Norwegian Medical Products Agency

Health Technology Assessment

Intravenous ketamine for treatment-resistant depression

ID2022_018

13/06/2025

Publisher	Norwegian Medical Products Agency (Direktoratet for medisinske produkter) Division for Health Economics and Analysis
Norwegian title	Intravenøs ketamin ved behandlingsresistent depresjon: en fullstendig metodevurdering
English title	Intravenous ketamine for treatment-resistant depression: a health technology assessment
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Type of report	Health technology assessment
No. of pages	118 (170 with appendix)
Commissioner	The Ordering Forum in the national system for managed introduction of health technologies within the specialist health care service
Keywords (MesH)	Depressive Disorder, Treatment-Resistant; Ketamine; Administration, Intravenous; Technology Assessment, Biomedical; Costs and Cost Analysis
Citation	Ohm IK, Flatby AV, Stoinska-Schneider A, Hafstad E. Intravenous ketamine for treatment-resistant depression: a health technology assessment [Intravenøs ketamin ved behandlingsresistent depresjon: en fullstendig metodevurdering.]. Oslo: Norwegian Medical Products Agency, 2024.

Table of contents

Key messages

Treatment-resistant depression affects approximately 30% of patients with major depressive disorder (MDD) and is associated with high morbidity, poor treatment outcomes, and increased mortality. Subanaesthetic doses of ketamine has emerged as a potential treatment option for treatment-resistant depression. Ketamine is currently only used off-label for treatment-resistant depression in limited settings in Norway.

This health technology assessment included 19 randomised controlled trials (RCTs) and 2 non-RCTs that compared the effect of single or multiple infusions of ketamine and esketamine with saline, midazolam, electroconvulsive therapy (ECT), esketamine, or low dose ketamine (<0.5 mg/kg). The main efficacy outcome was response, with additional outcomes of remission, relapse and depression severity scores. Safety outcome was (serious) adverse events. The main results are presented below with an assessment of our confidence in the results (GRADE).

- **Ketamine vs. ECT**: Multiple ketamine infusions probably improve response rates more than ECT (*moderate certainty evidence*).
- **Ketamine vs. saline**: Single ketamine infusions probably improve response rates more than saline (*moderate certainty evidence*).
- **Ketamine vs. midazolam**: Single ketamine infusions may/probably improve response rates more than midazolam (*low/moderate certainty evidence*).
- **Ketamine vs. esketamine**: There may be little or no difference in response rates between single infusions of ketamine and esketamine (*low certainty evidence*).
- **Ketamine ≥0.5 mg/kg vs. <0.5 mg/kg**: A single high dose ketamine infusion may improve response rates (slightly) more than low dose ketamine (*low certainty evidence*).

Results for multiple infusions and long-term efficacy (i.e., past three months after treatment) were generally inconclusive due to very low certainty. Common side effects included headache, nausea, and anxiety, which were generally mild.

We considered ECT to be the most suitable comparator for the health economic evaluation in the Norwegian setting and performed a cost-comparison analysis. The cost of a ketamine treatment series was estimated at NOK 18,000, compared to NOK 28,000–42,000 for ECT.

Title:
Intravenous ketamine for treatment-resistant depression: a health technology assessment

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Publisher:
Norwegian Medical Products Agency conducted the HTA based on commission from the Ordering Forum

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What is not answered in this report?
We do not address ethical or legal aspects related to intravenous ketamine infusions for treatment-resistant depression. We conducted a cost-comparison analysis, and absolute shortfall and disease severity were not assessed.

When was the literature search conducted?
August 2024

Executive summary

Introduction

Treatment-resistant depression affects approximately 30% of patients with major depressive disorder (MDD) and is often defined as insufficient response to at least two adequate antidepressant treatments. Treatment-resistant depression is associated with high morbidity, poor treatment outcomes, and increased mortality, underscoring the need for novel therapeutic strategies. Ketamine, which is traditionally used as an anaesthetic, has emerged as a potential treatment for treatment-resistant depression due to its rapid antidepressant effects at subanaesthetic doses. Despite its promise, ketamine remains controversial due to dissociative side effects and abuse potential. In Norway, ketamine is used off-label for treatment-resistant depression and has been limited to Østfold Hospital and private clinics. Esketamine, the s-enantiomer of ketamine, has received marketing authorisation from the European Medicines Agency for treatment-resistant depression, but currently lacks public financing approval in Norwegian specialist health care.

Objective

The HTA was commissioned to address the growing interest in ketamine as a potential therapy for treatment-resistant depression in Norwegian specialist healthcare. The goal was to systematically assess the efficacy and safety of intravenous ketamine and esketamine for treatment-resistant depression and conduct a health economic evaluation of ketamine compared to relevant treatment alternative to determine its cost-effectiveness in the Norwegian healthcare context.

Effectiveness and safety

Methods

We identified relevant publications of randomised controlled trials (RCTs) and cohort studies through a systematic search across major databases and trials registries. Our selection criteria included adults aged ≥18 years with moderate to severe treatment-resistant depression (e.g., MADRS ≥20), treated with intravenous ketamine (0.5–1 mg/kg) and esketamine. Relevant comparators included saline, midazolam, lower doses ketamine (<0.5 mg/kg), and electroconvulsive therapy (ECT). Outcomes focused on efficacy (e.g., response rates, remission, relapse, quality of life) and safety (e.g., adverse events). Risk of bias was assessed using the Cochrane Risk of Bias tool for randomized controlled studies (RoB2), and data were synthesised via meta-analyses. Certainty of evidence was evaluated using the GRADE framework.

Results

This HTA included 23 publications from 21 unique clinical trials, comprising 19 RCTs and 2 non-RCTs. The studies investigated ketamine (0.5–1 mg/kg) and esketamine for treatment-resistant depression across single and multiple infusion-protocols. A total of 1,761 participants were included, with ~50% women and a mean age between 25–66 years. None of the included studies had been conducted in Norway.

Efficacy

Of 19 included RCTs, 17 were included in the data analysis. Response was the primary outcome, and results for all comparisons and timepoints are shown in the table below.

Ketamine vs. ECT: Multiple ketamine infusions probably improve response rates, remission rates, and depression severity scores at end of treatment (three weeks) more than ECT, with

moderate certainty evidence. Long-term outcomes (e.g., relapse rates at six months) remain more uncertain.

Ketamine vs. saline: Single ketamine infusions probably improve response rates and reduce depression severity scores at one day to two months post-infusion, more than saline, with moderate certainty evidence. Multiple ketamine infusions also seem to improve response and remission rates, and depression severity scores at the end of treatment, but the evidence are more uncertain, varying from moderate to very low.

Ketamine vs. midazolam: Single ketamine infusions probably improve response and remission rates, and depression severity scores at one and seven days post-infusion more than midazolam, with moderate-certainty evidence. Results for multiple ketamine infusions are inconclusive due to very low certainty.

Ketamine vs. esketamine: There may be little or no difference in efficacy between ketamine and esketamine for response, remission, and depression severity scores, but the certainty of this evidence is low.

Ketamine ≥0.5 mg/kg vs. ketamine <0.5 mg/kg: Higher doses of ketamine may improve response and remission rates at one day post-infusion, and probably remission rate at seven days post-infusion, slightly more than lower doses of ketamine. The evidence for other outcomes is inconsistent. Our confidence in all these results range from moderate to very low.

Safety

Adverse events were common but generally mild, with headache, nausea, and anxiety being most frequently reported. Serious adverse events, including urinary problems and suicidal ideation, were rare but slightly higher in ketamine-treated groups compared to comparators. Safety outcomes suggest ketamine is mostly well tolerated but requires careful monitoring.

Intervention	Comparator	Time-point	% patients with response		RR (95% CI)	Result
			Ketamine	Comparator		
Multiple doses – RCT						
Ketamine 0.5 mg/kg	ECT	EoT	50%	34%	**1.44** (1.13; 1.82)	Ketamine probably improve the chance of response more than ECT at EoT (*moderate certainty evidence*)
Ketamine 0.5 mg/kg	Saline	EoT	35%	12%	**2.86** (0.85; 9.56)	It is uncertain whether ketamine improve the chance of response more than saline at EoT, because the certainty of this evidence is very low.
Ketamine 0.5 mg/kg	Midazolam	EoT	65%	47%	**1.26** (0.82; 1.91)	It is uncertain whether ketamine improve the chance of response more than midazolam at EoT because the certainty of this evidence is very low.
		1 month after EoT	36%	22%	**1.64** (0.36; 6.98)	It is uncertain whether ketamine improve the chance of response more than midazolam at 1 month after EoT because the certainty of this evidence is very low.
		3 months after EoT	54%	33%	**1.62** (0.63; 4.16)	It is uncertain whether ketamine improve the chance of response more than midazolam at 3 months after EoT because the certainty of this evidence is very low.
Single dose – RCTs						
Ketamine 0.5 mg/kg	Saline	1 day PI	42%	12%	**3.02** (1.31; 7.00)	Ketamine probably improve the chance of response more than saline at 1 day post-infusion (*moderate certainty evidence*)
Ketamine 0.5 mg/kg	Midazolam	1 day PI	60%	20%	**2.86** (1.31; 6.24)	Ketamine probably improve the chance of response more than midazolam at 1 day

Intervention	Comparator	Time-point	% patients with response		RR (95% CI)	Result
			Ketamine	Comparator		
						post-infusion (*moderate certainty evidence*)
		3 day PI	48%	14%	**2.96** (1.30; 6.75)	Ketamine may improve the chance of response more than midazolam at 3 days post-infusion (*low certainty evidence*)
		7 day PI	49%	24%	**2.19** (1.20; 4.00)	Ketamine probably improves the chance of response more than midazolam at 7 days post-infusion (*moderate certainty evidence*)
Ketamine 0.5 mg/kg	Esketamine 0.25 mg/kg	1 day PI	52%	50%	**1.03** (0.64; 1.68)	Ketamine may have little or no effect on response compared to esketamine at 1 day post-infusion (l*ow certainty evidence*)
		3 day PI	55%	44%	**1.25** (0.76; 2.06)	Ketamine may improve the chance of response slightly more than esketamine at 3 days post-infusion (low certainty evidence)
		7 day PI	62%	41%	**1.51** (0.92; 2.47)	Ketamine may improve the chance of response slightly more than esketamine at 7 days post-infusion (*low certainty evidence*)
Ketamine ≥0.5 mg/kg	Ketamine <0.5 mg/kg	1 day PI	53%	29%	**1.74** (1.00; 3.03)	Ketamine ≥0.5 mg/kg may improve the chance of response more than ketamine <0.5 mg/kg at 1 day post-infusion (*low certainty evidence*)
		3 day PI (HDRS)	48%	42%	**1.13** (0.96; 1.85)	It is uncertain whether ketamine ≥0.5 mg/kg improves the chance of response (HDRS or MADRS) more than ketamine <0.5 mg/kg at 3 day post-infusion because the certainty of this evidence is very low.
		3 day PI (MADRS)			**1.57** (0.77; 3.21)	
		7 day PI	52%	33%	**3.27** (0.91; 11.71)	Ketamine 0.5 mg/kg may improve the chance of response slightly more than ketamine <0.5 mg/kg at 7 days post-infusion (l*ow certainty evidence*)
Non-RCT						
Ketamine ≥0.5 mg/kg	No comparator	Post-induction	18%	-	-	-
Ketamine ≥0.5 mg/kg	No comparator	26 weeks	28%	-	-	-

Percent patients with response are calculated from total number of events of all studies included in the data analysis.
CI: confidence interval; EoT: end of treatment; PI: post-infusion; RCT: randomised controlled, trial; RR: risk ratio

Health economics

Methods

To evaluate the economic aspects of treatment with intravenous ketamine in Norwegian, we performed a cost-comparison analysis. We compared ketamine with ECT, which we regarded as the most relevant comparator in practice, and calculated average costs for single treatment sessions, as well as treatment-series.

Results

Personnel costs are the main component for both compared treatment alternatives. The average costs of a single intravenous ketamine treatment session were about NOK 3 000, while the cost associated with a ECT treatment was about NOK 4 700. The cost of a treatment series consisting of 6 infusion sessions with ketamine over the course of 3 weeks was equal to about NOK 18 000. Corresponding costs related to ECT were about NOK

28 000 with twice-weekly regimen, and approximately NOK 42 000 when treatment was given three times per week.

User perspectives

Patients with treatment-resistant depression face significant challenges, including social isolation, reduced quality of life, and limited treatment options, with current methods often failing to deliver desired results. Ketamine therapy has shown promise, though it requires preparation, follow-up, and a structured treatment plan tailored to individual needs. While not a universal solution, ketamine's potential inclusion in Norway's specialist healthcare system could reduce financial barriers and substantially improve outcomes for both patients and their families.

Discussion

This HTA evaluated the clinical efficacy, safety, and economic consequences of intravenous ketamine for treatment-resistant depression. Evidence from 17 RCTs and 2 non-RCTs suggests that ketamine may offer benefits in terms of response, remission, and depression severity scores compared to saline, midazolam, and ECT during the intensive treatment phase, though long-term effects remain uncertain. While ketamine appears to be well tolerated, adverse events such as headache, nausea, and urinary issues were reported, albeit with varying prevalence across studies. This highlights the need for careful patient monitoring and follow-up. Additionally, the dissociative effects of ketamine, which potentially contribute to its antidepressant efficacy, may be unsettling for some patients and require transparent communication between patient and health care providers during treatment planning.

The strengths of this HTA include its systematic approach, adherence to published protocols, and comprehensive evaluation of available evidence. However, several limitations were identified. Most included studies had small sample sizes, and coupled with methodological variability and short follow-up periods, this reduced our confidence in the evidence. The lack of studies conducted in Norway also limit the applicability of findings to Norwegian clinical settings. Moreover, differences in study populations, treatment protocols, and definitions of TRD introduced heterogeneity, which may have influenced the results.

From a health systems perspective, ketamine may offer an efficient alternative to ECT due to somewhat lower resource requirements. However, successful implementation in Norwegian specialist healthcare would require clinician training, standardised protocols, and equitable access to avoid socioeconomic disparities. Policymakers should also address concerns around ketamine’s potential for misuse and abuse, ensuring structured administration and monitoring to minimise risks outside clinical settings.

Given the lack of robust long-term data and variability in treatment protocols, further research is needed, including larger RCTs with extended follow-up periods and clinically relevant treatment setups. Real-world data collection will also be essential to inform policy decisions and optimise outcomes.

We chose the simplified cost analysis as health economic evaluation due to uncertainty of clinical effect beyond the acute phase of treatment. In addition, ketamine offered improved response rates and lower resource use compared to ECT in the intensive treatment phase.

Conclusion

Intravenous ketamine infusions are generally well tolerated, and improve overall response rates, remission rates, and depression severity scores, more than saline, midazolam and ECT shortly after the intensive treatment phase of patients with treatment-resistant depression. Long-term efficacy (i.e., past three months after treatment) is unclear due to low

certainty evidence. Intravenous ketamine is probably comparable or less costly than ECT provided sufficient capacity in terms of personnel.

Hovedbudskap

Behandlingsresistent depresjon rammer omtrent 30 % av pasientene med alvorlig depressiv lidelse og er assosiert med høy sykelighet, dårlige behandlingsresultater og økt dødelighet. Subanestetiske doser av ketamin har vist seg som et potensielt behandlingsalternativ for behandlingsresistent depresjon. I Norge brukes ketamin utenfor indikasjonsgodkjennelse (off-label) for behandlingsresistent depresjon, i begrensede settinger.

Denne metodevurderingen inkluderte 19 RCT-er og 2 ikke-randomiserte studier (ikke-RCT-er) som sammenliknet effekten av enkel eller flerdose ketamin og esketamin med saltvann, midazolam, elektrosjokkbehandling (ECT), esketamin, eller lavdose ketamin (<0,5 mg/kg). Hovedutfallsmålet var respons, i tillegg til andre utfallsmål som remisjon, tilbakefall og depresjonsalvorlighetsscore. Utfallsmål for sikkerhet var (alvorlige) uønskede hendelser. Hovedresultatene er presentert under med vurdering av vår tiltro til resultatene (GRADE).

- **Ketamin vs. ECT**: Flerdose ketamin forbedrer sannsynligvis responsrate mer enn ECT (*moderat tiltro*)
- **Ketamin vs. saltvann**: Enkeltdose ketamin forbedre sannsynligvis responsrate mer enn saltvann (*moderat tiltro*)
- **Ketamin vs. midazolam**: Enkeltdose ketamin forbedrer kanskje/sannsynligvis responsrate mer enn midazolam (*lav/moderat tiltro*)
- **Ketamin vs. esketamin**: Det kan væreliten til ingen forskjell i responsrate mellom ketamin og esketamin (*lav tiltro*)
- **Ketamin ≥0,5 mg/kg vs <0,5 mg/kg**: Enkelinfusjon med høydose ketamin kan forbedre responsrate (litt) mer enn lavdose ketamin (*lav tiltro*)

Resultater for flerdose ketamin og langtidseffekt (dvs., utover tre måneder etter behandling) var generelt sett for usikre til å trekke slutninger. Vanlige uønskede hendelser var generelt sett milde, og inkluderte bl.a. hodepine, kvalme og angst.

Vi anså ECT som den mest relevante komparatoren for helseøkonomisk evaluering i norsk setting og utførte en kostnadskonsekvensanalyse. Kostnaden for en behandlingsserie med ketamin var estimert å være NOK 18 000, sammenliknet med NOK 28 000-42 000 for ECT behandling.

Tittel:
Intravenøs ketamin ved behandlingsresistent depresjon: en fullstendig metodevurdering

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Hvem står bak denne publikasjonen?
Direktoratet for medisinske produkter, på oppdrag fra Bestillerforum for nye metoder

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Hva svarer rapporten ikke på?
Vi har ikke sett på etiske eller juridiske aspekter knyttet til intravenøs infusjon av ketamin ved behandlingsresistent depresjon. Vi utførte kostnadskonsekvensanalyse, og absolutt prognosetap og alvorlighetsgrad ble ikke kvantifisert.

Når ble litteratursøket avsluttet?
August 2024

Sammendrag

Innledning

Behandlingsresistent depresjon rammer omtrent 30 % av pasientene med alvorlig depressiv lidelse og defineres ofte som utilstrekkelig respons på minst to adekvate antidepressiva behandlinger. Behandlingsresistent depresjon er assosiert med høy sykelighet, dårlige behandlingsresultater og økt dødelighet, noe som understreker behovet for nye terapeutiske strategier. Ketamin, som tradisjonelt brukes som et anestesimiddel, har vist seg som en potensiell behandling for behandlingsresistent depresjon på grunn av rask antidepressiv effekt i subanestetiske doser. Ketamin er likevel et kontroversielt legemiddel på grunn av dissosiativ effekt og risiko for misbruk. I Norge brukes ketamin utenfor indikasjonsgodkjennelse (*off-label*) for behandlingsresistent depresjon, og terapi har stort sett vært begrenset til Østfold og privatklinikker. Esketamin, s-enantiomeren av ketamin har fått markedsføringstillatelse for behandlingsresistent depresjon, men mangler per i dag offentlig finansieringsgodkjenning i norsk spesialisthelsetjeneste.

Hensikt

Denne metodevurderingen ble bestilt for å adressere den økende interessen for ketamin som en potensiell terapi for behandlingsresistent depresjon i norsk spesialisthelsetjeneste. Målet var å systematisk vurdere effekten og sikkerheten til intravenøst ketamin og esketamin for behandlingsresistent depresjon, samt gjennomføre en helseøkonomisk evaluering for å fastslå kostnadseffektiviteten i en norsk helsekontekst.

Klinisk effekt og sikkerhet

Metode

Vi identifiserte relevante publikasjoner av randomiserte kontrollerte studier (RCT-er) og kohortstudier gjennom et systematisk søk i flere databaser og studieregistre. Våre seleksjonskriterier inkluderte voksne ≥18 år med moderat til alvorlig behandlingsresistent depresjon (f.eks. MADRS ≥20), behandlet med intravenøst ketamin (0,5–1 mg/kg) og esketamin. Relevante komparatorer inkluderte saltvann, midazolam, lavere doser ketamin (<0,5 mg/kg) og elektrokonvulsiv terapi (ECT). Utfallene var effekt (f.eks. responsrater, remisjon, tilbakefall, livskvalitet) og sikkerhet (f.eks. bivirkninger). Risiko for systematisk skjevheter ble vurdert ved hjelp av Cochrane Risk of Bias-verktøyet for randomiserte kontrollerte studier (RoB2), og data ble sammenstilt gjennom metaanalyser. Tiltro til dataene ble vurdert ved hjelp av GRADE-rammeverket.

Resultater

Denne metodevurderingen inkluderte 23 publikasjoner fra 21 unike kliniske studier, bestående av 19 RCT-er og 2 ikke-randomiserte studier (ikke-RCT-er). Studiene undersøkte ketamin (0,5–1 mg/kg) og esketamin for behandlingsresistent depresjon gjennom både enkelt- og flerinfusjonsprotokoller. Totalt 1 761 deltakere ble inkludert, hvorav ~50 % var kvinner, og gjennomsnittsalderen var mellom 25 og 66 år. Ingen av studiene er utført i Norge.

Effekt

Av 19 inkluderte RCT-er, ble 17 inkludert i dataanalysen. Respons var det primære utfallsmålet, og resultatene for alle sammenlikningene er vist i tabellen under.

Ketamin vs. ECT: Flere ketamin-infusjoner forbedrer sannsynligvis responsrate, remisjonsrate og depresjonsalvorlighet ved behandlingens slutt (tre uker) mer enn ECT. Vi har moderat tiltro til disse dataene. Langtidseffekter (f.eks. tilbakefallsrater etter seks måneder) forblir imidlertid usikre.

Ketamin vs. saltvann: Enkeltinfusjoner med ketamin forbedrer sannsynligvis responsrate depresjonsalvorlighet ved én dag til to måneder etter infusjon, mer enn saltvann. Vi har moderat tiltro til disse dataene. Flere ketamin-infusjoner virker også å gi forbedring i respons- og remisjonsrater og depresjonsalvorlighet ved behandlingens slutt, men evidensen er mer usikker, med moderat til veldig lav tiltro.

Ketamin vs. midazolam: Enkeltinfusjon med ketamin forbedrer sannsynligvis responsrate, remisjonsrate og depresjonsalvorlighet ved én og syv dager etter infusjon, mer enn midazolam. Vi har moderat tiltro til disse dataene. Resultatene for flere ketamin-infusjoner er uklare på grunn av svært lav tiltro til dataene.

Ketamin vs. esketamin: Det virker å være liten eller ingen forskjell i effekt mellom ketamin og esketamin for respons, remisjon og depresjonsalvorlighet, men tiltroen til disse dataene er lav

Ketamin ≥0,5 mg/kg vs. ketamin <0,5 mg/kg: Høyere doser av ketamin forbedrer kanskje responsrate og remisjonsrate ved én dag etter infusjon, og sannsynligvis remisjonsrate ved syv dager etter infusjon, litt mer enn lavere doser ketamin. Dataene for andre utfallsmål er inkonsistente. Vår tiltro til alle resultatene varierer fra moderat til veldig lav.

Sikkerhet
Uønskede hendelser var vanlig, men generelt milde, med hodepine, kvalme og angst som de hyppigst rapporterte. Alvorlige uønskede hendelser, deriblant urinveisproblemer og selvmordstanker, var sjeldne, men noe høyere i ketamin-gruppene sammenlignet med komparatorene. Resultatene for sikkerhet antyder at ketamin stort sett er godt tolerert, men krever nøye overvåkning.

Intervensjon	Komparator	Tid	% pasienter med respons		RR (95% CI)	Resultat
			Ketamin	Komparator		
Flerdose – RCT						
Ketamin 0.5 mg/kg	ECT	EoT	50%	34%	**1.44** (1.13; 1.82)	Ketamin øker sannsynligvis sjansen for respons mer enn ECT ved EoT (*moderat tiltro*)
Ketamin 0.5 mg/kg	Saltvann	EoT	35%	12%	**2.86** (0.85; 9.56)	Det er usikkert om ketamin øker sjansen for respons mer enn saltvann ved EoT, fordi tiltroen til dataene er svært lav.
Ketamin 0.5 mg/kg	Midazolam	EoT	65%	47%	**1.26** (0.82; 1.91)	Det er usikkert om ketamin øker sjansen for respons mer enn midazolam ved EoT fordi tiltroen til dataene er svært lav.
		1 mnd etter EoT	36%	22%	**1.64** (0.36; 6.98)	Det er usikkert om ketamin øker sjansen for respons mer enn midazolam ved 1 måned etter EoT fordi tiltroen til dataene er svært lav.
		3 mnd etter EoT	54%	33%	**1.62** (0.63; 4.16)	Det er usikkert om ketamin øker sjansen for respons mer enn midazolam ved 3 måneder etter EoT fordi tiltroen til dataene er svært lav.
Enkelt dose – RCT						
Ketamin 0.5 mg/kg	Saltvann	1 dag e.i.	42%	12%	**3.02** (1.31; 7.00)	Ketamin øker sannsynligvis sjansen for respons mer enn saltvann 1 dag etter infusjon (*moderat tiltro*)
Ketamin 0.5 mg/kg	Midazolam	1 dag e.i.	60%	20%	**2.86** (1.31; 6.24)	Ketamin øker sannsynligvis sjansen for respons mer enn midazolam 1 dag etter infusjon (*moderat tiltro*)
		3 dag e.i.	48%	14%	**2.96** (1.30; 6.75)	Ketamin kan øker sjansen for respons mer enn midazolam 3 dager etter infusjon (*lav tiltro*)

Intervensjon	Komparator	Tid	% pasienter med respons		RR (95% CI)	Resultat
			Ketamin	Komparator		
		7 dag e.i.	49%	24%	**2.19** (1.20; 4.00)	Ketamin øker sannsynligvis sjansen for respons mer enn midazolam 7 dager etter infusjon. (*moderat tiltro*)
Ketamin 0.5 mg/kg	Esketamin 0.25 mg/kg	1 dag e.i.	52%	50%	**1.03** (0.64; 1.68)	Ketamin kan ha liten eller ingen effekt på respons sammenlignet med esketamin 1 dag etter infusjon (*lav tiltro*)
		3 dag e.i.	55%	44%	**1.25** (0.76; 2.06)	Ketamin kan øke sjansen for respons litt mer enn esketamin 3 dager etter infusjon (*lav tiltro*)
		7 dag e.i.	62%	41%	**1.51** (0.92; 2.47)	Ketamin kan øke sjansen for respons litt mer enn esketamin 7 dager etter infusjon (*lav tiltro*)
Ketamin ≥0.5 mg/kg	Ketamin <0.5 mg/kg	1 dag e.i.	53%	29%	**1.74** (1.00; 3.03)	Ketamin ≥0,5 mg/kg kan øke sjansen for respons mer enn ketamin <0,5 mg/kg 1 dag etter infusjon (*lav tiltro*)
		3 dag e.i. (HDRS)	48%	42%	**1.13** (0.96; 1.85)	Det er usikkert om ketamin ≥0,5 mg/kg øker sjansen for respons (HDRS eller MADRS) mer enn ketamin <0,5 mg/kg 3 dager etter infusjon fordi tiltroen til dataene er svært lavt.
		3 day e.i. (MADRS)			**1.57** (0.77; 3.21)	
		7 dag e.i.	52%	33%	**1.57** (0.77; 3.21)	Ketamin 0,5 mg/kg kan øke sjansen for respons litt mer enn ketamin <0,5 mg/kg 7 dager etter infusjon (*lav tiltro*)
Ikke-RCT						
Ketamin ≥0.5 mg/kg	Ingen komparator	Etter induksjon	18%	-	-	-
Ketamin ≥0.5 mg/kg	Ingen komparator	26 uker	28%	-	-	-

Prosent pasienter med respons er kalkulert fra totalt antall hendelser fra alle studier som er inkludert i dataanalysen.
CI: konfidensintervall; EoT: behandlingsslutt (end of treatment); e.i.: etter infusjon; HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery and Åsberg Depression Rating Scale; RCT: randomisert kontrollert studie (randomised controlled, trial); RR: relative risiko

Helseøkonomi

Metode

For å evaluere de økonomiske aspektene ved behandling med intravenøst ketamin i Norge, utførte vi en kostnadssammenligning. Vi sammenlignet ketamin med ECT, som vi anser som den mest relevante komparatoren i klinisk praksis, og beregnet gjennomsnittskostnader for enkeltbehandlinger samt behandlingsserier.

Resultater

Personalkostnader er hovedkomponenten for begge behandlingsalternativene. Gjennomsnittlige kostnader for en intravenøs ketamin-behandling var omtrent NOK 3 000, mens kostnaden for en ECT-behandling var omtrent NOK 4 700. Kostnaden for en behandlingsserie bestående av seks ketamin-infusjoner over tre uker var omtrent NOK 18 000. Tilsvarende kostnader for ECT var omtrent NOK 28 000 ved to ukentlige behandlinger og cirka NOK 42 000 ved tre ukentlige behandlinger.

Brukerperspektiv

Pasienter med behandlingsresistent depresjon står overfor betydelige utfordringer, inkludert sosial isolasjon, redusert livskvalitet og begrensede behandlingsalternativer, der nåværende metoder ofte ikke gir ønskede resultater. Ketamin-behandling har vist lovende resultater, selv om den krever forberedelse, oppfølging og en strukturert behandlingsplan tilpasset individuelle behov. Selv om det ikke er en universell løsning, kan en potensiell inkludering av

ketamin i Norges spesialisthelsetjeneste redusere økonomiske barrierer og betydelig forbedre situasjonen for både pasienter og deres familier.

Diskusjon

Denne metodevurderingen har vurdert den kliniske effekten, sikkerheten og kostnadseffektiviteten til intravenøst ketamin for behandlingsresistent depresjon. Data fra 17 RCT-er og to ikke-randomiserte studier viser at ketamin kan gi bedret respons, remisjon og depresjonsalvorlighet sammenlignet med saltvann, midazolam og ECT i den intensive behandlingsfasen, selv om langtidseffektene forblir usikre. Ketamin virker å være godt tolerert, men uønskede hendelser som hodepine, kvalme og urinveisproblemer ble rapportert, dog med varierende hyppighet mellom studiene. Dette understreker behovet for nøye overvåkning av pasienter. Videre kan ketamins dissosiative effekt, som potensielt bidrar til den antidepressive effekten, oppleves som urovekkende for noen pasienter og det krever derfor åpen kommunikasjon mellom pasient og helsepersonell under behandlingsplanleggingen.

Denne metodevurderingen har flere styrker, som f.eks. en systematisk tilnærming, overholdelse av publisert protokoll, og en omfattende evaluering av tilgjengelig evidens. Det er imidlertid også flere begrensninger. De fleste inkluderte studiene hadde små studiepopulasjoner, og dette sammen med metodologisk variasjon og korte oppfølgingsperioder, har bidratt til å redusere vår tiltro til dataene. Mangelen på studier utført i Norge begrenser overførbarheten av funnene til norske kliniske forhold. Videre førte forskjeller i studiepopulasjoner, behandlingsprotokoller og definisjoner av behandlingsresistent depresjon til heterogenitet, som kan ha påvirket resultatene.

Fra et helseperspektiv kan ketamin være et godt alternativ til ECT på grunn av noe lavere ressurskrav. En vellykket implementering i norsk spesialisthelsetjeneste vil imidlertid kreve opplæring av klinikere, standardiserte protokoller og rettferdig tilgang for å unngå sosioøkonomiske forskjeller.

Gitt mangelen på robuste langtidsdata og variasjon i behandlingsprotokoller, er det behov for videre forskning, inkludert større RCT-er med lengre oppfølging og klinisk relevante behandlingsoppsett. Innsamling av data fra kliniske miljøer vil også være avgjørende for å informere politiske beslutninger og optimalisere resultater.

Vi valgte den forenklede kostnadsanalysen for helseøkonomisk evaluering på grunn av usikkerhet rundt klinisk effekt utover den akutte fasen av behandlingen. I tillegg ga ketamin forbedrede responsrater og lavere ressursbruk sammenlignet med ECT i den intensive behandlingsfasen.

Konklusjon

Intravenøse ketamin-infusjoner er generelt sett godt tolerert, og forbedrer responsrate, remisjonsrate og depresjonsscore mer enn saltvann, midazolam og ECT i kort tid etter intensiv behandlingsfase, hos pasienter med behandlingsresistent depresjon. Langtidseffekt (dvs., utover tre måneder etter behandling) er uklar på grunn av lav tiltro til resultatene. Intravenøs ketamin er sannsynligvis tilsvarende eller mindre dyr enn ECT, gitt tilstrekkelig kapasitet med hensyn til personell.

Preface

The Division of Health Economics and Analysis at the Norwegian Medical Products Agency (NOMA) was commissioned in March 2024 to perform a health technology assessment of intravenous ketamine for treatment-resistant depression. The health technology assessment was commissioned within the National System for Managed Introduction of New Health Technologies in the Specialist Health Care Service in Norway (Nye metoder). The report will be used as a tool for informed decision-making by the regional health authorities in the Decision Forum in the national system.

The Division of Health Economics and Analysis follows established framework when conducting health technology assessments, described in the methods manual (called «Slik oppsummerer vi forskning»). This entails that we can use standard formulations when we describe methods, results and discuss the findings.

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We thank internal reviewers Jon-Vidar Gaustad, Vida Hamidi and Gunn Eva Næss for providing comments to the report. We thank Professor Declan McLoughlin for sending us additional data that we requested. We also thank Ingmar Claussen, from Østfold Hospital (DPS nordre Østfold/Moss) for providing us with access to the empirical cost data.

Use of artificial intelligence

As part of NOMA's commitment to innovation and efficiency, we utilize artificial intelligence (AI) tools to support specific aspects of our work. In this HTA, we used screening software with AI-powered functions to make screening more efficient and ChatDMP, an AI-powered language model, to assist with drafting summaries, proofreading and enhancing the clarity, consistency, and readability of several sections of the document.

The input provided by ChatDMP was carefully reviewed, validated, and edited by our team to ensure accuracy, relevance, and alignment with the scope and objectives of this HTA. All final decisions and content were determined by the NOMA team.

Declared conflicts of interests

All authors, experts and reviewers have declared interests in a written form. No conflicts of interest have been reported.

NOMA is solely responsible for the content of this report.

Martin Lerner	Ingrid Kristine Ohm
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Glossary and list of abbreviations

Abbreviation	Explanation
CI	Confidence interval
Chemsex	Sexual activity while under the influence of drugs
DS	Depression severity
Drug abuse	Intentional use of drugs or substances in a harmful way or for non-medical purposes, often to achieve a feeling of euphoria or escape. May lead to substance use disorder or addiction.
Drug misuse	Using a medication or substance in a way that is not intended or prescribed
ECT	Electroconvulsive therapy
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HDRS/HAM-D	Hamilton Depression Rating Scale (*Appendix 1*)
ITT	Intention to treat
K-hole	Intense or severe dissociation upon ketamine use, with a feeling of intense detachment of perceptions from the reality
MADRS	Montgomery and Åsberg Depression Rating Scale (*Appendix 1*)
MD	Mean difference
MDD	Major depressive disorder
NOK	Norwegian kroner
PHQ-9	Patient Health Questionnaire-9 (*Appendix 1*)
QIDS-SR	Quick Inventory of Depressive Symptomatology – Self Report scale (*Appendix 1*)
QoL	Quality of life
RR	Relative risk = risk ratio
TRD	Treatment-resistant depression

List of tables

List of figures

1. Introduction

1.1 Major depressive disorder

1.1.1 Symptoms

Major depressive disorder is a mood disorder consisting of at least one major depressive episode with several depressive symptoms, lasting for at least two weeks (1). The disorder is characterised by disturbances in emotions and gives rise to symptoms such as dysphoria (depressed mood), intense sadness, and emotional numbness and distress (2). Other symptoms may include disturbances in ideation or cognition (e.g., loss of interest, reduced or impaired concentration, social distancing or isolation), and somatic function (e.g., sleep disturbances, changes in appetite, fatigue, or loss of energy) (2;3). As depression is a heterogenous disorder with several subtypes, clinical symptoms may vary greatly between patients (2).

According to the International Classification of Diseases and related health problems, 10th edition (ICD-10), which is currently used in Norway, the severity of depression can be categorised as follows (4;5):

- Mild depressive episodes: 4 depressive symptoms
- Moderate depressive episodes: 5-6 depressive symptoms
- Severe depressive episodes: ≥7 depressive symptoms

Depression severity is measured using tools like MADRS (Montgomery-Åsberg Depression Rating Scale), HDRS (Hamilton Depression Rating Scale), and QIDS (Quick Inventory of Depressive Symptomatology) by assessing various symptoms of depression, such as mood, sleep, appetite, and energy levels. These tools consist of structured questionnaires or rating scales, where clinicians or patients score each item, and the total score reflects the severity of depression. A list of these tools with their scoring range and depression category is shown in *Appendix 1*.

1.1.2 Epidemiology

Depression disorders are among the most common mental health disorders worldwide and affect around 50% more women than men (6). In Norway, the 12-month prevalence and lifetime prevalence were shown as 4-7% and 8-18% respectively, which are comparable to that of other countries in Europe and North America (7).

1.1.3 Aetiology

Major depressive disorder was previously thought to be mainly caused by disturbances in neurotransmitters, such as serotonin and dopamine (8). However, the aetiology of depression is now recognised to be a more complex multifactorial disorder, involving biological, genetic, environmental and psychosocial factors, that may influence the neuroregulatory systems of the brain (3;8).

Risk factors for depression include challenging life circumstances or traumatic events, such as illness, unemployment, divorce, or death of loved ones, as well as struggles with drug and/or alcohol addiction (3;8).

1.1.4 Treatment

The goal of treating major depressive disorder is to eliminate depressive symptoms, improve daily functioning and quality of life, all while minimising adverse effects of the treatment, and avoiding relapse (3;9). The treatment for depression should be tailored to the individual patient's needs and preferences (3;9;10). There are several treatment options available, often used in combination with each other, including psychotherapy, pharmacotherapy, and various electrical therapies, including electroconvulsive therapy (ECT) (3;9). Lifestyle interventions, such as physical activity and measures aimed to improve dietary and sleeping habits, are also recommended (3;9).

Psychotherapy, which may include cognitive behavioural therapy and interpersonal therapy, is a first-line option for treating mild and moderate depression (3;9). However, the effect of this therapy alone diminishes with increasing severity of the depressive episode (4;9).

Pharmacological therapy is often considered a first-line option for treating moderate and severe depression (1;9). Although there are several classes of antidepressive drugs, selective serotonin reuptake inhibitors (SSRIs, e.g., citalopram, fluoxetine, and sertraline) are the clear first choice (4;9). SSRIs act by increasing the concentration of serotonin in synaptic gaps in the brain (3). Usually, the antidepressive effect will be evident first after a few weeks of treatment (11). As the risk of suicide often increases in the early period of treatment, it is important to be aware of this risk and to ensure close follow-up of the patient (9;12;13).

ECT is mainly used for treating severe depression when other treatments have failed (9;14). A small electric current is used to produce a generalized cerebral seizure, while the patient is under general anaesthesia (14;15). ECT treatment is typically given 2-3 times a week, and usually consists of 6-12 treatments in total (9;14). Recommendations regarding the use of ECT treatment in Norway, are presented in a national guideline published by the Norwegian Directorate of Health (16). Other treatments for depression include transcranial Direct Current Stimulation (tDCS), repeated Transcranial Magnetic Stimulation (rTMS) and Vagus Nerve Stimulation (VNS) (4). In 2022, tDCS treatment was implemented in Norwegian specialist health care as a treatment option for patients with moderate or severe unipolar depression (17).

Although most people with depression experience remission, relapse is still common (3;4). The recurrence rate increases with time, and has been reported to be up to 40% after two years, up to 60% after five years, and almost 90% after 15 years (3;9).

1.1.5 Treatment-resistant depression

Many people with depression do not respond to the initial treatment and will require other therapies, e.g., other antidepressants, a combination of treatments, etc. (9;18). However, some patients, especially those with severe depression, do not respond to treatment even after trying several different therapies (18;19). Although there is no universal definition of treatment-resistant depression, it is usually defined as a lack of response after treatment with at least two antidepressants given at an adequate dose and for an adequate duration (18;20). Due to the unclear definition, there is a wide range of prevalence estimates for treatment-resistant depression (20-22). Many sources, however, seem to report a prevalence of around 30% of all patients with depression (18;22). As people with treatment-resistant depression tend to have low response to treatment and high rates of (co)morbidity and mortality, there is a need for novel treatment strategies (23).

1.2 Ketamine

Ketamine is a well-known, highly effective anaesthetic drug that has been commercially available since the 1970s (24;25). Due to its rapid onset effect, short half-life and general lack of clinically significant respiratory depression, ketamine has remained as a desirable anaesthetic, especially for emergency surgical procedures (24-26). Additionally, ketamine has also been known to have both analgesic and antidepressive effects, and subanaesthetic doses of ketamine have now (re)emerged as a potential therapy option for treatment-resistant depression (24;27). However, due to the dissociative effects with distortion of sensory perception and thought processes at even low doses, and potential for abuse, ketamine remains as a somewhat controversial treatment option for treatment-resistant depression (26;28).

The anaesthetic effect of ketamine is primarily attributed to it acting as a noncompetitive antagonist blocking N-methyl-D-aspartate (NMDA) receptors (25;26). Though several theories presume a similar mechanism for the antidepressive effect, the full picture is still largely unknown (28).

1.2.1 Ketamine in Norway

Ketamine is only authorised for use in Norway as an anaesthetic for brief diagnostic and/or surgical procedures, and as a supplement to other anaesthetics (29). However, ketamine in subanaesthetic doses is being used off-label as analgesia, especially for treating severe pain, e.g. in palliative care (25;27;30;31). Ketamine as an antidepressive agent for treatment-resistant depression is a fairly new treatment option and has only been offered at one public hospital in Norway, in addition to some private clinics.

In 2020, the S-enantiomer of ketamine: esketamine, was awarded marketing authorisation in Norway for treating adults with treatment-resistant depression, used in combination with other antidepressive drugs (32). However, the drug Spravato has currently not been approved for financing by the Norwegian specialist health care in the Regional Health Authority (RHA) Decision Forum, due to low quality evidence and high costs (33).

1.3 Why is it important to conduct this health technology assessment?

The commission for this HTA was based on a proposal from Østfold Hospital HF, where ketamine treatment for treatment-resistant depression is provided. In the proposal they argue that ketamine is a low-cost drug with significant therapeutic effect and few side effects, and that it is a valuable alternative to ECT (34). According to the Act relating to specialist health care (Spesialisthelsetjenesteloven), the regional health authorities must organize their service in line with priority criteria relating to benefit, resource use and severity (35). All new medicines and indications for use that the Norwegian specialist healthcare service are expected to finance, must first be assessed in an HTA relating to the priority criteria. As such, it is important to assess the efficacy and safety, as well as to perform a health economic evaluation compared to relevant treatment alternatives of treatment with ketamine for this patient group.

1.4 Objectives and research question

The aim of this HTA was to systematically identify, assess and analyse available research regarding efficacy and safety of intravenously administered ketamine and esketamine for treating treatment-resistant depression in adults. We also evaluated the methods against the priority setting criteria by conducting a health economic evaluation of the relevant treatment alternatives.

1.5 Project plan and preparatory work

Before we started working on this HTA, we first planned the work, and prepared a protocol for the commissioned HTA (36). In addition to being published at NOMA (36), the protocol is also published at the Nye Metoder webpage for this commission (37). Overall, the HTA was executed in accordance with the protocol. We deviated from the protocol when choosing to include two studies that technically did not meet the inclusion criteria for comparator, as described in section *2.2.2*.

1.5.1 External experts

At the start of the project, we recruited six clinical experts via the national system «Nye metoder», with expertise within psychiatry, as contributors in the project. We also recruited two patient representatives from Mental Helse, in line with the NOMA's guidelines (38). The expert group's role has been to provide input on the technologies, clinical practice, experience with the technologies, resource use, relevant publications, formation of the inclusion criteria in the PICO based on the research question. PICO stands for population, intervention, comparator, and outcome. The expert group has also read and provided clinical input on the report draft.

2. Clinical efficacy and safety

As prespecified in our protocol (36), this HTA was conducted in accordance with the handbook “Slik oppsummerer vi forskning” and “Cochrane Handbook for Systematic Reviews of Interventions” (39;40).

2.1 Methods

2.1.1 Selection criteria

Inclusion criteria used for selection of studies is described in *Table 1*.

Table 1: Inclusion criteria

Population	Adults ≥18 years with moderate or severe depression (e.g. MADRS score ≥20) that is treatment-resistant
Intervention	Intravenous ketamine: 0.5-1 mg/kg, single and multiple administrations Intravenous esketamine
Comparator	Inactive placebo: saline Active placebo: midazolam, ketamine <0.5 mg/kg Electroconvulsive therapy (ECT)
Outcomes	Efficacy: 1) Primary: objective response rate e.g. based on MADRS score and HDRS. 2) Secondary: response on treatment, mean reduction in e.g. MADRS and HDRS scores, remission rate, relapse rate, time to relapse, quality of life, hospitalisation, duration of hospitalisation, use of resources, e.g. direct cost and personnel time, long-term effect on efficacy on the above outcomes. Safety: adverse events, serious adverse events, reports of abuse, long term effect on safety on the above outcomes.
Study design	Randomised controlled trials Cohort studies for long-term data on efficacy and safety, and in geriatrics.
Publication year	No limitation
Country/context	All
Language	Norwegian, Swedish, Danish, English

HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery and Åsberg Depression Rating Scale

2.1.1.1 Exclusion criteria

We excluded the following types of studies and publications:

- Studies where the study population had psychosis
- Studies where ketamine or esketamine was given in other administration method than intravenous as comparator
- Case studies or case series
- Animal studies
- Preprints
- Systematic reviews
- Conference abstracts

Though we excluded both systematic reviews and conference abstracts, we did search for and screen these publications, for relevant primary studies and to give a general view of potential non-publication rate, respectively. This is described more extensively in section *2.1.3*.

2.1.2 Literature search

The librarian responsible for the search (EH) collaborated with the project team to develop an information retrieval strategy with the aim of finding completed and ongoing research that meets the predefined selection criteria for the assignment. The plan and search strategies were peer reviewed by a librarian colleague (GEN) prior to execution.

As a first step, while working on the protocol, we searched for ongoing and completed HTAs in the International HTA database, supplemented with relevant HTA organisations' websites. We also

searched the Epistemonikos database for published systematic reviews on the topic. For the main search, we used the following sources:

- Cochrane Central Register of Controlled Trials (Wiley)
- Embase (Ovid)
- MEDLINE (Ovid)
- Clinicaltrials.gov (U.S. National Institutes of Health, National Library of Medicine)
- International Clinical Trials Registry Platform (World Health Organization)

The search strategies for the electronic bibliographic databases were adapted to the interface of each individual database. The search strategy comprised both controlled vocabulary terms, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords, for the population and intervention concepts. Search terms and keywords within a search concept were combined with the Boolean logical operator "OR", and the search concepts with "AND". The treatment-resistant aspect of depression and number and dosage of infusions was not specified in the search but operationalised during screening. We did not restrict the search by language or publication year. We excluded case reports and animal studies in the search strategy, but did not otherwise limit the search to certain study designs or publication types. However, we kept records of conference abstracts, preprints and study registrations apart and screened them separately. Complete search strategies for all sources are available in *Appendix 2*.

We exported the search results from the bibliographic databases and study registries to the reference management tool EndNote (41). Here, we added a few titles missing in the imported records, replaced some faulty publication years and then removed duplicates by a standardized and semi-automated method comparing the record's title, author, and doi-fields. The remaining, unique records were then exported to EPPI-Reviewer software (42;43) for assessment of relevance against the selection criteria by two reviewers (IKO and AVF).

Supplementing the search in bibliographic databases, we asked the medical experts involved in this HTA work whether they knew of further relevant publications. We also checked the studies/study reports included in selected systematic reviews and HTAs published since 2022 for relevance. Furthermore, we used the related papers search functionality in EPPI-Reviewer (44;45) (bibliography and "recommended by" modes) with the publications meeting eligibility criteria after full-text review as input.

In a separate process, we used two approaches to identify relevant health economic models/evaluations. First, we applied the Economic Evaluation-classifier in EPPI-Reviewer (42;43) to the results from the main search. We also looked for publications on treatment-resistant depression in the CEA Registry and International HTA Database and ran a pragmatic search in MEDLINE (Ovid) and Embase (Ovid). The pragmatic search strategy combined the concepts of treatment-resistant depression and economic models.

2.1.3 Selection of studies

Studies found in the literature search were selected in a two-step selection strategy:

1) Screening: two researchers (IKO and AVF) independently screened titles and abstracts (where available) using the EPPI Reviewer software and included or excluded articles based on their relevance to our research question. When in doubt, references were included. Systematic reviews, conference abstracts, preprints and records from trial registries were screened separate from the journal articles.
2) Full-text assessment: two researchers (IKO and AVF) independently read the full-text articles of the references included in step 1 to assess which to include in our HTA.

Both steps adhered to the eligibility criteria listed in *Table 1*. Disagreements in either of the two steps were resolved through discussion.

The machine learning function *priority screening* was used in step 1 in order to screen titles and abstracts more efficiently. References deemed more relevant by the machine learning model were

pushed forward in the “queue” as the researchers’ decisions for inclusion and exclusion updated the model. One researcher (IKO) screened all references from the main search while the other researcher (AVF) stopped manual screening when a clear flattening of the inclusion curve was observed, and more than 200 references had been screened without finding a relevant study.

Two researchers (IKO and AVF) screened ongoing studies and systematic reviews. One researcher (AVF) screened the identified “related papers” and studies included in relevant systematic reviews. One team member (EH) conducted a preliminary sorting of conference abstracts and preprints. One researcher (AVF) confirmed the selection of abstracts that would have been considered relevant for full-text review.

2.1.4 Risk of bias assessment

Two colleagues (IKO and AVF) independently assessed risk of bias. Disagreements in the assessments were resolved through discussion or by consulting a third researcher (JVG). For assessment of RCTs, we used the revised Cochrane's Risk of Bias tool for randomized controlled studies (RoB2) (46). For non-RCTs, we planned to use the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (47). We assessed RoB2 based on our primary outcome. For studies that did not present data on response, we used depression severity scores (MADRS or HDRS) as a proxy, as these scores are used as the basis for other efficacy outcomes such as response, remission, and relapse.

2.1.5 Data extraction

One team member (IKO) extracted data from the included studies, and another team member (AVF) cross-checked the data against the publication. Disagreements were resolved through discussion. We used Excel to make data sheets for the data extraction. The relevant data that was extracted is described in *Table 2*.

Table 2: Relevant data extracted from included studies

About	Information extracted
The study	Author, publication year, study design, country, clinical trial identification number, funding source (industry or non-industry)
The participants	Numbers of participants randomized; numbers of participants included in analyses; age; ethnicity; number of female participants; time since diagnosis; number of previous MDD episodes, duration of current MDD episode, number of failed antidepressant treatments, number of patients with failed antidepressant treatments.
The treatments	Name of treatment; posology information, i.e.: dose level, frequency, duration, and route of administration
The outcomes	Name of relative treatment effect estimate (e.g., mean, median, change from baseline); point estimate; name of measure of precision (e.g., 95% CI, SD); disease severity at baseline, depression scoring tool (i.e., MADRS, HDRS), time points for measurements (follow-up), definition for outcomes such as response, remission and relapse.

CI: confidence interval; HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery and Åsberg Depression Rating Scale; MDD: major depressive disorder; SD: standard deviation

2.1.6 Data analyses

We assessed the included RCTs to be sufficiently similar in terms of study design, participants, interventions and comparisons to allow us to synthesise the data of efficacy outcomes in meta-analyses. Review Manager (RevMan) was used for all analyses and forest plots, and GRADEpro was used for summary of findings-tables (48;49). Safety data, as well as all results from the non-RCTs, were presented in a narrative summary.

2.1.6.1 Efficacy analyses

For all data analyses calculated in RevMan, we used the random-effects model, as we considered the clinical and methodological diversity between the included studies to potentially cause (statistical) heterogeneity (39;50;51). Furthermore, for all outcomes we used the inverse variance method, the Restricted Maximum-Likelihood heterogeneity estimator method, and the Wald-type summary effect confidence interval (CI) method. Note that for the analyses that only contained one study (i.e., not meta-analyses), this set up had no practical impact on the results.

We calculated dichotomous outcomes, i.e., event data such as response, remission and relapse, as risk ratio with 95% CI. Continuous outcomes, i.e., depression severity using MADRS and/or HDRS, quality of life and time to relapse, were calculated as mean difference with 95% CI. We applied intention-to-treat (ITT) analysis in which all randomised patients were included in the data analyses, regardless of which treatment they actually received or if they dropped out during the study. Note that when studies presented either responders or remitters as percent of the study population, we calculated the number of responders based on the individual study's analysis population (e.g. modified ITT), to avoid overestimating the number of patients with response or remission.

Summary of findings-tables with calculated anticipated risk difference were made with the GRADEpro software. Anticipated risk difference calculated based on wide confidence intervals can lead to unrealistic values because they reflect substantial uncertainty in the relative effect estimate. When the upper limit of the confidence interval for relative risk is significantly high, it amplifies the estimated risk difference, especially if the baseline risk in the comparison group is low. This combination can result in exaggerated absolute effects that are not clinically plausible, e.g., 1050 of 1000 patients. In such cases we refer to the upper limit as "all patients". Such outcomes highlight the imprecision of the evidence and should be interpreted with caution, particularly when the certainty of the evidence is rated as very low. These calculations are intended to provide a range of possible effects rather than definitive predictions, and the wide intervals underscore the need for further high-quality research to refine the estimates.

2.1.6.2 Safety analyses

We conferred with clinical experts on which types of adverse events they considered most clinically important. The experts agreed on a set of adverse events, as described in *Table 3*. We adhered to this list as best possible, and added headache, as this adverse event was often presented by clinical studies.

Table 3: Adverse events as suggested by clinical experts

Group	Adverse event
Most important severe adverse events	Respiratory failure (apnoea, laryngospasm)
	Severe cardiovascular events (e.g., arrythmia, heart failure, myocardial infarction, or stroke)
	Increased intracranial pressure
	Anaphylaxis
	Seizure
Other adverse events	Hyper- or hypotension
	Tachy- or bradycardia
	Emergence delirium (confusion upon "awakening")
	Psychosis (beyond expected dissociation)
	Mania
	Suicidal ideation (after treatment)
	Nausea/ vomiting
	Stomach pain
	Urinary problem (cystitis, haematuria, hydronephrosis, incontinence, difficulties emptying the bladder)
	Dizziness/ataxia
	Anxiety
	Increased or decreased saliva

Group	Adverse event
Less severe and expected side effects (*emerges often during and shortly after infusion*)	Visual disturbance (double vision, nystagmus, difficulties focusing the vision)
	Speech disturbance (difficulties finding the right words, dysarthria)
	Amnesia (of the infusion period)
	Involuntary movements (tonic-clonic movements)

2.1.6.3 Minimal important difference (MID)

A statistically significant result in a clinical trial does not necessarily reflect a clinically important effect. A threshold of minimal important difference (MID) would therefore be helpful to assess clinical relevance. As we did not prespecify a minimal important difference in our protocol, we consulted with our clinical expert group, on a MID threshold for continuous outcomes such as depression severity scores. The clinical experts had different opinions as to what a relevant cut-off value should be. While one expert argued for using similar limits as to that of other antidepressant therapies (we assume 20% improvement), another thought we should apply stricter limits, e.g., 50-60% improvement. After much deliberation, we decided to use both of the suggested MID thresholds, to explore how it would affect the interpretation of the results. We applied the MID thresholds by adding a red line to signify 50% improvement, and a blue line illustrating 20% improvement in the forest plots of statistically significant results of our depression severity scores. The placement of these lines in forest plots were roughly estimated by calculating 20% and 50% improvement of the mean depression severity scores of the comparators. Our interpretation of clinical importance is in accordance with these MID thresholds is in line with the EPOC suggestions (52).

2.1.7 GRADE: assessing the certainty of evidence

The certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach in accordance with the GRADE handbook (53). As we narratively described safety data, as well as the results from the non-RCTs, we only assessed certainty of evidence for the efficacy data from the included RCTs.

Though the level of confidence is a continuous measure, for all practical reasons, it is classified into four categories: high, moderate, low, and very low (*Table 4*). In the GRADE approach, RCTs are as a starting point, considered to provide high quality evidence (53). The subsequent rating may be reduced after further assessment of the following factors: 1) study limitations (risk of bias), 2) inconsistency, 3) indirectness, 4) imprecision, and 5) publication bias (53). Two researchers (IKO and AVF) assessed certainty of evidence, and any disagreement were resolved through discussion.

Table 4: GRADE definitions (52;53)

GRADE level	Symbol	Description
High certainty	⊕⊕⊕⊕	This research provides a very good indication of the likely effect, and we are very confident that the true effect lies close to that of the estimate of the effect. The likelihood that the effect will be substantially different† is low.
Moderate certainty	⊕⊕⊕	This research provides a good indication of the likely effect, and we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect. There is a possibility that it is substantially† different, though the likelihood is moderate.
Low certainty	⊕⊕	This research provides some indication of the likely effect, and we have limited confidence in the effect estimate: The likelihood that it will be substantially different† is high.
Very low certainty	⊕	This research does not provide a reliable indication of the likely effect, and we have very low confidence that the effect estimate is close to the true effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different: a large enough difference that it might affect a decision.

2.2 Results

2.2.1 The literature search and selection of studies

In August 2024, we conducted searches in bibliographic databases and trial registries. Following screening and full-text eligibility assessment of the initial search results, we used included articles per November 2024 to carry out a supplementary backwards-citation and related-papers search in OpenAlex via the EPPI Reviewer software (43). Across all searches, we retrieved a total of 6,245 records (*Figure 1*). After removing duplicates, conference abstracts, and preprints, 3,225 unique records remained.

During the title and abstract screening phase, 3,072 records were excluded for clearly not meeting the inclusion criteria. This left 153 full-text publications for further evaluation. Of these, 23 publications were included, while 130 were excluded. The reasons for exclusion were as follows: non-relevant publication type or study type: 56; already included article from the study: 41; wrong population; 20; wrong intervention: 4; wrong comparator: 3; duplicate: 3; wrong outcome: 2; other reason: 1. See *Appendix 3* for the full list of publications we excluded in full-text screening, and the reasoning behind the exclusions.

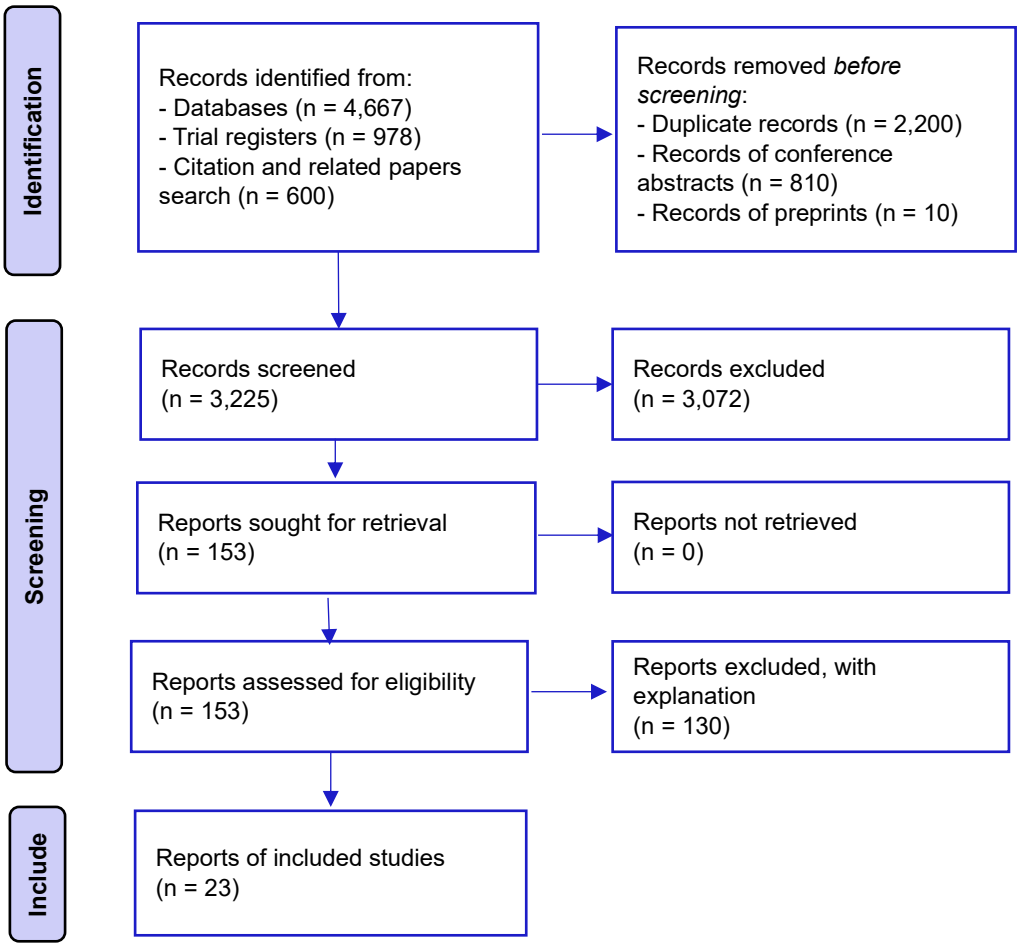


Figure 1: Flow chart on selection of studies

One researcher (IKO) screened all records while another researcher (AVF) screened 931 records. At this point, a clear flattening of the inclusion curve was observed, and 295 records had been screened without new inclusions.

2.2.2 Description of the included studies

We included 21 unique studies in this HTA, described in 23 publications (54-76). The studies by Correia-Melo (58), Kheirkhah (62), Sakurai (68) and Pfeiffer (66) did not technically meet our inclusion criteria for comparator (i.e. ECT, ketamine <0.5 mg/kg, saline or midazolam), but since all of their intervention groups met our inclusion criteria for intervention (i.e., intravenous ketamine 0.5-1 mg/kg, and/or intravenous esketamine), and we did not identify any relevant cohort studies with control groups, we chose to include them.

Nineteen of the included studies were RCTs (54-65;67;69-76), and two were non-RCTs (real-world studies) (66;68). All included studies are presented in *Table 5* and in more detail in *Appendix 4*. In brief, we included twelve RCTs that had given single ketamine infusions (56-59;62-64;67;69;71;73-76), and seven that had given multiple ketamine infusions (54;55;60;61;65;72). Overall, the studies were small, with a sample size less than 100 participants. The total number of participants across all included studies were 1761 (1459 in the RCTs and 302 in the non-RCTs), ranging from 20 to 403, of which ~50% were women. All participants had moderate to severe depression, and some form of treatment-resistant depression, as defined by the individual trials. The mean age of the participants ranged from 25 to 66 years. The studies were conducted in Europe (Sweden, Ireland, and Belgium, Poland and Germany) (60;71;75), the Americas (Brazil and USA) (55;58;59;61;63;64;66-70;72), Asia (Taiwan and Thailand) (56;57;65;73;74), and Africa and the Middle East (Egypt and Iran) (54;62;76). Only two of 21 studies were funded by the industry (71;72).

Table 5: Description of the included studies (n=21)

Publication author; year (ref)	Treatment; study population (n)	Administration frequency	Outcomes included in our data analysis
RCTs with single dose ketamine			
Chen 2018a (57) Su 2017 (73)	Ketamine 0.50 mg/kg; n=24 Ketamine 0.20 mg/kg; n=23 Saline; n=24	Single infusion	Response, MADRS
Chen 2018b (56)	Ketamine 0.50 mg/kg; n=8 Ketamine 0.20 mg/kg; n=8 Saline; n=8	Single infusion	Response
Correia-Melo 2020 (58)	Ketamine 0.5 mg/kg; n=29 Esketamine 0,25 mg/kg; n=34	Single infusion	Response, MADRS, remission
Fava 2020 (59) Salloum 2020 (69)	Ketamine 0.10 mg/kg; n=18 Ketamine 0.20 mg/kg; n=20 Ketamine 0.50 mg/kg; n=22 Ketamine 1.00 mg/kg; n=20 Midazolam 0.045 mg/kg; n=19	Single infusion	Response, remission, AE, SAE
Kheirkhah 2018 (62)	Ketamine 0.50 mg/kg; n=25, inj Ketamine 0.75 mg/kg; n=25, inj Ketamine 0.50 mg/kg; n=25, inf Ketamine 0.75 mg/kg; n=25, inf	Single dose	Response data not used due missing information
Lijffijt 2022 (63)	Ketamine 0.50 mg/kg; n=11 Ketamine 0.25 mg/kg; n=5 Ketamine 0.10 mg/kg; n=4 Midazolam 0.03 mg/kg; n=13	Single infusion	Response, remission, AE, SAE
Murrough 2013 (64)	Ketamine 0.50 mg/kg; n=48 Midazolam 0.045 mg/kg; n=25	Single infusion	Response, MADRS, relapse, AE

Publication author; year (ref)	Treatment; study population (n)	Administration frequency	Outcomes included in our data analysis
Rengasamy 2024 (67)	Ketamine 0.50 mg/kg; n=103 Saline; n=51	Single infusion	MADRS data not used due to missing information
Singh 2016a (71)	Esketamine 0.40 mg/kg; n=11 Esketamine 0.20 mg/kg; n=9 Saline; n=10	Single infusion	Response, MADRS
Su 2023 (74)	Ketamine 0.50 mg/kg; n=42 Midazolam 0.045 mg/kg.; n=42	Single infusion	Response, AE, SAE
Tiger 2020 (75)	Ketamine 0.50 mg/kg; n=20 Saline; n=10	Single infusion	Response, MADRS
Zolghadriha 2024 (76)	Ketamine 0.50 mg/kg; n=32 Saline; n=32	Single infusion	MADRS, AE
RCTs with multiple doses ketamine			
Ahmed 2023 (54)	Ketamine 0.50 mg/kg; n=18 Saline; n=18	1 infusion per week for 2 weeks	Response, MADRS, relapse, remission, AE, SAE
Anand 2023 (55)	Ketamine 0.50 mg/kg; n=200 ECT; n=203	2 infusions or 3 treatments per week for 3 weeks	Response, MADRS, remission, relapse, AE, SAE
Gallagher 2020 (60)	Ketamine 0.5 mg/kg; n=13 Midazolam 0.045 mg/kg; n=12	1 infusion per week for 4 weeks	Response, HDRS, remission, relapse
Ionescu 2019 (61)	Ketamine 0.50 mg/kg; n=13 Saline; n=13	2 infusions per week for 3 weeks	Response, HDRS, remission
Pattanaseri 2024 (65)	Ketamine 0.50 mg/kg; n=11 Midazolam 0.045 mg/kg; n=9	3 infusions per week for 1 weeks	Response, MADRS, remission, time to relapse
Shiroma 2020 (70)	Ketamine 0.50 mg/kg; n=28 Midazolam 0.045 mg/kg + ketamine 0.50 mg/kg; n=30	3 infusions per week for 2 weeks	Response, remission
Singh 2016b (72)	Ketamine 0.50 mg/kg; n=18 Saline; n=17 Ketamine 0.50 mg/kg; n=17 Saline; n=16	2 or 3 infusions per week for 4 weeks	Response, MADRS, remission
Non-randomised real-world studies			
Pfeiffer 2024 (66)	Ketamine; n=215	Infusion	Not used, narrative summary only
Sakurai 2020 (68)	Ketamine 0.50 mg/kg; n=87	Single infusion	Not used, narrative summary only

AE: adverse events, inj: (bolus) injection, inf: infusion, SAE: serious adverse events
Rows marked in grey indicate that the studies were not included in the data analysis

2.2.3 Risk of bias in the included studies

2.2.3.1 RCTs

Risk of bias in RCTs was assessed for the primary outcome, i.e., response, using the RoB2-checklist (46). Each study was rated as being at low, some concerns, or high risk of bias on five domains: 1) randomisation process, 2) deviations from intended interventions, 3) missing outcome data, 4) measurement of the outcome, and 5) selection of the reported result. The assessed risk of bias across all included RCTs is shown in *Figure 2*, and individual risk of bias assessments for all domains for each individual RCTs is shown in *Figure 3*.

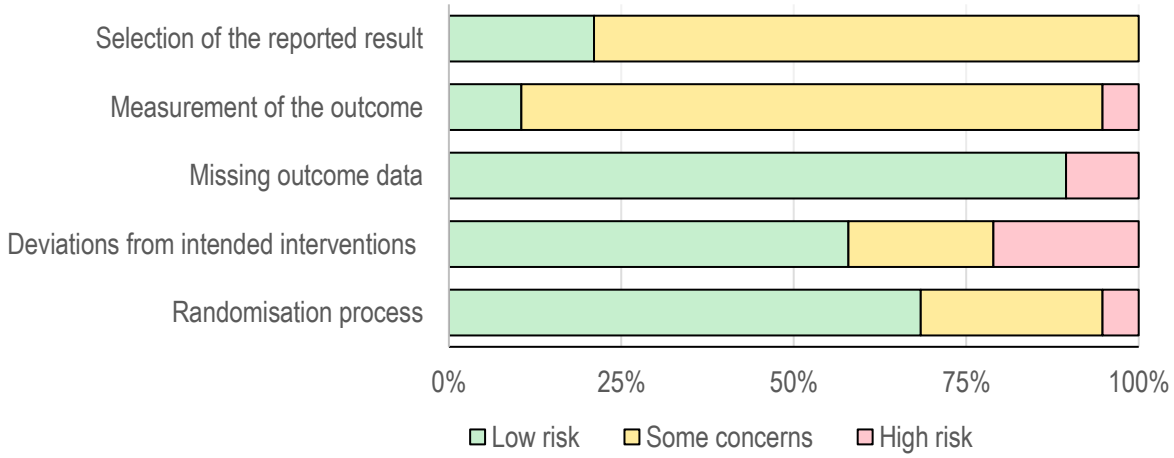


Figure 2: Risk of bias across included RCTs

For the domain “Randomisation process”, only one study was assessed to have high risk of bias due to statistic significant difference in baseline depression severity (MADRS scores) between the two groups (ketamine and saline) (74). Five studies were assessed to have some concerns, mainly due to a lack of information regarding the randomisation process and/or the allocation concealment (56;57;59;62;69;73;75).

For the domain “Deviations from interventions”, four studies were assessed to have high risk of bias due to a) several more of the patients in the control group than in the intervention group chose not to start the treatment, which likely affected the result (55), b) unclear which population was used in the analysis and we assume the missing data may have impacted the result (59;60;69), and c) unclear drop-out rate (71). Four of the studies were assessed to have some concerns due to no information regarding deviations from the intended intervention (54;61;65;70).

For the domain “Missing outcome data”, two studies were assessed to have high risk of bias due to missing data for some patients and/or missing data for some of the intervention groups (59;60;69). The rest of the studies were all assessed to have low risk of bias.

For the domain “Measurement of the outcome”, we assessed one study to have high risk of bias due to the authors arguing that the unexpected results may have been caused by the patients’ expectation of the treatment (70). Only two studies were assessed to have low risk of bias (58;62), whereas the majority were assessed to have some concerns. The reasoning is that although all of the included studies (except Anand 2023 (55)) were double or triple blinded, several studies showed that both patients and personnel could guess (quite accurately) which treatment was received/given, due to the dissociative effect of ketamine. This was especially true for studies where the comparator was saline, but also for midazolam and lower doses of ketamine (e.g., 0,1 mg/kg and 0,2 mg/kg). Furthermore, efficacy outcomes for depression are based on self-reported depression severity scores, e.g., structured interviews by using MADRS or HDRS, and it could therefore be possible that patients and personnel were influenced by knowledge of the intervention they received/gave. When assessing the

RoB2 questions that related to this, we chose to rate it possible but not likely that patients and personnel had been influenced by the knowledge of which intervention was received/given.

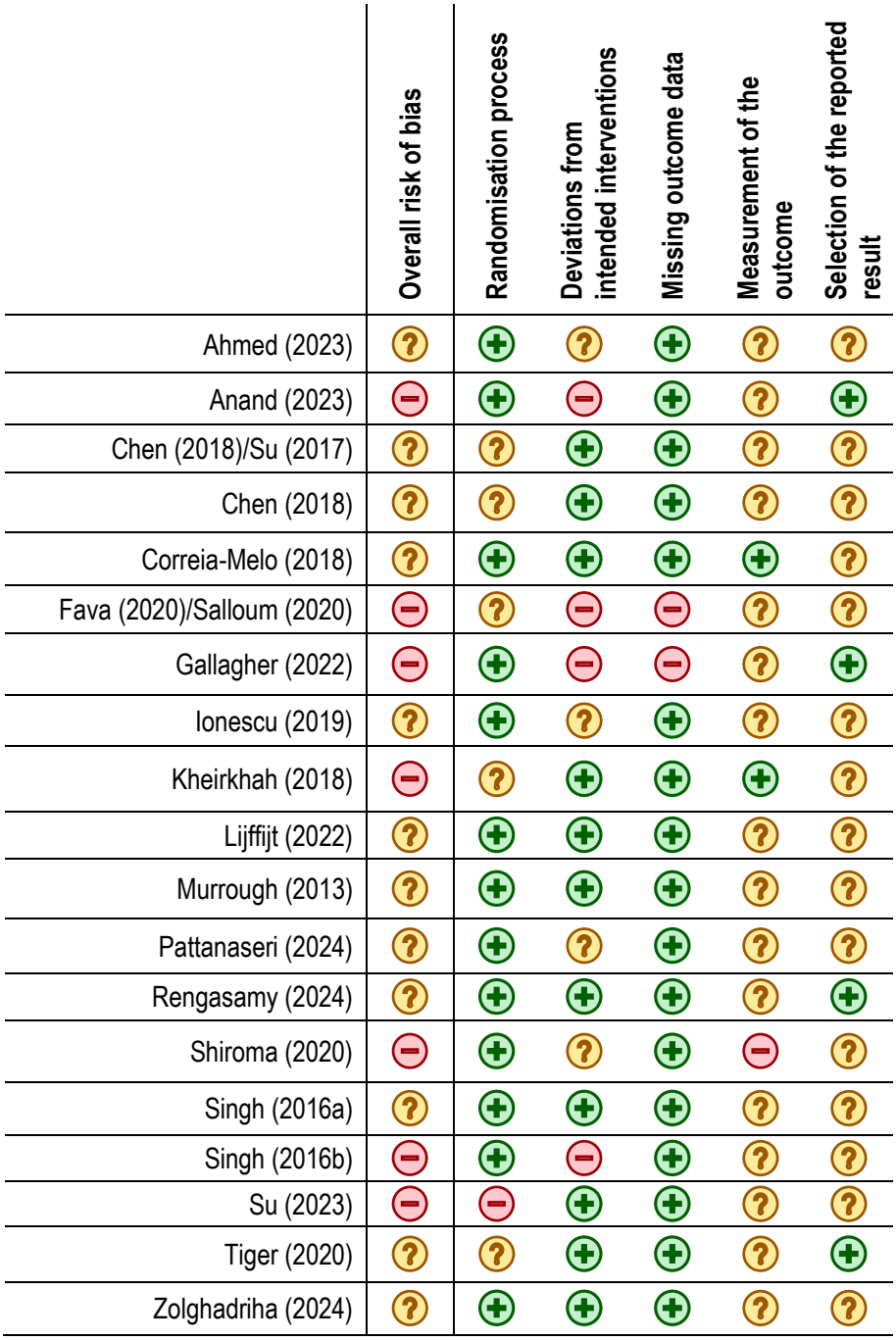


Figure 3: Risk of bias for each included RCT

For the last domain “Selection of the reported result”, we assessed four studies to have low risk of bias (55;60;67;75), and the rest of the studies to have some concerns. This was mainly due to the lack of information regarding prespecified analysis plan.

Finally, we assessed the overall risk of bias for each study, based on the results of our assessment for the five domains. None of the included RCTs were assessed to have low overall risk of bias; seven were assessed to have a high overall risk of bias, while the rest was ruled to have some overall concerns (*Figure 3*).

We found assessing risk of bias in the study by Kheirkhah (62) especially challenging. The study was very poorly described, and missing important description of methods and results. Due to the

intervention set-up and missing information however, the individual RoB2-domains were either ruled as “low risk of bias” or “some concerns”. According to the RoB2-checklist, this could warrant an overall ruling of “some concerns”, but as we found this to be a too generous ruling due to the lack of information and poor descriptions, we therefore set the overall risk of bias for Kheirkhah as “high”.

2.2.3.2 Non-RCTs

We planned to assess risk of bias in non-randomised, controlled studies using the ROBINS-I-tool. We only identified two relevant non-RCTs and these were retrospective chart reviews without control groups and therefore not appropriate for assessment with ROBINS-I. Methodological limitations of these studies are described narratively.

Since the studies lacked control groups, it is difficult to determine whether the observed effects of ketamine are due to the treatment itself or other factors, such as placebo effect, natural recovery, or concurrent treatments. Both studies rely on a retrospective review of patient records, which may introduce bias due to inconsistencies in how data is collected. Depression severity was assessed prior to infusion and not at specified time points following infusion and the dosing and administration schedule for ketamine was not standardized, making it difficult to compare results and draw general conclusions about optimal dosing and treatment frequency. The Patient Health Questionnaire-9 (PHQ-9) was used to assess depression severity by Pfeiffer *et al.* (66) while the 16-item Quick Inventory of Depressive Symptomatology-Self Report scale (QIDS-SR_{16}) was used by Sakurai *et al.* (68). Sakurai *et al.* reported a high discontinuation rate with 47.1% discontinuing treatment during or immediately after the induction phase (68). The main reason for discontinuation was reported to be insufficient effect.

The risk of bias is considered high for both studies and results must be interpreted with caution. Additionally, Pfeiffer *et al.* reported results from a veteran population, which makes generalization to a general TRD population difficult (66). Eighteen percent of the participants were female and 70% were diagnosed with post-traumatic stress disorder (PTSD) (66).

2.2.4 About the data analysis

We contacted the listed corresponding authors for eight of our included RCTs (57;59;60;63;64;69;70;72-74), for clarifications and/or additional data, due to either missing or inadequately described data. Only one corresponding author replied: Professor Declan McLoughlin (corresponding author of the study by Gallagher *et al.* 2022 (60)), who sent us the additional data that we had requested.

The studies by Kheirkhah *et al.* and Rengasamy *et al.* were both included in our HTA but were omitted from the data analysis (62;67). The study by Kheirkhah *et al.* was poorly described and missed important descriptions of the results (62). While we contacted the authors for clarification, they never replied, and we therefore chose to omit this study from our analyses. We included the study by Rengasamy *et al.* for the depression severity (HDRS) data (67), but as the publication lacked data on variance, and the authors never replied to our request, we had no choice but to omit this study from our analyses.

We kept all data from single and multiple infusions-studies separate in our data analysis, i.e., we did *not* include outcome data of the first infusion from multiple infusion-studies in the data analysis of single infusion-studies.

2.2.4.1 Presentation of results

Based on the included RCTs, we made seven comparisons for the single dose studies, and three for the multiple dose studies (*Table 6*). Additional data analysis regarding comparison of various doses of esketamine, and esketamine versus saline, are found in *Appendix 6*.

Table 6: Comparisons used in the data analysis of single and multiple ketamine doses (with links)

Comparisons	**Placement in report** (with hyperlinks)	**Outcomes** (with hyperlinks)
Single ketamine infusions		
Ketamine 0.5 mg/kg versus saline	Results section *2.2.7*	Response: *2.2.7.1* Depression severity: *2.2.7.2*
Ketamine ≥0.5 mg/kg versus midazolam	Results section *2.2.9*	Response: *2.2.9.1* Relapse after response: *2.2.9.2* Remission: *2.2.9.3* Depression severity: *0*
Ketamine 0.5 mg/kg versus esketamine 0.25 mg/kg	Results section *2.2.11*	Response: *2.2.11.1* Remission: *2.2.11.2* Depression severity: *2.2.11.3*
Ketamine ≥0.5 mg/kg versus ketamine <0.5 mg/kg	Results section *2.2.12*	Response: *2.2.12.1* Relapse after response: *2.2.12.2* Remission: *2.2.12.3* Relapse after remission: *2.2.12.4* Depression severity: *2.2.12.5*
Esketamine 0.4 mg/kg versus esketamine 0.2 mg/kg	*Appendix 6*	Response Depression severity
Esketamine 0.4 mg/kg versus saline	*Appendix 6*	Response Depression severity
Esketamine 0.2 mg/kg versus saline	*Appendix 6*	Response Depression severity
Multiple ketamine infusions		
Ketamine 0.5 mg/kg versus ECT	Results section *2.2.6*	Response: *2.2.6.1* Relapse after response: *2.2.6.2* Remission: *2.2.6.3* Depression severity: *2.2.6.4* Quality of life: *2.2.6.5*
Ketamine 0.5 mg/kg versus saline	Results section *2.2.8*	Response: *2.2.8.1* Remission: *2.2.8.2* Depression severity: *2.2.8.3*
Ketamine 0.5 mg/kg versus midazolam	Results section *2.2.10*	Response: *2.2.10.1* Relapse after response: *2.2.10.2* Remission: *2.2.10.3* Time to relapse: *2.2.10.4* Depression severity: *2.2.10.5*

ECT: electroconvulsive therapy.

2.2.5 Certainty of evidence - GRADE

We evaluated the certainty of the estimates of all outcomes using the GRADE approach, as described in the Method chapter (*GRADE: assessing the certainty of evidence*). Our GRADE judgements are presented in the summary of findings tables for all outcomes, as well as in *Appendix 5*.

2.2.6 Ketamine 0.5 mg/kg versus ECT – multiple infusions

Only one study contributed to the comparison between ketamine and ECT: Anand *et al.* 2023 (55). The intervention group was given two infusions of 0.5 mg/kg ketamine every week for three weeks, while the comparison group received three ECT sessions every week for three weeks (55).

2.2.6.1 Response

Data on response was only provided for end of treatment, which occurred within three days after the last treatment (i.e., of either ketamine infusion or ECT) (55). Response was defined as ≥50% decrease in MADRS score (55).

The risk ratio (95% CI; p-value) of response was 1.44 (1.13 to 1.82; p=0.003) at end of treatment, which is statistically significant in favour of ketamine 0.5 mg/kg. In other words, patients in this study who received multiple infusions of ketamine 0.5 mg/kg were 44% more likely to experience response at end of treatment, i.e., ≥50% reduction in MADRS scores, than patients who received multiple ECTs (*Figure 4*).

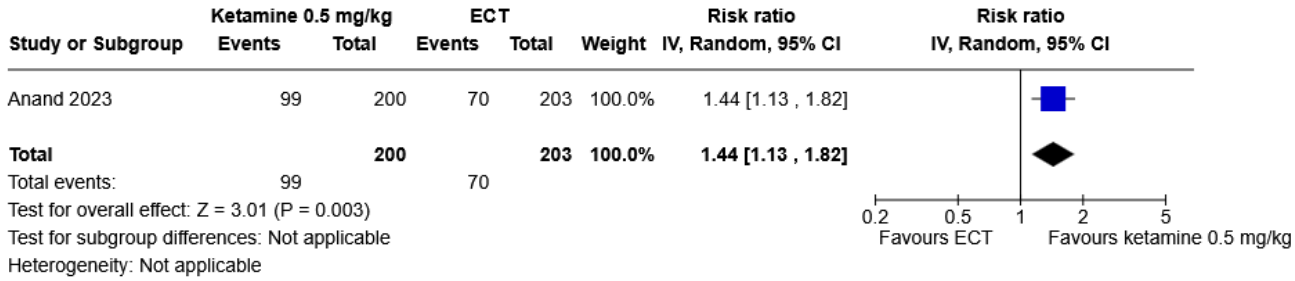


Figure 4: Multiple doses ketamine 0.5 mg/kg vs ECT: forest plot of response

If 345 of 1 000 patients treated with mutliple ECTs experienced response at end of treatment, then the anticipated risk difference would correspond to 152 more patients per 1 000 (i.e., 497 patients) treated with multiple ketamine 0.5 mg/kg infusions having response at end of treatment (*Table 7*). The 95% CI shows that it is statistically possible that between 45 more patients (i.e., 390 patients) and 283 more patients (i.e., 628 patients) would be anticipated to experience response at end of treatment when receiving multiple infusions of ketamine 0.5 mg/kg than when receiving multiple ECTs.

Table 7: Multiple doses ketamine 0.5 mg/kg vs ECT: summary of findings table for response

Outcome: response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ECT	Risk difference with ketamine 0.5 mg/kg			
EoT N=403 (1 RCT)	345 per 1 000	**152 more per 1 000** (45 more to 283 more)	**RR 1.44** (1.13 to 1.82)	⊕⊕⊕ Moderate [a]	Multiple ketamine 0.5 mg/kg infusions probably improve the chance of response more than ECT at EoT (*moderate certainty evidence*)

***GRADE**: a: study limitations (RoB); **CI:** confidence interval; **EoT**: end of treatment; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.6.2 Relapse after response

Data on relapse of responders was provided at one, three- and six months after end of treatment (55). Relapse was defined as MADRS score over 20 (55).

2.2.6.2.1 One month follow-up after end of treatment

At one month after end of treatment, the risk ratio (95% CI; p-value) of relapse of responders was 0.76 (0.48 to 1.21; p=0.25). In other words, patients in this study who responded on multiple infusions of

0.5 mg/kg ketamine were 24% less likely to relapse, compared to patients who responded on multiple ECTs (*Figure 5*). However, as the confidence interval includes values above 1, it is statistically possible that responders on multiple 0.5 mg/kg ketamine infusions are actually at equal or higher risk of relapsing one month after end of treatment, compared to responders on multiple ECTs.

If 329 of 1 000 patients treated with multiple ECTs experienced relapse after response at one month after end of treatment, then the anticipated risk difference would correspond to 79 fewer patients per 1 000 (i.e., 250 patients) treated with multiple ketamine 0.5 mg/kg infusions relapsing after response at one month after end of treatment (*Table 8*). The 95% CI shows that it is statistically possible that between 171 fewer patients (i.e., 158 patients) and 69 more patients (i.e., 398 patients) would be anticipated to relapse after response at one month after end of treatment when receiving multiple ketamine 0.5 mg/kg infusions than when receiving multiple ECTs.

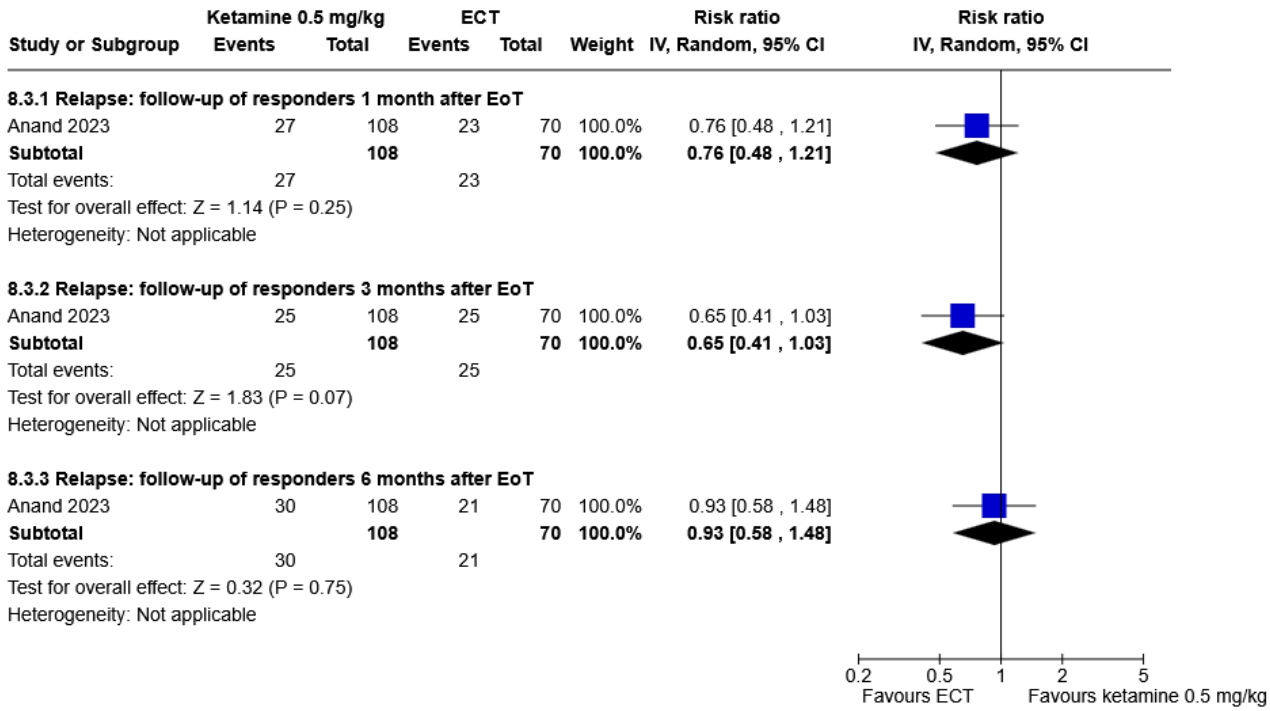


Figure 5: Multiple doses ketamine 0.5 mg/kg vs ECT: forest plot of relapse after response

2.2.6.2.2 Three months follow-up after end of treatment

At three months follow-up after end of treatment, the risk ratio (95% CI; p-value) of relapse of responders was 0.65 (0.41 to 1.03; p=0.07). In other words, patients in this study who responded on multiple 0.5 mg/kg ketamine infusions were 35% less likely to relapse three months after end of treatment, compared to responders on multiple ECTs (*Figure 5*). However, the confidence interval includes values above 1, so it is statistically possible that patients who respond on multiple 0.5 mg/kg ketamine infusions are actually at equal or greater risk of relapsing three months after end of treatment, compared to patients who responded on multiple ECTs.

If 300 of 1 000 patients treated with multiple ECTs relapsed after response at six months after end of treatment, then the anticipated risk difference would correspond to 21 fewer patients per 1 000 (i.e., 279 patients) treated with multiple ketamine 0.5 mg/kg infusions relapsing after response at six months after end of treatment (*Table 8*). The 95% CI shows that it is statistically possible that between 126 fewer patients (i.e., 174 patients) and 144 more patients (i.e., 444 patients) would be anticipated to relapse after response at six months after end of treatment when receiving multiple ketamine 0.5 mg/kg infusions than when receiving multiple ECTs.

Table 8: Multiple doses ketamine 0.5 mg/kg vs ECT: summary of findings table for relapse after response

Outcome: relapse after response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ECT	Risk difference with ketamine 0.5 mg/kg			
Follow-up of responders 1 month after EoT N=178 (1 RCT)	329 per 1 000	**79 fewer per 1 000** (171 fewer to 69 more)	**RR 0.76** (0.48 to 1.21)	⊕⊕ Low [a,d]	Multiple ketamine 0.5 mg/kg infusions may slightly reduce the risk of relapse more than ECT, 1 month after EoT (*low certainty evidence*)
Follow-up of responders 3 months after EoT N=178 (1 RCT)	357 per 1 000	**125 fewer per 1 000** (211 fewer to 11 more)	**RR 0.65** (0.41 to 1.03)	⊕⊕ Low [a,d]	Multiple ketamine 0.5 mg/kg infusions may slightly reduce the risk of relapse more than ECT, 3 months after EoT (*low certainty evidence*)
Follow-up of responders 6 months after EoT N=178 (1 RCT)	300 per 1 000	**21 fewer per 1 000** (126 fewer to 144 more)	**RR 0.93** (0.58 to 1.48)	⊕⊕ Low [a,d]	Multiple ketamine 0.5 mg/kg infusions may have little or no effect on the risk of relapse compared to ECT, 6 months after EoT (*low certainty evidence*)

***GRADE**: a: study limitations (RoB); d: imprecision*
***CI:** confidence interval; **EoT**: end of treatment; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.6.2.3 Six months follow-up after end of treatment

At six months follow-up after end of treatment, the risk ratio (95% CI; p-value) of relapse of responders was 0.93 (0.68 to 1.48; 0.75), which indicate minimal or no difference in effect between multiple ketamine 0.5 mg/kg infusions and multiple ECTs (p=0.75). In other words, patients in this study who responded on multiple 0.5 mg/kg ketamine infusions were 7% less likely to relapse six months after end of treatment, compared to patients who responded on multiple ECTs (*Figure 5*). However, as the confidence interval includes values above 1, it is statistically possible that responders on multiple 0.5 mg/kg ketamine infusions are actually at equal or higher risk of relapsing six months after end of treatment, compared to responders on multiple ECTs.

If 357 of 1 000 patients treated with multiple ECTs experienced relapse after response at three months after end of treatment, then the anticipated risk difference would correspond to 125 fewer patients per 1 000 (i.e., 232 patients) treated with multiple ketamine 0.5 mg/kg infusions relapsing after response at three months after end of treatment (*Table 8*). The 95% CI shows that it is statistically possible that between 211 fewer patients (i.e., 146 patients) and 11 more patients (i.e., 368 patients) would be anticipated to relapse after response at three months after end of treatment when receiving multiple ketamine 0.5 mg/kg infusions than when receiving multiple ECTs.

2.2.6.3 Remission

Data on remission was only provided for end of treatment, which occurred within three days after the last treatment (i.e., of either ketamine infusion or ECT) (55). Remission was defined as MADRS score ≤10 (55).

The risk ratio (95% CI; p-value) of remission was 2.03 (1.44 to 2.86) at end of treatment, which is statistically significant in favour of multiple infusions of ketamine 0.5 mg/kg (p<0.0001). In other words, patients in this study who received multiple ketamine 0.5 mg/kg infusions were over twice as likely to achieve remission at end of treatment, i.e., MADRS score ≤10, than patients who received multiple ECTs (*Figure 6*).

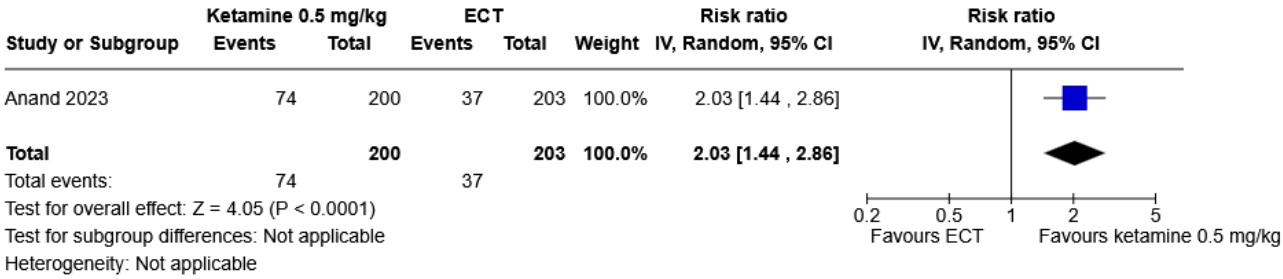


Figure 6: Multiple doses ketamine 0.5 mg/kg vs ECT: forest plot of remission

If 182 of 1 000 patients treated with multiple ECTs achieved remission at end of treatment, then the anticipated risk difference would correspond to 188 more patients per 1 000 (i.e., 370 patients) treated with multiple ketamine 0.5 mg/kg infusions achieve remission at end of treatment (*Table 9*). The 95% CI shows that it is statistically possible that between 80 more patients (i.e., 262 patients) and 339 more patients (i.e., 521 patients) would be anticipated to achieve remission at end of treatment when receiving multiple ketamine 0.5 mg/kg infusions than when receiving multiple ECTs.

Table 9: Multiple doses ketamine 0.5 mg/kg vs ECT: summary of findings table for remission

Outcome: remission	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ECT	Risk difference with ketamine 0.5 mg/kg			
End of treatment N=403 (1 RCT)	182 per 1 000	**188 more per 1 000** (80 more to 339 more)	**RR 2.03** (1.44 to 2.86)	⊕⊕⊕ Moderate [a]	Multiple ketamine 0.5 mg/kg infusions probably improve the chance of remission more than ECT at EoT. (*moderate certainty evidence*)

***GRADE**: a: study limitations (RoB)*
***CI:** confidence interval; **EoT**: end of treatment; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.6.4 Depression severity

Depression severity was measured by MADRS. Data was provided at end of treatment for all patients and for responders, as well as one, three- and six-months follow-up of responders after end of treatment (55). As described in *2.1.6.3 Minimal important difference (MID)*, we applied MID thresholds of 20% and 50% improvement in the forest plots of depression severity scores. Note that these thresholds are rough estimations and only relevant for the statistically significant results.

2.2.6.4.1 End of treatment for all patients

At end of treatment, the mean difference (95% CI; p-value) of depression severity of all patients was −2.50 (−4.45 to −0.55; p=0.01), which is statistically significant in favour of multiple infusions of ketamine 0.5 mg/kg. In other words, of the total patient population in this study, patients who received multiple 0.5 mg/kg ketamine infusions had lower MADRS scores, i.e. less severe depression, at end of treatment, compared to patients who received multiple ECTs (*Figure 7; Table 10*).

2.2.6.4.2 End of treatment for all responders

At end of treatment, the mean difference (95% CI; p-value) of depression severity of patients who had responded to treatment (either ketamine or ECT) was −1.18 (−3.64 to 1.28; p=0.35). In other words, of all patients who responded in this study, patients who received multiple 0.5 mg/kg ketamine infusions had lower MADRS scores, i.e. less severe depression, at end of treatment, compared to patients who received multiple ECTs (*Figure 7; Table 10*). However, as the confidence interval includes values above 0, it is statistically possible that responders on multiple 0.5 mg/kg ketamine infusions actually have equal or higher depression severity, i.e., MADRS scores, at end of treatment, compared to responders on multiple ECTs.

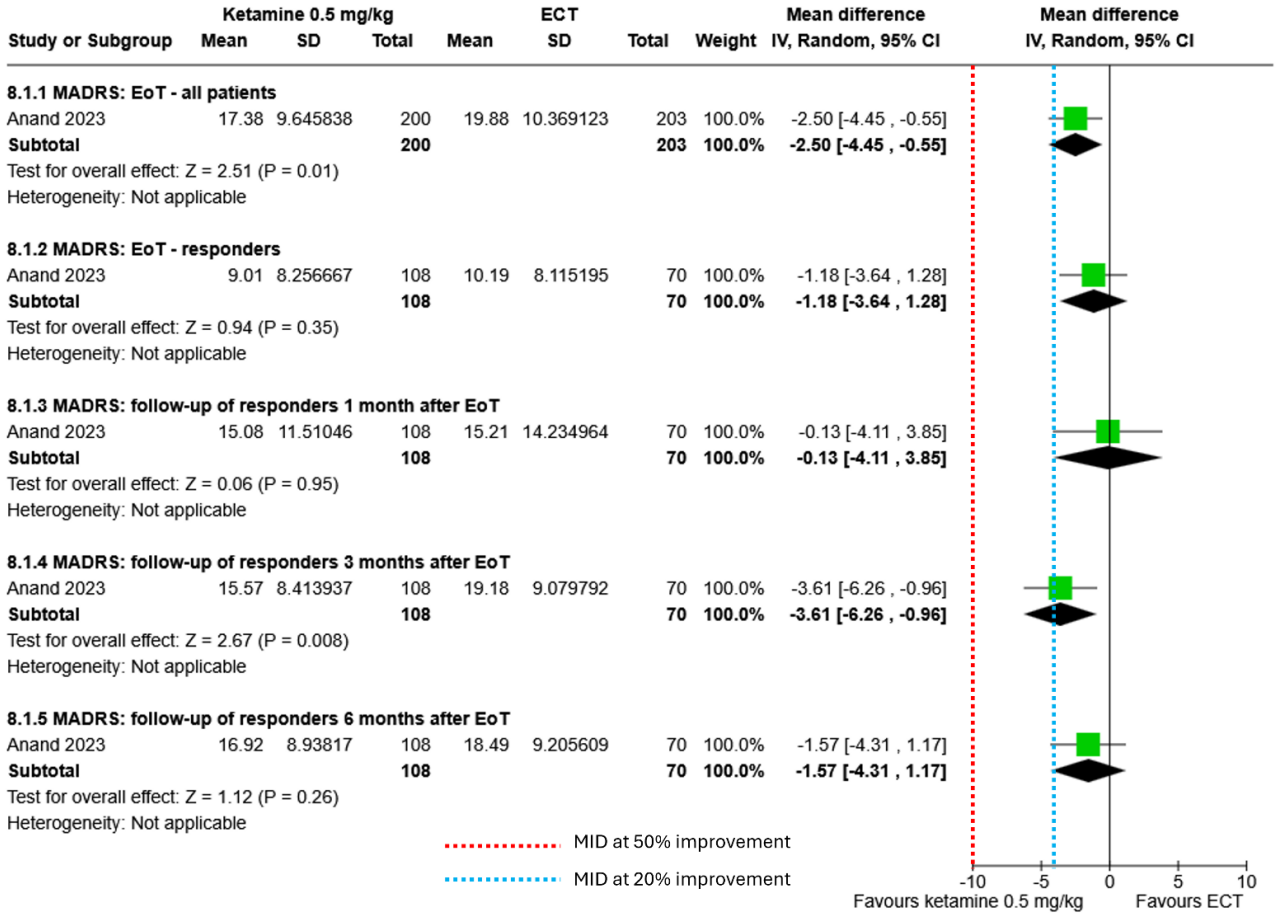


Figure 7: Multiple doses ketamine 0.5 mg/kg vs ECT: forest plot of depression severity.

2.2.6.4.3 One month follow-up of responders after end of treatment

At one month after end of treatment, the mean difference (95% CI; p-value) of depression severity of patients who had responded to treatment (either ketamine or ECT) was −0.13 (−4.11 to 3.86; p=0.95), indicating no difference in effect between treatment with multiple infusions of ketamine 0.5 mg/kg and multiple ECTs. In other words, of all patients who responded in this study, patients who received multiple 0.5 mg/kg ketamine infusions had similar MADRS scores, i.e. equal depression severity, at one month after end of treatment, compared to patients who received multiple ECTs (*Figure 7, Table 10*). However, as the confidence interval includes values above 0, it is statistically possible that responders on multiple 0.5 mg/kg ketamine infusions actually have lower or higher depression severity, i.e. MADRS scores, at end of treatment, compared to responders on multiple ECTs.

2.2.6.4.4 Three months follow-up of responders after end of treatment

At three months after end of treatment, the mean difference (95% CI; p-value) of depression severity of patients who had responded to treatment (either ketamine or ECT) was −3.61 (−6.26 to −0.96; p=0.008), which is statistically significant in favour of multiple infusions of ketamine 0.5 mg/kg. In other words, of all patients who responded in this study, patients who received multiple 0.5 mg/kg ketamine infusions had lower MADRS scores, i.e. less severe depression, at end of treatment, compared to patients who received multiple ECTs (*Figure 7; Table 10*).

2.2.6.4.5 Six months follow-up of responders after end of treatment

At six months after end of treatment, the mean difference (95% CI; p-value) of depression severity of patients who had responded to treatment (either ketamine or ECT) was −1.57 (−4.31 to 1.17; p=0.26). In other words, of all patients who responded in this study, patients who received multiple infusions of 0.5 mg/kg ketamine had lower MADRS scores, i.e. less severe depression, at end of treatment, compared to patients who received multiple ECTs (*Figure 7; Table 10*). However, as the confidence

interval includes values above 0, it is statistically possible that responders on multiple 0.5 mg/kg ketamine infusions actually have equal or higher depression severity, i.e., MADRS scores, at six months after end of treatment, compared to responders on multiple ECTs.

Table 10: Multiple doses ketamine 0.5 mg/kg vs ECT: summary of findings table for depression severity

Outcome: depression severity (MADRS)	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ECT	Risk difference with ketamine 0.5 mg/kg		
EoT - all patients (MADRS) N=403 (1 RCT)	Mean DS was **19.88**	MD **2.5 lower** (4.45 lower to 0.55 lower)	⊕⊕⊕ Moderate [a]	Multiple ketamine infusions probably reduce depression severity scores of all patients slightly more than multiple ECTs at EoT (*moderate certainty evidence*)
EoT - responders (MADRS) N=178 (1 RCT)	Mean DS was **10.19**	MD **1.18 lower** (3.64 lower to 1.28 higher)	⊕⊕ Low [a,d]	There may be little or no difference in depression severity scores of responders with treatment with multiple ketamine infusions and multiple ECTs at EoT (*low certainty evidence*)
Follow-up of responders 1 month after EoT (MADRS) N=178 (1 RCT)	Mean DS was **15.21**	MD **0.13 lower** (4.11 lower to 3.85 higher)	⊕⊕ Low [a,d]	There may be little or no difference in depression severity scores of responders with treatment with multiple ketamine infusions and multiple ECTs at 1 months after EoT (*low certainty evidence*)
Follow-up of responders 3 months after EoT (MADRS) N=178 (1 RCT)	Mean DS was **19.18**	MD **3.61 lower** (6.26 lower to 0.96 lower)	⊕⊕⊕ Moderate [a]	Multiple ketamine infusions probably reduce depression severity scores of all patients slightly more than multiple ECTs at 3 months after EoT (*moderate certainty evidence*)
Follow-up of responders 6 months after EoT (MADRS) N=178 (1 RCT)	Mean DS was **18.49**	MD **1.57 lower** (4.31 lower to 1.17 higher)	⊕⊕ Low [a,d]	There may be little or no difference in depression severity scores of responders with treatment with multiple ketamine infusions and multiple ECTs at 6 months after EoT (*low certainty evidence*)

***GRADE**: a: study limitations (RoB); d: imprecision.*
***CI:** confidence interval; **DS**: depression severity; **EoT**: end of treatment; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MD**: mean difference; **N**: number of study participants; **RCT**: randomised controlled trial*

Neither of the two statistically significant results of depression severity (i.e., EoT for all patients, and three months follow-up after EoT) were considered clinically important when applying MID thresholds of 50% (red line) and 20% (blue line) (*Figure 7*). As such, we interpret these results as “less important benefit” (*Table 10*), in accordance with the EPOC standardised statements for reporting of effect (52).

2.2.6.5 Quality of life

Quality of life was measured by 16-item Quality-of-Life scale, with a scale ranging from 16 to 112. Data was provided only for responders at end of treatment, and at one, three- and six-months after end of treatment (55).

2.2.6.5.1 End of treatment

At end of treatment, the mean difference (95% CI; p-value) of quality of life for responders was −0.90 (−1.46 to −0.34; p=0.002), which is statistically significant in favour of ECT. In other words, of all responders in this study, patients who received multiple ECTs had higher quality of life-scores, i.e. better quality of life, at end of treatment, compared to patients who received multiple infusions of 0.5

mg/kg ketamine (*Figure 8*;*Table 11*). However, the difference in mean total quality of life-score between the two groups was only about one point.

2.2.6.5.2 One month after end of treatment

At one month after end of treatment, the mean difference (95% CI; p-value) of quality of life for responders was −1.20 (−1.76 to −0.64; p<0.0001), which is statistically significant in favour of ECT. In other words, of all responders in this study, patients who received multiple ECTs had higher quality of life-scores, i.e. better quality of life, at one month after end of treatment, compared to patients who received multiple infusions of 0.5 mg/kg ketamine (*Figure 8*;*Table 11*). However, the difference in mean total quality of life-score between the two groups was only about one point.

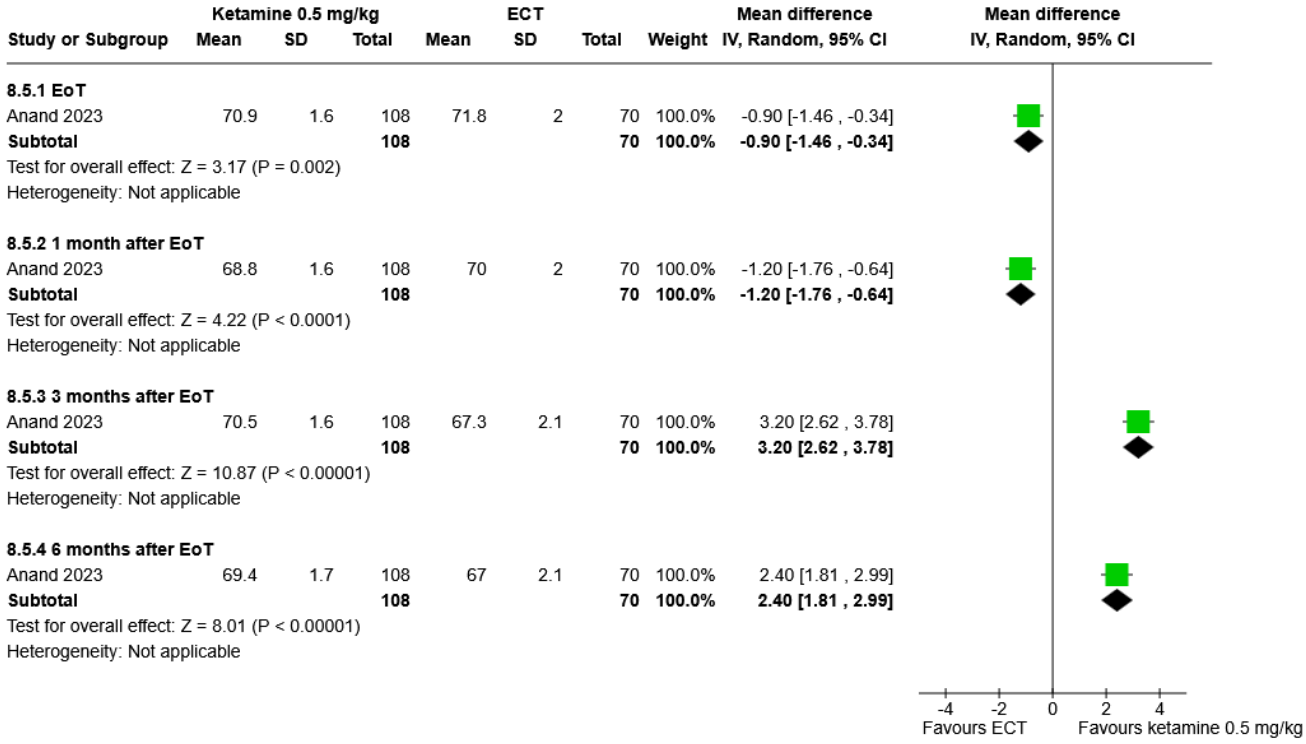


Figure 8: Multiple doses ketamine 0.5 mg/kg vs ECT: forest plot of quality of life

2.2.6.5.3 Three months after end of treatment

At three months after end of treatment, the mean difference (95% CI; p-value) of quality of life for responders was 3.20 (2.62 to 3.78; p<0.00001), which is statistically significant in favour of 0.5 mg/kg ketamine. In other words, of the all responders in this study, patients who received multiple infusions of 0.5 mg/kg ketamine had higher quality of life-scores, i.e. better quality of life, at three months after end of treatment, compared to patients who received multiple ECTs (*Figure 8*;*Table 11*). However, the difference in mean total quality of life-score between the two groups was only about three points.

2.2.6.5.4 Six months after end of treatment

At six months after end of treatment, the mean difference (95% CI; p-value) of quality of life for responders was 2.40 (1.81 to 2.99; p<0.00001), which is statistically significant in favour of 0.5 mg/kg ketamine. In other words, of the all responders in this study, patients who received multiple infusions of 0.5 mg/kg ketamine had higher quality of life-scores, i.e. better quality of life, at six months after end of treatment, compared to patients who received multiple ECTs (*Figure 8*;*Table 11*). However, the difference in mean total quality of life-score between the two groups was only about two points.

Table 11: Multiple doses ketamine 0.5 mg/kg vs ECT: summary of findings table for quality of life

Outcome: quality of life†	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ECT	Risk difference with ketamine 0.5 mg/kg		
EoT N=178 (1 RCT)	The mean QoL at EoT was **71.8**	MD **0.9 lower** (1.46 lower to 0.34 lower)	⊕⊕⊕ Moderate [a]	ECTs probably improve QoL more than multiple ketamine 0.5 mg/kg infusions at EoT (*moderate certainty evidence*)
1 month after EoT N=178 (1 RCT)	The mean QoL 1 month after EoT was **70.0**	MD **1.2 lower** (1.76 lower to 0.67 lower)	⊕⊕⊕ Moderate [a]	ECTs probably improve QoL more than multiple ketamine 0.5 mg/kg infusions at 1 months after EoT (*moderate certainty evidence*)
3 months EoT N=178 (1 RCT)	The mean QoL 3 months after EoT was **67.3**	MD **3.2 higher** (2.62 higher to 3.78 higher)	⊕⊕⊕ Moderate [a]	Multiple ketamine 0.5 mg/kg infusions probably improve QoL more than ECT at 3 months after EoT (*moderate certainty evidence*)
6 months after EoT N=178 (1 RCT)	The mean QoL 6 months after EoT was **67.0**	MD **2.4 higher** (1.81 higher to 2.99 higher)	⊕⊕⊕ Moderate [a]	Ketamine probably improve QoL more than ECT at 6 months after EoT (*moderate certainty evidence*)

†Assessed with 16-item Quality-of-Life scale, Scale from: 16 to 112
***GRADE**: a: study limitations (RoB); d: imprecision.*
***CI:** confidence interval; **MD**: mean difference; **N**: number of study participants; **QoL**: quality of life; **RCT**: randomised controlled trial*

2.2.6.6 Safety data

In the initial treatment phase, 25% of the patients who received multiple ketamine 0.5 mg/kg infusions and 32% of the patients who received multiple ECTs experienced at least one moderate or severe adverse event (*Table 12*) (55). In the follow-up phase, this was reduced to about 15% in both study groups. In the acute treatment phase, the most prevalent adverse event was headache, with an incidence of 8% and 7% the ketamine- and ECT-group, respectively. Few events were registered of the specific adverse events suggested to us by the clinical experts, and the distribution was fairly similar, though slightly higher in the ketamine-group. Of note, in the acute treatment phase suicidal ideation was twice as prevalent in the ketamine-group as in the ECT-group, though the numbers were very small (2% versus 1%). In the ECT-group, the prevalence of suicidal ideation was similar in both the acute treatment phase and the follow-up phase, whereas it was twice as high in the ketamine-group in the follow-up phase (4%). During the follow-up phase, the only suicide attempt registered in the study was by a patient in the ketamine-group (55).

Table 12: Multiple doses ketamine 0.5 mg/kg vs ECT: overview of adverse events

Anand *et al.* (55)	Acute treatment phase		Follow-up phase	
	Ketamine 0.5 mg/kg *(n=195)*	ECT *(n=170)*	Ketamine 0.5 mg/kg *(n=108)*	ECT *(n=70)*
Adverse events				
Number of patients with AE	49 (25%)	55 (32%)	17 (16%)	10 (14%)
Hypo- or hypertension	6 (3%)	4 (2%)	2 (2%)	0
Suicidal ideation	4 (2%)	2 (1%)	4 (4%)	1 (1%)
Headache	16 (8%)	12 (7%)	*n.d.*	*n.d.*
Serious adverse events				
Number of patients with AE	5 (3%)	4 (2%)	8 (7%)	3 (4%)
Cardiovascular event	1 (1%)	1 (1%)	1 (1%)	0
Suicidal ideation	3 (2%)	1 (1%)	4 (4%)	1 (1%)
Suicidal attempt	0	0	1 (1%)	0

2.2.7 Ketamine 0.5 mg/kg versus saline – single infusion

Four studies contributed to the comparison between single dose ketamine and saline: 1) Chen *et al.* 2018a, Su *et al.* 2017 (57;73), 2) Chen *et al.* 2018b (56), 3) Tiger *et al.* 2020 (75), and 4) Zolghadriha *et al.* 2024 (76). The intervention group was given a single infusion of 0.5 mg/kg ketamine, while the comparison group received a single infusion of saline (56;57;73;75;76).

2.2.7.1 Response

Three studies presented data on response, which was only provided at one day post-infusion (56;57;74;75). The included studies defined response as ≥50% reduction from baseline HDRS or MADRS.

The risk ratio (95% CI; p-value) of response was 3.02 (1.31 to 7.00; p=0.010) at one day post-infusion, which is statistically significant in favour of single infusions of ketamine 0.5 mg/kg. In other words, patients who received a single ketamine 0.5 mg/kg infusion were about three times more likely to experience response at one day post-infusion, i.e., ≥50% reduction in HDRS or MADRS scores, than patients who received a single saline infusion (*Figure 9*).

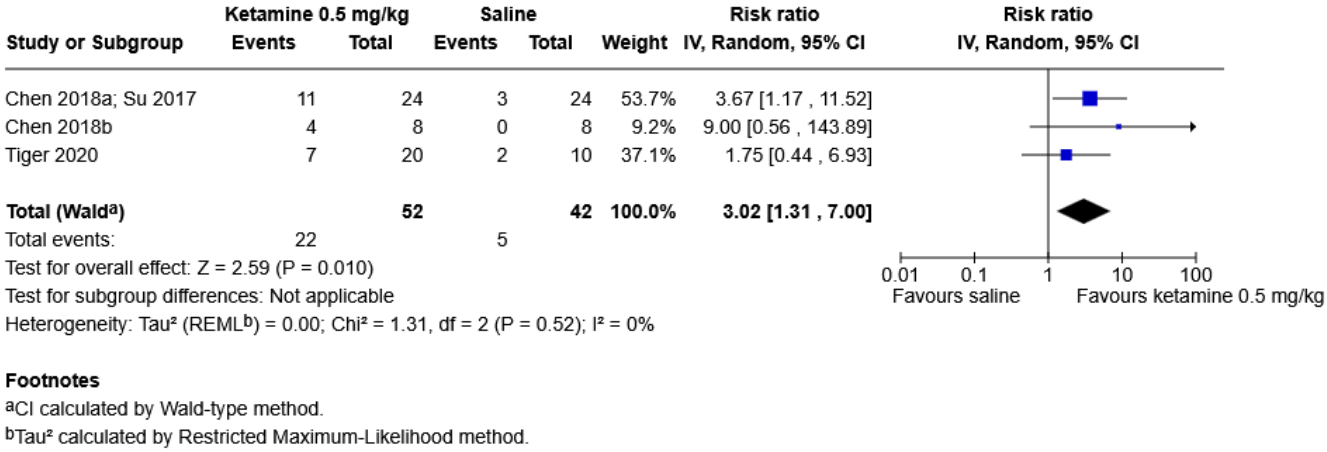


Figure 9: Single dose ketamine 0.5 mg/kg vs saline: forest plot of response

If 119 of 1 000 patients treated with a single saline infusion experienced response at one day post-infusion, then the anticipated risk difference would correspond to 240 more patients per 1 000 (i.e., 359 patients) treated with a single ketamine 0.5 mg/kg infusion having response at one day post-infusion (*Table 13*). The 95% CI shows that it is statistically possible that between 37 more patients (i.e., 156 patients) and 714 more patients (i.e., 833 patients) would be anticipated to experience response at one day post-infusion when receiving a single ketamine 0.5 mg/kg infusion than when receiving a single saline infusion.

Table 13: Single dose ketamine 0.5 mg/kg vs saline: summary of findings table for response

Outcome: response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with saline	Risk difference with ketamine 0.5 mg/kg			
1 day post infusion N=94 (3 RCTs)	119 per 1 000	**240 more per 1 000** (37 more to 714 more)	**RR 3.02** (1.31 to 7.00)	⊕⊕⊕ Moderate [b]	A single ketamine 0.5 mg/kg infusion probably improve the chance of response more than saline at 1 day post-infusion. (*moderate certainty evidence*)

***GRADE**: b: inconsistency*
***CI:** confidence interval; **HDRS**: Hamilton Depression Rating Scale; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.7.2 Depression severity

Three studies presented data on depression severity measured by MADRS at one or more of the following time points: one, three, and six to seven days, and one and two months post-infusion (57;73;75;76). As described in *2.1.6.3 Minimal important difference (MID)*, we applied MID thresholds of 20% and 50% improvement in the forest plots of depression severity scores. Note that these thresholds are rough estimations.

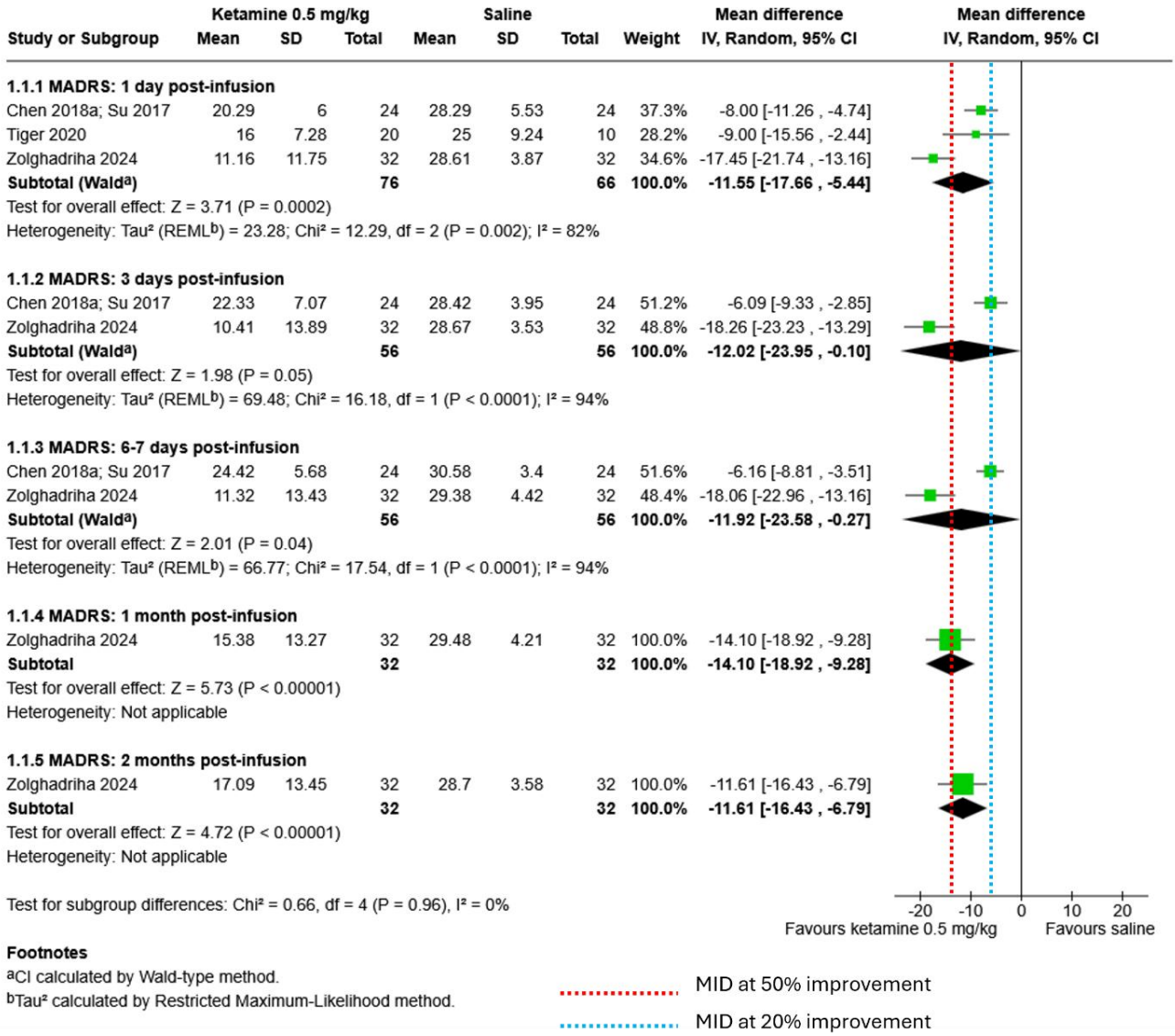


Figure 10: Single dose ketamine 0.5 mg/kg vs saline: forest plot of depression severity (MADRS).

2.2.7.2.1 One day post-infusion

At one day post-infusion, the mean difference (95% CI; p-value) of depression severity of all patients was −11.55 (−17.66 to −5.44; p=0.0002), which is statistically significant in favour of single infusions of ketamine 0.5 mg/kg. In other words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at one day post-infusion, compared to patients who received a single saline infusion (*Figure 10; Table 14*).

2.2.7.2.2 Three days post-infusion

At three days post-infusion, the mean difference (95% CI; p-value) of depression severity of all patients was −12.02 (−23.95 to −0.10; p=0.05), which is statistically significant in favour of single infusions of ketamine 0.5 mg/kg. In other words, patients who received a single 0.5 mg/kg ketamine

infusion had lower MADRS scores, i.e. less severe depression, at three days post-infusion, compared to patients who received a single saline infusion (*Figure 10; Table 14*).

2.2.7.2.3 Six to seven days post-infusion

At six to seven days post-infusion, the mean difference (95% CI; p-value) of depression severity of all patients was −11.92 (−23.58 to −0.27; p=0.04), which is statistically significant in favour of single infusions of ketamine 0.5 mg/kg. In other words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at six to seven days post-infusion, compared to patients who received a single saline infusion (*Figure 10; Table 14*).

Table 14: Single dose ketamine 0.5 mg/kg vs saline: summary of findings table for depression severity

Outcome: depression severity	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with saline	Risk difference with ketamine 0.5 mg/kg		
1 day post-infusion (MADRS) N=142 (3 RCTs)	-	MD **11.55 lower** (17.66 lower to 5.44 lower)	⊕⊕⊕ Moderate [b]	**MID50%**: A single ketamine 0.5 mg/kg infusion probably reduce the depression severity scores slightly more than saline (*moderate certainty evidence*)
				MID20%: A single ketamine 0.5 mg/kg infusion probably reduce the depression severity score more than saline (*moderate certainty evidence*)
3 days post-infusion (MADRS) N=112 (2 RCTs)	-	MD **12.02 lower** (23.95 lower to 0.1 lower)	⊕⊕⊕ Moderate [b]	**MID50%**: A single ketamine 0.5 mg/kg infusion probably reduce the depression severity scores slightly more than saline (*moderate certainty evidence*)
				MID20%: A single ketamine 0.5 mg/kg infusion probably reduce the depression severity score more than saline (*moderate certainty evidence*)
6-7 days post-infusion (MADRS) N=112 (2 RCTs)	-	MD **11.92 lower** (23.58 lower to 0.27 lower)	⊕⊕⊕ Moderate [b]	**MID50%**: A single 0.5 mg/kg ketamine infusion probably reduce the depression severity scores slightly more than saline (*moderate certainty evidence*)
				MID20%: A single ketamine 0.5 mg/kg infusion probably reduce the depression severity score more than saline (*moderate certainty evidence*)
1 month post-infusion (MADRS) N=64 (1 RCT)	Mean DS was **29,48**	MD **14.1 lower** (18.92 lower to 9.28 lower)	⊕⊕⊕ Moderate [d]	**MID50%**: A single ketamine 0.5 mg/kg probably reduce depression severity scores slightly more than saline (*moderate certainty evidence*)
				MID20%: A single ketamine 0.5 mg/kg infusion probably reduces the depression severity scores more than saline (*moderate certainty evidence*)
2 months post-infusion (MADRS) N=64 (1 RCT)	Mean DS was **28,7**	MD **11.61 lower** (16.43 lower to 6.79 lower)	⊕⊕⊕ Moderate [d]	**MID50%**: A single ketamine 0.5 mg/kg probably reduces depression severity scores slightly more than saline (*moderate certainty evidence*)
				MID20%: A single ketamine 0.5 mg/kg infusion probably reduces the depression severity scores more than saline (*moderate certainty evidence*)

***GRADE**: b: inconsistency; d: imprecision.*
***CI:** confidence interval; **DS**: depression severity; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MD**: mean difference; **N**: number of study participants; **RCT**: randomised controlled trial*

2.2.7.2.4 One month post-infusion

At one month post-infusion, the mean difference (95% CI; p-value) of depression severity of all patients was 14.10 (−18.92 to −9.28; p<0.00001), which is statistically significant in favour of single infusions of ketamine 0.5 mg/kg. In other words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at one month post-infusion, compared to patients who received a single saline infusion (*Figure 10; Table 14*).

2.2.7.2.5 Two months post-infusion

At two months post-infusion, the mean difference (95% CI; p-value) of depression severity of all patients was −11.61 (−16.43 to −6.79; p<0.00001), which is statistically significant in favour of single infusions of ketamine 0.5 mg/kg. In other words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at two months post-infusion, compared to patients who received a single saline infusion (*Figure 10; Table 14*).

None of the five statistically significant meta-analysis results of depression severity would be considered clinically relevant when interpreting the meta-analysis data with MID thresholds of 50% (red line) (*Figure 10*). Conversely, all would be considered clinically relevant when using a MID of 20% (blue line). When using the MID threshold of 50%, we interpret these results as “less important benefit”, in accordance with the EPOC standardised statements for reporting of effect (52). However, using the MID threshold of 20%, we interpret these results as “important benefit” (*Table 14*).

2.2.7.3 Safety data

Only one study presented data on adverse events (76). No adverse events were registered in the group that received single saline infusions, whereas all patients that received a single infusion of ketamine experienced some form of adverse event (*Table 15*) (76). Overall, the reported adverse events were mild in form of headache, nausea, and visual disturbances. Four patients in the ketamine-group experienced anxiety.

Table 15: Single dose ketamine 0.5 mg/kg vs saline: overview of adverse events

Zolghadriha *et al.* (76)	**Ketamine 0.5 mg/kg** *(n=32)*	**Saline** *(n=32)*
Nausea/vomiting	8 (25%)	0
Anxiety	4 (13%)	0
Visual disturbance	2 (6%)	0
Headache	32 (100%)	0

2.2.8 Ketamine 0.5 mg/kg versus saline – multiple infusion

Three studies contributed to the comparison between multiple doses of 0.5 mg/kg ketamine and saline: 1) Ahmed *et al.* 2023 (54), 2) Ionescu *et al.* 2019 (61), and 3) Singh *et al.* 2016b (72). The treatment frequency differed between the studies: In the study by Ahmed *et al.*, participants received one infusion every week for two weeks; in total two infusions (54), whereas participants in the Ionescu-study received two infusions every week for three weeks; in total six infusions (61). In the study by Singh *et al.* (2016b), there were four treatment groups, where two groups received two infusions (ketamine or saline) every week for four weeks; in total eight infusions, and the other two received three infusions (ketamine or saline) every week for four weeks; in total twelve infusions (72). In our analyses, we kept the data from the Singh 2016b-study separate, as if they were from two different studies, but still analysed them together in meta-analyses across the treatment regimes.

All studies reported relevant data on the outcomes, i.e., response, remission and/or depression severity, at one time point only, and given the different treatment durations, this varied greatly between the studies. In the Ahmed-study, response and depression severity were assessed one week after the second and final infusion (54), whereas all three outcomes were assessed four hours after the sixth and final infusion in the Ionescu-study (61). In contrast, in the Singh 2016b-study (2016b), data on response and remission were only presented at day 15, which was half-way though the scheduled treatment period of four weeks, while depression severity was reported on day 29 (72). Please note that we have chosen to use the term “end of treatment” when referencing all of the results below, although the time points in the Singh-study do not necessarily reflect the actual end of treatment.

2.2.8.1 Response

All three studies reported data on response at end of treatment, and defined it as ≥50% decrease or improvement in HDRS (54;61) or MADRS scores (72).

At end of treatment, the risk ratio (95% CI; p-value) of response was 2.86 (0.86 to 9.56; p=0.09) (see note above). In other words, patients who received multiple infusions of ketamine 0.5 mg/kg were almost three times more likely to experience response at end of treatment, i.e., ≥50% reduction in HDRS or MADRS scores, than patients who received multiple infusions of saline (*Figure 11*). However, as the confidence interval includes values below 1, it is *statistically* possible that treatment with multiple 0.5 mg/kg ketamine infusions actually have equal or less chance of response at end of treatment, compared to patients treated with multiple saline infusions.

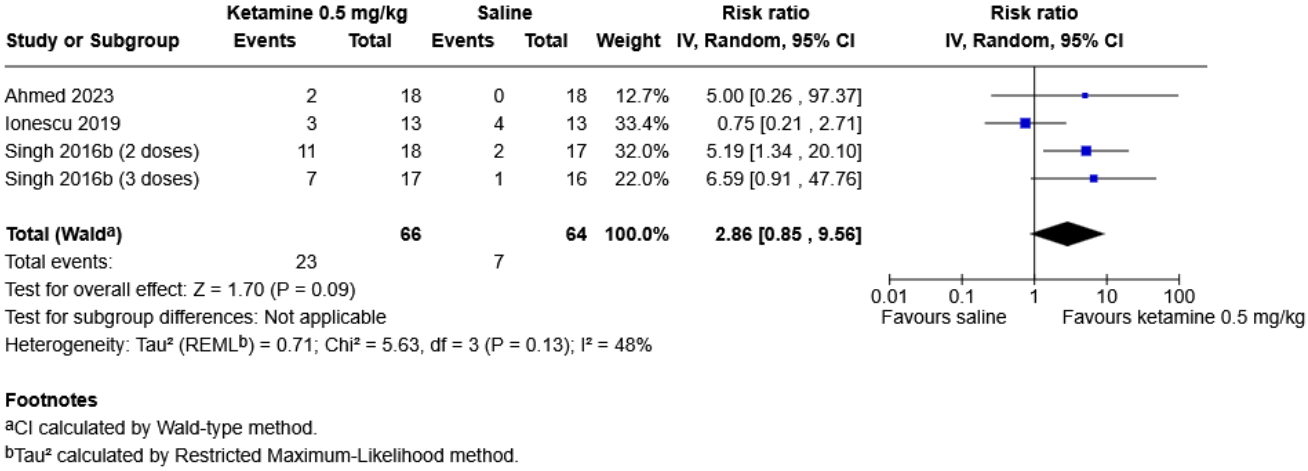


Figure 11: Multiple doses ketamine 0.5 mg/kg vs saline: forest plot of response

If 109 of 1 000 patients treated with multiple saline infusions experienced response at the end of treatment, then the anticipated risk difference would correspond to 203 more patients per 1 000 (i.e., 312 patients) treated with multiple infusions of ketamine 0.5 mg/kg having response (*Table* **16**). The 95% CI shows that it is statistically possible that between 16 fewer patients (i.e., 93 patients) and 936

more patients (i.e., all patients)[1] would be anticipated to experience response at end of treatment when receiving multiple 0.5 mg/kg ketamine infusions than when receiving multiple saline infusions.

Table 16: Multiple doses ketamine 0.5 mg/kg vs saline: summary of findings table for response

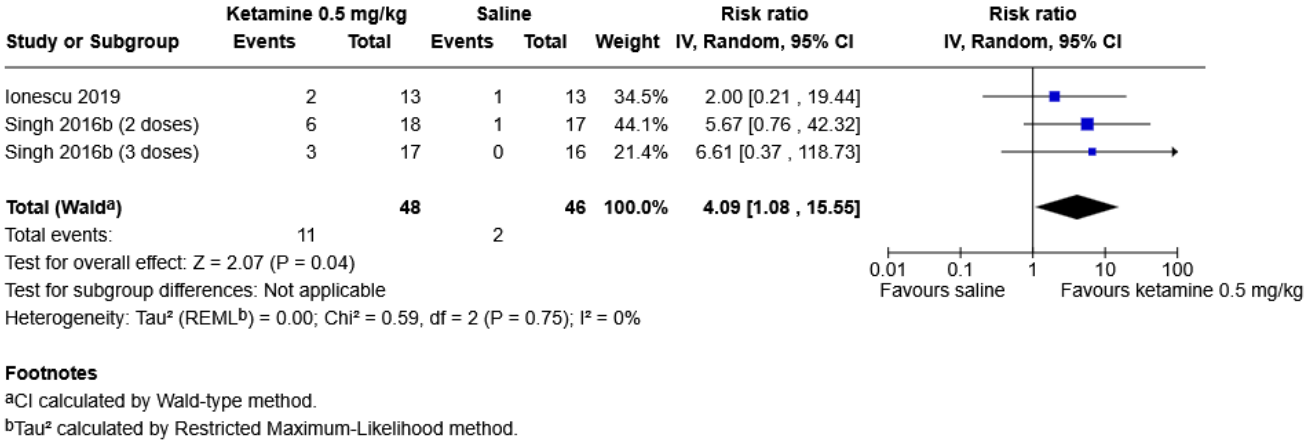
Outcome: response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with saline	Risk with ketamine 0.5 mg/kg			
EoT N=130 (3 RCTs)	109 per 1 000	**203 more per 1 000** (16 fewer to 936 more)	**RR 2.86** (0.85 to 9.56)	⊕ Very low [a,b,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions improve the chance of response more than saline at EoT, because the certainty of this evidence is very low.

***GRADE**: a: study limitations (RoB); b: inconsistency; d: imprecision.*
***CI:** confidence interval; **EoT**: end of treatment; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.8.2 Remission

Two studies reported data on remission, and only at one time point: at end of treatment. The definition of remission varied: the Ionescu-study defined remission as HDRS score ≤7 (61), while the Singh 2016b-study defined it as MADRS score <10 (72).

At end of treatment, the risk ratio (95% CI; p-value) of remission was 4.09 (1.08 to 15.55; P=0.04) (see note above), which is statistically significant in favour of multiple infusions of ketamine 0.5 mg/kg. In other words, patients who received multiple 0.5 mg/kg ketamine infusions were over four times more likely to achieve remission at end of treatment than patients who received multiple saline infusions (*Figure 12*).



Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Figure 12: Multiple doses ketamine 0.5 mg/kg vs saline: forest plot of remission

If 43 of 1 000 patients treated with multiple saline infusions achieved remission at end of treatment, then the anticipated risk difference would correspond to 134 more patients per 1 000 (i.e., 177 patients) treated with multiple infusions of ketamine 0.5 mg/kg achieve remission (*Table 17*). The 95% CI shows that it is statistically possible that between 3 more patients (i.e., 46 patients) and 633 more patients (i.e., 676 patients) would be anticipated to achieve remission at end of treatment when receiving multiple 0.5 mg/kg ketamine infusions than when receiving multiple saline infusions.

[1] *As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution.*

Table 17: Multiple doses ketamine 0.5 mg/kg vs saline: Summary of findings table for remission

Outcome: remission	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with saline	Risk with ketamine 0.5 mg/kg			
EoT N=94 (2 RCTs)	43 per 1 000	**134 more per 1 000** (3 more to 633 more)	**RR 4.09** (1.08 to 15.55)	⊕⊕ Low [a,d]	Multiple ketamine 0.5 mg/kg infusions may improve the chance of remission more than saline at EoT (*low certainty evidence*)

***GRADE**: a: study limitations (RoB); d: imprecision.*
***CI:** confidence interval; **EoT:** end of treatment; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.8.3 Depression severity

Two studies reported depression severity as measured by HDRS (54;61), and one study by MADRS (72). As described in *2.1.6.3 Minimal important difference (MID)*, we applied MID thresholds of 20% and 50% improvement in the forest plots of depression severity scores. Note that these thresholds are rough estimations and only relevant for the statistically significant results.

2.2.8.3.1 MADRS

At end of treatment, the mean difference (95% CI; p-value) of depression severity as measured by MADRS was −19.11 (−23.10 to −15.12; p<0.00001), which is statistically significant in favour of multiple infusions of ketamine 0.5 mg/kg. In other words, patients who received multiple 0.5 mg/kg ketamine infusions in this study had lower MADRS scores, i.e. less severe depression, at end of treatment, compared to patients who received multiple saline infusions (*Figure 13*;*Table 18*). Note that this data was reported by only one study, with two separate treatment regimens, i.e., two doses per week or three doses per week for four weeks (72).

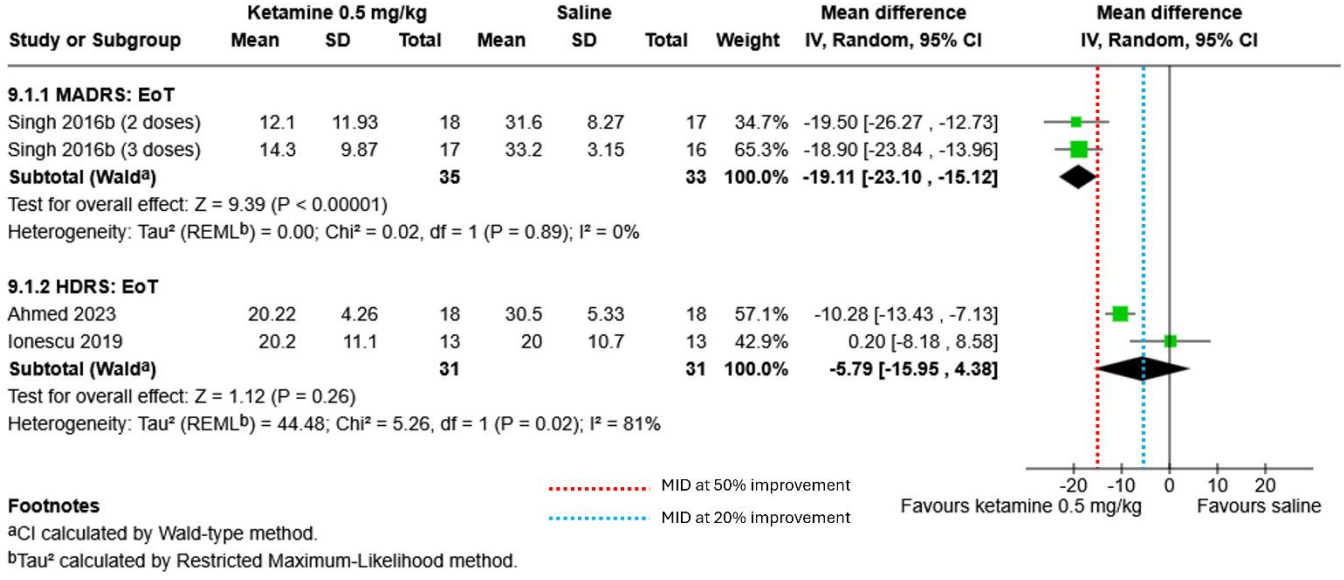


Figure 13: Multiple doses ketamine 0.5 mg/kg vs saline: forest plot of depression severity.

2.2.8.3.2 HDRS

At end of treatment, the mean difference (95% CI; p-value) of depression severity as measured by HDRS was −5.79 (−15.95 to 4.38; p=0.26). In other words, patients who received multiple 0.5 mg/kg ketamine infusions in this study had lower HDRS scores, i.e. less severe depression, at end of treatment, compared to patients who received multiple saline infusions (*Figure 13*;*Table 18*). However, as the confidence interval includes values above 0, it is *statistically* possible that patients who receive

multiple 0.5 mg/kg ketamine infusions actually have equal or higher depression severity, i.e., HDRS scores, at end of treatment, compared to patient who receive multiple saline infusions.

Table 18: Multiple doses ketamine 0.5 mg/kg vs saline: summary of findings table for depression severity

Outcome: depression severity (MADRS)	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with saline	Risk difference with ketamine 0.5 mg/kg		
EoT (MADRS) N=68 (1 RCTs)	-	MD **19.11 lower** (23.1 lower to 15.12 lower)	⊕⊕⊕ Moderate [a]	Multiple ketamine 0.5 mg/kg infusions probably reduce the depression severity (MADRS) scores more than saline at EoT (*moderate certainty evidence*)
EoT (HDRS) N=62 (2 RCTs)	-	MD **5.79 lower** (15.95 lower to 4.38 higher)	⊕ Very low [a,b,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions reduce the depression severity (HDRS) scores more than saline at EoT because the certainty of this evidence is very low.

***GRADE**: a: study limitations (RoB); b: inconsistency; d: imprecision.*
***CI:** confidence interval; **EoT**: end of treatment; **HDRS**: Hamilton Depression Rating Scale; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MD**: mean difference; **N**: number of study participants; **RCT**: randomised controlled trial*

The statistically significant meta-analysis result of depression severity (i.e., MADRS, EoT) would be considered clinically relevant with both MID threshold 20% (blue line) and 50% (red line) (*Figure 13*). As such, we interpret these results as "important benefit" (*Table 18*), in accordance with the EPOC standardised statements for reporting of effect (52).

2.2.8.4 Safety data

Only one study presented data on adverse events (72). Of all patients who received ketamine-infusions, 76-83% experienced at least one adverse event. In contrast, about 50% of patients who received saline infusions experienced at least one adverse event (72). Headache was the most common of the adverse events reported in the publication (72). While headache had a similar distribution between the ketamine- and the saline-groups for twice weekly administration, it was more prevalent in the ketamine-group for trice weekly administration (*Table 19*).

Table 19: Multiple doses ketamine 0.5 mg/kg vs saline: overview of adverse events

Singh 2016b *et al.* (72)	Twice weekly for 4 weeks		Trice weekly for 4 weeks	
	Ketamine 0.5 mg/kg *(n=18)*	Saline *(n=17)*	Ketamine 0.5 mg/kg *(n=17)*	Saline *(n=16)*
Adverse events – *most common events ≥20% patients in any group*				
Number of patients with AE	15 (83%)	9 (53%)	13 (76%)	8 (50%)
Nausea/vomiting	3 (17%)	1 (6%)	4 (24%)	2 (13%)
Anxiety	5 (28%)	0	1 (6%)	0
Headache	4 (22%)	5 (29%)	7 (41%)	1 (6%)
Serious adverse events				
Suicide attempt	1 (6%)	0	0	0
Anxiety	1 (6%)	0	0	0

One suicide attempt and one case of anxiety were the only serious adverse events presented in the publication by Singh et al. (2016b); both in the twice weekly ketamine-group (72).

2.2.9 Ketamine ≥0.5 mg/kg versus midazolam – single infusion

Four studies contributed to the comparison between single dose ketamine and midazolam: 1) Fava 2020/Salloum 2020 (59;69), 2) Lijffijt 2022 (63), 3) Murrough 2013 (64), and 4) Su 2023 (74). The intervention groups were given a single infusion of 0.5 and/or 1.0 mg/kg ketamine, while the comparison groups received a single infusion of 0.03 or 0.045 mg/kg midazolam. Fava/Salloum was the only study that investigated several doses of ketamine versus midazolam. In accordance with input from our clinical experts, we pooled the response data from the intervention groups that received 0.5 and 1.0 mg/kg ketamine in our data analysis and present the intervention group as ≥0.5 mg/kg ketamine. For all other outcomes, i.e., relapse on response, remission and depression severity, the intervention group is presented as 0.5 mg/kg ketamine.

2.2.9.1 Response

All four studies presented data on response, but at various time points (59;63;64;69;74). The included studies defined response as ≥50% reduction from baseline HDRS (59) or MADRS (63;64;74).

2.2.9.1.1 One day post-infusion

At one day post-infusion, the risk ratio (95% CI; p-value) of response was 2.86 (1.31 to 6.24; p=0.008), which is statistically significant in favour of single infusions of ketamine ≥0.5 mg/kg. In other words, patients who received a single ketamine ≥0.5 mg/kg infusion were almost three times more likely to experience response at one day post-infusion, i.e., ≥50% reduction in HDRS or MADRS scores, than patients who received a single midazolam infusion (*Figure 14*).

If 205 of 1 000 patients treated with a single midazolam infusion experienced response at one day post-infusion, then the anticipated risk difference would correspond to 380 more patients per 1 000 (i.e., 585 patients) treated with a single ketamine ≥0.5 mg/kg infusion having response at one day post-infusion (*Table 20*). The 95% CI shows that it is statistically possible that between 63 more patients (i.e., 268 patients) and 1072 more patients (i.e., all patients)[1] would be anticipated to experience response at one day post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single midazolam infusion.

2.2.9.1.2 Three days post-infusion

At three days post-infusion, the risk ratio (95% CI; p-value) of response was 2.96 (1.30 to 6.75; p=0.010), which is statistically significant in favour of single infusions of ketamine ≥0.5 mg/kg. In other words, patients who received a single ketamine ≥0.5 mg/kg infusion were almost three times as likely to experience response at three days post-infusion, i.e., ≥50% reduction in HDRS or MADRS scores, than patients who received a single midazolam infusion (*Figure 14*).

If 97 of 1 000 patients treated with a single midazolam infusion experienced response at three days post-infusion, then the anticipated risk difference would correspond to 191 more patients per 1 000 (i.e., 288 patients) treated with a single ketamine ≥0.5 mg/kg infusion having response at three days post-infusion (*Table 20*). The 95% CI shows that it is statistically possible that between 29 more patients (i.e., 126 patients) and 560 more patients (i.e., 657 patients) would be anticipated to experience response at three days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single midazolam infusion.

[1] *As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution*

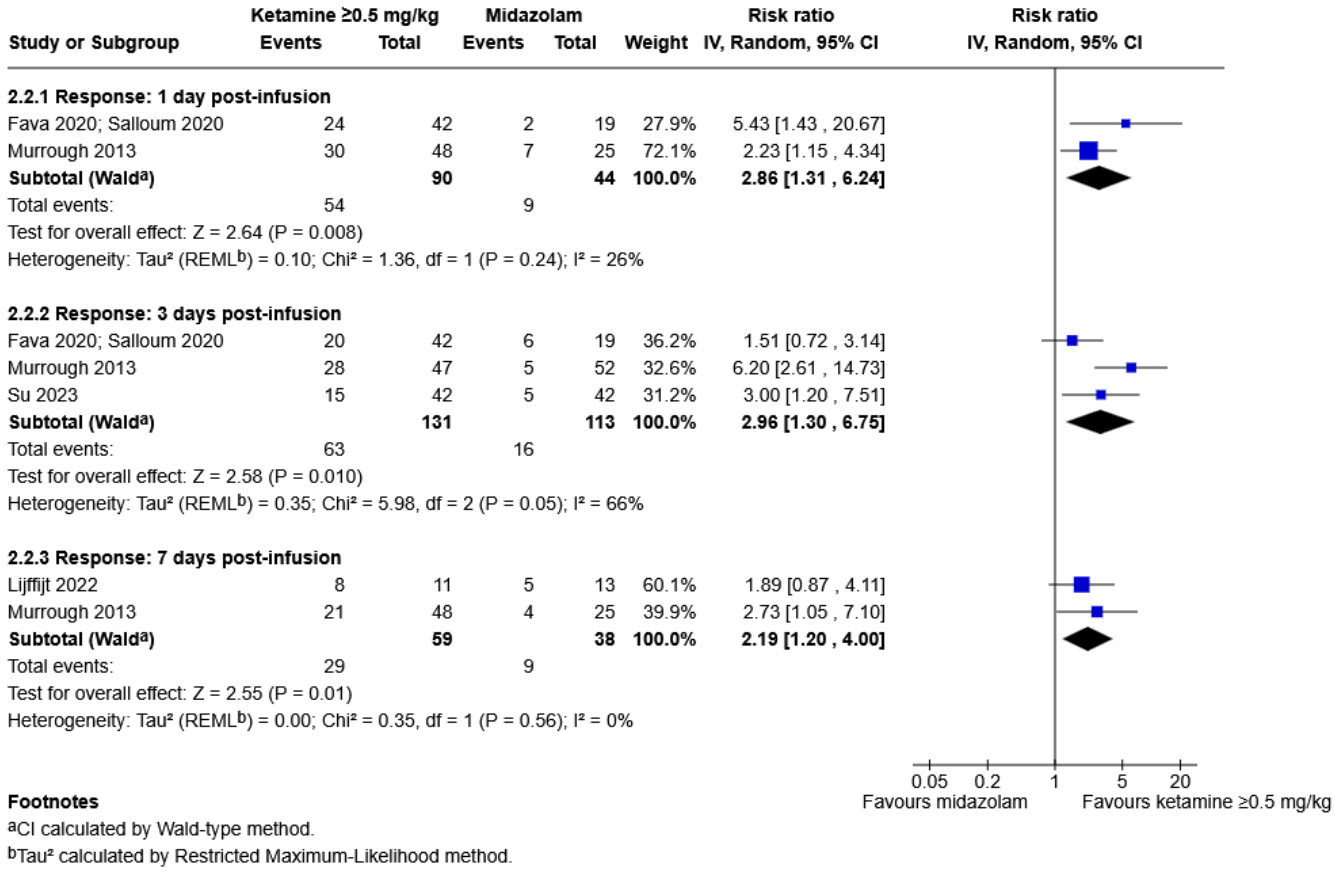


Figure 14: Single dose ketamine ≥0.5 mg/kg vs midazolam: forest plot of response

2.2.9.1.3 Seven days post-infusion

At seven days post-infusion, the risk ratio (95% CI; p-value) of response was 2.19 (1.20 to 4.00; p=0.01), which is statistically significant in favour of single infusions of ketamine ≥0.5 mg/kg. In other words, patients who received a single ketamine ≥0.5 mg/kg infusion were over twice as likely to experience response at three days post-infusion, i.e., ≥50% reduction in HDRS or MADRS scores, than patients who received a single midazolam infusion (*Figure 14*).

If 237 of 1 000 patients treated with a single midazolam infusion experienced response at seven days post-infusion, then the anticipated risk difference would correspond to 282 more patients per 1 000 (i.e., 519 patients) treated with a single ketamine ≥0.5 mg/kg infusion having response at seven days post-infusion (*Table 20*). The 95% CI shows that it is statistically possible that between 47 more patients (i.e., 284 patients) and 711 more patients (i.e., 948 patients) would be anticipated to experience response at seven days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single midazolam infusion.

Table 20: Single dose ketamine ≥0.5 mg/kg vs midazolam: summary of findings table for response

Outcome: response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with midazolam	Risk difference with ketamine ≥0.5 mg/kg			
1 day post-infusion N=134 (2 RCTs)	205 per 1 000	**380 more per 1 000** (63 more to 1 072 more)	**RR 2.86** (1.31 to 6.24)	⊕⊕⊕ Moderate [a]	Single ketamine ≥0.5 mg/kg infusions probably improve the chance of response more than midazolam at 1 day post-infusion. (*moderate certainty evidence*)

Outcome: response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with midazolam	Risk difference with ketamine ≥0.5 mg/kg			
3 days post-infusion N=244 (3 RCTs)	97 per 1 000	**191 more per 1 000** (29 more to 560 more)	**RR 2.96** (1.30 to 6.75)	⊕⊕ Low [a,b]	Single ketamine ≥0.5 mg/kg infusions may improve the chance of response more than midazolam at 3 days post-infusion. (*low certainty evidence*)
7 days post-infusion N=97 (2 RCTs)	237 per 1 000	**282 more per 1 000** (47 more to 711 more)	**RR 2.19** (1.20 to 4.00)	⊕⊕⊕ Moderate [d]	Single ketamine ≥0.5 mg/kg infusions probably improve the chance of response more than midazolam at 7 days post-infusion. (*moderate certainty evidence*)

***GRADE**: a: study limitations (RoB); b: inconsistency; d: imprecision.*
***CI:** confidence interval; **HDRS**: Hamilton Depression Rating Scale; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.9.2 Relapse after response

Only one study presented data on relapse after response, and only at 14 days post-infusion (64). The study defined relapse as increase in MADRS score to ≥20 in patients with response (64).

At 14 days post-infusion, the risk ratio (95% CI; p-value) of relapse of responders was 0.57 (0.17 to 1.88; p=0.36). In other words, patients in this study who responded on single infusions of 0.5 mg/kg ketamine were 43% less likely to relapse 14 days post-infusion, compared to patients who responded on single infusions of midazolam (*Figure 15*). However, as the confidence interval includes values above 1, it is statistically possible that responders on single 0.5 mg/kg ketamine infusions are actually at equal or higher risk of relapsing 14 days post-infusion, compared to responders on single midazolam infusions.

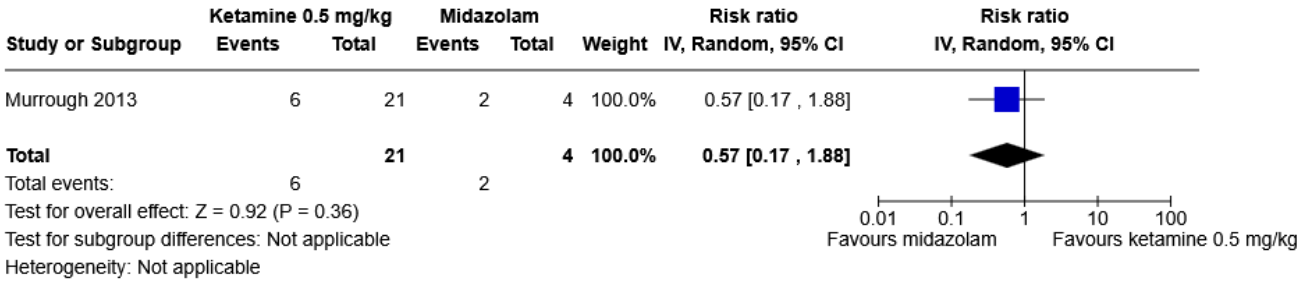


Figure 15: Single dose ketamine 0.5 mg/kg vs midazolam: forest plot of relapse after response

If 500 of 1 000 patients treated with single midazolam infusions experienced relapse after response at 14 days post-infusion, then the anticipated risk difference would correspond to 215 fewer patients per 1 000 (i.e., 285 patients) treated with single ketamine 0.5 mg/kg infusions relapsing after response at 14 days post-infusion (*Table 21*). The 95% CI shows that it is statistically possible that between 415 fewer patients (i.e., 85 patients) and 440 more patients (i.e., 940 patients) would be anticipated to relapse after response at 14 days post-infusion when receiving a single ketamine 0.5 mg/kg infusion than when receiving a single midazolam infusion.

Table 21: Single dose ketamine 0.5 mg/kg vs midazolam: summary of findings table for relapse after response

Outcome: relapse on response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with midazolam	Risk difference with ketamine 0.5 mg/kg			
14 days post-infusion N=25 (1 RCT)	500 per 1 000	**215 fewer per 1 000** (415 fewer to 440 more)	**RR 0.57** (0.17 to 1.88)	⊕⊕ Low [c,d]	Single 0.5 mg/kg ketamine infusions may reduce the risk of relapse after response slightly more than midazolam at 14 days post-infusion. (*low certainty evidence*)

***GRADE**: c: indirectness; d: imprecision.*
***CI:** confidence interval; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.9.3 Remission

Only one study presented data on remission, and only at seven days post-infusion (63). The study defined remission as MADRS score ≤9 (63).

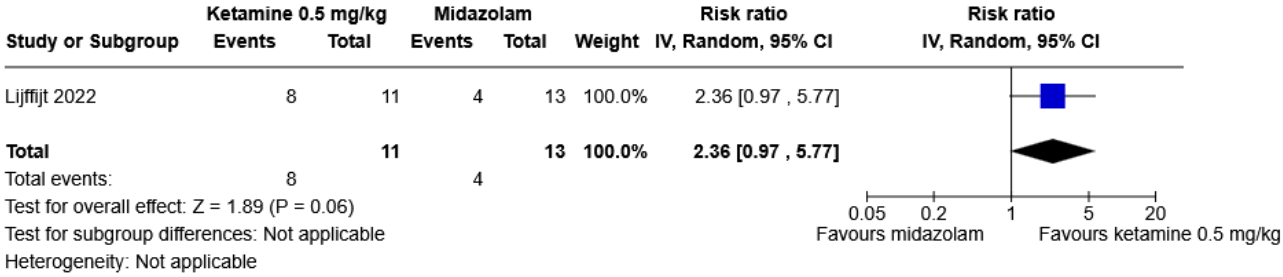


Figure 16: Single dose ketamine 0.5 mg/kg vs midazolam: forest plot of remission

At seven days post-infusion, the risk ratio (95% CI; p-value) of remission was 2.36 (0.97 to 5.77; p=0.06). In other words, patients who received a single 0.5 mg/kg ketamine infusion were over two times more likely to experience remission at seven days post-infusion than patients who received a single midazolam infusion (*Figure 16*).

Table 22: Single dose ketamine 0.5 mg/kg vs midazolam: summary of findings table for remission

Outcome: remission	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with midazolam	Risk difference with ketamine 0.5 mg/kg			
7 days post-infusion N=24 (1 RCT)	308 per 1 000	**418 more per 1 000** (9 fewer to 1 468 more)	**RR 2.36** (0.97 to 5.77)	⊕⊕⊕ Moderate [d]	Single ketamine 0.5 mg/kg infusions probably improve the chance of remission slightly more than midazolam at 7 days post-infusion (*moderate certainty evidence*)

***GRADE**: d: imprecision.*
***CI:** confidence interval; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

If 308 of 1 000 patients treated with single midazolam infusions achieved remission at seven days post-infusion, then the anticipated risk difference would correspond to 418 more patients per 1 000 (i.e., 726 patients) treated with single infusions of ketamine 0.5 mg/kg achieve remission (*Table 22*). The 95% CI shows that it is statistically possible that between 9 fewer patients (i.e., 299 patients) and

1468 more patients (i.e., all patients)[1] would be anticipated to achieve remission at seven days post-infusion when receiving a single 0.5 mg/kg ketamine infusion than when receiving a single midazolam infusion.

2.2.9.4 Depression severity

Only one study presented data on depression severity measured by MADRS at one and seven days post-infusion (64). As described in *2.1.6.3 Minimal important difference (MID)*, we applied MID thresholds of 20% and 50% improvement in the forest plots of depression severity scores. Note that these thresholds are rough estimations.

2.2.9.4.1 One day post-infusion

At one day post-infusion, the mean difference (95% CI; p-value) of depression severity of all patients was −7.95 (−12.67 to −3.23; p=0.0010), which is statistically significant in favour of single infusions of ketamine 0.5 mg/kg. In other words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at one day post-infusion, compared to patients who received a single midazolam infusion (*Figure 17*; *Table 23*).

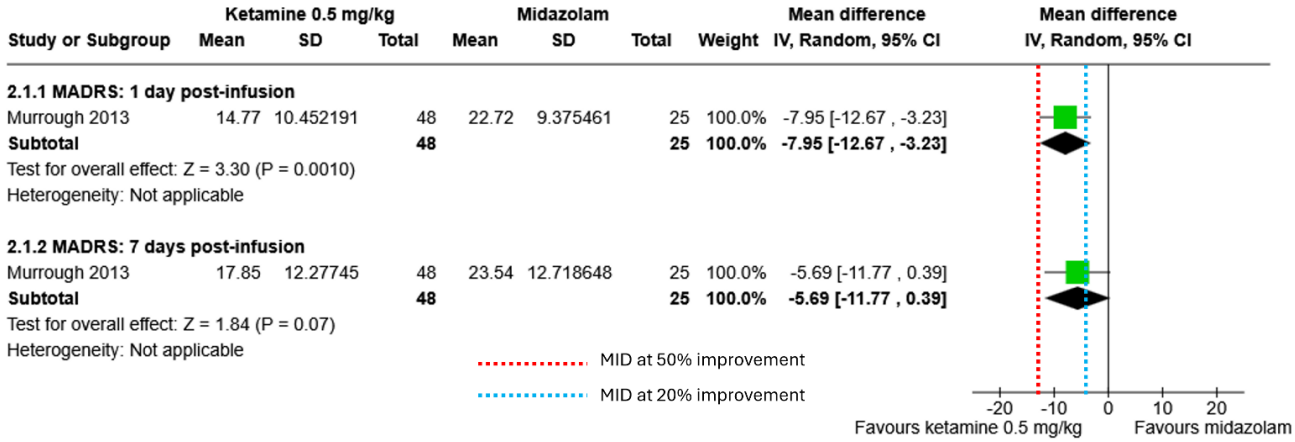


Figure 17: Single dose ketamine 0.5 mg/kg vs midazolam: forest plot of depression severity (MADRS).

2.2.9.4.2 Seven days post-infusion

At seven days post-infusion, the mean difference (95% CI; p-value) of depression severity of all patients was −5.69 (−11.77 to 0.39; p=0.07). In other words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at seven days post-infusion, compared to patients who received a single midazolam infusion (*Figure 17*;*Table 23*). However, as the confidence interval includes values above 0, it is statistically possible that patients receiving a single 0.5 mg/kg ketamine infusion actually have equal or higher depression severity, i.e., MADRS scores, at seven days post-infusion, compared to patients receiving a single midazolam infusion.

The statistically significant meta-analysis result of depression severity, i.e., at 1 day post-infusion would not be considered clinically relevant when interpreting the meta-analysis data with MID thresholds of 50% (red line) (*Figure 17*). However, it would be considered clinically relevant when using a MID of 20% (blue line). When using the MID threshold of 50%, we interpret these results as “less important benefit”, in accordance with the EPOC standardised statements for reporting of effect (52). However, using the MID threshold of 20%, we interpret these results as “important benefit” (*Table* **23**).

[1] As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution

Table 23: Single dose ketamine 0.5 mg/kg vs midazolam: summary of findings table for depression severity

Outcome: depression severity (MADRS)	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with midazolam	Risk difference with ketamine 0.5 mg/kg		
1 day post-infusion N=73 (1 RCT)	Mean DS was **22,72**	MD **7.95 lower** (12.67 lower to 3.23 lower)	⊕⊕⊕ Moderate [d]	**MID50%**: A single ketamine 0.5 mg/kg infusion probably reduces depression severity scores slightly more than midazolam at 1 day post-infusion (*moderate certainty evidence*)
				MID20%: A single ketamine 0.5 mg/kg infusion probably reduces depression severity scores more than midazolam at 1 day post-infusion (*moderate certainty evidence*)
7 days post-infusion N=73 (1 RCT)	Mean DS was **23,54**	MD **5.69 lower** (11.77 lower to 0.39 higher)	⊕⊕⊕ Moderate [d]	A single ketamine 0.5 mg/kg infusion probably reduces depression severity scores slightly more than midazolam at 7 days post-infusion (*moderate certainty evidence*)

***GRADE**: d: imprecision.*
***CI:** confidence interval; **DS**: depression severity; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MD**: mean difference; **MID**: Minimal Important Difference; **N**: number of study participants; **RCT**: randomised controlled trial*

2.2.9.5 Safety data

All four studies presented some data on adverse events (59;63;64;69;74). As presented in the study by Fava/Salloum, 40% of the study population who received a ≥0.5 ketamine (i.e., 0.5 mg/kg and 1.0 mg/kg) infusion experienced an adverse event, compared to 37% of patients who received a single midazolam-infusion (*Table 24*) (59;69). However, the number of adverse events that were reported was higher in the ketamine-groups (0.5 mg/kg and 1.0 mg/kg) than in the midazolam-group. Similar numbers were not presented in the other three studies.

One of the most common adverse events was nausea/vomiting, which was reported on by all four studies. The results differed, as the studies by Fava/Salloum and Murrough showed a higher prevalence of nausea among patients who received ketamine-infusions (59;64;69), while the opposite was shown in the studies by Lijffijt and Su (63;74). The study by Murrough reported similar prevalence of anxiety in both the ketamine- and midazolam-group, whereas in the Lijffijt-study the prevalence was over twice as high in the midazolam-group as in the ketamine-group (63;64).

Urinary problem was reported on by Lijffijt and Murrough, who both showed higher prevalence in the ketamine-group (17-18%) than in the midazolam-group (0-8%) (63;64).

Serious events of suicide were attempted by one patient in the midazolam-group in the Lijffijt-study (63), and two patients in the midazolam-group and one patient in the ketamine-group in the study by Su *et al.* (74).

Table 24: Single dose ketamine ≥0.5 mg/kg vs midazolam: overview of adverse events

	Fava/Salloum (59;69)		**Lijffijt** (63)		**Murrough** (64)**		**Su 2023** (74)	
	Ketamine* ≥0.5 *(n=42)*	**MDZ** *(n=19)*	**Ketamine 0.5** *(n=11)*	**MDZ** *(n=13)*	**Ketamine 0.5** *(n=48)*	**MDZ** *(n=25)*	**Ketamine 0.5** *(n=42)*	**MDZ** *(n=42)*
Adverse events								
Number of patients with AE	17 (40%)	7 (37%)	-	-	-	-	-	-
Number of AE	32 (76%)	10 (53%)	-	-	-	-	-	-
Cardiovascular event	-	-	1 (9%)	0	8 (17%)	4 (16%)	-	-
Hypo- or hypertension	1 (2%)	0	-	-	2 (4%)	0	-	-

	Fava/Salloum (59;69)		**Lijffijt** (63)		**Murrough** (64)**		**Su 2023** (74)	
	Ketamine* ≥0.5 *(n=42)*	**MDZ** *(n=19)*	**Ketamine 0.5** *(n=11)*	**MDZ** *(n=13)*	**Ketamine 0.5** *(n=48)*	**MDZ** *(n=25)*	**Ketamine 0.5** *(n=42)*	**MDZ** *(n=42)*
Brady- or tachycardia	1 (2%)	0	-	-	1 (2%)	0	-	-
Suicidal ideation	1 (2%)	0	-	-	-	-	-	-
Nausea/vomiting	8 (19%)	0	0	5 (38%)	7 (15%)	2 (8%)	2 (5%)†	4 (10%)†
Urinary problem	-	-	2 (18%)	1 (8%)	8 (17%)	0	-	-
Anxiety	-	-	1 (9%)	3 (23%)	14 (29%)	7 (28%)	-	-
Increased or decreased saliva	-	-	1 (9%)	3 (23%)	4 (8%)	3 (12%)	-	-
Visual disturbances	-	-	1 (9%)	1 (8%)	5 (10%)	2 (8%)	-	-
Involuntary movements	-	-	1 (9%)	2 (15%)	3 (6%)	2 (8%)	-	-
Headache	4 (10%)	0	2 (18%)	4 (31%)	15 (31%)	7 (28%)	-	-
Serious adverse events								
Suicidal attempt	0	0	0	1 (8%)	-	-	1 (2%)	2 (5%)

Doses as mg/kg.

**Numbers summarised from ketamine 0.5 mg/kg and 1.0 mg/kg groups.*

***Murrough: adverse events as reported on 1-7 days post-infusion.*

† Su: reports of nausea were registered during infusion

MDZ: midazolam. Midazolam dose was 0.045 mg/kg in all studies except for Lijffijt, where the dose was 0.03 mg/kg.

2.2.10 Ketamine 0.5 mg/kg versus midazolam – multiple infusions

Three studies contributed to the comparison between multiple doses of ketamine and midazolam: 1) Gallagher 2020 (60), 2) Pattanaseri 2024 (65), and 3) Shiroma 2020 (70). The treatment frequency differed between the studies: In the study by Gallagher *et al.*, participants received one infusion (ketamine or midazolam) every week for four weeks; in total four infusions (60), whereas the participants in the Pattanaseri-study received three infusions (ketamine or midazolam) for one week; in total three infusions (65). In the study by Shiroma *et al.,* participants received three infusions every week for two weeks. However, the set-up of this study was different, as the first five infusions in the comparator group was midazolam, followed by ketamine 0.5 mg/kg in the final sixth infusion (70). In order to use data from this study in our analyses, we only used data from the fifth infusion as our end-of-treatment time point.

2.2.10.1 Response

All three studies reported data on response at end of treatment, but only the studies by Pattanaseri *et al.* and Gallagher *et al.*, reported response data at one and three months follow-up after end of treatment, respectively (60;65;70). The studies differed in their definition of response: While both the Pattanaseri-study and the Shiroma-study defined response as ≥50% decrease in MADRS (65;70), the study by Gallagher *et al.* defined it as ≥60% decrease in HDRS from baseline and a HDRS score of ≤16 (60).

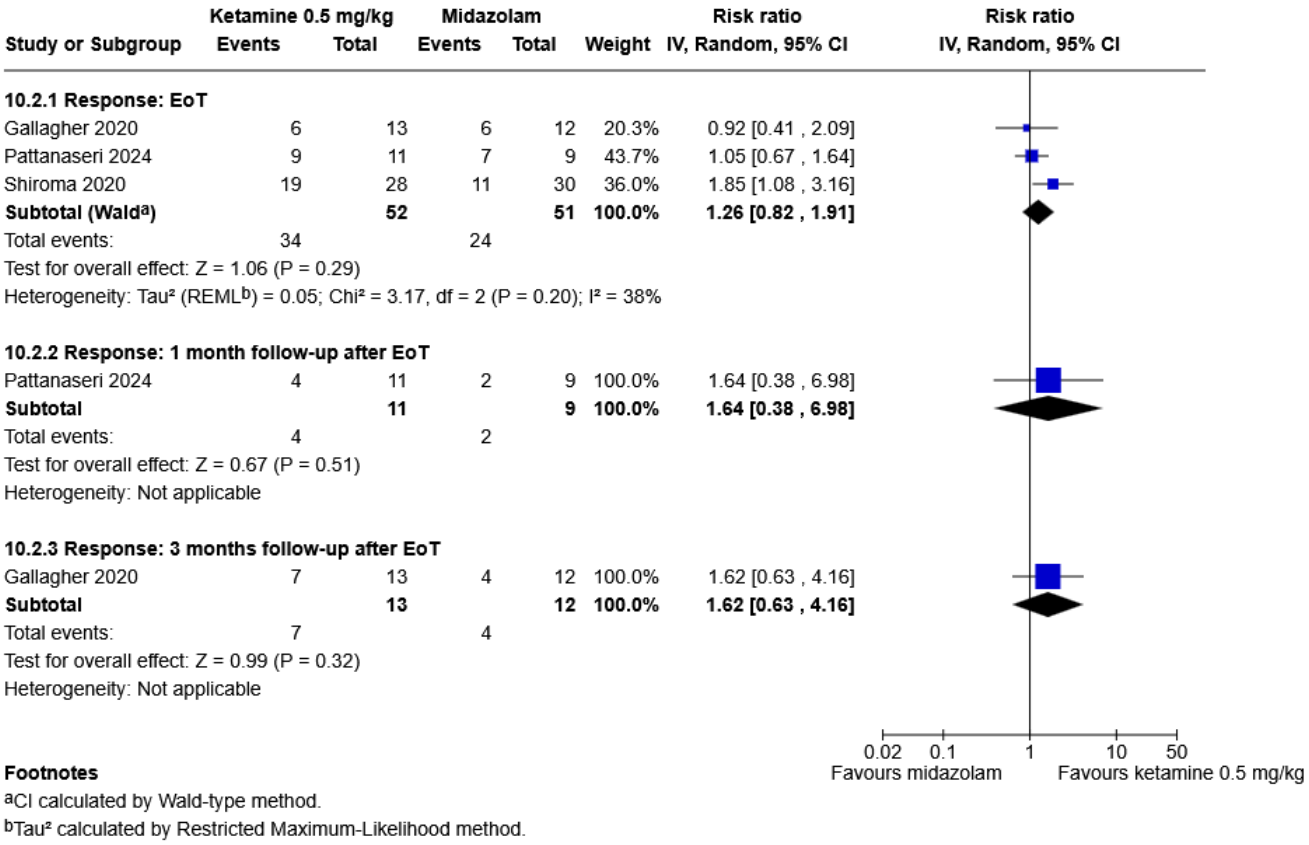


Figure 18: Multiple doses ketamine 0.5 mg/kg vs midazolam: forest plot of response

2.2.10.1.1 End of treatment

At end of treatment, the risk ratio (95% CI; p-value) of response was 1.26 (0.82 to 1.91; p=0.29). In other words, patients who received multiple infusions of ketamine 0.5 mg/kg were 26% more likely to experience response at end of treatment than patients who received multiple infusions of midazolam (*Figure 18*). However, as the confidence interval includes values below 1, it is statistically possible that treatment with multiple 0.5 mg/kg ketamine infusions actually have equal or less chance of response at end of treatment, compared to patients treated with multiple midazolam infusions.

If 471 of 1 000 patients treated with multiple midazolam infusions experienced response at end of treatment, then the anticipated risk difference would correspond to 122 more patients per 1 000 (i.e., 593 patients) treated with multiple infusions of ketamine 0.5 mg/kg having response (*Table 25*). The 95% CI shows that it is statistically possible that between 85 fewer patients (i.e., 386 patients) and 428 more patients (i.e., 899 patients) would be anticipated to experience response at end of treatment when receiving multiple 0.5 mg/kg ketamine infusions than when receiving multiple midazolam infusions.

2.2.10.1.2 One month follow-up after end of treatment

At one month after end of treatment, the risk ratio (95% CI; p-value) of response was 1.64 (0.38 to 6.98; p=0.51). In other words, patients who received multiple infusions of ketamine 0.5 mg/kg were 64% more likely to experience response at one month after end of treatment than patients who received multiple infusions of midazolam (*Figure 18*). However, as the confidence interval includes values below 1, it is statistically possible that treatment with multiple 0.5 mg/kg ketamine infusions actually have equal or less chance of response at one month after end of treatment, compared to patients treated with multiple midazolam infusions.

If 222 of 1 000 patients treated with multiple midazolam infusions experienced response at one month after end of treatment, then the anticipated risk difference would correspond to 142 more patients per 1 000 (i.e., 364 patients) treated with multiple infusions of ketamine 0.5 mg/kg having response (*Table 25*). The 95% CI shows that it is statistically possible that between 138 fewer patients (i.e., 84 patients) and 1329 more patients (i.e., all patients)[1] would be anticipated to experience response at one month after end of treatment when receiving multiple 0.5 mg/kg ketamine infusions than when receiving multiple midazolam infusions.

Table 25: Multiple doses ketamine 0.5 mg/kg vs midazolam: summary of findings table for response

Outcome: response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with midazolam	Risk difference with ketamine 0.5 mg/kg			
EoT N=103 (3 RCTs)	471 per 1 000	**122 more per 1 000** (85 fewer to 428 more)	**RR 1.26** (0.82 to 1.91)	⊕ Very low [a,b,c,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions improve the chance of response more than midazolam at EoT because the certainty of this evidence is very low.
1 month follow-up after EoT N=20 (1 RCT)	222 per 1 000	**142 more per 1 000** (138 fewer to 1 329 more)	**RR 1.64** (0.38 to 6.98)	⊕ Very low [a,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions improve the chance of response more than midazolam at 1 month after EoT because the certainty of this evidence is very low.
3 months follow-up after EoT N=25 (1 RCT)	333 per 1 000	**207 more per 1 000** (123 fewer to 1 053 more)	**RR 1.62** (0.63 to 4.16)	⊕ Very low [a,c,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions improve the chance of response more than midazolam at 3 months after EoT because the certainty of this evidence is very low.

***GRADE**: a: study limitations (RoB); b: inconsistency; c: indirectness; d: imprecision.*
***CI:** confidence interval; **EoT**: end of treatment; **HDRS**: Hamilton Depression Rating Scale; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

[1] As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution

2.2.10.1.3 Three months follow-up after end of treatment

At three months after end of treatment, the risk ratio (95% CI; p-value) of response was 1.62 (0.63 to 4.16; p=0.32). In other words, patients who received multiple infusions of ketamine 0.5 mg/kg were 62% more likely to experience response at three months after end of treatment than patients who received multiple infusions of midazolam (*Figure 18*). However, as the confidence interval includes values below 1, it is statistically possible that treatment with multiple 0.5 mg/kg ketamine infusions actually have equal or less chance of response at three months after end of treatment, compared to patients treated with multiple midazolam infusions.

If 333 of 1 000 patients treated with multiple midazolam infusions experienced response at three months after end of treatment, then the anticipated risk difference would correspond to 207 more patients per 1 000 (i.e., 540 patients) treated with multiple infusions of ketamine 0.5 mg/kg having response (*Table 25*). The 95% CI shows that it is statistically possible that between 123 fewer patients (i.e., 210 patients) and 1053 more patients (i.e., all patients)[1] would be anticipated to experience response at three months after end of treatment when receiving multiple 0.5 mg/kg ketamine infusions than when receiving multiple midazolam infusions.

2.2.10.2 Relapse after response

Only one study presented data on relapse after response, and only at three months after end of treatment (60). The study defined relapse as a ≥10 point increase in HDRS of patients with response and a HDRS score of ≥16 (60).

At three months after end of treatment, the risk ratio (95% CI; p-value) of relapse of responders was 1.00 (0.20 to 4.95; p=1.00). In other words, the patients in this study who responded on single infusions of 0.5 mg/kg ketamine had equal risk of relapsing three months after end of treatment, compared to patients who responded on single infusions of midazolam (*Figure 19*). However, as the confidence interval includes values above and below 1, it is statistically possible that responders on single 0.5 mg/kg ketamine infusions are actually at lower or higher risk of relapsing three months after end of treatment, compared to responders on single midazolam infusions.

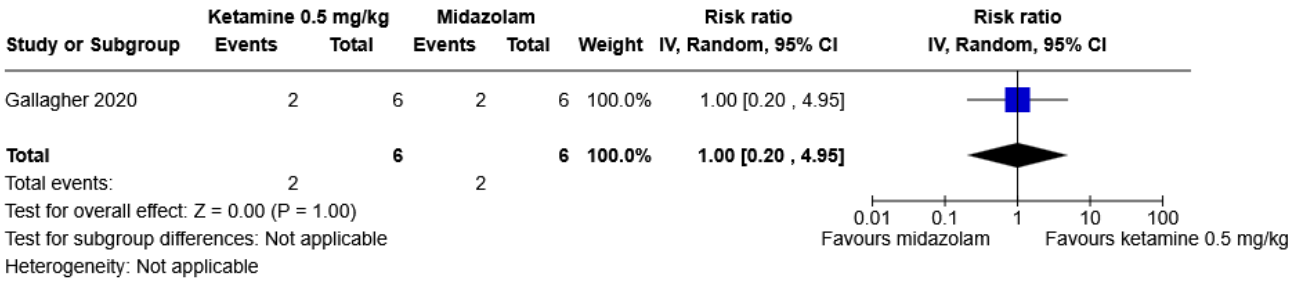


Figure 19: Multiple doses ketamine 0.5 mg/kg vs midazolam: forest plot of relapse after response

If 333 of 1 000 patients treated with multiple midazolam infusions relapsed after response at three months after end of treatment, then the anticipated risk difference would not differ from the number of patients treated with mutiple ketamine 0.5 mg/kg infusions relapsing after response at three months after end of treatment (*Table 26*). The 95% CI shows that it is statistically possible that between 267 fewer patients (i.e., 66 patients) and 1317 more patients (i.e., all patients)[1] would be anticipated to relapse after response at three months after end of treatment when receiving multiple ketamine 0.5 mg/kg infusions than when receiving multiple midazolam infusions.

[1] *As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution*

Table 26: Multiple doses ketamine 0.5 mg/kg vs midazolam: summary of findings table for relapse after response

Outcome: relapse on response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with midazolam	Risk difference with ketamine 0.5 mg/kg			
3 months after EoT N=12 (1 RCT)	333 per 1 000	**0 fewer per 1 000** (267 fewer to 1 317 more)	**RR 1.00** (0.20 to 4.95)	⊕ Very low [a,c,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions reduce the risk of relapse after response more than midazolam at 3 months after EoT because the certainty of this evidence is very low.

***GRADE**: a: study limitations (RoB); c: indirectness; d: imprecision.*
***CI:** confidence interval; **EoT**: end of treatment; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.10.3 Remission

All three studies reported data on remission at end of treatment, but the studies by Pattanaseri *et al.* and Gallagher *et al.*, also reported remission data at one and three months follow-up after end of treatment, respectively (60;65;70). The studies differed in their definition of response: While both the Pattanaseri-study and the Shiroma-study defined response as MADRS score ≤10 (65;70), the study by Gallagher *et al.* defined it as ≥60% decrease in HDRS from baseline and a HDRS score of ≤10 (60).

2.2.10.3.1 End of treatment

At end of treatment, the risk ratio (95% CI; p-value) of remission was 1.26 (0.76 to 2.09; p=0.38). In other words, patients who received multiple infusions of ketamine 0.5 mg/kg were 26% more likely to achieve remission at end of treatment than patients who received multiple infusions of midazolam (*Figure 20*). However, as the confidence interval includes values below 1, it is statistically possible that treatment with multiple 0.5 mg/kg ketamine infusions actually have equal or less chance of remission at end of treatment, compared to patients treated with multiple midazolam infusions.

If 333 of 1 000 patients treated with multiple midazolam infusions achieved remission at end of treatment, then the anticipated risk difference would correspond to 87 more patients per 1 000 (i.e., 420 patients) treated with multiple infusions of ketamine 0.5 mg/kg achieve remission (*Table 27*). The 95% CI shows that it is statistically possible that between 80 fewer patients (i.e., 253 patients) and 363 more patients (i.e., 696 patients) would be anticipated to achieve remission at end of treatment when receiving multiple 0.5 mg/kg ketamine infusions than when receiving multiple midazolam infusions.

2.2.10.3.2 One month follow-up after end of treatment

At one month after end of treatment, the risk ratio (95% CI; p-value) of remission was 2.45 (0.31 to 19.74; p=0.40). In other words, patients who received multiple infusions of ketamine 0.5 mg/kg were 2.5 times more likely to achieve remission at one month after end of treatment than patients who received multiple infusions of midazolam (*Figure 20*). However, as the confidence interval includes values below 1, it is statistically possible that treatment with multiple 0.5 mg/kg ketamine infusions actually have equal or less chance of remission at one month after end of treatment, compared to patients treated with multiple midazolam infusions.

If 111 of 1 000 patients treated with multiple midazolam infusions achieved remission at one month after end of treatment, then the anticipated risk difference would correspond to 161 more patients per 1 000 (i.e., 272 patients) treated with multiple infusions of ketamine 0.5 mg/kg achieve remission (*Table 27*). The 95% CI shows that it is statistically possible that between 77 fewer patients (i.e., 37

patients) and 2082 more patients (i.e., all patients)[1] would be anticipated to achieve remission at one month after end of treatment when receiving multiple 0.5 mg/kg ketamine infusions than when receiving multiple midazolam infusions.

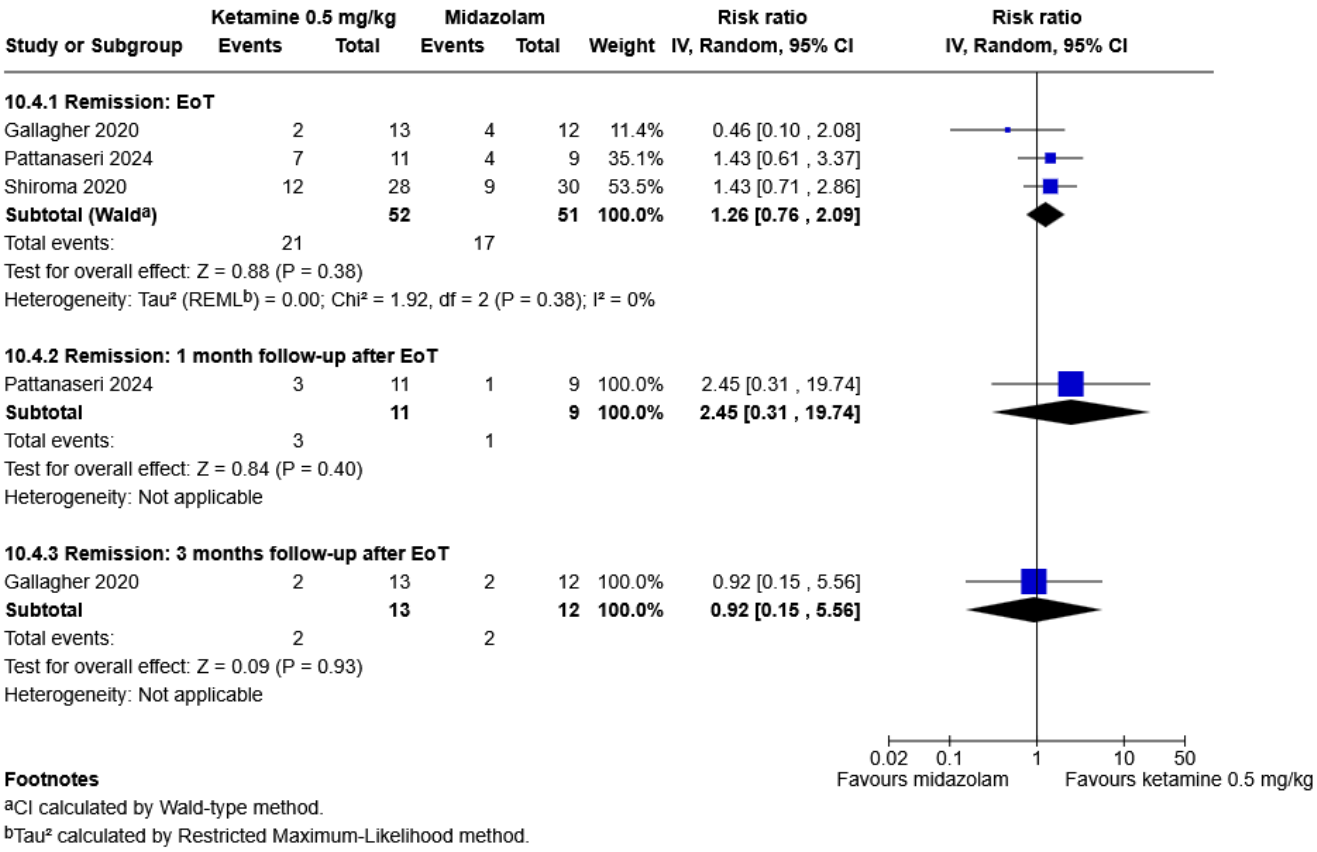


Figure 20: Multiple doses ketamine 0.5 mg/kg vs midazolam: forest plot of remission

2.2.10.3.3 Three months follow-up after end of treatment

At three months after end of treatment, the risk ratio (95% CI; p-value) of remission was 0.92 (0.15 to 5.56; p=0.93). In other words, patients who received multiple infusions of ketamine 0.5 mg/kg were 8% less likely to achieve remission at three months after end of treatment than patients who received multiple infusions of midazolam (*Figure 20*). However, as the confidence interval includes values on both sides of 1, it is statistically possible that treatment with multiple 0.5 mg/kg ketamine infusions actually have equal or higher chance of remission at three months after end of treatment, compared to patients treated with multiple midazolam infusions.

If 167 of 1 000 patients treated with multiple midazolam infusions achieved remission at three months after end of treatment, then the anticipated risk difference would correspond to 13 fewer patients per 1 000 (i.e., 154 patients) treated with multiple infusions of ketamine 0.5 mg/kg achieve remission (*Table 27*). The 95% CI shows that it is statistically possible that between 142 fewer patients (i.e., 24 patients) and 760 more patients (i.e., 927 patients) would be anticipated to achieve remission at three months after end of treatment when receiving multiple 0.5 mg/kg ketamine infusions than when receiving multiple midazolam infusions.

[1] As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution

Table 27: Multiple doses ketamine 0.5 mg/kg vs midazolam: summary of findings table for remission

Outcome: remission	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with midazolam	Risk difference with ketamine 0.5 mg/kg			
EoT N=103 (3 RCTs)	333 per 1 000	**87 more per 1 000** (80 fewer to 363 more)	**RR 1.26** (0.76 to 2.09)	⊕ Very low [a,b,c,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions improve the chance of remission more than midazolam at EoT because the certainty of this evidence is very low.
1 month follow-up after EoT N=20 (1 RCT)	111 per 1 000	**161 more per 1 000** (77 fewer to 2 082 more)	**RR 2.45** (0.31 to 19.74)	⊕ Very low [a,c,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions improve the chance of remission more than midazolam 1 month after EoT because the certainty of this evidence is very low.
3 months follow-up after EoT N=25 (1 RCT)	167 per 1 000	**13 fewer per 1 000** (142 fewer to 760 more)	**RR 0.92** (0.15 to 5.56)	⊕ Very low [a,c,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions improve the chance of remission more than midazolam 3 months after EoT because the certainty of this evidence is very low.

***GRADE**: a: study limitations (RoB); b: inconsistency; c: indirectness; d: imprecision.*
***CI:** confidence interval; **EoT**: end of treatment; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.10.4 Time to relapse

Only one study reported data on time to relapse: Pattanaseri *et al.*, which was assessed among patients who achieved response after end of treatment (65). The authors did not provide any explanation on how they defined relapse.

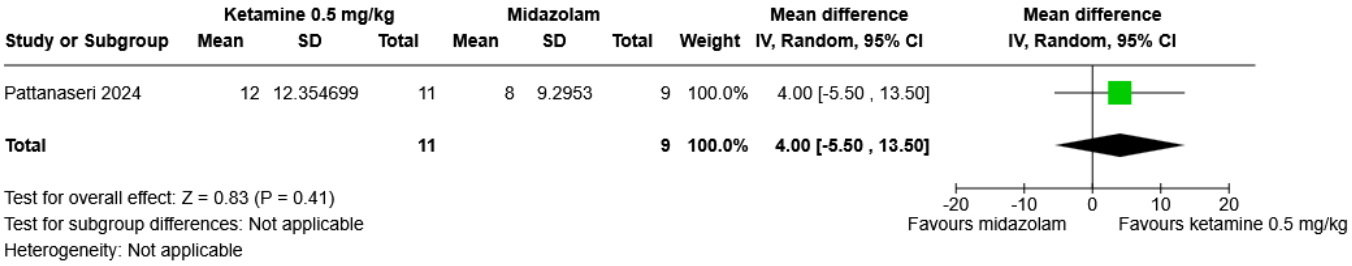


Figure 21: Multiple doses ketamine 0.5 mg/kg vs midazolam: forest plot of time to relapse

The mean (95% CI) for time to relapse was 8 days (0.97 to −15.26) for patients who received multiple infusions of midazolam, and 12 days (3.30 to −19.90) for patients who received multiple infusions of ketamine. The mean difference (95% CI; p-value) of time to relapse of responders was 4.00 (−5.50 to 13.50; p=0.41). In other words, patients who responded after receiving multiple 0.5 mg/kg ketamine infusions relapsed four days later (i.e., “favours midazolam” in the forest plot) compared to patients who responded after receiving multiple midazolam infusions (*Figure 21*;*Table 28*). However, as the confidence interval includes values below 0, it is statistically possible that responders on multiple 0.5 mg/kg ketamine infusions actually relapsed at equal time or earlier than patients who responded on multiple midazolam infusions.

Table 28: Multiple doses ketamine 0.5 mg/kg vs midazolam: summary of findings table for time to relapse

Outcome: time to relapse	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with midazolam	Risk difference with ketamine 0.5 mg/kg		
Time to relapse N=20 (1 RCT)	The mean time to relapse was **8 days**	MD **4 days higher** (5.5 lower to 13.5 higher)	⊕ Very low [a,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions delay relapse more than midazolam because the certainty of this evidence is very low.

***GRADE**: a: study limitations (RoB); d: imprecision.*
***CI:** confidence interval; **DS**: depression severity; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MD**: mean difference; **N**: number of study participants; **RCT**: randomised controlled trial*

2.2.10.5 Depression severity

Only one study presented data on depression severity measured by MADRS at end of treatment and one month follow-up after end of treatment (65) .

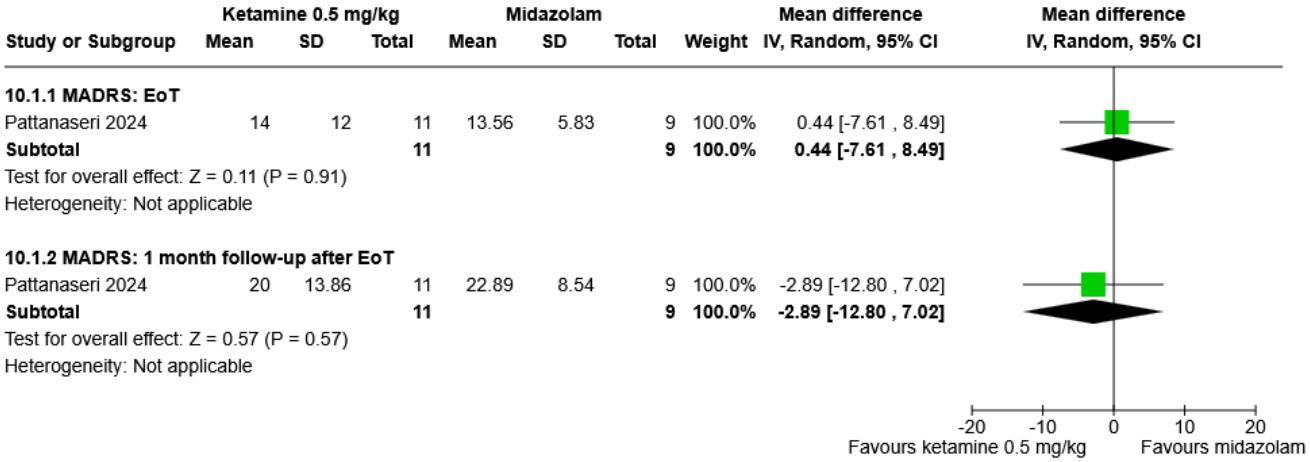


Figure 22: Multiple doses ketamine 0.5 mg/kg vs midazolam: forest plot of depression severity (MADRS)

2.2.10.5.1 End of treatment

At end of treatment, the mean difference (95% CI; p-value) of depression severity as measured by MADRS was 0.44 (−7.61 to 8.49; p=0.91). In other words, patients who received multiple 0.5 mg/kg ketamine infusions in this study had almost identical MADRS scores as patients who received multiple midazolam infusions, i.e., the severity of the depression was similar in both patient groups (*Figure 22*; *Table 29*). However, as the confidence interval includes values on both sides of 0, it is statistically possible that patients who receive multiple 0.5 mg/kg ketamine infusions actually have lower or higher depression severity, i.e., MADRS scores, at end of treatment, compared to patient who receive multiple midazolam infusions.

Table 29: Multiple doses ketamine 0.5 mg/kg vs midazolam: summary of findings table for depression severity

Outcome: depression severity (MADRS)	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with midazolam	Risk difference with ketamine 0.5 mg/kg		
EoT (MADRS) N=20 (1 RCT)	Mean DS was **13,56**	MD **0.44 higher** (7.61 lower to 8.49 higher)	⊕ Very low [a,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions reduce MADRS scores more than midazolam at EoT because the certainty of this evidence is very low.
1 month follow-up after EoT (MADRS) N=20 (1 RCT)	Mean DS was **22.89**	MD **2.89 lower** (12.8 lower to 7.02 higher)	⊕ Very low [a,d]	It is uncertain whether multiple ketamine 0.5 mg/kg infusions reduce MADRS scores more than midazolam 1 month after EoT scores because the certainty of this evidence is very low.

***GRADE**: a: study limitations (RoB); d: imprecision.*
***CI:** confidence interval; **DS**: depression severity; **EoT**: end of treatment; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MD**: mean difference; **N**: number of study participants; **RCT**: randomised controlled trial*

2.2.10.5.2 One month follow-up after end of treatment

At one month after end of treatment, the mean difference (95% CI; p-value) of depression severity as measured by MADRS was -2.89 (−12.80 to 7.02; p=0.57). In other words, patients who received multiple 0.5 mg/kg ketamine infusions had lower MADRS scores, i.e. less severe depression, at one month after end of treatment, compared to patients who received multiple midazolam infusions (*Figure* **22**;*Table 29*). However, as the confidence interval includes values over 0, it is statistically possible that patients who receive multiple 0.5 mg/kg ketamine infusions actually have equal or higher depression severity, i.e., MADRS scores, at one month after end of treatment, compared to patient who receive multiple midazolam infusions.

2.2.10.6 Safety data

Only one study reported data on adverse events, and we chose to only extract data on adverse events as reported one hour after the final fourth infusion (60). At this time, no events were registered of the specific adverse events suggested to us by the clinical experts, except for one event of anxiety in the ketamine-group (*Table 30*).

Table 30: Multiple doses ketamine 0.5 mg/kg vs midazolam: overview of adverse events

Gallagher *et al.* (60)	Ketamine 0.5 mg/kg 1dx4w *(n=8)*	Midazolam 0.045 mg/kg 1dx4w *(n=8)*
Cardiovascular event	0	0
Nausea/vomiting	0	0
Urinary problem	0	0
Anxiety	1	0
Increased or decreased saliva	0	0
Visual disturbance	0	0
Involuntary movements	0	0
Headache	0	0

1dx4w: one dose every week for four weeks.

2.2.11 Ketamine 0.5 mg/kg versus esketamine 0,25 mg/kg – single infusion

Only one study contributed to the comparison between ketamine and esketamine: Correia-Melo *et al.* 2020 (58). The intervention group was given a single infusions of 0.5 mg/kg ketamine, while the comparison group received a single infusion of 0.25 mg/kg esketamine (58).

2.2.11.1 Response

Data on response was provided at one, three and seven days post-infusion (58). The study by Correia-Melo defined response as ≥ 50% reduction from baseline MADRS scores (58).

2.2.11.1.1 One day post-infusion

At one day post-infusion, the risk ratio (95% CI; p-value) of response was 1.03 (0.64 to 1.68; p=0.89). In other words, patients who received a single ketamine 0.5 mg/kg infusion had almost equal chance of response at one day post-infusion, i.e., ≥50% reduction in MADRS scores, as patients who received a single 0.25 mg/kg esketamine infusion (*Figure 23*).

If 500 of 1 000 patients treated with a single 0.25 mg/kg esketamine infusion experienced response at one day post-infusion, then the anticipated risk difference would correspond to 15 more patients per 1 000 (i.e., 515 patients) treated with a single ketamine ≥0.5 mg/kg infusion having response at one day post-infusion (*Table 31*). The 95% CI shows that it is statistically possible that between 180 fewer patients (i.e., 320 patients) and 340 more patients (i.e., 840 patients) would be anticipated to experience response at one day post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single 0.25 mg/kg esketamine infusion.

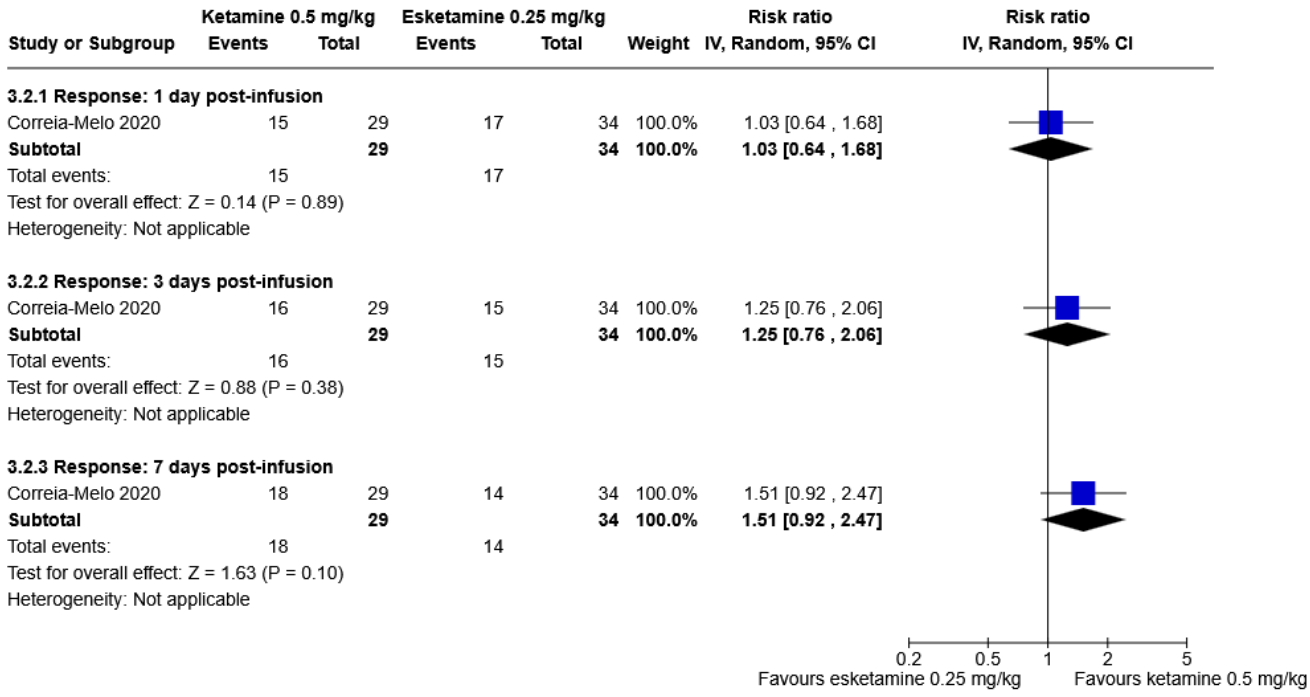


Figure 23: Single dose ketamine 0.5 mg/kg vs esketamine 0.25 mg/kg: forest plot of response

2.2.11.1.2 Three days post-infusion

At three days post-infusion, the risk ratio (95% CI; p-value) of response was 1.25 (0.76 to 2.06; p=0.38). In other words, patients who received a single ketamine 0.5 mg/kg infusion were 25% more likely to experience response, i.e., ≥50% reduction in MADRS scores, at three days post-infusion than patients who received a single 0.25 mg/kg esketamine infusion (*Figure 23*).

If 441 of 1 000 patients treated with a single 0.25 mg/kg esketamine infusion experienced response at three days post-infusion, then the anticipated risk difference would correspond to 110 more patients per 1 000 (i.e., 551 patients) treated with a single ketamine ≥0.5 mg/kg infusion having response at

three days post-infusion (*Table 31*). The 95% CI shows that it is statistically possible that between 106 fewer patients (i.e., 335 patients) and 468 more patients (i.e., 909 patients) would be anticipated to experience response at three days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single 0.25 mg/kg esketamine infusion.

2.2.11.1.3 Seven days post-infusion

At seven days post-infusion, the risk ratio (95% CI; p-value) of response was 1.51 (0.92 to 2.47; p=0.10). In other words, patients who received a single ketamine 0.5 mg/kg infusion were 51% more likely to experience response, i.e., ≥50% reduction in MADRS scores, at seven days post-infusion than patients who received a single 0.25 mg/kg esketamine infusion (*Figure 23*).

If 412 of 1 000 patients treated with a single 0.25 mg/kg esketamine infusion experienced response at seven days post-infusion, then the anticipated risk difference would correspond to 210 more patients per 1 000 (i.e., 622 patients) treated with a single ketamine ≥0.5 mg/kg infusion having response at seven days post-infusion (*Table 31*). The 95% CI shows that it is statistically possible that between 33 fewer patients (i.e., 379 patients) and 605 more patients (i.e., all patients)[1] would be anticipated to experience response at seven days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single saline infusion.

Table 31: Single dose ketamine 0.5 mg/kg vs esketamine 0.25 mg/kg: summary of findings table for response

Outcome: response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with esketamine 0.25 mg/kg	Risk difference with ketamine 0.5 mg/kg			
1 day post-infusion N=63 (1 RCT)	500 per 1 000	**15 more per 1 000** (180 fewer to 340 more)	**RR 1.03** (0.64 to 1.68)	⊕⊕ Low [c,d]	A single ketamine 0.5 mg/kg infusion may have little or no effect on response compared to esketamine 0.25 mg/kg at 1 day post-infusion (*low certainty evidence*)
3 days post-infusion N=63 (1 RCT)	441 per 1 000	**110 more per 1 000** (106 fewer to 468 more)	**RR 1.25** (0.76 to 2.06)	⊕⊕ Low [c,d]	A single ketamine 0.5 mg/kg infusion may improve the chance of response slightly more than esketamine 0.25 mg/kg at 3 days post-infusion (*low certainty evidence*)
7 days post-infusion N=63 (1 RCT)	412 per 1 000	**210 more per 1 000** (33 fewer to 605 more)	**RR 1.51** (0.92 to 2.47)	⊕⊕ Low [c,d]	A single ketamine 0.5 mg/kg infusion may improve the chance of response slightly more than esketamine 0.25 mg/kg at 7 days post-infusion (*low certainty evidence*)

***GRADE**: c: indirectness; d: imprecision.*
***CI:** confidence interval; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.11.2 Remission

Data on remission was provided at one, three and seven days post-infusion (58). The study by Correia-Melo *et al.* defined response as MADRS score ≤7 (58).

[1] *As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution*

2.2.11.2.1 One day post-infusion

At one day post-infusion, the risk ratio (95% CI; p-value) of remission was 0.82 (0.36 to 1.85; p=0.64). In other words, patients who received a single ketamine 0.5 mg/kg infusion were 18% less likely to achieve remission one day post-infusion, as patients who received a single 0.25 mg/kg esketamine infusion (*Figure 24*).

If 294 of 1 000 patients treated with a single 0.25 mg/kg esketamine infusion achieved remission at one day post-infusion, then the anticipated risk difference would correspond to 53 fewer patients per 1 000 (i.e., 241 patients) treated with a single ketamine ≥0.5 mg/kg infusion achieve remission at one day post-infusion (*Table 32*). The 95% CI shows that it is statistically possible that between 188 fewer patients (i.e., 106 patients) and 259 more patients (i.e., 553 patients) would be anticipated to achieve remission at one day post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single 0.25 mg/kg esketamine infusion.

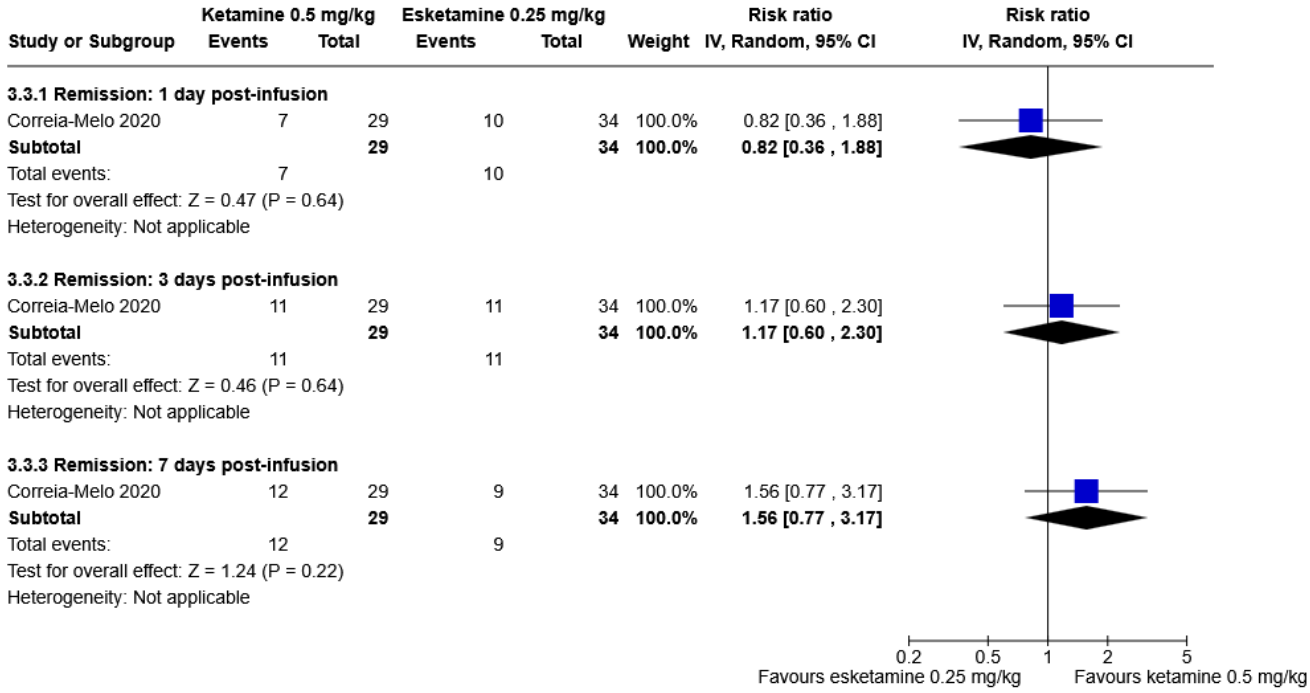


Figure 24: Single dose ketamine 0.5 mg/kg vs esketamine 0.25 mg/kg: forest plot of remission

2.2.11.2.2 Three days post-infusion

At three days post-infusion, the risk ratio (95% CI; p-value) of remission was 1.17 (0.60 to 2.30; p=0.64). In other words, patients who received a single ketamine 0.5 mg/kg infusion were 17% more likely to achieve remission three days post-infusion, as patients who received a single 0.25 mg/kg esketamine infusion (*Figure 24*).

If 324 of 1 000 patients treated with a single 0.25 mg/kg esketamine infusion achieved remission at three days post-infusion, then the anticipated risk difference would correspond to 55 more patients per 1 000 (i.e., 379 patients) treated with a single ketamine ≥0.5 mg/kg infusion achieve remission at three days post-infusion (*Table 32*). The 95% CI shows that it is statistically possible that between 129 fewer patients (i.e., 195 patients) and 421 more patients (i.e., 745 patients) would be anticipated to achieve remission at three days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single 0.25 mg/kg esketamine infusion.

2.2.11.2.3 Seven days post-infusion

At seven days post-infusion, the risk ratio (95% CI; p-value) of remission was 1.56 (0.77 to 3.17; p=0.22). In other words, patients who received a single ketamine 0.5 mg/kg infusion were 56% more

likely to achieve remission seven days post-infusion, as patients who received a single 0.25 mg/kg esketamine infusion (*Figure 24*).

If 265 of 1 000 patients treated with a single 0.25 mg/kg esketamine infusion achieved remission at seven days post-infusion, then the anticipated risk difference would correspond to 148 more patients per 1 000 (i.e., 204 patients) treated with a single ketamine ≥0.5 mg/kg infusion achieve remission at seven days post-infusion (*Table 32*). The 95% CI shows that it is statistically possible that between 61 fewer patients (i.e., 204 patients) and 574 more patients (i.e., 839 patients) would be anticipated to achieve remission at seven days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single 0.25 mg/kg esketamine infusion.

Table 32: Single dose ketamine 0.5 mg/kg vs esketamine 0.25 mg/kg: summary of findings table for remission

Outcome: remission	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with esketamine 0.25 mg/kg	Risk difference with ketamine 0.5 mg/kg			
1 day post-infusion N=63 (1 RCT)	294 per 1 000	**53 fewer per 1 000** (188 fewer to 259 more)	**RR 0.82** (0.36 to 1.88)	⊕⊕ Low [c,d]	A single ketamine 0.5 mg/kg infusions may improve the chance of remission slightly more than esketamine 0.25 mg/kg at 1 day post-infusion (*low certainty evidence*)
3 days post-infusion N=63 (1 RCT)	324 per 1 000	**55 more per 1 000** (129 fewer to 421 more)	**RR 1.17** (0.60 to 2.30)	⊕⊕ Low [c,d]	A single ketamine 0.5 mg/kg infusions may improve the chance of remission slightly more than esketamine 0.25 mg/kg at 3 day post-infusion (*low certainty evidence*)
7 days post-infusion N=63 (1 RCT)	265 per 1 000	**148 more per 1 000** (61 fewer to 574 more)	**RR 1.56** (0.77 to 3.17)	⊕⊕ Low [c,d]	A single ketamine 0.5 mg/kg infusions may improve the chance of remission slightly more than esketamine 0.25 mg/kg at 7 day post-infusion (*low certainty evidence*)

***GRADE**: c: indirectness; d: imprecision.*
***CI:** confidence interval; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.11.3 Depression severity

Data on depression severity, measured by MADRS, was provided at one, three and seven days post-infusion (58).

2.2.11.3.1 One day post-infusion

At one day post-infusion, the mean difference (95% CI; p-value) of depression severity of all patients was −1.33 (−6.93 to 4.27; p=0.64). In other words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at one day post-infusion, compared to patients who received a 0.25 mg/kg esketamine infusion (*Figure 25*; *Table 33*). However, as the confidence interval includes values over 0, it is statistically possible that patients who receive a single 0.5 mg/kg ketamine infusion actually have equal or higher depression severity, i.e., MADRS scores, at one day post-infusion, compared to patients who receive a single 0.25 mg/kg esketamine infusion.

2.2.11.3.2 Three days post-infusion

At three days post-infusion, the mean difference (95% CI; p-value) of depression severity of all patients was −2.62 (−9.01 to 3.77; p=0.42), which is statistically significant in favour of single infusions of ketamine 0.5 mg/kg. In other words, patients who received a single 0.5 mg/kg ketamine infusion

had lower MADRS scores, i.e. less severe depression, at three days post-infusion, compared to patients who received a single 0.25 mg/kg esketamine infusion (*Figure 25*; *Table 33*). However, as the confidence interval includes values over 0, it is statistically possible that patients who receive a single 0.5 mg/kg ketamine infusion actually have equal or higher depression severity, i.e., MADRS scores, at three days post-infusion, compared to patients who receive a single 0.25 mg/kg esketamine infusion.

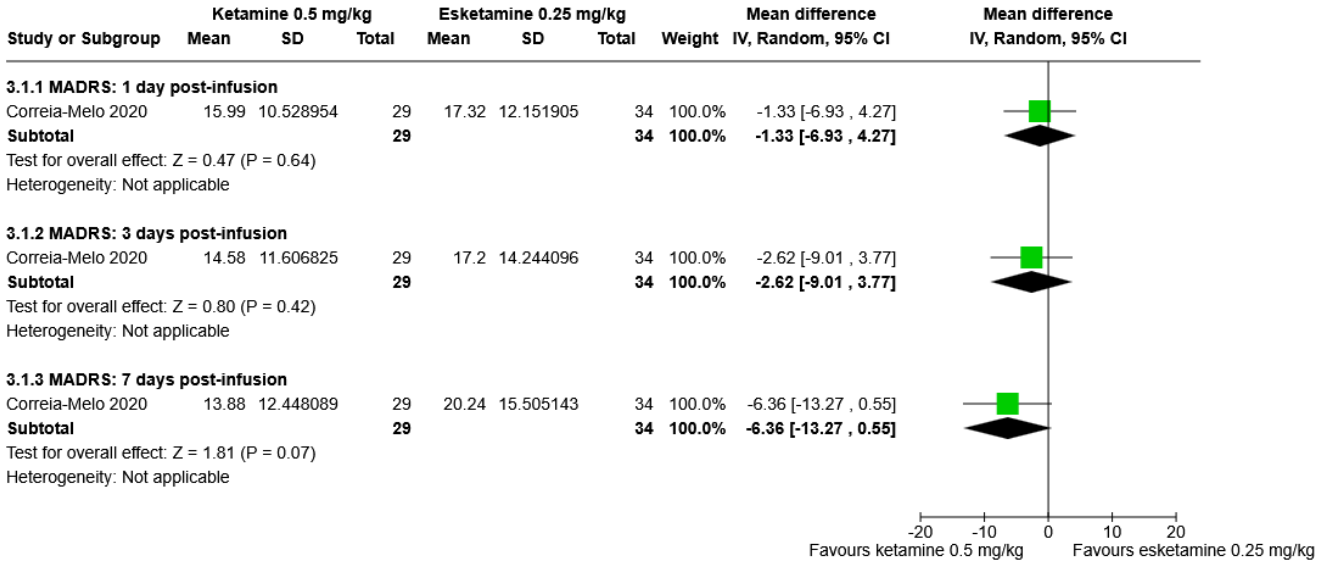


Figure 25: Single dose ketamine 0.5 mg/kg vs esketamine 0.25 mg/kg: forest plot of depression severity

2.2.11.3.3 Seven days post-infusion

At seven days post-infusion, the mean difference (95% CI; p-value) of depression severity of all patients was −6.36 (−13.27 to 0.55; p=0.07), which is statistically significant in favour of single infusions of ketamine 0.5 mg/kg. In other words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at seven days post-infusion, compared to patients who received a single 0.25 mg/kg esketamine infusion (*Figure 25*; *Table 33*). However, as the confidence interval includes values over 0, it is statistically possible that patients who receive a single 0.5 mg/kg ketamine infusion actually have equal or higher depression severity, i.e., MADRS scores, at seven days post-infusion, compared to patients who receive a single 0.25 mg/kg esketamine infusion.

Table 33: Single dose ketamine 0.5 mg/kg vs esketamine 0.25 mg/kg: summary of findings table for depression severity

Outcome: depression severity	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with esketamine 0.25 mg/kg	Risk difference with ketamine 0.5 mg/kg		
1 day post-infusion (MADRS) N=63 (1 RCT)	Mean DS was **17.32**	MD **1.33 lower** (6.93 lower to 4.27 higher)	⊕⊕ Low [c,d]	There may be little or no difference in depression severity scores with treatment with a single ketamine 0.5 mg/kg infusion and a single esketamine 0.25 mg/kg infusion at 1 day post-infusion (low certainty evidence)
3 days post-infusion (MADRS) N=63 (1 RCT)	Mean DS was **17.2**	MD **2.62 lower** (9.01 lower to 3.77 higher)	⊕⊕ Low [c,d]	A single ketamine 0.5 mg//kg infusion may reduce depression severity scores slightly more than a single esketamine 0.25 mg/kg infusion at 3 days post-infusion (*low certainty evidence*)

Outcome: depression severity	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with esketamine 0.25 mg/kg	Risk difference with ketamine 0.5 mg/kg		
7 days post-infusion (MADRS) N=63 (1 RCT)	Mean DS was **20.24**	MD **6.36 lower** (13.27 lower to 0.55 higher)	⊕⊕ Low [c,d]	A single ketamine 0.5 mg/kg infusion may reduce depression severity scores slightly more than a single esketamine 0.25 mg/kg infusion at 7 days post-infusion (*low certainty evidence*)

***GRADE**: c: indirectness; d: imprecision.*
***CI:** confidence interval; **DS**: depression severity; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MD**: mean difference; **N**: number of study participants; **RCT**: randomised controlled trial*

2.2.11.4 Safety data

The study by Correia-Melo et al. presented safety data on ketamine and esketamine-infusions as a narrative summary (58). According to the study, adverse events were distributed similarly between the ketamine- and the esketamine-groups, and no serious adverse events were observed in either group (58).

2.2.12 Ketamine ≥0.5 mg/kg versus ketamine <0.5 mg/kg – single infusion

Four studies contributed to the comparison between single dose ketamine ≥0.5 mg/kg versus ketamine <0.5 mg/kg: 1) Chen 2018a/Su 2017 (57;73), 2) Chen 2018b (56), 3) Fava 2020/Salloum (59;69), and 4) Lijffijt 2022 (63). Ketamine was given as single infusions in both intervention and comparator groups, in doses of 0.5 and/or 1.0 mg/kg, and 0.1, 0.2 or 0.25 mg/kg, respectively. The studies by Fava/Salloum and Lijffijt both investigated the effect of several doses of ketamin (59;63;69). In accordance with input from our clinical experts, we pooled data of the groups that received 0.1 and 0.2-0.25 mg/kg ketamine (comparator group), and the groups that received 0.5 and 1.0 mg/kg (intervention group).

2.2.12.1 Response

All four studies presented data on response, but at various time points (56;57;59;63;69;73). The included studies defined response as ≥50% reduction from baseline HDRS (56;57;59;73) or MADRS (63;69). The study by Fava/Salloum presented two different sets of response data in the two publications, based on different depression rating scales; MADRS (69) and HDRS (HDRS-6) (59). We chose to analyse and present both sets of response data, because 1) Fava *et al.* was the only publication to present response data at all time points (i.e., one, three and seven days post-infusion), whereas Salloum *et al.* only presented response data for one time point (i.e., three days post-infusion), and 2) the response data from Salloum *et al.* was used as a basis for relapse data, which was not presented in Fava *et al.* (59;69). Note that the publication by Salloum *et al.*, only presented data for 0.1 mg/kg ketamine, not 0.2 mg/kg (69), and that the control group is therefore smaller than what is seen for the data presented in Fava *et al.* (59).

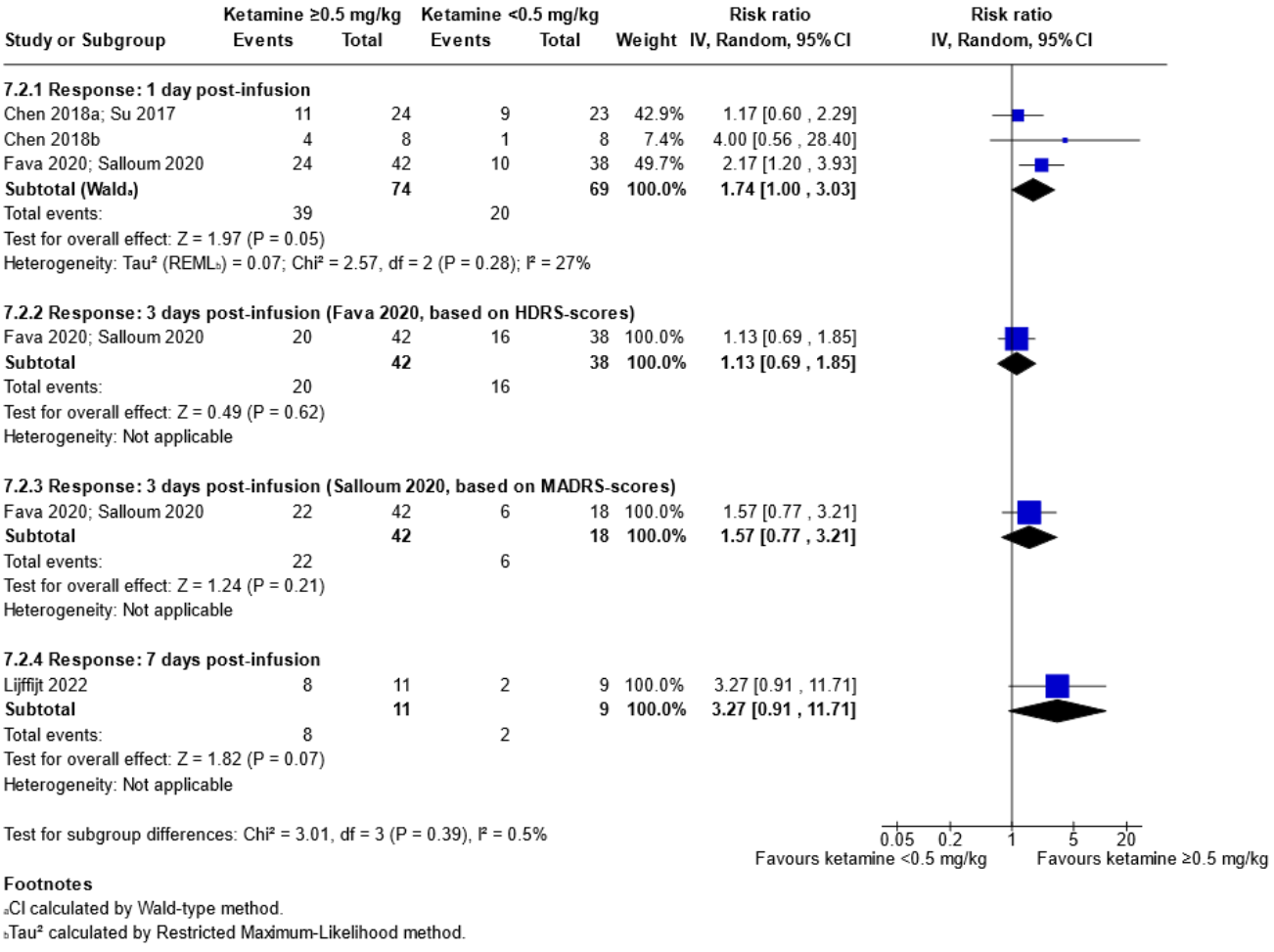


Figure 26: Single dose ketamine ≥0.5 mg/kg vs <0.5 mg/kg ketamine: forest plot of response

2.2.12.1.1 One day post-infusion

At one day post-infusion, the risk ratio (95% CI; p-value) of response was 1.74 (1.00 to 3.03; p=0.05), which is statistically significant in favour of single infusions of ketamine ≥0.5 mg/kg. In other words, patients who received a single ketamine ≥0.5 mg/kg infusion had 74% higher chance to experience response at one day post-infusion, i.e., ≥50% reduction in HDRS or MADRS scores, than patients who received a single <0.5 mg/kg ketamine infusion (*Figure 26*).

If 290 of 1 000 patients treated with a single <0.5 mg/kg ketamine infusion experienced response at one day post-infusion, then the anticipated risk difference would correspond to 214 more patients per 1 000 (i.e., 504 patients) treated with a single ketamine ≥0.5 mg/kg infusion having response at one day post-infusion (*Table 34*). The 95% CI shows that it is statistically possible that between 0 more patients (i.e., 290 patients) and 588 more patients (i.e., 878 patients) would be anticipated to experience response at one day post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single <0.5 mg/kg ketamine infusion.

2.2.12.1.2 Three days post-infusion

At three days post-infusion, the response data from the publication by Fava *et al.* (59), based on HDRS scores, showed a risk ratio (95% CI; p-value) of 1.13 (0.69 to 1.85; p=0.62). In other words, patients in this study who received a single ketamine ≥0.5 mg/kg infusion had 13% higher chance of experience response at three days post-infusion, i.e., ≥50% reduction in HDRS scores, than patients who received a single <0.5 mg/kg ketamine infusion (*Figure 26*). However, the confidence interval includes values below 1, so it is statistically possible that patients who receive a single ≥0.5 mg/kg ketamine infusion actually have equal or less chance of response three days post-infusion, compared to patients who received a single <0.5 mg/kg ketamine infusion.

If 421 of 1 000 patients treated with a single <0.5 mg/kg ketamine infusion experienced response at three days post-infusion, then the anticipated risk difference would correspond to 55 more patients per 1 000 (i.e., 476 patients) treated with a single ketamine ≥0.5 mg/kg infusion having response at three days post-infusion (*Table 34*). The 95% CI shows that it is statistically possible that between 131 fewer patients (i.e., 290 patients) and 358 more patients (i.e., 779 patients) would be anticipated to experience response at three days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single <0.5 mg/kg ketamine infusion.

At three days post-infusion, the response data from the publication by Salloum *et al.* (69), based on MADRS scores, showed a risk ratio (95% CI; p-value) of 1.57 (0.77 to 3.21; p=0.21). In other words, patients in this study who received a single ketamine ≥0.5 mg/kg infusion had 57% higher chance of experience response at three days post-infusion, i.e., ≥50% reduction in MADRS scores, than patients who received a single <0.5 mg/kg ketamine infusion (*Figure 26*). However, the confidence interval includes values below 1, so it is statistically possible that patients who receive a single ≥0.5 mg/kg ketamine infusion actually have equal or less chance of response three days post-infusion, compared to patients who received a single <0.5 mg/kg ketamine infusion.

If 333 of 1 000 patients treated with a single <0.5 mg/kg ketamine infusion experienced response at three days post-infusion, then the anticipated risk difference would correspond to 190 more patients per 1 000 (i.e., 523 patients) treated with a single ketamine ≥0.5 mg/kg infusion having response at three days post-infusion (*Table 34*). The 95% CI shows that it is statistically possible that between 77 fewer patients (i.e., 256 patients) and 737 more patients (i.e., all patients)[1] would be anticipated to experience response at three days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single <0.5 mg/kg ketamine infusion.

[1] *As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution*

2.2.12.1.3 Seven days post-infusion

At seven days post-infusion, the risk ratio (95% CI; p-value) of response was 3.27 (0.91 to 11.71; p=0.39). In other words, patients who received a single ketamine ≥0.5 mg/kg infusion were over three times as likely to experience response at seven days post-infusion, i.e., ≥50% reduction in MADRS scores, than patients who received a single <0.5 mg/kg ketamine infusion (*Figure 26*). However, the confidence interval includes values below 1, so it is statistically possible that patients who receive a single ≥0.5 mg/kg ketamine infusion actually have equal or less chance of response seven days post-infusion, compared to patients who received a single <0.5 mg/kg ketamine infusion.

If 222 of 1 000 patients treated with a single <0.5 mg/kg ketamine infusion experienced response at seven days post-infusion, then the anticipated risk difference would correspond to 504 more patients per 1 000 (i.e., 726 patients) treated with a single ketamine ≥0.5 mg/kg infusion having response at seven days post-infusion (*Table 34*). The 95% CI shows that it is statistically possible that between 20 fewer patients (i.e., 202 patients) and 2380 more patients (i.e., all patients)[1] would be anticipated to experience response at seven days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single <0.5 mg/kg ketamine infusion.

Table 34: Single dose ketamine ≥0.5 mg/kg vs <0.5 mg/kg ketamine: summary of findings table for response

Outcome: response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ketamine <0.5 mg/kg	Risk difference with ketamine ≥0.5 mg/kg			
1 day post-infusion N=143 (3 RCTs)	290 per 1 000	**214 more per 1 000** (0 fewer to 588 more)	**RR 1.74** (1.00 to 3.03)	⊕⊕ Low [a,d]	A single ketamine ≥0.5 mg/kg infusion may improve the chance of response more than a single ketamine <0.5 mg/kg infusion at 1 day post-infusion (*low certainty evidence*)
3 days post-infusion (Fava 2020, **based on HDRS-scores**) N=80 (1 RCT)	421 per 1 000	**55 more per 1 000** (131 fewer to 358 more)	**RR 1.13** (0.69 to 1.85)	⊕ Very low [a,d]	It is uncertain whether a single ketamine ≥0.5 mg/kg infusion improves the chance of response (HDRS ≤50%) more than <0.5 mg/kg ketamine at 3 day post-infusion because the certainty of this evidence is very low.
3 days post-infusion (Salloum 2020, **based on MADRS-scores**) N=60 (1 RCT)	333 per 1 000	**190 more per 1 000** (77 fewer to 737 more)	**RR 1.57** (0.77 to 3.21)	⊕ Very low [a,d]	It is uncertain whether a single ketamine ≥0.5 mg/kg infusion improves the chance of response (MADRS ≤50%) more than <0.5 mg/kg ketamine at 3 day post-infusion because the certainty of this evidence is very low.
7 days post-infusion N=20 (1 RCT)	222 per 1 000	**504 more per 1 000** (20 fewer to 2 380 more)	**RR 3.27** (0.91 to 11.71)	⊕⊕ Low [d]	A single ketamine 0.5 mg/kg infusion may improve the chance of response slightly more than a single ketamine <0.5 mg/kg infusion at 7 days post-infusion (*low certainty evidence*)

***GRADE**: a: study limitations (RoB); d: imprecision.*
***CI:** confidence interval; **HDRS**: Hamilton Depression Rating Scale; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

[1] As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution

2.2.12.2 Relapse after response

Only the study by Fava/Salloum presented data on relapse after response, at 5-7, 14 and 30 days post-infusion (59;69). Note that the ketamine dose in the comparator group is presented as 0.1 mg/kg, as data on 0.2 mg/kg were not reported in the paper by Salloum *et al.* (69). Also, as relapse data on day 5 and 7 were identical, these time points were grouped together. Salloum et al. defined relapse as a MADRS score of ≥22 on any subsequent visit (69).

2.2.12.2.1 Five to seven days post-infusion

At five to seven days post-infusion, the risk ratio (95% CI; p-value) of relapse of responders was 0.34 (0.08 to 1.53; p=0.16). In other words, patients in this study who responded on single infusions of ≥0.5 mg/kg ketamine were 66% less likely to relapse five to seven days post-infusion, compared to patients who responded on single infusions of 0.1 mg/kg ketamine (*Figure 27*). However, as the confidence interval includes values above 1, it is statistically possible that responders on single ≥0.5 mg/kg ketamine infusions are actually at equal or higher risk of relapsing five to seven days post-infusion, compared to responders on single 0.1 mg/kg ketamine infusions.

If 400 of 1 000 patients treated with single 0.1 mg/kg ketamine infusions experienced relapse after response at five to seven days post-infusion, then the anticipated risk difference would correspond to 264 fewer patients per 1 000 (i.e., 136 patients) treated with single ketamine ≥0.5 mg/kg infusions relapsing after response at five to seven days post-infusion (*Table 35*). The 95% CI shows that it is statistically possible that between 368 fewer patients (i.e., 32 patients) and 212 more patients (i.e., 612 patients) would be anticipated to relapse after response at five to seven days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single 0.1 mg/kg ketamine infusion.

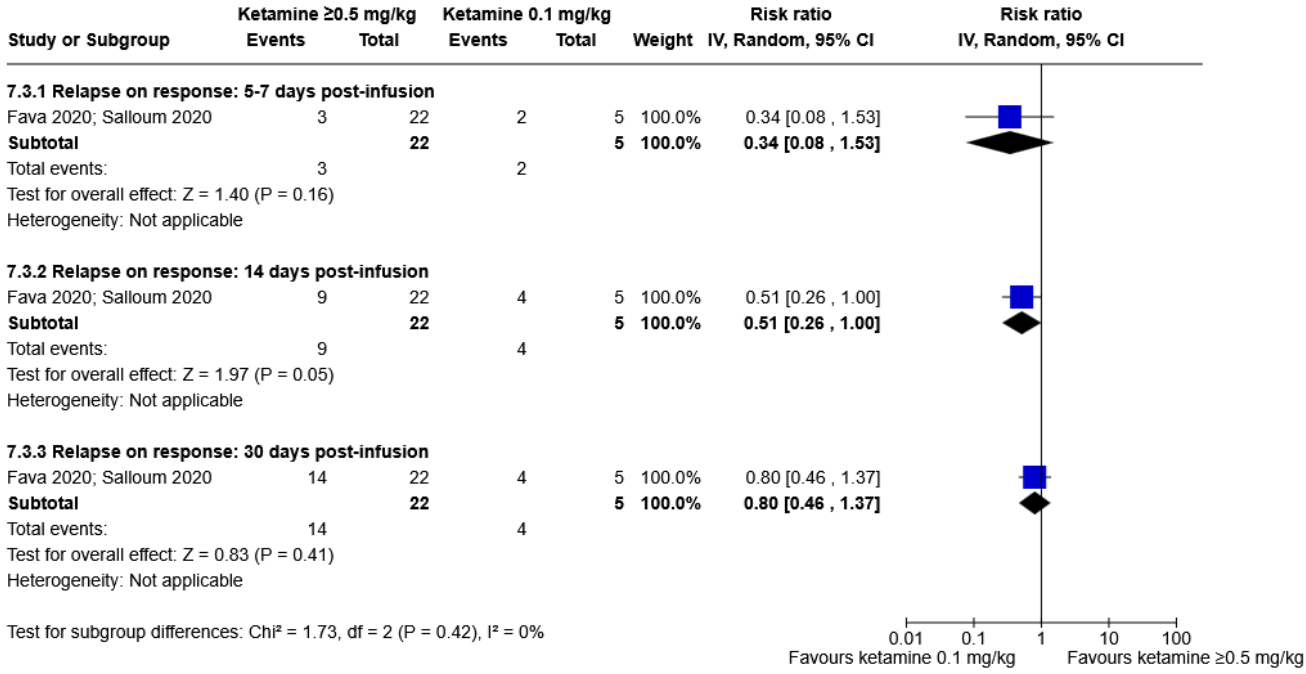


Figure 27: Single dose ketamine ≥0.5 mg/kg vs 0.1 mg/kg ketamine: forest plot of relapse after response

2.2.12.2.2 Fourteen days post-infusion

At 14 days post-infusion, the risk ratio (95% CI; p-value) of relapse of responders was 0.51 (0.26 to 1.00; p=0.05), which is statistically significant in favour of ≥0.5 mg/kg ketamine. In other words, patients in this study who responded on single infusions of ≥0.5 mg/kg ketamine were 49% less likely to relapse 14 days post-infusion, compared to patients who responded on single infusions of 0.1 mg/kg ketamine (*Figure 27*).

If 800 of 1 000 patients treated with single 0.1 mg/kg ketamine infusions experienced relapse after response at 14 days post-infusion, then the anticipated risk difference would correspond to 392 fewer patients per 1 000 (i.e., 408 patients) treated with single ketamine ≥0.5 mg/kg infusions relapsing after response at 14 days post-infusion (*Table 35*). The 95% CI shows that it is statistically possible that between 592 fewer patients (i.e., 208 patients) and 0 fewer patients (i.e., 800 patients) would be anticipated to relapse after response at 14 days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single 0.1 mg/kg ketamine infusion.

2.2.12.2.3 Thirty days post-infusion

At 30 days post-infusion, the risk ratio (95% CI; p-value) of relapse of responders was 0.80 (0.46 to 1.37; p=0.41). In other words, patients in this study who responded on single infusions of ≥0.5 mg/kg ketamine were 20% less likely to relapse 30 days post-infusion, compared to patients who responded on single infusions of 0.1 mg/kg ketamine (*Figure 27*). However, as the confidence interval includes values above 1, it is statistically possible that responders on single ≥0.5 mg/kg ketamine infusions are actually at equal or higher risk of relapsing five to seven days post-infusion, compared to responders on single 0.1 mg/kg ketamine infusions.

If 800 of 1 000 patients treated with single 0.1 mg/kg ketamine infusions experienced relapse after response at 30 days post-infusion, then the anticipated risk difference would correspond to 160 fewer patients per 1 000 (i.e., 640 patients) treated with single ketamine ≥0.5 mg/kg infusions relapsing after response at 30 days post-infusion (*Table 35*). The 95% CI shows that it is statistically possible that between 432 fewer patients (i.e., 368 patients) and 296 more patients (i.e., all patients)[1] would be anticipated to relapse after response at 30 days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single 0.1 mg/kg ketamine infusion.

Table 35: Single dose ketamine ≥0.5 mg/kg vs 0.1 mg/kg ketamine: summary of findings table for relapse after response

Outcome: relapse on response	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ketamine 0.1 mg/kg	Risk difference with ketamine ≥0.5 mg/kg			
5-7 days post-infusion N=27 (1 RCT)	400 per 1 000	**264 fewer per 1 000** (368 fewer to 212 more)	**RR 0.34** (0.08 to 1.53)	⊕⊕ Low [a,d]	A single ketamine ≥0.5 mg/kg infusion may reduce the risk of relapse slightly more than 0.1 mg/kg ketamine at 5-7 days post-infusion (*low certainty evidence*)
14 days post-infusion N=27 (1 RCT)	800 per 1 000	**392 fewer per 1 000** (592 fewer to 0 fewer)	**RR 0.51** (0.26 to 1.00)	⊕⊕ Low [a,d]	A single ketamine 0.5 mg/kg infusion may reduce the risk of relapse more than 0.1 mg/kg ketamine at 14 days post-infusion (*low certainty evidence*)
30 days post-infusion N=27 (1 RCT)	800 per 1 000	**160 fewer per 1 000** (432 fewer to 296 more)	**RR 0.80** (0.46 to 1.37)	⊕⊕ Low [a,d]	A single ketamine 0.5 mg/kg infusion may reduce the risk of relapse slightly more than 0.1 mg/kg ketamine at 30 days post-infusion (*low certainty evidence*)

***GRADE**: a: study limitations (RoB); d: imprecision.*
***CI:** confidence interval; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

[1] As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution

2.2.12.3 Remission

Only one study presented data on remission, at three and seven days post-infusion (59;69). Remission was defined as MADRS score ≤10 on day three post-infusion (69).

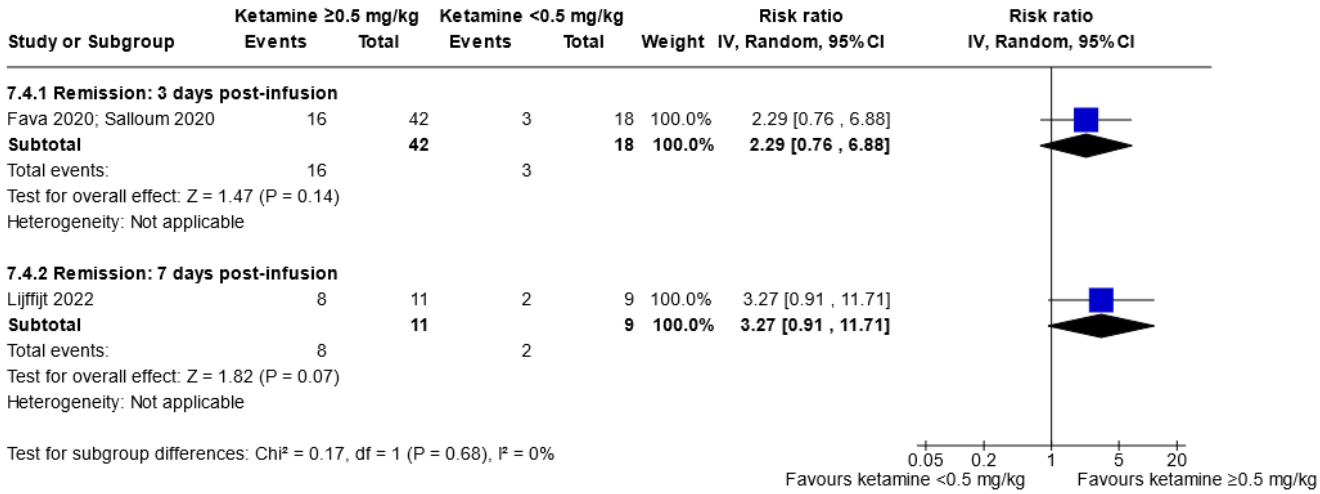


Figure 28: Single dose ketamine ≥0.5 mg/kg vs <0.5 mg/kg ketamine: forest plot of remission

2.2.12.3.1 Three days post-infusion

At three days post-infusion, the risk ratio (95% CI; p-value) of remission was 2.29 (0.76 to 6.88; p=0.14). In other words, patients in this study who received a single ketamine ≥0.5 mg/kg infusion were over twice as likely to achieve remission at three days post-infusion than patients who received a single <0.5 mg/kg ketamine infusion (*Figure 28*). However, the confidence interval includes values below 1, so it is statistically possible that patients who receive a single ≥0.5 mg/kg ketamine infusion actually have equal or less chance of remission three days post-infusion, compared to patients who received a single <0.5 mg/kg ketamine infusion.

If 167 of 1 000 patients treated with a single <0.5 mg/kg ketamine infusion achieved remission at three days post-infusion, then the anticipated risk difference would correspond to 215 more patients per 1 000 (i.e., 382 patients) treated with a single ketamine ≥0.5 mg/kg infusion achieve response at three days post-infusion (*Table 36*). The 95% CI shows that it is statistically possible that between 40 fewer patients (i.e., 127 patients) and 980 more patients (i.e., all patients)[1] would be anticipated to achieve remission at three days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single <0.5 mg/kg ketamine infusion.

Table 36: Single dose ketamine ≥0.5 mg/kg vs <0.5 mg/kg ketamine: summary of findings table for remission

Outcome: remission	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ketamine <0.5 mg/kg	Risk difference with ketamine ≥0.5 mg/kg			
3 days post-infusion N=60 (1 RCT)	167 per 1 000	**215 more per 1 000** (40 fewer to 980 more)	**RR 2.29** (0.76 to 6.88)	⨁⨁ Low [a,d]	A single ketamine ≥0.5 mg/kg infusion may improve the chance of remission slightly more than <0.5 mg/kg ketamine at 3 days post-infusion (*low certainty evidence*)

[1] As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution

Outcome: remission	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ketamine <0.5 mg/kg	Risk difference with ketamine ≥0.5 mg/kg			
7 days post-infusion N=20 (1 RCT)	222 per 1 000	**504 more per 1 000** (20 fewer to 2 380 more)	**RR 3.27** (0.91 to 11.71)	⊕⊕⊕ Moderate [d]	A single ketamine ≥0.5 mg/kg infusion probably improves the chance of remission slightly more than <0.5 mg/kg ketamine at 7 days post-infusion. (*moderate certainty evidence*)

***GRADE**: a: study limitations (RoB); d: imprecision.*
***CI:** confidence interval; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.12.3.2 Seven days post-infusion

At seven days post-infusion, the risk ratio (95% CI; p-value) of remission was 3.27 (0.91 to 11.71; p=0.0.07). In other words, patients in this study who received a single ketamine ≥0.5 mg/kg infusion were over three times as likely to achieve remission at seven days post-infusion than patients who received a single <0.5 mg/kg ketamine infusion (*Figure 28*). However, the confidence interval includes values below 1, so it is statistically possible that patients who receive a single ≥0.5 mg/kg ketamine infusion actually have equal or less chance of remission seven days post-infusion, compared to patients who received a single <0.5 mg/kg ketamine infusion.

If 222 of 1 000 patients treated with a single <0.5 mg/kg ketamine infusion achieved remission at seven days post-infusion, then the anticipated risk difference would correspond to 504 more patients per 1 000 (i.e., 726 patients) treated with a single ketamine ≥0.5 mg/kg infusion achieve response at seven days post-infusion (*Table 36*). The 95% CI shows that it is statistically possible that between 20 fewer patients (i.e., 202 patients) and 2380 more patients (i.e., all patients)[1] would be anticipated to achieve remission at seven days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single <0.5 mg/kg ketamine infusion.

2.2.12.4 Relapse after remission

Only one study presented data on remission, at five, seven, 14 and 30 days post-infusion (59;69). Salloum et al. defined relapse as a MADRS score of ≥22 on any subsequent visit (69).

2.2.12.4.1 Five days post-infusion

At five days post-infusion, the risk ratio (95% CI; p-value) of relapse of remitters was 0.56 (0.08 to 3.75; p=0.55). In other words, patients in this study who remitted on single infusions of ≥0.5 mg/kg ketamine were 44% less likely to relapse five days post-infusion, compared to patients who remitted on single infusions of <0.5 mg/kg ketamine (*Figure 29*). However, as the confidence interval includes values above 1, it is statistically possible that responders on single ≥0.5 mg/kg ketamine infusions are actually at equal or higher risk of relapsing five days post-infusion, compared to responders on single <0.5 mg/kg ketamine infusions.

If 333 of 1 000 patients treated with single <0.5 mg/kg ketamine infusions experienced relapse after remission at five days post-infusion, then the anticipated risk difference would correspond to 147 fewer patients per 1 000 (i.e., 186 patients) treated with single ketamine ≥0.5 mg/kg infusions relapsing after remission at five days post-infusion (*Table 37*). The 95% CI shows that it is statistically possible that between 307 fewer patients (i.e., 26 patients) and 917 more patients (i.e., all patients)[1] would be anticipated to relapse after response at five days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single <0.5 mg/kg ketamine infusion.

[1] As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution

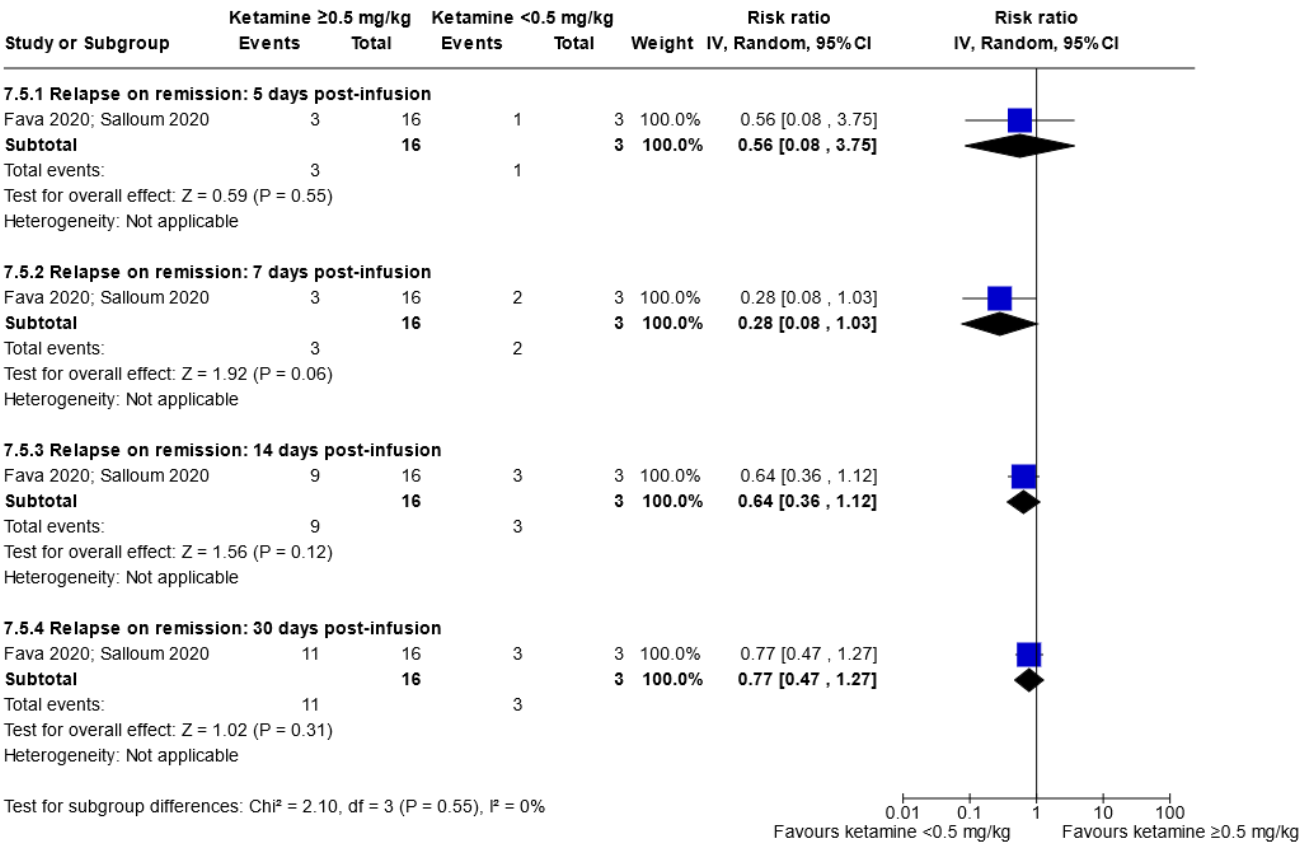


Figure 29: Single dose ketamine ≥0.5 mg/kg vs <0.5 mg/kg ketamine: forest plot of relapse after remission

2.2.12.4.2 Seven days post-infusion

At seven days post-infusion, the risk ratio (95% CI; p-value) of relapse of remitters was 0.28 (0.08 to 1.03; p=0.06). In other words, patients in this study who remitted on single infusions of ≥0.5 mg/kg ketamine were 72% less likely to relapse seven days post-infusion, compared to patients who remitted on single infusions of <0.5 mg/kg ketamine (*Figure 29*). However, as the confidence interval includes values above 1, it is statistically possible that responders on single ≥0.5 mg/kg ketamine infusions are actually at equal or higher risk of relapsing five days post-infusion, compared to responders on single <0.5 mg/kg ketamine infusions.

If 667 of 1 000 patients treated with single <0.5 mg/kg ketamine infusions experienced relapse after remission at seven days post-infusion, then the anticipated risk difference would correspond to 480 fewer patients per 1 000 (i.e., 187 patients) treated with single ketamine ≥0.5 mg/kg infusions relapsing after remission at seven days post-infusion (*Table 37*). The 95% CI shows that it is statistically possible that between 613 fewer patients (i.e., 54 patients) and 20 more patients (i.e., 687 patients) would be anticipated to relapse after response at seven days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single <0.5 mg/kg ketamine infusion.

Table 37: Single dose ketamine ≥0.5 mg/kg vs <0.5 mg/kg ketamine: summary of findings table for relapse after remission

Outcome: relapse on remission	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ketamine <0.5 mg/kg	Risk difference with ketamine ≥0.5 mg/kg			
5 days post-infusion N=19 (1 RCT)	333 per 1 000	**147 fewer per 1 000** (307 fewer to 917 more)	**RR 0.56** (0.08 to 3.75)	⊕ Very low [a,d]	It is uncertain whether a single ketamine 0.5 mg/kg infusion reduces the risk of relapse after remission more than <0.5 mg/kg ketamine at 5 days post-infusion because the certainty of this evidence is very low.
7 days post-infusion N=19 (1 RCT)	667 per 1 000	**480 fewer per 1 000** (613 fewer to 20 more)	**RR 0.28** (0.08 to 1.03)	⊕ Very low [a,d]	It is uncertain whether a single ketamine 0.5 mg/kg infusion reduces the risk of relapse after remission more than <0.5 mg/kg ketamine at 7 days post-infusion because the certainty of this evidence is very low.
14 days post-infusion N=19 (1 RCT)	1 000 per 1 000	**360 fewer per 1 000** (640 fewer to 120 more)	**RR 0.64** (0.36 to 1.12)	⊕ Very low [a,d]	It is uncertain whether a single ketamine 0.5 mg/kg infusion reduces the risk of relapse after remission more than <0.5 mg/kg ketamine at 14 days post-infusion because the certainty of this evidence is very low.
30 days post-infusion N=19 (1 RCT)	1 000 per 1 000	**230 fewer per 1 000** (530 fewer to 270 more)	**RR 0.77** (0.47 to 1.27)	⊕ Very low [a,d]	It is uncertain whether a single ketamine 0.5 mg/kg infusion reduces the risk of relapse after remission more than <0.5 mg/kg ketamine at 30 days post-infusion because the certainty of this evidence is very low.

***GRADE**: a: study limitations (RoB); d: imprecision.*
***CI:** confidence interval; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

2.2.12.4.3 14 days post-infusion

At 14 days post-infusion, the risk ratio (95% CI; p-value) of relapse of remitters was 0.64 (0.36 to 1.12; p=0.12). In other words, patients in this study who remitted on single infusions of ≥0.5 mg/kg ketamine were 36% less likely to relapse 14 days post-infusion, compared to patients who remitted on single infusions of <0.5 mg/kg ketamine (*Figure 29*). However, as the confidence interval includes values above 1, it is statistically possible that responders on single ≥0.5 mg/kg ketamine infusions are actually at equal or higher risk of relapsing 14 days post-infusion, compared to responders on single <0.5 mg/kg ketamine infusions.

If 1000 of 1 000 patients treated with single <0.5 mg/kg ketamine infusions experienced relapse after remission at 14 days post-infusion, then the anticipated risk difference would correspond to 360 fewer patients per 1 000 (i.e., 640 patients) treated with single ketamine ≥0.5 mg/kg infusions relapsing after remission at 14 days post-infusion (*Table 37*). The 95% CI shows that it is statistically possible that between 640 fewer patients (i.e., 360 patients) and 120 more patients (i.e., all patients)[1] would be

[1] As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution

anticipated to relapse after response at 14 days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single <0.5 mg/kg ketamine infusion.

2.2.12.4.4 30 days post-infusion

At 30 days post-infusion, the risk ratio (95% CI; p-value) of relapse of remitters was 0.77 (0.47 to 1.27; p=0.31). In other words, patients in this study who remitted on single infusions of ≥0.5 mg/kg ketamine were 23% less likely to relapse 30 days post-infusion, compared to patients who remitted on single infusions of <0.5 mg/kg ketamine (*Figure 29*). However, as the confidence interval includes values above 1, it is statistically possible that responders on single ≥0.5 mg/kg ketamine infusions are actually at equal or higher risk of relapsing 30 days post-infusion, compared to responders on single <0.5 mg/kg ketamine infusions.

If 1 000 of 1 000 patients treated with single <0.5 mg/kg ketamine infusions experienced relapse after remission at 30 days post-infusion, then the anticipated risk difference would correspond to 230 fewer patients per 1 000 (i.e., 770 patients) treated with single ketamine ≥0.5 mg/kg infusions relapsing after remission at 30 days post-infusion (*Table 37*). The 95% CI shows that it is statistically possible that between 530 fewer patients (i.e., 470 patients) and 270 more patients (i.e., all patients)[1] would be anticipated to relapse after response at 30 days post-infusion when receiving a single ketamine ≥0.5 mg/kg infusion than when receiving a single <0.5 mg/kg ketamine infusion.

2.2.12.5 Depression severity

Data on depression severity, measured by MADRS, was only provided by one study at one, three and five days post-infusion (57;73). Note that in this study, the doses of ketamine given in the intervention and comparator groups, were 0.5 and 0.2 mg/kg, respectively (57;73). As described in *2.1.6.3 Minimal important difference (MID)*, we applied MID thresholds of 20% and 50% improvement in the forest plots of depression severity scores. Note that these thresholds are rough estimations and only relevant for the statistically significant results.

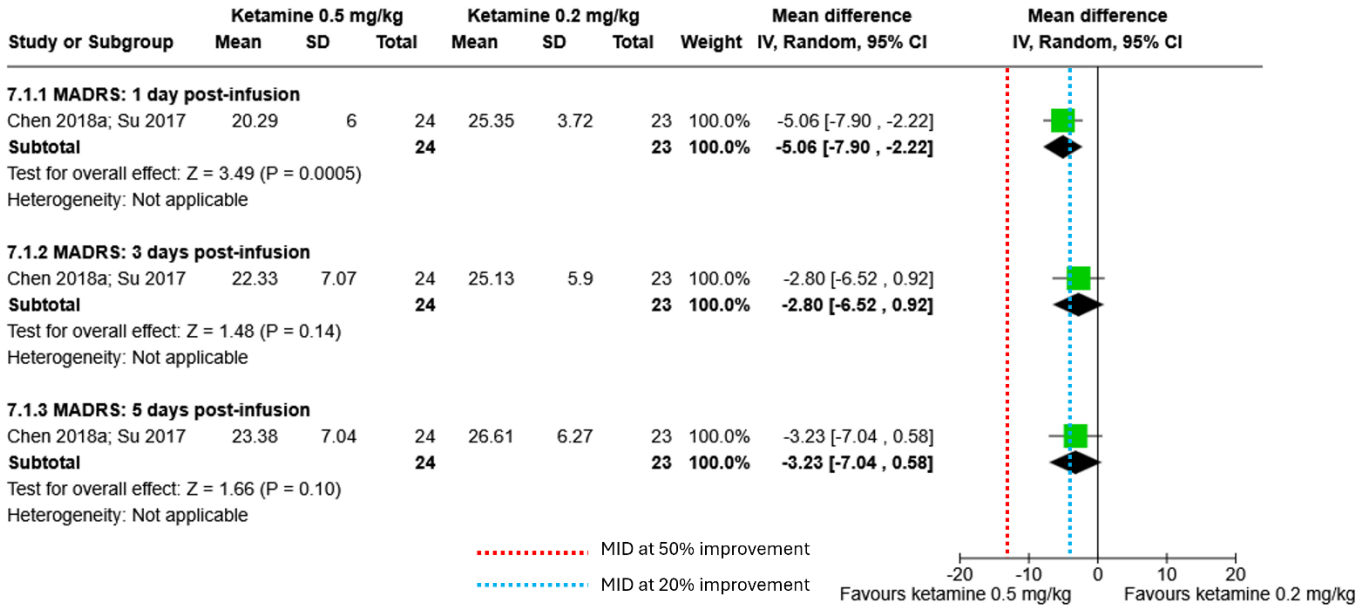


Figure 30: Single dose ketamine 0.5 mg/kg vs 0.2 mg/kg ketamine: forest plot of depression severity.

2.2.12.5.1 One day post-infusion

At one day post-infusion, the mean difference (95% CI; p-value) of depression severity was −5.05 (−7.90 to −2.22; p=0.0005), which is statistically significant in favour of ketamine 0.5 mg/kg. In other

[1] As the upper limit of the confidence interval has amplified the estimated risk difference, which result in an exaggerated absolute effect that is not clinically plausible. These calculations are only intended to provide a range of possible effects rather than definitive predictions and should be interpreted with caution

words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at one day post-infusion, compared to patients who received a 0.2 mg/kg ketamine infusion (*Figure 30;Table 38*).

2.2.12.5.2 Three days post-infusion

At three days post-infusion, the mean difference (95% CI; p-value) of depression severity was −2.80 (−6.52 to 0.92; p=0.14). In other words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at three days post-infusion, compared to patients who received a 0.2 mg/kg ketamine infusion (*Figure 30;Table 38*). However, as the confidence interval includes values over 0, it is statistically possible that patients who receive a single 0.5 mg/kg ketamine infusion actually have equal or higher depression severity, i.e., MADRS scores, at three days post-infusion, compared to patients who receive a single 0.2 mg/kg ketamine infusion.

Table 38: Single dose ketamine 0.5 mg/kg vs 0.2 mg/kg ketamine: summary of findings table for depression severity

Outcome: depression severity (MADRS)	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with ketamine 0.2 mg/kg	Risk difference with ketamine 0.5 mg/kg		
1 day post-infusion (MADRS) N=47 (1 RCT)	Mean DS was **25.35**	MD **5.06 lower** (7.9 lower to 2.22 lower)	⊕⊕⊕ Moderate [a,]	**MID50%**: A single ketamine 0.5 mg/kg infusion probably reduce the depression severity score slightly more than a single infusion of ketamine 0.2 mg/kg at 1 day post-infusion (*moderate certainty evidence*)
				MID20%: A single ketamine 0.5 mg/kg infusion probably reduce the depression severity scores more than a single ketamine 0.2 mg/kg infusion at 1 day post-infusion (*moderate certainty evidence*)
3 days post-infusion (MADRS) N=47 (1 RCT)	Mean DS was **25.13**	MD **2.8 lower** (6.52 lower to 0.92 higher)	⊕⊕ Low [a,d]	A single ketamine 0.5 mg/kg infusion may reduce the depression severity score slightly more than a single infusion of ketamine 0.2 mg/kg at 3 days post-infusion (*low certainty evidence*)
5 days post-infusion (MADRS) N=47 (1 RCT)	Mean DS was **26.61**	MD **3.23 lower** (7.04 lower to 0.58 higher)	⊕⊕ Low [a,d]	A single ketamine 0.5 mg/kg infusion may reduce the depression severity score slightly more than a single infusion of ketamine 0.2 mg/kg at 5 days post-infusion (*low certainty evidence*)

***GRADE**: a: study limitations (RoB); d: imprecision.*
***CI:** confidence interval; **DS**: depression severity; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MD**: mean difference; **N**: number of study participants; **RCT**: randomised controlled trial*

2.2.12.5.3 Five days post-infusion

At five days post-infusion, the mean difference (95% CI; p-value) of depression severity was −3.23 (−7.04 to 0.58; p=0.10). In other words, patients who received a single 0.5 mg/kg ketamine infusion had lower MADRS scores, i.e. less severe depression, at five days post-infusion, compared to patients who received a 0.2 mg/kg ketamine infusion (*Figure 30;Table 38*). However, as the confidence interval includes values over 0, it is statistically possible that patients who receive a single 0.5 mg/kg ketamine infusion actually have equal or higher depression severity, i.e., MADRS scores, at five days post-infusion, compared to patients who receive a single 0.2 mg/kg ketamine infusion.

The statistically significant meta-analysis result of depression severity, i.e., at 1 day post-infusion would not be considered clinically relevant when interpreting the meta-analysis data with MID thresholds of 50% (red line) (*Figure 30*). However, it would be considered clinically relevant when using a MID of 20% (blue line). When using the MID threshold of 50%, we interpret these results as "less important benefit", in accordance with the EPOC standardised statements for reporting of effect (52). However, using the MID threshold of 20%, we interpret these results as "important benefit" (*Table* **38**).

2.2.12.6 Safety data

Only two of the four studies presented data on adverse events (59;63;69). As presented in the study by Fava/Salloum, the number of patients who experienced adverse events were similar between the two groups (*Table 39*) (59;69). However, the percent of adverse events that were reported was higher in the <0.5 mg/kg ketamine groups (i.e., 0.1 mg/kg and 0.2 mg/kg) than in the ≥0.5 mg/kg ketamine groups (i.e., 0.5 mg/kg and 1.0 mg/kg). Similar numbers were not presented in the other study.

The most common adverse events were nausea/vomiting and headache, although few event were reported. For nausea/vomiting, the study by Fava/Salloum showed a higher prevalence among patients who received ≥0.5 mg/kg ketamine (59;69), while the opposite was shown in the study by Lijffijt (63). Urinary problem was only reported on by Lijffijt *et al.*, who showed a similar distribution between the two groups (63).

One patient in the <0.5 mg/kg ketamine-group attempted suicide in both the Fava/Salloum- and Lijffijt-studies (59;63;69).

Table 39: Single dose ketamine ≥0.5 mg/kg vs ketamine <0.5 mg/kg: overview of adverse events

	Fava/Salloum (59;69)		**Lijffijt** (63)	
	Ketamine ≥0.5 mg/kg *(n=42)*	**Ketamine <0.5 mg/kg** *(n=38)*	**Ketamine ≥0.5 mg/kg** *(n=11)*	**Ketamine <0.5 mg/kg** *(n=9)*
Adverse events				
Number of patients with AE	17 (40%)	16 (42%)	-	-
Number of AE	32 (76%)	36 (95%)	-	-
Cardiovascular event	-	-	1 (9%)	0
Hypo- or hypertension	1 (2%)	0	-	-
Brady- or tachycardia	1 (2%)	1 (3%)	-	-
Suicidal ideation	1 (2%)	1 (3%)	-	-
Nausea/vomiting	8 (19%)	4 (11%)	0	2 (22%)
Urinary problem	-	-	2 (18%)	1 (11%)
Anxiety	-	-	1 (9%)	1 (11%)
Increased or decreased saliva	-	-	1 (9%)	0
Visual disturbances	-	-	1 (9%)	2 (22%)
Involuntary movements	-	-	1 (9%)	0
Headache	4 (10%)	5 (13%)	2 (18%)	1 (11%)
Serious adverse events				
Suicidal attempt	0	1 (3%)	0	1 (11%)

AE: adverse eventsm n: number of patients
Ketamine ≥ 0.5 mg/kg: summarised from groups 0.5 mg/kg and 1.0 mg/kg.
Ketamine <0.5 mg/kg: summarised from groups 0.1, 0.2 and/or 0.25 mg/kg.

2.2.13 Results from non-RCTs

Since we did not identify any relevant cohort studies with control groups, results from two chart reviews without control groups are presented in this section to describe real-world long-term effects.

2.2.13.1 Sakurai *et al.*

The study by Sakurai *et al.* (2020) used real-world data of 87 patients that had been treated at the Intravenous Ketamine Clinic at Massachusetts General Hospital (USA), between October 2018 and November 2019 (68). Treatment consisted of an induction phase, where ketamine was administered twice per week for three weeks (i.e., six infusions in total), followed by a maintenance phase, where the ketamine administration varied according to the patients' needs (e.g., every 2-6 weeks depending on the duration of effect) (68). The ketamine-treatment was paid out-of-pocket by the patients themselves.

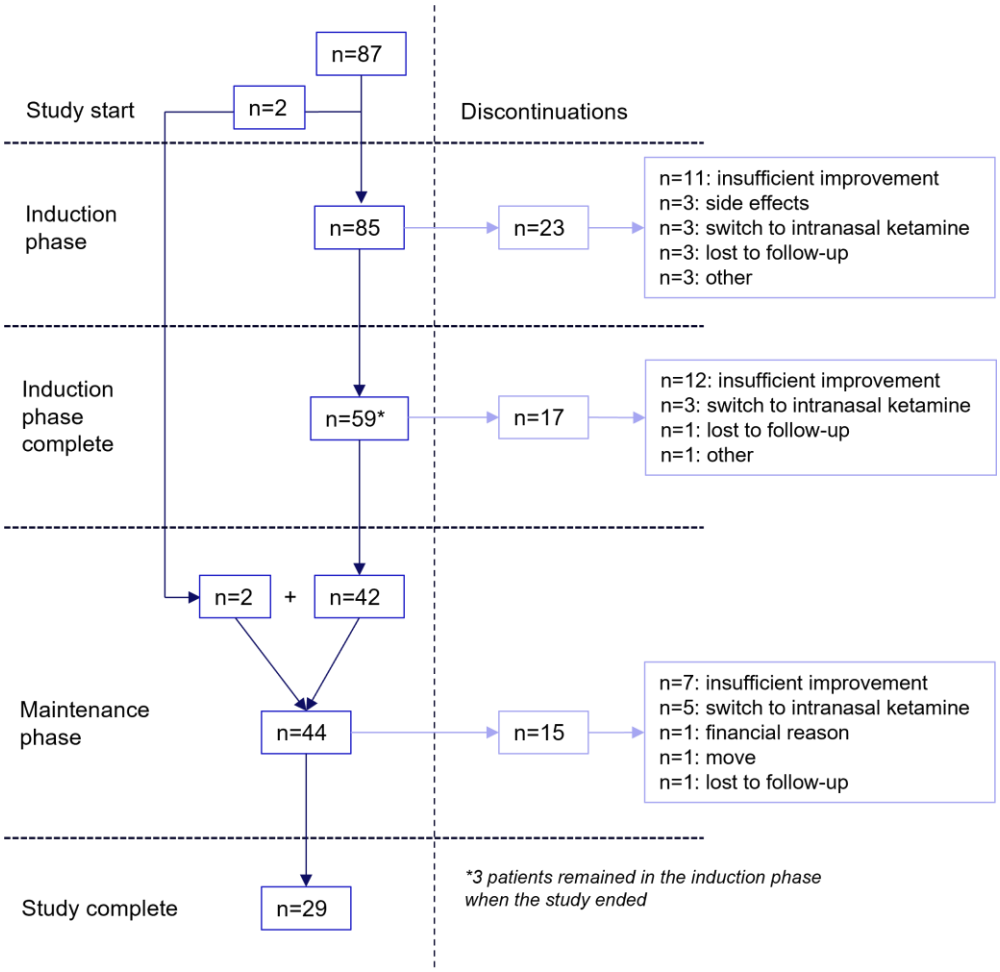


Figure 31: Study progression - Sakurai *et al. (68)*

The study progression is illustrated in *Figure 31*. In brief, 85 of the total 87 patients were ketamine naïve and started treatment with an induction phase (68). The remaining two patients started maintenance treatment, as they had prior response to ketamine (68). Of the 85 patients, 59 completed the induction phase, and 42 continued receiving ketamine as maintenance therapy (68). The total number of patients who received maintenance ketamine-treatment was 44, of which 29 were still receiving ketamine when the study ended, i.e., after 13 months (68).

Reason for discontinuation was mainly insufficient improvement. As shown in *Table 40*, 15 patients (18%) experienced response, defined as ≥50% reduction in QIDS-SR, during/after the induction phase, and six of the 15 (40%) continued having response during the maintenance phase (68). Twentynine patients (34%) experienced some improvement, defined as ≥35% reduction in QIDS-SR,

during/after the induction phase, and 13 of the 29 (45%) continued having improvement during maintenance phase (68).

Table 40: Overview response and improvement data - Sakurai *et al.* (68)

Phase	Response n/N	Response %	Improvement n/N	Improvement %
Induction	n=15/85	18%*	n=29/85	34%*
Maintenance (continued effect from induction)	n=6/15	40%**	n=13/29	45%**
	n=6/87	7%†	n=13/87	15%†

Response: ≥50% reduction in QIDS-SR
Improvement: ≥35% reduction in QIDS-SR
** Percent calculated from the total number of patients who received ketamine induction (n=85)*
*** Percent calculated from the number of patients who responded or improved during/after ketamine induction (n=15 and n=29)*
†Percent calculated from the total number of patients who received ketamine treatment. (n=87)

The study does not list any side effects or adverse events, other than mentioning that there were no reports on cognitive disturbances or urinary problems.

2.2.13.2 Pfeiffer *et al.*

The study used real-world data extracted from electronical medical records from the Veteran Health Administration (USA) (66). The patient population consisted of 215 American veterans that had been treated with intravenous ketamine infusions in 2020/2021. The treatment is likely to have been paid out-of-pocket by the patients themselves.

Only 4% (n=9) of the patients discontinued the ketamine-treatment after one infusion (66). Patients received on average 18 ketamine-infusions during the one year included in the study (66). As seen in *Table 41*, treatment infusions were more frequent in the first month, with five days between infusions, dropping gradually to 23-28 days between infusions at months 5-12 (66).

Table 41: Overview treatment duration and frequency - Pfeiffer *et al.* (66)

Treatment duration	Time between infusions
Month 1	5 days
Months 2-4	12-17 days
Months 5-12	23-28 days

The study reported data on response, defined as ≥50% reduction in PHQ-9 scores, and remission, defined as a PHQ-9 score ≤5, at 6, 12 and 26 weeks of treatment (*Table 42*). At 6 weeks, 26% and 15% experienced response and remission, respectively. These numbers remained relatively stable, with 25% and 28% achieving response, and 12% and 13% achieving remission, at 12 weeks and 26 weeks, respectively (66). The study reported no data on safety.

Table 42: Overview response and improvement data - Pfeiffer *et al.* (66)

Treatment duration	Response	Remission
6 weeks (n=164)	26%	15%
12 weeks (n=169)	25%	12%
26 weeks (n=171)	28%	13%

n: number of patients

3. Health economic evaluation

The health care systems function within financial frame of limited resources and given budgets. The purpose of health economic evaluation is to provide better basis for informed decision-making, and this way contribute to the more efficient use of the health sector's resources, in line with the national guidelines for prioritisation (77). The core of a health economic evaluation is to compare the costs and health effects of alternative interventions. By systematically analysing costs and outcomes of healthcare interventions, health economic evaluations ensure that healthcare resources are used efficiently and effectively, ultimately aiming to improve health outcomes and access to care.

In Norway decisions on the introduction, use or phasing out of methods, are based on three priority criteria: health benefit, resource use and severity. The prioritization criteria should be assessed jointly and weighed against each other. The greater the benefit of a measure and the more serious a condition is, the higher use of resources can be accepted (77).

A health economic evaluation is a comparative analysis of treatment strategies or interventions, where both the costs and health effects of the measures are assessed. The overall goal of a health economic evaluation is to achieve the most health possible with the resources available. The recommended analysis to support decisions on prioritising methods at the population level in Norway is cost per quality-adjusted life year. Such an analysis is particularly relevant when a health measure is more effective and simultaneously more costly compared to other relevant alternatives. However, in cases where documentation suggests that the effect and safety profile are approximately the same or non-inferior for intervention and comparator(s), a simplified assessment of economic consequences can be carried out (78).

3.1 Methods

3.1.1 General

There are several treatment options available for persons with treatment-resistant depression. They include psychotherapy, combination of multiple antidepressants, and various electrical therapies, including ECT (79). In this economic evaluation we assume that in practice, different medicines in combination with psychotherapy would have been tried and failed before considering treatment with ECT or ketamine. We therefore view ECT as the most relevant comparator for intravenous ketamine treatment in a Norwegian setting for this patient group.

We identified only one RCT that explored clinical effect and safety of intravenous ketamine compared to ECT (55). The patients in the ketamine group were given two infusions of 0.5 mg/kg ketamine every week for three weeks, while the comparison group received three ECT sessions every week for three weeks (55). The results indicated that multiple doses of ketamine probably improved the chances of response at the end of treatment (after three weeks). The RR was 1.44 (95% CI: 1.13 to 1.82). In other words, patients in this study who received multiple doses of ketamine were 44% more likely to experience response at end of treatment (see the results in *2.2.6*). The result was statistically significant, and we have assessed the certainty of this evidence to be moderate. The results on relapse after response in longer perspective than the end of treatment are more uncertain. Certainty of the evidence for these outcomes were assessed as low, we therefore chose to limit the time perspective to the end of treatment.

We have gathered cost data related to both treatment options in the Norwegian outpatient settings. We learned that the costs related to both therapies are overall at a comparable level, with ketamine being a somewhat less resource-consuming option. With the intervention being both better in terms of outcomes, albeit with some uncertainty, and less expensive than the comparator, with similar safety profile, we have chosen a cost-comparison analysis as the most appropriate type for economic assessment of treatment with intravenous ketamine compared with ECT. We based our analyses on cost data received from Norwegian public hospitals in outpatient settings, expressed in the Norwegian kroner (NOK). We compared both average costs of single treatment sessions for both alternatives, as

well as cost of treatment series. Since both treatments are overall well tolerated and have similar safety profile, we have not included costs related to treatment of side effects in our analyses. We carried out the analyses from the healthcare sector perspective. This approach aligns with priorities established within a fixed healthcare budget, as outlined in the Priority-setting White Paper (77) and implies that all relevant healthcare costs are included. Given the available evidence on relapse rates gathered in our systematic review, and tendency for recurrence of moderate or severe depression, we limited the time horizon for our analyses to the most intensive treatment phase for both treatment options, i.e. three weeks (end of treatment) in the RCT by Anand *et al.* (55).

3.1.2 Costs of the compared interventions

3.1.2.1 Cost of electroconvulsive therapy (ECT)

ECT is a treatment option for moderate to severe treatment-resistant depression when other treatments have failed, or for recurrent depression in patients who have had positive response to ECT before (80). During ECT, a controlled electric current from the electrodes placed on the patient's head is passed through the brain to induce a brief seizure, which usually last 15–45 seconds. This process is done under general anaesthesia to ensure that the patient does not feel pain or discomfort, and a muscle relaxant to prevent injury during the procedure (80). The ECT procedure itself takes approximately 15 minutes, but requires preparations, close monitoring of the patient and post-procedure care to facilitate recovery. The patient can feel a little tired in the minutes after the treatment and will need to rest for a while. Although ECT is usually well tolerated, some patients may experience also short-term side effects such as headaches, nausea and muscle pain. Memory problems are relatively common, but these are often transient and resolve within a few weeks or months after treatment (81).

To accurately calculate the costs of an ECT procedure, we requested estimations of real costs for an ECT procedure from the Norwegian hospitals. We have received estimates from Stavanger University Hospital (Stavanger universitetssjukehus) (82) and St. Olav's Hospital in Trondheim (Universitetssykehuset i Trondheim) (83). They both encompass direct costs related to the procedure (personnel costs, depreciation costs for the ECT unit, and consumables), as well as indirect costs (overheads). The estimates received from the hospitals represent some variation in the level of the costs but differ only slightly. To simplify the further analyses, we have calculated an arithmetic average of the two. ECT given in the hospital setting directly engages the following resources: depreciation costs for the ECT unit and following personnel resource use: an ECT-operator (a specialised physician, usually a psychiatrist (15 minutes), an anaesthesiologist (30 minutes), 1-2 intensive nurse(s) (90 minutes), additional personnel (15 minutes) (82;83).

In the RCT by Anand and colleagues the treatment series included three weeks with three treatments per week, i.e. nine treatment sessions over three weeks (55). Norwegian guidelines suggest that ECT should be offered twice per week rather than three times per week (80). We have therefore calculated results for both twice-weekly and thrice-weekly treatment regimens and presented the results as an interval.

3.1.2.2 Costs of treatment with intravenous ketamine

We have received detailed information and cost data related to intravenous ketamine treatment from the Østfold Hospital (84). The clinic has been treating patients with therapy-resistant depression with intravenous ketamine within research framework since 2020 (85) and developed the Norwegian protocol for this treatment alternative (86).

Intravenous ketamine treatment consists of two main elements: medicine use and psychotherapy. The infusion itself takes 40 minutes out of a total of about 120 minutes that are set aside per treatment session. Blood pressure, pulse and oxygen saturation are measured before and after the infusion. It is recommended that the patient has started with psychotherapy before starting ketamine treatment. Preparatory conversations before each treatment session and integration conversations during and after ketamine treatment are integral parts of the treatment plan. Preparatory conversations aim to

establish a safe treatment relationship and prepare the patient for the ketamine experience. During integration conversations experiences, feelings or insights from experiences related to the treatment are processed. Both preparatory and integration conversations, as well as continuous monitoring of the patient, are included in the cost estimates. Full effect of the treatment is achieved within 24 hours of infusion, the patients are therefore offered an additional teleconsultation the day after treatment session in the start-up phase (initial 3 weeks) and the costs of this consultation is also included in the estimates.

The treatment with ketamine requires involvement from the three personnel groups, and we have therefore based calculation of the personnel cost on hourly wages (including social costs) for these three groups, as outlined in *Table 43*.

Table 43: Wages used in the calculation of personnel costs (84).

Health personnel	Annual salary in NOK	Hourly wages in NOK	Hourly wages inclusive of the social costs in NOK
Administration staff/health secretary	527 000	270.26	424.8
Nurse	675 000	365.66	574.8
Physician (specialist in psychiatry)	1 320 000	668.02	1 050

NOK: Norwegian kroner

We have assumed that intravenous ketamine treatment is conducted by a doctor or nurse with a senior psychiatry consultant on-call. A second nurse is required to double-check the preparation of the infusion. An ordinary treatment session always includes two working hours for a nurse, and introductory conversation with a nurse (20 minutes) and a physician (20 minutes). An additional nurse double-checks the preparation of the infusion (2 x10 minutes).

In the calculations, we have included costs of the qualifying consultation for intravenous ketamine, the first treatment session and an ordinary treatment session (any subsequent treatment with intravenous ketamine). Based on these costs we have then calculated an average cost per treatment. We have also included costs of the consumables, i.e. cost of the ketamine solution, tubes, cannulas, needles, eye mask are included as a lump sum, based on an average use per treatment session (84). We have further assumed that a treatment clinic is already equipped with the necessary infrastructure like room with armchair, bed, blood pressure monitor, oxygen saturation (SpO2) measurement, etc., and therefore not included these investment costs separately. We have however included these in the indirect costs/overheads (hospital infrastructure, electricity, cleaning services, etc.) and accounted for additional 20% of the sum of the direct costs (personal costs and costs of consumables) and added these costs to the total. The details of resource use for the three consultation types are presented in *Table 44* below.

Table 44: Use of resources for treatment with intravenous ketamine

Health personnel and consumable materials	Qualification consultation	First treatment session	Every subsequent treatment session
Administration staff/health secretary	10 min	10 min	
Nurse	110 min	140 min + 20 min + 30 min	120 min + 20 min + 20min
Physician (specialist in psychiatry)	15 min	30 min	20 min

Health personnel and consumable materials	Qualification consultation	First treatment session	Every subsequent treatment session
Consumable materials (medicine, eye mask, venous cannula, extension tube, ect.)		306 NOK	306 NOK

3.2 Results

3.2.1 Costs of the compared interventions

In this chapter, we present the results of our cost-comparison analysis, first as the average costs related to the single alternative treatments and then as costs of the treatment series.

3.2.1.1 Cost of electroconvulsive therapy (ECT)

We received cost estimates of electroconvulsive therapy from two Norwegian hospitals: Stavanger University Hospital: NOK 4 151 (82), and from and St.Olav's Hospital in Trondheim: NOK 5 263 per procedure (83). Based on these two estimates we calculated an average cost of NOK 4 707 per ECT single procedure.

3.2.1.2 Costs of treatment with intravenous ketamine

We have received cost data related to intravenous ketamine treatment from the Østfold Hospital (84). Before a treatment series can be started, it is necessary with a separate consultation, during which the patient is prepared and accustomed with the therapy principles. Also, the first treatment session when a patient receives their first infusion requires different resource use than any subsequent session. The utilisation of resources for qualification consultation, the first treatment session and any subsequent treatment session are outlined in *Table 45*.

Table 45: Cost of treatment with intravenous ketamine

Cost in NOK	Qualification consultation	First treatment session	Every subsequent treatment session
Personal costs	1 381	2 416	1 883
Consumable materials (medicine, eye mask, venous cannula, extension tube, etc.)		306	306
Indirect costs / overheads	277	544	438
Total	1 665	3 266	2 627

Source: Østfold Hospital (84)

Based on the above costs, we have calculated an average cost of a single intravenous ketamine session to equal NOK 3 011 in the initial 3-weeks treatment phase.

3.2.1.3 Costs of treatment series for a patient with treatment-resistant depression

We have compared the cost of treatment series with intravenous ketamine with ECT in the initial, intensive treatment phase, i.e. the initial three weeks of the treatment. We have used the average costs of an ECT session and intravenous ketamine calculated above.

The cost of a treatment series consisting of six infusion sessions with ketamine over the course of three weeks is equal to NOK 18 064. Corresponding costs related to ECT were NOK 28 243 with twice-weekly regimen, and NOK 42 364 when treatment was given three times per week. The results are presented in *Table 46*.

Table 46: Cost of treatment series with intravenous ketamine compared with electroconvulsive therapy in the intensive treatment phase

Cost in NOK	ECT – 2 times a week	ECT – 3 times a week	IV Ketamine treatment
Number of treatments in the initial phase	6	9	6
Average cost/treatment session	4 707	4 707	3 011
Costs of the treatment series	28 243	42 364	18 064

ECT: electroconvulsive therapy; IV: intravenous

4. Patient perspectives

4.1 Introduction

Patient perspectives relate to issues relevant for patients, individuals, and caregivers. Since patients with treatment-resistant depression can provide unique perspectives about experiences, attitudes, preferences, values, and expectations concerning health, illness, service delivery and treatments, their perspectives may extend far beyond the original setting of the proposed new method.

4.2 Methods

In this HTA, considerations regarding patients' experiences and perspectives were managed with the help of two patient representatives assigned by "Mental Helse", an organisation for mental health in Norway. We collected their perspectives through a questionnaire and a digital interview. The patient representatives were also invited to participate in digital meetings as part of the external working group.

The patient representatives provided their perspectives and experiences related to:

- The burden of living with treatment-resistant depression
- Reflections about the current course of treatment
- Expectations of and/or experiences with ketamine treatment

4.3 The burden of living with treatment-resistant depression

Treatment-resistant depression has a severe impact on patients' quality of life. Many experience social isolation, loss of employment, and a significant reduction in joy and meaning in their daily lives. The condition leads to an increased risk of suicidal thoughts and actions, and the patient group has a considerably shorter life expectancy than the general population. There is still a significant amount of prejudice and stigma associated with mental illness, and the idea that one can simply "pull oneself together" can add to the burden. It is not possible to think or exercise one's way out of severe, treatment-resistant depression. This does not mean that personal effort is unimportant, but in order to be able to take charge of one's life, a helping hand is often needed.

Friends and relatives can find themselves in a demanding situation, characterized by worry and constant vigilance, particularly due to the risk of suicide. Many relatives develop mental health issues themselves as a result of the strain of living closely with someone suffering from severe depression and report a lack of support from the healthcare system. When treatment options fail to deliver the desired effects, hopelessness and frustration can exacerbate the situation for both patients and their next of kin.

4.4 Reflections about the current course of treatment

Antidepressants often have many side-effects and must be taken daily. This can be particularly challenging for patients with low capacity for adherence, which is a symptom of depression. ECT often requires hospitalization and can lead to extensive and long-lasting side effects. When depression is described as "treatment resistant", it entails that previous treatments have not had the desired effect, and we need more tools in the toolbox.

4.5 Expectations and experiences with ketamine therapy

According to the patient representative, patients treated with ketamine report rapid improvement in suicidal thoughts, increased energy, and an enhanced ability to address their own challenges. Some report that ketamine is the only treatment that has been effective after trying all other therapy options. Many experience significant improvements in quality of life, with the possibility of returning to work and engaging in social activities. Unlike other treatments such as ECT, ketamine does not require hospitalization, is perceived to be less invasive and has fewer long-term side effects. Ketamine's side effects, such as anxiety and "K-hole" experiences, are perceived by patients to be tolerable. Still, the

treatment method requires preparation and follow-up, as ketamine treatment can induce psychedelic experiences and bring up past traumas.

Furthermore, patient representatives also highlight that ketamine treatment should be accompanied with psychotherapy after each treatment session to maximize the benefits of the treatment. While ketamine can provide rapid improvement, full effect of ketamine therapy is unlikely to be achieved after the first dose, and lasting change will require significant personal effort and a structured treatment plan that is tailored to the individual patient's needs, such as adjusting the dosing and frequency of sessions. On the question regarding potential for misuse/abuse, it is argued that while it is possible to misuse ketamine, the potential is lower than for other psychiatric medications since the drug is only administered in controlled settings and not prescribed to use at home. For misuse or abuse to be possible, ketamine would have to be acquired illegally.

It is important to note, however, that ketamine is not a miracle cure, and it is not seen as such by the patient population. Ketamine treatment is not universally effective, as the underlying causes of treatment-resistant depression may vary. It is also important to note that this treatment is not relevant as a coercive treatment, as this may do more harm than good, due to ketamine's dissociative effect.

Ketamine therapy is currently only available in private clinics, and this creates financial barriers for many patients who could benefit from the treatment, especially those who are unemployed. A potential introduction to the Norwegian specialist health care service will therefore be of particular importance for this patient group. When patients recover, their families also benefit, especially through reduced fear of suicide.

5. Discussion

5.1 Discussion efficacy and safety

5.1.1 Key findings from the systematic review of efficacy and safety

We have systematically reviewed the literature on clinical efficacy and safety of intravenous ketamine for treatment-resistant depression. The evidence base comprised of 17 of 19 included RCTs, studying the effect of ≥0.5 mg/kg ketamine compared with ECT, saline, midazolam, esketamine, and/or ketamine <0.5 mg/kg (54-61;63-65;69-76), in addition to two non-RCTs (66;68). The majority of studies were small, with a sample size less than 100 participants. Twelve of the included RCTs administered single ketamine-infusions (56-59;63;64;69;71;73-76), and seven used multiple ketamine-infusions (54;55;60;61;65;70;72). We performed meta-analyses on four pre-selected outcomes: response, remission, relapse (i.e., after response and/or remission), and depression severity scores, in addition to narratively summarising safety data from the RCTs and the results of the non-RCTs.

5.1.1.1 Summary of findings – RCTs

5.1.1.1.1 Ketamine versus ECT

The comparison of ketamine versus ECT was only based on one study, but overall results seem to be in favour of ketamine. We found that patients treated with multiple infusions of 0.5 mg/kg ketamine probably have a higher chance of response, remission, and lower depression severity scores at end-of-treatment (i.e., after three weeks with a total of six infusions), than patients treated with multiple ECTs (moderate certainty evidence). However, the results at later time points are more uncertain and scattered, and it is therefore difficult to see any clear picture with regards to long-term effect. We also found that ECT may improve quality of life more than ketamine at end of treatment and one month after end of treatment, and conversely, that ketamine may improve quality of life more than ECT at three and six months after end of treatment (moderate certainty evidence).

5.1.1.1.2 Ketamine versus saline

Overall, the results of the comparison between single infusions of ketamine and saline seem to be in favour of ketamine. We found that patients treated with a single infusion of 0.5 mg/kg ketamine may have a higher chance of response at one day post-infusion, compared with patients treated with single infusions of saline. However, we have low confidence in this estimate. We also found that single ketamine infusions probably reduce depression severity scores (MADRS) more than single saline infusions, at one and two months post-infusion (moderate certainty evidence). Note that this result was only based on one study. At earlier time points (1-7 days post-infusion), however, the results were more uncertain and scattered, and we have low confidence in the estimates.

The results regarding the comparison of multiple infusions of ketamine and saline were overall in line with the results for single infusions, although less clear. We found that patients treated with multiple infusions of 0.5 mg/kg ketamine may have a higher chance of remission and lower depression severity MADRS scores, at end of treatment. However, our confidence in these estimates vary greatly, from moderate to very low. Furthermore, it is uncertain whether multiple infusions of 0.5 mg/kg ketamine improve the chance of response or lower the depression severity HDRS score at end of treatment, more than multiple infusions of saline, because the certainty of evidence is very low.

5.1.1.1.3 Ketamine versus midazolam

The results of the comparison between single infusions of ketamine and midazolam, seem overall to be in favour of ketamine. We found that patients treated with single infusions of 0.5 mg/kg ketamine probably have a higher and slightly higher chance of response and remission, respectively, at seven days post-infusion, than patients treated with single midazolam infusions (moderate certainty evidence). Note that these results were only based on one study. Similar results were found for depression severity scores at one and seven days post-infusion. Results for response at earlier time

points (i.e., one and three days post-infusion), and relapse after response, indicated some effect of ketamine, but our confidence in these results were low.

In contrast, the results of all outcomes of the comparison between multiple infusions of ketamine and midazolam are uncertain, because our confidence in all these results is very low.

5.1.1.1.4 Ketamine versus esketamine

Overall, the comparison of single dose ketamine versus esketamine seem to indicate no important difference in effect. We found that single infusions of 0.5 mg/kg ketamine have little or no difference, or may slightly improve response, remission and depression severity scores compared with single infusions of esketamine 0.25 mg/kg. All results are based on only one study with a small sample size, and we have low confidence in these effect estimates.

5.1.1.1.5 Ketamine versus ketamine

Finally, the results of the comparison between single dose ≥0.5 mg/kg ketamine versus <0.5 mg/kg ketamine are scattered and somewhat unclear. We found that patients treated with single infusions of ≥0.5 mg/kg ketamine probably have a slightly higher chance of remission at seven days post-infusion, than patients treated with single infusions of <0.5 mg/kg ketamine (moderate certainty evidence). This result is however based on only one study. Moreover, treatment with ≥0.5 mg/kg ketamine may increase the chance of response at one day post-infusion and decrease the risk of relapse after response at 14 days post-infusion, more than <0.5 mg/kg ketamine, but we have low confidence in these estimates. For all other outcomes and time points, the results were more uncertain and scattered, and it is therefore difficult to see any clear picture with regards to effect.

5.1.1.1.6 Long term data on safety and efficacy in RCTs

Few of the included RCTs provided data on safety, and none provided long-term data. Overall, ketamine infusions for treatment-resistant depression were well tolerated with few adverse events and serious adverse events. The most common adverse events were headache, nausea/vomiting, and anxiety, although the actual prevalence varied greatly between the studies. Urinary problems were only listed by three studies (60;63;64), and prevalence ranged from 0 to 16% in the ketamine groups, and 0 to 8% in the midazolam groups. Suicidal ideation and attempt ranged from 0 to 5% in the ketamine groups, and 0 to 1% in the comparator groups (i.e., ECT and midazolam).

Of the included RCTs with multiple infusions of ketamine, the longest continuous treatment period was four weeks (60;72). The study of ketamine versus ECT by Anand *et al.*, had the longest overall follow-up of six months, for data on relapse and depression severity scores (55). In terms of data on response and remission, the study of ketamine versus midazolam by Gallagher *et al.* had the longest follow-up at three months (60). None of these results, either at three or six months follow-up, were statistically significant.

5.1.1.2 Summary of findings – non-RCTs

The results of the two non-RCTs with real-world data showed similar response rates (about 20%) at the first 3-6 weeks of treatment. While the response rate presented in Sakurai *et al*. dropped in the maintenance phase, both the response rates and the remission rates presented in Pfeiffer *et al.*, remained stable over a period of 26 weeks (six months). None of the studies presented data on safety.

5.1.2 Overall completeness and applicability of evidence

All of the included RCTs investigated the effect of intravenous ketamine and/or esketamine on study populations with moderate to severe treatment-resistant depression, which is in line with our selection criteria and the commission given by the National System for Managed Introduction of New Health Technologies in the Specialist Health Care Service in Norway. Most studies included at least some data on response, remission, relapse and/or depression severity scores, at various time points during and after the treatment. However, none of our included studies provided data on hospitalisation, use of

resources, or abuse. Only two studies provided data on quality of life and time to relapse, i.e., Anand *et al.* (55), and Pattanaseri *et al.* (65), respectively.

5.1.2.1 Patient variability

Although the included studies matched our selection criteria (PICOS), they still exhibited considerable variability. When looking closer at the various study populations, two major factors stood out: age and definition of treatment-resistant depression.

In terms of age, most studies were conducted with patients in their 30s and 40s, but the mean age still ranged from 25 years old to 66 years old. When the standard deviations are taken into account, the ages will effectively span from 18 years old to over 70 years old. These variations in age mimic the real-world population, as depression is not prevalent at only one specific age. As such, any decisions based on this HTA regarding the use of ketamine for treatment-resistant depression, should not be limited to one specific age group. Methodological diversities and inter-variabilities between the study populations, e.g., with regards to age, could potentially increase heterogeneity and introduce bias in our results. A study by Pennybaker *et al.* (2021), showed that although younger age was associated with faster response, it did not seem to affect durability or total efficacy on treatment with multiple infusions of ketamine (87). Moreover, as a recent systematic review and network meta-analysis found no indications of age being an effect modifier (88), it seems unlikely that our results would be influenced by the varying ages in our included studies.

As previously mentioned, there is no universal definition of treatment-resistant depression, but it is usually defined as a lack of response after treatment with at least two antidepressants (given at an adequate dose and for an adequate duration) in the current depressive episode. This definition, which is used in Norway, was applied by eleven of our included studies (54;55;57;59;63;68-70;72-74;76). However, of the remaining ten studies, four defined treatment resistance as failure of one or more antidepressants (58;67;71;75), three defined it as failure of three or more antidepressants (56;61;64), and three lacked a definition of treatment resistance altogether (60;62;66). The issue with different definitions of treatment resistance is that the study populations are potentially different in terms of disease severity and duration. Our inclusion criteria of moderate to severe depression, should in theory ensure that all patients have more or less the same depression severity. Still, we see great variation between studies in terms of disease duration, i.e., time since first diagnosis and duration of current depressive episode, and number of failed antidepressant therapies.

5.1.2.2 Clinical applicability

None of the included studies were conducted in Norway and only one was from a closely relating neighbouring country (Sweden). We are therefore uncertain about how applicable the results are to a Norwegian clinical setting. Moreover, a majority (twelve) of the included studies only investigated single infusions of ketamine, which is not a standard clinical practice. Our two non-RCTs, that were based on real-world patient data, administered ketamine infusions more frequent in the first few weeks, i.e., induction phase, with more and more infrequent infusions as time passed, i.e., maintenance phase. This treatment set-up is more in line with what has been described at the Østfold Hospital and private clinics that provide ketamine treatment in Norway. As such, the results of the seven RCTs that have investigated multiple infusions of ketamine, would in theory be more relevant to clinical practice. At first glance, the efficacy results of the multiple infusions of ketamine versus saline and midazolam seem be in favour of ketamine, which is line with the data on single infusions. However, our confidence in these results on multiple infusions are mostly low and very low, the results from single dose ketamine versus the same comparators had better GRADE-assessments (moderate to low). As such, we advise against disregarding our results on single ketamine infusions in favour of the results on multiple ketamine infusions, just because multiple infusions are more clinically relevant.

We included several comparators in our selection criteria, based on input from the clinical experts: saline, midazolam, ECT, esketamine and lower doses of ketamine. Of these, only ECT have approval for adults with treatment-resistant depression in Norway and is therefore the only comparator that would be a clinically relevant alternative to ketamine-treatment. Esketamine by nasal administration

(Spravato® by Janssen-Cilag AS), has been awarded marketing authorisation for treatment-resistant depression (in Europe and consequently Norway), but was denied reimbursement by the Norwegian specialist health care (through the New Methods system) in 2022 after evaluation of cost-effectiveness in a single technology assessment (33). Our commission only specified intravenous administration of ketamin and esketamine, and consequently we did not include nasal administration as a comparator. Therefore, we warn against extrapolating the results in this HTA to assume anything regarding effect of esketamine by intranasal administration.

5.1.2.3 Minimal clinically important difference

As mentioned in chapter *2.1.6.3 Minimal important difference*, a statistically significant result in a clinical trial does not necessarily reflect a clinically important effect, and using a MID threshold may assist the interpretation of clinical importance. Due to different opinions as to what a relevant MID threshold should be, we used both suggested thresholds of 50% and 20% improvement, respectively, to explore how the interpretation of the results would be affected. We found that only one of the statistically significant meta-analysis results of depression severity would be considered clinically important according to a 50% threshold, i.e., multiple infusions of ketamine versus saline. In contrast, all depression severity results, apart from ketamine versus ECT, would be considered clinically important when using MID at 20% improvement. This highlights the importance of having a well-defined threshold as assistance when interpreting results. We acknowledge that readers may view our results differently than we have, using their own opinions on thresholds of clinical relevance, and that this may be in contrast to how we have interpreted the results.

5.1.2.4 Choice of statistical method

The type of statistical methods used in data analysis can greatly affect the results and consequently influence their interpretation. Cochrane recommends using the Hartung-Knapp-Sidik-Jonkman (HKSJ) method for the summary effect CI when using a random-effects model to analyse data from more than two studies, and when the data has a between-study variance over zero ($\tau^2>0$) (89;90). Conversely, when analysing data of two studies or less, and when the between-study variance is zero ($\tau^2=0$), Cochrane recommends the Wald-type method (89;90). As described in chapter *2.1.6 Data analyses*, we used the random-effects model with the Wald-type method for all of our data analyses. While most of our results met the Cochrane's criteria for using the Wald-type method, five analyses should, according to Cochrane, have been analysed using the HKSJ method: 1) depression severity of single infusion of ketamine versus saline at one day post-infusion, 2) response of multiple infusions of ketamine versus saline at end of treatment, 3) response of single infusion of ketamine versus midazolam at three days post-infusion, 4) response of multiple infusion of ketamine versus midazolam at end of treatment, and 5) response of single infusion of ketamine ≥0.5 mg/kg versus ketamine<0.5 mg/kg at one day post-infusion. To explore the effect our choice of summary-effect-CI method would have on our results, we analysed them using both the Wald and the HKSJ-method. As shown in *Appendix 7*, the HKSJ method makes the 95% CI wider around all the meta-analysis effect estimates, than when using the Wald-type method. The three results that were statistically significant when using the Wald-type method, are consequently no longer statistically significant when using HKSJ method (Appendix 7*: ketamine versus saline*; *ketamine versus ketamine*). As such we are aware that consistently using the Wald-type method for all of our analyses is not in accordance with the Cochrane recommendation, and that the statistical significance of three of our results may be caused by using a method that is not sufficiently conservative. We therefore advise readers and decisionmakers to look at the results broadly, rather than focusing too much on single results.

5.1.2.5 Statistical significance on a group level

While statistical significance has traditionally been used as a benchmark for evaluating study results, it is crucial not to rely on this as the sole indicator of scientific validity or clinical relevance. As highlighted by Amrhein *et al.* (2019), the dichotomous interpretation of results as "significant" or "non-significant" based on arbitrary thresholds (e.g., $p < 0.05$, or 95% CI that do not include 1 or 0) can obscure important nuances and lead to misinterpretation of data (91). Statistical significance does not

necessarily equate to clinical significance, and a non-significant result does not necessarily imply the absence of an effect. Instead, policymakers should focus on the magnitude and precision of effect estimates, as well as the broader context of evidence, including study design, sample size, and methodological quality. By shifting the focus away from rigid p-value thresholds, decision-making can be better informed by the totality of evidence rather than isolated statistical metrics.

5.1.3 Generalisability in a clinical setting

The goal of a systematic review is to summarise available evidence that meet a defined set of criteria. Regardless of the amount and quality of evidence that can be included in a systematic review, it is important to remember that systematic reviews, as well as single studies, typically report treatment effects that do not necessarily reflect the treatment effect (i.e., clinical effect) for an individual patient. In other words, our findings are probably most usefully interpreted at the health system-level, rather at an individual patient-level.

5.1.4 Can we trust the evidence?

Details of our GRADE assessments are presented in *Appendix 5*. All of our results were downgraded by at least one level, making “moderate certainty” our highest confidence rating. Most results were downgraded by one or two levels for imprecision, due to 95% CI and/or low power (i.e., small sample size). Of the RCTs included in our data analyses, only the study by Anand *et al.* (55) had a sample size over 50 in each treatment arm, whereas ten RCTs had a sample size below 20 in each arm.

Many of the results were also downgraded by one level for study limitations, i.e., risk of bias. Our assessment of risk of bias is described in detail in the chapter *2.2.3 Risk of bias in the included studies*. One challenge when assessing risk of bias was the question of blinding. We found that although all studies (except one) were blinded, several studies reported that both the participants and the personnel still guessed and identified the treatments that were given, due to ketamine’s dissociative effect. This was especially true when saline was used as a comparator, but also with midazolam and ketamine in lower doses. As there are no objective outcome measures for depression, participants who identified which treatment they received, could in theory have been influenced by this knowledge in their reporting on depression severity.

The certainty of evidence is an assessment of how much confidence we have that the effect estimates are close to or accurately represent the "true" effects of the interventions. The main advantage of using the GRADE approach is that it makes our judgements transparent and open to criticism. However, even though GRADE provides a structure to evaluate the certainty of evidence in a systematic manner, the assessments are still made by our subjective judgement. We therefore acknowledge that others may rate or perceive the certainty of the evidence differently than we have.

5.1.5 Strengths and limitations

A general strength of this HTA is that the work has been performed in a systematic manner in accordance with our published protocol (36). Throughout the process, at least two researchers have been involved in the screening and selection of studies, extraction of data, as well as assessment of risk of bias and certainty of the evidence (GRADE). As such, we are confident that we have taken reasonable steps to conduct a trustworthy HTA.

As our literature search was performed in August 2024, we cannot exclude the possibility that other relevant studies may have been published since that time. However, our search strategy was thorough, and we are confident that we have identified all relevant studies published prior to August 2024. That said, we have only included studies that used some form of the term “treatment-resistant depression” when describing the study population (in their inclusion criteria or elsewhere in the study). This may have caused us to inadvertently exclude studies where the authors have not described the population as treatment-resistant, although it still could be considered as such. However, our goal was to perform a systematic review with reproducible methods, which means that we had to apply systematic criteria for study selection and not “guess” which study populations would be relevant.

A clear limitation to our work is that the majority of the included studies were very small in terms of sample size. Ideally, this would not be an issue when pooling data from several small studies in a meta-analysis. However, although we included 17 RCTs in our HTA, their methodological differences meant that we could not analyse them all together. Effectively, most of our results were only based on one study, and the meta-analyses consisted of only two or three RCTs, of which the sample size in each arm was still very low (under 100). This increases the uncertainties of the effect estimates.

We made a conscious decision to adhere strictly to the commission and only include studies with *intravenous* ketamine and/or esketamine treatment. As intranasal administration of esketamine recently was awarded marketing authorisation for treatment-resistant depression, this would also have been a relevant comparator to intravenous ketamine and/or esketamine treatment. We are however unsure how many studies would have been relevant if we had included this comparator in our HTA. The clinical experts informed us that ketamine treatment is also often given intramuscularly or subcutaneously, and that the effect is comparable to that of intravenous administration. If we had chosen to include intramuscular and subcutaneous administration to our inclusion criteria, we would most likely have had several more studies in this HTA. On one hand, that could potentially have increased the sample size in the various data analyses. On the other hand, it would also have introduced more methodological differences and potential heterogeneity in our evidence pool, which could have influenced the results. As clinical experts have stated that intravenous, intramuscular, and subcutaneous administrations of ketamine can be used interchangeably, we suggest that any decisions regarding the use of ketamine in the Norwegian specialist healthcare still allow clinicians to use professional judgment with regards to these three administration forms.

Ideally, we should have analysed all multiple treatment-studies with similar treatment features, e.g., treatment duration and number of infusions. However, this was not feasible in this HTA, as all seven of our multiple treatment-studies were different, spanning from one to four treatment weeks, and from two to twelve ketamine-infusions in total. The only way to analyse them in meta-analyses was to use “end of treatment” as a common denominator, even though actual end of treatment differed between the studies. As such, we should expect more variation within the data, than what would be expected if all treatment durations and number of infusions were the same. Consequently, we cannot say anything regarding which treatment set-up is more effective.

Although RCTs are often referred to as the gold standard of medical research, they are also criticised for not always being broadly applicable to the population they study, due to narrow eligibility criteria, shorter treatment durations, etc. (92). In contrast, retrospective register studies that provide data on the treatment of real-world patients may give a more realistic picture regarding effect of the treatment. However, these studies are considered to be of lower quality than RCTs, with increased risk of selection bias, confounding, etc., due to non-randomisation. In our HTA, we chose to include non-RCTs to increase the chance of finding long-term data on efficacy and safety, as well as data on people aged ≥65. While neither provided data specifically on a geriatric study population, the studies by Pfeiffer and Sakurai had a follow-up of six and eleven months, respectively (66;68). As previously described, the response data reported in both non-RCTs were lower than what has been shown in RCTs. In the study by Sakurai *et al.*, the authors argue that one possible explanation is that the patients who received the ketamine treatment paid out-of-pocket, as it was not covered by the insurance (USA). As such, the financial burden may have influenced some patients to discontinue the treatment early if they did not perceive the effect as sufficiently beneficial to justify continued treatment. In Norway, ketamine treatment is currently not provided by the specialist health care system and has been geographically and financially limited to patients who either live in Østfold or have resources to pay out-of-pocket at private clinics. As pointed out by both clinical experts and patient representatives, this set-up allows for a socioeconomic disparity among Norwegian patients with treatment-resistant depression.

5.1.6 Consistency with other literature reviews and studies

Although our literature search found several systematic reviews that have investigated the efficacy and safety of ketamine and/or esketamine treatment for depression, only a few focused on a

(seemingly) treatment-resistant population. One systematic review (Iran, 2022) investigated the effect of glutamate receptor modulators, including ketamine, on treatment-resistant depression, and included 38 RCTs, of which 23 were related to ketamine treatment (93). Two Canadian reviews, from CADTH (now Canada's drug agency; CDA) (2024) and Worksafe (2022), focused on the efficacy and/or safety of ketamine for adults with treatment-resistant depression or PTSD (94;95). While the HTA from CADTH was based on four systematic reviews and seven RCTs (94), the systematic review from WorkSafe, was only based on one other systematic review (95). When looking closer at the studies included by these three systematic reviews, not all seem to have been performed in a treatment-resistant population. This is in contrast to our HTA, where we have taken action to ensure that the studies we included were performed on treatment-resistant populations. Although we have included some of the same RCTs, several studies included in the systematic reviews would have been excluded in our HTA, due to stricter selection criteria, e.g., for administration method and study design. As all three systematic reviews presented their results in a narrative manner, i.e., no meta-analysis was performed, it is difficult to compare our results with that of other systematic reviews and HTAs. Still, the results from the systematic reviews overall seem to be in line with the results presented in this HTA.

In 2021, The Cochrane Collaboration published a systematic review and meta-analysis of ketamine and other glutamate receptor modulators for the treatment of depression (96). Though not studied specifically in a treatment-*resistant* population, the review included several of the same studies as in this HTA. Overall, the results from the comparisons of ketamine versus saline, midazolam and esketamine were similar to that of our results. The results of ketamine versus ECT however, differed from ours. The study by Anand *et al.* that we included for the ECT-comparison (55), was not yet published when the Cochrane systematic review (as well as the other above-mentioned reviews) was performed. Conversely, the ECT-study that the Cochrane review included, did not meet our inclusion criteria for population (i.e., the population was not specifically treatment-resistant) (96).

While several RCTs show clear effect of ketamine for treatment-resistant depression compared to saline or midazolam, some studies, e.g., Ionescu *et al.* and Lii *et al.* (61;97), report that ketamine does not outperform the comparators. In the study by Ionescu *et al.*, the authors argue that one possible explanation of the similar results for ketamine and midazolam could be that the study population had a high level of treatment-resistance, and that the ketamine dose of 0.5 mg/kg may have been too low to elicit any significant effect (61). The study by Lii *et al.* aspired to investigate the effect of ketamine in a completely blinded population, which they achieved by administering ketamine or saline to moderately to severely depressed patients who underwent elective surgery, while under general anaesthesia (97). The results showed no difference between the two groups, which may suggest that the antidepressant effect of ketamine is best achieved while the recipient is awake to consciously experience the dissociation that is associated with ketamine treatment (97).

Though there are not many systematic reviews of real-world data, we have identified one that sought out to evaluate the real-world clinical effectiveness of ketamine in patients with treatment-resistant depression (98). The review by Alnefeesi *et al*. presented a mean response rate and remission rate of 45% and 30%, respectively (98), which is overall higher than what is presented in the non-RCTs included in this HTA. While one of our included non-RCTs (Sakurai *et al*.) was also included in the review by Alnefeesi *et al*, our second non-RCT (Pfeiffer *et al*.), was first published in 2024, which was after the Alnefeesi-review (2022). As the Alnefeesi-review included in total 79 studies (34 had response data, 23 had remission data), the data pool is substantially larger than in our HTA with only two non-RCTs. This discrepancy is easily explained by differing inclusion criteria. In contrast to our HTA, Alnefeesi *et al*. have no restrictions in terms of dose, administration form, and isomeric forms of ketamine, i.e., racemic, R-ketamine and S-ketamine (esketamine) (98). Furthermore, Alnefeesi *et al*. have opened for the inclusion of several different study types of non-RCTs, including case studies and case reports (98). Finally, similar to the systematic reviews of RCTs, the studies included in the review by Alnefeesi *et al*. are not solely conducted in treatment-resistant populations. This is in contrast to our HTA, where we have consciously only included studies where treatment-resistant populations are specified.

5.2 Discussion health economics

To evaluate the health economic aspects of intravenous ketamine for treatment-resistant depression in Norwegian health care settings, we have performed a cost-comparison analysis that compared ketamine to electroconvulsive therapy. Electroconvulsive treatment (ECT) is a relevant treatment option for this subpopulation of patients who do not achieve adequate effect from other treatments after trying a combination of several antidepressants and structured psychological treatment, or/and quetiapine and lithium used in combination with an antidepressant (80). In agreement with our clinical experts, we considered ECT to be the most appropriate comparator for our analysis.

We have chosen this simplified form of assessment of economic consequences for several reasons. During our work with the systematic review of clinical efficacy and safety, it became apparent that infusions of ketamine are likely to give a higher chance of response, remission, and lower depression severity scores at end-of-treatment (i.e., after three weeks with a total of six infusions), than treatment with multiple ECTs (nine treatment sessions over the course of three weeks). However, the fact that these results apply only to the intensive treatment phase, adds to the uncertainty about long-term effects. Both treatments are overall well tolerated and have similar safety profile, with side effects that are transient and treatable (55). The cost data made available from the Norwegian clinical practice also indicated that ketamine treatment is likely to be less resource consuming than ECT. With the studied intervention being both more beneficial and less expensive than the comparator, we regarded a cost-comparison analysis to be the most suitable approach to economic analysis, despite its limitations.

We have limited the time perspective for our analysis to the most intensive treatment phase for both treatment options, i.e. three weeks (end of treatment in the study by Ananad et al.) (55). The available evidence on clinical efficacy at later time points is uncertain (after one month and three months: ketamine 0.5 mg/kg may slightly reduce the risk of relapse; after six months: ketamine 0.5 mg/kg may make little or no difference to the risk of relapse) (55). The tendency for recurrence of moderate or severe depression makes it difficult to make assumptions about long-term effects. Therefore, we have not included the costs of maintenance therapies beyond three weeks in the analyses. Thoughtful planning on how to maintain treatment results for patients who respond to the initial treatment series, following either of the two treatment alternatives, becomes advisable (80;86). The authors of the Norwegian treatment protocol for intravenous ketamine recommend that after the intensive phase with six infusions, patients who respond are offered another six maintenance infusions given once a month. After 12 infusions in total, the treatment is completed. Patients with insufficient response end their treatment after the initial phase (86). The guidance on ECT for patients with depression recommends maintenance treatment with antidepressants for prevention of relapse after completed intensive series with ECT. However, for patients who do not achieve desired effects with antidepressants or who have preferences towards ECT instead of pharmaceutical therapy, maintenance treatment with ECT, for example one session every four weeks, can also be an option (80).

Our results indicate that the costs of ECT and ketamine treatments are overall comparable in monetary terms, with ketamine treatment probably being a slightly cheaper option. Apart from nominal costs, it is the use of personnel time that is an important resource use aspect. ECT procedure requires use of general anaesthesia, and although the procedure itself takes a relatively short time, it involves two physicians (the ECT operator and anaesthesiologist), and one to two nurses specialised in intensive care who prepare and monitor the patient in the time following ECT. For ordinary (not the first) ketamine treatment we included personnel cost for a physician (20 min) and the time of one nurse being with the patient during treatment (120 min). There is also a question of sufficient capacity at the treatment clinic, something that cannot directly be addressed in health economic evaluation.

We have assumed outpatient settings for calculations of cost estimates for ECT and ketamine treatments. This approach enables evaluation of costs isolated form other elements of care services and make them comparable. In clinical practice however, based on information from our clinical experts, ECT is often offered to hospitalised patients and ketamine treatment can be an alternative offered both on in- and outpatient basis.

Cost estimates that we have calculated are subject to some uncertainty and possible variation in the clinical setting. Although ketamine therapy cost estimates are based on one source only, they are comprehensive and built on empirical data gathered over a period of few years and amount to an average of NOK 3 011 for a treatment session. For reference, the prices from Oxford Health NHS Foundation Trust in the UK for self-pay ketamine service account to very similar cost levels. The price of initial assessment appointment with psychiatrist before ketamine treatment is £225 (about NOK 3,147), and each intravenous ketamine infusion also costs £225 (99).

The cost of a treatment series consisting of 6 infusion sessions with ketamine over the course of 3 weeks is equal to NOK 18 064, while the costs related to ECT were NOK 28,243 – 42,364, depending on number of treatments given per week. Another treatment alternative for patients with TRD, that was approved for reimbursement in specialist healthcare in Norway is transcranial direct current stimulation (tDCS). A treatment series with tDCS for 4-weeks costs about NOK 16,000 in a home-based setting, and about NOK 81,000 in an outpatient setting (100).

In our analyses, we have only included direct costs related to the compared treatment alternatives, not accounting for possible changes in use of health care resources due to effects of these therapies. For patients with moderate or severe depression who experience response or remission, the reduction in costs of health care can be significant in terms of avoided hospitalisations, doctor consultations and reduced use of pharmaceuticals. In the broader perspective, both personal and societal economy can benefit from patients being able to return to their working life as result of successful therapies. The societal costs related to production losses due to depression can be significant. Over NOK 12 billion was disbursed by NAV (the Norwegian Labour and Welfare Administration) in 2020 as sickness benefits related to depression (101).

We have not included costs related to training of health personnel for the compared alternative treatments. The clinicians who administer ketamine infusions are doctors or nurses who, in addition to the technical skills, should have a good understanding of the mechanisms of action of ketamine and how these can affect the patient's psychotherapeutic progress (86).

As our economic analysis is not model-based, we have not calculated the absolute shortfall for patients with treatment-resistant depression to quantify the severity principle. In the single technology assessment of intranasal esketamine for the same indication performed by NOMA in 2020, the calculated shortfall was 6.2-12.6 QALY (78).

We have abstained from calculating the budgetary consequences of the introduction of intravenous ketamine treatment for the healthcare system for several reasons.

Estimating the number of patients eligible for the treatment with intravenous ketamine in Norway is very challenging. According to the Norwegian Public Health institute every tenth Norwegian will have some form of depressive disorder in 12 months (102). It is estimated that as many as 30% of people with depression do not reach adequate response to a minimum of two antidepressants (22). For these patients there are several treatment options available that include psychotherapy, combination of multiple antidepressants, and various electrical and magnetic field therapies, including electroconvulsive therapy (ECT) and adequacy of therapies must be assessed individually (79). The choice of approach to treatment-resistant depression is dependent on many factors: severity of symptoms, previous history of the patient, and response to previous treatment, the skills and experiences of the treating physician with various forms of therapies, and not least on the patient’s preferences. Not all patients with TRD who wish to commence treatment with intravenous ketamine would be counted as eligible. The exclusion criteria for this treatment alternative, listed in the treatment protocol from Østfold, are both somatic and psychiatric conditions, such as pregnancy, kidney, liver or bladder disease, primary psychotic disorders, ongoing manic or hypomanic symptoms, or current harmful use of alcohol or illegal drugs, among many others (86). We have used ECT as a comparator in our analysis, but we do not know the number of patients currently receiving ECT as these treatments are not recorded in any registers, and it is therefore difficult to estimate the extent of the treatment in recent years. In 2015, 4,600 ECT treatments were performed on approximately 520 patients (80). Although we used ECT as a comparator, including intravenous ketamine treatment as a

standard alternative for patients with treatment-resistant depression, will not automatically imply that ECT and other treatments for TRD will be replaced by ketamine. Adding this treatment option should rather be seen as an additional tool that might help patients for whom other options have been tried and failed. In the documentation submitted by the suppliers of intranasal esketamine the assumption was that about 2,800 (920-4,700) patients would be eligible for the treatment in Norway (78), but we are unsure how many patients will be eligible for treatment with intravenous ketamine in Norway.

There is scarcity of studies that investigate the economic impact of ketamine treatment for patients with TRD, but one study from the U.S. found that expanding access to ketamine for these patients can increase the number of patients in treatment and result in savings in societal perspective (103).

5.3 Implications of the findings for practice

The findings of this HTA suggest that intravenous ketamine may be a promising treatment option for patients with treatment-resistant depression. During the intensive treatment phase, ketamine appears to provide lower depression severity scores, with higher chance of response and remission, compared to saline, midazolam, and ECT. However, the evidence regarding long-term effects is limited, and the certainty of the evidence varies across comparisons and outcomes (see section *5.1.4 Can we trust the evidence?*).

5.3.1 Clinical practice

The lack of robust long-term data highlights the importance of careful patient selection and follow-up. Clinicians should be aware of the potential for transient and low risk side effects (e.g., headache and nausea), as well as more severe and serious adverse events (e.g., urinary problems), and ensure that patients are adequately monitored during and after treatment. Furthermore, given the variability in treatment protocols across studies and the lack of national treatment guidelines, clinicians will have to tailor the administration of ketamine (e.g., dosing and frequency of infusions) to the individual patient's needs.

5.3.2 Health System Considerations

From a healthcare system perspective, intravenous ketamine may offer an efficient alternative to ECT for some patients with treatment-resistant depression. Our cost-comparison analysis suggests that ketamine treatment is likely to be less resource-intensive than ECT during the intensive treatment phase, primarily due to the absence of general anaesthesia and fewer personnel requirements. However, the introduction of ketamine treatment in the specialist healthcare system would require training for healthcare professionals, development of standardised treatment protocols, and infrastructure adjustments to ensure safe administration. Additionally, equitable access to ketamine treatment must be prioritised to avoid socioeconomic disparities, as current availability is limited to select geographical areas and costly private clinics.

5.3.3 Patient-Centred Care

Patient preferences and experiences should also play a central role in decision-making regarding ketamine treatment. Ketamine's dissociative effects may contribute to its antidepressant efficacy but can also be unsettling for some patients. Transparent communication about the potential benefits and risks of treatment is essential to ensure informed consent. Moreover, the absence of long-term data necessitates discussions with patients about the uncertainty surrounding maintenance treatment and relapse prevention.

5.3.4 Potential for misuse and abuse

The psychoactive and dissociative effects make ketamine susceptible to misuse and abuse (104;105), and this potential is important to consider when evaluating ketamine for treatment-resistant depression. As none of the studies included in this HTA reported any data on addiction, we have been unable to assess the potential risk of developing an addiction to ketamine following ketamine infusions for treatment-resistant depression.

Addiction may arise when using ketamine to self-medicate or for recreational purposes. In recent years, Europe has seen a rising incidence of recreationally used ketamine, especially among younger people in the party and nightlife scene and for chemsex (104-107). In a large global sample of over 130 000 people, about 6% reported having used ketamine in their lifetime, and about 3% had used ketamine in the last 12 months (108). Within the latter cohort (i.e., having used ketamine in the last year), less than one-third reported having a mental health diagnosis (of which depression was the most common diagnosis), suggesting self-medication (108). The actual numbers of recreational ketamine users in Europe are still low (107). Analysis of wastewater in 82 European cities showed overall substantially lower levels of ketamine than other recreational drugs, such as cocaine, cannabis and amphetamines (109). The highest mass loads of ketamine were however detected in cities in Norway, in addition to Belgium, the Netherlands and Hungary (109). In Norway, ketamine is not considered a narcotic substance, but prescription is still strictly controlled (110). In 2024, Norwegian customs authorities reported the seizure of 33 kilograms of ketamine, which is a tenfold increase from 2021, highlighting its presence in illegal drug markets (111). This is also in line with other European countries, as increased ketamine seizures have been reported in recent years (107).

Persistent use of ketamine can lead to severe health consequences, including cognitive impairments, urinary tract dysfunction, and addiction (112-115). It is important to note however, that misuse and abuse cases often see substantially higher doses and more frequent administration of ketamine than what is used in a clinical setting. The risk of misuse may be mitigated in clinical settings where ketamine is solely prescribed and administered by healthcare professionals. Structured protocols, careful patient selection, and regular monitoring are essential to minimise the risk of diversion or non-medical use. If ketamine is to be implemented in the Norwegian specialist health care for treatment-resistant depression, policymakers should consider input from clinical experts and patient representatives to ensure implementation of the treatment in a way that prevent misuse outside of clinical environments.

5.3.5 Policy Implications

The findings of this HTA highlight the need for policymakers to consider whether intravenous ketamine should be included as a treatment option for treatment-resistant depression within the Norwegian specialist healthcare system. However, given the uncertainties in long-term outcomes and the variability in treatment protocols, any implementation should be accompanied by robust monitoring systems to collect real-world data on safety, efficacy, and cost-effectiveness. Additionally, policymakers should consider the broader societal benefits of effective treatment of this population, including reduced healthcare utilisation and improved productivity.

5.4 Knowledge gaps

This HTA set out to identify, assess and analyse available research regarding efficacy and safety of intravenously administered ketamine and esketamine for adults with treatment-resistant depression.

Although we included 19 RCTs and two non-RCTs in this work, the evidence base is still too limited to draw conclusions with high confidence in the effect estimates. Consequently, there is a need for further research. First and foremost, to ensure sufficient power to detect a true effect of ketamine, future RCTs should include significantly larger study populations than what is used in the majority of the studies included in this HTA. Furthermore, studies should incorporate a clinically relevant treatment set-up, i.e., a treatment protocol for multiple infusions of ketamine with an induction and maintenance phase, rather than administering single ketamine infusions. Future research should also have longer study duration, i.e., at least a year, with additional follow-up. It is, however, expensive and resource-intensive to conduct large RCTs, and as ketamine is no longer patent protected, it will not be profitable for the producer to finance these types of clinical studies. This is supported by the fact that only two of 21 included publications (*Appendix 4*) and one of 29 ongoing studies (*Appendix 9*) are financed by the pharmaceutical industry. While public funding and research grants are crucial for advancing research on ketamine for the treatment of depression, they have their limitations that can restrict the scope of studies, particularly in terms of complexity and long-term follow-up. In late 2024,

Østfold Hospital was awarded almost 25 million NOK by the National Program for Clinical Treatment Research in Specialist Health Services (*KLINBEFORSK: Nasjonalt program for klinisk behandlingsforskning i spesialisthelsetjenesten*) in Norway, to conduct a study on ketamine for treatment-resistant depression (116). The study, that is planned to span over three years and include ten hospitals across Norway (116), is likely to be an important addition to the evidence base and provide valuable information regarding the applicability of ketamine-treatment in Norway. The assessment of the cost-health benefit ratio of using ketamine compared to relevant treatment alternatives can be assessed when data on efficacy over a longer time perspective are available.

6. Conclusion

Overall, intravenous ketamine infusions increase response rates and remission rates, and decrease depression severity scores, more than saline, midazolam and ECT shortly after the intensive treatment phase of patients with treatment-resistant depression. We have moderate and low confidence in these results. It is not possible to draw clear conclusions regarding ketamine's long-term efficacy (i.e., past three months after treatment) for this patient group due to low and very low confidence in limited data. In terms of safety, intravenous ketamine infusions are mostly well tolerated, but treatment should still be monitored due to potential harmful side-effects.

For the comparison between intravenous esketamine and intravenous ketamine, the results indicate little to no difference of efficacy and safety for patients with treatment-resistant depression. Still, low certainty and scarcity of evidence limit the applicability of these results.

From a health economic perspective, treatment with intravenous ketamine is probably comparable or less costly than treatment with ECT for patients with treatment-resistant depression provided sufficient capacity in terms of personnel.

Even though not all treatment-resistant patients may benefit from treatment with ketamine, it could still be a valuable additional treatment option for a patient group that may have tried and failed several currently available therapies.

7. References

1. Rush JA. Major depressive disorder in adults: Approach to initial management [Web page]. USA: UpToDate [updated 13.05.2024; cited 06.06.2024]. Available from: https://www.uptodate.com/contents/major-depressive-disorder-in-adults-approach-to-initial-management
2. Lyness JM. Unipolar depression in adults: Clinical features [Web page]. USA: UpToDate [updated 19.10.2023; cited 22.05.2024]. Available from: https://www.uptodate.com/contents/unipolar-depression-in-adults-clinical-features
3. Røssberg JI, Malt U. Depresjon [Web page]. Norway: Store medisinske leksikon [updated 11.01.2024; cited 22.05.2024]. Available from: https://sml.snl.no/depresjon
4. Ødegaard KJ. T5.5 Depresjoner [Web page]. Norway: Norsk Legemiddelhåndbok [updated 02.10.2022; cited 06.06.2024]. Available from: https://www.legemiddelhandboka.no/T5.5/Depresjoner
5. Norwegian Directorate of Health, World Health Organisation. ICD-10: Psykiske lidelser og atferdsforstyrrelse: kliniske beskrivelser og diagnostiske retningslinjer (Blåboka). Norway: Norwegian Directorate of Health. Available from: https://www.ehelse.no/kodeverk-og-terminologi/ICD-10-og-ICD-11
6. World Health Organisation. Depressive disorder (depression) [Web page]. WHO [updated 31.03.2023; cited 07.06.2024]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression
7. Reneflot A, Aarø LE, Aase H, Reichborn-Kjennerud T, Tambs K, Øverland S. Psykisk helse i Norge [Report]. Norway: Norwegian Institute of Public Health; 2018. Available from: https://www.fhi.no/publ/2018/psykisk-helse-i-norge/
8. Bains N, Abdijadid S. Major Depressive Disorder [Web page]. USA: StatPearls Publishing [updated 10.04.2023; cited 23.05.2024]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559078/
9. MacKinnon DF. Depression in adults [Web page]. UK: BMJ Best Practice [updated 08.05.2024; cited 22.05.2024]. Available from: https://bestpractice.bmj.com/topics/en-gb/55
10. Norwegian Directorate of Health. Nasjonalt pasientforløp for utredning og behandling i psykisk helsevern, voksne [Web document]. Oslo, Norway: Norwegian Directorate of Health; 2018. Available from: https://www.helsedirektoratet.no/nasjonale-forlop/psykiske-lidelser-voksne
11. Helsebiblioteket, BMJ. Depresjon hos voksne [Web page]. Oslo: Norwegian Directorate of Health [updated 09.03.2021; cited 12.06.2024]. Available from: https://www.helsenorge.no/sykdom/psykiske-lidelser/depresjon/depresjon-voksne/
12. Felleskatalogen. Cipralex (Orifarm) [Web page]. Oslo: Felleskatalogen [cited 12.06.2024]. Available from: https://www.felleskatalogen.no/medisin/cipralex-orifarm-574078#komplett-felleskatalogtekst
13. Felleskatalogen. Zoloft (2care4) [Web page]. Oslo: Felleskatalogen [cited 12.06.2024]. Available from: https://www.felleskatalogen.no/medisin/zoloft-2care4-639548
14. Malt U, Grønli OK. ECT [Web page]. Norway: Store medisinske leksikon [updated 19.10.2023; cited 07.06.2024]. Available from: https://sml.snl.no/ECT
15. Kellner CH. Overview of electroconvulsive therapy (ECT) for adults [Web page]. USA: UpToDate [updated 10.08.2022; cited 07.06.2024]. Available from: https://www.uptodate.com/contents/overview-of-electroconvulsive-therapy-ect-for-adults
16. Norwegian Directorate of Health. Nasjonal faglig retningslinje om bruk av elektrokonvulsiv behandling - ECT [National guideline]. Oslo, Norway: Norwegian Directorate of Health; 2017. IS-2629. Available from: https://www.helsedirektoratet.no/tema/elektrokonvulsiv-behandling-ect
17. Nye metoder. Transkraniell likestrømsstimulering [Web page]. Oslo: Nye metoder [cited 12.06.2024]. Available from: https://www.nyemetoder.no/metoder/transkraniell-likestromsstimulering/
18. Kvam T-M, Stewart LH, Blomkvist AW, Andreassen OA. Ketamin ved depresjon – evidens og forslag til praksis. Tidsskr Nor Legeforen 2021;141. DOI: 10.4045/tidsskr.21.0480

19. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19(2):179-200. DOI: 10.1016/s0193-953x(05)70283-5
20. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, et al. The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. J Clin Psychiatry 2021;82(2). DOI: 10.4088/JCP.20m13699
21. Thase M, Connolly KR. Unipolar treatment-resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis [Web page]. USA: UpToDate [updated 11.01.2023; cited 07.06.2024]. Available from: https://www.uptodate.com/contents/unipolar-treatment-resistant-depression-in-adults-epidemiology-risk-factors-assessment-and-prognosis
22. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry 2023;22(3):394-412. DOI: 10.1002/wps.21120
23. Borbely E, Simon M, Fuchs E, Wiborg O, Czeh B, Helyes Z. Novel drug developmental strategies for treatment-resistant depression. Br J Pharmacol 2022;179(6):1146-86. DOI: 10.1111/bph.15753
24. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacol Rev 2018;70(3):621-60. DOI: 10.1124/pr.117.015198
25. Rosenbaum SB, Gupta V, Patel P, Palacios JL. Ketamine [Web page]. USA: StatPearls Publishing [updated 30.01.2024; cited 24.06.2024]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470357/
26. Øye I. Ketamin – medienes nye motedop? Tidsskr Nor Legeforen 2000;12(120):1464-6.
27. UpToDate Lexidrug. Ketamine: drug information [Web page]. USA: UpToDate [cited 25.06.2024]. Available from: https://www.uptodate.com/contents/ketamine-drug-information
28. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. Mol Psychiatry 2018;23(4):801-11. DOI: 10.1038/mp.2017.255
29. Felleskatalogen. Ketalar [Web page]. Norway: Felleskatalogen [updated 05.12.2023; cited 25.06.2024]. Available from: https://www.felleskatalogen.no/medisin/ketalar-pfizer-560507
30. Norsk Legemiddelhåndbok. L22.3.1.4 Ketamin [Web page]. Norway: Norsk Legemiddelhåndbok [updated 02.12.2016; cited 28.06.2024]. Available from: https://www.legemiddelhandboka.no/L22.3.1.4/Ketamin
31. Norsk Legemiddelhåndbok. T21.1.1.2 Medikamentell behandling - WHO smertetrapp [Webpage]. Norway: Norsk Legemiddelhåndbok [updated 11.04.2023; cited 14.08.2024]. Available from: https://www.legemiddelhandboka.no/T21.1.1.2/Medikamentell_behandling_-_WHO_smertetrapp#p-2125
32. Felleskatalogen. Spravato [Web page]. Oslo: Felleskatalogen [cited 14.08.2024]. Available from: https://www.felleskatalogen.no/medisin/spravato-janssen-670393
33. Nye metoder. Esketamin (Spravato) [Web page]. Norway: Nye Metoder [cited 14.08.2024]. Available from: https://www.nyemetoder.no/metoder/esketamin-spravato/#tidligere-beslutninger
34. Clausen I. Forslag om nasjonal metodevurdering - ketamin [Technology proposal]. Norway: Nye metoder; 2022. Available from: https://www.nyemetoder.no/48dea9/siteassets/documents/forslag/viktig-informasjon--se-pa-dette-forst-og-husk-a-krysse-av10.docx
35. Lov om spesialisthelsetjenesten m.m. (spesialisthelsetjenesteloven). LOV-1999-07-02-61. Available from: https://lovdata.no/dokument/NL/lov/1999-07-02-61/KAPITTEL_5#KAPITTEL_5
36. Ohm I, Flatby A, Stoinska-Schneider A, Hafstad E. Intravenous ketamine for treatment-resistant depression [Protocol]. Oslo, Norway: Norwegian Medical Products Agency; 2024. ID2022_018. Available from: https://www.dmp.no/offentlig-finansiering/metodevurdering-av-medisinske-produkter/metodevurdering-av-legemidler/prosjektplaner

37. Nye metoder. ID2022_018 Ketamin [Webpage]. Norway: Nye metoder [cited 06.02.2025]. Available from: https://www.nyemetoder.no/metoder/ketamin/
38. Norwegian Medical Products Agency. Brukerinnspill når vi vurderer nytte og kostnad ved nye legemidler og medisinsk utstyr [Webpage]. Norway: NOMA [updated 04.09.2024; cited 29.04.2025]. Available from: https://www.dmp.no/offentlig-finansiering/metodevurdering-av-medisinske-produkter/brukerinnspill-nar-vi-vurderer-nytte-og-kostnad-ved-nye-legemidler
39. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4. Cochrane: 2023. Available from: https://training.cochrane.org/handbook
40. Område for helsetjenester i Folkehelseinstituttet. Slik oppsummerer vi forskning. Metodeboka [Nettdokument]. Oslo: Område for helsetjenester i Folkehelseinstituttet [updated 22. apr. 2022; cited 1. aug. 2022]. Available from: https://www.fhi.no/nettpub/metodeboka/
41. The EndNote Team. EndNote 20. Philadelphia, PA: Clarivate Analytics; 2013.
42. Thomas J, Brunton J, Graziosi S. EPPI-Reviewer 4.0: software for research synthesis. [Software]. EPPI Centre Software. London: Social Science Research Unit, Institute of Education, University of London; 2010.
43. Thomas J, Graziosi S, Brunton J, Ghouze Z, O'Driscoll P, Bond M, et al. EPPI-Reviewer: advanced software for systematic reviews, maps and evidence synthesis. London: EPPI Centre, UCL Social Research Institute, University College London; 2023.
44. OpenAlex in EPPI-Reviewer [web page]. London: EPPI Centre, UCL Social Research Institute, University College London [cited]. Available from: https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3754
45. Priem J, Piwowar H, Orr R. OpenAlex: A fully-open index of scholarly works, authors, venues, institutions, and concepts. arXiv:220501833 2022.
46. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj 2019;366:l4898. DOI: 10.1136/bmj.l4898
47. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. DOI: 10.1136/bmj.i4919
48. Review Manager (RevMan). Version 8.14.0 ed: The Cochrane Collaboration January 24, 2025.
49. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime; 2025. Available from: https://www.gradepro.org/
50. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Chapter 13: Fixed-Effect Versus Random-Effects Models. In: Introduction to Meta-Analysis2009. Available from: https://meta-analysis.com/download/Meta-analysis%20Fixed-effect%20vs%20Random-effects%20models.pdf?srsltid=AfmBOorjPdirXz9jbICd3oYMYUsjnSqL4M71nRKBuZ1HrhM4-g_p7aad
51. Dettori JR, Norvell DC, Chapman JR. Fixed-Effect vs Random-Effects Models for Meta-Analysis: 3 Points to Consider. Global Spine J 2022;12(7):1624-6. DOI: 10.1177/21925682221110527
52. (EPOC) CEPaOoC. Reporting the effects of an intervention in EPOC reviews. . UK: Cochrane; 2018. Available from: https://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/Resources-for-authors2017/how_to_report_the_effects_of_an_intervention.pdf
53. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook. Cochrane; 2013. Available from: https://gdt.gradepro.org/app/handbook/handbook.html#h.svwngs6pm0f2
54. Ahmed GK, Elserogy YM, Elfadl GMA, Ghada Abdelsalam K, Ali MA. Antidepressant and anti-suicidal effects of ketamine in treatment-resistant depression associated with psychiatric and personality comorbidities: A double-blind randomized trial. Journal of Affective Disorders 2023;325:127-34. DOI: 10.1016/j.jad.2023.01.005
55. Anand A, Mathew SJ, Sanacora G, Murrough JW, Goes FS, Altinay M, et al. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. New England Journal of Medicine 2023;388(25):2315-25. DOI: 10.1056/NEJMoa2302399

56. Chen MH, Li CT, Lin WC, Hong CJ, Tu PC, Bai YM, et al. Persistent antidepressant effect of low-dose ketamine and activation in the supplementary motor area and anterior cingulate cortex in treatment-resistant depression: A randomized control study. Journal of Affective Disorders 2018;225:709-14. DOI: 10.1016/j.jad.2017.09.008
57. Chen MH, Li CT, Lin WC, Hong CJ, Tu PC, Bai YM, et al. Rapid inflammation modulation and antidepressant efficacy of a low-dose ketamine infusion in treatment-resistant depression: A randomized, double-blind control study. Psychiatry Research 2018;269:207-11. DOI: 10.1016/j.psychres.2018.08.078
58. Correia-Melo FS, Leal GC, Vieira F, Jesus-Nunes AP, Mello RP, Magnavita G, et al. Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: A randomized, double-blind, non-inferiority study. Journal of Affective Disorders 2020;264:527-34. DOI: 10.1016/j.jad.2019.11.086
59. Fava M, Freeman MP, Flynn M, Judge H, Hoeppner BB, Cusin C, et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Molecular Psychiatry 2020;25(7):1592-603. DOI: 10.1038/s41380-018-0256-5
60. Gallagher B, Foley M, Slattery CM, Gusciute G, Shanahan E, McLoughlin DM. Ketamine as an adjunctive therapy for major depression - a randomised controlled pragmatic pilot trial (Karma-Dep Trial). Hrb Open Research 2020;3:90. DOI: 10.12688/hrbopenres.13182.2
61. Ionescu DF, Bentley KH, Eikermann M, Taylor N, Akeju O, Swee MB, et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: A randomized, double blind, placebo controlled trial. Journal of Affective Disorders 2019;243:516-24. DOI: 10.1016/j.jad.2018.09.037
62. Kheirkhah F, Tayyebi G, Rabiee SM, Moghadamnia AA, Bijani A. Efficacy of different doses of ketamine as a bolus in major depressive disorder. Caspian Journal of Internal Medicine 2018;9(3):220-7. DOI: 10.22088/cjim.9.3.220
63. Lijffijt M, Murphy N, Iqbal S, Green CE, Iqbal T, Chang LC, et al. Identification of an optimal dose of intravenous ketamine for late-life treatment-resistant depression: a Bayesian adaptive randomization trial. Neuropsychopharmacology 2022;47(5):1088-95. DOI: 10.1038/s41386-021-01242-9
64. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. American Journal of Psychiatry 2013;170(10):1134-42. DOI: 10.1176/appi.ajp.2013.13030392
65. Pattanaseri K, Lortrakul J, Jaisin K, Srifuengfung M, Sa-Nguanpanich N, Viravan N, et al. A randomized controlled pilot study of daily intravenous ketamine over three days for treatment-resistant depression. BMC Psychiatry 2024;24(1):512. DOI: 10.1186/s12888-024-05951-5
66. Pfeiffer PN, Geller J, Ganoczy D, Jagusch J, Carty J, Festin FED, et al. Clinical Outcomes of Intravenous Ketamine Treatment for Depression in the VA Health System. Journal of Clinical Psychiatry 2024;85(1):08. DOI: 10.4088/JCP.23m14984
67. Rengasamy M, Mathew S, Howland R, Griffo A, Panny B, Price R. Neural connectivity moderators and mechanisms of ketamine treatment among treatment-resistant depressed patients: a randomized controlled trial. EBioMedicine 2024;99:104902. DOI: 10.1016/j.ebiom.2023.104902
68. Sakurai H, Jain F, Foster S, Pedrelli P, Mischoulon D, Fava M, et al. Long-term outcome in outpatients with depression treated with acute and maintenance intravenous ketamine: A retrospective chart review. Journal of Affective Disorders 2020;276:660-6. DOI: 10.1016/j.jad.2020.07.089
69. Salloum NC, Fava M, Hock RS, Freeman MP, Flynn M, Hoeppner B, et al. Time to relapse after a single administration of intravenous ketamine augmentation in unipolar treatment-resistant depression. Journal of Affective Disorders 2020;260:131-9. DOI: 10.1016/j.jad.2019.09.017
70. Shiroma PR, Thuras P, Wels J, Albott CS, Erbes C, Tye S, et al. A randomized, double-blind, active placebo-controlled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. Transl Psychiatry Psychiatry 2020;10(1):206. DOI: 10.1038/s41398-020-00897-0

71. Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, et al. Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study. Biological Psychiatry 2016;80(6):424-31. DOI: 10.1016/j.biopsych.2015.10.018
72. Singh JB, Fedgchin M, Daly EJ, De Boer P, Cooper K, Lim P, et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. American Journal of Psychiatry 2016;173(8):816-26. DOI: 10.1176/appi.ajp.2016.16010037
73. Su TP, Chen MH, Li CT, Lin WC, Hong CJ, Gueorguieva R, et al. Dose-Related Effects of Adjunctive Ketamine in Taiwanese Patients with Treatment-Resistant Depression. Neuropsychopharmacology 2017;42(13):2482-92. DOI: 10.1038/npp.2017.94
74. Su TP, Li CT, Lin WC, Wu HJ, Tsai SJ, Bai YM, et al. A Randomized, Double-Blind, Midazolam-Controlled Trial of Low-Dose Ketamine Infusion in Patients With Treatment-Resistant Depression and Prominent Suicidal Ideation. International Journal of Neuropsychopharmacology 2023;26(5):331-9. DOI: 10.1093/ijnp/pyad014
75. Tiger M, Veldman ER, Ekman CJ, Halldin C, Svenningsson P, Lundberg J. A randomized placebo-controlled PET study of ketamine's effect on serotonin_{1B} receptor binding in patients with SSRI-resistant depression. Transl Psychiatry Psychiatry 2020;10(1):159. DOI: 10.1038/s41398-020-0844-4
76. Zolghadriha A, Anjomshoaa A, Jamshidi MR, Taherkhani F. Rapid and sustained antidepressant effects of intravenous ketamine in treatment-resistant major depressive disorder and suicidal ideation: a randomized clinical trial. BMC Psychiatry 2024;24(1):341. DOI: 10.1186/s12888-024-05716-0
77. Norwegian Ministry of Health and Care Services. Principles for priority setting in health care. Summary of a white paper on priority setting in the Norwegian health care sector. 2017.
78. Norwegian Medicines Agency. Hurtig metodevurdering for legemidler finansiert i spesialisthelsetjeneste. ID2019_116 Esketamin (Spravato) - behandling ved behandlingsresistent depresjon. Vurdering av innsendt dokumentasjon. . 2020. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.dmp.no/globalassets/documents/offentlig-finansiering-og-pris/metodevurderinger/s/spravato_behandling-ved-behandlingsresistens-depresjon_2020.pdf
79. NEL. Norsk Elektronisk Legehåndbok. Psykiatri Tilstander og sykdommer. Depresjoner. Terapi nasjonale rettningslinjer [cited]. Available from: https://legehandboka.no/premium/handboken/kliniske-kapitler/psykiatri/tilstander-og-sykdommer/depresjoner/depresjon#terapi-nasjonale-retningslinjer
80. Helsedirektoratet. National guidelines on use of ECT. Nasjonal faglig retningslinje om bruk av elektrokonvulsiv behandling - ECT 2027.
81. Store Norske Leksikon. Store medisinske leksikon, ECT [cited]. Available from: https://sml.snl.no/ECT
82. Helse Stavanger. Peronnlig kommunikasjon med Benedikt Römer, Alderpsykiatrisk avdeling og Casper Nielsen, Avdeling Affektiv og Psykose, Stavanger universitessjukehus. 2025.
83. St. Olavs Hospital. Personnlig kommunikasjon med Gunvor Garberg Moen, Alderspsykiatrisk avdeling, St. Olavs Hospital 2025.
84. Sykehuset Østfold. Personlig kommuniskasjon med Ingmar Claussen, DPS nordre Østfold i Moss. 2025.
85. Kvam T, Stewart L, Blomkvist A, OA A. Ketamine for depression – evidence and proposals for practice. Tidsskrift for den norske legeforening 2021.
86. Sykehuset Østfold. Protokoll for intravenøs ketaminbehandling for pasienter med terapiresistent depresjon. Utarbeidet av Ketaminenheten ved DPS Nordre, Sykehuset Østfold. 2024.
87. Pennybaker S, Roach BJ, Fryer SL, Badathala A, Wallace AW, Mathalon DH, et al. Age affects temporal response, but not durability, to serial ketamine infusions for treatment refractory depression. Psychopharmacology (Berl) 2021;238(11):3229-37. DOI: 10.1007/s00213-021-05939-z
88. Terao I, Kodama W. Comparative antidepressant effects and safety of intravenous racemic ketamine, psilocybin and theta burst stimulation for major depressive

disorder: A systematic review and network meta-analyses of randomized controlled trials. Psychiatry and Clinical Neurosciences Reports 2024;3(4):e70042. DOI: https://doi.org/10.1002/pcn5.70042
89. Veroniki A-A, McKenzie J. Demonstration of New Random-Effects Methods in RevMan (webinar 2) [Webinar presentation]. Toronto, Canada: Cochrane; 2025. Available from: https://training.cochrane.org/sites/training.cochrane.org/files/public/uploads/Demonstration%20of%20new%20random-effects%20methods%20in%20RevMan_0.pdf
90. Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions Version 64 [Cochrane [cited 27.06.2024]. Available from: https://training.cochrane.org/handbook/current/chapter-10
91. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature 2019;567(7748):305-7. DOI: 10.1038/d41586-019-00857-9
92. Saldanha IJ, Skelly AC, Ley KV, Wang Z, Berliner E, Bass EB, et al. Strengths and Limitations of RCTs. In: Inclusion of Nonrandomized Studies of Interventions in Systematic Reviews of Intervention Effectiveness: An Update. Rockville (MD): Agency for Healthcare Research and Quality (US); 2022.
93. Shamabadi A, Ahmadzade A, Aqamolaei A, Mortazavi SH, Hasanzadeh A, Akhondzadeh S. Ketamine and Other Glutamate Receptor Modulating Agents for Treatment-Resistant Depression: A Systematic Review of Randomized Controlled Trials. Iranian journal of psychiatry 2022;17(3):320-40. DOI: 10.18502/ijps.v17i3.9733
94. CADTH. Ketamine for adults with treatment-resistant depression or posttraumatic stress disorder: a 2023 update. Canada: Canadian Agency for Drugs and Technologies in Health (CADTH); 2024. Available from: https://www.cadth.ca/ketamine-adults-treatment-resistant-depression-or-posttraumatic-stress-disorder-2023-update
95. WorkSafe BCE-BPG, Martin CW. Esketamine as treatment for depression and PTSD. Canada: WorkSafeBC; 2023. Available from: https://www.worksafebc.com/en/resources/health-care-providers/guides/esketamine-treatment-depression-ptsd?lang=en&origin=s&returnurl=https%3A%2F%2Fwww.worksafebc.com%2Fen%2Fforms-resources%23sort%3DDate%26q%3DEsketamine%2520as%2520Treatment%2520for%2520Depression%2520and%2520PTSD%26f%3Alanguage-facet%3D%5BEnglish%5D%26tags%3DGuide%7C2d7eb4b30f6a4a319e0d40565c9abbab%2CHealth%2520Care%2520Provider%7C13468b0b3f074f6bade3f57ac3cdfb8e%2CSystematic%2520Review%7Cf78c29d570c14ec3b5a394385905df70&highlight=Esketamine%20as%20Treatment%20for%20Depression%20and%20PTSD
96. Dean RL, Marquardt T, Hurducas C, Spyridi S, Barnes A, Smith R, et al. Ketamine and other glutamate receptor modulators for depression in adults with bipolar disorder. The Cochrane database of systematic reviews 2021;10(10):CD011611. DOI: 10.1002/14651858.CD011611.pub3
97. Lii TR, Smith AE, Flohr JR, Okada RL, Nyongesa CA, Cianfichi LJ, et al. Randomized trial of ketamine masked by surgical anesthesia in patients with depression. Nature Mental Health 2023;1(11):876-86. DOI: 10.1038/s44220-023-00140-x
98. Alnefeesi Y, Chen-Li D, Krane E, Jawad MY, Rodrigues NB, Ceban F, et al. Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis. J Psychiatr Res 2022;151:693-709. DOI: 10.1016/j.jpsychires.2022.04.037
99. NHS Oxford Health. Interventional Psychiatry Service, Oxford Health NHS Foundation Trust, pricing[cited 08.04.2025]. Available from: https://www.oxfordhealth.nhs.uk/ips/ketamine-trd/pricing/
100. Gaustad J-V, Kleven L, Kornør H, Harboe I, Flatby AV, Aakhus E, et al. Transkraniell likestrømsbehandling for depresjon og afasi: fullstendig metodevurdering. [Transcranial direct current stimulation for depression and aphasia. A health technology assessment]. Oslo: Folkehelseinstituttet, 2022. . 2022. Available from: chrome-

extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2022/transkraniell-likestromsbehandling-for-depresjon-og-afasi-rapport-2022.pdf
101. Oslo Economics. Sykdomsbyrden av behandlingsresistent depresjon. En studie av sykdomsbyrde og samfunnskostnader i Norge 2022. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://osloeconomics.no/wp-content/uploads/2022/10/Sykdomsbyrden-av-depresjon-i-Norge.pdf
102. Health NIoP. Psykiske plager og lidelser hos voksne. Folkeheserapporten. 2023. Available from: https://www.fhi.no/he/folkehelserapporten/psykisk-helse/psykiske-lidelser-voksne/?term=#forekomst-av-psykiske-plager
103. Lu T, D'Angelo S, Tayebali Z, Dempsey M, Giombi K, Khavjou O. Impact analysis of expanded access to ketamine for treatment-resistant depression. J Comp Eff Res 2025;14(6):e240233. DOI: 10.57264/cer-2024-0233
104. Bavato F, Quednow BB. Ketamine addiction in Europe: Any risks on the horizons? Eur Neuropsychopharmacol 2025;94:39-40. DOI: 10.1016/j.euroneuro.2025.02.015
105. Marongiu S, van Eijk M, Gresnigt FMJ, Croes EA, Franssen EJF. Rising incidence of recreational ketamine use: Clinical cases and management in emergency settings. Toxicol Rep 2025;14:101940. DOI: 10.1016/j.toxrep.2025.101940
106. Gandolfo P, Soeiro T, Jouve E, Revol B, Daveluy A, Bertin C, et al. Patterns of ketamine use among people with substance use disorder in France: Multisource analysis of the data from the French Addictovigilance Network. Fundam Clin Pharmacol 2024;38(5):978-87. DOI: 10.1111/fcp.12995
107. European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2024: Trends and Developments [Report]. Lisbon, Portugal: EUDA; European Union Drugs Agency; 2024. Available from: https://www.euda.europa.eu/publications/european-drug-report/2024_en
108. Barrios KP, Connolly DJ, Ferris JA, Maier LJ, Barratt MJ, Winstock AR, et al. Ketamine use in a large global sample: Characteristics, patterns of use and emergency medical treatment. J Psychopharmacol 2025;39(1):8-22. DOI: 10.1177/02698811241273850
109. European Union Drugs Agency. Wastewater analysis and drugs — a European multi-city study [Report]. Lisbon, Portugal: EUDA; European Union Drugs Agency; 2025. Available from: https://www.euda.europa.eu/publications/html/pods/waste-water-analysis_en
110. Forskrift om narkotika (narkotikaforskriften). FOR-2013-02-14-199. Available from: https://lovdata.no/dokument/SF/forskrift/2013-02-14-199#KAPITTEL_1
111. Norwegian customs. Rekordmengder marihuana beslaglagt i 2024: – Vi ser en tydelig trend [Web page]. Norway: Tolletaten [updated 22.01.2025; cited 16.04.2025]. Available from: https://www.toll.no/no/om-tolletaten/aktuelt-fra-tolletaten/rekordstore-mengder-beslaglagt-i-2024
112. Morgan CJ, Curran HV. Ketamine use: a review. Addiction 2012;107(1):27-38. DOI: 10.1111/j.1360-0443.2011.03576.x
113. Schak KM, Vande Voort JL, Johnson EK, Kung S, Leung JG, Rasmussen KG, et al. Potential Risks of Poorly Monitored Ketamine Use in Depression Treatment. Am J Psychiatry 2016;173(3):215-8. DOI: 10.1176/appi.ajp.2015.15081082
114. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. Urology 2007;69(5):810-2. DOI: 10.1016/j.urology.2007.01.038
115. Strous JFM, Weeland CJ, van der Draai FA, Daams JG, Denys D, Lok A, et al. Brain Changes Associated With Long-Term Ketamine Abuse, A Systematic Review. Front Neuroanat 2022;16:795231. DOI: 10.3389/fnana.2022.795231
116. Trømborg IW. Sykehuset Østfold har fått 24,9 millioner til forskning på ketamin [Web page]. Norway: Sykehuset Østfold [updated 11.12.2024; cited 23.04.2025]. Available from: https://www.sykehuset-ostfold.no/nyheter/sykehuset-ostfold-har-fatt-249-millioner-til-forskning-pa-ketamin/
117. Mongomery S, Åsberg M, Malt U. MADRS - Montgomery and Åsberg Depression Rating Scale [Depression rating tool]. Norway: Den norske legeforening; 1992. Available from: https://www.legeforeningen.no/contentassets/478e85c05e654494896c9d78110ae963/montgommery-asberg-depression-rating-scale-madrs.pdf

118. Hamilton Depression Rating Scale (HAM-D or HDRS) calculator [Web calculator]. QxMD [cited 28.04.2025]. Available from: https://qxmd.com/calculate/calculator_146/hamilton-depression-rating-scale-ham-d-or-hdrs
119. Scoring Instructions for the Depression Questionnaire Quick Inventory of Depressive Symptomatology (QIDS-SR16) [Depression rating tool]. USA: GSK; 2014. Available from: https://alnursing.org/wp-content/uploads/2020/03/Depression-Questionnaire-QIDS-SR-16.pdf
120. Patient Health Questionnaire-9 (PHQ-9) [Web calculator]. QxMD [cited 28.04.2025]. Available from: https://qxmd.com/calculate/calculator_271/patient-health-questionnaire-9-phq-9
121. Li CT, Chen MH, Lin WC, Hong CJ, Yang BH, Liu RS, et al. The effects of low-dose ketamine on the prefrontal cortex and amygdala in treatment-resistant depression: A randomized controlled study. Hum Brain Mapp 2016;37(3):1080-90. DOI: 10.1002/hbm.23085
122. Price RB, Spotts C, Panny B, Griffo A, Degutis M, Cruz N, 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 2022;179(12):959-68. DOI: 10.1176/appi.ajp.20220216
123. Echegaray MVF, Mello R, Correia-Melo FS, Leal GC, Jesus-Nunes AP, Vieira F, et al. P.454 Dissociative symptoms predict antidepressant response after infusion of ketamine in treatment-resistant depression. European Neuropsychopharmacology 2019;29(Supplement 6):S321-S2. DOI: 10.1016/j.euroneuro.2019.09.466
124. Heifets B, Lii T, Smith A, Flohr J, Nyongesa C, Cianfichi L, et al. Clinical Outcomes and Biomarkers From a Randomized Trial of Ketamine Masked by Surgical Anesthesia in Depressed Patients. Biological Psychiatry 2024;95(10 Supplement):S47. DOI: 10.1016/j.biopsych.2024.02.117
125. Ionescu D. A randomized, double blind, placebo controlled trial of repeat-dose ketamine augmentation for chronic suicidal thinking. Neuropsychopharmacology 2017;43(Supplement 1):S5-S6. DOI: 10.1038/npp.2017.263
126. Murrough JW. Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site, randomized, parallel-arm, midazolam-controlled, clinical trial. Biological Psychiatry 2013;1):142S.
127. Murrough JW, Iosifescu DV, Chang L, Al Jurdi RK, Green C, Perez A, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site, randomised controlled trial. European Neuropsychopharmacology 2013;2):S411-S2. DOI: 10.1016/S0924-977X(13)70651-5
128. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CM, Iqbal S, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site, randomized, parallel-arm, midazolam-controlled, clinical trial. Neuropsychopharmacology 2012;1):S151-S2. DOI: 10.1038/npp.2012.219
129. Price R, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Charney DS, et al. Effects of intravenous ketamine on explicit and implicit suicdal cognition: A randomized controlled trial in treatment-resistant depression. Biological Psychiatry 2013;1):142S-3S.
130. Singh J, Fedgchin M, Daly E, De Boer P, Cooper K, Lim P, et al. Onset of efficacy of ketamine in treatmentresistant depression: A double-blind, randomised, placebo-controlled, dose frequency study. European Neuropsychopharmacology 2014;2):S387-S8.
131. Singh J, Fedgchin M, Daly E, De Boer P, Cooper K, Lim P, et al. A double-blind, randomized, placebo-controlled, parallel group, dose frequency study of intravenous ketamine in patients with treatment-resistant depression. Biological Psychiatry 2014;1):44S. DOI: 10.1016/j.biopsych.2014.03.014
132. Singh J, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, et al. Efficacy and safety of intravenous esketamine in patients with treatment-resistant depression: A double-blind, double-randomization, placebocontrolled phase 2a study. Neuropsychopharmacology 2013;2):S369-S70. DOI: 10.1038/npp.2013.280
133. Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in

treatment-resistant depression. Depression & Anxiety 2014;31(4):335-43. DOI: 10.1002/da.22253

Appendix 1: Depression severity scales

	MADRS score (117)	HDRS-17 score* (118)	QIDS-SR (119)	PHQ-9 (120)
No or little depression	0-6	<7	0-5	0-4
Mild depression	7-19	7-17	6-10	5-9
Moderate depression	20-34	18-24	11-15	10-14
Moderately severe	-	-	-	15-19
Severe depression	≥35	≥25	16-20	20-27
Very severe	-	-	≥21	-

HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery and Åsberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report scale

** Note that the scores may differ according to which HDRS-type that is being used.*

Appendix 2: Search strategy

Scoping search
Epistemonikos (2024-08-14)

Advanced search – Title/Abstract Publication type: Broad Synthesis (BS), Systematic review (SR)	
((bipolar OR bi-polar OR depression* OR depressive OR MDD OR TRBD OR TRBPD OR TRD) AND (esketamin* OR ketamin* OR s-ketamin*) AND (infusion* OR intravenous* OR perfusion* OR "IV ketamine" OR "ketamine IV" OR "IV esketamine" OR "esketamine IV" OR "I.V. ketamine" OR "ketamine I.V." OR "I.V. esketamine" OR "esketamine I.V."))	BS: 2 SR: 97

International HTA database (2024-08-14)

Basic search	
(("Depressive Disorder, Treatment-Resistant"[mh] OR bipolar OR bi-polar OR depressed OR depression* OR depressive OR MDD OR TRBD OR TRBPD OR TRD) AND ("Ketamine"[mh] OR ketamin* OR esketamin*))	20

Supplementary search on websites of HTA organizations:

- Agency for Healthcare Research and Quality (AHRQ)
- National Institute for Health and Care Excellence (NICE)
- Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)
- Västra Götalandsregionen, HTA-centrum

Main search
Cochrane Central Register of Controlled Trials (2024-08-26, Issue 7 of 12, July 2024)

ID	Search	Hits
#1	[mh ^"Bipolar disorder"] OR [mh ^"Major Depression"] OR [mh ^"Depressive Disorder, Treatment-Resistant"] OR (bipolar OR bi-polar OR depressed OR depression* OR depressive OR melancholia OR MDD OR TRD OR TRBD OR TRBPD) OR (anhedoni* OR cyclothym* or dysphori* OR dysthymi* OR (seasonal NEAR/2 disorder*))	127768
#2	[mh ^Ketamine] OR (ketamin* OR Ketalar* OR esketamin* OR Ketanest* OR s-ketamin* OR ((NMDA OR N-methyl-D-aspart* OR n-methyl-dextro-aspart*) NEAR/6 (antagonist* OR block* OR inhibitor*)))	9636
#3	[mh "Administration, Intravenous"] OR (drip OR intravenous* OR infusion* OR perfusion* OR ((esketamin* OR ketamin*) NEXT (IV OR I.V.)))	177572
#4	#1 AND #2 AND #3 in Trials	1244
#5	"Trial registry record":pt	524689
#6	#4 NOT #5	760

Search syntax abbreviations:

- mh: Medical Subject Heading

- NEAR/n: positional operator that lets you retrieve records that contain your terms (in any order) within a specified number (n) of words of each other.
- NEXT: finds the terms when they appear next to each other.
- pt: Publication Type (search field)

Embase 2024-08-26

Embase <1974 to 2024 August 23> Advanced search		
1	exp Depression/ or (bipolar or bi-polar or depressed or depression* or depressive or melanchol* or MDD or TRD or TRBD or TRBPD).ti,bt,ab,kf. or (anhedoni* or cyclothym* or dysphori* or dysthymi* or (seasonal adj2 disorder*)).ti,bt,kf,ab.	1059850
2	Ketamine/ or Esketamine/ or "n methyl dextro aspartic acid receptor blocking agent"/ or (6740-88-1 or 33643-46-8).rn. or (ketamin* or esketamin*).ti,bt,du,dy,kf,ab. or ((NMDA or N-methyl-D-aspart* or n-methyl-dextro-aspart*) adj6 (antagonist* or block* or inhibitor*)).ti,bt,kf,ab. or (anhedoni* or cyclothym* or dysphori* or dysthymi* or (seasonal adj2 disorder*)).ti,bt,kf,ab.	126289
3	(Anesject* or Brevinaze* or Keiran* or Keta or KetaTM or Ketalar* or Ketolar* or Ketaject* or Ketoject* or Ketaline* or Ketamax* or Ketamine Abcur or Ketased* or Ketmin* or Cal?psol* or Kal?psol* or Ketasol* or Ketotal* or (Ketanest* or Eskelan* or Esgamda* or Esketiv* or Eskesia* or Sinmelan* or Spravato or Vesierra*)).tn.	2176
4	("bipolar depression/drug therapy/ketamine" or "bipolar depression/drug therapy/esketamine" or "major depression/drug therapy/ketamine" or "major depression/drug therapy/esketamine" or "treatment resistant depression/drug therapy/ketamine" or "treatment resistant depression/drug therapy/esketamine").xt.	1516
5	exp Intravenous Drug Administration/ or (infusion* or intravenous* or perfusion* or ((esketamin* or ketamin*) adj3 (IV or "I.V."))).ti,bt,kf,ab.	1314087
6	((1 and (2 or 3)) or 4) and 5	3467
7	(case report or "in a patient").ti.	528645
8	Animal experiment/ not (human experiment/ or human/)	2663895
9	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti.	2400327
10	or/7-9	4399239
11	6 not 10 [not case reports, not animal studies]	2688

Search syntax abbreviations:

- ab: Abstract (search field)
- ADJn: positional operator that lets you retrieve records that contain your terms (in any order) within a specified number (n) of words of each other.
- bt: Book Title (search field)
- du: Drug Index Terms (search field)
- dy: Drug Index Terms Word (search field)
- kf: Keyword Heading Word (search field)
- rn: Registry Number / Name of Substance (search field)
- ti: Title (search field)
- tn: Drug Trade Name (search field)
- xt: Triple Subheading (search field)

MEDLINE (2024-06-28)

Ovid MEDLINE(R) ALL <1946 to August 23, 2024> Advanced search		
1	Depression/ or exp Mood Disorders/ or (bipolar or bi-polar or depressed or depression* or depressive or melanchol* or MDD or TRD or TRBD or TRBPD).ti,bt,kf,ab. or (anhedoni* or cyclothym* or dysphori* or dysthymi* or (seasonal adj2 disorder*)).ti,bt,kf,ab.	705063
2	Ketamine/ or Esketamine/ or Receptors, N-Methyl-D-Aspartate/ai, de or (6740-88-1 or 33643-46-8).rn. or (ketamin* or esketamin* or s-ketamin*).ti,bt,nm,rn,kf,ab. or ((NMDA or N-methyl-D-aspart* or n-methyl-dextro-aspart*) adj6 (antagonist* or block* or inhibitor*)).ti,bt,kf,ab.	49850
3	(Anesject* or Brevinaze* or Keiran* or Keta or KetaTM or Ketalar* or Ketolar* or Ketaject* or Ketoject* or Ketaline* or Ketamax* or Ketamine Abcur or Ketased* or Ketmin* or Cal?psol* or Kal?psol* or Ketasol* or Ketotal* or (Ketanest* or Eskelan* or Esgamda* or Esketiv* or Eskesia* or Sinmelan* or Spravato or Vesierra*)).nm,rn.	4121
4	exp Administration, Intravenous/ or (infusion* or intravenous* or perfusion* or ((esketamin* or ketamin*) adj3 (IV or "I.V."))).ti,bt,kf,ab.	820899
5	1 and (2 or 3) and 4	1657
6	(case report or "in a patient").ti.	435057
7	exp animals/ not humans.sh.	5251605
8	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti.	2232325
9	or/6-8	6093244
10	5 not 9 [not case reports, not animal studies]	1239

Search syntax abbreviations:

- /: Medical Subject Heading (MeSH)
- ab: Abstract (search field)
- ADJn: positional operator that lets you retrieve records that contain your terms (in any order) within a specified number (n) of words of each other.
- ai: antagonists & inhibitors (MeSH Qualifiers)
- de: drug effects (MeSH Qualifiers)
- exp: retrieves named and narrower MeSH in the tree structure
- bt: Book Title (search field)
- kf: Keyword Heading Word (search field)
- nm: Name of Substance Word (search field)
- rn: Registry Number / Name of Substance (search field)
- ti: Title (search field)

Clinicaltrials.gov (2024-08-26)

[Condition/disease:] Bipolar Disorder OR Major Depression OR Treatment Resistant Depression OR bipolar OR depressed OR depression OR depressive OR melancholia OR MDD OR TRBD OR TRD OR TRBPD [Intervention/treatment:]: Ketamine Infusion OR Ketamine OR Esketamine OR (NMDA AND (antagonist OR antagonists OR blockade OR blocker OR blockers OR blocking OR inhibiting OR inhibitor OR inhibitors))	368

International Clinical Trials Registry Platform (2024-08-26)

Advanced Recruitment status: ALL	
[Condition:] bipolar OR bi-polar OR depressed OR depression OR depressions OR depressive OR melancholia OR melancholic OR melancholy OR MDD OR TRBD OR TRD OR TRPBD [Intervention:] Ketamine OR Esketamine OR (NMDA AND (antagonist OR antagonists OR blockade OR blocker OR blockers OR blocking OR inhibiting OR inhibitor OR inhibitors))	517

EU Clinical Trials Register (2024-09-30)

EU Clinical Trials Register -> January 2023 Clinical Trials Register Screened online (IKO)	
((bipolar OR bi-polar OR depressed OR depression OR depressions OR depressive OR melancholia OR melancholic OR melancholy OR MDD OR TRBD OR TRD OR TRPBD) AND (Ketamine OR Esketamine OR (NMDA AND (antagonist OR antagonists OR blockade OR blocker OR blockers OR blocking OR inhibiting OR inhibitor OR inhibitors))))	71
Clinical Trials 2023-> Search for clinical trials - EMA (euclinicaltrials.eu) Screened online (IKO)	
[Contain any of these terms:] Esketamine	10
[Contain any of these terms:] Ketamine	12

Economic Evaluations/Models

EPPI-Reviewer
We applied the EPPI-Reviewer built-in classifier for economic evaluations on all records from our main search. 78 records had a classifier score above 70 (range 0-100).

CEA Registry
keyword:"treatment-resistant depression"

INAHTA
"Depressive Disorder, Treatment-Resistant"[mh]

Search syntax abbreviations:
[mh]: Medical Subject Heading

Ovid Embase og MEDLINE

Embase <1974 to 2024 October 08> Ovid MEDLINE(R) ALL <1946 to October 04, 2024> Advanced search		
1	Depressive Disorder, Treatment-Resistant/ use medall	2435
2	exp Treatment Resistant Depression/ use oemezd	6105
3	((intractable or pharmacoresistant or refractory or resistant) and (((bi-polar or bipolar) adj3 disorder*) or depress*)).ti,bt.	9522
4	or/1-3 [population - narrow]	13547
5	Models, Economic/ use medall	11341
6	Economic Model/ use oemezd	3733

7	((cost* or decision* or economic* or Markov) adj10 model*).ti,bt,ab. or (model* and QALY).ab.	256436
8	or/5-7 [economic modelling]	263172
9	4 and 8 [narrow population - economic modelling]	106
10	conference abstract.pt.	5247599
11	preprint.pt.	171308
12	9 not (10 or 11)	79
13	remove duplicates from 12	50

Search syntax abbreviations:

- /: Medical Subject Heading (MeSH)
- ab: Abstract (search field)
- ADJn: positional operator that lets you retrieve records that contain your terms (in any order) within a specified number (n) of words of each other
- exp: retrieves named and narrower MeSH in the tree structure
- bt: Book Title (search field)
- medall: MEDLINE segment
- oemezd: Embase segment
- pt: publication type
- ti: Title (search field)

Appendix 3: Studies excluded in full-text screening

Reference	Reason for exclusion
Abbar M, Demattei C, El-Hage W, Llorca PM, Samalin L, Demaricourt P, et al.. Ketamine for the acute treatment of severe suicidal ideation: double blind, randomised placebo controlled trial. BMJ 2022;376:e067194. DOI: 10.1136/bmj-2021-067194	Non-relevant population
Abdallah CG, Dutta A, Averill CL, McKie S, Akiki TJ, Averill LA, et al.. Ketamine, but Not the NMDAR Antagonist Lanicemine, Increases Prefrontal Global Connectivity in Depressed Patients. Chronic Stress 2018;2:Jan-Dec. DOI: 10.1177/2470547018796102	Non-relevant population
Abdallah CG, Roache JD, Gueorguieva R, Averill LA, Young-McCaughan S, Shiroma PR, et al.. Dose-related effects of ketamine for antidepressant-resistant symptoms of posttraumatic stress disorder in veterans and active duty military: a double-blind, randomized, placebo-controlled multi-center clinical trial. Neuropsychopharmacology 2022;47(8):1574-81. DOI: 10.1038/s41386-022-01266-9	Non-relevant population
Aepfelbacher J, Panny B, Price RB. Experiences of Awe Mediate Ketamine's Antidepressant Effects: Findings From a Randomized Controlled Trial in Treatment-Resistant Depression. Biological Psychiatry Global Open Science 2024;4(4):100316. DOI: 10.1016/j.bpsgos.2024.100316	Non-relevant comparator
Alexander L, Hawkins PCT, Evans JW, Mehta MA, Zarate CA, Jr. Preliminary evidence that ketamine alters anterior cingulate resting-state functional connectivity in depressed individuals. Transl Psychiatry Psychiatry 2023;13(1):371. DOI: 10.1038/s41398-023-02674-1	Non-relevant publication or study type
Aligeti S, Quinones M, Salazar R. Rapid resolution of suicidal behavior and depression with single low-dose ketamine intravenous push even after 6 months of follow-up. Journal of Clinical Psychopharmacology 2014;34(4):533-5. DOI: 10.1097/JCP.0000000000000146	Non-relevant publication or study type
Allen AP, Naughton M, Dowling J, Walsh A, Ismail F, Shorten G, et al.. Serum BDNF as a peripheral biomarker of treatment-resistant depression and the rapid antidepressant response: A comparison of ketamine and ECT. Journal of Affective Disorders 2015;186:306-11. DOI: 10.1016/j.jad.2015.06.033	Non-relevant publication or study type
Amiaz R, Saporta R, Noy A, Berkenstadt H, Weiser M. Can Quetiapine Prolong the Antidepressant Effect of Ketamine?: A 5-Year Follow-up Study. Journal of Clinical Psychopharmacology 2021;41(6):673-5. DOI: 10.1097/JCP.0000000000001489	Non-relevant publication or study type
Araujo-de-Freitas L, Santos-Lima C, Mendonca-Filho E, Vieira F, Franca R, Magnavita G, et al.. Neurocognitive aspects of ketamine and esketamine on subjects with treatment-resistant depression: A comparative, randomized and double-blind study. Psychiatry Research 2021;303:114058. DOI: 10.1016/j.psychres.2021.114058	Already included article from this study
Basso L, Bonke L, Aust S, Gartner M, Heuser-Collier I, Otte C, et al.. Antidepressant and neurocognitive effects of serial ketamine administration versus ECT in depressed patients. Journal of Psychiatric Research 2020;123:1-8. DOI: 10.1016/j.jpsychires.2020.01.002	Non-relevant publication or study type
Beanes G, Caliman-Fontes AT, Souza-Marques B, Silva HDS, Leal GC, Carneiro BA, et al.. Effects of GRIN2B , GRIA1 , and BDNF Polymorphisms on the Therapeutic Action of Ketamine and Esketamine in Treatment-Resistant Depression Patients: Secondary Analysis From a Randomized Clinical Trial. Clinical Neuropharmacology 2022;45(6):151-6. DOI: 10.1097/WNF.0000000000000517	Already included article from this study
Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al.. Antidepressant effects of ketamine in depressed patients. Biological Psychiatry 2000;47(4):351-4. DOI: 10.1016/s0006-3223(99)00230-9	Non-relevant population
Brody BD, Park N, Christian A, Shaffer CW, Smetana R, Kotbi N, et al.. Ketamine for major depressive disorder during an inpatient psychiatric admission: Effectiveness, adverse events, and lessons learned. Journal of Affective Disorders 2024;351:293-8. DOI: 10.1016/j.jad.2024.01.207	Non-relevant publication or study type
Burrows M, Kotoula V, Dipasquale O, Stringaris A, Mehta MA. Ketamine-induced changes in resting state connectivity, 2 h after the drug administration in patients with remitted depression. Journal of Psychopharmacology 2023;37(8):784-94. DOI: 10.1177/02698811231189432	Non-relevant population

Reference	Reason for exclusion
Caliman-Fontes AT, Leal GC, Correia-Melo FS, Paixao CS, Carvalho MS, Jesus-Nunes AP, et al.. Brain-derived neurotrophic factor serum levels following ketamine and esketamine intervention for treatment-resistant depression: secondary analysis from a randomized trial. Trends in Psychiatry & Psychotherapy 2023;45:e20210298. DOI: 10.47626/2237-6089-2021-0298	Already included article from this study
Chaudhary P, Shah P, Mehta P. Retrospective data analysis to determine the effectiveness of intravenous ketamine therapy on patients suffering from depression with suicidal ideation. Industrial Psychiatry Journal 2023;32(1):86-92. DOI: 10.4103/ipj.ipj_231_21	Non-relevant publication or study type
Chen MH, Bai YM, Wu HJ, Li CT, Lin WC, Tsai SJ, et al.. Role of klotho on antidepressant and antisuicidal effects of low-dose ketamine infusion among patients with treatment-resistant depression and suicidal ideation. Journal of Affective Disorders 2023;340:471-5. DOI: 10.1016/j.jad.2023.08.061	Already included article from this study
Chen MH, Chang WC, Lin WC, Tu PC, Li CT, Bai YM, et al.. Functional Dysconnectivity of Frontal Cortex to Striatum Predicts Ketamine Infusion Response in Treatment-Resistant Depression. International Journal of Neuropsychopharmacology 2020;23(12):791-8. DOI: 10.1093/ijnp/pyaa056	Already included article from this study
Chen MH, Li CT, Lin WC, Hong CJ, Tu PC, Bai YM, et al.. Cognitive function of patients with treatment-resistant depression after a single low dose of ketamine infusion. Journal of Affective Disorders 2018;241:1-7. DOI: 10.1016/j.jad.2018.07.033	Already included article from this study
Chen MH, Lin WC, Li CT, Tsai SJ, Wu HJ, Bai YM, et al.. Baseline Working Memory Predicted Response to Low-Dose Ketamine Infusion in Patients with Treatment-Resistant Depression. Pharmacopsychiatry 2022;55(2):109-14. DOI: 10.1055/a-1589-6301	Already included article from this study
Chen MH, Lin WC, Li CT, Wu HJ, Bai YM, Tsai SJ, et al.. Effects of low-dose ketamine infusion on vascular endothelial growth factor and matrix metalloproteinase-9 among patients with treatment-resistant depression and suicidal ideation. Journal of Psychiatric Research 2023;165:91-5. DOI: 10.1016/j.jpsychires.2023.07.022	Already included article from this study
Chen MH, Lin WC, Tsai SJ, Li CT, Cheng CM, Wu HJ, et al.. Effects of treatment refractoriness and brain-derived neurotrophic factor Val66Met polymorphism on antidepressant response to low-dose ketamine infusion. European Archives of Psychiatry & Clinical Neuroscience 2021;271(7):1267-74. DOI: 10.1007/s00406-021-01264-w	Already included article from this study
Chen MH, Lin WC, Wu HJ, Bai YM, Li CT, Tsai SJ, et al.. Happiness During Low-Dose Ketamine Infusion Predicts Treatment Response: Reexploring the Adjunctive Ketamine Study of Taiwanese Patients With Treatment-Resistant Depression. Journal of Clinical Psychiatry 2020;81(6):10. DOI: 10.4088/JCP.20m13232	Already included article from this study
Chen MH, Lin WC, Wu HJ, Bai YM, Li CT, Tsai SJ, et al.. Efficacy of low-dose ketamine infusion in anxious vs nonanxious depression: revisiting the Adjunctive Ketamine Study of Taiwanese Patients with Treatment-Resistant Depression. Cns Spectrums 2021;26(4):362-7. DOI: 10.1017/S1092852920001194	Already included article from this study
Chen MH, Lin WC, Wu HJ, Bai YM, Li CT, Tsai SJ, et al.. Interest-activity symptom severity predicts response to ketamine infusion in treatment-resistant depression. Psychopharmacology 2021;238(3):857-65. DOI: 10.1007/s00213-020-05737-z	Already included article from this study
Chen MH, Lin WC, Wu HJ, Cheng CM, Li CT, Hong CJ, et al.. Antisuicidal effect, BDNF Val66Met polymorphism, and low-dose ketamine infusion: Reanalysis of adjunctive ketamine study of Taiwanese patients with treatment-resistant depression (AKSTP-TRD). Journal of Affective Disorders 2019;251:162-9. DOI: 10.1016/j.jad.2019.03.075	Already included article from this study
Chen MH, Su TP, Li CT, Lin WC, Wu HJ, Tsai SJ, et al.. Effects of melancholic features on positive and negative suicidal ideation in patients with treatment-resistant depression and strong suicidal ideation receiving low-dose ketamine infusion. European Archives of Psychiatry & Clinical Neuroscience 2024;274(4):759-66. DOI: 10.1007/s00406-023-01735-2	Already included article from this study
Chen MH, Wu HJ, Li CT, Lin WC, Bai YM, Tsai SJ, 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. Journal of Affective Disorders 2021;281:865-71. DOI: 10.1016/j.jad.2020.11.045	Already included article from this study
Chen MH, Wu HJ, Li CT, Lin WC, Tsai SJ, Hong CJ, et al.. Low-dose ketamine infusion for treating subjective cognitive, somatic, and affective depression symptoms of treatment-resistant depression. Asian Journal of Psychiatry 2021;66:102869. DOI: 10.1016/j.ajp.2021.102869	Already included article from this study

Reference	Reason for exclusion
Chen MH, Wu HJ, Li CT, Lin WC, Tsai SJ, Hong CJ, et al.. Is one or two infusions better in the first week of low-dose ketamine treatment for medication-resistant depression? A post hoc pooled analysis of randomized placebo-controlled and open-label trials. Journal of Psychiatric Research 2021;144:448-54. DOI: 10.1016/j.jpsychires.2021.11.006	Already included article from this study
Chen MH, Wu HJ, Li CT, Lin WC, Tsai SJ, Hong CJ, et al.. Low-dose ketamine infusion in treatment-resistant double depression: Revisiting the adjunctive ketamine study of Taiwanese patients with treatment-resistant depression. Human Psychopharmacology 2022;37(2):e2820. DOI: 10.1002/hup.2820	Already included article from this study
Chisamore N, Danayan K, Rodrigues NB, Di Vincenzo JD, Meshkat S, Doyle Z, et al.. Real-world effectiveness of repeated intravenous ketamine infusions for treatment-resistant depression in transitional age youth. Journal of Psychopharmacology 2023;37(8):775-83. DOI: 10.1177/02698811231171531	Non-relevant publication or study type
Danayan K, Chisamore N, Rodrigues NB, Vincenzo JDD, Meshkat S, Doyle Z, et al.. Real world effectiveness of repeated ketamine infusions for treatment-resistant depression with comorbid borderline personality disorder. Psychiatry Research 2023;323:115133. DOI: 10.1016/j.psychres.2023.115133	Non-relevant publication or study type
de la Salle S, Phillips JL, Blier P, Knott V. Electrophysiological correlates and predictors of the antidepressant response to repeated ketamine infusions in treatment-resistant depression. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2022;115:110507. DOI: 10.1016/j.pnpbp.2021.110507	Non-relevant publication or study type
Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al.. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Archives of General Psychiatry 2010;67(8):793-802. DOI: 10.1001/archgenpsychiatry.2010.90	Non-relevant publication or study type
DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, et al.. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. Journal of Clinical Psychiatry 2010;71(12):1605-11. DOI: 10.4088/JCP.09m05327blu	Non-relevant intervention
Echegaray MVF, Mello RP, Magnavita GM, Leal GC, Correia-Melo FS, Jesus-Nunes AP, et al.. Does the intensity of dissociation predict antidepressant effects 24 hours after infusion of racemic ketamine and esketamine in treatment-resistant depression? A secondary analysis from a randomized controlled trial. Trends in Psychiatry & Psychotherapy 2023;17:17. DOI: 10.47626/2237-6089-2022-0593	Already included article from this study
Ekstrand J, Fattah C, Persson M, Cheng T, Nordanskog P, Akeson J, et al.. Racemic Ketamine as an Alternative to Electroconvulsive Therapy for Unipolar Depression: A Randomized, Open-Label, Non-Inferiority Trial (KetECT). International Journal of Neuropsychopharmacology 2022;25(5):339-49. DOI: 10.1093/ijnp/pyab088	Non-relevant population
Fancy F, Rodrigues NB, Di Vincenzo JD, Chau EH, Sethi R, Husain MI, et al.. Real-World Effectiveness of Repeated Ketamine Infusions for Treatment-Resistant Bipolar Depression. Focus 2023;21(4):420-9. DOI: 10.1176/appi.focus.23021022	Non-relevant publication or study type
Fancy F, Rodrigues NB, Di Vincenzo JD, Chau EH, Sethi R, Husain MI, et al.. Real-world effectiveness of repeated ketamine infusions for treatment-resistant bipolar depression. Bipolar Disorders 2023;25(2):99-109. DOI: 10.1111/bdi.13284	Duplicate
Farmer CA, Gilbert JR, Moaddel R, George J, Adeojo L, Lovett J, et al.. Ketamine metabolites, clinical response, and gamma power in a randomized, placebo-controlled, crossover trial for treatment-resistant major depression. Neuropsychopharmacology 2020;45(8):1398-404. DOI: 10.1038/s41386-020-0663-6	Non-relevant publication or study type
Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, et al.. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA Psychiatry 2014;71(6):681-8. DOI: 10.1001/jamapsychiatry.2014.62	Non-relevant population
Feeney A, Hock RS, Freeman MP, Flynn M, Hoeppner B, Iosifescu DV, et al.. The effect of single administration of intravenous ketamine augmentation on suicidal ideation in treatment-resistant unipolar depression: Results from a randomized double-blind study. European Neuropsychopharmacology 2021;49:122-32. DOI: 10.1016/j.euroneuro.2021.04.024	Already included article from this study
Finnegan M, Galligan T, Ryan K, Shanahan E, Harkin A, Daly L, et al.. Ketamine Versus Midazolam for Depression Relapse Prevention Following Successful Electroconvulsive Therapy: A Randomized Controlled Pilot Trial. Journal of ECT 2019;35(2):115-21. DOI: 10.1097/YCT.0000000000000560	Non-relevant intervention

Reference	Reason for exclusion
Freeman MP, Hock RS, Papakostas GI, Judge H, Cusin C, Mathew SJ, et al.. Body Mass Index as a Moderator of Treatment Response to Ketamine for Major Depressive Disorder. Journal of Clinical Psychopharmacology 2020;40(3):287-92. DOI: 10.1097/JCP.0000000000001209	Already included article from this study
Freeman MP, Papakostas GI, Hoeppner B, Mazzone E, Judge H, Cusin C, et al.. Sex differences in response to ketamine as a rapidly acting intervention for treatment resistant depression. Journal of Psychiatric Research 2019;110:166-71. DOI: 10.1016/j.jpsychires.2019.01.010	Already included article from this study
Ghasemi M, Kazemi MH, Yoosefi A, Ghasemi A, Paragomi P, Amini H, et al.. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. Psychiatry Research 2014;215(2):355-61. DOI: 10.1016/j.psychres.2013.12.008	Non-relevant population
Gil T, Bonetti TC. Efficacy of intravenous esketamine in reducing suicidal ideation and major depressive symptoms: A real-world evidence study. Journal of Affective Disorders Reports 2024;17(no pagination). DOI: 10.1016/j.jadr.2024.100809	Non-relevant publication or study type
Gilbert JR, Ballard ED, Galiano CS, Nugent AC, Zarate CA, Jr. Magnetoencephalographic Correlates of Suicidal Ideation in Major Depression. Biological Psychiatry : Cognitive Neuroscience and Neuroimaging 2020;5(3):354-63. DOI: 10.1016/j.bpsc.2019.11.011	Non-relevant publication or study type
Grunebaum MF, Ellis SP, Keilp JG, Moitra VK, Cooper TB, Marver JE, et al.. Ketamine versus midazolam in bipolar depression with suicidal thoughts: A pilot midazolam-controlled randomized clinical trial. Bipolar Disorders 2017;19(3):176-83. DOI: 10.1111/bdi.12487	Non-relevant population
Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, et al.. Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial. American Journal of Psychiatry 2018;175(4):327-35. DOI: 10.1176/appi.ajp.2017.17060647	Non-relevant population
Gutierrez G, Kang MJY, Vazquez G. IV low dose ketamine infusions for treatment resistant depression: Results from a five-year study at a free public clinic in an academic hospital. Psychiatry Research 2024;335:115865. DOI: 10.1016/j.psychres.2024.115865	Non-relevant publication or study type
Haile CN, Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Foulkes A, et al.. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. International Journal of Neuropsychopharmacology 2014;17(2):331-6. DOI: 10.1017/S1461145713001119	Already included article from this study
Hashimoto K. Detrimental Side Effects of Repeated Ketamine Infusions in the Brain. American Journal of Psychiatry 2016;173(10):1044-5. DOI: 10.1176/appi.ajp.2016.16040411	Non-relevant publication or study type
Henderson TA. Practical application of the neuroregenerative properties of ketamine: real world treatment experience. Neural Regeneration Research 2016;11(2):195-200. DOI: 10.4103/1673-5374.177708	Non-relevant publication or study type
Hietamies TM, McInnes LA, Klise AJ, Worley MJ, Qian JJ, Williams LM, et al.. The effects of ketamine on symptoms of depression and anxiety in real-world care settings: A retrospective controlled analysis. Journal of Affective Disorders 2023;335:484-92. DOI: 10.1016/j.jad.2023.04.141	Non-relevant publication or study type
Ionescu DF, Swee MB, Pavone KJ, Taylor N, Akeju O, Baer L, et al.. Rapid and Sustained Reductions in Current Suicidal Ideation Following Repeated Doses of Intravenous Ketamine: Secondary Analysis of an Open-Label Study. Journal of Clinical Psychiatry 2016;77(6):e719-25. DOI: 10.4088/JCP.15m10056	Non-relevant publication or study type
Jesus-Nunes AP, Leal GC, Correia-Melo FS, Vieira F, Mello RP, Caliman-Fontes AT, et al.. Clinical predictors of depressive symptom remission and response after racemic ketamine and esketamine infusion in treatment-resistant depression. Human Psychopharmacology 2022;37(4):e2836. DOI: 10.1002/hup.2836	Already included article from this study
Jha MK, Wilkinson ST, Krishnan K, Collins KA, Sanacora G, Murrough J, et al.. Ketamine vs Electroconvulsive Therapy for Treatment-Resistant Depression: A Secondary Analysis of a Randomized Clinical Trial. JAMA Network Open 2024;7(6):e2417786. DOI: 10.1001/jamanetworkopen.2024.17786	Already included article from this study
Jiang Q, Qi Y, Zhou M, Dong Y, Zheng W, Zhu L, et al.. Effect of esketamine on serum neurotransmitters in patients with postpartum depression: a randomized controlled trial. BMC Anesthesiology 2024;24(1):293. DOI: 10.1186/s12871-024-02681-9	Non-relevant population

Reference	Reason for exclusion
Jollant F, Demattei C, Fabbro P, Abbar M. Clinical predictive factors and trajectories of suicidal remission over 6 weeks following intravenous ketamine for suicidal ideation. Journal of Affective Disorders 2024;347:1-7. DOI: 10.1016/j.jad.2023.11.043	Non-relevant population
Juby VM, Paruk S, Tomita M, Chiliza B. Ketamine for depressive symptoms: A retrospective chart review of a private ketamine clinic. The South African Journal Of Psychiatry : SAJP : The Journal Of The Society Of Psychiatrists Of South Africa 2024;30:2176. DOI: 10.4102/sajpsychiatry.v30i0.2176	Non-relevant outcome
Keilp JG, Madden SP, Marver JE, Frawley A, Burke AK, Herzallah MM, et al.. Effects of Ketamine Versus Midazolam on Neurocognition at 24 Hours in Depressed Patients With Suicidal Ideation. Journal of Clinical Psychiatry 2021;82(6):02. DOI: 10.4088/JCP.21m13921	Non-relevant population
Kheirabadi G, Vafaie M, Kheirabadi D, Mirlouhi Z, Hajiannasab R. Comparative Effect of Intravenous Ketamine and Electroconvulsive Therapy in Major Depression: A Randomized Controlled Trial. Advanced Biomedical Research 2019;8:25. DOI: 10.4103/abr.abr_166_18	Non-relevant population
Kopelman J, Keller TA, Panny B, Griffo A, Degutis M, Spotts C, et al.. Rapid neuroplasticity changes and response to intravenous ketamine: a randomized controlled trial in treatment-resistant depression. Transl Psychiatry Psychiatry 2023;13(1):159. DOI: 10.1038/s41398-023-02451-0	Non-relevant outcome
Kwasny A, Cubala WJ, Wlodarczyk A. Anhedonia and depression severity measures during ketamine administration in treatment-resistant depression. Frontiers in psychiatry Frontiers Research Foundation 2024;15:1334293. DOI: 10.3389/fpsyt.2024.1334293	Non-relevant publication or study type
Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, Zarate CA. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. Transl Psychiatry Psychiatry 2014;4:e469. DOI: 10.1038/tp.2014.105	Non-relevant publication or study type
Lenze EJ, Farber NB, Kharasch E, Schweiger J, Yingling M, Olney J, et al.. Ninety-six hour ketamine infusion with co-administered clonidine for treatment-resistant depression: A pilot randomised controlled trial. World Journal of Biological Psychiatry 2016;17(3):230-8. DOI: 10.3109/15622975.2016.1142607	Non-relevant intervention
Li CT, Chen MH, Lin WC, Hong CJ, Yang BH, Liu RS, et al.. The effects of low-dose ketamine on the prefrontal cortex and amygdala in treatment-resistant depression: A randomized controlled study. Human Brain Mapping 2016;37(3):1080-90. DOI: 10.1002/hbm.23085	Already included article from this study
Li W, Zhou Y, Liu W, Wang C, Lan X, Zhang Z, et al.. Long-term outcomes of repeated ketamine infusions in patients with unipolar and bipolar depression: A naturalistic follow-up study. Journal of Affective Disorders 2022;300:172-8. DOI: 10.1016/j.jad.2021.12.084	Non-relevant publication or study type
Li WC, Chen LF, Su TP, Li CT, Lin WC, Wu HJ, et al.. Right dorsolateral prefrontal cortex volumetric reduction is associated with antidepressant effect of low-dose ketamine infusion: A randomized, double-blind, midazolam-controlled PET-MRI clinical trial. Journal of Affective Disorders 2023;335:105-10. DOI: 10.1016/j.jad.2023.05.024	Already included article from this study
Liang Y, You Z, Chen X, Liu G, Li W, Wang C, et al.. Long-term quality of life after repeated ketamine infusions in anxious and nonanxious patients with depression. Journal of Affective Disorders 2024;349:394-9. DOI: 10.1016/j.jad.2024.01.084	Non-relevant publication or study type
Lii TR, Smith AE, Flohr JR, Okada RL, Nyongesa CA, Cianfichi LJ, et al.. Randomized trial of ketamine masked by surgical anesthesia in patients with depression. Nature Mental Health 2023;1(11):876-86. DOI: 10.1038/s44220-023-00140-x	Non-relevant intervention
Lin WC, Chen MH, Su TP, Li CT, Wu HJ, Tsai SJ, et al.. Effects of Low-Dose Ketamine Infusion on the Positive and Negative Domains of Hopelessness and Suicidal Thoughts. Journal of Clinical Psychiatry 2024;85(3):08. DOI: 10.4088/JCP.24m15257	Already included article from this study
Lin WC, Su TP, Li CT, Tsai SJ, Tu PC, Bai YM, et al.. Current suicide risk, but not lifetime history of attempted suicide, predicts treatment response to low-dose ketamine infusion: Post Hoc analysis of adjunctive ketamine study of Taiwanese patients with treatment-resistant depression. Experimental & Clinical Psychopharmacology 2024;32(1):84-9. DOI: 10.1037/pha0000658	Already included article from this study
Lin WC, Su TP, Li CT, Wu HJ, Bai YM, Liu YL, et al.. Association of Neurofilament Light Chain With the Antidepressant Effects of Low-Dose Ketamine Infusion Among Patients With Treatment-Resistant Depression. International Journal of Neuropsychopharmacology 2023;26(9):649-53. DOI: 10.1093/ijnp/pyad045	Already included article from this study

Reference	Reason for exclusion
Lin WC, Su TP, Li CT, Wu HJ, Tsai SJ, Bai YM, et al.. Baseline cognitive function predicts full remission of suicidal symptoms among patients with treatment-resistant depression and strong suicidal ideation after low-dose ketamine infusion. Journal of Psychopharmacology 2023;37(8):795-801. DOI: 10.1177/02698811231182107	Already included article from this study
Lu BY, Agapoff JR, Olson D, Tawata W, Williams SR, Ona C, et al.. Effectiveness and Safety of Intravenous Ketamine for Severely Depressed Patients Unable to Receive Electroconvulsive Therapy Due to Medical Risks. The Primary Care Companion to CNS Disorders 2020;22(3):04. DOI: 10.4088/PCC.19l02535	Non-relevant publication or study type
McIntyre RS, Rodrigues NB, Lee Y, Lipsitz O, Subramaniapillai M, Gill H, et al.. The effectiveness of repeated intravenous ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: Results from the Canadian Rapid Treatment Center of Excellence. Journal of Affective Disorders 2020;274:903-10. DOI: 10.1016/j.jad.2020.05.088	Non-relevant publication or study type
McMillan R, Sumner R, Forsyth A, Campbell D, Malpas G, Maxwell E, et al.. Simultaneous EEG/fMRI recorded during ketamine infusion in patients with major depressive disorder. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2020;99:109838. DOI: 10.1016/j.pnpbp.2019.109838	Non-relevant publication or study type
McGrory CL, Ryan KM, Gallagher B, McLoughlin DM. Vascular endothelial growth factor and pigment epithelial-derived factor in the peripheral response to ketamine. Journal of Affective Disorders 2020;273:380-3. DOI: 10.1016/j.jad.2020.04.013	Already included article from this study
Mello RP, Echegaray MVF, Jesus-Nunes AP, Leal GC, Magnavita GM, Vieira F, et al.. Trait dissociation as a predictor of induced dissociation by ketamine or esketamine in treatment-resistant depression: Secondary analysis from a randomized controlled trial. Journal of Psychiatric Research 2021;138:576-83. DOI: 10.1016/j.jpsychires.2021.05.014	Already included article from this study
Milak MS, Rashid R, Dong Z, Kegeles LS, Grunebaum MF, Ogden RT, et al.. Assessment of Relationship of Ketamine Dose With Magnetic Resonance Spectroscopy of Glx and GABA Responses in Adults With Major Depression: A Randomized Clinical Trial. JAMA Network Open 2020;3(8):e2013211. DOI: 10.1001/jamanetworkopen.2020.13211	Non-relevant population
Mouwen A, Walsh S. Treatment-resistant bipolar disorder managed with ketamine infusions as monotherapy. JAAPA 2021;34(12):1. DOI: 10.1097/01.JAA.0000800660.07463.0f	Non-relevant publication or study type
Murphy N, Tamman AJF, Lijffijt M, Amarneh D, Iqbal S, Swann A, et al.. Neural complexity EEG biomarkers of rapid and post-rapid ketamine effects in late-life treatment-resistant depression: a randomized control trial. Neuropsychopharmacology 2023;48(11):1586-93. DOI: 10.1038/s41386-023-01586-4	Already included article from this study
Murrough JW, Burdick KE, Levitch CF, Perez AM, Brallier JW, Chang LC, et al.. Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial. Neuropsychopharmacology 2015;40(5):1084-90. DOI: 10.1038/npp.2014.298	Already included article from this study
Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het R, et al.. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biological Psychiatry 2013;74(4):250-6. DOI: 10.1016/j.biopsych.2012.06.022	Non-relevant publication or study type
Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM, et al.. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychological Medicine 2015;45(16):3571-80. DOI: 10.1017/S0033291715001506	Non-relevant publication or study type
Nugent AC, Ballard ED, Gilbert JR, Tewarie PK, Brookes MJ, Zarate CA, et al.. The Effect of Ketamine on Electrophysiological Connectivity in Major Depressive Disorder. Frontiers in psychiatry Frontiers Research Foundation 2020;11:519. DOI: 10.3389/fpsyt.2020.00519	Non-relevant publication or study type
Nugent AC, Diazgranados N, Carlson PJ, Ibrahim L, Luckenbaugh DA, Brutsche N, et al.. Neural correlates of rapid antidepressant response to ketamine in bipolar disorder. Bipolar Disorders 2014;16(2):119-28. DOI: 10.1111/bdi.12118	Non-relevant publication or study type
O'Brien B, Green CE, Al-Jurdi R, Chang L, Lijffijt M, Iqbal S, et al.. Bayesian adaptive randomization trial of intravenous ketamine for veterans with late-life, treatment-resistant depression. Contemporary Clinical Trials Communications 2019;16:100432. DOI: 10.1016/j.conctc.2019.100432	Non-relevant publication or study type
Otto ME, Bergmann KR, de Kam ML, Recourt K, Jacobs GE, van Esdonk MJ. Item response theory in early phase clinical trials: Utilization of a reference model to analyze the Montgomery-Asberg Depression Rating Scale. CPT: Pharmacometrics & Systems Pharmacology 2023;12(10):1425-36. DOI: 10.1002/psp4.13018	Non-relevant publication or study type

Reference	Reason for exclusion
Pathak U, Ahuja SK, Dwivedi R, Mishra N, Kumar P, Mishra DK, et al.. Antisuicidal efficacy of ketamine infusion in suicidal patients of depressive disorder. Indian Journal of Psychiatry 2021;63(5):483-9. DOI: 10.4103/indianjpsychiatry.indianjpsychiatry_80_21	Non-relevant population
Pennybaker S, Roach BJ, Fryer SL, Badathala A, Wallace AW, Mathalon DH, et al.. Age affects temporal response, but not durability, to serial ketamine infusions for treatment refractory depression. Psychopharmacology 2021;238(11):3229-37. DOI: 10.1007/s00213-021-05939-z	Non-relevant publication or study type
Phillips JL, Norris S, Talbot J, Birmingham M, Hatchard T, Ortiz A, et al.. Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized Controlled Trial. American Journal of Psychiatry 2019;176(5):401-9. DOI: 10.1176/appi.ajp.2018.18070834	Non-relevant publication or study type
Phillips JL, Norris S, Talbot J, Birmingham M, Hatchard T, Ortiz A, et al.. Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized Controlled Trial. Focus 2020;18(2):236-43. DOI: 10.1176/appi.focus.18206	Duplicate
Phillips JL, Norris S, Talbot J, Hatchard T, Ortiz A, Birmingham M, et al.. Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. Neuropsychopharmacology 2020;45(4):606-12. DOI: 10.1038/s41386-019-0570-x	Non-relevant publication or study type
Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, et al.. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depression & Anxiety 2014;31(4):335-43. DOI: 10.1002/da.22253	Already included article from this study
Price RB, Wallace ML, Mathew SJ, Howland RH. One-Year Outcomes Following Intravenous Ketamine Plus Digital Training Among Patients with Treatment-Resistant Depression: A Secondary Analysis of a Randomized Clinical Trial. JAMA Network Open 2023;6(5):e2312434. DOI: 10.1001/jamanetworkopen.2023.12434	Non-relevant comparator
Reed JL, Nugent AC, Furey ML, Szczepanik JE, Evans JW, Zarate CA, et al.. Effects of Ketamine on Brain Activity During Emotional Processing: Differential Findings in Depressed Versus Healthy Control Participants. Biological Psychiatry : Cognitive Neuroscience and Neuroimaging 2019;4(7):610-8. DOI: 10.1016/j.bpsc.2019.01.005	Non-relevant publication or study type
Riva-Posse P, Reiff CM, Edwards JA, Job GP, Galendez GC, Garlow SJ, et al.. Blood pressure safety of subanesthetic ketamine for depression: A report on 684 infusions. Journal of Affective Disorders 2018;236:291-7. DOI: 10.1016/j.jad.2018.02.025	Non-relevant publication or study type
Rodrigues NB, McIntyre RS, Lipsitz O, Cha DS, Lee Y, Gill H, et al.. Changes in symptoms of anhedonia in adults with major depressive or bipolar disorder receiving IV ketamine: Results from the Canadian Rapid Treatment Center of Excellence. Journal of Affective Disorders 2020;276:570-5. DOI: 10.1016/j.jad.2020.07.083	Non-relevant publication or study type
Rodrigues NB, McIntyre RS, Lipsitz O, Lee Y, Cha DS, Nasri F, et al.. Safety and tolerability of IV ketamine in adults with major depressive or bipolar disorder: results from the Canadian rapid treatment center of excellence. Expert Opinion on Drug Safety 2020;19(8):1031-40. DOI: 10.1080/14740338.2020.1776699	Non-relevant publication or study type
Rodrigues NB, Siegel A, Lipsitz O, Cha DS, Gill H, Nasri F, et al.. Effectiveness of intravenous ketamine in mood disorder patients with a history of neurostimulation. Cns Spectrums 2022;27(3):315-21. DOI: 10.1017/S1092852920002187	Non-relevant publication or study type
Sakurai H, Hoeppner B, Jain F, Foster S, Pedrelli P, Mischoulon D, et al.. Use of Staging Models for Treatment-Resistant Depression Is Not Helpful in Predicting Nonresponse to Acute Intravenous Ketamine Treatment. Journal of Clinical Psychopharmacology 2022;42(2):140-5. DOI: 10.1097/JCP.0000000000001524	Non-relevant publication or study type
Saligan LN, Farmer C, Ballard ED, Kadriu B, Zarate CA, Jr. Disentangling the association of depression on the anti-fatigue effects of ketamine. Journal of Affective Disorders 2019;244:42-5. DOI: 10.1016/j.jad.2018.10.089	Non-relevant publication or study type
Salloum NC, Fava M, Freeman MP, Flynn M, Hoeppner B, Hock RS, et al.. Efficacy of intravenous ketamine treatment in anxious versus nonanxious unipolar treatment-resistant depression. Depression & Anxiety 2019;36(3):235-43. DOI: 10.1002/da.22875	Already included article from this study
Sharma RK, Kulkarni G, Kumar CN, Arumugham SS, Sudhir V, Mehta UM, et al.. Antidepressant effects of ketamine and ECT: A pilot comparison. Journal of Affective Disorders 2020;276:260-6. DOI: 10.1016/j.jad.2020.07.066	Non-relevant population

Reference	Reason for exclusion
Shiroma PR, Thuras P, Wels J, Albott CS, Erbes C, Tye S, et al.. Neurocognitive performance of repeated versus single intravenous subanesthetic ketamine in treatment resistant depression. Journal of Affective Disorders 2020;277:470-7. DOI: 10.1016/j.jad.2020.08.058	Already included article from this study
Singh B, Vande Voort JL, Pazdernik VK, Frye MA, Kung S. Treatment-resistant depression patients with baseline suicidal ideation required more treatments to achieve therapeutic response with ketamine/esketamine. Journal of Affective Disorders 2024;351:534-40. DOI: 10.1016/j.jad.2024.01.262	Non-relevant comparator
Sos P, Klirova M, Novak T, Kohutova B, Horacek J, Palenice T. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. Activitas Nervosa Superior Rediviva 2013;55(1-2):57-63.	Non-relevant population
Sos P, Klirova M, Novak T, Kohutova B, Horacek J, Palenicek T. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. Neuroendocrinology Letters 2013;34(4):287-93.	Duplicate
Talaei A, Farid H, Mahdavi M, Salehi M, Karimani A, Afzaljavan F. A Comparison between Single and Double-Dose Intravenous Ketamine Administration in Bipolar Mood Disorder: A Double-Blind Controlled Clinical Trial. Iranian Journal of Psychiatry 2023;18(4):396-405. DOI: 10.18502/ijps.v18i4.13627	Non-relevant population
Thomas RK, Baker G, Lind J, Dursun S. Rapid effectiveness of intravenous ketamine for ultraresistant depression in a clinical setting and evidence for baseline anhedonia and bipolarity as clinical predictors of effectiveness. Journal of Psychopharmacology 2018;32(10):1110-7. DOI: 10.1177/0269881118793104	Non-relevant publication or study type
Tu PC, Chang WC, Su TP, Lin WC, Li CT, Bai YM, et al.. Thalamocortical functional connectivity and rapid antidepressant and antisuicidal effects of low-dose ketamine infusion among patients with treatment-resistant depression. Molecular Psychiatry 2024;06:06. DOI: 10.1038/s41380-024-02640-3	Already included article from this study
Veldman ER, Mamula D, Jiang H, Tiger M, Ekman CJ, Lundberg J, et al.. P11 (S100A10) as a potential predictor of ketamine response in patients with SSRI-resistant depression. Journal of Affective Disorders 2021;290:240-4. DOI: 10.1016/j.jad.2021.04.055	Already included article from this study
Vestring S, Galuba V, Kern E, Voita S, Berens F, Nasiri D, et al.. Ketamine in multiple treatment-resistant depressed inpatients: A naturalistic cohort study. Journal of Affective Disorders 2024;350:895-9. DOI: 10.1016/j.jad.2024.01.165	Non-relevant publication or study type
Wilkowska A, Wlodarczyk A, Galuszko-Wegielnik M, Wiglusz MS, Cubala WJ. Intravenous Ketamine Infusions in Treatment-Resistant Bipolar Depression: An Open-Label Naturalistic Observational Study. Neuropsychiatric Disease & Treatment 2021;17:2637-46. DOI: 10.2147/NDT.S325000	Non-relevant publication or study type
Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, Pankow H, et al.. Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism. American Journal of Psychiatry 2018;175(12):1205-15. DOI: 10.1176/appi.ajp.2018.18020138	Non-relevant publication or study type
Xiao C, Zhou J, Li A, Zhang L, Zhu X, Zhou J, et al.. Esketamine vs Midazolam in Boosting the Efficacy of Oral Antidepressants for Major Depressive Disorder: A Pilot Randomized Clinical Trial. JAMA Network Open 2023;6(8):e2328817. DOI: 10.1001/jamanetworkopen.2023.28817	Non-relevant population
Xu AJ, Niciu MJ, Lundin NB, Luckenbaugh DA, Ionescu DF, Richards EM, et al.. Lithium and Valproate Levels Do Not Correlate with Ketamine's Antidepressant Efficacy in Treatment-Resistant Bipolar Depression. Neural Plasticity 2015;2015:858251. DOI: 10.1155/2015/858251	Non-relevant publication or study type
Yadav GR, Jaiswal S. Efficacy of Ketamine in Antidepressants-Resistant Cases of MDD. International Journal of Pharmaceutical and Clinical Research 2024;16(1):372-82.	Though the article meets our inclusion criteria, we chose to exclude it due to it presenting results in a contradictory manner, as well as being published in a journal reported to be predatory.
Yonezawa K, Uchida H, Yatomi T, Ohtani Y, Nomoto-Takahashi K, Nakajima S, et al.. Factors Associated with Antidepressant Effects of Ketamine: A Reanalysis of Double-Blind Randomized Placebo-Controlled Trial of Intravenous Ketamine for Treatment-Resistant Depression. Pharmacopsychiatry 2024;57(1):35-40. DOI: 10.1055/a-2179-8884	Already included article from this study

Reference	Reason for exclusion
Zarate CA, Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, et al.. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biological Psychiatry 2012;71(11):939-46. DOI: 10.1016/j.biopsych.2011.12.010	Non-relevant publication or study type
Zarate CA, Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, et al.. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Archives of General Psychiatry 2006;63(8):856-64. DOI: 10.1001/archpsyc.63.8.856	Non-relevant publication or study type
Zheng W, Gu LM, Yang XH, Zhou YL, Wang CY, Lan XF, et al.. Association of anhedonia and suicidal ideation in patients with treatment-refractory depression after intravenous ketamine infusions. International Journal of Psychiatry in Clinical Practice 2023;27(2):145-50. DOI: 10.1080/13651501.2022.2138444	Non-relevant publication or study type
Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Lan XF, et al.. A preliminary study of adjunctive ketamine for treatment-resistant bipolar depression. Journal of Affective Disorders 2020;275:38-43. DOI: 10.1016/j.jad.2020.06.020	Non-relevant publication or study type
Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al.. Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. Journal of Psychiatric Research 2018;106:61-8. DOI: 10.1016/j.jpsychires.2018.09.013	Non-relevant publication or study type
Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al.. Investigation of medical effect of multiple ketamine infusions on patients with major depressive disorder. Journal of Psychopharmacology 2019;33(4):494-501. DOI: 10.1177/0269881119827811	Non-relevant publication or study type
Zhou Y, Chen X, Ning Y. Repeated infusions of ketamine for treatment-resistant bipolar depression in real-world practice. Bipolar Disorders 2023;25(6):515-6. DOI: 10.1111/bdi.13372	Non-relevant publication or study type

Appendix 4: Characteristics of included studies

Author, year (ref)	About the study	Recruited patients; TRD definition	About the treatment	Patient characteristics baseline
Ahmed 2023 (54)	NCT04101474 Double-blind RCT Public funding Egypt	Recruited outpatients. Failed response to ≥2 ADs	**Ketamine 0.50 mg/kg**; n=18 1 infusion per week for 2 weeks	**Age**: 36.11±13.83. **Female**: n=8 **Time since diagnosis:** 3.78±3.57 **Number of MDD episodes**: 3.22±1.8 **Number of failed AD treatment**: 5.06±1.16 **Depression severity (HDRS)**: 28.28±4.45
			Saline; n=18 1 infusion per week for 2 weeks	**Age**: 36.61±13.65. **Female**: n=7. **Time since diagnosis**: 4.06±3.03. **Number of MDD episodes**: 2.33±1.6 **Number of failed AD treatment**: 4.49±0.9 **Depression severity (HDRS)**: 31.22±5.26
Anand 2023 (55)	NCT03113968 Open label RCT Public funding USA	Recruited in- or outpatients referred to ECT. Failed response to ≥2 AD treatments in their lifetime.	**Ketamine 0.50 mg/kg**; n=200 2 infusions per week for 3 weeks	**Age**: 45.6±14.8. **Female**: n=106 **Number of MDD episodes**: 5 (2-16) **Duration current MDD** *(months)*: 24 (12-75) **Depression severity (MADRS)**: 32.3±6.2
			ECT; n=203 3 treatments per week for 3 weeks	**Age**: 47.1±14.1. **Female**: n=100 **Number of MDD episodes**: 5 (2-18) **Duration current MDD** *(months)*: 24 (10-72) **Depression severity (MADRS)**: 32.6±6.0
Chen 2018a (57) **Su 2017** (73)	UMIN000016985 Double-blind RCT Public funding Taiwan	Recruited outpatients. Failed response to >2 ADs.	**Ketamine 0.50 mg/kg**; n=24 single infusion	**Age**: 48.46±11.01. **Female**: n=21 **Time since diagnosis**: 13.17±8.92 **Depression severity (MADRS)**: 33.96±7.35
			Ketamine 0.20 mg/kg; n=23 single infusion	**Age**: 44.96±12.31. **Female**: n=17 **Time since diagnosis**: 9.70±8.68 **Depression severity (MADRS)**: 35.09±6.66

Author, year (ref)	About the study	Recruited patients; TRD definition	About the treatment	Patient characteristics baseline
			Saline; n=24 single infusion	**Age**: 48.63±8.12. **Female**: n=15 **Time since diagnosis**: 10.85±6.83 **Depression severity (MADRS)**: 34.96±4.86
Chen 2018b (56)	Double-blind RCT Public funding Taiwan	Not description of recruitment. Failed response to ≥3 ADs and ≥1 AD treatment during their current depressive episode**.	**Ketamine 0.50 mg/kg**; n=8 single infusion	**Age**: 51.13±13.59. **Female**: n=8 **Time since diagnosis**: 11.88±9.40 **Depression severity (HDRS)**: 24.0±1.93
			Ketamine 0.20 mg/kg; n=8 single infusion	**Age**: 49.75±11.08. **Female**: n=5 **Time since diagnosis**: 11.63±6.61 **Depression severity (HDRS)**: 27.13±3.23
			Saline; n=8 single infusion	**Age**: 46.25±8.14. **Female**: n=5 **Time since diagnosis**: 12.44±8.73 **Depression severity (HDRS)**: 24.63±4.63
Correia-Melo 2020 (58)	UMIN000032355 Double-blind RCT Public funding Brazil	Recruited outpatients. Failed response to ≥1 ADs	**Ketamine 0.5 mg/kg**; n=29 single infusion	**Age**: 48.7±15.1. **Female**: n=19 **Number of MDD episodes**: 5.86±5.74 **Duration current MDD** *(months)*: 24.86±43.54 **Depression severity (MADRS)**: 32.9±5.3
			Esketamine 0.25 mg/kg; n=34 single infusion	**Age**: 45.5±14.5. **Female**: n=19 **Number of MDD episodes**: 8.03±6.53 **Duration current MDD** *(months)*: 32.89±65.70 **Depression severity (MADRS)**: 33.1±9.3
Fava 2020 (59) **Salloum 2020** (69)	NCT01920555 Double-blind RCT Public funding USA	Recruited outpatients. Failed response to ≥2 treatment courses during the current depressive episode (including the current ADT).	**Ketamine 0.10 mg/kg**; n=18 single infusion	**Age**: 43.1±11.9. **Female**: n=10 **Number of failed AD treatment**: 3.3±1.3 **Depression severity (HDRS)**: 12.6±1.8
			Ketamine 0.20 mg/kg; n=20 single infusion	**Age**: 45.5±14.6. **Female**: n=9 **Number of failed AD treatment**: 3.7±1.6 **Depression severity (HDRS)**: 12.8±2.5
			Ketamine 0.50 mg/kg; n=22 single infusion	**Age**: 48.6±12.9. **Female**: n=11 **Number of failed AD treatment**: 2.7±1.2 **Depression severity (HDRS)**: 12.6±1.5
			Ketamine 1.00 mg/kg; n=20	**Age**: 47.4±10.1. **Female**: n=8

Author, year (ref)	About the study	Recruited patients; TRD definition	About the treatment	Patient characteristics baseline
			single infusion	**Number of failed AD treatment**: 2.9±1.2 **Depression severity (HDRS)**: 12.6±2.1
			Midazolam 0.045 mg/kg; n=19 single infusion	**Age**: 45.6±13.8. **Female**: n=11 **Number of failed AD treatment**: 2.9±1.4 **Depression severity (HDRS)**: 13.1±2.3
Gallagher 2022 (60)	NCT03256162 Double-blind RCT Public funding Ireland	Recruited inpatients. No definition of TRD.	**Ketamine 0.5 mg/kg**; n=13 1 infusion per week for 4 weeks	**Age**: .48.9±13.1. **Female**: n=8 **Number of MDD episodes**: 5 (2-10) **Duration current MDD** *(days)*: 42 (14-330) **Depression severity (HDRS)**: 28.4±4.3
			Midazolam 0.045 mg/kg; n=12 1 infusion per week for 4 weeks	**Age**: 52.3±12.5. **Female**: n=5 **Number of MDD episodes**: 70 (1-20) **Duration current MDD** *(days)*: 75 (14-720) **Depression severity (HDRS)**: 27.4±4.3
Ionescu 2019 (61)	* Double-blind RCT Public funding USA	Recruited in academic site. Failed response of >3 failed ADs during the current episode (including the current regimen).	**Ketamine 0.50 mg/kg**; n=13 2 infusions per week for 3 weeks	**Age**: 45.5±13.6. **Female**: n=7 **Number of MDD episodes**: 5.2±8.2 **Duration current MDD** *(months)*: 132.5±154.6 **Number of failed AD treatment**: 6.6±2.9 **Depression severity (HDRS)**: 31.6±5.2
			Saline; n=13 2 infusions per week for 3 weeks	**Age**: 45.3±11.7. **Female**: n=3 **Number of MDD episodes**: 5.4±5.2 **Duration current MDD** *(months)*: 91.6±126.4 **Number of failed AD treatment**: 8.2±3.1 **Depression severity (HDRS)**: 26.3±4.8
Kheirkhah 2018 (62)	IRCT2015030921072N2 Double-blind RCT Public funding Iran	Recruited in academic site. No definition of TRD.	**Ketamine 0.50 mg/kg**; n=25 single bolus injection	**Age**: 40.84±11.75. **Female**: n=10 **Depression severity (HDRS)**: 32.64±8.27
			Ketamine 0.75 mg/kg; n=25 single bolus injection	**Age**: 42.84±12.17. **Female**: n=11 **Depression severity (HDRS)**: 35.32±10.04
			Ketamine 0.50 mg/kg; n=25 single infusion	**Age**: 39.0±11.49. **Female**: n=14 **Depression severity (HDRS)**: 33.16±9.27
			Ketamine 0.75 mg/kg; n=25	**Age**: 39.72±10.18. **Female**: n=15

Author, year (ref)	About the study	Recruited patients; TRD definition	About the treatment	Patient characteristics baseline
			single infusion	**Depression severity (HDRS)**: 33.52±7.6
Lijffijt 2022 (63)	NCT02556606 Double-blind RCT Public funding USA	Recruited outpatients and referrals. Failed response to ≥2 trials of ADs.	**Ketamine 0.50 mg/kg**; n=11 single infusion	**Age**: 60.91±4.97. **Female**: n=3 **Time since diagnosis**: 34.55±16.31 **Number of MDD episodes**: 2.36±1.12 **Duration current MDD** *(years)*: 11.09±6.43 **Depression severity (MADRS)**: 32.55±2.42
			Ketamine 0.25 mg/kg; n=5 single infusion	**Age**: 61.8±6.06. **Female**: n=3 **Time since diagnosis**: 31.20±22.28 **Number of MDD episodes**: 1.40±0.55 **Duration current MDD** *(years)*: 13.20±5.54 **Depression severity (MADRS)**: 35.80±2.05
			Ketamine 0.10 mg/kg; n=4 single infusion	**Age**: 66.75±6.85. **Female**: n=0 **Time since diagnosis**: 27.67±7.64 **Number of MDD episodes**: 2.0±0.82 **Duration current MDD** *(years)*: 10.25±7.41 **Depression severity (MADRS)**: 35.5±4.93
			Midazolam 0.03 mg/kg; n=13 single infusion	**Age**: 62.15±5.54. **Female**: n=4 **Time since diagnosis**: 30.67±15.46 **Number of MDD episodes**: 2.3±0.95 **Duration current MDD** *(years)*: 8.23±7.03 **Depression severity (MADRS)**: 35.00±5.64
Murrough 2013 (64)	NCT00768430 Double-blind RCT Public funding USA	Recruited in academic site. Failed response to ≥3 ADs.	**Ketamine 0.50 mg/kg**; n=48 single infusion	**Age**: 46.9±12.8. **Female**: n=26 **Time since diagnosis**: 24.2±12.5 **Number of MDD episodes**: 3.7±3.7 **Number of failed AD treatment**: 5.1±2.0 **Depression severity (MADRS)**: 32.6±6.1
			Midazolam 0.045 mg/kg; n=25 single infusion	**Age**: 42.7±11.6. **Female**: n=11 **Time since diagnosis**: 19.7±14.8 **Number of MDD episodes**: 4.0±3.4 **Number of failed AD treatment**: 4.44±1.88

Author, year (ref)	About the study	Recruited patients; TRD definition	About the treatment	Patient characteristics baseline
				Depression severity (MADRS): 31.1±5.6
Pattanaseri 2024 (65)	NCT05026203 Double-blind RCT Public funding Thailand	Recruited referred patients. Failed response to ≥2 antidepressants and one psychological intervention.	**Ketamine 0.50 mg/kg**; n=11 3 infusions per week for 1 week	**Age**: 32.36±10.62. **Female**: n=7 **Time since diagnosis**: 7.64±5.97 **Number of failed AD treatment**: 6.18±3.89 **Depression severity (MADRS)**: 33.73±7.9
			Midazolam 0.045 mg/kg; n=9 3 infusions per week for 1 week	**Age**: 25.67±5.61. **Female**: n=7 **Time since diagnosis**: 5.22±2.91 **Number of failed AD treatment**: 4.44±1.88 **Depression severity (MADRS)**: 35.33±6.08
Pfeiffer 2024 (66)	Retrospective study Public funding USA	Recruited outpatients. No definition of TRD.	**Ketamine**; n=215 Infusion	**Age**: 50.0±14. **Female**: n=38 †**Number of failed AD treatment:** 6.1±2.7 ‡**Depression severity (PHQ-9)**: 18.6±5.7
Rengasamy 2024 (67)	NCT03237286 Double-blind RCT Public funding USA	No description of recruitment. Failed response to ≥1 ADs within the current depressive episode. ***	**Ketamine 0.50 mg/kg**; n=103 single infusion	**Age**: 34.6±10.9. **Female**: n=62 **Depression severity (MADRS)**: 32.7±5.3
			Saline; n=51 single infusion	**Age**: 33.6±10.1. **Female**: n=33 **Depression severity (MADRS)**: 32.4±5.1
Sakurai 2020 (68)	Retrospective study No information on funding USA. Japan	Recruited outpatients. No definition of TRD.	**Ketamine 0.50 mg/kg**; n=87 single infusion	**Age**: 46.0±19.1. **Female**: n=48 **Duration current MDD** *(years)*: 6.4±11.1 **Number of failed AD treatment**: 7.4±3.7 **Depression severity (QIDS-SR)**: 17.0±5.1
Shiroma 2020 (70)	Double-blind RCT Public funding USA	Recruited outpatients. Failed response to ≥2 ADs during current episode.	**Ketamine 0.50 mg/kg**; n=28 3 infusions per week for 2 weeks	**Age**: 54.4±13.8. **Female**: n=3 **Number of MDD episodes**: 5.3±2.6 **Duration current MDD** *(weeks)*: 78.3±39.6 **Number of failed AD treatment**: 4.6±1.9 **Depression severity (MADRS)**: n.a.
			Midazolam 0.045 mg/kg + ketamine 0.50 mg/kg; n=30 3 infusions per week for 2 weeks†	**Age**: 51.2±12.5. **Female**: n=5 **Number of MDD episodes**: 6.1±3.8 **Duration current MDD** *(weeks)*: 84.9±35.3. **Number of failed AD treatment**: 4.5±2.0. **Depression severity (MADRS)**: n.a.

Author, year (ref)	About the study	Recruited patients; TRD definition	About the treatment	Patient characteristics baseline
Singh 2016a (71)	NCT01640080 Double-blind RCT Industry funding Belgium. Germany. Poland	No description of recruitment. Failed response to ≥1 AD drug in the current episode and failed response to ≥1 AD either in the current or in a previous episode.	**Esketamine 0.40 mg/kg**; n=11 single infusion	**Age**: 41.8±11.63. **Female**: n=7 **Depression severity (MADRS)**: 33.7±5.82
			Esketamine 0.20 mg/kg; n=9 single infusion	**Age**: 44.7±13.38. **Female**: n=5 **Depression severity (MADRS)**: 33.1±3.55
			Saline; n=10 single infusion	**Age**: 42.7±10.89. **Female**: n=6 **Depression severity (MADRS)**: 33.9±4.15
Singh 2016b (72)	NCT01627782 Double-blind RCT Industry funding USA	No description of recruitment. Failed response to ≥2 ADs (with ≥1 AD failure in the current episode)	**Ketamine 0.50 mg/kg**; n=18 2 infusions per week for 4 weeks	**Age**: 45.7±9.6. **Female**: n=12 **Depression severity (MADRS)**: 33.3±4.9
			Saline; n=17 2 infusions per week for 4 weeks	**Age**: 40.3±11.8. **Female**: n=12 **Depression severity (MADRS)**: 35.6±3.8
			Ketamine 0.50 mg/kg; n=17 3 infusions per week for 4 weeks	**Age**: 43.3±12. **Female**: n=12 **Depression severity (MADRS)**: 35.4±5.3
			Saline; n=16 3 infusions per week for 4 weeks	**Age**: 46.1±10.5. **Female**: n=9 **Depression severity (MADRS)**: 36.8±5.8
Su 2023 (74)	UMIN000033916 UMIN000033760 Double-blind RCT Public funding Taiwan	Recruited outpatients. Failed response to ≥2 ADs.	**Ketamine 0.50 mg/kg**; n=42 single infusion	**Age**: 34.26±13.34. **Female**: n=28 **Depression severity (MADRS)**: 35.83±4.53
			Midazolam 0.045 mg/kg.; n=42 single infusion	**Age**: 36.88±12.21. **Female**: n=31 **Depression severity (MADRS)**: 38.26±3.83
Tiger 2020 (75)	Double-blind RCT Public funding Sweden	Internet based recruitment. Treated for at least 4 weeks with an SSRI in adequate doses without treatment response.	**Ketamine 0.50 mg/kg**; n=20 single infusion	**Age**: 39.2. **Female**: n=8 **Depression severity (MADRS)**: 26.3±6.58
			Saline; n=10 single infusion	**Age**: 37.1. **Female**: n=6 **Depression severity (MADRS)**: 30.8±4.92
Zolghadriha 2024 (76)	IRCT20210806052096N1 Single-blind RCT Public funding Iran	Recruited referrals. Failed response to ≥2 ADs.	**Ketamine 0.50 mg/kg**; n=32 single infusion	**Age**: 38.77±9.13. **Female**: n=14 **Number of MDD episodes**: 5.36±1.31 **Duration current MDD** *(weeks)*: 12.49±2.93 **Depression severity (MADRS)**: 35.16±8.13
			Saline; n=32 single infusion	**Age**: 40.06±7.65. **Female**: n=12 **Number of MDD episodes**: 6.02±1.70

Author, year (ref)	About the study	Recruited patients; TRD definition	About the treatment	Patient characteristics baseline
				Duration current MDD *(weeks)*: 13.62±3.02 **Depression severity (MADRS)**: 32.51±5.66

**Ionescu have listed an NCT-number in the article. but it is likely not correct. as it refers to a non-RCT when checked on clinicaltrials.gov*
***Described in a separate article by Li et al. 2016 (121)*
**** Described in a separate article by Price et al. 2022 (122)*
† Number of different antidepressant trials in the past 20 years
‡ Depression severity (PHQ-9) score at the first infusion
The studies by Kheirkhah (2018) and Rengasamy (2024) (both marked in grey), were not used in the data-analysis due to ineligible data.
Baseline characteristics are presented as absolute number. mean ± standard deviation. or median (range). Age and Time since diagnosis is presented as years.
***AD**: antidepressant; **HDRS**: Hamilton Depression Rating Scale; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MDD**: Major Depressive Disorder; **PHQ-9**: Patient Health Questionnaire-9; **QIDS-SR**: Quick Inventory of Depressive Symptomatology – Self Report scale*

Appendix 5: Grading the certainty of the evidence (GRADE)

For GRADEing the certainty of evidence, we assessed the following factors: 1) study limitations (risk of bias), 2) inconsistency, 3) indirectness, 4) imprecision, and 5) publication bias

Response

Appendix table 1: Assessment of certainty for results on response

Treatment		Time point	No. studies	Relative (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention	Comparator				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	
Multiple ketamine 0.5 mg/kg	Multiple ECT	EoT	1 RCT	**RR 1.44** (1.13 to 1.82)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE
Single ketamine 0.5 mg/kg	Single saline	1 day post-infusion	3 RCTs	**RR 3.02** (1.31 to 7.00)	-	↓[2]	-	-	-	⊕⊕⊕ MODERATE
Multiple ketamine 0.5 mg/kg	Multiple saline	EoT	3 RCTs	**RR 2.86** (0.85 to 9.56)	↓[1]	↓[2]	-	↓[4]	-	⊕ VERY LOW
Single ketamine 0.5 mg/kg	Single midazolam	1 day post-infusion	2 RCTs	**RR 2.86** (1.31 to 6.24)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE
		3 days post-infusion	2 RCTs	**RR 2.01** (1.03 to 3.90)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
		7 days post-infusion	1 RCT	**RR 2.19** (1.20 to 4.00)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE
Multiple ketamine 0.5 mg/kg	Multiple midazolam	EoT	3 RCTs	**RR 1.26** (0.82 to 1.91)	↓[1]	↓[2]	↓[3]	↓[4]	-	⊕ VERY LOW
		1 month after EoT	1 RCT	**RR 1.64** (0.38 to 6.98)	↓[1]	-	-	↓↓[4]	-	⊕ VERY LOW

Treatment		Time point	No. studies	Relative (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention	Comparator				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	
		3 months after EoT	1 RCT	**RR 1.62** (0.63 to 4.16)	↓[1]	-	↓[3]	↓[4]	-	⊕ VERY LOW
Single ketamine 0.5 mg/kg	Single esketamine 0.25 mg/kg	1 day post-infusion	1 RCT	**RR 1.03** (0.64 to 1.68)	-	-	↓[3]	↓[4]	-	⊕⊕ LOW
		3 days post-infusion	1 RCT	**RR 1.25** (0.76 to 2.06)	-	-	↓[3]	↓[4]	-	⊕⊕ LOW
		7 days post-infusion	1 RCT	**RR 1.51** (0.92 to 2.47)	-	-	↓[3]	↓[4]	-	⊕⊕ LOW
Single ketamine ≥0.5 mg/kg	Single ketamine <0.5 mg/kg	1 day post-infusion	3 RCTs	**RR 1.74** (1.00 to 3.03)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
		3 days post-infusion*	1 RCT	**RR 1.13** (0.69 to 1.85)	↓[1]	-	-	↓↓[4*]	-	⊕ VERY LOW
		3 days post-infusion†	1 RCT	**RR 1.57** (0.77 to 3.21)	↓[1]	-	-	↓↓[4*]	-	⊕ VERY LOW
		7 days post-infusion	1 RCT	**RR 3.27** (0.91 to 11.71)	-	-	-	↓↓[4]	-	⊕⊕ LOW
Single esketamine 0.4 mg/kg	Single esketamine 0.2 mg/kg	4 days post-infusion	1 RCT	**RR 0,95** (0,50 - 1,82)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE
Single esketamine 0.4 mg/kg	Single saline	4 days post-infusion	1 RCT	**RR 0,39** (0,19 - 0,82)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE
Single esketamine 0.2 mg/kg	Single saline	4 days post-infusion	1 RCT	**RR 0,37** (0,16 - 0,86)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE

Treatment		Time point	No. studies	Relative (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention	Comparator				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	

***CI**: confidence interval; **ECT**: electroconvulsive therapy; **EoT**: end of treatment; **RCT**: randomised controlled trials; **RR**: relative risk*

** Data based on HDRS-scores from Fava et al. 2020*

† Data based on MADRS-scores from Salloum et al. 2020

↓ Downrated by one level; ↓↓ Downrated by two levels; - No change

Reasons for downrating:

1: high risk of bias

2: effect estimates are inconsistent with each other and some differences in study population and definitions of treatment resistance across studies

3: hospitalised patient population, i.e. not in line with how treatment is used in Norway, and/or lack of definition for treatment resistance or definition is not in line with definition used in Norway

4: (very) few study participants, i.e., low strength, and/or 95% CI cross 1

* We rated down additionally due to unclear results presented in the publications by Fava 2020 and Salloum 2020.

Relapse after response

Appendix table 2: Assessment of certainty for results on relapse after response

Treatment		Time point	No. studies	Relative (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention n/N	Comparator n/N				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	
Multiple ketamine 0.5 mg/kg	Multiple ECT	1 month after EoT	1 RCT	**RR 0.76** (0.48 to 1.21)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
		3 months after EoT	1 RCT	**RR 0.65** (0.41 to 1.03)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
		6 months after EoT	1 RCT	**RR 0.93** (0.58 to 1.48)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
Single ketamine 0.5 mg/kg	Single midazolam	14 days post-infusion	1 RCTs	**RR 0.57** (0.17 to 1.88)	-	-	↓[3]	↓[4]	-	⊕⊕ LOW
Multiple ketamine 0.5 mg/kg	Multiple midazolam	3 months after EoT	1 RCTs	**RR 1.00** (0.20 to 4.95)	↓[1]	-	↓[3]	↓↓[4]	-	⊕ VERY LOW
Single ketamine 0.5 mg/kg	Single ketamine <0.5 mg/kg	5-7 days post-infusion	1 RCT	**RR 0.34** (0.08 to 1.53)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
		14 days post-infusion	1 RCT	**RR 0.51** (0.26 to 1.00)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
		30 days post-infusion	1 RCT	**RR 0.80** (0.46 to 1.37)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW

***CI**: confidence interval; **ECT**: electroconvulsive therapy; **EoT**: end of treatment; **RCT**: randomised controlled trials; **RR**: relative risk*

↓ Downrated by one level; - No change

Reasons for downrating:

1: high risk of bias

3: hospitalised patient population, i.e. not in line with how treatment is used in Norway, and/or lack of definition for treatment resistance or definition is not in line with definition used in Norway

4: (very) few study participants, i.e., low strength, and/or 95% CI cross 1

Remission

Appendix table 3: Assessment of certainty for results on remission

Treatment		Time point	No. studies	Relative (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention	Comparator				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	
Multiple ketamine 0.5 mg/kg	Multiple ECT	EoT	1 RCT	**RR 2.03** (1.44 to 2.86)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE
Multiple ketamine 0.5 mg/kg	Multiple saline	EoT	2 RCTs	**RR 4.09** (1.08 to 15.55)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
Single ketamine 0.5 mg/kg	Single midazolam	7 days post-infusion	1 RCT	**RR 2.36** (0.97 to 5.77)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE
Multiple ketamine 0.5 mg/kg	Multiple midazolam	EoT	3 RCTs	**RR 1.26** (0.76 to 2.09)	↓[1]	↓[2]	↓[3]	↓[4]	-	⊕ VERY LOW
		1 month after EoT	1 RCT	**RR 2.45** (0.31 to 19.74)	↓[1]	-	↓[3]	↓↓[4]	-	⊕ VERY LOW
		3 months after EoT	1 RCT	**RR 0.92** (0.15 to 5.56)	↓[1]	-	↓[3]	↓↓[4]	-	⊕ VERY LOW
Single ketamine 0.5 mg/kg	Single esketamine 0.25 mg/kg	1 day post-infusion	1 RCT	**RR 0.82** (0.36 to 1.88)	-	-	↓[3]	↓[4]	-	⊕⊕ LOW
		3 days post-infusion	1 RCT	**RR 1.17** (0.60 to 2.30)	-	-	↓[3]	↓[4]	-	⊕⊕ LOW
		7 days post-infusion	1 RCT	**RR 1.56** (0.77 to 3.17)	-	-	↓[3]	↓[4]	-	⊕⊕ LOW
Single ketamine ≥0.5 mg/kg	Single ketamine <0.5 mg/kg	3 days post-infusion	1 RCT	**RR 2.29** (0.76 to 6.88)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
		7 days post-infusion*	1 RCT	**RR 3.27** (0.91 to 11.71)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE

***CI**: confidence interval; **ECT**: electroconvulsive therapy; **EoT**: end of treatment; **RCT**: randomised controlled trials; **RR**: relative risk. ↓ Downrated by one level; ↓↓ Downrated by two levels; - No change*
Reasons for downrating:
1: high risk of bias
2: effect estimates are inconsistent with each other and some differences in study population and definitions of treatment resistance across studies
3: hospitalised patient population, i.e. not in line with how treatment is used in Norway, and/or lack of definition for treatment resistance or definition is not in line with definition used in Norway
4: few study participants, i.e., low strength, and/or 95% CI cross 1

Relapse after remission

Appendix table 4: Assessment of certainty for results on relapse after remission

Treatment		Time point	No. studies	Relative (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention n/N	Comparator n/N				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	
Single ketamine ≥0.5 mg/kg	Single ketamine <0.5 mg/kg	5 days post-infusion	1 RCT	**RR 0.56** (0.08 to 3.75)	↓[1]	-	-	↓↓[4]	-	⊕ VERY LOW
		7 days post-infusion	1 RCT	**RR 0.28** (0.08 to 1.03)	↓[1]	-	-	↓↓[4]	-	⊕ VERY LOW
		14 days post-infusion	1 RCT	**RR 0.64** (0.36 to 1.12)	↓[1]	-	-	↓↓[4]	-	⊕ VERY LOW
		30 days post-infusion	1 RCT	**RR 0.77** (0.47 to 1.27)	↓[1]	-	-	↓↓[4]	-	⊕ VERY LOW

***CI**: confidence interval; **RCT**: randomised controlled trials; **RR**: relative risk*

↓ Downrated by one level; ↓↓ Downrated by two levels; - No change

Reasons for downrating:

1: high risk of bias

4: very few study participants, i.e., low strength, and/or 95% CI cross 1

Depression severity

Appendix table 5: Assessment of certainty for results on depression severity

Treatment		Time point	No. studies	Risk difference (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention n/N	Comparator n/N				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	
Multiple ketamine 0.5 mg/kg	Multiple ECT	EoT all patients	1 RCT	MD **2.5 lower** (4.45 lower to 0.55 lower)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE
		EoT responders	1 RCT	MD **3.61 lower** (6.26 lower to 0.96 lower)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
		1 month after EoT	1 RCT	MD **1.18 lower** (3.64 lower to 1.28 higher)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
		3 months after EoT	1 RCT	MD **0.13 lower** (4.11 lower to 3.85 higher)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE
		6 months after EoT	1 RCT	MD **1.57 lower** (4.31 lower to 1.17 higher)	↓[1]	-	-	-	-	⊕⊕ LOW
Single ketamine 0.5 mg/kg	Single saline	1 day post-infusion	3 RCTs	MD **11.55 lower** (17.66 lower to 5.44 lower)	-	↓[2]	-	-	-	⊕⊕⊕ MODERATE
		3 days post-infusion	2 RCTs	MD **12.02 lower** (23.95 lower to 0.1 lower)	-	↓[2]	-	-	-	⊕⊕⊕ MODERATE
		6-7 days post-infusion	2 RCTs	MD **11.92 lower** (23.58 lower to 0.27 lower)	-	↓[2]	-	-	-	⊕⊕⊕ MODERATE

Treatment		Time point	No. studies	Risk difference (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention n/N	Comparator n/N				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	
		1 month post-infusion	1 RCT	MD **14.1 lower** (18.92 lower to 9.28 lower)	-	-	-	↓[4]*	-	⊕⊕⊕ MODERATE
		2 months post-infusion	1 RCT	MD **11.61 lower** (16.43 lower to 6.79 lower)	-	-	-	↓[4]*	-	⊕⊕⊕ MODERATE
Multiple ketamine 0.5 mg/kg	Multiple saline	EoT: MADRS	1 RCT	MD 19.11 lower (23.1 lower to 15.12 lower)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE
		EoT: HDRS	2 RCTs	MD **5.79 lower** (15.95 lower to 4.38 higher)	↓[1]	↓[2]	-	↓[4]	-	⊕ VERY LOW
Single ketamine 0.5 mg/kg	Single midazolam	1 day post-infusion	1 RCT	MD **7.95 lower** (12.67 lower to 3.23 lower)	-	-	-	↓[4]*	-	⊕⊕⊕ MODERATE
		7 days post-infusion	1 RCT	MD **5.69 lower** (11.77 lower to 0.39 higher)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE
Multiple ketamine 0.5 mg/kg	Multiple midazolam	EoT	1 RCT	MD **0.44 higher** (7.61 lower to 8.49 higher)	↓[1]	-	-	↓↓[4]	-	⊕ VERY LOW
		1 month after EoT	1 RCT	MD **2.89 lower** (12.8 lower to 7.02 higher)	↓[1]	-	-	↓↓[4]	-	⊕ VERY LOW
Single ketamine 0.5 mg/kg	Single esketamine 0.25 mg/kg	1 day post-infusion	1 RCT	MD **1.33 lower** (6.93 lower to 4.27 higher)	-	-	↓[3]	↓[4]	-	⊕⊕ LOW
		3 days post-infusion	1 RCT	MD **2.62 lower** (9.01 lower to 3.77 higher)	-	-	↓[3]	↓[4]	-	⊕⊕ LOW

Treatment		Time point	No. studies	Risk difference (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention n/N	Comparator n/N				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	
		7 days post-infusion	1 RCT	MD **6.36 lower** (13.27 lower to 0.55 higher)	-	-	↓[3]	↓[4]	-	⊕⊕ LOW
Single ketamine ≥0.5 mg/kg	Single ketamine <0.5 mg/kg	1 day post-infusion	1 RCT	MD **5.06 lower** (7.9 lower to 2.22 lower)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE
		3 days post-infusion	1 RCT	MD **2.8 lower** (6.52 lower to 0.92 higher)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
		5 days post-infusion†	1 RCT	MD **3.23 lower** (7.04 lower to 0.58 higher)	↓[1]	-	-	↓[4]	-	⊕⊕ LOW
Single esketamine 0.4 mg/kg	Single esketamine 0.2 mg/kg	1 day post-infusion	1 RCT	MD **0.46 lower** (-3.93; 3.01)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE
		3 days post-infusion	1 RCT	MD **0,86 lower** (-3,59; 5,31)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE
Single esketamine 0.4 mg/kg	Single saline	1 day post-infusion	1 RCT	MD **13,03 lower** (-15,72; -10,34)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE
		3 days post-infusion	1 RCT	MD **9,96 lower** (-13,68; -6,24)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE
Single esketamine 0.2 mg/kg	Single saline	1 day post-infusion	1 RCT	MD **12,57 lower** (-15,24; -9,90)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE
		3 days post-infusion	1 RCT	MD **10,82 lower** (-14,11; -7,53)	-	-	-	↓[4]	-	⊕⊕⊕ MODERATE

Treatment		Time point	No. studies	Risk difference (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention n/N	Comparator n/N				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	

***CI**: confidence interval; **ECT**: electroconvulsive therapy; **EoT**: end of treatment; **MD**: mean difference; **RCT**: randomised controlled trials*

↓ Downrated by one level; ↓↓ Downrated by two levels; - No change

Reasons for downrating:

1: high risk of bias

2: effect estimates are inconsistent with each other and some differences in study population and definitions of treatment resistance across studies

3: Definition for treatment resistance or definition is not in line with definition used in Norway

4: few study participants, i.e., low strength, and/or 95% CI cross 0

*Downgraded by one because the effect estimates consist of only one study with few participants, despite having a narrow 95% CI and sufficient power.

Quality of life

Appendix table 6: Assessment of certainty for results on quality of life

Treatment		Time point	No. studies	Relative (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention n/N	Comparator n/N				Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	
Multiple ketamine 0.5 mg/kg	Multiple ECT	EoT	1 RCT	MD **0.9 lower** (1.46 lower to 0.34 lower)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE
		1 month after EoT	1 RCT	MD **1.2 lower** (1.76 lower to 0.67 lower)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE
		3 months after EoT	1 RCT	MD **3.2 higher** (2.62 higher to 3.78 higher)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE
		6 months after EoT	1 RCT	MD **2.4 higher** (1.81 higher to 2.99 higher)	↓[1]	-	-	-	-	⊕⊕⊕ MODERATE

***CI**: confidence interval; **ECT**: electroconvulsive therapy; **EoT**: end of treatment; **MD**: mean difference; **RCT**: randomised controlled trials*

↓ Downrated by one level; - No change

Reasons for downrating:

1: high risk of bias

Time to relapse

Appendix table 7: Assessment of certainty for results on time to relapse

Treatment		No. studies	Relative (95% CI)	Assessment of certainty in the effect estimates					Certainty
Intervention n/N	Comparator n/N			Study limitation	Inconsistency	Indirectness	Imprecision	Publication bias	
Multiple ketamine 0.5 mg/kg	Multiple midazolam	1 RCT	MD **4 days higher** (5.5 lower to 13.5 higher)	↓[1]	-	-	↓↓[4]	-	⊕ VERY LOW

***CI**: confidence interval; **MD**: mean difference; **RCT**: randomised controlled trials*

↓ Downrated by one level; ↓↓ Downrated by two levels; - No change

Reasons for downrating:

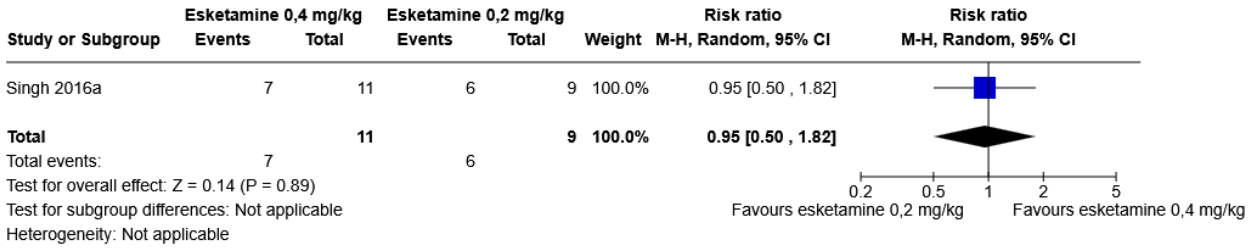
1: high risk of bias

4: very few study participants, i.e., low strength, and/or 95% CI cross 0

Appendix 6: Additional efficacy and safety data

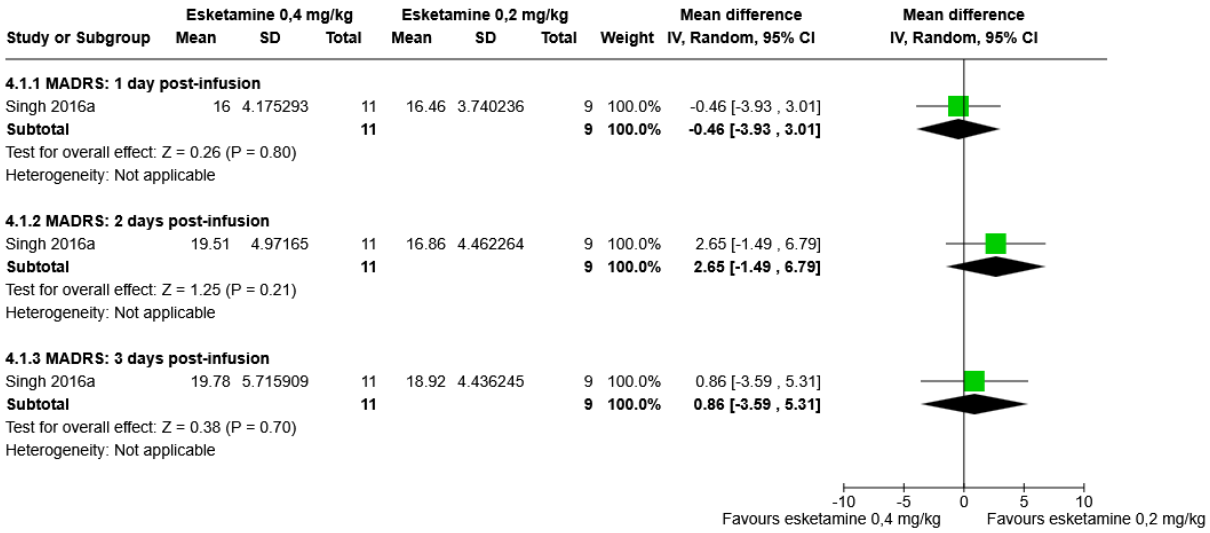
Esketamine 0.4 mg/kg versus esketamine 0.2 mg/kg – single dose

Response



Appendix figure 1: Single dose esketamine 0.4 mg/kg vs esketamine 0.2 mg/kg: forest plot of response 4 days post-infusion

Depression severity



Appendix figure 2: Single dose esketamine 0.4 mg/kg vs esketamine 0.2 mg/kg: forest plot of depression severity

Appendix table 8: Single dose esketamine 0.4 mg/kg vs esketamine 0.2 mg/kg: summary of findings table for all outcomes

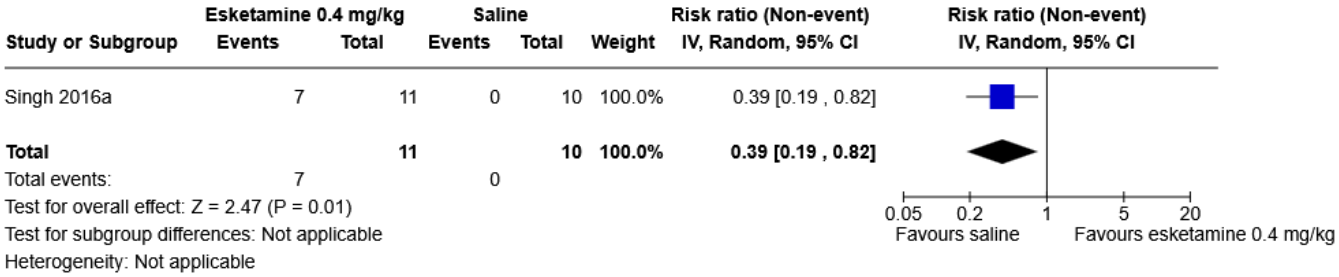
Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with esketamine 0.2 mg/kg	Risk with esketamine 0.4 mg/kg			
Response **4 days post-infusion** N=20 (RCT)	667 per 1 000	**633 per 1 000** (333 to 1 000)	**RR 0.95** (0.50 to 1.82)	⊕⊕⊕ Moderate [d]	A single esketamine 0.4 mg/kg infusion probably makes little or no difference to response compared to esketamine 0.2 mg/kg at 4 days post-infusion (*moderate certainty evidence*)

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with esketamine 0.2 mg/kg	Risk with esketamine 0.4 mg/kg			
Depression severity 1 day post-infusion (MADRS) N= 20 (1 RCT)	Mean DS was **16.46**	MD **0.46 lower** (3.93 lower to 3.01 higher)	-	⊕⊕⊕ Moderate [d]	A single esketamine 0.4 mg/kg infusion probably makes little or no difference to depression severity scores compared to esketamine 0.2 mg/kg at 1 day post-infusion (*moderate certainty evidence*)
Depression severity 2 days post-infusion (MADRS) N= 20 (1 RCT)	Mean DS was **16.86**	MD **2.65 higher** (1.49 lower to 6.79 higher)	-	⊕⊕⊕ Moderate [d]	A single esketamine 0.4 mg/kg infusion probably makes little or no difference to depression severity scores compared to esketamine 0.2 mg/kg at 2 days post-infusion (*moderate certainty evidence*)
Depression severity 3 days post-infusion (MADRS) N=20 (1 RCT)	Mean DS was **18.92**	MD **0.86 higher** (3.59 lower to 5.31 higher)	-	⊕⊕⊕ Moderate [d]	A single esketamine 0.4 mg/kg infusion probably makes little or no difference to depression severity scores compared to esketamine 0.2 mg/kg at 3 days post-infusion (*moderate certainty evidence*)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect of the intervention (and its 95% CI).*
***GRADE**: d: imprecision*
***CI:** confidence interval; **DS**: depression severity; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MD**: mean difference; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

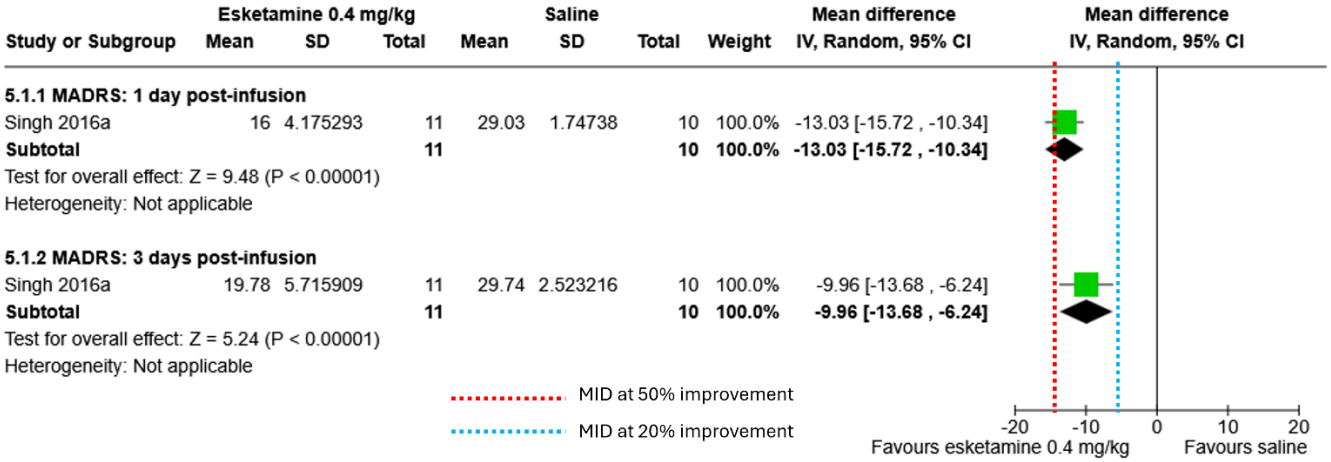
Esketamine 0.4 mg/kg versus saline – single dose

Response



Appendix figure 3: Single dose esketamine 0.4 mg/kg vs saline: forest plot of response 4 days post-infusion.
Note: the outcome is presented as non-event, i.e., the risk of *not* experiencing response.

Depression severity



Appendix figure 4: Single dose esketamine 0.4 mg/kg vs saline: forest plot of depression severity

Appendix table 9: Single dose esketamine 0.4 mg/kg vs saline: summary of findings table for all outcomes

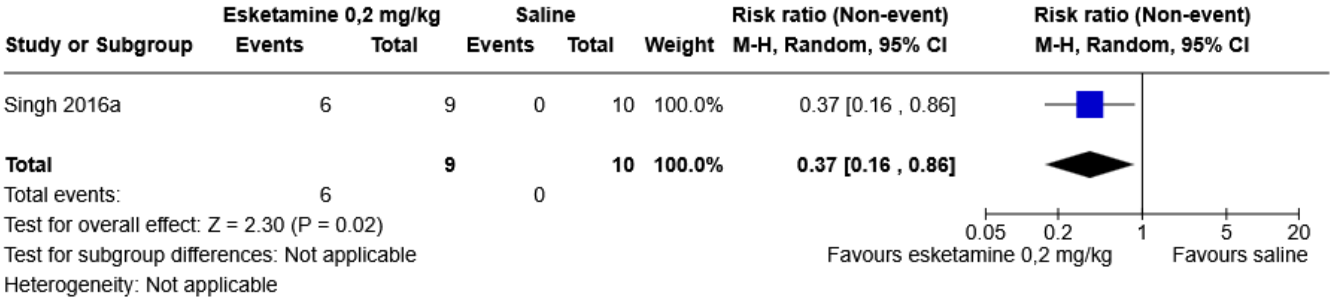
Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with saline	Risk with esketamine 0.4 mg/kg			
Response non-event 4 days post-infusion N=21 (RCT)	1000 per 1 000	**390 fewer per 1 000** (190 fewer to 820 fewer)	**RR 0.39** (0.19 to 0.82)	⊕⊕⊕ Moderate [d]	A single esketamine 0,4 mg/kg infusion probably improve the chance of response more than a single saline infusion at 4 days post-infusion (*moderate certainty evidence*)
Depression severity 1 day post-infusion (MADRS) N= 21 (1 RCT)	Mean DS was **29.03**	MD **13.03 lower** (15.72 lower to 10.34 lower)	-	⊕⊕⊕ Moderate [d]	**MID50%**: A single esketamine 0.4 mg/kg infusion probably slightly reduces depression severity scores more than a single saline infusion (*moderate certainty evidence*) **MID20%**: A single esketamine 0.4 mg/kg infusion probably reduces the depression severity scores more than a single saline infusion (*moderate certainty evidence*)

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with saline	Risk with esketamine 0.4 mg/kg			
Depression severity 3 days post-infusion (MADRS) N=21 (1 RCT)	Mean DS was **29.74**	MD **9.96 lower** (13.68 lower to 6.24 lower)	-	⊕⊕⊕ Moderate [d]	**MID50%**: A single esketamine 0.4 mg/kg infusion probably slightly reduces depression severity scores more than a single saline infusion (*moderate certainty evidence*)
					MID20%: A single esketamine 0.4 mg/kg infusion probably reduces the depression severity scores more than a single saline infusion (*moderate certainty evidence*)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect of the intervention (and its 95% CI).*
***GRADE**: d: imprecision*
***CI:** confidence interval; **DS**: depression severity; **MADRS**: Montgomery and Åsberg Depression Rating Scale; N: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

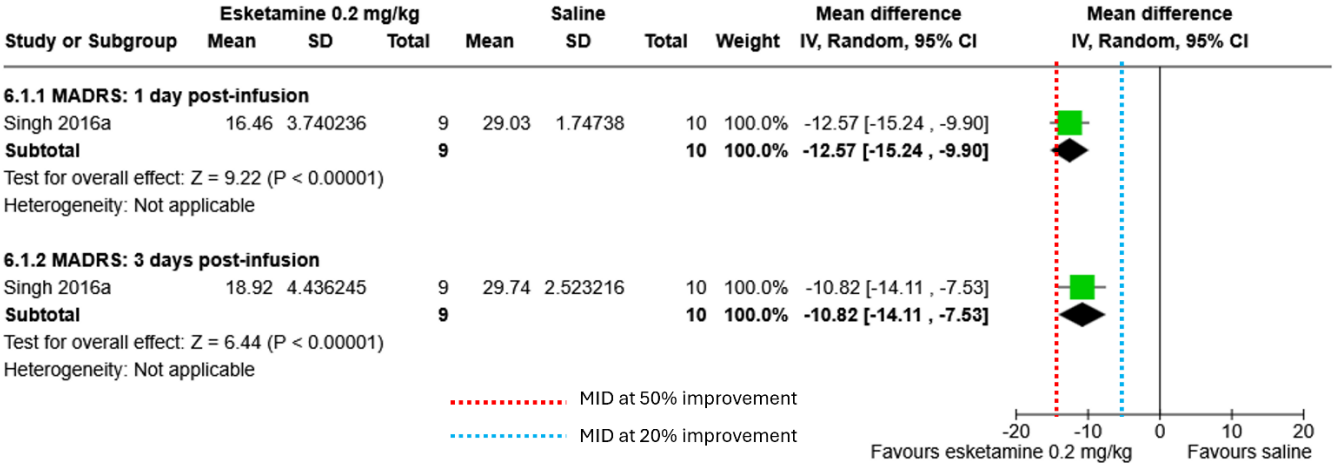
Esketamine 0.2 mg/kg versus saline – single dose

Response



Appendix figure 5: Single dose esketamine 0.2 mg/kg vs saline: forest plot of response 4 days post-infusion.
Note: the outcome is presented as non-event, i.e., the risk of not experiencing response

Depression severity



Appendix figure 6: Single dose esketamine 0.2 mg/kg vs saline: forest plot of depression severity

Appendix table 10: Single dose esketamine 0.2 mg/kg vs saline: summary of findings table for all outcomes

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with saline	Risk with esketamine 0.2 mg/kg			
Response non-event 4 days post-infusion N=19 (RCT)	1000 per 1 000	**370 fewer per 1 000** (160 fewer to 860 fewer)	**RR 0.37** (0.16 to 0.86)	⊕⊕⊕ Moderate [d]	A single esketamine 0,2 mg/kg infusion probably improve the chance of response more than a single saline infusion at 4 days post-infusion (*moderate certainty evidence*)
Depression severity 1 day post-infusion (MADRS) N= 19 (1 RCT)	Mean DS was **29.03**	MD **12.57 lower** (15.24 lower to 9.9 lower)	-	⊕⊕⊕ Moderate [d]	**MID50%**: A single esketamine 0.2 mg/kg infusion probably slightly reduces depression severity scores more than a single saline infusion (*moderate certainty evidence*)
					MID20%: A single esketamine 0.2 mg/kg infusion probably reduces the depression severity scores more than a single saline infusion (*moderate certainty evidence*)

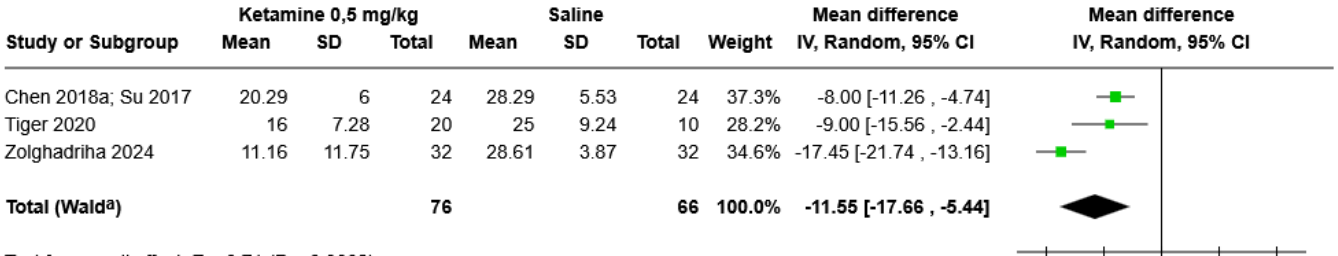
Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effects
	Risk with saline	Risk with esketamine 0.2 mg/kg			
Depression severity 3 days post-infusion (MADRS) N=19 (1 RCT)	Mean DS was **29.74**	MD **10.82 lower** (14.11 lower to 7.53 lower)	-	⊕⊕⊕ Moderate [d]	**MID50%**: A single esketamine 0.2 mg/kg infusion probably slightly reduces depression severity scores more than a single saline infusion (*moderate certainty evidence*)
					MID20%: A single esketamine 0.2 mg/kg infusion probably reduces the depression severity scores more than a single saline infusion (*moderate certainty evidence*)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect of the intervention (and its 95% CI).*
***GRADE**: d: imprecision*
***CI:** confidence interval; **DS**: depression severity; **MADRS**: Montgomery and Åsberg Depression Rating Scale; **MD**: mean difference; **N**: number of study participants; **RCT**: randomised controlled trial; **RR:** relative risk*

Appendix 7: How results change due to choice of statistical methods

Ketamine 0.5 mg/kg vs saline – single dose

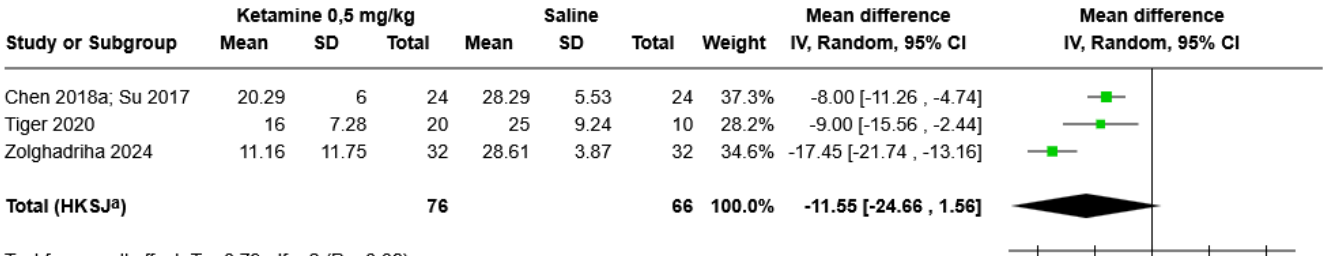
Depression severity



Test for overall effect: Z = 3.71 (P = 0.0002)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 23.28; Chi² = 12.29, df = 2 (P = 0.002); I² = 82%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Appendix figure 7: Single ketamine vs saline - depression severity with Wald-type method



Test for overall effect: T = 3.79, df = 2 (P = 0.06)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 23.28; Chi² = 12.29, df = 2 (P = 0.002); I² = 82%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

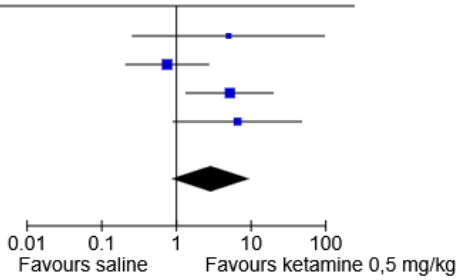
Appendix figure 8: Single ketamine vs saline - depression severity with HKSJ method

Ketamine 0.5 mg/kg vs saline – multiple doses

Response

Study or Subgroup	Ketamine 0,5 mg/kg Events	Total	Saline Events	Total	Weight	Risk ratio IV, Random, 95% CI
Ahmed 2023	2	18	0	18	12.7%	5.00 [0.26 , 97.37]
Ionescu 2019	3	13	4	13	33.4%	0.75 [0.21 , 2.71]
Singh 2016b (2 doses)	11	18	2	17	32.0%	5.19 [1.34 , 20.10]
Singh 2016b (3 doses)	7	17	1	16	22.0%	6.59 [0.91 , 47.76]
Total (Wald[a])		**66**		**64**	**100.0%**	**2.86 [0.85 , 9.56]**
Total events:	23		7			

Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.71; Chi² = 5.63, df = 3 (P = 0.13); I² = 48%

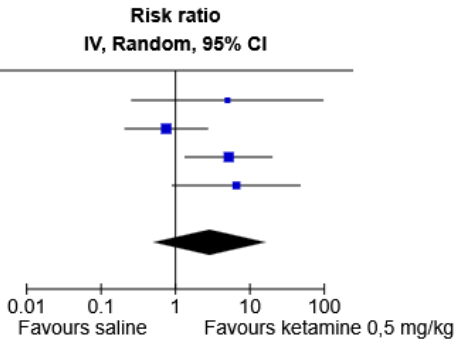


Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Appendix figure 9: Multiple ketamine vs saline - response with Wald-type method

Study or Subgroup	Ketamine 0,5 mg/kg Events	Total	Saline Events	Total	Weight	Risk ratio IV, Random, 95% CI
Ahmed 2023	2	18	0	18	12.7%	5.00 [0.26 , 97.37]
Ionescu 2019	3	13	4	13	33.4%	0.75 [0.21 , 2.71]
Singh 2016b (2 doses)	11	18	2	17	32.0%	5.19 [1.34 , 20.10]
Singh 2016b (3 doses)	7	17	1	16	22.0%	6.59 [0.91 , 47.76]
Total (HKSJ[a])		**66**		**64**	**100.0%**	**2.86 [0.50 , 16.39]**
Total events:	23		7			

Test for overall effect: T = 1.91, df = 3 (P = 0.15)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.71; Chi² = 5.63, df = 3 (P = 0.13); I² = 48%



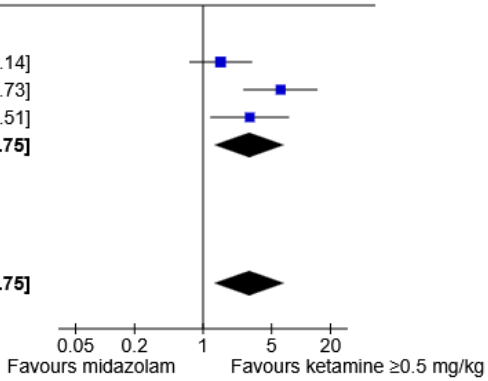
Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Appendix figure 10: Multiple ketamine vs saline - response with HKSJ method

Ketamine 0.5 mg/kg vs midazolam – single dose

Response

Study or Subgroup	Ketamine ≥0.5 mg/kg Events	Total	Midazolam Events	Total	Weight	Risk ratio IV, Random, 95% CI
2.7.1 Response: 3 days post-infusion						
Fava 2020; Salloum 2020	20	42	6	19	36.2%	1.51 [0.72 , 3.14]
Murrough 2013	28	47	5	52	32.6%	6.20 [2.61 , 14.73]
Su 2023	15	42	5	42	31.2%	3.00 [1.20 , 7.51]
Subtotal (Wald[a])		**131**		**113**	**100.0%**	**2.96 [1.30 , 6.75]**
Total events:	63		16			
Test for overall effect: Z = 2.58 (P = 0.010)						
Heterogeneity: Tau² (REML[b]) = 0.35; Chi² = 5.98, df = 2 (P = 0.05); I² = 66%						
Total (Wald[a])		**131**		**113**	**100.0%**	**2.96 [1.30 , 6.75]**
Total events:	63		16			
Test for overall effect: Z = 2.58 (P = 0.010)						
Test for subgroup differences: Not applicable						
Heterogeneity: Tau² (REML[b]) = 0.35; Chi² = 5.98, df = 2 (P = 0.05); I² = 66%						



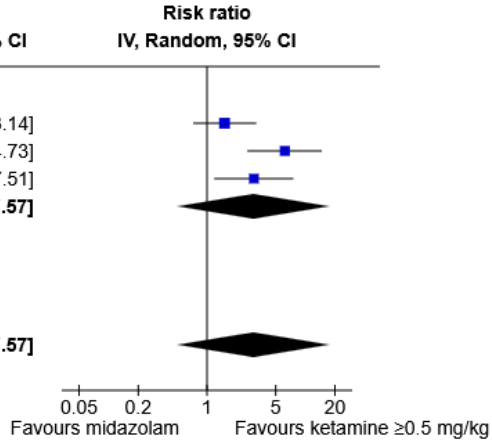
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

Appendix figure 11: Single ketamine vs midazolam - response with Wald-type method

Study or Subgroup	Ketamine ≥0.5 mg/kg Events	Total	Midazolam Events	Total	Weight	Risk ratio IV, Random, 95% CI
2.7.1 Response: 3 days post-infusion						
Fava 2020; Salloum 2020	20	42	6	19	36.2%	1.51 [0.72 , 3.14]
Murrough 2013	28	47	5	52	32.6%	6.20 [2.61 , 14.73]
Su 2023	15	42	5	42	31.2%	3.00 [1.20 , 7.51]
Subtotal (HKSJ[a])		**131**		**113**	**100.0%**	**2.96 [0.50 , 17.57]**
Total events:	63		16			
Test for overall effect: T = 2.62, df = 2 (P = 0.12)						
Heterogeneity: Tau² (REML[b]) = 0.35; Chi² = 5.98, df = 2 (P = 0.05); I² = 66%						
Total (HKSJ[a])		**131**		**113**	**100.0%**	**2.96 [0.50 , 17.57]**
Total events:	63		16			
Test for overall effect: T = 2.62, df = 2 (P = 0.12)						
Test for subgroup differences: Not applicable						
Heterogeneity: Tau² (REML[b]) = 0.35; Chi² = 5.98, df = 2 (P = 0.05); I² = 66%						



Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

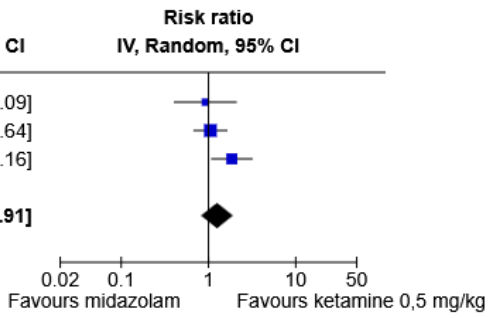
Appendix figure 12: Single ketamine vs midazolam - response with HKSJ method

Ketamine 0.5 mg/kg vs midazolam – multiple doses

Response

Study or Subgroup	Ketamine 0,5 mg/kg Events	Total	Midazolam Events	Total	Weight	Risk ratio IV, Random, 95% CI
Gallagher 2020	6	13	6	12	20.3%	0.92 [0.41 , 2.09]
Pattanaseri 2024	9	11	7	9	43.7%	1.05 [0.67 , 1.64]
Shiroma 2020	19	28	11	30	36.0%	1.85 [1.08 , 3.16]
Total (Wald[a])		**52**		**51**	**100.0%**	**1.26 [0.82 , 1.91]**
Total events:	34		24			

Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.05; Chi² = 3.17, df = 2 (P = 0.20); I² = 38%

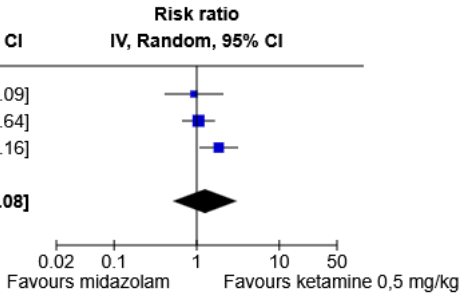


Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Appendix figure 13: Multiple ketamine vs midazolam - response with Wald-type method

Study or Subgroup	Ketamine 0,5 mg/kg Events	Total	Midazolam Events	Total	Weight	Risk ratio IV, Random, 95% CI
Gallagher 2020; McGrory 2020	6	13	6	12	20.3%	0.92 [0.41 , 2.09]
Pattanaseri 2024	9	11	7	9	43.7%	1.05 [0.67 , 1.64]
Shiroma 2020	19	28	11	30	36.0%	1.85 [1.08 , 3.16]
Total (HKSJ[a])		**52**		**51**	**100.0%**	**1.26 [0.51 , 3.08]**
Total events:	34		24			

Test for overall effect: T = 1.09, df = 2 (P = 0.39)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.05; Chi² = 3.17, df = 2 (P = 0.20); I² = 38%



Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

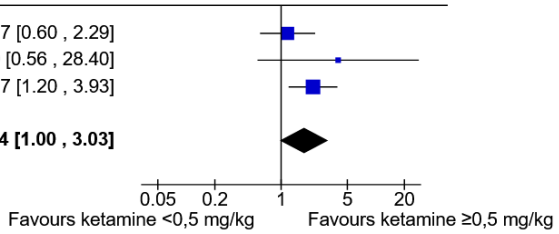
Appendix figure 14: Multiple ketamine vs midazolam - response with HKSJ method

Ketamine ≥0.5 mg/kg vs ketamine <0.5 mg/kg – single dose

Response

Study or Subgroup	Ketamine ≥0,5 mg/kg Events	Total	Ketamine <0,5 mg/kg Events	Total	Weight	Risk ratio IV, Random, 95% CI
Chen 2018a; Su 2017	11	24	9	23	42.9%	1.17 [0.60 , 2.29]
Chen 2018b	4	8	1	8	7.4%	4.00 [0.56 , 28.40]
Fava 2020; Salloum 2020	24	42	10	38	49.7%	2.17 [1.20 , 3.93]
Total (Wald[a])		**74**		**69**	**100.0%**	**1.74 [1.00 , 3.03]**
Total events:	39		20			

Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.07; Chi² = 2.57, df = 2 (P = 0.28); I² = 27%



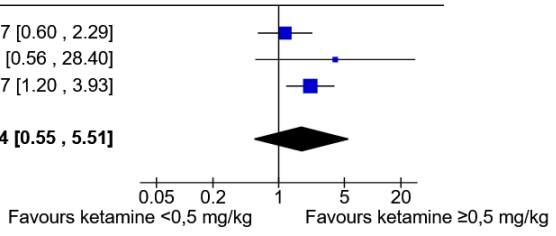
Footnotes

[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Appendix figure 15: Single ketamine vs ketamine - response with Wald-type method

Study or Subgroup	Ketamine ≥0,5 mg/kg Events	Total	Ketamine <0,5 mg/kg Events	Total	Weight	Risk ratio IV, Random, 95% CI
Chen 2018a; Su 2017	11	24	9	23	42.9%	1.17 [0.60 , 2.29]
Chen 2018b	4	8	1	8	7.4%	4.00 [0.56 , 28.40]
Fava 2020; Salloum 2020	24	42	10	38	49.7%	2.17 [1.20 , 3.93]
Total (HKSJ[a])		**74**		**69**	**100.0%**	**1.74 [0.55 , 5.51]**
Total events:	39		20			

Test for overall effect: T = 2.08, df = 2 (P = 0.17)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.07; Chi² = 2.57, df = 2 (P = 0.28); I² = 27%



Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Appendix figure 16: Single ketamine vs ketamine - response with HKSJ method

Appendix 8: Conference abstracts and preprints

The literature searches retrieved 810 conference abstracts and ten preprints. One team member (EH) assessed these against the project's selection criteria. A researcher who had also reviewed published journal articles and ongoing studies (AVF) verified the selection and confirmed that the proposed abstracts would have been retrieved in full text if they were not conference abstracts. In many cases, the conference abstracts lacked sufficient information to determine whether the study met our selection criteria. We have not contacted the relevant authors to obtain additional information. None of the preprints and nine abstracts met the criteria. Based on a comparison of author names from the conference abstracts and journal articles, PICO, and the number of participants, we linked all of them (123-132) to five studies/scientific articles, included in this HTA (58;61;64;71;72;97).

Conference abstract	Included publication
Echegaray MVF, Mello R, Correia-Melo FS, Leal GC, Jesus-Nunes AP, Vieira F, et al. P.454 Dissociative symptoms predict antidepressant response after infusion of ketamine in treatment-resistant depression. Eur Neuropsychopharmacol 2019;29(Supplement 6):S321-S2. DOI: 10.1016/j.euroneuro.2019.09.466	Correia-Melo 2020 (58)
Ionescu D. A randomized, double blind, placebo controlled trial of repeat-dose ketamine augmentation for chronic suicidal thinking. Neuropsychopharmacology 2017;43(Supplement 1):S5-S6. DOI: 10.1038/npp.2017.263	Ionescu 2019 (61)
Murrough JW. Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site, randomized, parallel-arm, midazolam-controlled, clinical trial. Biol Psychiatry 2013;1):142S.	Murrough 2013 (64)
Murrough JW, Iosifescu DV, Chang L, Al Jurdi RK, Green C, Perez A, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site, randomised controlled trial. Eur Neuropsychopharmacol 2013;2):S411-S2. DOI: 10.1016/S0924-977X(13)70651-5	Murrough 2013 (64)
Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CM, Iqbal S, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site, randomized, parallel-arm, midazolam-controlled, clinical trial. Neuropsychopharmacology 2012;1):S151-S2. DOI: 10.1038/npp.2012.219	Murrough 2013 (64)
Price R, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Charney DS, et al. Effects of intravenous ketamine on explicit and implicit suicidal cognition: A randomized controlled trial in treatment-resistant depression. Biol Psychiatry 2013;1):142S-3S.	Price 2014* (133), Murrough 2013 (64)
Singh J, Fedgchin M, Daly E, De Boer P, Cooper K, Lim P, et al. Onset of efficacy of ketamine in treatment resistant depression: A double-blind, randomised, placebo-controlled, dose frequency study. Eur Neuropsychopharmacol 2014;2):S387-S8.	Singh 2016 (72)
Singh J, Fedgchin M, Daly E, De Boer P, Cooper K, Lim P, et al. A double-blind, randomized, placebo-controlled, parallel group, dose frequency study of intravenous ketamine in patients with treatment-resistant depression. Biol Psychiatry 2014;1):44S. DOI: 10.1016/j.biopsych.2014.03.014	Singh 2016 (72)
Singh J, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, et al. Efficacy and safety of intravenous esketamine in patients with treatment-resistant depression: A double-blind, double-randomization, placebo controlled phase 2a study. Neuropsychopharmacology 2013;2):S369-S70. DOI: 10.1038/npp.2013.280	Singh 2016 (71)

**Price 2014: excluded, see Appendix 3*

Appendix 9: Ongoing studies

Study ID / Title	Country	Status / estimated end	Treatments	Study design/ Enrollment (n)	Main outcome
ChiCTR2000037607 A Study to Evaluate the Efficacy and Safety of Esketamine in Treatment-resistant Depression	China	Recruiting /May 2024	Arm 1: IV esketamine 0.5 mg/kg Arm 2: IV midazolam 0.02 mg/kg	RCT phase 3 N=240	Not specified
ChiCTR2300071697 The efficacy. safety and mechanism of esketamine vs electroconvulsive therapy in the treatment of suicidal risk of patients with major depressive episode	China	Not started. /December 2027	Arm 1: IV esketamine 0.5 mg/kg Arm 2: Modified electroconvulsive therapy (MECT)	RCT phase 4 N=300	Beck Scale for Suicidal Ideation / Depression score on HDRS/MADRS
CTRI/2020/01/022914 Electroconvulsive therapy versus ketamine for improving symptoms in treatment resistant depression	India	Open to Recruitment	Arm 1: IV ketamine 0.5 mg/kg x 6 infusions Arm 2: ECT x 6 sessions	RCT N=60	Depression score on HDRS
CTRI/2021/07/035210 A clinical trial to compare the effectiveness of repeated ketamine infusions and electroconvulsive therapy in patients of depression with suicidality and how it relates to the kynurenine pathway.	India	Not Yet Recruiting	Arm 1: IV ketamine 0.5 mg/kg x 6 infusions Arm 2: Modified ECT x 6 sessions	RCT N=30	Becks Scale for Suicidal Ideation
CTRI/2021/10/037093 Study on the effectiveness of Ketamine in persons suffering from bipolar depression	India	Not Yet Recruiting	Arm 1: IV ketamine Arm 2: IV midazolam	RCT N=80	Depression score on HDRS
CTRI/2021/10/037627 A Clinical trial to study the efficacy and safety of Ketamine on patient with Severe depression.	India	Not Yet Recruiting	Arm 1: IV ketamine 0.5 mg/kg every 72 hours for two weeks Arm 2: IV saline every 72 hours for two weeks	RCT phase 3 N=52	Depression score on HDRS
CTRI/2022/11/047630 Ketamine vs ECT in patients with severe depression.	India	Not Yet Recruiting	Arm 1: IV ketamine 0.5 mg/kg x 3 infusions Arm 2: Modified ECT x 3 sessions	RCT phase 2/3 N=60	Depression score on HDRS
CTRI/2023/06/053779	India	Not Yet Recruiting	Arm 1: IV ketamine 0.5 mg/kg x 6 infusions Arm 2: Modified ECT x 6 sessions	RCT N=60	Not specified

Study ID / Title	Country	Status / estimated end	Treatments	Study design/ Enrollment (n)	Main outcome
A study comparing the effectiveness of Ketamine and ECT as an add-on therapy for severe depressive episodes with suicidal ideation.					
DRKS00022836 Treatment of Major Depressive Disorder with Ketamine - retrospective data analysis	Germany	Recruiting planned	Arm 1: Ketamine	Observational N=50 subjects / 600 treatments	Not specified
DRKS00025974 The effect of interventions focussing on or leading away from actual symptoms on well-being in different states of altered neuroplasticity	Germany	Recruiting ongoing	Arm 1: Depressed Patients - treatment as usual (TAU) In randomized order SIGMA or MBI as intervention Arm 2: Depressed Patients treated with ketamine In randomized order SIGMA or MBI as intervention Arm 3: Depressed Patients treated with rTMS In randomized order SIGMA or MBI as intervention Arm 4: Healthy controls In randomized order SIGMA or MBI as intervention	RCT crossover N=88	WHO-5 well-being-score
IRCT20141209020258N182 The effect of single dose of ketamine injection in reducing suicidal ideation in type 1 bipolardisorder patients in the depressive phase	Iran	Recruitment complete/ May 2024	Arm 1: IV ketamine 0.5 mg/kg Arm 2: IV saline	RCT phase 2-3 N=124	Beck Suicidal Ideation Scale
NCT04032301 Repeated Ketamine Infusions for Comorbid PTSD and MDD in Veterans	USA	Active. not recruiting	Arm 1: IV Ketamine x 6 Arm 2: IV Saline x 6	RCT phase 1 N=67	Depression score on MADRS
NCT04480918 University of Iowa Interventional Psychiatry Service Patient Registry	USA	Recruiting/ august 2050	Arm 1: Electroconvulsive Therapy (ECT) Arm 2: Transcranial Magnetic Stimulation (TMS) Arm 3: IV Ketamine Arm 4: Intranasal Esketamine Arm 5: Deep Transcranial Magnetic Stimulation (dTMS) (only for OCD)	Observational N=1000	Depression score on MADRS
NCT04877977 Long-term Observation of Participants With Mood Disorders	USA	Recruiting/ October 2028	NA	Observational N=1000	Score on Beck Depression Inventory (suicide item removed)
NCT04939649 Ketamine as an Adjunctive Therapy for Major Depression (2)	Ireland	Completed /August 2024	Arm 1: IV ketamine 0.5mg/kg x 8 Arm 2: IV midazolam 0.045mg/kg x 8	RCT phase 3 N=63	Depression score on MADRS

Study ID / Title	Country	Status / estimated end	Treatments	Study design/ Enrollment (n)	Main outcome
NCT05004896 Ketamine for Treatment-Resistant Bipolar Disorder	Canada	Recruiting / December 2025	Arm 1: IV ketamine 0.5-0.75 mg/kg x 4 Arm 2: IV midazolam 0.02-0.03 mg/kg x 4	RCT phase 2 N=100	Depression score on MADRS
NCT05046184 Elucidating the Neurocircuitry of Irritability With High-Field Neuroimaging to Identify Novel Therapeutic Targets	USA	Recruiting /November 2026	Arm 1: Healthy controls Arm 2: IV ketamine 0.5mg/kg x 4 Arm 3: IV midazolam 0.02 mg/kg x 4	RCT phase 2 N=180	Resting state functional connectivity/ depression score on MADRS
NCT05327699 Glutamatergic Adaptation to Stress as a Mechanism for Anhedonia and Treatment Response With Ketamine	USA	Recruiting /December 2026	Arm 1: IV ketamine 0.5mg/kg Arm 2: IV saline	RCT early phase 1 N=140	Change in glutamate concentration in the medial prefrontal cortex. no mention of MADRS or HDRS
NCT05565352 Observation of Ketamine Treatment Safety and Tolerability in Adult Psychiatry Clinic Medical University of Gdańsk Inpatients	Poland	Enrolling /December 2027	Arm 1: IV ketamine 0.5mg/kg x 8 Arm 2: Intranasal ketamine x 8 Arm 2: Oral ketamine 2.0mg/kg- 2.5mg/kg x 8	Observational N=140	Adverse events / depression score on MADRS
NCT06034821 Comparative Effectiveness of ECT vs. KETAMINE Over the Lifespan	USA/ Canada	Enrolling /March 2030	Arm 1: IV ketamine 0.5mg/kg x 8 Arm 2: ECT x 12	RCT phase 4 N=1500	Scale for Suicidal Ideation / depression score on MADRS
NCT06090422 Ketamine for Combined Depression and Alcohol Use Disorder	Norway	Not yet recruiting /July 2027	Arm 1: IV ketamine 0.8mg/kg x 4 Arm 2: IV midazolam 0.02mg/kg x 4	RCT phase 1-2 N=34	Depression score on MADRS
NCT06228391 Ketamine Treatment for PTSD and MDD in TBI	USA	Not yet recruiting /March 2027	Arm 1: IV ketamine 0.5mg/kg x 6 Arm 2: IV midazolam 0.045mg/kg x 6	RCT phase 2 N=40	Depression score on MADRS
NCT06231563 Ketamine for Veterans With Parkinson's Disease	USA	Not yet recruiting /June 2029	Arm 1: IV ketamine 0.5mg/kg Arm 2: IV remimazolam 0.25mg/kg	RCT phase 2 N=80	Depression score on MADRS
NCT06278779 Comparative Effectiveness Study of Two Forms of Ketamine for Treatment-resistant Depression	Australia	Recruiting /April 2027	Arm 1: intranasal esketamine x 8 + maintenance phases Arm 2: IV ketamine 0.5 mg/kg -1.5mg/kg x 8 + maintenance phases	RCT phase 4 N=162	Depression score on MADRS
NCT06355180 Esketamine Treatment for Depressive Episodes With Suicidal Ideation in Mood Disorders	China	Not yet recruiting /December 2026	Arm 1: IV esketamine 0.2 mg/kg x 6 Arm 2: Modified electroconvulsive therapy (MECT) x 6	RCT phase 4 N=340	Scale for Suicidal Ideation / depression score on MADRS

Study ID / Title	Country	Status / estimated end	Treatments	Study design/ Enrollment (n)	Main outcome
NCT06410599 Pharmacologic Treatment Augmentation in Chronic Depression	Germany	Not yet recruiting /July 2026	Arm 1: IV ketamine 0.5mg/kg x 6 + TAU Arm 2: IV saline x 6 + Cognitive Behavioral Analysis System of Psychotherapy (CBASP) Arm 3: IV ketamine 0.5mg/kg x 6 + CBASP	RCT phase 2 N=60	Depression score on MADRS
NCT06431386 Behavioural Activation Therapy and Esketamine for Resistant Depression	Canada	Recruiting /August 2026	Arm 1: Intranasal esketamine 56-84 mg x 8+ Behavioural Activation Therapy (BA) Arm 2: Intranasal esketamine 56-84 mg x 8	RCT N=40	Depression score on MADRS
NCT06480500 i-CBT and IV Ketamine for Suicidality in Treatment-Resistant Depression: A Randomized. Midazolam-Controlled Clinical Trial	Canada	Recruiting /July 2025	Arm 1: IV ketamine 0.5-0.85mg/kg x 6 + Internet-based Cognitive Behavioural Therapy (i-CBT) Arm 2: IV midazolam 0.02-0.035mg/kg x 6 + i-CBT	RCT phase 2 N=110	Suicidality severity on C-SSRS / depression score on MADRS
NL-OMON43144 A Randomized. Double-Blind. Placebo-Controlled. 2-Period. 2- Treatment Cross-Over Study to Evaluate the Effects of Ketamine on Resting State Functional Brain Connectivity in Major Depressive Disorder Patients who fail to respond to a Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin Noradrenaline Reuptake Inhibitor (SNRI)	Netherlands	Recruitment stopped	Arm 1: IV ketamine Arm 2: “Placebo”	RCT crossover N=	Changes in functional connectivity / depression score on MADRS

Appendix 10: Progress log

Progress log	Date/processing time
Proposal for topic sent / horizon scanning alert published on nyemetoder.no	06.01.2022
Commission given by the Ordering Forum in the national system	18.03.2024
Request for recruiting experts sent by NOMA	25.03.2024
Recruitment of experts completed	19.04.2024
Process of declaring confidentiality and impartiality	12.04.2024 - 14.05.2024
Start-up meeting with clinical experts and patient representative	14.06.2024
PICO determined = official start date (t=0)	28.06.2024
Project plan published	24.09.2024
New patient representative recruited	19.02.2025
Report draft sent to the external expert group	30.04.2025
Report draft sent to internal review/quality control	22.05.2025
Report draft sent for approval in DMP	05.06.2025
Report completed by NOMA	13.06.2025
Processing time at NOMA (days from t=0)	351 days
HTA sent to commissioner / received by the Secretariat for “Nye Metoder”	13.06.2025