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| **Unique ID** | a.1 | **Study ID** | Ren et al., 2024 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV esketamine (0.25mg/kg) plus propofol | **Comparator** | IV saline plus propofol | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Remission of suicidal ideation | **Results** | | **Weight** | 1 |

| Domain | Signalling question | Response | Comments |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | Eligible patients randomly assigned to either experimental or control group using a computer-generated random number sequence. Both patients and physicians were unaware of group assignment. |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | N | Comparable age between participants. No significant differences in sex. Other baseline characteristics (antidepressant medication, HAM-24, BPRS and MoCA scores before ECT) were similar. |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | Double blind study |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | Y | All analyses were conducted based on intention-to-treat (ITT) sample that comprised all randomized subjects. |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | To achieve a statistical power of 80% at a sig. level,103 subjects were needed in each group. Final sample size was 114 in each group. 6 dropped out from the experimental group, leaving 108 subjects. 12 dropped out from control group, leaving 102 subjects. Mean data was available for outcomes. |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | Concerns regarding the validity and persuasiveness of results on SI. SI was only assessed using the suicidal item on the HAMD and not confirmed by other instruments, like the C-SSRS. |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | Both groups were similarly assessed for SI |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | N | Subject and experimenter were both blinded and unaware of the group assignments and the specific anesthetics regimen.The Anesthesiologists and psychiatrists involved in ECT were not involved in the follow-up surveys. |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | Y | Power analysis was completed based on pilot study data prior to the initation of the current study |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | N | See description for 4.1 |
| | 5.3 ... multiple eligible analyses of the data? | PN | Outcomes analyzed by kaplan-meier curve and compared using the log-rank test. Generalized linear mixed model estimated in repeated measures analysis used for assessing trend changes over time in mean difference. |
| | **Risk of bias judgement** | **Low** | |
| **Overall bias** | **Risk of bias judgement** | **Low** | |

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| **Unique ID** | a.2 | **Study ID** | Fineberg et al., 2023 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV ketamine (0.5mg/kg) | **Comparator** | IV midazolam (0.4mg/kg) | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| Domain | Signalling question | Response | Comments |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | Participants randomized by Yale Investigational Drug Service (IDS); randomization done at a 1:1 ketamine to midazolam ratio, with fixed block size. Clinical staff and pts blinded. |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |

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| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | N | No sig. group differences in gender, age, race, education, or baseline clinical variables |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | See 1.1 description |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | NI | Exploratory assignment used; Unclear if study was a protocol analysis or an intention-to-treat analysis. |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | N | All data was available for 12 control and 10 experimental subjects. Some data was missing at various timepoints at each of the clinical scales (Day 1 - one midazolam pt; Day 3 - two midazolam participants). For BAI, data missing from one additional midazolam pt at day 3. For SAS-SR, data from one additional midazolam participant at Day 14 |
| | **Risk of bias judgement** | **Some concerns** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | Y | See 2.7 description |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | N | for suicidal ideation, the Beck Scale for Suicidal Ideation was appropriately used |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | Both groups have the same measurment of ascertainment at the same time intervals |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | N | clinical raters were blinded to infusion medication and to intra-infusion experience |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | PN | As an exploratory analysis, it is unclear if the statistical plan outlined was before or after outcome data |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | N | Only BSS score used to measure outcome |
| | 5.3 ... multiple eligible analyses of the data? | N | Only used change in BSS score |
| | **Risk of bias judgement** | **Some concerns** | |
| **Overall bias** | **Risk of bias judgement** | **Some concerns** | |

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| **Unique ID** | a.3 | **Study ID** | Su et al., 2023 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV Ketamine (0.5mg/kg) | **Comparator** | IV Midazolam (0.045mg/kg) | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| Domain | Signalling question | Response | Comments |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | PY | randomized double blind controlled trial; does not state how the participants were randomized |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | N | The baseline scores and psychiatri comorbidities of all outcomes did not differ between groups |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | NI | No relevant information provided |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | PN | No relevant information on whether participants dropped out after randomization.All figures and tables indicate that all 84 participants were involved in the analysis post-randomization |
| | **Risk of bias judgement** | **Some concerns** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | Y | Number of remissions of SI based on total CSSRS-ISS score and MADRS score |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |

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| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | Both the MADRS and the CSSRS-ISS are appropiate outcome measures. The limitations section does not list these two as lacking validity or being vulnerable to intervention effects |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | PN | Same measurement thresholds and methods were used for the both groups. |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | PN | The study is double-blind.However, there is no further information on whether the outcome assessor was present during the intervention. |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | NI | No mention of a statistical analysis plan. |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | PN | Remission of SI was examined by looking at CSSRS. Overall SI was examined by looking at the MADRS. While they both are looking at SI, they are different outcomes.All measurements follow the same time points, regardless of randomization group |
| | 5.3 ... multiple eligible analyses of the data? | N | |
| | **Risk of bias judgement** | **Some concerns** | |
| **Overall bias** | **Risk of bias judgement** | **Some concerns** | |

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| **Unique ID** | a.4 | **Study ID** | Ahmed et al., 2023 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV ketamine (0.5mg/kg in 50mL salinee) | **Comparator** | IV saline (50mL) | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | double-blind randomized via the Sequentially Numbered, Opaque, Sealed Envelope technique |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | PN | no significant differences in the demographic information of the groups.Duration of illness was slightly longer in the placebo group than the ketamine group. There was also no significant difference between groups in other clinical variables and ECT history. The difference in duration of illness is likely not related to a problem with the randomization process. |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | All infusions were overseen by a research physician (trained anesthesiologist or psychiatrist). Article and trial protocol does not provide information on whether carers and/or people delivering intervention aware of assigned intervention. |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | PY | No dropouts which may indicate an intention-to-treat analysis where all participants that were randomized were analyzed |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | No missing data; see 2.6 description |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | The SPS is a pre-specified outcome measure |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | PN | The SPS was used in both groups and at comparable time points |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | NI | See 2.1 description; only pharmacy was aware of the intervention received. However, the article does not indicate who the assessor was and whether they were present during the infusion |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | PN | It is unlikely that the research psychiatrist and/or the anesthesiologist (that were present during the intervention) were administering the SPS |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | PY | EPI info statistical package version 7 was used to determine the sample size. 17 samples were required for each arm. Additional statistical analysis plans are provided but it is unclear if this was completed before data was unblinded. |

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| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | N | |
| | 5.3 ... multiple eligible analyses of the data? | N | One possible way the outcome can be measured (SPS) |
| | **Risk of bias judgement** | **Low** | |
| **Overall bias** | **Risk of bias judgement** | **Low** | |

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| **Unique ID** | a.5 | **Study ID** | Zhou et al., 2023 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV esketamine (0.25mg/kg) | **Comparator** | IV midazolam (0.02mg/kg) | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | randomized controlled trial; double blind |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | PN | Tx group were similar with respect to their demographic and baseline clinical characteristics |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | double blind via a computer-generated randomization scheme, and assigned the participants to interventions but did not participate in participant enrollment or assessment scale |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | PY | Out of 54 randomized, 5 pts were lost to follow-up and another 5 refuse to complete assessments at some point post-randomization. Implies an intention-to-treat analysis. |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | Y | |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | Power analysis estimate was determined before the initiation of the study. Statistical analysis was most likely pre-specified. |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | Both groups use the same measurement of the outcome using C-SSRS Ideation and Intensity, MADRS and SSI-5 |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | N | Outcome assessors are not aware of the intervention |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | PY | See 4.1 description |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | PN | Multiple measurements are made; however, all subsets are fully reported. |
| | 5.3 ... multiple eligible analyses of the data? | PN | All eligible reported results for the outcome measurement correspond to all intended analyses. |
| | **Risk of bias judgement** | **Low** | |
| **Overall bias** | **Risk of bias judgement** | **Low** | |

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| **Unique ID** | a.6 | **Study ID** | Abbar et al., 2022 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV ketamine (0.5mg/kg) | **Comparator** | IV saline | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Remission of suicidal ideation | **Results** | | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | RCT; blocks of random size stratified by centre and by diagnostic category. Participants were assigned a unique identification code. |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | PN | Table 1 indicates that baseline characteristics (demographics and clinical charcacteristics) are not significant. |
| | **Risk of bias judgement** | **Low** | |
| | 2.1.Were participants aware of their assigned intervention during the trial? | N | Double-blind |

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| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | Double-blind |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| **Bias due to deviations from intended interventions** | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | Y | Intention-to-treat population, which indicated an appropriate analysis |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | 17/83 participants assigned to placebo discontinued treatment. 13/73 participants assigned to ketamine discontinued treatment |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | N | |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | N | Only the nurse prepared the infusion and was aware of the randomization result. The nurse was not involved in other parts of the study. |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | PY | Statistical analysis plan present, indicating that it was finalized before unblinded outcome data were available |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | PN | SI remission was determined by looking at SSI. Change in SSI and rates of suicidal attempts (CSSRS) were examined as a secondary outcom; all eligible reported results for the outcome domain correspond to all intended outcome measurements |
| | 5.3 ... multiple eligible analyses of the data? | PN | The authors provides all relevant primary and secondary outcomes. |
| | **Risk of bias judgement** | **Low** | |
| **Overall bias** | **Risk of bias judgement** | **Low** | |

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| **Unique ID** | a.7 | **Study ID** | Ionescu et al., 2022 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV ketamine (0.5mg/kg) | **Comparator** | IV saline | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal Ideation | **Results** | | **Weight** | 1 |

| Domain | Signalling question | Response | Comments |
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| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | randomly permuted blocks (4 patients per block) and stratified by study site and standard of care antidepressant type |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | PN | Tx groups were similar based on demographics, baseline clinical ratings, psychiatric hx, and standard-of care antidepressant use. It is likely that baseline differences did not suggest a problem. |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | Double blind |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | Y | The analysis included all patients who completed the double blind tx and either entered the followup phase or had adverse events evaulated after the double blind trx phase |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | Y | |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| | 4.1 Was the method of measuring the outcome inappropriate? | PN | pre-specified outcome; likely appropriate |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | Both groups have the same ascertainment method |

| | | | |
|---|---|---|---|
| **Bias in measurement of the outcome** | 4.3 Were outcome assessors aware of the intervention received by study participants? | PN | Outcome assessors unaware; raters for efficacy assessments different from raters for safety assessments. Efficacy raters were not allowed to provide patient care |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | PY | Statistical methods section implies that the methods were created before study initiation |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | PN | CGI-SS-r, CGGI-SS-I, MADRS suicidal thoughts, clinician-reported FoST, and patient-reported FoST were reported. Thus, there is evidence that all eligible reported results orrespond to intended outcome measurements. |
| | 5.3 ... multiple eligible analyses of the data? | PN | all eligible reported results for the outcome measurement correspond to all intended analyses |
| | **Risk of bias judgement** | **Low** | |
| **Overall bias** | **Risk of bias judgement** | **Low** | |

| | | | | | |
|---|---|---|---|---|---|
| **Unique ID** | a.8 | **Study ID** | Domany et al., 2022 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | Intranasal ketamine (100mg/ml 20mg) | **Comparator** | Intranasal saline | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | randomized (1:1), Double-blind |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | PN | There was no differences between groups at baseline in any of the demographic or assessment scales, indicating that there were no baseline differences that may have suggested a problem with the randomization process |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | The research psychiatrist applied the drug to patients and was unaware. |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | PY | An appropriate analysis was used; The paper does not exclude any participants throughout the study post-randomization |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | Y | Baseline measures and outcome measures provided (mean values) |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | Most scales to examine the outcome are valid. However, one scale (BSS) which looks at change in SI, is noted to have some limitations. Most notably, it conflates trait and state factors. |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | Both groups have the same measurement or ascetainment of the outcome |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | PN | The pharmacist was the only non-blinded member. The author provides no information on whether the assessor was present during the intervention.Hence, it is unclear if this may have impacted outcome measurements. |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Some concerns** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | Y | The analysis intentions preceded the availability of the outcome data. |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | PN | Both the BSS and MADRS-SI results are available; all eligible reported results for the outcome domain correspond to all intended outcome measurements |
| | 5.3 ... multiple eligible analyses of the data? | PN | All eligible reported results for the outcome measurements correspond to all intended analyses |
| | **Risk of bias judgement** | **Low** | |
| **Overall bias** | **Risk of bias judgement** | **Some concerns** | |

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|---|---|---|---|---|---|
| **Unique ID** | a.9 | **Study ID** | Vieira et al., 2021 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV esketamine (0.25mg/kg) | **Comparator** | IV ketamine (0.5mg/kg) | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | PN | The article states that the clinical baseline characteristics were considered "well-balanced" |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | All randomized individuals completed study. No dropouts post-randomization |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | NI | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | PN | No deviations noted suggesting that deviations were not present |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | Y | All randomized individuals completed study. No dropouts post-randomization |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | MADRS item 10 are used to measure SI. The limitations section does not note the MADRS to be having low validity. |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | All participants underwent the same post-randomization measurements of the outcome. |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | PN | Outcome assessors were unaware due to this being a double-blind study. However, it is unclear whether the assessors were present during the infusion. |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Some concerns** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | PN | Statistical analysis plan was presented in the supplementary material. Most of the plan was likely finalized before unblinded outcome data were available. However, it is noted that a post-hoc Dunn test was used to obtain pairwise comparisons, indicating that this test was determined after unblinded outcome data was available. |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | N | One outcome measure |
| | 5.3 ... multiple eligible analyses of the data? | PY | Dunn's posthoc analysis completed; chi-square/fischer's exact test were used to compare categorical variables; Student's t-tests were used to examine continuous variables |
| | **Risk of bias judgement** | **Some concerns** | |
| **Overall bias** | **Risk of bias judgement** | **Some concerns** | |

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|---|---|---|---|---|---|
| **Unique ID** | a.10 | **Study ID** | Kheirabadi et al., 2020 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IM racemic R-ketamine (0.5mg/kg) | **Comparator** | Oral R-ketamine (1mg/kg) or ECT (6-9 sessions) | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | Patients randomly allocated to 3 arms via a block randomization method by a nurse who had no further role in the study. Impossibility of blinding to the type of intervention. |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | PN | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | N | No significant difference between the 3 groups regarding age and sex. No difference in BSSI and HDRS baseline scores |
| | **Risk of bias judgement** | **Some concerns** | |
| | 2.1.Were participants aware of their assigned intervention during the trial? | PY | See 1.1 description |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | PY | |

| | | | |
|---|---|---|---|
| **Bias due to deviations from intended interventions** | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NI | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | PY | |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Some concerns** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | ANOVA tests were used on collected data. 1-way ANOVA was used on quantitative data. Both of these tests were pre-specified. The Tukey test for post-hoc analysis indicates that it was planned after. While this may not necessarily qualify as "inappropriate," it may be relevant. According to a.8, BSS may have some limitations but does not say that the measure lacks validity |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | All participants, regardless of randomization, underwent the same measurements |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | PY | The article claims that only the nurse gave the intervention to participants. However, the participants would be aware of their intervention. It is unclear if the assessors were present during administration of intervention. |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NI | At this point, there is much literature on the effects of ketamine in reducing SI and depression. If a patient or assessor was aware that they received ketamine, it may have impacted ratings. |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | PY | |
| | **Risk of bias judgement** | **High** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | PN | See 4.1 description |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | PN | Mean + SD, ANOVA; 1-way ANOVA for quantitative data; Tukey test for posthoc analysis; Kruskal-Wallis test; all stated analysis plans were completed. |
| | 5.3 ... multiple eligible analyses of the data? | PY | |
| | **Risk of bias judgement** | **Some concerns** | |
| **Overall bias** | **Risk of bias judgement** | **High** | |

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|---|---|---|---|---|---|
| **Unique ID** | a.11 | **Study ID** | Fu et al., 2023 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | Intrnasal esketamine (84mg) | **Comparator** | Intranasal placebo | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| Domain | Signalling question | Response | Comments |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | Eligible subjects randomized (1:1) based on a computer-generated randomization schedule. Randomization balanced using randomly permuted blocks and stratified by study center and type of standard of care antidepressant |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | PY | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | PN | No significant differences between intervention groups at baseline (Table 1) |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | Patients self-administered the drug, under the supervision of a site staff member 2x weekly for 4 weeks. |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | PN | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | PY | proof-of-concepts trial; all randomized patients who received at least one dose of the intervention was included in the safety analysis set. Full efficacy analysis included all patients in the safety analysis set who had bot a baseline and greater or equal to 1 postbaseline evaluation with the MADRS or CGI-SS-r. Follow-up analysis set included all pts who completed trx phase and either entered the follow-up phase or provided adverse event data after the double blind trx phase. |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | 164/192 completed the day 90 follow-up |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |

| | | | |
|---|---|---|---|
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | no limitations noted re measure of outcome (sibat) |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | PN | Outcome assessors were NOT aware of the intervention. However, it is unclear if the assessors were physically present during the treatment of either group medication. |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Some concerns** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | PY | prespecified subgroup analyses conducted according to an ANCOVA model.See 2.6 description for more details. |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | N | One measure used (SIBAT) which includes assessments, both clinician- and patient-reported modules (CGI-SS-r, CGI-SR-I, and FoST) |
| | 5.3 ... multiple eligible analyses of the data? | PN | All reported results for the outcome measurement correspond to all intended analyses |
| | **Risk of bias judgement** | **Low** | |
| **Overall bias** | **Risk of bias judgement** | **Low** | |

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|---|---|---|---|---|---|
| **Unique ID** | a.12 | **Study ID** | Lin et al., 2023 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV ketamine (0.5mg/kg) | **Comparator** | IV Saline or midazolam (0.045mg/kg) | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | Both original studies of this posthoc analysis was a randomized controlled trial |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | PY | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | N | Table 1 shows that baseline demographic characteristics and clinical data between groups is not significant, siggesting that there is no problem with the randomization process. |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | PN | In one of the studies (Li et al., 2016), an independent research nurse was the only person who was aware of the random allocation.The nurse was not allowed to share this information with the research team (including the nurse that applied the IV infusion. The other study (Su et al., 2017) did not provide additional information regarding the randomization process |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | PN | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | PY | intention to treat; all study participants included in study were used in analysis; no dropouts |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | 17-item HDRS item 3; MADRS item 10 - study 1 and 2CSSRS-ISS - study 2 |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | PY | See 4.1 description. This post hoc analysis includes the results from 2 studies. The two studies do not have the same method of measuring the outcome |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | NA | |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **High** | |
| | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | N | Since this is a post-hoc analysis, the statistics plan is not pre-specified. |

| | | | |
|---|---|---|---|
| **Bias in selection of the reported result** | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | PN | While there are multiple outcome measures, the authors present all results, regardless of significance.All eligible reported results for the outcome domain correspond to all intended outcome measurements |
| | 5.3 ... multiple eligible analyses of the data? | PN | |
| | **Risk of bias judgement** | **Some concerns** | |
| **Overall bias** | **Risk of bias judgement** | **Some concerns** | |

| | | | | | |
|---|---|---|---|---|---|
| **Unique ID** | a.13 | **Study ID** | Canuso et al., 2021 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | Intranasal esketamine (84mg) | **Comparator** | Intranasal placebo | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | Randomized (1:1), double-blind |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | N | No significant difference in baseline demographics, clinical rating, and psychiatric history |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | PN | different raters were used to conduct efficacy and safety assessments |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | PN | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | PY | The safety analysis data set included all randomized patients who received at least 1 dose of study drug; the efficacy analysis data set included all patients in the safety analysis data set who had baseline and at least 1 postbaseline evaluation for the MADRS or CGI-SS-r. The follow-up analysis included all pts who completed the double blind tx phase and either entered folowup or provided adverse event data after the double blind tx phase. |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | 5 pts excluded; most randomized patients (esketamine: 192/229; placebo: 187/227) completed 4-week double blind tx |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | N | SIBAT is an appropriate measure of SI |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | N | Both groups underwent the same measurement of outcome |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | PN | According to the article, functional unblinding was avoided by having different raters conduct efficacy and safety assessments. It is unclear which group of ratings were present during the study intervention. |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | N | Posthoc analyses were completed on pooled data from ASPIRE I and ASPIRE II trials |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | N | One outcome measure (SIBAT) which consists of various measures as outlined in the article (CGI-SS-r, CGI-SS-I, clinician- and self- reported FoST) |
| | 5.3 ... multiple eligible analyses of the data? | PN | Same as Fu et al. |
| | **Risk of bias judgement** | **Some concerns** | |
| **Overall bias** | **Risk of bias judgement** | **Low** | |

| | | | | | |
|---|---|---|---|---|---|
| **Unique ID** | a.14 | **Study ID** | Feeney et al., 2021 | **Assessor** | SS; reviewed by MG |
| **Ref or Label** | | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV ketamine (0.1,0.5,1mg/kg doses) | **Comparator** | IV midazolam | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Suicidal ideation | **Results** | | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| | 1.1 Was the allocation sequence random? | Y | randomized double blind |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |

| | | | |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | NI | baseline values not provided; it is unclear if there were baseline differences in clinical/demographics |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | double-blind randomized |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | PY | Yes; the post-hoc analysis includes any individuals from the original study that had a significant baseline SI score |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias due to missing outcome data** | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | Article notes that the study had a high rate of participant retention out to 30 days post-infusion |
| | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | Only the MADRS suicide item is used. While this measure is appropriate, the analysis is relatively limited due to one method of ascertainment. |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | PN | Both groups have the same procedure and follow the same measures at the same timepoints |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | N | article notes "remote raters" to maintain blinding |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | PN | As a post-hoc analysis, this data was produced after unblinded outcome data were available |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | N | One outcome measure (MADRS suicide item) |
| | 5.3 ... multiple eligible analyses of the data? | N | |
| | **Risk of bias judgement** | **Some concerns** | |
| **Overall bias** | **Risk of bias judgement** | **Low** | |

| | | | | | |
|---|---|---|---|---|---|
| **Unique ID** | a.15 | **Study ID** | | **Assessor** | SS |
| **Ref or Label** | Leal et al., 2023 | **Aim** | assignment to intervention (the 'intention-to-treat' effect) | | |
| **Experimental** | IV arketamine (0.5mg/kg) | **Comparator** | IV saline | **Source** | Journal article(s); Trial protocol |
| **Outcome** | Depression | **Results** | | **Weight** | 1 |

| **Domain** | **Signalling question** | **Response** | **Comments** |
|---|---|---|---|
| **Bias arising from the randomization process** | 1.1 Was the allocation sequence random? | Y | Yes; the participants were randomly assigned using a list of random numbers. It is important to note that all participants eventually received both interventions. |
| | 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? | Y | |
| | 1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? | NI | There is no analysis or discussion of the differences among baseline characteristics. It is unclear if any baseline differences suggest a problem with the randomization process. |
| | **Risk of bias judgement** | **Some concerns** | |
| **Bias due to deviations from intended interventions** | 2.1.Were participants aware of their assigned intervention during the trial? | N | This was a double-blind study. The investigator and the participants were blinded. The same investigator that was reponsible for determining which intervention group each participant received (via the random number selection) was not involved in the clinical follow-up evaluations throughout the study |
| | 2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | N | |
| | 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context? | NA | |
| | 2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome? | NA | |
| | 2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups? | NA | |
| | 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? | Y | The researchers utilized appropriate and well-established statistical techniques (Linear-Mixed Effects Models, post-hoc tests, and significance thresholds) in order to examine and estimate the effect of the intervention. |
| | 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized? | NA | |
| | **Risk of bias judgement** | **Low** | |
| | 3.1 Were data for this outcome available for all, or nearly all, participants randomized? | PY | 13 individuals were assessed for eligibility. 3 participants were excluded for not meeting the inclusion criteria.The remaining 10 participants were all analyzed, with no dropouts. |

| | | | |
|---|---|---|---|
| **Bias due to missing outcome data** | 3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data? | NA | |
| | 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? | NA | |
| | 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in measurement of the outcome** | 4.1 Was the method of measuring the outcome inappropriate? | PN | Using validated tools like the MADRS as a measurement for depression is appropriate.The CGI-S (Clinical Global Impression - Severity) and CGI-I (Clinical Global Impression - Improvement) is a validated scale for the secondary measure of efficacy. The MADRS was measured at various timepoints, allowing for a comprehensive assessment of changes in depression severity.The authors provide a specific definition for "response" and "remission," providing a objective and clinically way to measure improvements. Lastly, the study assesses side effects like dissociation using the CADSS, pulse oximetry, and blood pressure for safety purposes. |
| | 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups? | PN | It does not appear that the measurment of the outcome differed between the intervention groups. There is consistency and effort to maintain the blindness. |
| | 4.3 Were outcome assessors aware of the intervention received by study participants? | PN | See 2.1 description |
| | 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? | NA | |
| | 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received? | NA | |
| | **Risk of bias judgement** | **Low** | |
| **Bias in selection of the reported result** | 5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? | NI | It is unclear if a specific analysis plan was finalized before unblinded outome data were available. This is an exploratory study, which suggests flexibility in the analysis approach. Furthermore, the use of a linear mixed effects model, specific outcome measures, and safety assessments suggests that the authors may have had a clear statistical approach in mind. The usage of post hoc paiwise analyses with Tukey's correction suggests that although the overall analysis may haave been pre-specified, the authors may have performed additional comparisons after observing the data. |
| | 5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? | PN | The study utilized the MADRS to measure depression measures and timepoints.The CGI-S and CGI-I was used to examine efficacy. The CADSS measures dissociative symptoms. All measures were reported. |
| | 5.3 ... multiple eligible analyses of the data? | NI | The article does not provide sufficent information on whether multiple eligible. There is no evidence of multiple versions of analysis of the same outcome. |
| | **Risk of bias judgement** | **Some concerns** | |
| **Overall bias** | **Risk of bias judgement** | **Some concerns** | |