Comparative Efficacy and Safety of Adjunctive CT-152 in Major Depressive Disorder: A Frequentist Network Meta-Analysis

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Introduction

- Major depressive disorder (MDD) is a debilitating disease that is characterized by persistent depressed mood, loss of interest or pleasure in previously enjoyable activities, recurrent thoughts of death, and physical and cognitive symptoms[1]
- In 2008, the World Health Organization identified MDD as the third leading cause of disease burden globally, projecting that it will become the leading cause by 2030[2]
- Treatment of MDD typically includes antidepressant (ADT) medications, psychotherapy, or a combination of both[1,3]
- CT-152 recently received Food and Drug Administration 510(k)-clearance as a prescription digital therapeutic adjunct to an ADT medication for symptoms of MDD
- This study was conducted to compare the efficacy and safety of adjunctive (Adj.) CT-152 with adjunctive pharmacological and non-pharmacological interventions (digital treatments and cognitive behavioral therapies, CBT) for the treatment of MDD

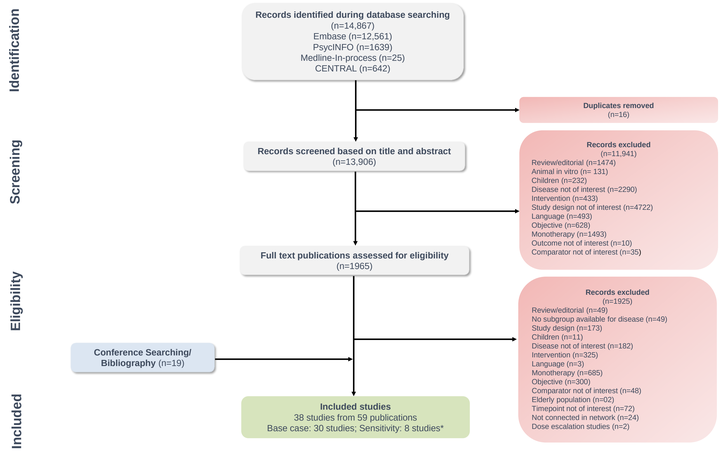
Methodology

- This study adhered to National Institute for Health and Care Excellence (NICE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic literature reviews (SLRs), following standard methodology with a transparent, reproducible, and unbiased approach
- EMBASE®, PubMed®, Cochrane®, and PsycINFO® were searched for English language articles published from inception to June 2023 for randomized controlled trials evaluating adjunctive digital, pharmacological, and non-pharmacological treatments in MDD
- Two independent reviewers performed the data collection and extraction activities, with conflicts resolved by a third independent reviewer
- A feasibility analysis was performed to evaluate clinical and statistical heterogeneity across the studies, using interpretation methods proposed by Higgins and colleagues[4]
- Frequentist (base-case) and Bayesian approaches, including both random-effects and fixed-effects network meta-analyses (NMA), were used to evaluate efficacy and safety over six weeks (aligned with MIRAI trial design)
- A sensitivity analysis was performed based on the heterogeneity evaluation carried out in the feasibility analysis

Results

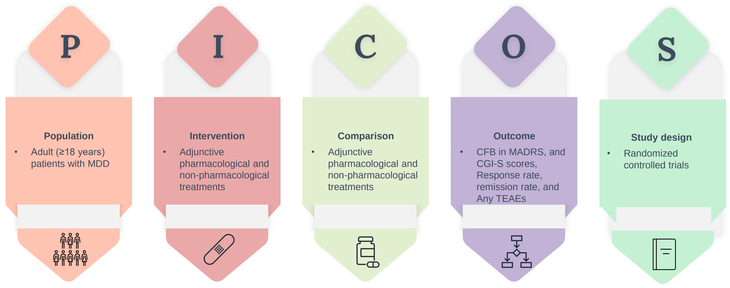
- Overall, 30 studies assessing 12,830 patients were included in the NMA. **Figure 1** and **Figure 2**, respectively, provide the PRISMA flow and the eligibility criteria for the NMA
- As a first step, a feasibility assessment (**Figure 3**) was conducted to evaluate the heterogeneity among the included studies, revealing low to moderate heterogeneity across outcomes, with only a few studies being outliers based on clinical variables (**Figure 4**). The global network for the NMA is presented in **Figure 5**
- In terms of continuous outcomes, adjunctive CT-152 demonstrated a reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) total scores compared to adjunctive ADTs (weighted mean difference, WMD: 0.95) and atypical antipsychotics (AAPs) (WMD, 0.24) (**Figure 6a**)
- For the Clinical Global Impressions-Severity scale (CGI-S), CT-152 showed a similar reduction compared to AAPs (WMD, 0.01), ADTs (WMD, -0.33), and deprexis (WMD, -0.20) (**Figure 6b**)
- Regarding categorical outcomes, remission rates were similar for CT-152 as compared to AAPs (risk ratio, RR, 0.91) and ADTs (RR, 1.04), CBT (RR, 1.61) (**Figure 6c**)
- Response rates also showed similar findings for CT-152 versus AAPs (RR, 1.04) and ADTs (RR, 1.23) (**Figure 6d**)
- In terms of safety (any treatment-emergent adverse events, TEAE), CT-152 demonstrated a statistically significant ($p<0.05$) superior profile compared to AAPs (odds ratio, OR, 0.32) and ADTs (OR, 0.37) (**Figure 6e**)
- In addition to the base-case (Frequentist) random-effects NMA, fixed-effects NMA, Bayesian NMA, and sensitivity analyses were conducted based on outlier studies for sample size, race, age, and prior ADT control status. These approaches demonstrated consistent results across all methodologies, confirming the robustness of the NMA

Figure 1: PRISMA flow of studies through SLR and NMA



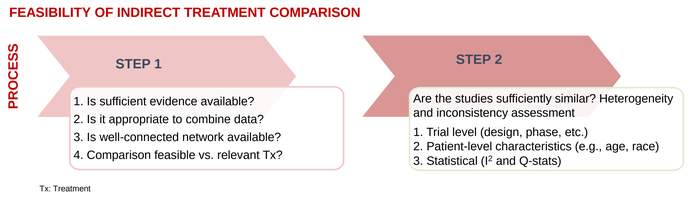
*seven studies not meeting trial design criteria and one study using fixed-dose combinations were excluded from the base case; CENTRAL: Cochrane Central Register of Controlled Trials; EMBASE: Excerpta Medica Database; NMA: Network Meta-Analysis; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: Systematic Literature Review

Figure 2: Eligibility criteria for SLR and NMA



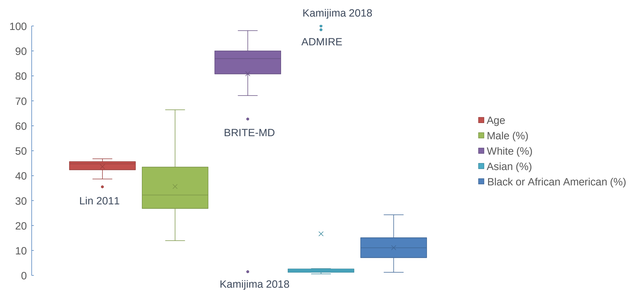
CFB: Change from Baseline; CGI-S: Clinical Global Impressions-Severity; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: Major Depressive Disorder; TEAE: Treatment-Emergent Adverse Events

Figure 3: Process of conducting feasibility assessment



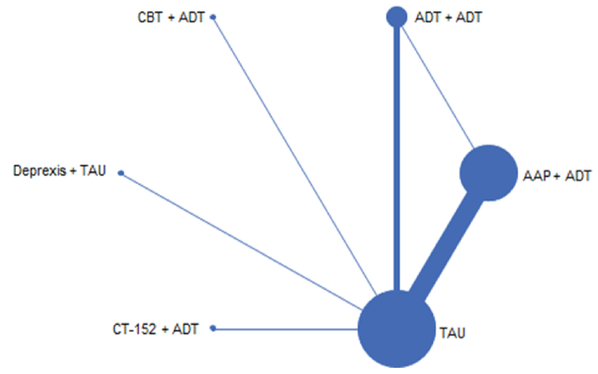
Tx: Treatment

Figure 4: Box plot assessments of included studies



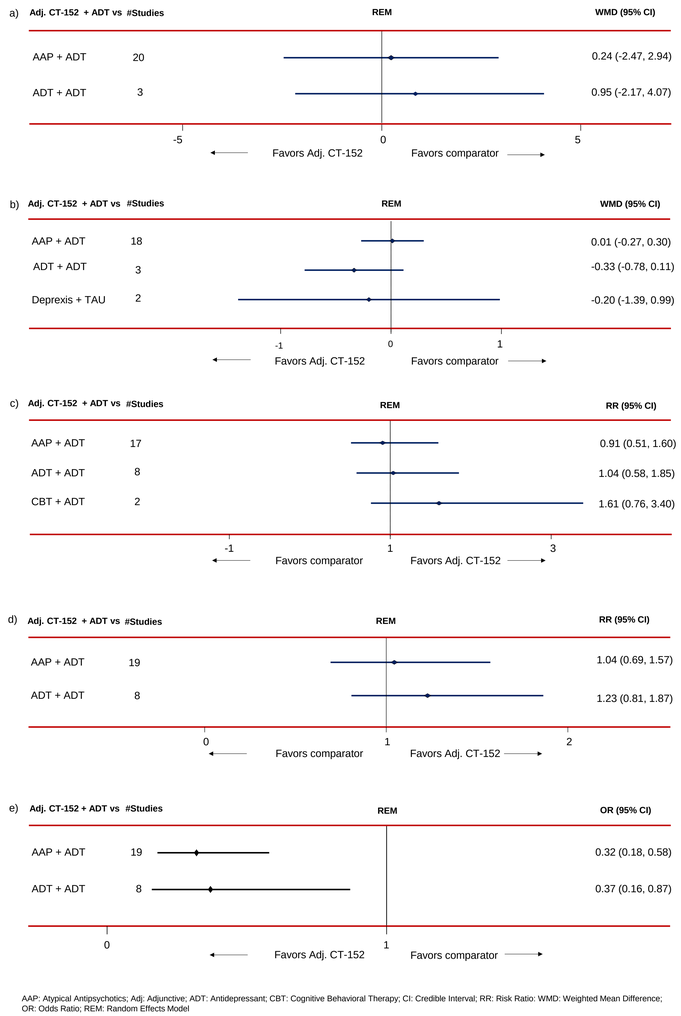
'X' denotes the mean estimates of the demographic data

Figure 5: Global network of 30 studies considered for the base case of NMA



AAP: Atypical Antipsychotics; ADT: Antidepressant; CBT: Cognitive Behavioral Therapy; TAU: Treatment As Usual

Figure 6: Forest plot of treatment comparison for a) MADRS total scores, b) CGI-S scores, c) Remission rate, d) Response rate, e) Any treatment-emergent adverse events



AAP: Atypical Antipsychotics; Adj: Adjunctive; ADT: Antidepressant; CBT: Cognitive Behavioral Therapy; CI: Credible Interval; RR: Risk Ratio: WMD: Weighted Mean Difference; OR: Odds Ratio; REM: Random Effects Model

CONCLUSIONS

❖ Adjunctive treatment with CT-152 demonstrated similar efficacy in terms of MADRS total score (versus adjunctive AAPs and ADTs), CGI-S scores (versus adjunctive AAPs, ADTs and deprexis), response rate (versus adjunctive AAPs, and ADTs) and remission rate (versus adjunctive AAPs, ADTs and CBT)

❖ Adjunctive treatment with CT-152 exhibited a statistically significant and superior safety profile in terms of any TEAEs when compared with adjunctive AAPs, ADTs

❖ The alignment of Frequentist, fixed-effects, NMA results with random-effects, Bayesian approaches and sensitivity analysis reinforces CT-152 efficacy and safety, enhancing confidence in its clinical application and relevance in modern treatment strategies for MDD

List of Abbreviations

AAP: Atypical Antipsychotics; ADT: Antidepressant; CENTRAL: Cochrane Central Register of Controlled Trials; CBT: Cognitive Behavioral Therapies; CFB: Change From Baseline; CrI: Credible Interval; EMBASE: Excerpta Medica Database; ITC: Indirect Treatment Comparison; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: Major Depressive Disorder; NICE: National Institute for Health and Care Excellence; NMA: Network Meta-Analyses; OR: Odds Ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR: Risk Ratio; REM: Random Effect Model; SGA: Subgroup Available; SLR: Systematic Literature Review; TAU: Treatment As Usual; TEAE: Treatment-Emergent Adverse Events; Tx: Treatment; WMD: Weighted Mean Difference

References

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Disclosures

ML, TC and AK, are employees of Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA
BS, and PR are employees of Pharmacoevidence, SAS Nagar Mohali, India, which was funded by Otsuka to conduct this analysis

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