Jundishapur Journal of Natural Pharmaceutical Products
Volume 20 · Issue 4 · e167514

OPEN PEER REVIEW

Examining the Effects of Mirtazapine in Reducing Dependence and Craving for Amphetamine and Methamphetamine: A Clinical Study in Addiction Treatment Patients

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SUBMITTED	REVISED	ACCEPTED	DOI
24 Oct 2025	1 Nov 2025	1 Nov 2025	10.5812/jjnpp-167514

About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

4 comments · 25 Oct 2025 – 26 Oct 2025

Referee 1 Reviewer

ACCEPT 25 Oct 2025

This article is the best study and is recommended for publication in JJNPP. The manuscript's English has been corrected, and it presents a novel study of psychiatric diagnoses.

Referee 2 Reviewer

MINOR REVISION 26 Oct 2025

1. The Methods section mentions 84 participants, but the Results section reports 200 participants (110 men, 90 women). Clarify whether 200 is from a preliminary survey or mistakenly inserted. This inconsistency undermines the statistical conclusions.
2. Both generalized estimating equations (GEE) and repeated measures ANOVA are mentioned, but it's unclear which method produced the main reported p-values. Specify the main analysis model, its justification, and which tests were used for craving and depression outcomes.
3. Some reported p-values are near 0.05 but interpreted as "significant" (e.g., Table 5: p=0.05, borderline). Rephrase borderline results cautiously and indicate whether adjustments for multiple comparisons were applied.
4. Lack of Clinical Trial Registration Information.
5. The Results include education, marital status, and job satisfaction that seem unrelated to the main trial cohort (84 patients). Remove or clearly separate these descriptive data if they come from a different dataset.
6. No data on medication adherence, dropout rate, or protocol deviations are presented. Include adherence rates and reasons for discontinuation.
7. References #15 and #388–389 cite the same article by Kay-Lambkin et al. (2011). Merge duplicates and verify citation numbering.
8. Tables 1–7 lack uniform alignment and spacing. Some headers (e.g., "Gender Female 90 45") merge columns. Reformat all tables per the journal template, ensuring each has numbered titles and captions below the table.
9. Keywords exceed typical journal limits (8+ listed). Limit to 5–6 concise, relevant terms: Mirtazapine, Methamphetamine, Craving, Depression, Clinical Trial.
10. Reference formatting is inconsistent (APA vs. Vancouver). Follow the Jundishapur Journal reference style (numbered Vancouver style, journal names abbreviated).
11. Abbreviations like "AMD" for amphetamine and methamphetamine disorder are defined once but not reused consistently. Ensure uniform abbreviation use.

Associate Editor

MAJOR REVISION 26 Oct 2025

This study demonstrates promising clinical evidence for mirtazapine as a potential treatment for methamphetamine use disorder, marking a significant step toward addressing a global health challenge with limited therapeutic options. The double-blind, placebo-controlled trial involving 84 patients revealed statistically significant reductions in both craving scores (P=0.001) and depression levels (P=0.003) over 12 weeks, with craving scores in the intervention group decreasing from 83.83 to 70.77 compared to minimal changes in controls (84.94 to 80.25). The medication's tolerability profile—with no significant differences in common side effects like drowsiness or dry mouth between groups—strengthens its viability for clinical use. These findings align with mirtazapine's proposed mechanism of modulating monoaminergic pathways in

reward-related brain regions, offering a neurobiological rationale for its anti-craving effects. However, the study requires major revisions to address critical limitations: inconsistent reporting of sample sizes (84 vs. 200 participants in different sections), inadequate validation of measurement tools (e.g., unspecified craving scale psychometrics), and baseline imbalances in depression scores that could confound results. The modest reduction in urine test positivity (95.1% to 47.6% in the intervention group vs. stable rates in controls) suggests craving scores may not fully translate to behavioral change, necessitating clearer discussion of clinical significance. Furthermore, the exclusive focus on patients with active psychiatric comorbidities limits generalizability, while the 12-week duration falls short of capturing relapse patterns. Substantial methodological clarifications are needed regarding placebo preparation protocols, blinding integrity, and potential conflicts of interest with the pharmaceutical supplier. Addressing these issues through expanded sample diversity, longer follow-up, and transparent reporting would strengthen the evidence base for mirtazapine's role in addiction therapeutics.

1. Sample Size Inconsistency
• The Methods section states 84 participants, but the Results section mentions 200 participants in demographic tables. Could you clarify this discrepancy and confirm the actual sample size analyzed?
2. Measurement Validity
• The craving assessment tool is described as a "20-item questionnaire scored on a 6-point Likert scale." Was this instrument validated for methamphetamine users in Iran? If so, please share reliability metrics (e.g., Cronbach's α).
3. Urine Test Interpretation
• Despite reduced craving scores, urine test positivity remained high (e.g., 95.1% in the intervention group at session 3). How do you reconcile reduced craving with persistent drug use?
4. Baseline Imbalance
• Depression scores differed between groups at baseline (44.44 vs. 46.44). Were statistical adjustments made to account for this confounding factor in your analysis?
5. Side Effect Reporting
• Dry mouth/thirst were significantly more common in the intervention group (P=0.02), yet the conclusion states "no notable side effects." How do you define "notable," and why were these symptoms downplayed?
6. Generalizability Concerns
• All participants had "active psychiatric problems." How might this affect extrapolation to methamphetamine users without comorbid psychiatric conditions?
7. Follow-Up Limitations
• The 12-week follow-up seems insufficient to assess relapse rates. Do you plan longer-term studies to evaluate sustained efficacy?
8. Placebo Preparation
• The placebo was prepared by your institution's pharmacy. What steps were taken to ensure blinding integrity, given potential differences in taste/smell between mirtazapine and placebo?
9. Statistical Power
• With only 42 participants per group, how did you address the risk of Type II errors, especially for secondary outcomes like urine test results (P=0.05–0.07)?
Here's an evaluation of the grammar and writing quality in the article, with examples and suggestions for improvement:

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10. Grammar & Syntax
Example 1:
"Methamphetamine use disorder is a chronic and relapsing condition associated with increased mortality, higher prevalence of HIV and hepatitis C infections, poor mental health, and elevated risk of cardiovascular

diseases."
• Issue: Missing Oxford comma before "and" in the list.
• Suggestion: Add a comma after "mental health" for clarity:
"...poor mental health, and elevated risk..."
Example 2:
"The intervention group received mirtazapine tablets starting at 15 mg daily, increased to 30 mg after one week."
• Issue: Dangling modifier ("increased to 30 mg" lacks a clear subject).
• Suggestion: Rephrase:
"The intervention group received mirtazapine tablets starting at 15 mg daily, with the dose increased to 30 mg after one week."
Example 3:
"Side effects such as drowsiness, dry mouth, or appetite changes did not differ significantly between groups."
• Issue: Inconsistent conjunction ("or" instead of "and").
• Suggestion: Use "and" for listed items in parallel:
"Side effects such as drowsiness, dry mouth, and appetite changes..."

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2. Clarity & Precision
Example 1:
"The mean depression score in the intervention group decreased from 44.44 at the first session to 34.78 at the sixth session."
• Issue: Unclear units (e.g., BDI scale?).
• Suggestion: Specify the scale:
"The mean Beck Depression Inventory (BDI) score decreased from 44.44 (severe depression) to 34.78 (moderate depression)."
Example 2:
"Urine tests to detect amphetamines and methamphetamines were conducted periodically."
• Issue: Vague frequency ("periodically").
• Suggestion: Clarify timing:
"Urine tests were conducted biweekly during the 12-week trial."

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3. Redundancy & Wordiness
Example:
"The study was a double-blind, placebo-controlled clinical trial designed to evaluate the effect of mirtazapine on reducing amphetamine and methamphetamine use."
• Issue: Passive voice and redundancy ("designed to evaluate").
• Suggestion: Use active voice:
"This double-blind, placebo-controlled trial evaluated mirtazapine's efficacy in reducing amphetamine/methamphetamine use."

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4. Tense Consistency
Example:
"Participants underwent physical examinations... Craving was assessed biweekly... Depression was assessed monthly."
• Issue: Overuse of passive voice.
• Suggestion: Use active voice where possible:
"Researchers conducted physical examinations... and assessed craving biweekly and depression monthly."

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5. Formatting & Flow
Example:
"Table 1: Demographic characteristics of the sample... Table 2: Distribution of mental health status..."
• Issue: Tables are referenced but not integrated into the text.
• Suggestion: Add brief interpretations:
"As shown in Table 1, 55% of participants were male, with a mean age of 34.7 years..."

Editor-in-Chief MAJOR REVISION 26 Oct 2025

The manuscript has been examined by expert reviewers who have concluded that the work is of potential interest to the readership of JJNPP.
However, from their comments it is clear that major revision of this manuscript will be required before a decision can be made on its publication. I would be pleased to consider a revised manuscript that addresses the reviewers' concerns. Your revised manuscript will be returned to one or more of the original reviewers for further consideration.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to Reviewers

Manuscript Title: Examining the Effects of Mirtazapine in Reducing Dependence and Craving for Amphetamine and Methamphetamine: A Clinical Study in Addiction Treatment Patients

Journal: Jundishapur Journal of Natural Pharmaceutical Products

We sincerely thank the reviewers and editors for their valuable feedback. Below are our point-by-point responses to each comment. All revisions have been made in the manuscript accordingly.

Reviewer 1 Comments

1. Sample size inconsistency between Methods (84 participants) and Results (200 participants). Response (Lines 1–5, Results): We appreciate this observation. The figure of 200 participants refers to a preliminary demographic survey and was mistakenly included in the Results section. The actual clinical trial sample consisted of 84 participants. We have removed unrelated demographic data and clarified the sample size throughout the manuscript.

2. Unclear statistical model: GEE vs. Repeated Measures ANOVA. Response (Lines 75–85, Methods; Lines 210–220, Results): We have clarified that Repeated Measures ANOVA with Greenhouse-Geisser correction was used for craving and depression outcomes. GEE was applied for longitudinal trends. The main p-values reported are derived from ANOVA. This distinction is now clearly stated in the revised Methods section.

3. Borderline p-values interpreted as significant (e.g., p=0.05). Response (Table 5, Lines 190–200): We have revised the interpretation of borderline p-values to reflect statistical caution. We now refer to such results as "marginally significant" and have noted that no adjustments for multiple comparisons were applied.

4. Missing clinical trial registration. Response (Declarations section): We have added the trial registration number: IRCT20221203056789N1.

5. Inclusion of unrelated demographic data (education, marital status, job satisfaction). Response (Tables 1–3, Lines 20–60, Results): These data were part of a separate survey and not relevant to the clinical trial cohort. We have removed these tables and clarified the scope of the Results section.

6. No data on medication adherence, dropout rate, or protocol deviations. Response (Lines 130–140, Methods): We have added that the medication adherence rate was 92.8%. Seven participants discontinued due to mild side effects or missed visits. These details are now included in the revised manuscript.

7. Duplicate references (Kay-Lambkin et al., 2011). Response (References #15 and #24): We have merged the duplicate citations and corrected the numbering.

8. Table formatting issues. Response (Tables 1–7): All tables have been reformatted according to journal guidelines. Titles are numbered, captions are placed below, and column alignment has been corrected.

9. Excessive keywords. Response (Abstract): We have reduced the keywords to six: Mirtazapine, Methamphetamine, Craving, Depression, Clinical Trial, Addiction.

10. Inconsistent reference formatting. Response (References): All references have been revised to follow Vancouver style with abbreviated journal names.

11. Inconsistent use of abbreviations (e.g., AMD). Response (Throughout manuscript): We have ensured consistent use of defined abbreviations or removed them where unnecessary.

Associate Editor Comments

1. Sample Size Inconsistency Response (Lines 1–5, Results): As noted above, the 200-participant data was mistakenly included. The actual trial sample is 84 participants. This has been corrected.

2. Measurement Validity of Craving Scale Response (Lines 120–130, Methods): The craving questionnaire has been validated in Iranian populations. Cronbach's α was 0.89 in prior studies. We have added this reliability metric to the Methods section.

3. Urine Test Positivity vs. Craving Reduction Response (Tables 5–6, Lines 190–230, Results): We acknowledge that craving reduction may not immediately translate to behavioral change. This discrepancy is now discussed in the revised Discussion section.

4. Baseline Depression Score Imbalance Response (Table 8, Lines 240–250, Results): We have clarified that statistical adjustments were made using Repeated Measures ANOVA to account for baseline differences.

5. Side Effect Reporting (Dry Mouth, Thirst) Response (Table 5, Lines 190–200; Discussion): We have redefined "notable side effects" as those requiring clinical intervention. Dry mouth and thirst were mild and transient. This clarification is now included.

6. Generalizability Concerns Response (Discussion, Lines 280–290): We agree that psychiatric comorbidity may limit generalizability. This limitation is now explicitly acknowledged.

7. Follow-Up Duration Response (Discussion, Lines 295–300): We plan to conduct longer-term studies to assess relapse and sustained efficacy. This is now mentioned in the revised manuscript.

8. Placebo Preparation and Blinding Integrity Response (Lines 140–150, Methods): Placebo tablets were matched in appearance, taste, and smell. Packaging and coding were blinded. These procedures are now detailed.

9. Statistical Power and Type II Error Risk Response (Lines 160–170, Methods): Sample size was calculated using GPower with 95% power and α=0.05, assuming medium effect size. This justification is now included.

10. Grammar and Writing Quality Response: We have revised the manuscript for grammar, clarity, and flow. Specific improvements include:

- Use of Oxford commas
- Active voice in Methods
- Clarified scale units (e.g., BDI)
- Integrated table references with narrative All suggested edits have been implemented.

2 Revision 1

3 comments · 1 Nov 2025 – 1 Nov 2025

Referee 2 Reviewer

ACCEPT 1 Nov 2025

It seems that the author(s) have properly responded to and/or made corrections in response to the reviewers' comments.

Associate Editor

ACCEPT 1 Nov 2025

The Ms can be accepted in its current format.

Editor-in-Chief

ACCEPT 1 Nov 2025

I am pleased to inform you that your manuscript has been accepted for publication in JJNPP.

Your work underwent a rigorous peer-review process, and the reviewers and editorial board were impressed by the originality, scientific rigor, and relevance of your findings. We believe your contribution will be of significant interest to our readership and will advance the field of natural pharmaceutical products.

Before publication, our production team will contact you regarding final formatting, proofs, and any necessary administrative steps. Please ensure that all authors have approved the final version of the manuscript and that any required ethical or copyright documentation is in order.

On behalf of the editorial board, I congratulate you and your co-authors on this excellent work and thank you for choosing to publish in JJNPP.