Original Paper

Risks and benefits of psilocybin use in people with bipolar disorder: An international web-based survey on experiences of 'magic mushroom' consumption

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Abstract

Background: Psilocybin, the primary psychoactive component of psychedelic 'magic mushrooms', may have potential for treating depressive symptoms, and consequent applications for bipolar disorder (BD). Knowledge of the risks and benefits of psilocybin in BD is limited to case studies.
Aim: To support the design of clinical trials, we surveyed experiences of psilocybin use in people with BD.
Methods: An international web-based survey was used to explore experiences of psilocybin use in people with a self-reported diagnosis of BD. Quantitative findings were summarised using descriptive statistics. Qualitative content analysis was used to investigate free-text responses, with a focus on positive experiences of psilocybin use.
Results: A total of 541 people completed the survey (46.4% female, mean 34.1 years old). One-third (32.2%; $n=174$) of respondents described new/increasing symptoms after psilocybin trips, prominently manic symptoms, difficulties sleeping and anxiety. No differences in rates of adverse events overall were observed between individuals with BD I compared to BD II. Use of emergency medical services was rare ($n=18$; 3.3%), and respondents (even those who experienced adverse effects) indicated that psilocybin use was more helpful than harmful. Quantitative findings elaborated on perceived benefits, as well as the potential for psilocybin trips to contain both positively and negatively received elements.
Conclusions: The subjective benefits of psilocybin use for mental health symptoms reported by survey participants encourage further investigation of psilocybin-based treatments for BD. Clinical trials should incorporate careful monitoring of symptoms, as data suggest that BD symptoms may emerge or intensify following psilocybin use.

Keywords

Bipolar disorder, psilocybin, psychedelics

Background

Bipolar disorder (BD) is a chronic illness that affects approximately 2.5% of the world's population (Clemente et al., 2015; Merikangas et al., 2011). While manic symptoms are the defining feature of BD, patients with BD typically spend more time depressed (Judd et al., 2002, 2003), and patients themselves rate depression as the most burdensome mood state (Mączka et al., 2010). Depressive symptoms (even subsyndromal) are associated with functional impairments, suicidality and negative impacts to quality of life (Altshuler et al., 2006; Bonnín et al., 2012; Hadjipavlou and Yatham, 2008; Pallaskorpi et al., 2017; Piccinni et al., 2007), and are equally or more disabling than hypomania and mania (Ruggero et al., 2007).

Currently available pharmacotherapies for depression in BD have limitations (Frye et al., 2014; Yalin and Young, 2020). Lithium and antipsychotics are associated with significant side effects (Kemp, 2014; Ketter et al., 2014), while antidepressants carry the risk of breakthrough manic symptoms (Tondo et al., 2010). Even with treatment, many patients do not adequately respond or regain full functioning (Huxley and Baldessarini, 2007; Wingo et al., 2010). Novel therapeutic approaches for depressive symptoms in BD are urgently needed (Frye et al., 2014; Yalin and Young, 2020), and patients have nominated the identification of alternative treatments as a research priority (Nestsiarovich et al., 2017).

Psilocybin therapy, which typically includes a brief course of psychotherapy paired with one or two administrations of the 5HT2A receptor agonist and psychedelic drug psilocybin (Johnson et al., 2008), is a promising treatment for a variety of

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mental health conditions including major-depressive disorder and treatment-resistant unipolar depression (Carhart-Harris et al., 2016, 2018, 2021; Davis et al., 2021a,b; Gukasyan et al., 2022), substance use disorders (Bogenschutz and Johnson, 2016; Johnson et al., 2014) and depression and anxiety secondary to a serious medical illness like cancer (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016) and HIV (Anderson et al., 2020). Psilocybin has also been shown to induce long-lasting improvements in wellbeing in healthy humans (Griffiths et al., 2008). Together, these findings suggest that psilocybin therapy could have beneficial effects for depressive symptoms in BD as well as for the quality of life impacts and co-morbid substance use disorders that are very common and debilitating in this population.

Unfortunately, clinical psychedelic trials have excluded individuals with BD (and often, those with a family history of BD) for fear of precipitating manic episodes (Studerus et al., 2011). The rationale for supporting these exclusions, however, is rarely provided and appears to be anecdotal as no systematic study of psychedelic use in people with BD has been reported. A recent review of published case reports found 17 possible cases where psychedelic use was followed by either adverse outcomes in people with known BD or development of manic symptoms in someone without a known history of BD (Gard et al., 2021). While this suggests that ingestion of a psychedelic compound can trigger a manic episode in susceptible individuals, the relative dearth of such case reports compared to the widespread non-prescribed use of such substances invite larger-scale investigation of this risk (Krebs and Johansen, 2013; Yockey and King, 2021). Further, the biases inherent in published case reports, and the concomitant factors such as other drug use and lack of psychosocial support precludes strong conclusions from being formed about the safety of psilocybin ingestion in people with BD.

In addition, the small number of published case reports make it difficult to draw inferences about possible predictors of adverse outcomes that could be used to inform more granular risk management protocols for clinical trials. For example, exclusion of people with BD are predicated on concerns about mania, however, the clinical presentation of BD II is dominated by depressive symptoms (Judd et al., 2003), and individuals with this diagnosis have no past history of manic episodes. In comparison, people with a diagnosis of BD I have demonstrated vulnerability to developing full-threshold manic episodes, and may be at elevated risk of a treatment emergent affective switch into mania in response to use of serotonergic antidepressants than individuals with BD II (Bond et al., 2010); it is not known whether the same between-group differences may be observed in response to psilocybin use.

The absence of information regarding experiences of psilocybin use in BD both inhibits planning for clinical trials and restricts the ability of clinicians to hold productive conversations regarding psychedelic use with patients. To begin to redress this, we conducted an international, web-based survey. Our aim was to describe the intentions, practices and experiences of adults with self-reported BD who had at least one psychedelic 'trip' using psilocybin. To explore possible risks, we specifically asked about adverse events including worsening of BD symptoms and hospitalisations following psilocybin use.

Methods

Study design

Data collection occurred from October 2020 through the conclusion of January 2021. The study received ethics approval from the University of California, San Francisco Institutional Review Board (IRB#20-30885). All participants received written information on the study and indicated their consent before proceeding. Data in the study were treated confidentially and stored on a secure server in the United States.

Participants

Inclusion/exclusion criteria. To be included in the study, participants were required to: (a) be 18 years or older, (b) have a self-reported BD diagnosis and (c) have used psilocybin to achieve 'a full psychedelic trip'. Individuals with experiences limited to psilocybin 'microdosing', a common practice that does not produce psychedelic effects (Kuypers et al., 2019), were not eligible. A disclaimer was presented with accompanying photos to ask participants to comment on their experiences of psilocybin containing mushroom use only, and not Amanita muscaria (a different psychoactive mushroom).

Recruitment. Recruitment occurred via a variety of online channels. In an attempt to encourage demographically diverse groups of people to participate, our team created a colourful, informative and welcoming study ad (Williams et al., 2020), which was promoted on the social media accounts (Facebook, Instagram, Twitter) of the Bonding and Attunement in Neuropsychiatric Disorders Lab at the University of San Francisco California and the Collaborative RESearch Team to study psychosocial issues in Bipolar Disorder (CREST.BD) at the University of British Columbia. Advertisements were also placed on relevant websites, forums, Facebook groups and subreddits on the website Reddit; that is those related to psilocybin use or BD, as well as on forums that attract diverse groups of people with BD or with an interest in psychedelics. Paid advertisements on Twitter were used, targeting people of all genders aged 18 and over, who were interested in accounts sharing content related to mental health and psilocybin. Finally, blog posts describing the study and expressly welcoming people of marginalised racial and ethnic identities to participate in our project were hosted on the CREST.BD website and emails were sent to a mailing list of people who have expressed interest in CREST.BD studies. No honorarium was provided to participate in this study.

Measures

An online survey including a mix of multiple choice, multiple answer, Likert style and free-text questions was developed by the authors (see Supplemental File 1). The CREST.BD Community Advisory Group (comprised of individuals living with BD) was consulted regarding the wording and presentation of survey items. The questionnaire was split into three sections: (1) demographics (e.g. age, gender, ethnicity, location, education and

employment) and frequency of psilocybin use, (2) intentions when using (and whether these were achieved), the experience of adverse events and use of emergency medical services and (3) mental health history, including BD diagnoses, adherence to prescribed medications, and perceptions of the impact of psilocybin use (helpfulness and harmfulness).

Data collection occurred online via the survey platform Qualtrics. An automated prompt would notify participants of missed items; however, they were not required to respond to all items to complete the survey. No restrictions were placed on the length of answers to free-text items.

Data analysis

Prior to analysis, multiple submissions from the same IP address were investigated for duplicate responses. If two entries from the same IP address provided identical responses, the most complete entry was retained. In cases where any responses to survey items differed, both entries were retained, as we could not determine whether these reflected multiple submissions from the same individual, or submissions from two different people who happened to be using the same computer (e.g. roommates).

Quantitative analysis. Descriptive statistics were used to summarise responses. Percentages were calculated based on the number of participants who participated in the survey (i.e. inclusive of missing responses).

To characterise the individuals most at risk of experiencing negative outcomes of psilocybin use, individuals who endorsed experiencing any negative outcome were compared to those who did not on a number of variables. *T*-tests were used to compare these groups in regards to age, perceived helpfulness and perceived harmfulness. Effect sizes (Cohen's *d*) were reported. For perceived harmfulness and helpfulness, Levene's Test for Equality of Variances was significant, and as such equal variances were not assumed. Chi-square tests were used to compare categorical variables, including gender (male vs. female), BD diagnosis (BD I vs. BD II), psychosis-spectrum diagnoses, number of lifetime psychiatric hospitalisations, number of psilocybin trips and changes to prescribed medication use. The Phi coefficient statistic (ϕ) was reported as an effect size measure for 2×2 comparisons (gender, BD diagnosis, psychosis spectrum diagnoses), and Cramer's V reported as an effect size measure for $>2 \times 2$ comparisons (number of lifetime hospitalisations, number of psilocybin trips, changes to prescribed medication use).

Qualitative analysis. A qualitative analysis was conducted on free-text responses to an open-ended question at the conclusion of the study: 'Is there anything else you would like us to know about your experience(s) of using psilocybin/hallucinogenic 'magic' mushrooms?' Responses to general items may highlight issues of subjective importance not addressed by closed questions, either by elaborating on responses to closed items or flagging new issues (Decorte et al., 2019; O'Cathain and Thomas, 2004). We note that for reasons of feasibility and relevance it is not standard practice to report on all comments provided for open-ended items, rather, authors may choose to specifically interrogate prominent issues raised by respondents. In line with good practice recommendations for analysis of general items, authors EM, AA and KS conducted a preliminary review of responses ($n = 314$) to determine the analytic foci (Decorte et al., 2019; O'Cathain and Thomas, 2004).

A decision was made to analyse responses describing positive experiences with psilocybin for several reasons. Firstly, the large proportion of responses which commented on positive experiences was noteworthy ($n = 214$), given prior research that responses to open-ended questions are often made by individuals with negative experiences (Miller and Dumford, 2014; Oshodi et al., 2019). Secondly, this qualitative data addressed gaps in the quantitative elements of the survey, which largely focused on behaviours surrounding psilocybin use and negative impacts. The relatively small number of comments which focused on exclusively negative experiences of psilocybin use ($n = 25$) were observed to elaborate on adverse effects that were asked about in quantitative portions of the survey. For example, participants commented on their psilocybin-related experiences of anxiety (e.g. 'I had a very bad trip because I became hyper aware of my racing heart'), psychosis-like phenomena (e.g. 'had severe auditory echoes/hallucinations'), and mood symptoms (e.g. 'was really moody not depressed for about a week after coming from a stable place'). A small number commented on aspects of set and setting that the individual believed to play a role. For reasons of feasibility, the small number of responses, the overlap of content with the more robust quantitative data analysis, and the fact that issues of 'set and setting' were to be deliberately followed up on in qualitative interviews with a subsample of survey respondents (see Future Directions), exclusively negative responses were not subject to formal qualitative analysis here.

Analyses were conducted using the qualitative data management software NVivo (QSR International, 2016). Content analysis was employed as follows (Hsieh and Shannon, 2005): In the first stage, two researchers (KS and AA) became immersed in survey data by reading and rereading survey responses. Deductive coding was used to generate a preliminary framework describing aspects of positive experiences with psilocybin. In the second stage of analysis, consensus discussion was used to refine the coding framework and solidify shared understanding. Authors KS, EM and AA independently applied the preliminary coding framework to the same random sample of 10% of responses to this item, then met to discuss points of divergence and convergence, as well as suggest changes to the framework. This process was repeated with an additional 10% sample. In the third stage of analysis, coders independently applied the coding framework to a random sample of responses (EM, $n = 104$; AA, $n = 105$; KS, $n = 105$). Coders met to review each other's results, with disagreements resolved via a process of consensus discussion. Integrated findings were then reviewed and discussed within the wider team.

Findings were selected for presentation in this paper on the basis of frequency and salience; illustrative verbatim comments are provided. We reported numbers of responses to contextualise findings (Maxwell, 2010), and provide transparency (Chivanga, 2016; Hannah and Lautsch, 2010). However, such numbers do not represent the number of participants with such experiences, only those who felt driven to express them.

Results

Sample

A total of 743 responses were collected. Of these, two declined to consent, and 58 failed to respond to a single screening question. One hundred and eight were excluded because they did not meet inclusion criteria; 11 were younger than 18 years old, 42 reported no BD diagnosis, and 55 reported no use of psilocybin-containing magic mushrooms. Of eligible consenting entries, 24 did not respond to items beside the screening questions and were excluded. Ten duplicate responses were removed. A remainder of 541 responses were analysed.

Table 1 summarises demographic characteristics. Respondents were 46.4% female ($n=251$), primarily residing in the United States (71.5%, $n=387$) or Canada (13.3%, $n=72$), of white ethnicity (60.1%, $n=325$), with a mean age of 34.1 years (SD = 11.1; range 19–74). The majority of respondents (63.2%; $n=342$) were in paid employment. Students made up 17% ($n=92$) of the sample. Most respondents had partially or fully completed some form of postsecondary education (82.1%; $n=444$). The most reported diagnostic subtype was BD II (45.1%, $n=244$).

Experiences of psilocybin use

Quantitative findings. Experiences of psilocybin use are summarised in Table 2. The modal range of full psilocybin trips reported was 2–5 (40.1%; $n=217$). Of participants who were taking psychiatric medication at the time of their psilocybin trip ($n=212$), only 33.5% ($n=70$) reported changing the way they used it (i.e. ceasing medication or altering dosage before psilocybin consumption). 43.4% ($n=235$) of respondents indicated they were not taking any psychiatric medications at the time of psilocybin use.

Negative or unwanted outcomes during or in the 14 days after a psilocybin trip were reported by 32.2% ($n=174$) of respondents (summarised in Figure 1; note, respondents could indicate the experience of multiple adverse outcomes). New or increasing manic symptoms were the most common side effect (14.2%; $n=77$), followed by difficulties falling or staying asleep (10.4%; $n=56$), anxiety symptoms (9.4%; $n=51$) and depressive symptoms (8.9%; $n=48$).

Eighteen people (3.3%) reported use of emergency services (emergency department, psychiatric hospitalisation or medical hospitalisation) during or in the 14 days after a psilocybin trip. For these individuals, the most common negative outcomes of psilocybin use were new or increasing manic symptoms (72.2%; $n=13$), followed by delusional beliefs (66.7%; $n=12$), anxiety (50%; $n=9$), difficulties falling or staying asleep (50%; $n=9$), hallucinations (44.4%; $n=8$) and depressive symptoms (16.7%; $n=3$). Only one individual who used emergency services following their psilocybin trip did not report experiencing any of these adverse events.

Individuals who reported negative outcomes did not differ from those who did not experience side effects in terms of age, $t(471)=1.73$, $p=0.08$, $d=0.17$ or gender $\chi^2(1, N=442)=0.33$, $p=0.57$, $\phi=0.03$. Nor did these groups differ in terms of BD subtype diagnosis (BD I vs BD II; this analysis did not include the $n=20$ individuals who endorsed being diagnosed with both subtypes), $\chi^2(1, N=383)=1.96$, $p=0.16$, $\phi=0.07$, psychotic spectrum diagnoses, $\chi^2(1, N=444)=2.72$, $p=0.10$, $\phi=0.\ 08$, number of lifetime psychiatric hospitalisations, $\chi^2(4, N=475)=5.2$, $p=0.27$, $V=0.11$, number of lifetime psilocybin trips, $\chi^2(4, N=475)=1.17$, $p=0.88$, $V=0.05$, or adherence to prescribed psychiatric medication $\chi^2(2, N=444)=4.93$, $p=0.09$, $V=0.11$.

Participants reported a range of motivations for psilocybin use (summarised in Table 2). Most commonly, participants reported using psilocybin to aid personal development, that is existential exploration, personal growth or self-awareness (60.6%; $n=328$). The least commonly endorsed motivation was escapism, that is to avoid pain or discomfort (19.2%; $n=104$). Just over half of respondents (53.2%; $n=288$) described an intention to treat symptoms of a mental health or substance use condition. The majority of respondents indicated that they achieved their personal goals for psilocybin use (see Figure 2), although the precise proportion varied, with the highest agreement (90.4%) seen in respondents who nominated curiosity as a goal, and the lowest (60.6%) being respondents who nominated escapism as a goal.

On average, respondents rated the harmfulness of psilocybin trips as 1.6 out of 5 (SD = 0.9), where 1 is 'Not at all harmful' and 5 is 'Extremely harmful'. The mean perceived helpfulness of psilocybin trips was 4 out of 5 (SD = 1.1), where 1 is 'Not at all helpful' and 5 is 'Extremely helpful'. Individuals who reported side effects perceived psilocybin on average as more harmful (2.1 ± 1.2) than those who did not experience side effects (1.3 ± 0.5), $t(193.5)=-8.57$, $p<0.000$, $d=1.02$. Similarly, those who reported side effects perceived psilocybin as less helpful (3.6 ± 1.3) than those who did not experience side effects (4.2 ± 0.9), $t(252.4)=5.17$, $p<0.000$, $d=0.56$. Despite between-group differences, individuals who experienced side effects still on average perceived psilocybin positively in terms of its harmfulness and helpfulness.

Qualitative findings. Over half (58%; $n=314$) of participants responded to the final open-ended free-text item. As per our rationale, qualitative analysis of this item focused on characterising positive experiences with psilocybin. Comments describing neutral ($n=3$) or exclusively negative ($n=25$) experiences are not summarised here. Other comments unrelated to this focus ($n=72$) included research-related comments, thoughts on psilocybin that did not describe personal experiences, or description of the context of psilocybin use (e.g. setting, dosage, use of psychiatric medication).

Of participants who described positive experiences ($n=214$), the subjective benefits of psilocybin were wide-ranging. While benefits could be transitory and contained within the trip (e.g. pleasant imagery, enhanced creativity and positive mood), others were longer lasting.

Mental health benefits. A number of respondents described improvements in mental health ($n=86$), such as a reduction in depressive and anxiety symptoms, mood lability or substance use. Some individuals described ongoing mental health symptoms, but an enhanced ability to cope with these. For example, 'When I'm feeling the negative effects of my bipolar II disorder (depression and anxiety), I can sometimes put myself in the same headspace I was in when I took psilocybin and it helps calm me down and put things in perspective'.

Table 1. Demographic and clinical characteristics for the total sample and individual subgroups who did and did not report experiencing side effects of psilocybin use.

Variable	Total sample ($n=541$)	No psilocybin side effects ($n=301$)	Psilocybin side effects ($n=174$)
Gender ($n=525$)			
Female	251 (46.4%)	147 (48.8%)	83 (47.7%)
Male	238 (44%)	141 (46.8%)	71 (40.8%)
Non-binary	21 (3.9%)	7 (2.3%)	12 (6.9%)
Prefer to self-describe/prefer not to say	15 (2.8%)	6 (2%)	8 (4.6%)
Mean age ($n=538$)	34.1 (SD=11.1)	34.8 (SD=10.7)	33 (SD=11.6)
Racial/ethnic identity ($n=436$)			
White	325 (60.1%)	195 (64.8%)	105 (60.3%)
Black	10 (1.8%)	5 (1.7%)	4 (2.3%)
Asian	10 (1.8%)	6 (2%)	2 (1.1%)
Hispanic	25 (4.6%)	13 (4.3%)	10 (5.7%)
Indigenous	4 (0.7%)	1 (0.3%)	2 (1.1%)
Multiple/mixed identities	47 (8.7%)	30 (10%)	16 (9.2%)
Other	15 (2.7%)	6 (2%)	6 (3.4%)
Country of residence ($n=541$)			
United States	387 (71.5%)	216 (71.8%)	128 (73.6%)
Canada	72 (13.3%)	44 (14.6%)	21 (12.1%)
Latin America	6 (1.1%)	2 (0.7%)	1 (0.6%)
Europe	51 (9.4%)	25 (8.3%)	18 (10.3%)
Australia	11 (2%)	6 (2%)	1 (0.6%)
Asia	3 (0.6%)	2 (0.7%)	0 (0%)
Middle East	4 (0.7%)	1 (0.3)	3 (1.7%)
Africa	7 (1.3%)	5 (1.7%)	2 (1.1%)
Highest level of education ($n=525$)			
High school	65 (12.4%)	31 (10.3%)	21 (12.1%)
Some postsecondary	222 (41%)	131 (43.5%)	74 (42.5%)
Undergraduate degree	142 (26.2%)	84 (27.9%)	45 (25.9%)
Postgraduate	80 (14.8%)	45 (15%)	29 (16.7%)
Other	16 (3%)	10 (3.3%)	5 (2.9%)
Employment status* ($n=524$)			
In paid employment	342 (63.2%)	198 (65.8%)	109 (62.6%)
Student	92 (17%)	46 (15.3%)	39 (22.4%)
Receiving disability benefits or unemployed	106 (19.6%)	64 (21.3%)	33 (19%)
Other (e.g. retired, caregiver, volunteer)	39 (7.4%)	24 (8%)	13 (7.5%)
BD subtype diagnosis* ($n=447$)			
BD I	182 (33.6%)	109 (36.2%)	71 (40.8%)
BD II	244 (45.1%)	163 (54.2%)	80 (45.9%)
Other BD	44 (8.1%)	24 (8%)	20 (11.5%)
Psychotic disorder (e.g. schizophrenia, mania with psychosis)	49 (9.1%)	26 (8.6%)	23 (13.2%)
Additional mental health concerns	155 (28.7%)	101 (33.6%)	54 (31%)
Number of lifetime psychiatric hospitalisations ($n=244$)			
Once only	107 (19.8%)	68 (22.6%)	39 (22.4%)
2–3 times	97 (17.9%)	65 (21.6%)	31 (17.8%)
4–10 times	34 (6.3%)	16 (5.3%)	18 (10.3%)
11 or more	6 (1.1%)	3 (1%)	3 (1.7%)

*Response options were not mutually exclusive.

Spiritual and psychological growth. Other benefits were not directly related to clinical conceptualisations of mental ill-health. Psychedelic trips were described by some individuals as facilitating the processing of traumatic experiences ($n=13$), for example, 'The experience brought up past traumatic memories that I was able to process in a healthy way'. Spiritual experiences and an enhanced sense of connection with other people, nature and the world were also described ($n=14$), for example 'I was finally able to see the true beauty in nature and in life. My attitude thereafter has significantly changed towards my existence and the role

Table 2. Psilocybin use and impacts.

Experiences of psilocybin use (n=valid responses)	Total sample (n=541)	No psilocybin side effects (n=301)	Psilocybin side effects (n=174)
Number of trips (n=497)			
Once	73 (13.5%)	42 (14%)	24 (13.8%)
2–5 times	217 (40.1%)	130 (43.2%)	79 (45.4%)
6–12 times	123 (22.7%)	75 (24.9%)	43 (24.7%)
13–35 times	59 (10.9%)	40 (13.3%)	18 (10.3%)
More than 35 times	25 (4.6%)	14 (4.7%)	10 (5.7%)
Mean perceived harmfulness, ranked 1–5 (n=432)	1.6 (SD=0.9)	1.3 (SD=0.5)	2.12 (SD=1.18)
Mean perceived helpfulness, ranked 1–5 (n=448)	4 (SD=1.1)	4.2 (SD=0.9)	3.60 (SD=1.26)
Use of psychiatric medication surrounding psilocybin trips (n=447)			
N/A (Not taking medication)	235 (43.4%)	150 (49.8%)	83 (47.7%)
No change to medication use	142 (26.2%)	96 (31.9%)	46 (26.4%)
Changed medication use	70 (12.9%)	36 (12%)	33 (19%)
Use of emergency services during or in the 14 days after any psilocybin trips* (n=497)			
Emergency department visit	9 (1.7%)	1 (0.3%)	8 (4.6%)
Psychiatric hospitalisation	10 (1.8%)	0 (0%)	10 (5.7%)
Medical hospitalisation	3 (0.6%)	0 (0%)	3 (1.7%)
Motivations for use (n=498)*			
Personal development	328 (60.4%)	194 (64.5%)	117 (67.2%)
Fun	296 (54.5%)	176 (58.5%)	105 (60.9%)
Mental health treatment	288 (53%)	183 (60.8%)	93 (53.4%)
Curiosity	284 (52.7%)	161 (53.5%)	106 (60.9%)
Spiritual growth	254 (47.5%)	151 (50.2%)	94 (54%)
Cognitive enhancement	200 (37%)	120 (39.9%)	73 (42%)
Interpersonal bonding (one other person)	189 (34.4%)	106 (35.2%)	68 (39.1%)
Community bonding (a group of people)	137 (25.3%)	83 (27.6%)	47 (27%)
Escapism	104 (19.2%)	49 (16.3%)	48 (27.6%)
Other	56 (10.4%)	35 (11.6%)	19 (10.7%)

*Response options were not mutually exclusive.

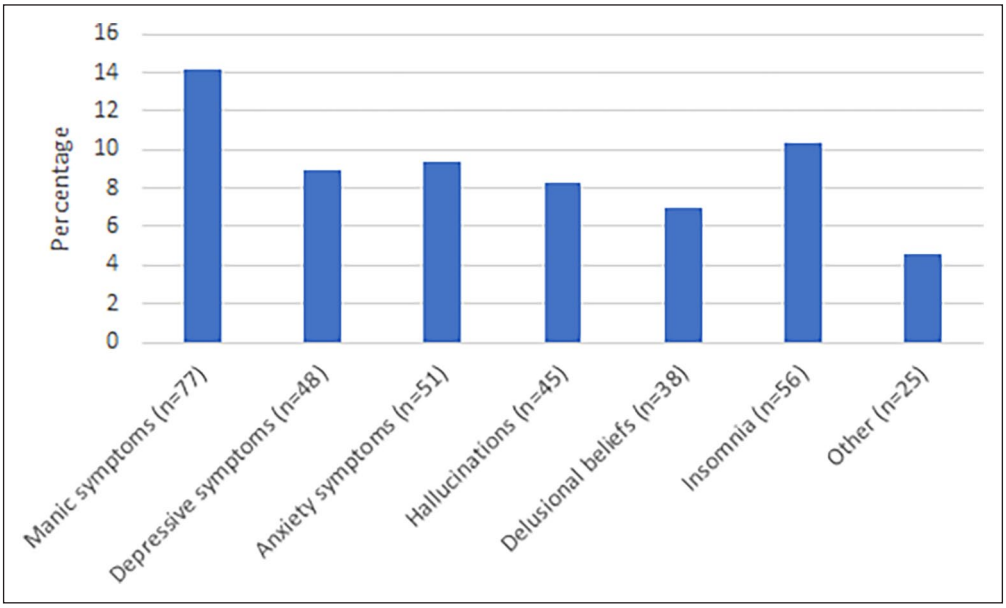

Figure 1. Percentage of total sample (n=541) who reported experiencing negative or unwanted outcomes during or in the 14 days after psilocybin use.

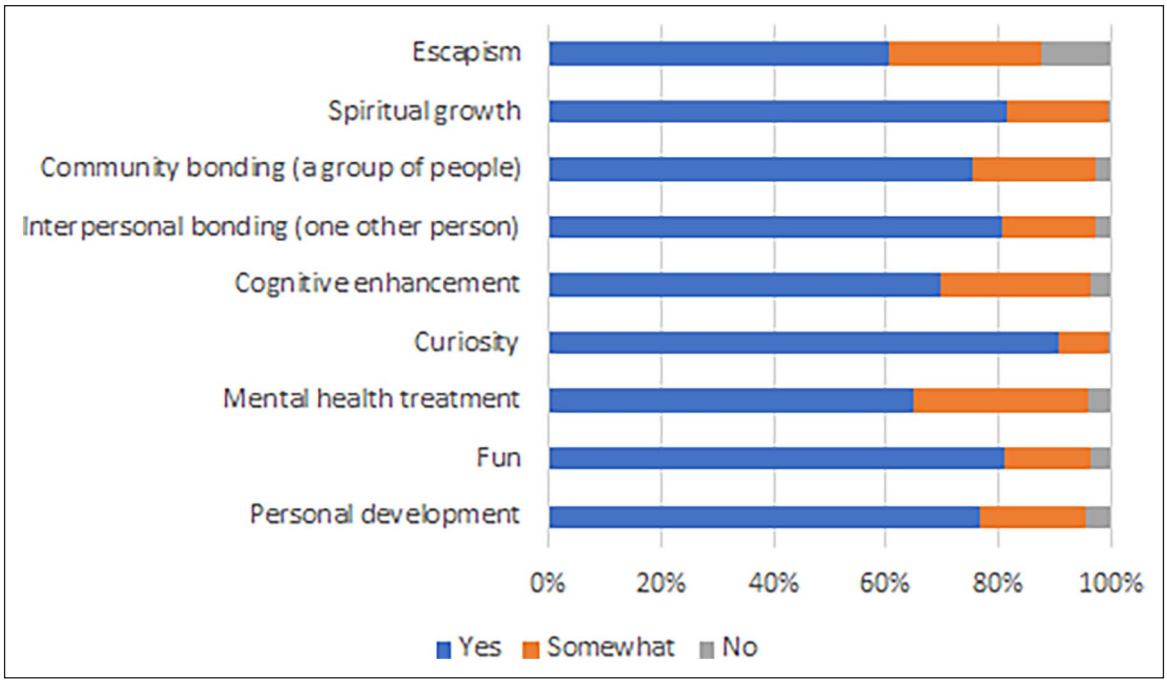

Figure 2. Percentage of participants who reported achieving their aims for psilocybin use.

I play in my life and the world'. Prominently ($n=38$), individuals experienced psilocybin use as facilitating psychological growth by helping respondents be introspective, adopt new perspectives, develop self-compassion and confront difficult issues. For example, 'Helped me immensely with viewing people and events with new perspectives. I no longer see things black/white. . . In reality we live in a complex world'.

Mixed experiences. It should be noted that a substantial proportion of individuals with positive experiences of psilocybin use also described negative experiences ($n=43$). In some cases, participants reported a history of distinct 'good' and 'bad' trips ($n=9$), for example 'I had two trips. One was fantastic. The other was bad and included about an hour of severe anxiety'. Other respondents specified both negative and positive aspects of the same psilocybin trip ($n=27$). For these individuals, psilocybin trips could include physical side effects, intense anxiety, escalation in mood symptoms (particularly mania) and distressing hallucinations or beliefs. In some cases, participants could pinpoint factors that may have contributed to negative outcomes, for example 'I was at home by myself and was not in a good state of mind when I took the mushrooms, and they just amplified my anxiety'. A number of participants expressed a desire for precautions (e.g. the assistance of a 'trip sitter', someone who is not taking the substance you are taking whose role is to keep you safe) to help manage or prevent adverse effects, for example 'I think in a therapeutic setting, things could have been much different than me just eating a large amount of mushrooms after work one day'. In a minority of cases, participants stated that these negatives would deter them from using mushrooms again. However, many respondents noted that such negatives were paired with psychological or mental health benefits, for example 'These breakdowns are ultimately insightful despite being painful'. Respondents sometimes qualified the benefits of such trips as 'worth' any challenging aspects. For instance, one respondent noted that their distressing experiences taught them coping skills: 'I can now treat my endogenous hallucinations like a trip and just relax and remember it's temporary, and they don't distress me or disrupt my life'.

Discussion

Main findings

The hallucinogenic compound psilocybin could have potential for treating depressive symptoms in BD, yet little empirical evidence exists regarding its impacts for this population. Quantitative findings from this survey highlight the existence of adverse side-effects of psilocybin use in approximately a third of this population, suggesting that a cautious approach to this novel treatment is required. However, this should be balanced with quantitative and qualitative findings suggesting that people with BD perceived wide-ranging benefits of psilocybin use.

Negative or unwanted impacts of psilocybin use were most commonly new or increasing manic symptoms, sleep difficulties and anxiety. Sleep disturbances are of particular concern for people with BD, given accumulating prospective evidence demonstrating their association with the recurrence of mood episodes, particularly mania (Cretu et al., 2016; Gruber et al., 2011; Perlman et al., 2006; Sylvia et al., 2011), but also extending to hypomania and depression (Andrade-Gonzalez et al., 2020; Lam and Wong, 2005). In addition, anxiety is a common prodrome for both depressive and manic/hypomanic episodes in patients with BD I and II (Andrade-Gonzalez et al., 2020; Lam and Wong, 2005). As mentioned earlier, it may be expected that individuals with BD I are more vulnerable to adverse effects of psilocybin

use; however, in the present sample people with BD I and BD II were equally as likely to report the experience of any adverse or unwanted outcome overall. Although by definition only people with a diagnosis of BD I have experienced mania, it is not unheard of for an individual with diagnosed BD II to go on to experience a manic episode – indeed, there is a documented example of this occurring when an individual with BD II consumed psilocybin (Gard et al., 2021). In the absence of more conclusive evidence regarding differential risk profiles, we suggest a cautious approach remains warranted for both subgroups. It is important to qualify these reports with an acknowledgement that serious adverse events (i.e. use of emergency medical services) were exceedingly rare in this survey. Published case reports of adverse events associated with psilocybin use in BD may be weighted towards such rare instances (Gard et al., 2021). In addition, as impaired decision making (such as problematic substance use) is a core feature of mania (Adida et al., 2008; Meade et al., 2008), it is possible that some adverse events may have occurred due to fluctuations in BD symptoms that led to psilocybin use, but that the psilocybin use itself was not the true cause.

Of note, respondents in this survey on balance indicated that they found psilocybin more helpful than harmful. Qualitative analysis of free-text responses reinforced and added detail to this notion, as individuals with mixed experiences of psilocybin use largely emphasised that the positive impacts offset the (often transient) negatives. Our finding is thematically similar to a large-scale online survey ($n = 1993$) asking psilocybin users from the general population about their single most psychologically difficult or challenging psilocybin experience; 84% of respondents still endorsed benefiting from their 'worst trips' (Carbonaro et al., 2016), with degree of difficulty correlated with enduring increase in wellbeing. In light of such related findings, our preliminary evidence on the relative subjective benefits and harms of psilocybin for people with BD calls for nuanced consideration of the safety profile and impacts of this substance moving forward.

Our study detailed, for the first time, adherence to psychiatric medications amongst people with BD who use psilocybin. Although we did not observe an association between the experience of side effects of psilocybin consumption and use (or discontinuation) of psychiatric medications as prescribed, a limitation of our survey is that we did not enquire about negative physical health outcomes, which may have impacted individuals who maintained their usual psychiatric medications. Given that psychedelic compounds act as 5-HT2A serotonergic agonists, the occurrence of serotonin syndrome related to concurrent use of other serotonergic agents (e.g. selective serotonin reuptake inhibitor-type [SSRI] antidepressants) is a valid concern (Barnett and Greer, 2021); however, recorded cases of serotonin syndrome secondary to classic psychedelic compounds are rare (Malcom and Thomas, 2021). Research investigating interactions between psychedelics and common pharmacological treatments (e.g. mood stabilisers, antipsychotics) for BD is rare, but user-led reports offer some suggestions about potentially dangerous interactions. Analysis of reports from three websites (Erowid.org, Shroomery.org and Reddit.com) suggest that concurrent use of classic psychedelics (e.g. psilocybin and lysergic acid diethylamide) and the mood stabiliser lithium, but not lamotrigine, may be associated with seizures (Nayak et al., 2021). Further research is required to support informed decision-making in self-directed psilocybin users, as well as protocols for psilocybin therapy in clinical trials.

Current procedures for psilocybin clinical trials may need to be modified to account for risks specific to populations with BD. For example, after a session of psilocybin, participants are typically transported home by a family member or caregiver (Carhart-Harris et al., 2016). Given the not-infrequent experience of symptom escalation reported by participants in the present survey, a BD psilocybin trial would benefit from assertive follow-up with participants/a nominated contact at a minimum. Some individuals with BD may require monitoring within the facility (with availability of appropriate pharmacological treatments to ensure adequate sleep takes place following a session). Other risk mitigation strategies include careful screening for prodromal hypomanic symptoms before psilocybin administration and monitoring for adherence to prescription medication. The emerging study of methods to integrate challenging psychedelic experiences also has relevance to the design of clinical trials in this population, given the number of individuals reporting increases in anxiety, depressive symptoms and psychosis-like experiences (Gorman et al., 2021). Attention to psychological state prior to administration ('set') and interpersonal/physical characteristics of the administration environment ('setting') may help minimise the experience of distressing reactions to psychedelics (Johnson et al., 2008; Studerus et al., 2012). More research on potential risk factors is required to appropriately tailor risk management procedures in BD clinical trials: the present survey was not able to rule out the influence of alternative precipitating factors for adverse events, including polysubstance use, preexisting subthreshold mood elevation and set/setting. The likelihood of adverse events in a more carefully controlled clinical setting may differ from those reported in non-prescribed/recreational use.

Given limited evidence and the complex regulatory status of psychedelic treatments (Johnson et al., 2018), it may be some time before prescription of psilocybin as a pharmacological treatment for BD is possible. However, findings in the present study demonstrate that numerous people with BD are currently using this substance, most commonly with the intent of promoting personal development, recreational purposes (fun or curiosity), self-medicating mental health symptoms or achieving spiritual growth. Clinicians should therefore be alert to the possibility of psilocybin use in patients with BD and discuss potential side effects and mitigation strategies within a harm reduction framework (Gorman et al., 2021). Collaborative exploration of attitudes towards use of prescribed medications is also necessary given the high risk of relapse associated with nonadherence in BD (Crowe et al., 2011; Jawad et al., 2018).

Our qualitative characterisation of the perceived benefits of psilocybin for mental health is echoed by a growing body of literature describing positive impacts of psilocybin for symptoms of anxiety (Grob et al., 2011; Moreno et al., 2006), depression (Carhart-Harris et al., 2018; Davis et al., 2021a,b; Osório et al., 2015) and substance use (Bogenschutz and Johnson, 2016). Some respondents in the present survey study also noted reduced mood lability (rapid, frequent and disproportionate mood changes), a feature which has been shown to predict subsequent relapse and worse clinical/functional outcomes in patients with BD (Howes et al., 2011; Patel et al., 2015; Stange et al., 2016; Strejilevich et al., 2013). Although such qualitative findings have limitations in that they are subjective and derived from a small, relatively homogenous sample, they lend weight to calls to investigate psilocybin therapy in people with BD. Taken together,

these subjective benefits suggest investigation of the utility of psilocybin for acute depressive episodes and as a prophylactic maintenance treatment, as well as identify potentially relevant outcomes to measure in future clinical trials.

Of note, non-clinical benefits to wellbeing were also described by participants, including most prominently, psychological growth. While there is some literature to show quantitative improvements in wellbeing in healthy humans following psilocybin administration (Griffiths et al., 2008), inherently personal insightful or spiritual experiences are more difficult to measure nomothetically (although measures have been developed in an effort to better describe these, for example the Mystical Experiences Questionnaire, (MacLean et al., 2012) and the Psychological Insight Questionnaire (Davis et al., 2021a,b). Qualitative research in both clinical and healthy samples, however, has detailed meaningful and mystical experiences during psychedelic trips, and subsequent impacts on wellbeing or clinical outcomes (Belser et al., 2017; Breeksema et al., 2020). Of relevance to BD, a qualitative study of psilocybin therapy for treatment-resistant depression highlighted that developing a sense of connection (to oneself and others) and acceptance of negative emotions served as a protective buffer against symptom impacts (Watts et al., 2017). Although the mechanistic pathways of psilocybin are not well understood, such qualitative research draws attention to the potential role of personal and spiritual growth in mediating clinical improvements. However, it should be noted that this qualitative research examined experiences under the more tightly controlled context of psilocybin therapy; subjective benefits of non-prescribed/recreational use in individuals with BD (as described in the present survey) may be influenced by different factors. Future clinical trials of psilocybin in BD will therefore benefit from applying mixed-methods designs (i.e. both qualitative and quantitative data collection) in order to explore biological and psychological change processes.

Future directions

The present survey represents the initial phase of a sequential mixed-methods project (Ivankova et al., 2006), with the overarching aim of improving understanding of psilocybin use and outcomes among people with BD. In the second phase, a series of qualitative interviews were conducted with a subset of respondents, with the aim of elaborating on perceived risks and benefits, as well as circumstances (i.e. set and setting) surrounding psilocybin consumption. Together, findings will inform the design of an open-label, dose escalation study investigating the safety and feasibility of psilocybin therapy to treat depressive symptoms in BD II (ClinicalTrials.gov Identifier: NCTT05065294).

Limitations

Strengths include the relatively large sample size and mixed-methods approach. Nonetheless, there are some limitations. Use of online surveys for data collection has limitations, as it is possible that individuals who do not meet eligibility criteria chose to participate. For example, as diagnosis was self-reported, it is possible that individuals who did not meet diagnostic criteria for BD completed the survey. There is little research on the characteristics of people who self-identify as having BD. However, face-to-face structured clinical interviews with a random sample ($n = 100$) of people applying to join a BD case registry confirmed that 93% had a lifetime DSM-IV BD diagnosis (Kupfer et al., 2002). In the present study we opted to minimise barriers to participation for this potentially stigmatised group of individuals who have used illicit substances (such as requiring the provision of contact details or the completion of a gold-standard diagnostic interview); however, this must be balanced with the fact that we cannot verify diagnosis.

Relatedly, online surveys may be vulnerable to inattentive responding, duplicate responses, bot responses and missing data (Buchanan and Scofield, 2018). However, we did not offer incentives for completion of this study, which can can minimise the risk of such poor-quality responses (Griffin et al., 2021; Yarrish et al., 2019). Further, we undertook efforts to remove duplicate responses based on IP addresses. We also note that the response rate to qualitative items is reassuring, as such items are unlikely to be completed by bots or inattentive/low-effort responders. Future research may benefit from incorporating additional data integrity verification questions and cleaning procedures to deter 'mischievous' responders who intentionally provide inaccurate responses, such as overreporting undesirable outcomes like substance use (Cimpian et al., 2018; Palamar and Acosta, 2020).

To minimise response burden and maximise survey completion rates, we did not ask people to describe each individual experience of psilocybin consumption. This limited our ability to analyse contextual factors surrounding the experience of positive and negative events (such as use of/discontinuation of particular psychiatric medications). We believe that asking for such granular detail would not have been feasible, given the modal rate of psilocybin use was 2–5 occasions. Future research may benefit from asking participants to focus on and describe a singular experience, such as the most beneficial or the most harmful. Despite our efforts to recruit demographically diverse groups of people, the sample was overwhelmingly White and North American. This pattern follows a long history of homogenous sampling within psychedelic research (Michaels et al., 2018), which decreases the generalisability of findings to Black, Indigenous and people of colour (BIPOC) and may serve to exclude these populations from therapeutic benefits. Recently published recommendations to support the inclusion of BIPOC and other underrepresented communities in psychedelic research include offering face-to-face education about the study and ways their safety and confidentiality would be protected, so that community members have a chance to develop trust and rapport (Williams et al., 2020). Details about the study's structure, as well as open question-and-answer periods, should be included. Finally, psychedelic research groups should prioritise hiring professionals from underrepresented populations to aid marginalised communities in identifying with the research cause and processes.

Specific to the analysis of qualitative survey responses, we were not able to ask follow-up questions, limiting the depth of analysis. To address this, follow-up qualitative interviews were conducted with a purposive subsample of respondents. Further, individuals who self-select into answering open-ended items may be more articulate or have a greater interest in the survey topic. Potentially, as much of the survey focused on negative experiences (side effects, use of emergency medical services), participants may have inferred that the researchers held preconceived notions of psilocybin as harmful. As such, participants may have been more

motivated to express positive experiences to challenge this assumption, encourage further research or due to concerns that research findings would be used to undermine future research or law reform (Decorte et al., 2019). It is also important to reiterate here that the analysis of qualitative responses deliberately focused on positive experiences to complement the quantitative focus on adverse events and medication use; a small proportion of individuals ($n=25$) spontaneously discussed negative experiences. We again note that the frequency of comments provided in response to open-ended items is better taken as a proxy of how salient these issues were to respondents, and how driven they were to comment on them. They do not necessarily indicate how prevalent positive and negative experiences of psilocybin use were for this population. Despite limitations, our results add to a body of work showing that the near ubiquitous, but rarely analysed 'any other comments' question may provide important insights.

Conclusion

This survey is the first to characterise the use and impacts of psilocybin amongst people with BD. Respondents described subjective benefits for mental health symptoms and wellbeing, adding to a growing body of literature suggesting positive impacts of psilocybin use. However, data also suggest that symptoms of BD may be precipitated by psychedelic 'trips'. As such, more intensive follow-up and safeguards should be employed with this population than is typical of psilocybin studies to date. Despite this, serious adverse events were rare, and participants overall reported psilocybin to be more helpful than harmful. Taken together, the findings encourage further investigation of psilocybin-based treatments for BD in the context of carefully monitored clinical trials.

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Data availability

Data are not publicly available in accordance with ethics approval given by the ethics board from the participating university. Interested investigators may submit inquiries to the corresponding author.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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