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Prevalence and associations of challenging, difficult or distressing experiences using classic psychedelics

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ABSTRACT

Previous studies have investigated challenging, difficult, or distressing classic psychedelic experiences, but little is known about the prevalence and associations of such experiences. Using nationally representative data of the US adult population (N = 2822), this study examined the prevalence and associations of challenging, difficult, or distressing experiences using classic psychedelics, in a subsample of respondents who reported lifetime classic psychedelic use (n = 613). Of the 613 respondents who reported lifetime classic psychedelic use, the majority of them (59.1 %) had never had a challenging, difficult, or distressing experience using a classic psychedelic, but 8.9 % of respondents reported functional impairment that lasted longer than one day as a result of such experiences. Notably, 2.6 % reported seeking medical, psychiatric, or psychological assistance in the days or weeks following their most challenging, difficult, or distressing classic psychedelic experience. In covariate-adjusted regression models, co-use of lithium, co-use of other mood stabilizers, and six set and setting variables (no preparation, disagreeable physical environment, negative mindset, no psychological support, dose was too large, major life event prior to experience) were associated with the degree of difficulty; and co-use of lithium, co-use of other mood stabilizers, and three set and setting variables (negative mindset, no psychological support, major life event prior to experience) were associated with overall risk of harm. In summary, this study provides insight into the prevalence and associations of challenging, difficult, or distressing classic psychedelic experiences. The findings broadly correspond with findings from previous studies and can inform harm reduction efforts and future experimental research designs.

The evidence to date suggests that serotonin 2A agonist classic psychedelics such as psilocybin have a good safety profile and may be effective in the treatment of certain psychiatric disorders when combined with therapy (Luoma et al., 2020; Nutt et al., 2010; Rucker et al., 2022). For example, results from three randomized controlled trials suggest that psilocybin administration, in conjunction with psychological support, can reduce depressive symptoms in patients with major depressive disorder (Carhart-Harris et al., 2021; Davis et al., 2021; von Rotz et al., 2023). Such findings contribute to a growing body of evidence in support of potential mental health benefits (Reiff et al., 2020), but relatively little remains known about potential risks associated with classic psychedelic use, including use outside of the carefully selected samples and highly controlled settings in which clinical trials are occurring (Anderson et al., 2020).

The leading guidelines on classic psychedelic research suggest a number of precautions to minimize risks. For example, it is recommended that individuals who take certain medications (e.g., lithium) that may alter the effects of classic psychedelics are screened out. The guidelines also suggest that risks can be further reduced by ensuring an appropriate set (i.e., psychological state) and setting (i.e., physical setting), including a positive mindset, an aesthetically appealing physical environment, and psychological support (Johnson et al., 2008). The

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acute classic psychedelic experience may still, however, elicit acute anxiety or panic and paranoia among other psychologically difficult states, even when overseen in a controlled and supportive setting (Barrett et al., 2016; Cohen, 1960; Strassman, 1984; Gashi et al., 2021). The long-term effects of such experiences are not well-understood (Barrett et al., 2016; Carbonaro et al., 2016), but previous research suggests that it may be associated with a higher risk of harm to oneself or others (Carbonaro et al., 2016), which makes it an important area for harm reduction research.

The prevalence of challenging, difficult, or distressing experiences using classic psychedelics has not yet been examined in nationally representative samples free of significant self-selection bias, but the frequency and intensity of such experiences appear to be higher in naturalistic surveys than in laboratory studies (Carbonaro et al., 2016), which may be related to extra-pharmacological factors (e.g., psychological support, structured setting). The research to date suggests that a number of psychological traits and states may predict challenging, difficult, or distressing experiences using classic psychedelics (Barrett et al., 2017; Haijen et al., 2018). Yet relatively little remains known about the associations between certain medication co-use, set and setting, and challenging, difficult, or distressing classic psychedelic experiences. Here, using a subsample (n = 613) of lifetime classic psychedelic users from a representative sample of the US adult population with regard to sex, age, and ethnicity (N = 2822), we aimed to conduct exploratory research on the prevalence and associations of challenging, difficult, or distressing experiences using classic psychedelics.

1. Materials and methods

1.1. Participants and procedure

Using linear multiple regression (fixed model, R2 increase) in GPower, we calculated that a sample size of 395 classic psychedelic users would achieve 80 % power to detect a small effect size with an alpha of 0.05. Based on recent data on the prevalence of lifetime classic psychedelic use in the US adult population (Simonsson et al., 2021), we estimated that around 2800 participants would be necessary to get approximately 395 lifetime classic psychedelic users in the sample. We therefore aimed to recruit 2800 participants in total.

The participants were 18 years or older and current residents of the United States (US). The sample (N = 2822) was recruited on Prolific Academic (https://app.prolific.co) in October (1st–9th) 2021 and was stratified across three demographic characteristics — sex (male, female), age (18–27, 28–37, 38–47, 48–57, and 58+), and ethnicity (White, Mixed, Asian, Black, Other) – to reflect the demographic distribution of the US adult population. The recruitment materials did not mention classic psychedelics to avoid potential self-selection bias (see Supplemental Materials for recruitment materials). Respondents who reported having used a classic psychedelic at least once in their lifetime (n = 613; see Supplemental Table 1 for key demographics) were asked to complete a number of items related to challenging, difficult, or distressing experiences using classic psychedelics. Study completion resulted in $2.20 payment and study procedures were approved by the Institutional Review Board at the University of Wisconsin – Madison. The data and Stata syntax are available at figshare: https://doi.org/10.6084/m9.figshare.21972953 [Data] and https://doi.org/10.6084/m9.figshare.21972956.v1 [Syntax].

1.2. Measures

1.2.1. Lifetime classic psychedelic use

All respondents were asked to report which, if any, of the following classic psychedelics they had ever used: ayahuasca, *N*,*N*-dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), mescaline, peyote, San Pedro, and psilocybin ("magic mushrooms"). Respondents who reported that they had used any of these substances were coded as positive for lifetime classic psychedelic use, whereas those indicating that they had never used any of these substances were coded as negative.

1.2.2. Challenging, difficult, or distressing experiences

Respondents who reported lifetime classic psychedelic use were asked three items related to challenging, difficult, or distressing experiences using classic psychedelics (adapted from items used in Goldberg et al., 2021): "I personally have had challenging, difficult, or distressing experiences as a result of using classic psychedelics" (Never, Rarely, Occasionally, Regularly, Frequently); "My challenging, difficult, or distressing experiences using classic psychedelics impaired my ability to function" (Not applicable; I have not had difficulties, Not at all, Somewhat, Moderately, Severely); and "How long did your impairment last?" (I did not experience impairment, 1 day or less, For a few days to 1 week, >1 week to 1 month, >1 month to 1 year, >1 year). Respondents were also asked whether the challenging, difficult or distressing experiences were associated with a specific classic psychedelic (multiple-choice). Using a modified version of the 11-item Meditation-Related Adverse Effects Scale – Mindfulness-Based Program (MRAES-MBP (Britton et al., 2018)),[1] respondents were also asked whether they had experienced any of the listed enduring adverse effects as a result of classic psychedelics (e.g., "I felt distant or cut off from other people", "I experienced repeated, disturbing memories, thoughts, or images of a stressful experience from the past"). The responses were rated on a 5-point Likert scale: (1) Never, (2) For a few days to 1 week, (3) >1 week to 1 month, (4) >1 month to 1 year, (5) >1 year. Prior research using the MRAES-MBP has shown that endorsement of challenging, difficult, or distressing experiences is higher when specific experiences are queried versus when a single, more general item is used (Goldberg et al., 2021). Therefore, respondents who reported never having had challenging, difficult, or distressing experiences using classic psychedelics on the single item were still asked to complete the MRAES-MBP. Finally, a single item assessed whether participants felt glad to have used classic psychedelics (adapted from item used in Goldberg et al., 2021):

> Consider the various experiences you have had using classic psychedelics, including any challenging, difficult, or distressing experiences. How much do you agree with the following statement: "I am glad I have used classic psychedelics."

The responses were rated on a 1- (Strongly disagree) to 6-point (Strongly agree) Likert scale.

Most challenging, difficult, or distressing experience.

Respondents who reported lifetime classic psychedelic use were asked to look back on their most challenging, difficult, or distressing experience using a classic psychedelic and complete the 26-item Challenging Experiences Questionnaire (CEQ (Barrett et al., 2016)), which asks respondents to rate the extent to which they experienced any of the listed phenomena (e.g., "isolation and loneliness", "I had the profound experience of my own death", "I experienced a decreased sense of sanity"). The responses were rated on a 0- (None; not at all) to 5-point (Extreme) Likert scale. The internal consistency was excellent (alpha = 0.97).

After completing the CEQ, respondents were asked whether the challenging, difficult, or distressing experience was associated with variables related to the set and setting (list modified from (Carbonaro et al., 2016); see response items in Supplemental Materials), whether there was anything that was helpful in responding to or managing the experience (list derived from Carbonaro et al., 2016), and whether there were thoughts or attempts to hurt themselves or others in the days or weeks following the experience. Respondents were also asked whether they sought medical, psychiatric, or psychological assistance in the days

[1] The decision to use a modified version of the MRAES-BMP was informed by the phenomenological and neurophysiological overlaps that exist between psychedelic and meditative states (Millière et al., 2018).

or weeks following the challenging, difficult, or distressing experience and whether they were using any specific medications (i.e., tricyclic antidepressants, SSRIs, SNRIs, MAOIs, St John's Wort, or any other medications or supplements with serotonin activity; haloperidol or any other antipsychotic medications; lithium or any other mood stabilizers; or methadone or buprenorphine/suboxone) at the time of the challenging, difficult, or distressing experience. These medications were assessed because research on their drug-drug interactions with classic psychedelics is ongoing (e.g., ClinicalTrials.gov Identifier: NCT04161066) or because individuals who use them are typically excluded from participation in clinical trials using classic psychedelics (e.g., ClinicalTrials.gov Identifier: NCT02037126), which corresponds with contemporary guidelines (Johnson et al., 2008).

1.3. Statistical analyses

We used multiple linear (for continuous dependent variables) and logistic (for dichotomous) regression models to evaluate associations related to respondents' most challenging, difficult, or distressing classic psychedelic experience. All analyses were conducted using Stata version 17.

2. Results

2.1. Challenging, difficult, or distressing experiences

Table 1 shows descriptive statistics of challenging, difficult, or distressing experiences using classic psychedelics. As indicated in the table, a little more than half of the respondents (59.1 %) reported never having had a challenging, difficult, or distressing classic psychedelic experience. Approximately one in twenty (4.6 %) reported severely impaired ability to function and roughly one in ten (8.9 %) reported impairment that lasted longer than one day. A majority (57.1 %) reported at least one of the listed enduring symptoms (feeling anxious being the most common) and most agreed (from slightly agree to strongly agree) with the gratitude statement ("I am glad I have used classic psychedelics"). Lastly, LSD was most commonly associated with challenging, difficult, or distressing classic psychedelic experiences (24.0 %; 31.5 % of lifetime LSD users), followed by tryptamines (15.3 %; 19.7 % of lifetime tryptamine users) and phenethylamines (4.1 %; 14.7 % of lifetime phenethylamine users).[2]

Table 1
Challenging, difficult, or distressing experiences.

	(%)	(N)
Frequency of experiences		
Never	59.1	362
Rarely	23.3	143
Occasionally	13.1	80
Regularly	3.6	22
Frequently	1.0	6
Impaired ability to function		
Not applicable: I have not had difficulties	38.7	237
Not at all	32.6	200
Somewhat	16.0	98
Moderately	8.2	50
Severely	4.6	28
Length of impairment		
I did not experience impairment	57.3	351
1 day or less	33.8	207
For a few days to 1 week	4.4	27
>1 week to 1 month	1.1	7
>1 month to 1 year	2.3	14
>1 year	1.1	7
Symptoms lasting at least a few days		
At least one of the symptoms below reported	57.1	350
Feeling anxious	36.1	221
Difficulty sleeping	27.9	171
Difficulty thinking or making decisions	24.0	147
Feeling disconnected from everything	23.7	145
Feeling distant or cut off from other people	20.1	123
Bothered by little things	18.4	113
Headaches and/or body pain	16.3	100
Re-experience of stressful event in the past	15.7	96
Trouble enjoying things	14.4	88
Sensitive hearing	14.4	88
Other significant symptoms	8.7	53
Experiences associated with a specific classic psychedelic		
LSD	24.0	147
Tryptamines	15.3	94
Phenethylamines	4.1	25
Glad to have used classic psychedelics		
Strongly disagree	5.9	36
Disagree	6.9	42
Slightly disagree	8.7	53
Slightly agree	23.2	142
Agree	28.2	173
Strongly agree	27.2	167

Note: Percentages are calculated as the proportion of the total sample of classic psychedelic users (n = 613). All percentages were rounded to the nearest 0.1 %. (N) refers to the counts of respondents on each row.

2.2. Most challenging, difficult, or distressing experience

Table 2 displays variables related to the most challenging, difficult, or distressing experience using a classic psychedelic. As seen in the table, approximately one in nine (11.3 %) reported co-use of at least one type of medication at the time of their most challenging, difficult, or distressing experience using a classic psychedelic. The five most commonly reported set and setting variables associated with respondents' most challenging, difficult, or distressing classic psychedelic experience were: no preparation, negative mindset, no psychological support, disagreeable social environment, and disagreeable physical environment. The five most commonly reported helpful interventions during respondents' most challenging, difficult, or distressing classic psychedelic experience were: trying to calm the mind, changing location, asking for help from friend, changing social environment, and smoking cannabis. In the days or weeks following their most challenging, difficult, or distressing experience using a classic psychedelic, roughly one in fifteen (6.7 %) reported thoughts or attempts of hurting themselves or others (4.6 %, thoughts of hurting oneself; 2.6 % thoughts of hurting others; 1.5 %, attempts to harm oneself; 0.7 %, attempts to harm others) while nearly one in forty (2.6 %) reported seeking medical, psychiatric, or psychological assistance.

Table 3 presents results from the multiple linear regression models examining the associations between medication co-use, set and setting, and CEQ scores (see Supplemental Table 2 for unadjusted analyses). As shown in the table, both co-use of lithium and co-use of other mood stabilizers during respondents' most challenging, difficult, or distressing experience using a classic psychedelic were associated with higher CEQ scores. No associations were observed with other types of medication co-use. No preparation, disagreeable physical environment, negative mindset, no psychological support, dose was too large, and major life event prior to experience were associated with higher CEQ scores. No associations were observed with other set and setting variables.

Table 4 displays results from the multiple logistic regression models examining the associations between medication co-use, set and setting, and overall risk of harm (i.e., thoughts or attempts to hurt themselves or others; see Supplemental Table 3 for unadjusted analyses). As demonstrated in the table, both co-use of lithium and co-use of other mood stabilizers during respondents' most challenging, difficult, or distressing classic psychedelic experience were associated with higher odds of overall risk of harm. No associations were observed with other types of

[2] Classic psychedelics are commonly divided into three categories: tryptamines (ayahuasca, DMT, psilocybin), lysergamides (LSD), phenethylamines (mescaline, peyote, San Pedro).

Table 2
Most challenging, difficult, or distressing experience.

	(%)	(N)
Medication co-use during most challenging, difficult, or distressing experience		
At least one of the medications below reported	11.3	69
Tricyclic antidepressants	1.5	9
SSRIs	5.2	32
SNRIs	1.8	11
MAOIs	0.8	5
St John's Wort	0.5	3
Other medications or supplements with serotonin activity	1.8	11
Haloperidol	0.8	5
Other antipsychotic medications	1.1	7
Lithium	1.3	8
Other mood stabilizers	2.6	16
Methadone or buprenorphine/suboxone	1.1	7
Set and setting during most challenging, difficult, or distressing experience		
No preparation	29.7	182
Negative mindset	15.7	96
No psychological support	15.5	95
Disagreeable social environment	15.0	92
Disagreeable physical environment	14.5	89
Dose was too large	13.2	81
Major life event prior to experience	6.7	41
Disagreeable musical environment	4.9	30
Other	4.7	29
Combining with other drug	4.4	27
Helpful interventions during most challenging, difficult, or distressing experience		
Trying to calm the mind	41.9	257
Changing location	27.4	168
Asking for help from friend	20.2	124
Changing social environment	20.2	124
Smoking cannabis	18.4	113
Changing music	16.2	99
Changing environment in other way	12.6	77
Drinking alcohol	8.8	54
Using the body to shift the experience	7.8	48
Taking other drug	3.6	22
Risk of harm following most challenging, difficult, or distressing experience		
At least one of the harm risks below reported	6.7	41
Thoughts of hurting oneself	4.6	28
Thoughts of hurting others	2.6	16
Attempts to harm oneself	1.5	9
Attempts to harm others	0.7	4
Sought assistance following most challenging, difficult, or distressing experience		
Yes	2.6	16
No	97.4	597

Note: The number of observations was 613. All percentages were rounded to the nearest 0.1 %. (N) refers to the counts of respondents on each row. All questions (except for the last question) were multiple-choice and results show how many respondents selected each specific option.

medication co-use. Negative mindset, no psychological support, and major life event prior to experience were associated with higher odds of overall risk of harm. No associations were observed with other set and setting variables.

3. Discussion

The present study investigated the prevalence and associations of challenging, difficult, or distressing experiences using classic psychedelics, in a representative sample of the US adult population with regard to sex, age, and ethnicity. Of the 613 respondents who reported lifetime classic psychedelic use, the majority of them (59.1 %) had never had a challenging, difficult, or distressing experience using a classic psychedelic, but 8.9 % reported functional impairment that lasted longer than one day as a result of such experiences. Notably, 2.6 % reported seeking medical, psychiatric, or psychological assistance in the days or weeks following their most challenging, difficult, or distressing experience,

Table 3
Medication co-use, set and setting, and CEQ scores.

	CEQ scores	
	β	*p*
Medication co-use		
Tricyclic antidepressants	0.03	0.531
SSRIs	0.03	0.431
SNRIs	−0.04	0.371
MAOIs	0.09	0.068
St John's Wort	0.00	0.993
Other medications or supplements with serotonin activity	−0.01	0.903
Haloperidol	−0.02	0.685
Other antipsychotic medications	0.02	0.665
Lithium	0.11	0.041
Other mood stabilizers	0.10	0.018
Methadone or buprenorphine/suboxone	0.01	0.879
Set and setting		
No preparation	0.09	0.010
Negative mindset	0.14	<0.001
No psychological support	0.25	<0.001
Disagreeable social environment	0.04	0.263
Disagreeable physical environment	0.09	0.029
Dose was too large	0.24	<0.001
Major life event prior to experience	0.13	<0.001
Disagreeable musical environment	0.05	0.192
Other	0.00	0.973
Combining with other drug	−0.06	0.099

Note: The number of observations was 613. β = standardized coefficients; medication co-use variables were simultaneously entered into the regression; set and setting variables were simultaneously entered into the regression.

Table 4
Medication co-use, set and setting, and risk of harm.

	Overall risk of harm	
	aOR (CI 95 %)	*p*
Medication co-use		
Tricyclic antidepressants	5.06 (0.55–46.34)	0.151
SSRIs	2.11 (0.61–7.37)	0.240
SNRIs	4.79 (0.72–31.83)	0.105
MAOIs	3.26 (0.17–63.93)	0.436
St John's Wort	***	***
Other medications or supplements with serotonin activity	0.55 (0.04–6.84)	0.641
Haloperidol	***	***
Other antipsychotic medications	0.91 (0.08–10.78)	0.938
Lithium	22.34 (1.78–279.65)	0.016
Other mood stabilizers	5.84 (1.40–24.34)	0.015
Methadone or buprenorphine/suboxone	2.10 (0.17–26.40)	0.564
Set and setting		
No preparation	1.17 (0.56–2.45)	0.681
Negative mindset	4.56 (2.10–9.94)	<0.001
No psychological support	2.85 (1.27–6.42)	0.011
Disagreeable social environment	0.33 (0.11–1.01)	0.051
Disagreeable physical environment	0.88 (0.33–2.35)	0.803
Dose was too large	1.60 (0.66–3.88)	0.299
Major life event prior to experience	2.93 (1.17–7.35)	0.022
Disagreeable musical environment	2.67 (0.87–8.21)	0.087
Other	0.52 (0.06–4.30)	0.546
Combining with other drug	1.33 (0.35–4.99)	0.672

Note: The number of observations was 613. aOR = adjusted Odds Ratios; medication co-use variables were simultaneously entered into the regression; set and setting variables were simultaneously entered into the regression. ***Due to collinearity in Stata, Haloperidol and St John's Wort were dropped from regression with medication co-use.

which broadly corresponds with findings from previous research (Carbonaro et al., 2016).

When respondents were asked about their most challenging,

difficult, or distressing experience using a classic psychedelic, trying to calm the mind was the most commonly reported helpful intervention, which broadly corresponds with findings from previous research (Carbonaro et al., 2016). As part of the preparation for a classic psychedelic experience, it may therefore be useful to introduce exercises that users can utilize to calm the mind such as mindfulness-based practices (for reviews on the potential synergies between classic psychedelics and mindfulness meditation, see Eleftheriou and Thomas, 2021; Payne et al., 2021).

In covariate-adjusted regression models, co-use of lithium, co-use of other mood stabilizers, and six set and setting variables (no preparation, disagreeable physical environment, negative mindset, no psychological support, dose was too large, major life event prior to experience) were associated with the degree of difficulty during respondents' most challenging classic psychedelic experience. These findings strengthen the support for the main guidelines on safety in classic psychedelic research (Johnson et al., 2008), especially as co-use of lithium, co-use of other mood stabilizers, and three set and setting variables (negative mindset, no psychological support, major life event prior to experience) were also associated with higher odds of overall risk of harm. Notably, the associations related to the set and setting are consistent with findings from previous research (Carbonaro et al., 2016) while the associations related to lithium co-use correspond with previous findings on links between lithium co-use and classic psychedelic-related seizures (Simonsson et al., 2022; Nayak et al., 2021). It therefore appears prudent for both clinical trials and legalization initiatives to strictly follow contemporary guidelines (Johnson et al., 2008), at least until future research has provided a greater understanding of potential risks.

There are several limitations in the present study that need to be considered when interpreting the findings. First, the associations reported in this study cannot be used to infer causality due to the cross-sectional design. Second, the sampling platform (Prolific Academic) used in this study only allowed the sample to be stratified across three demographics – sex, age and ethnicity – to reflect the demographic distribution of the US adult population. It may not necessarily have been representative on other variables (e.g., indicators of socioeconomic status). Third, the respondents were asked to complete self-report measures, which are susceptible to a range of biases. Future research should use longitudinal research designs and objective measures to investigate potential causal links between classic psychedelic use and psychological risks among naturalistic users.

4. Conclusion

In summary, this study provides insight into the prevalence and associations of challenging, difficult, or distressing experiences using classic psychedelics. The findings broadly correspond with findings from previous studies and can be used to inform both ongoing harm reduction efforts and future experimental research designs.

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CRediT authorship contribution statement

OS conceptualized and designed the study, with input from SBG and PSH. OS analyzed the data and wrote the manuscript, with comments from SBG, PSH, RC, and WO.

Declaration of competing interest

PSH is on the scientific advisory board of Bright Minds Biosciences Ltd., Eleusis Benefit Corporation, and Reset Pharmaceuticals Inc. OS and RC are co-founders of Eudelics AB. The remaining authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.01.073.

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