# INPLASY

## Suicidal Ideation in Treatment-Resistant Depression: A Meta-Analysis of Pooled Severity Estimates and Clinical Heterogeneity

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## INTRODUCTION

*R*eview question / Objective We conducted a meta-analysis to establish reference severity benchmarks of SI in patients with TRD using two widely employed assessment tools: MADRS item 10 and the C-SSRS. By quantifying both the central tendency and the variability of SI severity in TRD populations, this study aims to provide clinically interpretable benchmark estimates to inform and facilitate cross-study comparisons and contextualize the severity of suicidality in future clinical trials and observational research. We hypothesized that SI would be frequently reported at a clinically meaningful level of severity across studies, reflecting its ubiquity in treatment-resistant illness.

Given the recognized heterogeneity of TRD populations, we also anticipated substantial between-study variability, reflecting differences in patient characteristics and study methodologies. Finally, sensitivity analyses were undertaken to evaluate the robustness of pooled estimates and to explore the potential influence of small-study effects. By quantifying both the central tendency and the variability of SI severity in TRD, this study aims to provide a clinically meaningful frame of reference while highlighting the complexity and heterogeneity of suicidality in TRD. A clearer characterization of this dimension may ultimately support improved patient stratification and more targeted therapeutic approaches in future research and clinical practice.

**Condition being studied** Treatment resistant depression and suicidal ideation.

## METHODS

**Participant or population** Psychiatric patients with treatment resistant depression.

**Intervention** Evaluation of suicidal ideation in TRD patients.

**Comparator** No comparator.

**Study designs to be included** RCT for the metaanalysis, metaanalysi, open label, pooled analysis for the revision part.

**Eligibility criteria** Both randomized controlled trials and observational studies (including open-label, naturalistic, retrospective, or case–control designs) were considered, provided that baseline data allowed characterization of SI severity in individuals with TRD. This inclusive approach was adopted because the primary objective of the meta-analysis was to characterize SI severity in the TRD population at study entry, rather than to evaluate treatment efficacy. Studies were excluded if they did not clearly document treatment resistance, lacked baseline assessment of SI, included mixed diagnostic samples without extractable TRD-specific data, or assessed suicidal only as an outcome without reporting baseline severity.

**Information sources** A systematic literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science and PsycINFO to identify relevant titles and abstracts published between January 2015 and December 2025. The following search strategy was used in PubMed and adapted for the other databases: "treatment-resistant depression" "TRD" OR "resistant depression" OR "treatment refractory depression" AND ("suicide" OR "suicid*" OR "mortality" OR "suicidal ideation" OR "suicidal attempt").

**Main outcome(s)** Suicidal ideation evaluated with C-SSRS and MADRS item 10.

**Quality assessment / Risk of bias analysis** We managed screening, data extraction, and risk-of-bias assessment in Covidence (Veritas Health Innovation, Melbourne, Australia). All search results were exported to Covidence (Veritas Health Innovation, Melbourne, Australia) for record management. Covidence automatically removed duplicates prior to screening. Two reviewers (IB, AVM) independently screened titles/abstracts and then full texts against pre-specified eligibility criteria within Covidence; conflicts were resolved by consensus or, when necessary, a third reviewer. Furthermore, the assessment of inter-rater reliability yielded an overall Cohen's kappa coefficient of 0.92, reflecting an almost perfect level of agreement between the two independent reviewers across all domains. When multiple treatment arms were reported, baseline data were pooled to avoid double counting. When standard deviations were not reported, they were calculated from standard errors, confidence intervals, or interquartile ranges when possible. Publication bias was evaluated using funnel plots and Egger's regression test. Baseline was defined as the assessment closest to treatment initiation.

**Strategy of data synthesis** Two meta-analyses were conducted to estimate the pooled mean values of the MADRS item 10 score and the C-SSRS score in patients with TRD and SI. Publication bias was evaluated by visual inspection of funnel plots and formally tested using Egger's regression test, while between-study heterogeneity was evaluated using Cochran's Q test and quantified with the $I^2$ statistic. Pooled estimates and corresponding 95% confidence intervals were calculated using a random-effects model. In all the aforementioned analyses, an alpha significance level of 0.05 was used. Statistical analyses and graphical outputs (forest plots and funnel plots) were performed using R version 4.5.2.

Although both MADRS item 10 and the C-SSRS ideation severity scale are ordinal measures, pooling mean values is a common approach in psychiatric meta-analyses when the scales contain multiple ordered categories and are routinely treated as approximately continuous in clinical research. This approach allows estimation of average severity levels across studies while maintaining comparability with existing literature.

**Subgroup analysis** Two subgroups analysis based on C-SSRS and Madras scores.

**Sensitivity analysis** The assessment of inter-rater reliability yielded an overall Cohen's kappa coefficient of 0.92, reflecting an almost perfect level of agreement between the two independent reviewers across all domains.

**Country(ies) involved** Italy.

**Keywords** TRD, suicidal ideation, MADRS, C-SSRS.

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