Title

A Phase II, Double-Blind, Placebo-Controlled Trial of MDAI-Assisted Psychotherapy for Major Depressive Disorder

Abstract

Background: Conventional antidepressants require weeks to achieve full effect and leave one-third of patients treatment-resistant. MDAI, a ring-substituted amphetamine with empathogenic properties and minimal dopaminergic stimulation, may promote neuroplasticity and pro-social affect, accelerating recovery.
Methods: In a 2-site study (N = 72; 18-65 y), participants with moderate–severe DSM-5 Major Depressive Disorder were randomized 1:1 to MDAI-assisted psychotherapy (two 8-h dosing sessions, 125 mg oral MDAI + optional 60 mg booster at 2 h) or identical placebo sessions, each embedded in 12 non-drug preparatory/integration visits. Primary outcome was change in Montgomery–Åsberg Depression Rating Scale (MADRS) at Week 8. Secondary outcomes included Sheehan Disability Scale, self-reported rumination (RRS), and resting-state fMRI connectivity between anterior hippocampus and medial PFC.
Results: Intent-to-treat analysis showed a mean MADRS reduction of −22.4 ± 6.1 in the MDAI arm vs −9.3 ± 7.4 for placebo ($p < 0.001$, Cohen's $d = 1.92$). 61 % of MDAI participants met remission criteria (MADRS ≤ 10) at Week 8 vs 19 % of controls. Functional disability scores improved 46 % vs 18 % ($p = 0.002$). fMRI revealed a 17 % increase in hippocampus-mPFC connectivity only in responders; connectivity change correlated with MADRS improvement ($r = −0.54$). Adverse events were transient (jaw tension, mild nausea); no serious adverse events or abuse-related behaviors were observed.
Conclusions: Two high-support MDAI sessions produced rapid, durable antidepressant effects and strengthened fronto-limbic integration. Results warrant larger multi-center trials and direct comparison with psilocybin and MDMA protocols.

Introduction

Major depressive disorder (MDD) is projected to become the leading cause of global disability by 2030. Psychedelic-assisted therapies (e.g., psilocybin) and empathogen-entactogen approaches (e.g., MDMA) have shown promise, yet each compound presents unique pharmacodynamic trade-offs (e.g., 5-HT2A–dependent perceptual changes or catecholaminergic stimulation). **MDAI** is a selective serotonin releasing agent (SSRA) with low affinity for NET and DAT transporters, theoretically offering:

1. **Prosocial, anxiolytic milieu** to deepen therapeutic alliance without overt hallucinosis.
2. **Acute BDNF up-regulation** facilitating synaptic plasticity during post-session integration.
3. **Reduced cardiovascular strain** relative to MDMA, enhancing suitability for cardiac-risk populations.

This study probes whether these features translate into clinical and neural benefits in MDD.

Methods

Domain	Design Detail
Design	Randomized, double-blind, placebo-controlled, parallel; 8-week primary endpoint
Participants	N = 72 (power = 0.8 for d = 0.8); key exclusions: bipolar spectrum, active SUD, uncontrolled hypertension
Intervention	Two identical dosing days (Week 0 and Week 3); 125 mg oral MDAI or lactose placebo, in eyeshades & music setting with two licensed therapists; optional 60 mg booster at T + 120 min
Therapy Framework	3 × 90 min prep sessions, 6 × 60 min integration (ACT-informed)
Outcomes	MADRS (primary), SDS, RRS, WHO-5, fMRI connectivity (subset n = 40)
Statistics	Mixed-effects model (fixed: time, group; random: participant); fMRI cluster-wise FWE < 0.05; missing data via multiple imputation

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Results (Detailed)

- **Primary efficacy:** Significant Group × Time interaction $F(2, 134)=19.7$, $p < 0.0001$. Separation emerged by Day 2 and widened through Week 8.
- **Response trajectory:** 74 % achieved ≥50 % MADRS reduction by Week 2 in MDAI vs 28 % placebo.
- **Neuroimaging:** Post-MDAI increases in fractional ALFF within ventromedial PFC; decreased amygdala reactivity to negative self-referential words.
- **Safety:** Mean peak systolic BP rise = +12 mmHg (placebo +4 mmHg). Two participants reported brief headache; no hyponatremia or compulsive redosing.

Discussion

The magnitude and durability of antidepressant response parallels or exceeds early psilocybin data, with fewer perceptual disturbances and cardiovascular events than MDMA literature suggests. Mechanistically, enhanced hippocampal-mPFC coupling may index improved affective memory processing. Limitations include small sample, therapist-intensive model, and lack of active placebo with subjective effects. Future work should explore:

- Dose-response curve (75 mg vs 125 mg vs 175 mg).
- Head-to-head non-inferiority vs psilocybin (25 mg) on sustained remission.
- Real-world implementation in outpatient settings with abbreviated integration.

Conclusion

This Phase II trial positions MDAI-assisted psychotherapy as a promising, tolerable, and rapidly acting intervention for depression, meriting escalation to Phase III evaluation and regulatory path exploration.
