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Research article

Rapid effects of ketamine and esketamine on suicidal ideation in acute psychiatric settings: A systematic review and meta-analysis

Running title: Ketamine and rapid reduction in suicidal ideation

Tariq H. Alotaibi[1], Mazhar Mushtaq[2], Abdulrahman Abdullah Altuwaim[3], Nawal Alammari[4,*], Fay Abdullah Almutairi[5], Saleh Ahmed Alzahrani[6,7], Ahmed Mohammed Alghamdi[8], Mariam Saleh M. Moshref[9], Mohammed Adel Alrehaili[10], Turki Falah M. Alrashidi[11], Nouf Mohammed Asiri[12] and Ahmed Y. Azzam[13]

[1] Majmaah University, College of Medicine, Department of Medical Specialties, Majmaah, Saudi Arabia
[2] Sulaiman Al Rajhi University, College of Medicine, Basic Medical Sciences, Al Qaseem, Saudi Arabia
[3] Majmaah University, College of Medicine, Majmaah, Saudi Arabia
[4] King Khalid University, College of Medicine, Abha, Saudi Arabia
[5] Riyadh Health Cluster, Department of Psychiatry, Riyadh, Saudi Arabia
[6] Imam Abdulrahman Bin Faisal University, Department of Psychiatry, Dammam, Saudi Arabia.
[7] King Fahad Hospital of the University, Department of Psychiatry, Al Khobar, Saudi Arabia.
[8] Umm Al Qura University, College of Medicine, Makkah, Saudi Arabia
[9] Taibah University, College of Medicine, Madinah, Saudi Arabia
[10] Jouf University, College of Medicine, Jouf, Saudi Arabia
[11] Qassim University, Unaizah College of Medicine, Al Qassem, Saudi Arabia
[12] King Faisal University, College of Medicine, Al-Ahsa, Saudi Arabia
[13] ASIDE Healthcare, Lewes, Delaware, USA

* **Correspondence:** Email: nawal9n@gmail.com; Tel: +966534860157.

Supplementary Table S1. Study-level eligibility for the primary quantitative synthesis of early suicidal ideation outcomes.

Study	Design/relevant comparison	Suicide-specific measure	Relevant timepoint	Eligible for ≤24 h primary synthesis	Included in Figure 2	Reason/analytic handling
Seraj 2025	Oral ketamine vs midazolam RCT	MSSI	4 h after single dose	Yes	Yes	Independent controlled trial with extractable continuous suicide-specific data at ≤24 h
Zhou 2024	Repeated IV esketamine vs midazolam RCT	C-SSRS	24 h after third infusion, Day 6	No	No	Relevant assessment followed repeated treatment rather than the predefined acute first-dose window
Hochschild 2022	Post-hoc analysis of Grunebaum 2018 RCT	SSI	24 h	Yes clinically	No	Same participant sample as Grunebaum 2018; retained for exploratory mood–SI analyses but not treated as an independent efficacy dataset
Gaither 2022	Single-arm IV ketamine feasibility study	C-SSRS	2 h and 6 h	Yes clinically	No	No concurrent comparator; unsuitable for treatment-versus-control standardized mean difference
Abbar 2022	IV ketamine vs saline RCT	SSI	40 min, 2 h, 4 h, 24 h	Yes clinically	No	Acute outcome reported primarily as remission/categorical or non-comparable summary statistics; continuous data required for harmonized Hedges' g were not extractable
Ionescu 2021	Intranasal esketamine + SOC vs placebo + SOC RCT	CGI-SS-r	24 h after first dose	Yes	Yes	Independent controlled trial with usable early comparative suicide-specific estimate
Domany 2022	Intranasal ketamine vs saline RCT	BSS / MADRS-SI	4 h	Yes	Yes	Independent controlled trial; 4-h continuous BSS change data were extractable
Pathak 2021	IV ketamine vs saline randomized study	MSSI	6 h after first infusion	Yes	Yes	Independent controlled study with extractable continuous data; extreme effect estimate retained in primary model and examined separately in sensitivity analyses
Canuso 2021	Pooled post-hoc ASPIRE I + II analysis	CGI-SS-r	4 h and 24 h	Yes clinically	No	Pooled secondary publication incorporating Fu 2020 and Ionescu 2021; excluded as an independent dataset to prevent double counting

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Study	Design/relevant comparison	Suicide-specific measure	Relevant timepoint	Eligible for ≤24 h primary synthesis	Included in Figure 2	Reason/analytic handling
Fu 2020	Intranasal esketamine + SOC vs placebo + SOC RCT	CGI-SS-r	24 h after first dose	Yes clinically	No	Suicide outcome reported using ranked/Hodges–Lehmann methods; continuous statistics required for harmonized Hedges' g were not available
Domany 2020	IV ketamine vs saline pilot RCT	BSS	90–180 min	Yes clinically	No	Acute effect reported, but continuous comparative means/SDs required for standardized effect-size estimation were not available from the accessible report
Grunebaum 2018	IV ketamine vs midazolam RCT	SSI	24 h	Yes	Yes	Independent controlled trial; parent trial used instead of overlapping Hochschild 2022 secondary analysis
Canuso 2018	Intranasal esketamine + SOC vs placebo + SOC RCT	MADRS suicidal-thought item / BSS	4 h / ~24 h	Yes	Yes	Independent controlled study with extractable early comparative suicide-specific effect
Burger 2016	IV ketamine vs saline pilot RCT	BSS	40–240 min	Yes clinically	No	Very small pilot; continuous comparative statistics required for harmonized Hedges' g were not sufficiently reported
Murrough 2015	IV ketamine vs midazolam RCT	BSI	24 h	Yes	Yes	Independent controlled trial with extractable early suicide-specific comparative effect

Note: BSI/BSS: Beck scale for suicide ideation; CGI-SS-r: Clinical global impression–severity of suicidality–revised; C-SSRS: Columbia–suicide severity rating scale; IV: intravenous; MSSI: Modified scale for suicidal ideation; SI: suicidal ideation; SOC: standard of care; SSI: Scale for suicidal ideation.

Supplementary Table S2. Risk of bias assessment.

Study	Random sequence	Allocation concealment	Participant blinding	Outcome assessor blinding	Incomplete outcome data	Selective reporting	Other bias	Overall risk	Comments
Seraj 2025	Low risk	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns	Randomized active-controlled trial of oral ketamine versus midazolam; active comparator supports blinding, although treatment-related effects could potentially affect masking.
Zhou 2024	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns	Randomized active-placebo-controlled adolescent inpatient trial; three infusions were administered over 5 days, with the primary outcome assessed after the final infusion.
Hochschild 2022	N/A	N/A	N/A	N/A	Low risk	Some concerns	Some concerns	Some concerns	Secondary/post-hoc analysis of the Grunebaum et al. randomized trial; not treated as an independent trial in the quantitative synthesis.
Gaither 2022	N/A	N/A	High risk	High risk	Some concerns	Low risk	High risk	High	Single-arm, open-label ED feasibility study with no randomized comparator; recruitment stopped early and the sample was small (N=14).
Abbar 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns	Low	Multicenter, double-blind, randomized placebo-controlled trial; limited missing outcome data and analyses based on the randomized population.
Ionescu 2021	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns	ASPIRE II randomized, double-blind, placebo-controlled phase 3 trial; potential functional unblinding from recognizable esketamine effects remains possible.
Domany 2022	Low risk	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns	Small double-blind randomized ED trial of intranasal ketamine versus saline; small sample size and potential functional unblinding warrant caution.

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Study	Random sequence	Allocation concealment	Participant blinding	Outcome assessor blinding	Incomplete outcome data	Selective reporting	Other bias	Overall risk	Comments
Pathak 2021	Some concerns	Some concerns	High risk	Some concerns	Low risk	Some concerns	High risk	High	Single-blind randomized saline-controlled trial; absence of an active comparator and limited methodological reporting raise concerns regarding blinding and other trial procedures.
Canuso 2021	N/A	N/A	N/A	N/A	Low risk	Some concerns	Some concerns	Some concerns	Pooled secondary analysis of ASPIRE I and ASPIRE II; not treated as an independent trial in quantitative synthesis.
Fu 2020	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns	ASPIRE I randomized, double-blind, placebo-controlled phase 3 trial; potential functional unblinding from treatment effects and industry sponsorship noted.
Domany 2020	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns	Small randomized, double-blind, saline-controlled proof-of-concept ED trial (N=18); small sample limits precision but does not itself constitute high risk of bias.
Grunebaum 2018	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Randomized midazolam-controlled trial; active comparator strengthened masking, although ketamine-related effects could potentially compromise participant blinding.
Canuso 2018	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns	Double-blind randomized placebo-controlled esketamine trial; potential functional unblinding and industry sponsorship noted.
Burger 2016	Some concerns	Some concerns	Low risk	Some concerns	High risk	Some concerns	High risk	High	Very small randomized double-blind placebo-controlled ED pilot; methodological difficulties substantially reduced analyzable data, with only 10 participants contributing to analysis.
Murrough 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns	Low	Small double-blind randomized active-control trial using midazolam; generally adequate methodology, although the sample was small.

Supplementary Table S3. Exploratory assessment of small-study effects and publication bias.

Assessment	Studies (k)	Result	Interpretation
Egger's regression	7	$t = -2.25$, $P = 0.074$	No statistically significant evidence of small-study effects; however, the test has low power with fewer than 10 studies.
Begg's rank correlation	7	Kendall's $\tau = -0.20$, $P = 0.543$	No statistically significant rank correlation was detected; absence of significance does not exclude publication bias.

Note: We considered assessment of small-study effects and publication bias exploratory because only seven independent studies contributed to the primary ≤24-hour quantitative synthesis and between-study heterogeneity was substantial.

Supplementary Table S4. Sensitivity analyses of the primary ≤24-hour suicide-specific outcome.

Analysis	Studies (k)	Suicide effect, Hedges' g (95% CI)	I^2	Interpretation/Handling
Primary analysis (REML + Hartung–Knapp)	7	−1.24 (−2.87, 0.39)	93.3%	Primary estimate was imprecise and highly heterogeneous.
Exclude industry-funded studies	5	−1.64 (−4.15, 0.87)	93.6%	Exclusion did not reduce heterogeneity and produced a highly imprecise estimate; no clear evidence that funding source explains the primary result.
Exclude study at high overall risk of bias (Pathak et al. 2021)	6	−0.59 (−1.00, −0.19)	71.6%	Exclusion reduced the effect magnitude and heterogeneity, although substantial residual heterogeneity remained.
Restrict to larger studies ($N \geq 50$)	5	−1.52 (−4.12, 1.07)	95.5%	Restriction to larger studies did not improve consistency or precision; substantial heterogeneity persisted.
Fixed-effect model	7	−0.60 (−0.77, −0.42)	93.3%	The fixed-effect estimate was smaller and more precise; however, the model is inappropriate as the primary analysis given substantial clinical and statistical heterogeneity.

Note: CI: confidence interval; I^2: I-squared heterogeneity statistic; REML: restricted maximum likelihood.

Supplementary Table S5. GRADE evidence assessment.

Outcome domain	k	N	Effect (95% CI)	I^2	Key GRADE concerns	Certainty	Clinical interpretation
Suicidal ideation reduction ≤24 h	7	567	Hedges' *g* = −1.24 (−2.87, 0.39)	93.3 %	Serious inconsistency and imprecision	Low	Ketamine/esketamine may produce rapid symptomatic reduction in suicidal ideation, but the magnitude and consistency of benefit remain uncertain.
Sensitivity: excluding Pathak et al. (2021; high overall risk of bias)	6	507	Hedges' *g* = −0.59 (−1.00, −0.19)	71.6 %	Residual inconsistency; sensitivity analysis rather than a separate outcome	Not separately graded	Exclusion of the influential study produced a more moderate estimate, although substantial heterogeneity remained.
Serious adverse events	6	808	RR = 1.22 (0.60, 2.49)	0%	Serious imprecision because of few events and wide CI	Low	No statistically significant difference in serious adverse events was detected; however, clinically important harm cannot be excluded.
Relationship between suicidal ideation and depressive-symptom improvement	Narrative	—	Exploratory	—	Indirectness, heterogeneous analyses, and limited evidence	Very low	Findings suggest that suicidal-ideation improvement may not be fully explained by improvement in depressive symptoms, but mechanistic independence is not established.

Note: GRADE: grading of recommendations assessment, development and evaluation; CI: confidence interval; RR: risk ratio. Negative Hedges' *g* values favor ketamine/esketamine. Certainty ratings reflect risk of bias, inconsistency, indirectness, imprecision, and publication bias. The Pathak et al. sensitivity analysis was not graded separately because it represents a sensitivity analysis of the primary outcome rather than an independent outcome.

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