Supplemental Online Content

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eTable 1. Treatment Effects on Problems Related to Drinking
eTable 2. Adverse Events
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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Treatment Effects on Problems Related to Drinking

a. Final Visit (including all week 36 assessments)

	Timepoint	Diphenhydramine			Psilocybin			Treatment Effect		
		n	Mean	Standard Deviation	n	Mean	Standard Deviation	g	95% CI	P-Value
Physical	*Baseline*	45	4.76	2.25	47	4.45	2.05			
	Week 36	40	3.08	2.42	44	1.30	1.86	0.83	0.38 to 1.28	<0.001
Inter-Personal	*Baseline*	45	3.64	2.87	47	3.51	2.59			
	Week 36	40	2.08	2.41	44	1.16	2.01	0.42	-0.02 to 0.85	0.061
Intra-Personal	*Baseline*	45	6.67	2.12	47	6.55	2.07			
	Week 36	40	4.22	2.71	44	2.43	2.36	0.71	0.27 to 1.15	0.002
Impulse Control	*Baseline*	45	2.87	2.12	47	2.49	2.03			
	Week 36	40	1.70	1.80	44	0.75	1.64	0.55	0.12 to 0.99	0.013
Social Responsibility	*Baseline*	45	3.67	2.88	47	3.26	2.48			
	Week 36	40	1.93	2.34	44	0.95	1.80	0.47	0.04 to 0.91	0.035
Total Problems	*Baseline*	45	21.60	9.61	47	20.26	8.89			
	Week 36	40	13.00	10.48	44	6.59	8.80	0.67	0.23 to 1.11	0.003

b. MMRM Results

	Timepoint	Diphenhydramine			Psilocybin			Treatment Effect		
		n	Mean	SD	n	Mean	SD	g	95% CI	P-value
Physical	*Baseline*	45	4.76	2.25	47	4.45	2.05			
	Week 12	22	2.62	2.65	26	2.63	2.38	-0.01	-0.56 to 0.57	.984
	Week 24	25	2.60	2.93	16	0.59	2.32	0.74	0.10 to 1.39	.016
	Week 36	24	2.52	2.90	21	0.24	2.59	0.83	0.22 to 1.44	.006
Inter-Personal	*Baseline*	45	3.64	2.87	47	3.51	2.59			
	Week 12	22	1.93	2.50	26	2.03	2.24	-0.04	-0.53 to 0.61	.886
	Week 24	25	2.29	2.84	16	1.47	2.36	0.31	-0.32 to 0.94	.317
	Week 36	24	1.85	2.82	21	1.14	2.64	0.26	-0.33 to 0.85	.382
Intra-Personal	*Baseline*	45	6.67	2.12	47	6.55	2.07			
	Week 12	22	4.36	3.18	26	4.17	2.84	0.06	-0.50 to 0.63	.826
	Week 24	25	4.00	3.52	16	1.55	2.80	0.75	0.10 to 1.40	.015
	Week 36	24	3.80	3.48	21	1.45	3.13	0.71	0.10 to 1.31	.019
Impulse Control	*Baseline*	45	2.87	2.12	47	2.49	2.03			
	Week 12	22	1.32	1.92	26	1.41	1.72	-0.05	-0.52 to 0.62	.867
	Week 24	25	1.33	2.16	16	0.68	1.72	0.33	-0.31 to 0.96	.287
	Week 36	24	1.46	2.13	21	0.55	1.93	0.45	-0.15 to 1.04	.134
Social Responsibility	*Baseline*	45	3.67	2.88	47	3.26	2.48			
	Week 12	22	2.08	2.48	26	1.96	2.22	0.05	-0.51 to 0.62	.856
	Week 24	25	1.84	2.81	16	1.39	2.33	0.17	-0.46 to 0.80	.578
	Week 36	24	1.60	2.79	21	1.10	2.59	0.19	-0.40 to 0.77	.528
Total Problems	Baseline	45	21.60	9.61	47	20.26	8.89			
	Week 12	22	12.00	11.00	26	12.06	9.87	-0.01	-0.56 to 0.57	.984
	Week 24	25	11.69	12.34	16	5.65	10.07	0.53	-0.11 to 1.16	.088
	Week 36	24	10.86	12.25	21	4.29	11.22	0.56	-0.04 to 1.15	.062

Caption: Problems related to alcohol were assessed using the Short Index of Problems (SIP-2R). Mean total scores and subscale scores are shown, along with sample sizes and standard deviations used to calculate Hedge's g and 95% confidence intervals for between-group comparisons at the baseline assessment *(covariate in the model)*, and each follow-up timepoint assessed *(weeks 12, 24, 36)*. P values are uncorrected for multiple comparisons. Supplemental Table 2a shows results of post-hoc analysis including all data collected at the final visit of the double-blind observation period, regardless of whether it occurred within the pre-specified window. Supplemental Table 2b shows results of Mixed Models for Repeated Measures (MMRM) analyses including only data from visits occurring within pre-specified windows (See SAP).

eTable 2: Adverse Events

a. AEs occurring after first Administration of Medication (Week 4) through Week 36

SOC	PT	PSILO (N = 48)	PSILO %	DIPHEN (N = 45)	DIPHEN %	TOTAL (N=93)	TOTAL %	P-VALUE
BLOOD AND LYMPHATIC SYSTEM DISORDERS								
	Anemia	0	0.0	1	2.2	1	1.1	0.48
	Thrombocytosis	0	0.0	1	2.2	1	1.1	0.48
CARDIAC DISORDERS								
	Palpitations	1	2.1	0	0.0	1	1.1	1.00
EYE DISORDERS								
	Cataract	1	2.1	0	0.0	1	1.1	1.00
	Photopsia	1	2.1	0	0.0	1	1.1	1.00
GASTROINTESTINAL DISORDERS								
	Abdominal pain	1	2.1	0	0.0	1	1.1	1.00
	Abdominal pain upper	2	4.2	0	0.0	2	2.2	0.50
	Constipation	0	0.0	1	2.2	1	1.1	0.48
	Diarrhea	0	0.0	2	4.4	2	2.2	0.48
	Diverticulitis	1	2.1	0	0.0	1	1.1	1.00
	Dyspepsia	1	2.1	0	0.0	1	1.1	1.00
	Food poisoning	1	2.1	0	0.0	1	1.1	1.00
	Mallory-Weiss syndrome	0	0.0	1	2.2	1	1.1	0.48
	Nausea	10	20.8	4	8.9	14	15.1	0.15
	Toothache	1	2.1	0	0.0	1	1.1	1.00
	Vomiting	2	4.2	1	2.2	3	3.3	1.00
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
	Asthenia	1	2.1	0	0.0	1	1.1	1.00
	Fatigue	1	2.1	0	0.0	1	1.1	1.00
	Influenza like Illness	0	0.0	1	2.2	1	1.1	0.48
	Oedema	0	0.0	1	2.2	1	1.1	0.48
	Pain	1	2.1	3	6.7	4	8.3	0.35
	Peripheral swelling	0	0.0	1	2.2	1	1.1	0.48
	Pyrexia	0	0.0	1	2.2	1	1.1	0.48
IMMUNE SYSTEM DISORDERS								
	Dermatitis contact	0	0.0	1	2.2	1	1.1	0.48
	Food allergy	1	2.1	0	0.0	1	1.1	1.00

SOC	PT	PSILO (N = 48)	PSILO %	DIPHEN (N = 45)	DIPHEN %	TOTAL (N=93)	TOTAL %	P-VALUE
INFECTIONS AND INFESTATIONS								
	Bronchitis	0	0.0	3	6.7	3	3.2	0.11
	Bronchitis bacterial	0	0.0	1	2.2	1	1.1	0.48
	Corona virus infection	2	4.2	0	0.0	2	2.2	0.50
	Eye infection	0	0.0	1	2.2	1	1.1	0.48
	Fungal infection	0	0.0	1	2.2	1	1.1	0.48
	Gingivitis	1	2.1	1	2.2	2	2.2	1.00
	Influenza	1	2.1	2	4.4	3	3.2	0.61
	Pneumonia	2	4.2	0	0.0	2	2.2	0.50
	Upper respiratory tract infection	2	4.2	0	0.0	2	2.2	0.50
	Viral upper resp. tract infection	2	4.2	3	6.7	5	5.4	0.67
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS								
	Alcohol poisoning	2	4.2	0	0.0	2	2.2	0.50
	Limb injury	1	2.1	0	0.0	1	1.1	1.00
	Muscle strain	1	2.1	0	0.0	1	1.1	1.00
	Traumatic lung injury	0	0.0	1	2.2	1	1.1	0.48
INVESTIGATIONS								
	Biopsy cervix	1	2.1	0	0.0	1	1.1	1.00
	Blood pressure diastolic increased	1	2.1	0	0.0	1	1.1	1.00
	Blood pressure increased	1	2.1	0	0.0	1	1.1	1.00
METABOLISM AND NUTRITION DISORDERS								
	Hyponatremia	0	0.0	1	2.2	1	1.1	0.48
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS								
	Arthralgia	0	0.0	1	2.2	1	1.1	0.48
	Back pain	1	2.1	3	6.7	4	4.3	0.35
	Musculoskeletal pain	1	2.1	1	2.2	2	2.2	1.00
	Myalgia	1	2.1	0	0.0	1	1.1	1.00
	Pain in extremity	0	0.0	1	2.2	1	1.1	0.48
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED								
	Malignant melanoma	0	0.0	1	2.2	1	1.1	0.48
NERVOUS SYSTEM DISORDERS								
	Dizziness	1	2.1	1	2.2	2	2.2	1.00
	Headache	21	43.8	2	4.4	23	24.7	**< 0.01**
	Hypoesthesia	0	0.0	1	2.2	1	1.1	0.48

SOC	PT	PSILO (N = 48)	PSILO %	DIPHEN (N = 45)	DIPHEN %	TOTAL (N=93)	TOTAL %	P-VALUE
	Migraine	0	0.0	1	2.2	1	1.1	0.48
	Psychomotor hyperactivity	1	2.1	0	0.0	1	1.1	1.00
	Sedation	0	0.0	1	2.2	1	1.1	0.48
	Sinus headache	0	0.0	2	4.4	2	2.2	0.23
PSYCHIATRIC DISORDERS								
	Alcohol withdrawal syndrome	1	2.1	2	4.4	3	3.2	0.61
	Anger	0	0.0	1	2.2	1	1.1	0.48
	Anxiety	7	14.6	1	2.2	8	8.6	**0.06**
	Depressed mood	3	6.3	2	4.4	5	5.4	1.00
	Depression	2	4.2	2	4.4	4	4.3	1.00
	Dysphoria	1	2.1	0	0.0	1	1.1	1.00
	Illusion	1	2.1	0	0.0	1	1.1	1.00
	Insomnia	3	6.3	2	4.4	5	5.4	1.00
	Restlessness	0	0.0	1	2.2	1	1.1	0.48
	Suicidal Ideation	4	8.3	3	6.7	7	7.5	1.00
RENAL AND URINARY DISORDERS								
	Urinary incontinence	1	2.1	0	0.0	1	1.1	1.00
REPRODUCTIVE SYSTEM AND BREAST DISORDERS								
	Testicular pain	1	2.1	0	0.0	1	1.1	1.00
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS								
	Cough	0	0.0	1	2.2	1	1.1	0.48
	Dyspnea	1	2.1	0	0.0	1	1.1	1.00
	Hyperventilation	1	2.1	0	0.0	1	1.1	1.00
	Lower resp. tract congestion	0	0.0	2	4.4	2	2.2	0.23
	Nasal congestion	1	2.1	0	0.0	1	1.1	1.00
	Oropharyngeal pain	1	2.1	2	4.4	3	3.2	0.61
	Rhinorrhea	0	0.0	1	2.2	1	1.1	0.48
	Sinus congestion	0	0.0	1	2.2	1	1.1	0.48
SOCIAL CIRCUMSTANCES								
	Sexual abuse	0	0.0	1	2.2	1	1.1	0.48
SURGICAL AND MEDICAL PROCEDURES								
	Arthoscopic surgery	0	0.0	1	2.2	1	1.1	0.48
	Endodontic procedure	0	0.0	1	2.2	1	1.1	0.48
	Skin cosmetic procedure	1	2.1	0	0.0	1	1.1	1.00

b. Treatment-Emergent Adverse Events Occurring within 48 Hours of Medication Administration

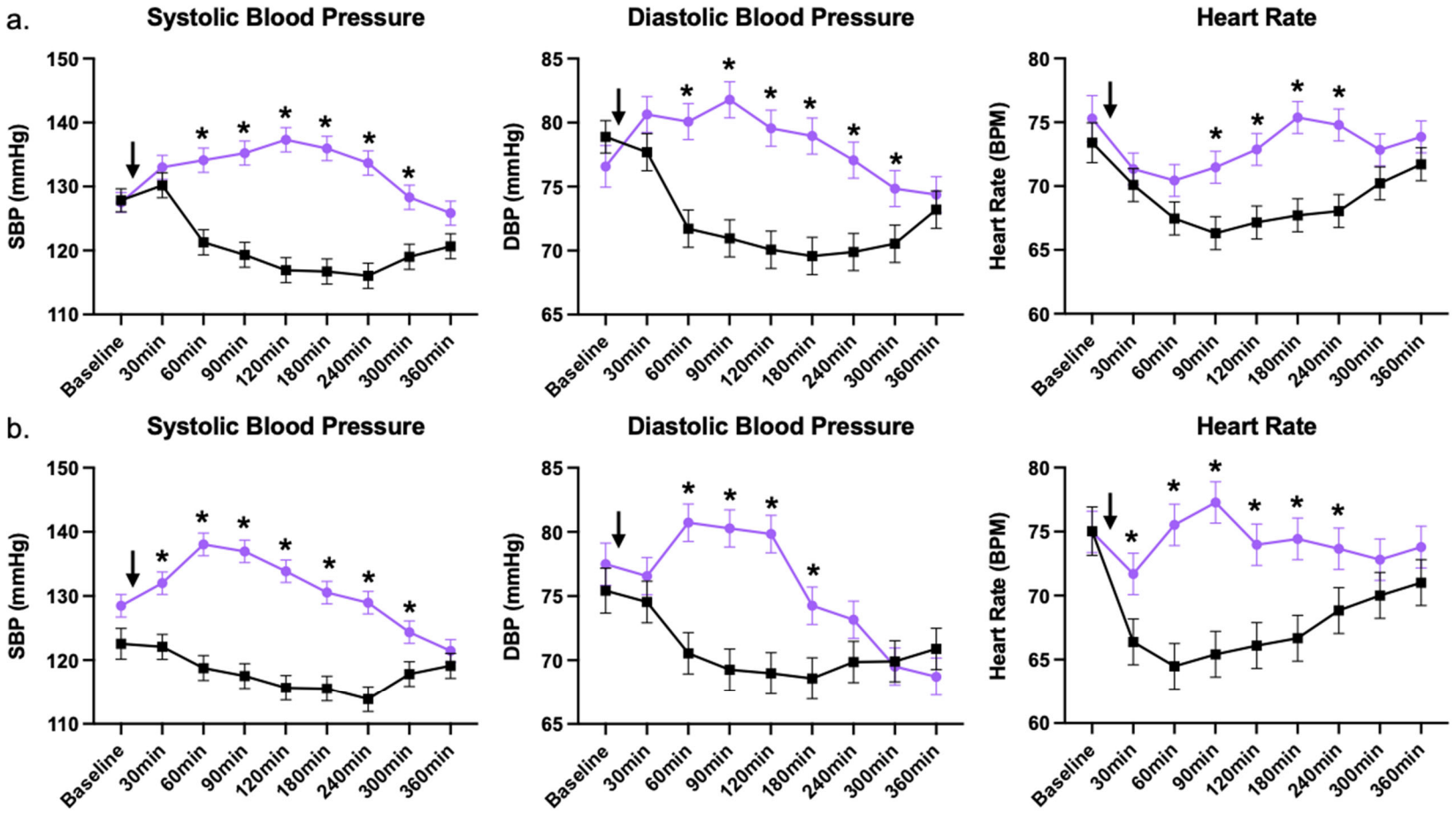
SOC	PT	PSILO (N = 48)	PSILO %	DIPHEN (N = 45)	DIPHEN %	TOTAL (N=93)	TOTAL %	P-VALUE
CARDIAC DISORDERS								
	Palpitations	1	2.1	0	0.0	1	1.1	1.00
GASTROINTESTINAL DISORDERS								
	Abdominal pain	1	2.1	0	0.0	1	1.1	1.00
	Abdominal pain upper	1	2.1	0	0.0	1	1.1	1.00
	Dyspepsia	1	2.1	0	0.0	1	1.1	1.00
	Nausea	10	20.8	3	6.7	13	14.1	**0.07**
	Vomiting	2	4.2	1	2.2	3	3.3	1.00
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
	Asthenia	1	2.1	0	0.0	1	1.1	1.00
	Fatigue	1	2.1	0	0.0	1	1.1	1.00
	Edema	0	0.0	1	2.2	1	1.1	0.48
	Pain	1	2.1	1	2.2	2	2.2	1.00
INVESTIGATIONS								
	Blood pressure diastolic increased	1	2.1	0	0.0	1	1.1	1.00
	Blood pressure increased	1	2.1	0	0.0	1	1.1	1.00
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS								
	Arthralgia	0	0.0	1	2.2	1	1.1	0.48
	Back pain	1	2.1	1	2.2	2	2.2	1.00
	Musculoskeletal pain	1	2.1	0	0.0	1	1.1	1.00
NERVOUS SYSTEM DISORDERS								
	Dizziness	1	2.1	1	2.2	2	2.2	1.00
	Headache	21	43.8	1	2.2	22	23.9	**< 0.01**
	Psychomotor hyperactivity	1	2.1	0	0.0	1	1.1	1.00
	Sedation	0	0.0	1	2.2	1	1.1	0.48
PSYCHIATRIC DISORDERS								
	Anger	0	0.0	1	2.2	1	1.1	0.48
	Anxiety	4	8.3	0	0.0	4	4.3	0.12
	Depressed mood	0	0.0	1	2.2	1	1.1	0.48
	Depression	1	2.1	0	0.0	1	1.1	1.00
	Dysphoria	1	2.1	0	0.0	1	1.1	1.00
	Illusion	1	2.1	0	0.0	1	1.1	1.00
	Insomnia	3	6.3	2	4.4	5	5.4	1.00

SOC	PT	PSILO (N = 48)	PSILO %	DIPHEN (N = 45)	DIPHEN %	TOTAL (N=93)	TOTAL %	P-VALUE
	Restlessness	0	0.0	1	2.2	1	1.1	0.48
	Suicidal Ideation	1	2.1	0	0.0	1	1.1	1.00
RENAL AND URINARY DISORDERS								
	Urinary incontinence	1	2.1	0	0.0	1	1.1	1.00
	Hyperventilation	1	2.1	0	0.0	1	1.1	1.00
	Oropharyngeal pain	0	0.0	1	2.2	1	1.1	0.48
SURGICAL AND MEDICAL PROCEDURES								
	Endodontic procedure	0	0.0	1	2.2	1	1.1	0.48

Caption: Table 3a lists frequency and percentage of participants experiencing adverse events for all adverse events occurring during the 32-week double-blind observation period following the first administration of study medication. Table 3b lists frequency and percentage of participants experiencing adverse events during the 48 hours following study drug administration (Session 1 or Session 2) the first administration of study medication Adverse events are organized by MedDRA System Class (SOC) and preferred term (PT). P-values from Fisher's exact tests are shown for descriptive purposes. Values less than 0.1 are shown in bold.

There were 34 duplicates AEs (PTs occurring more than once in an individual) during the double-blind follow-up period and 14 duplicates within 48 hours of drug administration. For the entire 32-week period, the duplicates were Diarrhea (2 AEs in the diphenhydramine group), Nausea (3 AEs in the psilocybin group, 1 AE in the diphenhydramine group), Upper respiratory tract infection (1 AE in the psilocybin group), Viral upper respiratory tract infection (1 AE in the diphenhydramine group), Alcohol poisoning (1 AE in the psilocybin group), Back pain (1 AE in the psilocybin group, 2 AEs in the diphenhydramine group), Dizziness (1 AE in the diphenhydramine group), Headache (12 AEs in the psilocybin group, 1 AE in the diphenhydramine group), Alcohol withdrawal syndrome (2 AEs in the diphenhydramine group), Anxiety (1 AE in the psilocybin group, 1 AE in the diphenhydramine group), Depressed mood (1 AE in the diphenhydramine group), Depression (1 AE in the psilocybin group), and Suicidal ideation (1 AE in the psilocybin group, 1 AE in the diphenhydramine group). For the 48 hours following drug administration, the duplicates were Nausea (3 AEs in the psilocybin group), Dizziness (1 AE in the diphenhydramine group), and Headache (9 AEs in the psilocybin group, 1 AE in the diphenhydramine group).

eFigure. Treatment Effects on Cardiovascular Outcomes



Caption: Mean and SE estimates for participants who received psilocybin (purple) and diphenhydramine (black) are illustrated for baseline (just prior to medication administration; covariate in each model), and eight timepoints following medication administration *(30, 60, 90, 120, 180, 240, 300, 360min after treatment administration)*. Participants who receive psilocybin are shown Arrows represent double-blind medication administration sessions.

*p<0.05 for Treatment x Time interactions in first medication session (systolic blood pressure: $F_{(7, 651)}$= 10.02, p<0.001; diastolic blood pressure: $F_{(7, 651)}$= 5.48, p<0.001; and heart rate: $F_{(1, 85)}$= 2.89, p=0.01) and second medication session (systolic blood pressure: $F_{(7, 544)}$= 10.59, p<0.001; diastolic blood pressure: $F_{(7, 544)}$= 11.16, p<0.001; and heart rate: $F_{(7, 545)}$= 4.74, p<0.001].