.0		8/20	40.0	
Day 3	8/20	40.0		8/20	40.0	
Day 5	7/19	36.8		6/19	31.6	
Day 7	6/19	31.6		11/19	57.9	
Day 14	8/19	42.1		9/19	47.4	

SD, standard deviation. MADRS, Montgomery–Åsberg Depression Rating Scale. HADS, Hospital Anxiety and Depression Scale. Clinical response is defined as ≥50% reduction in MADRS scores from screening baseline. Remission is defined as MADRS score ≤12.

https://doi.org/10.1038/s44220-023-00140-x

Extended Data Table 2 | Average Daily Inpatient Opioid Use

Measure	Ketamine			Placebo		
	Mean	SD	Inpatient n*	Mean	SD	Inpatient n*
Average Daily Inpatient Opioid Use, in MME						
Day 1	81.6	59.6	14	69.2	62.2	16
Day 2	83.3	65.2	8	77.6	71.3	13
Day 3	87.5	101	6	59.7	84.0	12
Day 5	195	n/a	1	36.7	41.4	8
Day 7	n/a	n/a	0	0	n/a	1
Day 14	n/a	n/a	0	n/a	n/a	0

SD, standard deviation. MME, morphine milligram equivalents. *Includes only patients who remained hospitalized for the entire day.

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Software and code

Policy information about availability of computer code

Data collection	Screening and outcomes data were entered into Stanford REDCap (version 13.4.10), a secure online data capture platform (http://redcap.stanford.edu) developed and operated by Stanford Medicine Research IT team.
Data analysis	RStudio (version 2022.07.1 for MacOS) was used for data analysis. Prism GraphPad (version 9.5.0 for MacOS) was used for figure-making. R code used for data analysis is publicly available at https://osf.io/zdkr8/ (DOI 10.17605/OSF.IO/ZDKR8).

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Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Information about birth sex, but not gender, was collected for demographic characterization of our sample. We obtained data on participant birth sex from electronic health records, which rely on patient self report. This data is summarized as a number and percentage for each study arm in the demographics table.
Population characteristics	The mean age of trial participants was 51 years; they were mostly female (70%), white (65%), non-Hispanic (87.5%), employed (62.5%), and never smoked (65%). At screening, both groups had moderate levels of depression (ketamine: mean Montgomery-Asberg Depression Rating Scale score = 27.7, placebo: 30.6) and moderate levels of treatment resistance (ketamine: mean Maudsley Staging Method score = 8.3, placebo: 7.5).
Recruitment	Adults undergoing elective non-cardiac, non-intracranial surgery were recruited from preoperative clinics at Stanford University Medical Center. The 8-item Patient Health Questionnaire (PHQ-8) was distributed to patients through a perioperative mental health screening service. To be eligible for the study, patients must score ≥ 10 on the PHQ-8, corresponding with at least moderate depression. Research staff screened electronic health records (EHR) of patients scheduled for surgery who scored ≥ 10 points on the PHQ-8; those without exclusion criteria documented in the EHR were introduced to the study and consented for an additional screening visit. Surgical clinics also referred patients with symptomatic depression who expressed interest in the trial. These patients were contacted by research staff for a telephone pre-screen, and qualifying patients were consented for an additional screening visit. At this visit, research staff collected information on demographics, medical, and psychiatric history, including level of antidepressant treatment resistance assessed by the Maudsley Staging Method (MSM). Inclusion and exclusion criteria were assessed via a hybrid approach of corroborating EHR data with patient self-report. Self-selection bias may have favored patients with less severe depression, as these patients are more likely to engage with research staff and complete all screening procedures. However, our eligibility criteria set minimum depression severity scores to reduce the impact of this type of bias.
Ethics oversight	This was an investigator-initiated, university-sponsored trial. The trial protocol was approved by the institutional review board at Stanford University and all participants gave written informed consent.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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Life sciences study design

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Sample size	Our sample size estimation was derived from an a priori power analysis for the primary outcome. In a randomized controlled trial of ketamine versus active placebo performed by Phillips et al., participants had a mean decrease of 10.9 points (standard deviation [SD] 8.9) in MADRS total score relative to pre-infusion scores compared with a mean decrease of 2.8 points (SD 3.6) with midazolam29. For reference, the minimum clinically important difference on the MADRS is estimated to range from 3 to 9 points30. Using these results, we computed an estimated total sample size of 38 participants at a two-sided alpha level of 0.05 and 80% power to detect this difference if using parametric testing. An additional 2 participants were added to account for potential attrition, for a total of 40 participants. Interim analyses were not performed.
Data exclusions	No data was excluded for primary and secondary and exploratory analyses.
Replication	At every screening and follow-up time point, all outcomes were independently measured once. No replication experiments were conducted.

Randomization	Twenty participants were randomly allocated to a single dose of intravenous ketamine (0.5 mg/kg diluted into 40 ml of normal saline, infused over 40 minutes using a programmable pump). Another twenty participants were randomly allocated to 40 ml of normal saline infused similarly over 40 minutes. Pharmacy staff randomized participants using computerized block randomization with 5 blocks of 8.
Blinding	The participant, investigators, and direct care providers (e.g., anesthesiologists) were masked to treatment assignment. Prior to participant unmasking at the end of the follow up period, a masking assessment of participants was performed.

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Clinical trial registration	NCT03861988
Study protocol	The full trial protocol will be submitted along with the manuscript and SAP.
Data collection	Data was collected by 1) review of electronic health records, 2) in-person interviews on Stanford University campus and Stanford Hospital, 3) telephone and video-based interviews. Participant recruitment occurred between February 2020 and August 2022. Data collection occurred between February 2020 and September 2022.
Outcomes	The primary outcome was the MADRS score measured 1, 2, and 3 days post-infusion, as previous studies have found the greatest antidepressant effect occurs within the first 72 hours of a single ketamine infusion. The MADRS is a clinical rating scale used widely in antidepressant trials; it consists of 10 items which measure the severity of depression in individuals, with a total score ranging from 0 to 60, and higher scores indicating more severe depression15. Trained clinical research personnel administered the MADRS. The secondary outcome was clinical response, defined as ≥50% reduction in MADRS scores from screening baseline. Remission, defined as MADRS score ≤12 in our study, was treated as an exploratory outcome.