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Supplementary Material

Article Title: Eight-Week Randomized, Double-Blind, Placebo-Controlled 2-Site Trial Assessing the Efficacy and Safety of Mixed Amphetamine Salt as an Adjunctive Therapy for Bipolar Depression

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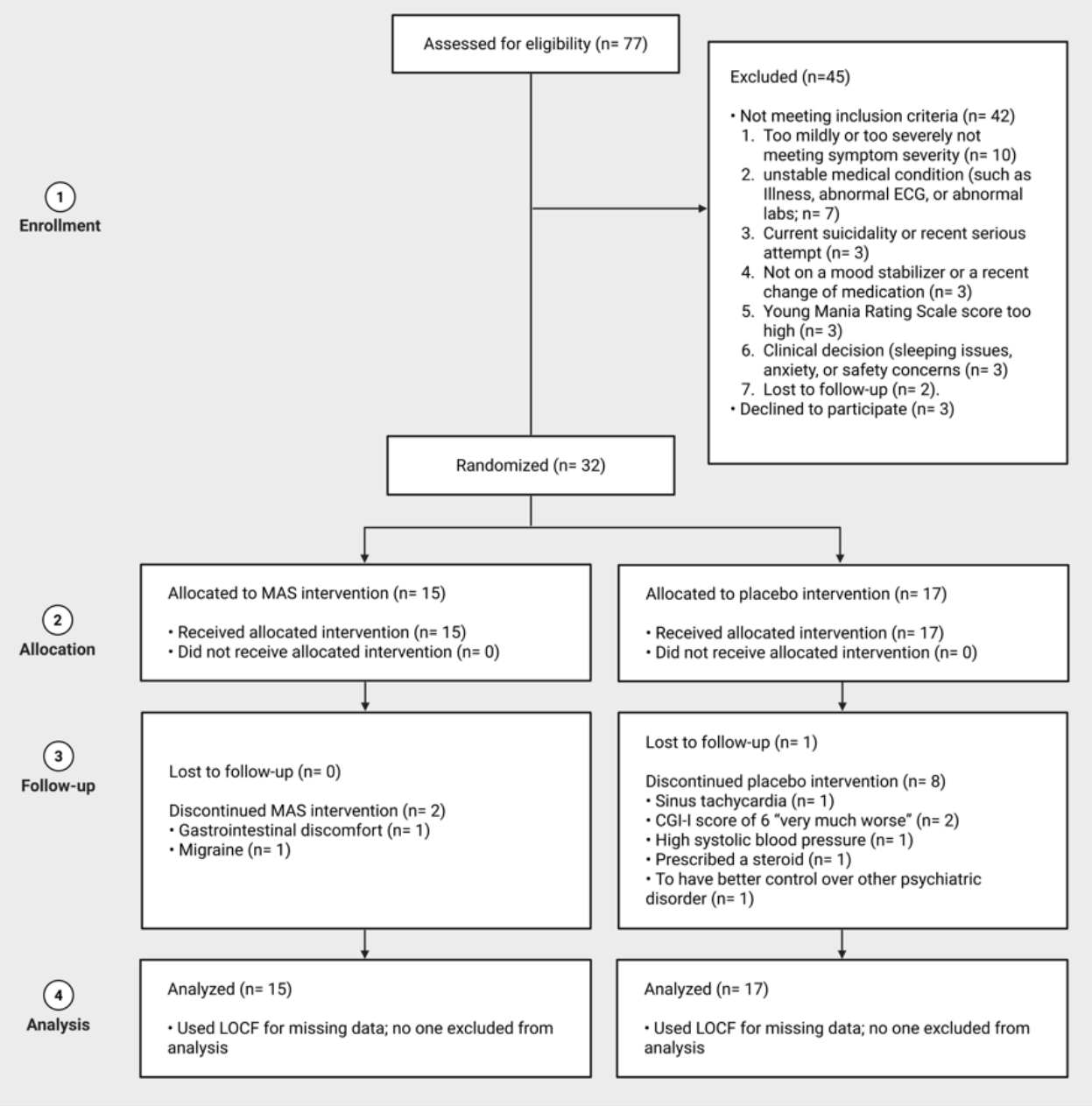
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SUPPLEMENTARY FILE

Supplementary Figure 1: CONSORT diagram of enrollment, randomization, follow-up, and analysis for MAS vs placebo trial, with reasons for exclusions shown. LOCF: Last Observation Carried Forward; CGI: Clinical Global Impression.



Supplementary Table 1. Psychiatric comorbidities of participants randomized to MAS or placebo

Characteristic	Placebo (N=17)	MAS (N=15)	Total (N=32)	p value[1]
Psychiatric comorbidity, n (%)[2,3]				
Any anxiety disorder	12 (71%)	8 (53%)	20 (62%)	0.47
Generalized anxiety disorder, current	11 (65%)	6 (40%)	17 (53%)	0.29
Generalized anxiety disorder, lifetime	13 (76%)	6 (40%)	19 (59%)	**0.07**
Panic disorder, current	1 (6%)	1 (7%)	2 (6%)	1.00
Social phobia, current	0 (0%)	2 (13%)	2 (6%)	0.21
Anxiety disorder NOS, current	0 (0%)	1 (7%)	1 (3%)	0.47
Specific phobia, lifetime[4]	0 (0%)	1 (10%)	1 (5%)	0.45
Obsessive-compulsive disorder, current	0 (0%)	2 (13%)	2 (6%)	0.21
Posttraumatic stress disorder, current	5 (29%)	2 (13%)	7 (22%)	0.40
Posttraumatic stress disorder, lifetime	6 (35%)	4 (27%)	10 (31%)	0.71
Any lifetime substance use disorder	7 (41%)	4 (27%)	11 (34%)	0.47
Alcohol use disorder, lifetime	6 (35%)	3 (20%)	9 (28%)	0.44
Other substance use disorder, lifetime[5]	2 (12%)	1 (7%)	3 (9%)	1.00
Polysubstance use disorder, lifetime	1 (6%)	0 (0%)	1 (3%)	1.00
Nicotine use, lifetime[7]	5 (29%)	4 (29%)	9 (29%)	1.00
Attention-deficit/hyperactivity disorder, current[6]	3 (18%)	8 (57%)	11 (35%)	**0.031**

[1] Fisher's exact test.
[2] Values are presented as n (%). Percentages are based on available data within each randomized group; participants may contribute to more than one category.
[3] Psychiatric comorbidity was ascertained using the SCID for DSM-IV-TR. Active current substance use disorders were exclusionary per protocol; all substance use disorders reported here were in sustained remission at screening.
[4] Lifetime specific phobia was not recorded at the Lindner Center of HOPE (n=10); percentages are based on the 22 participants with available data.
[5] Other lifetime substance use disorders included cannabis (n=2) and an unspecified substance (n=1).
[6] Attention-deficit/hyperactivity disorder was based on a clinical diagnosis documented at screening and was not confirmed by structured diagnostic interview. Data were unavailable for one participant randomized to MAS.
[7] Lifetime nicotine misuse was obtained from the BiBCQ or medical record rather than the SCID. Data were unavailable for one participant randomized to MAS.
Abbreviations: MAS, mixed amphetamine salts; NOS, not otherwise specified; SCID, Structured Clinical Interview for DSM-IV-TR.

Supplementary Table 2.

Detailed additional exclusion criteria due to unstable medical or laboratory abnormality	
Category	Exclusion Criterion
Cardiovascular	• History of structural cardiac abnormality, cardiomyopathy, serious heart-rhythm abnormality, coronary artery disease, stroke, or other serious cardiovascular problems • ECG with clinically significant arrhythmias, conduction abnormalities, or voltage criteria for left ventricular hypertrophy (unless cleared by cardiology consultation) • Uncontrolled hypertension (>160/100 mmHg) • Tachycardia (heart rate >110 bpm)
Neurological/ Vascular	• History of grand-mal seizure • Tourette syndrome • Established vasculopathy or history of Raynaud's phenomena
Ophthalmological	• Narrow-angle glaucoma
Renal	• Chronic kidney disease >stage IIIa (GFR 40–59 mL/min)
General Medical	• Clinically unstable medical disease • Clinically significant laboratory abnormality • Hypersensitivity to amphetamines or other ingredients of Mydayis® • Current positive test for SARS-CoV-2
Reproductive	• Pregnancy • Lactation • Childbearing potential without established contraception
Concomitant Medications	• Daily lorazepam >2 mg/day or dose-equivalent benzodiazepine: Clonazepam >1 mg/day, alprazolam 1–2 mg/day, or diazepam >20 mg/day
Administrative	• Administrative reasons and/or clinician judgment

Supplementary Methods:

Two prespecified sensitivity analyses of the primary outcome excluded non-completers and depression-related non-completers, respectively. Missing MADRS values were additionally addressed by multiple imputation. Thirty imputed datasets were generated by multivariate imputation by chained equations using predictive mean matching, with variables imputed in monotone visit sequence. Imputation models drew on study site, treatment assignment, age at consent, baseline MADRS, and the interim double-blind MADRS assessments. Imputation diagnostics (trace plots and comparisons of observed and imputed distributions) indicated no anomalies. The primary model was refit in each imputed dataset, and estimates were pooled across datasets using Rubin's rules.

To assess sensitivity to departures from the missing-at-random assumption, a delta-adjusted (pattern-mixture) analysis was performed in which the imputed percent reductions of participants who discontinued for worsening depression were penalized by a fixed offset before model fitting. Because higher percent reduction denotes greater improvement, offsets were negative, encoding the assumption that these participants would have improved less than a missing-at-random model implies; the offset was varied from 0 to −30 percentage points, and the pooled treatment effect was estimated at each level.

Supplementary Table 3. Ordinal logistic regression models of last available concentration-item severity (N=32)

Variable	MADRS concentration item OR (95% CI)	*p*	QIDS concentration item OR (95% CI)	*p*
MAS vs placebo	0.18 (0.03–1.06)	0.058	0.50 (0.10–2.60)	0.41
Age at consent, per year	1.05 (0.98–1.13)	0.14	1.03 (0.96–1.11)	0.36
Baseline concentration-item score	1.42 (0.85–2.37)	0.18	9.69 (2.32–40.50)	**0.002**
Nagelkerke R^2	**0.316**		**0.467**	

The outcome variables included the last available MADRS concentration-difficulties item and QIDS concentration/decision-making item. Both items were collapsed into three ordered levels to address sparse endpoint cells: MADRS scores were grouped as 0, 1-2, and ≥3; QIDS scores were grouped as 0, 1, and 2-3. Estimates are odds ratios with 95% confidence intervals from separate ordinal logistic regression models. Bolded p values are statistically significant at $p < 0.05$.

Supplementary Table 4. Logistic regression models of CGI-BP response adjusted for concentration-item and overall depressive symptom change

Variable	MADRS models				QIDS models			
	Δ concentration		Δ concentration + Δ total		Δ concentration		Δ concentration + Δ total	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*p*	OR (95% CI)	*P*
MAS vs placebo	18.2 (2.42-136.7)	**0.001**	0.75 (0.04-15.7)	0.88	23.7 (2.08-269.3)	**0.003**	1.61 (0.10-25.8)	0.77
Age at consent, year	0.94 (0.87-1.02)	0.11	1.02 (0.91-1.13)	0.78	0.93 (0.86-1.02)	0.11	1.00 (0.91-1.10)	0.97
Change in concentration item	0.73 (0.48-1.10)	0.13	1.36 (0.63-2.96)	0.51	0.15 (0.03-0.80)	**0.01**	0.56 (0.10-3.11)	0.60
Change in total MADRS score	—	—	0.69 (0.52-0.91)	**0.001**	—	—	0.76 (0.60-0.97)	**0.009**
Nagelkerke R^2	0.405		0.793		0.545		0.778	

The outcome variable is CGI-BP improvement, defined as “much improved” or “very much improved.” Estimates are odds ratios with 95% confidence intervals from binary logistic regression models. The MADRS and QIDS concentration models included treatment, age, and change in the respective concentration item. The expanded models additionally included change in total MADRS score. For the change-score predictors, OR < 1.00 indicated lower odds of improvement per one-point worsening. Bolded *p* values indicate statistical significance at $p < 0.05$. CGI-BP, Clinical Global Impressions-Bipolar Disorder scale; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS, Quick Inventory of Depressive Symptomatology.

Supplementary Table 5: Participant retention and reasons for attrition by study phase and randomized treatment assignment:

Study phase	Visit	Placebo		MAS		*p* value
		Active participants, n/N (%)	Reason for attrition after visit	Active participants, n/N (%)	Reason for attrition after visit	
Blinded	Week 1	17/17 (100%)	Depression; other medical; unknown	15/15 (100%)	—	
	Week 2	14/17 (82%)	Transition to open phase; depression; other medical	15/15 (100%)	—	
	Week 3	11/17 (65%)	—	15/15 (100%)	—	
	Week 4	11/17 (65%)	Other medical	15/15 (100%)	—	
	Week 5	10/17 (59%)	Depression	15/15 (100%)	Transition to open phase	
	Week 6	9/17 (53%)	—	14/15 (93%)	—	
	Week 7	9/17 (53%)	—	14/15 (93%)	Other medical	
	Week 8	9/17 (53%)	—	13/15 (87%)	—	0.060[a]
Open label	Week 1	10/10 (100%)	—	14/14 (100%)	—	
	Week 2	10/10 (100%)	Unknown	14/14 (100%)	Unknown	
	Week 3	9/10 (90%)	Personal	13/14 (93%)	Hypomanic; unknown	
	Week 4	8/10 (80%)	—	11/14 (79%)	Depression; unknown	
	Week 5	8/10 (80%)	Personal	9/14 (64%)	—	
	Week 6	7/10 (70%)	—	9/14 (64%)	Depression; other medical	
	Week 7	7/10 (70%)	—	7/14 (50%)	—	
	Week 8	7/10 (70%)	—	7/14 (50%)	—	0.42[a]

Active participants are participants who completed the specified visit. Reasons for attrition are shown at each participant's last completed visit and describe attrition before the subsequent visit. Blinded-phase percentages use the randomized denominators (placebo N=17; MAS N=15). Open-label percentages use the number entering the open-label phase (placebo n=10; MAS n=14), classified according to original randomized treatment assignment. "Transition to open phase" indicates early discontinuation of the blinded phase followed by entry into the open-label phase. MAS, mixed amphetamine salts.

[a] Fisher exact test comparing the proportion of active participants between treatment groups at the end of each phase.

Supplementary Table 6. Sensitivity analyses of the primary MADRS % reduction outcome across alternative analytic populations and missing-data approaches

Analytic approach	n	MAS effect, percentage points (95% CI)	p
All randomized (primary)	32	46.9 (18.6 to 75.2)	0.002
Blind-phase completers	22	42.0 (20.8 to 63.3)	0.001
Excl. depression-related discontinuations	29	38.5 (17.4 to 59.5)	0.001
Multiple imputation (MI)	32	39.1 (21.4 to 56.8)	<0.001
Delta-adjusted MI (penalty 10 to 30 %-points)	32	40.9 to 44.6	<0.001

Estimates are MAS (vs. placebo) coefficients from linear regression of MADRS percent reduction, adjusted for age. All randomized = primary last observation used analysis; completers = restricted to blind-phase completers; excl. depression-related discontinuers = primary analysis with the three withdrawals related to worsening-depression removed. Multiple imputation pooled 30 imputed datasets by Rubin's rules; delta-adjusted imputation additionally penalized the imputed MADRS reductions of the depression-related withdrawals by 10 to 30 percentage points (range spans those penalties). The adjunctive-MAS effect remained statistically significant across all three models.