Supplemental Content

12-month Follow-up Psychiatric Medications and Therapy

At the 12-month follow-up visit (n=25), 10 (40.0%) participants reporting taking psychiatric medication(s); all 10 participants had taken psychiatric drugs before study participation. The number of participants prescribed a medication for a given indication was as follows: 1 (4.0%) for PTSD, 2 (8.0%) for depression, 3 (12.0%) for generalized anxiety disorder (GAD), 5 (20%) for insomnia, 1 (4.0%) for ADHD, 1 (4.0%) anxiety/sleep disturbance, 1 (4.0%) for occasional anxiety. Of these, two participants were taking medications for multiple indications - one person reported taking five medications, including for depression, insomnia, GAD; another was taking four medications, including for ADHD, insomnia, and GAD. The only individual taking a medication at 12-month follow-up for PTSD was taking Lithium, which had been tapered off after study enrollment. This person had a CAPS-IV Total score of 78 (Baseline) and 10 (12-month follow-up). Eleven participants were in therapy, with only one being in the same type of therapy as before the study participation.

Table S1. Treatment-Emergent Adverse Events during Blinded, Open-label, and 12-month Follow-up Segments †, Intent-to-Treat Set

System Organ Classes	40 mg MDMA (n = 6)	100 mg MDMA (n = 9)	125 mg MDMA (n = 13)	Open-Label MDMA (n = 26)	12-month Follow-up †† (n = 25)
Cardiac disorders	---	---	---	---	---
Ear and labyrinth disorders	---	---	---	---	---
Endocrine disorders	---	---	---	---	---
Eye disorders	---	1 (11.1)		1 (3.8)	---
Gastrointestinal disorders	---		4 (30.8)	1 (3.8)	---
General disorders and administration site conditions	1 (16.7)	1 (11.1)	2 (15.4)	1 (3.8)	---
Infections and infestations	---	---	---	---	---
Injury, poisoning and procedural complications	---	2 (22.2)	---	---	1 (4.0)
Metabolism and nutrition disorders	---	---	---	---	---
Musculoskeletal and connective tissue disorders	---	---	3 (23.1)	3 (11.5)	---
Nervous system disorders	---	---	---	2 (7.7)	---
Neoplasms benign, malignant and unspecified	---	---	---	1 (3.8)	---
Psychiatric disorders	---	3 (33.3)	4 (30.8)	4 (15.4)	3 (12.0)
Reproductive system and breast disorders	---	---	---	---	1 (4.0)
Respiratory, thoracic and mediastinal disorders	---	---	---	---	---
Skin and subcutaneous tissue disorders	---	---	---	---	---
Vascular disorders	---	1 (11.1)	---	1 (3.8)	---

† Frequency of participants reporting adverse events, each participant counted once per system organ class at each segment

†† After End of Stage 1 (100 mg and 125 mg) or Stage 2 (40 mg) only serious AEs and AEs that affected psychiatric status were collected.

Table S2. Vital Signs during Experimental Sessions, Intent-to-Treat Set

Measurement	40 mg MDMA (n = 6)	100 mg MDMA (n = 9)	125 mg MDMA (n = 13)	Open Label (100-125 mg) (n = 26)
Systolic Blood Pressure (mmHg)				
Pre-drug				
Mean (SD)	124.7 (14.14)	121.4 (20.16)	127.6 (14.04)	127.4 (15.56)
Min/Max	100/154	96/161	108/165	100/164
Peak				
Mean (SD)	134.3 (15.47)	138.6 (23.55)	150.0 (17.52)	147.9 (19.37)
Min/Max	112/163	100/180	114/181	105/178
Final				
Mean (SD)	123.6 (12.52)	116.7 (13.50)	122.5 (15.87)	124.6 (17.16)
Min/Max	107/148	92/140	86/160	86/158
Diastolic Blood Pressure (mmHg)				
Pre-drug				
Mean (SD)	80.0 (9.96)	79.0 (13.45)	81.6 (8.90)	80.3 (10.01)
Min/Max	62/95	58/102	54/98	56/97
Peak				
Mean (SD)	86.1 (9.28)	84.4 (11.38)	92.9 (13.07)	90.2 (10.94)
Min/Max	72/96	65/101	70/135	64/112
Final				
Mean (SD)	79.9 (9.74)	74.4 (7.72)	77.4 (10.96)	78.5 (10.87)
Min/Max	68/96	61/88	53/99	54/100
Heart Rate (Beats Per Minute)				
Pre-drug				
Mean (SD)	79.1 (11.00)	70.8 (17.40)	73.9 (17.55)	79.4 (14.71)
Min/Max	66/103	46/118	50/115	56/116
Peak				
Mean (SD)	87.5 (11.51)	97.0 (21.50)	105.8 (17.38)	104.5 (17.87)
Min/Max	69/103	65/140	73/160	63/143
Final				
Mean (SD)	80.1 (15.50)	81.4 (13.21)	87.4 (16.15)	85.8 (13.65)
Min/Max	56/103	63/114	59/120	60/120
Body Temperature (°C)				
Pre-drug				
Mean (SD)	36.4 (0.50)	35.9 (1.0)	36.3 (0.52)	36.2 (0.74)
Min/Max	35.8/37.2	33.9/37.9	35.4/37.2	34.3/37.5
Peak				
Mean (SD)	37.1 (0.33)	37.0 (0.64)	37.2 (0.35)	37.1 (0.54)
Min/Max	36.6/37.6	35.5/38.7	36.5/37.8	36.0/38.5
Final				
Mean (SD)	37.0 (0.38)	36.5 (0.74)	36.8 (0.45)	36.7 (0.62)
Min/Max	36.5/37.6	34.8/38.1	35.9/37.5	35.2/37.8

Table S3. Suicidal Ideation and Behavior across the Treatment Period and Endpoints [†], Intent-to-Treat Set

Dose		Pre-Drug [††]	During-Drug [†††]	Integration Visit 1	Contact Day 2	Contact Day 7	Integration Visit 2	Integration Visit 3
				Experimental Session 1 No. (%)				
40 mg	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	2 (40.0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	6	6	6	6	6	6	5
100 mg	PI	5 (55.6)	2 (22.2)	3 (33.3)	3 (33.3)	3 (33.3)	3 (33.3)	5 (55.6)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	9	9	9	9	9	9	9
125 mg	PI	3 (23.1)	0 (0)	0 (0)	1 (8.3)	4 (33.3)	4 (33.3)	6 (50.0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	13	13	13	12	12	12	12
				Experimental Session 2 No. (%)				
40 mg	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	5	5	5	5	5	5	5
100 mg	PI	3 (33.3)	3 (33.3)	3 (33.3)	4 (50.0)	2 (25.0)	3 (42,9)	7 (77.8)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	9	9	9	8	8	7	9
125 mg	PI	3 (25.0)	5 (41.7)	0 (0)	3 (25.0)	3 (25.0)	7 (58.3)	9 (75.0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	12	12	12	12	12	12	12
				Experimental Session 3 No. (%)				
100 mg	PI	3 (33.3)	2 (22.2)	1 (11.1)	2 (25.0)	1 (11.1)	3 (33.3)	3 (33.3)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	9	9	9	8	9	9	9
125 mg	PI	1 (8.3)	3 (25.0)	1 (8.3)	2 (16.7)	2 (16.7)	1 (10.0)	4 (33.3)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	12	12	12	12	11	10	12
				Experimental Session 4 No. (%)				
40 mg/ Open-label	PI	0 (0)	1 (20.0)	1 (20.0)	1 (20.0)	0 (0)	0 (0)	1 (20.0)
	SI	0 (0)	1 (20.0)	1 (20.0)	1 (20.0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	5	5	5	5	4	5	5
				Experimental Session 5 No. (%)				
40 mg/ Open-label	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	5	5	5	5	5	5	5
				Experimental Session 6 No. (%)				
40 mg/ Open-label	PI	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	3	3	4	4	4	4	4

Endpoints No. (%)								
Dose		**Baseline ††††**	**Primary**	**End of Stage 1**	**Open-label Dose**	**Secondary**	**End of Stage 2**	**12-month Follow-up**
40 mg	PI	0 (0)	1 (20.0)		100-125 mg	0 (0)	1 (25.0)	0 (0)
	SI	0 (0)	0 (0)	---		0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)			0 (0)	0 (0)	0 (0)
	N	6	5			5	4	5
100 mg	PI	6 (66.7)	4 (44.4)	1 (11.1)				1 (11.1)
	SI	0 (0)	0 (0)	0 (0)	---	---	---	0 (0)
	PB	0 (0)	0 (0)	0 (0)				0 (0)
	N	9	9	9				9
125 mg	PI	7 (53.8)	6 (45.4)	5 (41.7)				2 (18.2)
	SI	0 (0)	1 (8.3)	0 (0)	---	---	---	0 (0)
	PB	0 (0)	0 (0)	0 (0)				0 (0)
	N	13	12	12				11

Abbreviations: PI, Positive Ideation on C-SSRS; SI, Serious Ideation on C-SSRS; PB, Positive Behavior on C-SSRS; N, Number of Participants

† According to the C-SSRS scoring guide, scores of four or five on the suicidal ideation category are considered serious ideation, and scores of one or greater are considered positive behavior or ideation

†† Pre-drug measurement taken day of experimental session prior to drug administration

††† During-drug observation measured at experimental session endpoint, approximately 6 hours after drug administration

†††† Baseline represents measures taken during Preparatory Sessions and before drug administration in Experimental Session 1

Table S4. Summary of Changes in Amendments

Protocol Amendment	Study Design Change
Amendment 1	Obfuscation in informed consent – refer to 40 mg as comparator dose, not low dose. No one enrolled in original or A1 (n=28)
Amendment 2	Added optional titration dose available for the second and third sessions of open-label cross over (n=28)
Amendment 2	Posttraumatic Growth Inventory added (n = 26)
Amendment 2	RBANS and PASAT added as measures (n = 26)
Amendment 3	Addition of a second active-dose group of 100 mg (previously 40 and 125 mg only) (n = 23)
Amendment 3	Expanded exclusion from excluding borderline personality disorders to excluding all personality disorders. (n = 23)
Amendment 3	Changed definition of therapy team to be more inclusive (n = 23)
Amendment 4	Increased planned subjects from 17 to 23 (n = 17)
Amendment 5	Permitted Active dose 1 (e.g. 100 mg) subjects to receive 125 mg in third MDMA session (n = 14)
Amendment 6	(Clarification letter only) Permits addition of three subjects to be randomized

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4, 5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Table S4
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9, Table 2-5
Sample size	7a	How sample size was determined	NA/Pilot study
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	4, 7

		assessing outcomes) and howsssssssssss	
	11b	If relevant, description of the similarity of interventions	6-7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10-11
	13b	For each group, losses and exclusions after randomisation, together with reasons	Tables 2-6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 2-6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12-13, Table S1
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16
Other information			
Registration	23	Registration number and name of trial registry	4, 6
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	6, 18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.