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5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety

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ABSTRACT

Background: A recent epidemiological study suggested that 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) used for spiritual and recreational reasons is associated with subjective improvement in depression and anxiety. Further exploration of the potential psychotherapeutic effects of 5-MeO-DMT could inform future clinical trials. **Objectives:** We examined self-reported improvement in depression and anxiety among people who use 5-MeO-DMT in a group setting with structured procedures guiding dose and administration of 5-MeO-DMT. Such procedures also include activities for the preparation of, and support during/following sessions, which are similar to procedures used in clinical trials of hallucinogen administration. Next, we examined whether depression or anxiety were improved following use, and whether the acute subjective effects (mystical/challenging) or beliefs about the 5-MeO-DMT experience were associated with improvements in these conditions. **Methods:** Respondents ($n = 362$; $M_{age} = 47.7$; Male = 55%; White/Caucasian = 84%) completed an anonymous web-based survey. **Results:** Of those reporting having been diagnosed with depression (41%) or anxiety (48%), most reported these conditions were improved (depression = 80%; anxiety = 79%) following 5-MeO-DMT use, and fewer reported they were unchanged (depression = 17%; anxiety = 19%) or worsened (depression = 3%; anxiety = 2%). Improvement in depression/anxiety conditions were associated with greater intensity of mystical experiences and higher ratings of the spiritual significance and personal meaning of the 5-MeO-DMT experience. There were no associations between depression or anxiety improvement and the intensity of acute challenging physical/psychological effects during the 5-MeO-DMT experience. **Conclusions:** Future prospective controlled clinical pharmacology studies should examine the safety and efficacy of 5-MeO-DMT administration for relieving depression and anxiety.

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Introduction

Anxiety and depression are common mental health conditions (1), with global lifetime prevalence of approximately 13% and 10%, respectively (1,2). In the United States (US), past year prevalence of any mood disorder is 10% and is 19% for any anxiety disorder (3–5). Additionally, the public health burden of depression and anxiety contributes to occupational impairment, such as reduced workforce participation and lost productivity (6), and increases the risk for chronic physical conditions (e.g., cardiovascular disease) (7,8). Given high prevalence rates and the public health and personal burden, several interventions have been developed to address these conditions, which include a combination of psychotherapy and pharmacotherapy (9,10). Despite supportive evidence for these interventions, many people do not have access to

such services (11), and many people who have access continue to experience symptoms despite intervention (12–16), highlighting the need for more research.

One emerging area of research has examined the possible psychotherapeutic action of classic psychedelics as an adjunct to psychotherapy (17,18). Classic psychedelics are a class of hallucinogens, which act primarily as agonists of the 5-HT_{2A} receptor and are capable of producing profound changes in sensory perceptions, mood, and cognitions (19–22). Recent studies examining psilocybin administered as an adjunct to structured supportive psychotherapy have demonstrated efficacy in decreasing symptoms of depression and anxiety (18,22–24). For example, two placebo-controlled studies showed that psilocybin-assisted

supportive psychotherapy was efficacious in decreasing depression and anxiety in the context of cancer-related psychiatric distress following a single administration, with the suggestion of sustained effects for at least 6 months (23,24). Moreover, a recent open label study in patients with treatment-resistant depression showed that psilocybin contributed to reductions in depression and anxiety symptoms at 1 week and was sustained in the 3-month follow-up (17). Although more work is needed to fully understand the neurological and psychological mechanisms of action, efficacy appears to be associated with the intensity of acute mystical-type phenomena experienced during psilocybin sessions (23–27).

If future trials with larger samples continue to show positive therapeutic effects and a favorable safety profile (for a review see 18), psilocybin could potentially garner regulatory approval for use as an adjunct to psychotherapy in the US and elsewhere. However, despite these advances, the widespread dissemination of psilocybin-assisted psychotherapy is potentially challenging, given that drug administration sessions consist of a 7- to 10-hour day with two therapist guides and a medical monitor, which may be difficult to implement in traditional outpatient mental health settings. Therefore, short-acting psychedelics may warrant examination as potential therapeutics in order to overcome these barriers. One possible substance is 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), which is a short-acting (30–90 minutes) tryptamine found in the venom and skin of *Bufo alvarius* toads and can also be synthetically produced (19,28,29). According to a recent epidemiological survey study, 5-MeO-DMT is used infrequently, primarily for spiritual exploration, has a safe profile of use and low potential for psychiatric or biomedical consequences, and might have psychotherapeutic effects (30). For example, most respondents reported having anxiety (63%) or depression (61%), with over two-thirds (69% to 77%) claiming improvement in symptoms following 5-MeO-DMT use (30).

Although epidemiological findings regarding the association of 5-MeO-DMT use and improvements in anxiety and depression are encouraging, no laboratory studies administering 5-MeO-DMT to humans have been conducted. However, some people use 5-MeO-DMT in a group setting in the US, with established procedures that stipulate the dose and administration of 5-MeO-DMT, and provide guidelines for the preparation of, and support during/following sessions similar to those procedures used in clinical trials (31). Such a group provides a unique opportunity to examine the possible therapeutic effects of 5-MeO-DMT in a naturalistic group setting. Therefore, using data from a survey study of people who use 5-MeO-DMT

in this group, the primary aim of this current analysis is to examine whether use of 5-MeO-DMT is associated with spontaneous and unintended improvements in depression and anxiety among people who have used 5-MeO-DMT in this specific structured setting. The second aim of this study is to examine whether acute subjective effects (i.e., mystical or challenging), or beliefs about the 5-MeO-DMT experience are associated with improvement in depression and anxiety.

Method

Respondents, setting, and procedure

Potential respondents for this study came from an email distribution list of people in the US that use 5-MeO-DMT in a group setting. The administrator of this group was approached through a mutual friend of the authors (none of whom were involved with the group otherwise) to inquire about the possibility of surveying members. After several meetings the administrator agreed to help with recruiting members of the group. Established in 2007, during a time when the use of 5-MeO-DMT was uncontrolled and legal in the US (scheduling occurred in 2011; 32), this group was started with the intention of creating a safe and practical context for the use of 5-MeO-DMT. The group uses synthesized 5-MeO-DMT, which is tested in a laboratory via gas chromatography mass spectrometry (range = 98–100% pure). New members of the group must be at least 21 years of age, referred and sponsored by someone who is already a member, undergo a verbal health screening, and participate in a 2-h orientation session that provides details about the effects of 5-MeO-DMT before participation. Group members must also be willing to be present for and assist others who receive 5-MeO-DMT in their group session, commit to assisting with their physical and emotional safety, and agree to keep information about the group members confidential. Group sessions, which are conducted in a variety of geographic locations (primarily in the Western US), have a similar structure, include between 5 and 12 people (1–2 of these individuals administer and guide the sessions), and last approximately 6–7 h depending on the number of people present.

Each group session begins with preparation of the environment for the session (e.g., co-creating a calm space by providing for the physical comfort for attendees, playing pre-recorded music, etc.), followed by a “check-in” with each attendee (e.g., providing name, how they are feeling, and stating a specific intention for the session), and a brief ritual invocation of the purpose for the session. Next, one attendee is provided a specific dose of 5-MeO-DMT by means of inhalation (via custom crafted, argon gas, piston vaporizer) while the

other attendees quietly and mindfully attend to the person and assist the facilitators as necessary to provide safety for the individual. Doses are selected based in part on each individual's known sensitivities and prior experience with other psychedelic substances (e.g., psilocybin, LSD, etc.). For those with limited prior experience with psychedelics or with greater sensitivity, a lower dose range (between 5 and 7mg) is used. A medium dose range (8-12mg) is used for those with moderate experience with psychedelic substances, and a higher dose range (13-15mg+) is used for those with a regular practice of ingesting these substances. Each individual's experience lasts approximately 35–45 min. This procedure is repeated with the next attendee, until all attendees have received 5-MeO-DMT. The conclusion of the session includes a “closing circle” or “check-out” (e.g., each attendee briefly shares their thoughts about the experience, how their intention may have been fulfilled, and any emotions they are having after the experience). Finally, a brief “benediction” or prayer/meditation is offered before leaving the session. Attendees are invited to spend time “integrating” their experiences with others (e.g., attending a future gathering with other group members to discuss their experiences) and individually (e.g., spending time journaling about their experiences or contemplating their experience in nature in the days after the session).

Following attendance at a session each member is given the opportunity to receive a monthly electronic newsletter from the group administrator. Potential respondents for this study were any group member who participated in at least one 5-MeO-DMT group session between 2007 and 2017 and who provided an email address and agreed to receive the group's newsletter. During the span of four months (from April 2017 to August 2017) an administrator of the email distribution list sent a recruitment notice embedded in the newsletter (approximately 1 email/month) to everyone on the list. The recruitment notice contained information about the study, the amount of time required to complete the survey (approximately 20 min) and informed potential respondents that their participation would be anonymous. Potential respondents were also informed that we would donate \$2USD per person (up to \$250) to the Multidisciplinary Association for Psychedelic Studies in consideration of their time completing the survey (MAPS was not otherwise involved in the study). Once at the secure internet site (hosted by surveygizmo.com), each respondent was presented with the informed consent document, which repeated the aims of the study and described eligibility criteria for the survey (i.e., being ≥ 18 years old, able to read/understand English, and have used 5-MeO-DMT at least once). No identifying information (e.g., name, address) was collected as part of

the study. All procedures were approved by the Bowling Green State University's human subject's review board.

Measures

5-MeO-DMT survey

The primary survey used for this study included an extensive series of questions about the patterns of use, acute subjective effects, and potential consequences and benefits of using 5-MeO-DMT in this group setting (data will be presented in a forthcoming paper). As it pertains to the current analysis, the respondents were asked to report their number of lifetime doses of 5-MeO-DMT, frequency of use, time since last use, the dose used, and their primary reason for using 5-MeO-DMT.

Depression and anxiety measure

This questionnaire included a series of questions about whether respondents had a specific psychiatric condition, including depression or anxiety (categorical response options: yes, no, unsure), and whether their conditions had changed (categorical response options: better, stayed the same, worsened) after 5-MeO-DMT use.

Acute mystical experiences

The Mystical Experiences Questionnaire (MEQ30) was used to assess acute subjective effects that may occur after ingesting a hallucinogen (33,34). Respondents were asked to think back on their first experience with 5-MeO-DMT and then to rate the intensity with which they experienced each of 30 effects at any point during their 5-MeO-DMT session on a 6-point scale from 0 = “None; not at all” to 5 = “Extreme.” The MEQ30 is comprised of 4 subscales (1): Mystical (2); Positive mood (3); Transcendence of time/space; and (4) Ineffability (33). A total score is also scored which assesses the overall intensity of mystical experience. Internal consistency of each scale was: Mystical (Cronbach's $\alpha = .96$), Positive mood (Cronbach's $\alpha = .93$), Transcendence (Cronbach's $\alpha = .91$), Ineffability (Cronbach's $\alpha = .92$), Total Scale (Cronbach's $\alpha = .97$).

Acute challenging experiences

The Challenging Experiences Questionnaire (CEQ) was included to assess the psychologically and physically difficult experiences that may occur after ingesting a hallucinogen (35). Respondents were asked to think

back on their first experience with 5-MeO-DMT and then to rate the intensity with which they experienced each of 26 challenging effects at any point during their 5-MeO-DMT session on a 6-point scale from 0 = “None; not at all” to 5 = “Extreme.” The CEQ is comprised of 7 subscales (1): Fear (2), Grief (3), Physical Distress (4), Insanity (5), Isolation (6), Death, and (7) Paranoia (35). We also calculated a total CEQ score to assess the overall intensity of challenging effects each respondent experienced during the 5-MeO-DMT session. Internal consistency of each scale in the current sample was: Fear (Cronbach’s alpha = .91), Grief (Cronbach’s alpha = .83), Physical distress (Cronbach’s alpha = .67), Insanity (Cronbach’s alpha = .80), Isolation (Cronbach’s alpha = .87), Death (Cronbach’s alpha = .84), Paranoia (Cronbach’s alpha = .68), Total Scale (Cronbach’s alpha = .92).

Beliefs about the 5-MeO-DMT experience

Three items were also included from the Persisting Effects Questionnaire (24,26,31), in which participants rate the extent to which their first 5-MeO-DMT experience was personally meaningful (on a scale from 0 = “No more than routine, everyday experiences” to 7 = “The single most meaningful experience of my life”), and spiritually significant (on a scale from 0 = “Not at all” to 5 = “The single most spiritually significant experience of my life”). The third item assessed the degree to which each respondent believed their 5-MeO-DMT experience had led to changes in their personal well-being or life satisfaction (on a scale from -3 = “Decreased very much” to 3 = “Increased very much”).

Demographics and substance use questions

We examined the age, gender, ethnicity, sexual orientation, country/region of residence, employment status, level of education, and relationship status of each respondent as well as recent consumption of a variety of substances (e.g., alcohol, cannabis, psilocybin).

Data analyses

We began by conducting frequency counts and descriptive analyses of demographic characteristics, 5-MeO-DMT use characteristics, acute subjective mystical and challenging effects, beliefs about the 5-MeO-DMT experience, and rates of depression and anxiety. Next, the sample was split into two groups based on whether a respondent reported being diagnosed with depression or anxiety. We then split the depression subsample

based on whether they reported that their depression was “Better” or whether they reported “No Change”/“Worse” depression following 5-MeO-DMT use. Next, a series of chi-square analyses and two-sided *t*-tests were used to compare all study variables between these two groups (Better vs. No Change/Worse) including all demographic characteristics, mean ratings of acute subjective mystical and challenging effects, mean ratings of beliefs about the positive effects of 5-MeO-DMT, mean dose of 5-MeO-DMT respondents had used, and mean number of lifetime uses of 5-MeO-DMT. Next, this same analysis was conducted in the anxiety subsample and we compared all study variables between the two anxiety subgroups as a function of whether anxiety had improved or not (i.e., Better vs. No Change/Worse). Because of the limitations associated with using significance tests as a standalone statistical procedure (36) and the limitations of using a corrected alpha in exploratory studies (e.g., 37,38), a standard alpha of .05 was used to determine the significance of statistical tests and we calculated effect sizes (Cohen’s *d*) for each test to assist with interpretation of meaningful effects. Analyses were conducted using SPSS v.24 (39).

Results

Respondent characteristics

During the recruitment period, 519 people clicked the secure link to the online survey and were presented with information about the study. Of these individuals, 380 (73%) consented and completed all of the main study questionnaires related to 5-MeO-DMT use. Of these 380 respondents, we excluded 16 because of duplicate IP addresses (in order to ensure that no more than one survey was submitted per person) and 2 for careless responding. The final sample was comprised of 362 respondents (70% of those who clicked the link).

As shown in Table 1, the sample was comprised primarily of older (Mean age = 47.7, *SD* = 13.3), white/Caucasian (84%), heterosexual (79%), college graduates (75%), approximately half of whom were female (45%). In terms of 5-MeO-DMT use history, most respondents (63%) had used only 1–3 times in their lifetime and used about once per year or less frequently (64%). Additionally, almost all participants (90%) reported that their use of 5-MeO-DMT had decreased or stayed the same over the past year and over one-half (56%) reported they last used at least 6 months ago, with 43% reporting that at least one year had passed since they last used 5-MeO-DMT. Moreover, at the time of survey most respondents (73%)

Table 1. Demographic characteristics among the total sample and among those with depression or anxiety as a function of whether conditions improved or did not improve following 5-MeO-DMT use.

Demographic Variables	Total Sample (n = 362)	Participants with depression (n = 149; 41%)		Participants with Anxiety (n = 173; 48%)	
	M(SD) or %	Better (n = 120; 80%) M(SD) or %	No Change Or Worse (n = 29; 19%) M(SD) or %	Better (n = 136; 79%) M(SD) or %	No Change Or Worse (n = 37; 21%) M(SD) or %
Age	47.7 (13.3)	43.5 (11.6)	50.7 (14.7)	44.2 (12.5)	49.1 (13.8)
Gender					
Female	45%	50%	57%	45%	57%
Male	55	50	43	55	43
Ethnicity					
White	84%	85%	86	82%	87%
Non-White	16	15	14	18	13
Sexual Orientation					
Heterosexual	79%	69%	83%	74%	81%
Non-Heterosexual	21	31	17	26	19
Employment					
Employed	64%	59%	55%	65%	65%
Other (e.g., retired/disabled)	36	41	45	35	35
Education					
Less than Bachelor's	25%	28%	17%	28%	35%
Bachelor's or higher	75	73	83	72	65

reported that their first 5-MeO-DMT session was among the top five or single most personally meaningful experience of their life, and 80% reported that their session was one of the top five or single most spiritually significant experience of their life. Large proportions of the sample had used alcohol (77%) or cannabis (74%) in the three months prior to completing the survey, and smaller proportions had used other psychedelics in the past three months (psilocybin = 33%; LSD = 20%; ayahuasca = 15%; dimethyltryptamine = 11%).

Factors associated with improvement in anxiety and depression following 5-MeO-DMT use

Table 1 shows that 41% ($n = 149$) of the sample reported that they had depression, 48% ($n = 173$) had anxiety, and 34% ($n = 117$) had both depression and anxiety. Of those with depression ($n = 149$), 80% ($n = 120$) reported that their depression was better following 5-MeO-DMT use, 17% ($n = 25$) reported no change in depression, and 3% ($n = 4$) stated that they experienced a worsening in this condition, following 5-MeO-DMT use. Of those with anxiety ($n = 173$), 79% ($n = 136$) reported that their anxiety was better following 5-MeO-DMT use, 19% ($n = 33$) reported no change in anxiety, and 2% ($n = 4$) stated that they experienced a worsening in this condition. Interestingly, only 6 respondents reported that they used 5-MeO-DMT specifically for help with anxiety and only 1 respondent reported using for help with depression. There were no differences in demographic characteristics in either the depression and anxiety groups between those

who did or did not report an improvement in these conditions (null chi-square findings not presented; available upon request). However, those who reported their depression was better following 5-MeO-DMT use were significantly younger ($M = 43.5$, $SD = 11.6$) than those who reported their depression was the same or worsened after use ($M = 50.7$, $SD = 14.7$), $t(147) = 2.86$, $p = .018$, Cohen's $d = .60$. Similarly, those who reported their anxiety was better following 5-MeO-DMT use were significantly younger ($M = 44.2$, $SD = 12.5$) than those who reported their anxiety was the same or worsened after use ($M = 49.1$, $SD = 13.8$), $t(170) = 2.03$, $p = .044$, Cohen's $d = .38$.

There were no differences in ratings of acute challenging experiences during their first 5-MeO-DMT session between those who did or did not report an improvement in depression or anxiety following 5-MeO-DMT use (see Table 2). Additionally, those who reported an improvement in their depression or anxiety reported significantly higher MEQ30 scores (Depression group: MEQ30 total score and positive mood subscale; Anxiety group: MEQ30 total score, and all MEQ30 subscales) during their first 5-MeO-DMT session compared to those reporting no improvements in their depression or anxiety. Similarly, improvers in both groups reported higher ratings of the personal meaning and spiritual significance of the 5-MeO-DMT session and higher ratings regarding the degree to which that experience contributed to a sense of well-being/life satisfaction compared to those whose depression or anxiety had not improved.

Table 2. Means and standard deviations of acute mystical and challenging experiences, and ratings of personal meaning, spiritual significant, and effects on well-being/life-satisfaction, among the total sample and among those with depression or anxiety as a function of whether conditions improved or did not improve following 5-MeO-DMT use.

Variables	Total Sample (n = 362)	Participants with Depression (n = 149; 41%)				Participants with Anxiety (n = 173; 48%)			
		Better (n = 120; 80%)	No Change Or Worse (n = 29; 19%)	t-stat	d	Better (n = 136; 79%)	No Change Or Worse (n = 37; 21%)	t-stat	d
Acute Mystical Experiences									
Mystical	4.3(1.0)	4.3(0.8)	4.0(1.3)	-1.9	0.39	4.4(0.7)	3.9(1.3)	-2.8**	0.51
Positive Mood	4.3(1.1)	4.4(0.8)	3.6(1.4)	-4.0***	0.84	4.5(0.8)	3.8(1.3)	-3.8***	0.70
Transcendence	4.4(0.9)	4.5(0.8)	4.3(1.0)	-1.1	0.23	4.5(0.8)	4.0(1.2)	-2.6**	0.48
Ineffability	4.4(1.0)	4.5(0.9)	4.2(1.3)	-1.3	0.27	4.5(0.8)	4.1(1.2)	-2.5*	0.47
MEQ Total Score	4.3(0.9)	4.4(0.7)	4.0(1.1)	-2.5*	0.51	4.4(0.6)	4.0(1.2)	-3.3**	0.61
Acute Challenging Experiences									
Isolation	0.4(0.9)	0.5(1.0)	0.7(1.0)	1.1	0.22	0.5(1.0)	0.4(0.7)	-0.5	0.10
Fear	1.0(1.3)	1.1(1.3)	1.4(1.7)	1.4	0.29	1.1(1.3)	1.1(1.5)	0.2	0.04
Grief	0.9(1.1)	1.2(1.1)	1.3(1.6)	0.2	0.04	1.1(1.1)	1.0(0.9)	-0.9	0.16
Physical Distress	0.9(0.9)	1.1(0.9)	1.0(1.1)	-0.4	0.08	1.1(1.0)	0.8(1.0)	-1.2	0.23
Insanity	0.5(1.0)	0.7(1.2)	0.8(1.2)	0.4	0.08	0.6(1.1)	0.6(1.3)	-0.3	0.06
Death/Dying	1.5(1.7)	1.9(1.9)	1.8(1.9)	-0.2	0.05	1.7(1.8)	1.3(1.8)	-1.3	0.24
Paranoia	0.0(0.3)	0.1(0.2)	0.2(0.8)	1.7	0.35	0.0(0.2)	0.1(0.2)	1.2	0.23
CEQ Total Score	0.8(0.8)	0.8(0.1)	1.0(0.2)	0.5	0.10	0.8(0.1)	0.7(0.1)	-1.2	0.22
Ratings of Meaning and Effects of 5-MeO-DMT									
Personal	5.8(1.0)	5.9(1.0)	5.4(1.5)	-2.3*	0.48	5.9(0.9)	5.5(1.1)	-2.6**	0.49
Meaning									
Spiritual	4.0(0.9)	4.2(0.8)	3.7(1.2)	-2.7**	0.57	4.2(0.8)	3.8(1.0)	-2.8**	0.52
Significance									
Subjective	2.3(1.0)	2.6(0.6)	1.3(1.6)	-6.9***	1.44	2.7(0.6)	1.7(1.6)	-6.0***	1.12
Wellbeing									

*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 MEQ and CEQ subscales can range from 0–5. Ratings of personal meaning can range from 0–7, ratings of spiritual significance can range from 0–5, and ratings of subjective wellbeing can range from -3 to +3.

Abbreviations: MEQ = Mystical Experiences Questionnaire; CEQ = Challenging Experiences Questionnaire

Discussion

The present study suggests that 5-MeO-DMT administered in a naturalistic group setting is associated with improvements in depression and anxiety among a sample of individuals using 5-MeO-DMT for spiritual purposes. For example, approximately 80% of respondents with anxiety or depression in this sample reported improvements in these conditions after using 5-MeO-DMT. Results also indicated that the intensity of acute mystical effects of 5-MeO-DMT were associated with improvements in depression and anxiety. These results are consistent with laboratory studies that found positive psychotherapeutic effects of psilocybin as an adjunct to supportive psychotherapy (18,22–24) and suggests the importance of the acute mystical effects of psychedelic substances as one of the mechanisms by which they exert psychotherapeutic effects (24–26,40).

We also examined whether acute challenging effects of 5-MeO-DMT were related to reported changes in depression and anxiety. Results suggest that there were no differences in the intensity of acute challenging experiences between those who did or did not report an improvement in depression or anxiety, which could be because respondents reported only a “slight” intensity of challenging

experiences, thus attenuating any possible relations. This finding is consistent with findings from laboratory-based studies of psilocybin which utilize similar preparatory and integration activities (17,24,26,31), thus highlighting the importance of the structure and the setting within which psychedelics are administered.

Furthermore, the findings from the present study support the idea that psychologically challenging effects that occur during a psychedelic session could be neutral or positively associated with personally meaningful or spiritually significant psychedelic experiences (35,41). Results also indicated that those who had higher ratings of the personal meaning and spiritual significance of their 5-MeO-DMT session had greater self-reported improvements in their depression and anxiety, which is also consistent with prior psilocybin studies (23,24,27). Improvement in depression and anxiety was also positively associated with younger age, suggesting that the psychotherapeutic effects may be attenuated among those who are older and may have been struggling with the chronic effects of depression and anxiety for a longer period of time. However, this hypothesis warrants further investigation using a rigorous controlled design.

The results from this study should be considered in light of several limitations. First, we included only English-

speaking respondents, most of whom were white, heterosexual, college graduates who use 5-MeO-DMT in the western US, thus restricting the generalizability of these findings. Additionally, the study is cross-sectional, and used an online data collection procedure, thus limiting our ability to draw any temporal and thus causal inferences and restricting our sample to only those who were willing to participate in online research. This study is also lacked a standardized assessment for anxiety or depression, and we used other self-report measures, and thus is limited by retrospective recall bias. Had we included standardized or observer/clinician administered assessments we may have found a different pattern of results, perhaps also identifying subthreshold clinical levels of anxiety or depression. Nevertheless, an advantage of using self-report measures and a single item assessment of depression or anxiety history is that it may have overcome limitations associated with social desirability bias or other difficulties respondents may have had acknowledging the presence of specific psychiatric conditions. Moreover, the study used a donation as an incentive to participate which could have created unique volunteer bias.

This study is also limited because, given our small sample size, we did not examine the associations of changes among those who reported a history of being diagnosed with both anxiety *and* depression in order to retain power in our analyses. Given the high comorbidity of these conditions, and recent transdiagnostic approaches to treatment (40), it could be that such classifications are arbitrary, which is supported by our similar pattern of results across those with either condition. Nevertheless, future studies should examine this question using a larger sample. Additionally, because of the nature of this specific group of people who use 5-MeO-DMT and the context within in which this group prepares for, administers, and integrates these psychedelic experiences, we cannot determine the extent to which any changes in depression or anxiety are accounted for by the connections fostered within this community and the social support provided therein. Moreover, many people in this sample reported past three-month alcohol or cannabis use, smaller proportions reported use of other psychedelic substances (e.g., psilocybin or LSD), and we did not measure whether respondents had been taking prescription medications, thus restricting our ability to provide conclusive evidence that only 5-MeO-DMT use was responsible for any anxiolytic or anti-depressive effects reported in this sample. We also recognize that our sample may be inclined to report on positive associations between 5-MeO-DMT use and other variables because they view the substance favorably, possibly skewing our findings.

Future controlled laboratory studies are a critical next step.

Despite these methodological limitations, these results underscore the need for further study of this psychedelic compound. When administered in a naturalistic group setting, 5-MeO-DMT appears to be associated with spontaneous and unintended improvements in self-reported depression and anxiety, which were related to more intense acute mystical effects and increases in ratings of the personal meaning and spiritual significance of the 5-MeO-DMT session, as well as higher ratings of the degree to which the session contributed to improved well-being and life satisfaction (42). Taken together, these data highlight the importance of examining the long-term effects of 5-MeO-DMT, which may enhance mood in general or may be particularly mood enhancing for those experiencing clinically significant negative affect. Davis et al (30) found that 5-MeO-DMT had a safe profile of use and low risk for health and legal consequences, but further investigation is warranted in healthy volunteers. Therefore, we recommend that studies evaluate the safety of 5-MeO-DMT using prospective experimental designs so that future studies can examine the therapeutic potential of this psychedelic substance.

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