

Naturalistic Use of Mescaline Is Associated with Self-Reported Psychiatric Improvements and Enduring Positive Life Changes

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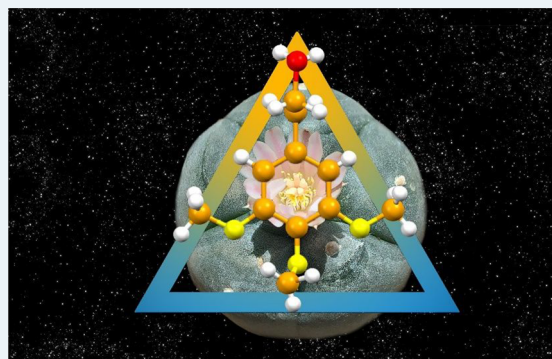
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ABSTRACT: Mescaline is a naturally occurring psychoactive alkaloid that has been used as a sacrament by Indigenous populations in spiritual ritual and healing ceremonies for millennia. Despite promising early preliminary research and favorable anecdotal reports, there is limited research investigating mescaline's psychotherapeutic potential. We administered an anonymous online questionnaire to adults ($N = 452$) reporting use of mescaline in naturalistic settings about mental health benefits attributed to mescaline. We assessed respondents' self-reported improvements in depression, anxiety, post-traumatic stress disorder (PTSD), and alcohol and drug use disorders (AUD and DUD). Of the respondents reporting histories of these clinical conditions, most (68–86%) reported subjective improvement following their most memorable mescaline experience. Respondents who reported an improvement in their psychiatric conditions reported significantly higher ratings of acute psychological factors including mystical-type, psychological insight, and ego dissolution effects compared to those who did not report improvements (Cohen's d range 0.7 – 1.5). Many respondents (35–50%) rated the mescaline experience as the single or top five most spiritually significant or meaningful experience(s) of their lives. Acute experiences of psychological insight during their mescaline experience were associated with increased odds of reporting improvement in depression, anxiety, AUD and DUD. Additional research is needed to corroborate these preliminary findings and to rigorously examine the efficacy of mescaline for psychiatric treatment in controlled, longitudinal clinical trials.

KEYWORDS: *psychedelics, mescaline, mental health, psychological insight, mystical-type experience*



Psychiatric conditions such as mood, anxiety-spectrum, and substance use disorders are commonplace and contribute substantially to the global disease burden.¹ Nearly 30% of people meet diagnostic criteria for a psychiatric disorder at some point in their lifetimes,¹ and psychiatric disorders comprise the leading cause of years lived with disability.² Psychiatric conditions also increase the risk of developing comorbid medical conditions such as type 2 diabetes and coronary vascular disease,³ and the public health burden involves high costs associated with lengthy hospitalization and a substantial loss in productivity.⁴ Treatment of psychiatric conditions typically focuses on a combination of psychotherapy and pharmacotherapy.⁵ The impact of these treatments, however, is complicated by disparities in access to care⁶ and treatment nonresponse by many who do receive intervention,⁷ necessitating further research into effective psychiatric treatment.

Contemporary research involving classic psychedelics has shown promise in treating a variety of mental health conditions including major depression, existential distress associated with a serious illness, post-traumatic stress disorder (PTSD), and

addiction.⁸ Classic psychedelics such as psilocybin, lysergic acid diethylamide (i.e., LSD), and ayahuasca (containing dimethyltryptamine and naturally occurring beta-carbolines) are known to stimulate significant perceptual, cognitive, and affective changes via agonist activity at the serotonin-2A receptor, although many other neurotransmitter systems likely contribute to their subjective effects.⁹ The precise neurobiological effects of psychedelic-assisted psychotherapy remain unidentified but appear related to functional changes in brain regions responsible for emotional processing and self-reference.¹⁰ Psychiatric improvement following psychotherapeutic psilocybin administration has also been associated with the intensity of acute psychological factors including mystical-type^{11–13} and psychological insight experiences.^{14–17} These

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Table 1. Demographic Characteristics among the Total Sample and among Those with Depression, Anxiety, PTSD, Alcohol Misuse or Alcohol Use Disorder, and Drug Misuse or Use Disorder as a Function of Whether Conditions Improved or Did Not Improve Following Mescaline Use^a

demographic variables	total sample (n = 452)		respondents with depression (n = 184)		respondents with anxiety (n = 210)		respondents with PTSD (n = 72)		respondents with alcohol misuse/ AUD (n = 72)		respondents with drug misuse/ DUD (n = 85)	
	M (SD) or %		better (n = 159)	no change/worse (n = 25)	better (n = 167)	no change/worse (n = 43)	better (n = 55)	no change/worse (n = 17)	better (n = 48)	no change/worse (n = 24)	better (n = 58)	no change/worse (n = 27)
age	38 (14.4)		35.5 (13.3)	41.4 (14.1)	35.5 (13.3)	40.8 (14.7)	45.6 (14.7)	39.8 (15.7)	39.8 (15.6)	45.3 (13.6)	33.5 (11.4)	38.3 (15.4)
gender												
female	20%		19%	20%	30%	16%	22%	18%	13%	17%	14%	4%
male	76%		70%	76%	61%	75%	66%	65%	83%	75%	79%	82%
transgender or gender-fluid	4%		11%	4%	9%	10%	12%	17%	4%	8%	7%	14%
ethnicity												
White	83%		84%	92%	80%	84%	82%	67%	81%	92%	79%	100%
non-White	17%		16%	8%	20%	16%	18%	33%	19%	8%	0%	21%
sexual orientation												
heterosexual	82%		84%	76%	73%	86%	63%	71%	78%	83%	77%	82%
non-heterosexual	18%		16%	26%	27%	14%	37%	29%	22%	17%	23%	18%
location												
North America	60%		65%	60%	64%	58%	71%	59%	62%	75%	60%	67%
Europe	20%		11%	28%	13%	23%	6%	18%	19%	8%	19%	19%
other	20%		24%	12%	23%	19%	23%	23%	19%	17%	21%	14%
employment												
employed	68%		68%	65%	66%	60%	56%	59%	65%	70%	66%	67%
other (e.g., retired/disabled)	32%		32%	35%	34%	40%	44%	41%	35%	30%	34%	33%
education												
less than Bachelor's	48%		52%	56%	51%	42%	59%	55%	65%	50%	70%	67%
Bachelor's or higher	52%		48%	44%	49%	58%	41%	45%	35%	50%	30%	33%

^aAbbreviations: PTSD = post-traumatic stress disorder; AUD = alcohol use disorder; DUD = drug use disorder. Values in italics (in the anxiety and drug misuse/DUD group) indicate a significant between-group difference ($p < 0.05$).

Table 2. Means and Standard Deviations of Acute Subjective Experiences and Persisting Effects among the Total Sample and among Those with Depression, Anxiety, PTSD, Alcohol Misuse/AUD, or Drug Misuse/DUD as a Function of Whether Conditions Improved or Did Not Improve Following Mescaline Use^a

variables	total sample (N = 452)	depression (n = 184)				anxiety (n = 210)				PTSD (n = 72)			
		better (n = 159)	no change or worse (n = 25)	t-stat	d	better (n = 167)	no change or worse (n = 43)	t-stat	d	better (n = 55)	no change or worse (n = 17)	t-stat	d
psychological insight (PIQ)	2.4(1.2)	2.9(1.0)	1.5(0.9)	-6.6***	1.5	3.0(0.9)	1.7(1.0)	-8.5***	1.4	3.2(1.0)	2.3(1.1)	-3.1***	0.9
mystical-type effects (MEQ)	3.2(1.1)	3.5(1.0)	2.2(1.0)	-6.0***	1.3	3.5(0.9)	2.4(1.2)	-6.9***	1.0	3.7(0.8)	2.7(1.4)	-3.7***	0.9
challenging effects (CEQ)	0.6(0.7)	0.7(0.6)	0.8(0.9)	0.9	NS	0.7(0.6)	0.9(0.9)	1.8	NS	0.7(0.6)	1.1(1.1)	2.1*	0.5
ego dissolution (EDI)	2.4(1.3)	2.6(1.2)	1.6(1.0)	-3.8***	1.0	2.7(1.2)	1.7(1.0)	-4.8***	0.9	2.6(1.3)	2.1(1.3)	-1.5	NS
personal meaning	4.6(1.4)	4.9(1.3)	3.6(1.3)	-4.5***	1.0	4.8(1.4)	4.1(1.2)	-3.0**	0.5	5.1(1.2)	4.2(1.4)	-2.4*	0.7
spiritual significance	4.4(1.9)	4.9(1.6)	3.3(1.8)	-4.5***	0.9	4.8(1.6)	3.6(2.0)	-4.2***	0.7	4.8(1.4)	4.5(2.0)	-0.7	NS
psychologically challenging	2.8(2.1)	4.9(1.6)	2.3(1.8)	-1.5	NS	2.8(2.0)	2.5(2.1)	-0.8	NS	2.7(2.1)	2.9(2.0)	0.5	NS
psychologically insightful	4.1(1.7)	4.7(1.6)	2.9(1.5)	-5.4***	1.2	4.5(1.6)	3.5(1.7)	-3.5**	0.6	4.9(1.6)	3.4(2.0)	-3.1**	0.8
well-being/life satisfaction	2.1(1.1)	2.5(0.7)	0.7(0.9)	-10.6***	2.2	2.5(0.7)	1.1(1.1)	-9.1***	1.5	2.5(0.8)	1.5(1.4)	-3.6**	0.9
life's purpose	1.8(1.1)	2.1(1.0)	0.7(0.8)	-6.8***	1.6	2.2(1.0)	1.0(1.0)	-6.8***	1.2	2.2(1.0)	1.3(1.2)	-3.1**	0.8
life's meaning	1.8(1.2)	2.0(1.1)	0.6(0.7)	-6.0***	1.5	2.1(1.0)	1.0(1.0)	-6.4***	1.1	2.3(1.0)	1.2(1.1)	-3.9***	1.1
social relationships	1.6(1.3)	2.0(1.0)	0.6(0.8)	-6.5***	1.6	2.1(1.0)	0.7(1.2)	-7.6***	1.3	2.2(0.9)	1.5(1.2)	-2.7**	0.7
attitudes about life	1.9(1.1)	2.3(0.8)	0.8(0.8)	-8.4***	1.9	2.3(0.8)	1.1(1.2)	-7.8***	1.2	2.4(1.0)	1.5(1.1)	-3.4**	0.9
attitudes about self	1.8(1.1)	2.0(1.0)	0.8(0.8)	-6.4***	1.3	2.2(1.0)	1.1(0.9)	-7.2***	1.2	2.3(1.1)	1.5(1.2)	-2.6*	0.7
relationship to nature	2.0(1.0)	2.3(0.9)	1.1(0.9)	-6.1***	1.3	2.4(0.9)	1.3(1.1)	-6.5***	1.1	2.4(1.0)	1.6(1.1)	-2.9**	0.8
behaviors	1.5(1.1)	1.9(1.0)	0.5(0.8)	-6.9***	1.6	2.0(1.0)	0.7(1.1)	-7.8***	1.2	2.2(1.0)	1.1(1.2)	-3.5**	1.0
how spiritual you are	1.6(1.2)	1.9(1.1)	0.6(0.8)	-5.8***	1.4	1.9(1.0)	0.9(1.1)	-5.7***	1.0	2.0(1.2)	1.1(1.2)	2.8**	0.8
attitudes about death	1.2(1.2)	1.5(1.3)	0.5(0.8)	-3.6***	0.9	1.5(1.2)	0.5(0.8)	-5.2***	1.0	1.7(1.3)	0.8(1.2)	-2.6*	0.7
views re: true nature of reality	1.7(1.2)	1.9(1.1)	0.8(0.8)	-4.7***	1.1	2.0(1.1)	1.1(1.2)	-4.4***	0.8	2.2(1.2)	0.9(1.1)	-3.8***	1.1

^a* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Note: Cohen's d was calculated to estimate effect sizes and is interpreted as 0.2 = small, 0.5 = medium. 0.8 = large. Scores on the PIQ, MEQ, and CEQ range from 0 to 5, and ratings of subjective well-being can range from -3 to +3.

findings suggest important psychological factors responsible for facilitating clinical improvements in addition to environmental variables such as interpersonal support, preparation, and therapeutic integration.

The psychiatric benefits of certain classic psychedelics (e.g., psilocybin) have been well studied in recent years, paving the way for more research into other classic psychedelics. For example, a recent study assessed patterns of use, motivation for consumption, and acute subjective effects among users of the classic psychedelic 3,4,5-trimethoxyphenethylamine (mescaline).¹⁸ Mescaline is a naturally occurring phenethylamine and a serotonin-2A/2C receptor agonist that can be prepared synthetically or extracted from the peyote or San Pedro cactus.¹⁹ A relatively low-potency psychedelic requiring active doses in the 200–400 mg range, mescaline produces subjective effects typically lasting 8 to 12 h.^{20,21} The medical uses of mescaline were first reported to the Western world in the late 19th century,²² but archeological evidence suggests that native North American peoples have used peyote ceremonially for nearly 6000 years.^{20,23} Peyote has long been used in the treatment of chronic alcoholism among members of the Native American Church.²⁴ Native American Church members who

use peyote also show significant improvements in psychological well-being when compared with control groups.²⁵ These findings support more recent anecdotal reports of symptom reduction following mescaline use described in online forums and communities.^{26,27} Furthermore, in a recent epidemiological survey of mescaline users,¹⁸ approximately two-thirds or more of the respondents who reported having a psychiatric condition prior to their mescaline experience also reported that the condition had improved following their mescaline experience.

Although preliminary data suggest that mescaline users report positive improvements in psychiatric conditions after use,¹⁸ no study has yet explored the possible mechanisms of change related to these psychiatric improvements or assessed the long-term effects associated with mescaline consumption. Therefore, the primary objective of this study was¹⁸ to explore the potential therapeutic and enduring effects of mescaline, and the mechanisms that may contribute to therapeutic effects. Specifically, we examined whether mescaline use was associated with improvements in self-reported depression, anxiety, PTSD, and alcohol/drug use disorders and whether acute subjective effects (i.e., mystical-type or psychological

Table 3. Means and Standard Deviations of Acute Subjective Experiences and Persisting Effects among the Total Sample and among Those with Alcohol Misuse/AUD or Drug Misuse/DUD as a Function of Whether Conditions Improved or Did Not Improve Following Mescaline Use^a

variables	total sample (N = 452)	alcohol misuse/AUD (n = 72)			drug misuse/DUD (n = 85)				
		better (n = 48)	no change or worse (n = 2)	t-stat	d	better (n = 58)	no change or worse (n = 27)	t-stat	d
psychological insight (PIQ)	2.4(1.2)	3.2(1.0)	1.9(1.2)	-5.0***	1.2	3.2(0.9)	2.0(1.0)	-5.7***	1.3
mystical type effects (MEQ)	3.2(1.1)	3.8(0.8)	3.0(1.1)	-3.5**	0.8	3.8(0.8)	2.9(1.2)	-4.4***	0.9
challenging effects (CEQ)	0.6(0.7)	0.7(0.6)	0.5(0.4)	-1.2	NS	0.8(0.6)	0.6(0.4)	-0.9	NS
ego dissolution (EDI)	2.4(1.3)	3.0(1.1)	2.2(1.3)	-2.5*	0.7	2.9(1.2)	2.1(1.1)	-2.7**	0.7
personal meaning	4.6(1.4)	5.1(1.3)	4.3(1.8)	-2.3*	0.5	4.8(1.3)	4.2(1.5)	-2.0	NS
spiritual significance	4.4(1.9)	5.2(1.4)	4.0(2.1)	-3.0**	0.7	4.9(1.4)	3.6(2.2)	-3.4**	0.7
psychologically challenging	2.8(2.1)	3.3(2.3)	2.4(2.4)	-1.5	NS	3.0(2.0)	2.1(1.9)	-1.9	NS
psychologically insightful	4.1(1.7)	5.0(1.5)	3.7(2.1)	-3.0**	0.7	4.7(1.5)	3.5(1.6)	-3.4**	0.8
well-being/life satisfaction	2.1(1.1)	2.6(0.8)	1.6(1.1)	-5.0***	1.0	2.5(0.7)	1.6(1.2)	-4.4***	0.9
life's purpose	1.8(1.1)	2.5(0.8)	1.2(1.2)	-5.6***	1.3	2.3(1.0)	1.3(1.1)	-4.1***	1.0
life's meaning	1.8(1.2)	2.4(0.8)	1.1(1.1)	-6.0***	1.4	2.1(1.0)	1.0(1.0)	-5.4***	1.1
social relationships	1.6(1.3)	2.3(0.8)	0.8(1.3)	-5.9***	1.4	2.2(0.9)	0.9(1.6)	-4.6***	1.0
attitudes about life	1.9(1.1)	2.5(0.7)	1.3(1.5)	-4.8***	1.0	2.4(0.8)	1.5(1.5)	-3.8***	0.8
attitudes about self	1.8(1.1)	2.4(0.9)	1.0(1.1)	-5.7***	1.4	2.3(0.9)	1.2(1.1)	-4.9***	1.1
relationship to nature	2.0(1.0)	2.7(0.7)	1.5(1.1)	-5.6***	1.3	2.6(0.7)	1.6(1.1)	-5.2***	1.1
behaviors	1.5(1.1)	2.3(0.9)	0.8(1.3)	-5.5***	1.3	2.1(1.0)	0.9(1.4)	-4.5***	1.0
how spiritual you are	1.6(1.2)	2.3(1.0)	1.2(1.1)	-4.4***	1.1	2.1(1.0)	1.2(1.2)	-3.6**	0.8
attitudes about death	1.2(1.2)	1.8(1.3)	0.7(1.1)	-3.9***	0.9	1.6(1.3)	0.8(1.2)	-3.0**	0.6
views re: true nature of reality	1.7(1.2)	2.4(1.0)	1.4(1.1)	-3.6**	1.0	2.1(1.1)	1.4(1.2)	-2.8**	0.6

^a* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Note: Cohen's d was calculated to estimate effect sizes and is interpreted as 0.2 = small, 0.5 = medium, 0.8 = large. Scores on the PIQ, MEQ, and CEQ range from 0 to 5, and ratings of subjective well-being can range from -3 to +3.

insight) were associated with improvements in these clinical domains.

RESULTS

Respondent Characteristics. During the recruitment period, 2025 individuals clicked on the recruitment advertisement, and 788 of them consented to participate in the survey. A total of 477 people completed all primary study questionnaires and reported valid responses. We removed data from 22 respondents who could not provide information regarding type of mescaline used and an additional three who reported being younger than 18 years old, leaving us with a final sample of 452 people.

Respondents were primarily White (83%), male (76%), and heterosexual (82%). The average age was 38 (SD = 14.4). Almost one-half (46%) of the sample reported lifetime use of mescaline between 1 and 3 times, with 70% reporting that they used yearly or less than once per year. Demographic characteristics across psychiatric subgroups did not differ significantly except for the volunteers who reported that their anxiety and drug misuse/DUD conditions improved after mescaline. Within the anxiety group, respondents who reported that their anxiety improved were significantly younger ($M = 35.5$; $SD = 13.3$) than those who reported that their conditions did not improve or worsened after use [$(M = 40.8$; $SD = 14.7)$, $t(2.21) = 3.17$, $p = 0.04$]. Within the drug misuse/DUD group, a larger proportion of White respondents reported that their condition did not improve or worsened (100%) compared with those who reported that their

condition improved (79%; $\chi(1) = 6.5$, $p = 0.01$). There were no other significant differences in demographic characteristics in the psychiatric subgroups between those who did or did not report an improvement in their respective conditions following mescaline.

Moreover, at the time of the survey, approximately one-third of the entire sample reported that their most memorable experience with mescaline was among the top five or single most (29% and 35%, respectively) personally meaningful or spiritually significant experiences of their lives. Of those respondents who reported that their psychiatric condition improved (compared with groups who reported No Change/Worse) after mescaline, 36–42% and 35–50%, respectively, rated the experience as the single or top five most meaningful experiences of their lives and the single or top five most spiritually significant experiences of their lives.

Factors Associated with Improvement in Mood, Anxiety, and Substance Use Outcomes Following Mescaline Use. Table 1 shows that nearly half the study sample reported having depression (41%; $n = 184$) or anxiety, (46%; $n = 210$) at the time of their most memorable mescaline use. A smaller proportion of the sample reported having PTSD (16%; $n = 72$), alcohol misuse or alcohol use disorder (AUD; 16%; $n = 72$), and drug misuse or drug use disorder (DUD; 19%; $n = 85$). Of those respondents reporting a prior psychiatric condition, the majority reported improvements in these conditions following mescaline as follows: depression (86%; $n = 184$), anxiety (80%; $n = 167$), PTSD (76%; $n = 55$), alcohol misuse or AUD (76%; $n = 48$), and drug misuse or

Table 4. Analysis of Odds Ratio Estimates for Acute Subjective Mescaline Effects Predicting “Better” or “No Change/Worse” in Reference Psychiatric Condition^a

predictor	depression		anxiety		PTSD		alcohol misuse/AUD		drug misuse/DUD	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
psychological insight	2.60**	1.43–4.58	3.25	1.91–5.54***	1.30	0.63–2.71	2.6**	1.34–5.14	3.34**	1.47–7.59
mystical-type	2.23	0.94–5.26	1.61	0.82–3.14	3.72*	1.20–11.51	1.2	0.47–3.39	1.53	0.49–4.75
ego dissolution	0.81	0.38–1.72	0.94	0.52–1.68	1.30	0.24–1.18	0.9	0.47–1.82	0.88	0.43–1.83

^aOR = odds ratio; CI = confidence interval; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

DUD (68%; $n = 58$). Interestingly, only a small minority of these respondents, 2–5%, reported an explicit intention to address or resolve their psychiatric conditions during their mescaline experience.

As shown in Tables 2 and 3, those respondents who reported an improvement in their psychiatric conditions reported significantly higher acute mystical-type (MEQ-30), psychological insight (PIQ), and ego dissolution effects (EDI) compared with their counterparts who did not report improvements (Cohen's d range 0.7–1.5). However, there were no significant differences in ratings of ego dissolution effects among those who did and did not report reductions in their PTSD symptoms after mescaline use. Additionally, with regard to enduring positive effects, those whose psychiatric conditions reportedly improved had higher ratings of the following variables: current sense of personal well-being or life satisfaction, life's purpose, life's meaning, social relationship as a whole, attitudes about life, attitudes about self, relationship to nature, positive behavioral changes, spirituality, attitudes about death, and views regarding the true nature of reality (Cohen's d range 0.6–2.2). Moreover, improvers in nearly all psychiatric subgroups rated their mescaline experience as more highly personally meaningful, spiritually significant, and psychologically insightful compared with those whose psychiatric conditions did not improve (Cohen's d range 0.5–1.2). There were no differences in ratings of acute psychologically challenging experiences between those who did or did not report improvements in psychiatric conditions after their most meaningful mescaline experience except within the PTSD subgroup. The respondents whose PTSD reportedly improved after mescaline reported lower ratings of acute challenging experiences than did their counterparts who reported no change or worsening in this condition.

On the basis of the significant subgroup differences (“better” versus “no change”/“worse”) in ratings of acute subjective effects (i.e., PIQ, MEQ-30, and EDI), we conducted a series of logistic regressions to determine if these acute effects were associated with improvements in respondents' reference psychiatric conditions following mescaline use (see Table 4). In the final models, a greater intensity of insight (PIQ), but not mystical-type (MEQ-30) or ego dissolution (EDI) experiences, was associated with increased odds of reporting improvement in depression (OR = 2.60, 95% CI, 1.43–4.58), alcohol misuse/AUD (OR = 3.25, 95% CI, 1.91–5.54), and drug misuse/DUD (OR = 3.34, 95% CI, 1.47–7.59). In the PTSD subgroup, the intensity of mystical-type (MEQ-30), but not insight (PIQ) or ego dissolution (EDI), was associated with increased odds of symptom improvement (OR = 3.72, 95% CI, 1.20–11.51).

DISCUSSION

This report from an online survey study provides detailed information from an international sample of 452 adults who reported improvements in psychiatric conditions following naturalistic use of mescaline. This is the first international survey study to examine the use of mescaline and its benefits on various psychiatric indices. Results indicate that mescaline use was associated with self-reported improvements in a variety of domains including mood, anxiety, and substance use disorders. Nearly half of all respondents reported having depression (41%) or anxiety (46%) at the time of their most memorable mescaline use, with a smaller proportion, approximately one-fifth, reporting having PTSD or drug or alcohol misuse or use disorders. A growing evidence base suggests that psychedelics used in naturalistic and human laboratory settings holds considerable promise for the treatment of a variety of clinical conditions.^{16,17,28,29} The transdiagnostic applications are wide ranging and include major depression,^{10,15,30} existential distress,^{13,31–34} substance use disorders,^{29,35,36} and PTSD,³¹ with sustained therapeutic effects observed in many cases.^{13,33,37} Although most respondents (95–98%) in our study did not report an explicit intention to address or change these conditions during their mescaline experience, it is possible that general intentions for psychological or spiritual exploration may have contributed to symptom improvement among this study sample.

The exploration of psychological mechanisms involved in the therapeutic process of psychedelic experiences is still in early phases. Several group differences in the present study highlight potentially relevant clinical factors and suggest compelling explanatory mechanisms to be explored in future controlled trials. For example, ratings of acute effects (mystical-type, psychological insight, and ego dissolution) and enduring effects (enhanced sense of personal well-being and life purpose, improved attitudes about life and self, and positive behavioral changes) differed significantly between those volunteers who reported that their psychiatric conditions improved and those who reported that their conditions did not improve or worsened following mescaline use. The effect sizes of these between-group differences were medium to large. Interestingly, acute phenomenological experiences of psychological insight, as indexed by a recently validated outcome measure,³⁸ was the only significant predictor of clinical improvement across several diagnostic categories in this study after controlling for the influence of acute mystical-type and ego dissolution experiences. This measure assessed the degree to which respondents gained new awareness into their emotions, behaviors, memories, or relationships during the mescaline experience.³⁸ These findings are compatible with two recent studies employing path analysis models that documented stronger associations between acute gains in psychological insight and clinical change, compared with acute mystical-type

experience.^{14,17} A large number of studies have documented a consistent relationship between mystical-type experiences and clinical outcomes.^{11–13,15,33,35,39–41} However, more nuanced and process-oriented models bolstered by the findings of the present study propose that although accessing acute self-transcendent states may be therapeutically necessary and valuable, what may ultimately be required for lasting therapeutic change is the assimilation of these transpersonal experiences with personal insights into one's psychological coping patterns.⁴² These experiential factors may enable individuals to re-examine their lives in the service of personal healing, consistent with reports of "quantum change"⁴³ or spontaneous spiritual conversion experiences.⁴⁴ Furthermore, we did not directly assess the role of emotionally cathartic experiences in this study, a phenomenon which has been documented in prior experimental studies with psychedelics^{41,45} and may be particularly relevant for clinical populations who use psychedelics. Cognitive insight in relation to one's intra- and interpersonal patterns may be insufficient to produce lasting change in the absence of emotional expression or processing. The coactivation of psychological insight and affective processing during the acute phase of a psychedelic experience may support the development of greater psychological flexibility⁴⁶ and emotion regulation⁴⁷ in the face of future stressors and serve to counteract the maladaptive use of experiential avoidance strategies.⁴⁸

It is intriguing to note that mescaline use was associated with improvements in PTSD symptoms in our study sample. Only one clinical trial has documented improvements in PTSD symptoms following the use of a classic serotonergic psychedelic,³¹ and no studies have explored the use of classic psychedelics to directly target PTSD as a primary outcome or clinical indication. Interestingly, the intensity of acute mystical-type experience in the PTSD group was associated with increased odds of symptom improvement in our logistic regression model. This is somewhat at odds with mounting evidence supporting the use of the entactogenic drug 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy for the treatment of PTSD,⁴⁹ wherein mystical experiences are less common⁵⁰ and the hypothesized mechanisms include enhanced fear extinction and reconsolidation of affective memories associated with the trauma.⁵¹ However, according to prevailing cognitive theories, traumatic experiences can profoundly violate a person's global beliefs about self, future, and the world, resulting in pervasive negative cognitions that maintain PTSD over time.^{52,53} A tentative explanation for the potential therapeutic effects of mescaline may relate to mescaline's combined psychedelic and entactogenic properties.⁵⁴ Phenomenological states of awe and interconnectedness^{55–57} may harmonize with feelings of emotional openness, trust, and safety to facilitate meaningful and constructive shifts in one's schemas, avoidance patterns, and appraisals of threat and safety. We hope that investigators will systematically explore the application of mescaline and other classic psychedelics toward the treatment of PTSD in future experimental trials.

In addition, it is notable that approximately 35–50% of respondents rated their naturalistic mescaline experience to be either the single most or among the top five most meaningful or spiritual experiences of their lives. These results align with other naturalistic^{16,17,28,29} and human laboratory studies that establish the potential of psychedelics to facilitate highly meaningful and spiritually significant experiences and improve

a variety of psychological outcomes.^{11–13,15,33,37} The slightly higher range of responses (52–96%) recorded in human laboratory studies suggests that the careful monitoring and therapeutic support associated with controlled administration of psychedelics in contemporary trials may potentiate the impact of psychedelics on psychological outcomes. It should also be noted that a considerably high proportion of respondents (73–80%) who reported on their use of 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) in a naturalistic survey study endorsed that their first 5-MeO-DMT experience, taking place in a group context with trained facilitators, was among the top five most meaningful or spiritual experiences of their lives.²⁸ These sessions involved similar structured preparation and integration activities to those utilized in human laboratory trials, underscoring the therapeutic value associated with these practices. Lastly, our results support the notion that psychologically challenging effects that occur during a psychedelic experience may be neutral or positively associated with the meaningfulness or spiritual significance of psychedelic experiences.^{28,58,59}

It is important to note the methodological limitations of our study and to urge caution when interpreting these findings. As this was a cross-sectional study, we cannot infer causality regarding the impact of mescaline on psychiatric conditions. Results are also limited by possible self-selection by individuals favorably disposed toward psychedelic experiences. For example, that recruitment occurred primarily via social media, email, and word-of-mouth, it is possible that respondents were biased in their predisposition to be publicly or privately affiliated with others who have used psychedelics. Additionally, it is possible that nonpharmacological variables including respondents' mindsets, positive expectancies, and environmental factors shaped their views and responses to our survey questions.^{60,61} The retrospective nature of respondents' reports is also subject to recall bias. Moreover, we did not administer standardized or psychometrically validated clinical measures of depression, anxiety, PTSD, AUD, and DUD and, instead, used a single item assessment to assess this history. Therefore, we were not able to verify the clinical information that respondents reported, and they do not represent absolute diagnoses. An additional design limitation is that we did not analyze outcomes with respect to psychiatric comorbidity; given the high rates of co-occurring disorders in the general population,⁶² it is likely that many of our respondents presented with multiple diagnoses that were not captured in this study. A final and important shortcoming of our study was that respondents were predominately young White males, which greatly limits the generalizability of these findings to other demographic groups. Across psychedelic research trials, Black, Indigenous, and People of Color are greatly underrepresented, and the field remains severely lacking in diversity and inclusion. It behooves the research community to assert more proactive efforts to recruit these individuals in future naturalistic and experimental trials.

Given these limitations, the present findings must be interpreted with caution. Nevertheless, the results from our study indicate that when administered in a naturalistic setting, mescaline may facilitate unintended improvements in self-reported depression, anxiety, PTSD, and substance use disorders. As documented in our previous report with this study sample,¹⁸ respondents in our study reported very low rates of adverse experiences, corroborating empirical evidence that mescaline carries a low risk for harmful health

consequences.^{63,64} These observations also contribute important preliminary data to our growing understanding of core therapeutic processes associated with mescaline use and suggest an important pathway through which psychological insight and mystical-type experience might influence subsequent clinical improvements. Our findings provide further support for a potential psychological mechanism of action of the clinically beneficial effects of mescaline on depression, anxiety, substance use disorders, and PTSD. Additional research is needed to systematically examine these processes in rigorous trials employing prospective, longitudinal designs. It is our hope that future investigators will continue to examine the therapeutic potential and explanatory mechanisms of this interesting psychedelic substance.

METHODS

This study is a secondary data analysis from a larger epidemiological study assessing individuals' patterns of use, motivations for consumption, benefits/consequences, and acute subjective effects of mescaline use among an international sample of volunteers.¹⁸ Respondents were recruited via Internet advertisements provided on several Web sites (e.g., www.facebook.com, www.reddit.com) and was distributed widely via email invitation to organizations (e.g., Chacruna) that may have newsletters, blogs, or listservs of potential respondents. Lastly, recruitment via word-of-mouth (i.e., snowballing) was evidenced by "shares" of our postings by nonstudy team members on Facebook and other social media. Recruitment occurred between January and October 2019. Potential respondents were presented with information regarding the purpose of the study, the anonymous nature of the study, and the approximate time required to complete the survey (45–60 min). Respondents were not provided compensation for their responses. Inclusion criteria consisted of having reading and writing fluency in English, being at least 18 years of age, and having ingested mescaline on at least one occasion. We did not collect identifying information. All procedures were approved by the Local Standing Ethical Committee at Maastricht University in The Netherlands.

Measures. Mescaline Survey. The primary survey utilized in this study included a wide-ranging series of questions detailed in a recent report¹⁸ about respondents' pattern of use, acute subjective effects, and potential consequences and benefits of their use of mescaline in the context of their most "memorable" experience.

Mental Health Measure. This questionnaire included a series of questions about whether respondents had been diagnosed with a mental health condition in the past, including depression, anxiety, PTSD, alcohol misuse or AUD, or drug misuse or DUD (categorical response options: yes, no, or unsure). Respondents could select multiple categories. The questionnaire also queried whether respondents' conditions had changed after mescaline consumption (categorical response options: better, stayed the same, or worsened).

Acute Mescaline Effects. Psychological Insight Questionnaire (PIQ). The PIQ consists of 23 items with two subscales: avoidance and maladaptive patterns, and goals and adaptive patterns.²⁸ Respondents were asked to reflect on their most memorable mescaline use and to rate the degree to which they experienced a broad range of insights on a 6-point scale from 0 = "None; not at all" to 5 = "Extremely (more than ever before in my life)." We used an overall total scale mean for

analyses. This measure showed excellent internal consistency in the current sample (Cronbach's $\alpha = 0.95$)

Mystical Experiences Questionnaire (MEQ-30). The MEQ-30 is a 30-item self-report questionnaire that measures the phenomenological effects occasioned by a psychedelic.⁵² Respondents were asked to think back on their most meaningful experience with mescaline and then to rate the intensity of the effects they experienced during that session on a 6-point scale from 0 = "None; not at all" to 5 = "Extreme (more than ever before in my life)." The MEQ-30 contains four factors: mystical, positive mood, transcendence of time/space, and ineffability. We used an overall total scale mean for analyses. This measure has shown good reliability (Cronbach's α ranging from 0.80 to 0.93) and demonstrated excellent internal consistency (of the total score) within our study sample (Cronbach's $\alpha = 0.96$).

Challenging Experiences Questionnaire (CEQ). The CEQ is a 26-item self-report instrument that measures the intensity of challenging experiences that may occur after ingesting a psychedelic.⁵⁷ Respondents were asked to consider their most meaningful experience with mescaline and then to report on the intensity of any psychologically or physically challenging effects they experienced using a 5-point scale from 0 = "None; not at all" to 5 = "Extreme (more than ever before in my life)." The CEQ contains seven total factors: fear, death, insanity, isolation, physical distress, and paranoia. We also calculated a total mean score to assess the overall intensity of challenging experiences during the respondents' mescaline sessions. This measure has shown good reliability in previous studies (Cronbach's α ranging from 0.70–0.89) and showed excellent internal consistency (of the total score) within the present sample (Cronbach's $\alpha = 0.92$).

Ego Dissolution Inventory (EDI). The EDI is an 8-item self-report measure that assesses the extent to which an individual experiences dissolution of ego boundaries after ingesting a psychedelic.⁶⁵ We asked respondents to reflect on their most memorable mescaline experience and to rate the degree of ego dissolution they experienced. We modified the original sliding scale from 0 to 100% to a Likert scale from 0 = "None; not at all" to 5 = "Extreme" in the present study. We used a total mean score in analyses. The measure has shown good convergent validity (Spearman's rho ranging from 0.83–0.89) and demonstrated excellent internal consistency within our sample (Cronbach's $\alpha = 0.91$).

Persisting Effects Questionnaire (PEQ). The PEQ¹¹ assesses self-rated changes in one's attitude, mood, behavior, and experience of spirituality after a psychedelic experience. The structure of the PEQ also enables it to capture longitudinal effects. Respondents were asked to consider their most meaningful experience with mescaline and then to report on the degree to which the session was personally meaningful, spiritually significant, psychologically challenging, and psychologically insightful. They were asked to rate these four items on a scale of from 0 = "No more than routine, everyday experiences" to 7 = "The single most [personally meaningful, spiritually significant, psychologically challenging, or psychologically insightful] experience of my life," respectively. Additionally, we asked respondents to rate whether their experience with mescaline had led to any enduring changes in their current sense of well-being or life satisfaction, life's purpose, life's meaning, social relationships, attitudes about life, attitudes about death, and views regarding the true nature of reality and the universe using a scale from

−3 = “Strong negative changes that I consider undesirable” to +3 = “Strong positive changes that I consider desirable”. Each item was used individually in analyses.

Data Analyses. The first step of our analysis involved calculating frequency counts and analyzing descriptive data regarding demographics, patterns of mescaline use, acute subjective effects (i.e., mystical-type, ego dissolution, psychological insight and challenging effects), beliefs about the mescaline experience, and rates of reported psychiatric conditions. We then split the sample into five psychiatric subgroups based on whether respondents reported having prior diagnoses of depression, anxiety, PTSD, alcohol misuse or AUD, or drug misuse or DUD conditions. We then split these psychiatric subgroups based on whether respondents reported that their psychiatric conditions became “Better”, or “Worse”/“No Change” after their most memorable mescaline experience. Next, we conducted a series of chi-square analyses and *t*-tests to compare variables (e.g., demographic characteristics, mean ratings of acute subjective effects and mean ratings of beliefs about the positive effects of mescaline) as a function of outcome (e.g., Better versus No Change/Worse) within each psychiatric subgroups. We subsequently conducted a series of logistic regression analyses to determine whether any significant between-group findings on any measures of acute effects, identified in the previous step, were predictive of whether respondents did or did not report improvements in their conditions in each psychiatric subgroup. We utilized a standard alpha of 0.05 to determine statistical significance. We also calculated Cohen’s *d* effect sizes and odds ratios to facilitate interpretation of significant effects.

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