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Attenuation of psilocybin mushroom effects during and after SSRI/SNRI antidepressant use

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Abstract

Background: Psilocybin is being studied for depression, but little is known about how it interacts with common antidepressants. Limited data suggest that psilocybin's effects may be diminished by serotonergic antidepressants acutely and even after a medication washout period.

Aims: To learn the extent to which antidepressants may diminish the effects of psilocybin-containing mushrooms both concurrently and after discontinuation of antidepressants.

Methods: Online retrospective survey of individuals with use of psilocybin mushrooms (1) with an antidepressant and/or (2) within 2 years of discontinuing an antidepressant. Participants who took mushrooms with an antidepressant and either took the same dose pre-antidepressant or took the same dose with other people not on antidepressant reported the strength of drug effects relative to their expectation. Participants who took mushrooms following discontinuation of an antidepressant also reported the presence of weakened effects.

Results: In reports ($n = 611$) of taking mushrooms with an antidepressant, probabilities [95% CI] of weaker than expected drug effects were 0.47 [0.41–0.54] (selective serotonergic reuptake inhibitors, SSRIs), 0.55 [0.44–0.67] (serotonin norepinephrine reuptake inhibitors, SNRIs) and 0.29 [0.2–0.39] (bupropion). Following SSRI/SNRI discontinuation ($n = 1{,}542$ reports), the probability of reduced drug effects was not significantly different from the earliest post-discontinuation timepoint (within 1 week) until 3–6 months, probability = 0.3 [0.20–0.46], $p = 0.001$. A sensitivity analysis found that removing responses involving fluoxetine, which has an especially long half-life, did not significantly alter this result.

Conclusions: SSRI/SNRIs appear to weaken psilocybin drug effects relative to a non-serotonergic antidepressant. This dampening effect may last as long as 3 months following antidepressant discontinuation.

Keywords

Antidepressant, serotonin, psychedelic, psilocybin, drug interactions

Introduction

A growing body of research suggests that psilocybin-assisted therapy can produce rapid and robust antidepressant effects in patients with major depressive disorder (MDD) (Carhart-Harris et al., 2018, 2021a; Davis et al., 2021). Psilocybin-assisted treatment is currently in phase II/III clinical trials for efficacy and safety in MDD and treatment-resistant depression, and it has the potential to become a widely used treatment if early results are successfully and safely replicated at scale. Although psilocybin and other serotonin 2A ($5HT_{2A}$) receptor agonists (i.e., classic psychedelics) may soon make their debut in clinical practice, relatively little is known about their interactions with other psychotropic drugs that are commonly used in patients with depression and other mental health conditions (Sarparast et al., 2022).

The current standard of practice in psilocybin-assisted therapy trials is to discontinue serotonergic antidepressants, and in some cases, other psychotropic drugs for at least four to five half-lives prior to treatment. In part, this practice stems from the need to determine the independent therapeutic efficacy of psychedelics, but is also done to avoid reduced efficacy or adverse effects of psychedelics with concurrent use of an antidepressant (e.g., serotonin syndrome – discussed below). Much of the evidence to support these potential interactions comes from studies of another $5HT_{2A}$ agonist, lysergic acid diethylamide (LSD), which has a somewhat distinct receptor-binding profile including dopamine agonist properties (Nichols, 2016). An early indication of clinically significant interaction was noted by Grof and Dytrych (1965), in which patients taking the monoamine oxidase inhibitor (MAOI) nialamide for several weeks were found to be insensitive

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to the effects of LSD. This effect lasted at least 14 days before eventually resolving. A later survey study of 32 LSD users, who reported chronic (>3 weeks) use of a selective serotonergic reuptake inhibitor (SSRI), found that 88% reported reduced or absent subjective effects of LSD (Bonson et al., 1996). A separate smaller study found similar effects with MAOIs, and conversely a potentiation of LSD effects with tricyclic antidepressants and lithium (Bonson and Murphy, 1995). A recent analysis of online forum posts also suggested a high rate of seizures when classic psychedelics were used concurrently with lithium (Nayak et al., 2021). A recent study administered psilocybin to healthy participants who had taken the SSRI escitalopram for 14 days and found that the combination did not affect total scores on the Mystical Experience Questionnaire (MEQ) or self-reported subjective "good drug effects," but did reduce the ineffability and nadir effects factors of the MEQ, reports of "any drug effects," cardiovascular effects, pupillary dilation, and ratings of negative subjective drug effects including anxious ego dissolution and fear (Becker et al., 2022). Given that 14-day SSRI pretreatment is insufficient for clinically significant antidepressant-induced serotonin receptor downregulation, it is unclear whether these findings would generalize to those with depression or longer-term SSRI use. The finding may also not generalize to other drug classes like serotonin norepinephrine reuptake inhibitors (SNRIs).

Other findings suggest that antidepressant use may decrease efficacy of psychedelics even after a medication taper has been completed, though data are mixed. In a secondary analysis of data from a trial of psilocybin versus escitalopram for MDD, participants in the high-dose psilocybin treatment condition who tapered off of an antidepressant immediately prior to their participation had significantly less clinical improvement when compared to participants without recent use of antidepressants (Carhart-Harris et al., 2021b). A more recent study of psilocybin in a treatment-resistant sample, however, did not find an association between recent antidepressant discontinuation and treatment effects (Goodwin et al., 2022).

Other clinically significant interactions are possible, though they are also poorly understood. There is a theoretical risk of serotonin syndrome, a potentially life-threatening condition caused by excessive levels of serotonin, which can result in a range of symptoms such as agitation, confusion, muscle rigidity, high fever, seizures and, in severe cases, can lead to organ failure and death. This can be caused by the use of certain medications or supplements that increase synaptic serotonin signaling, such as antidepressants, and risk increases with use of multiple such agents concurrently (Malcolm and Thomas, 2021). To date, only three cases of serotonin syndrome have ever been reported with a potential connection to psilocybin—members of a family in Japan who had simultaneously ingested *Psilocybe venenata* (Suzuki, 2016). There have been no reported cases of serotonin syndrome following ingestion of synthetic psilocybin. Seizures may occur with other classic psychedelics such as LSD, as suggested by one case report of a child experiencing grand mal seizures following ingestion of what was thought to be LSD during ongoing treatment with fluoxetine (Picker et al., 1992).

While current research practices and potential clinical applications are guided by an assumption that daily serotonergic pharmacotherapies should be discontinued before psychedelic administration, little is known about their potential interactions. If there are little to no increased risks from interactions or reductions of psychedelic effects, then the current practice of discontinuation of daily serotonergic pharmacotherapies may not be warranted. However, if there are risks of interaction or reductions of psychedelic effects, then modification of psychedelic doses or tapering and discontinuation of daily serotonergic pharmacotherapies may be optimal. If discontinuation is warranted, then it is important to know for how long discontinuation should occur.

We present the findings of a large retrospective survey study in which we sought to investigate the phenomena described above specifically with respect to psilocybin. Our primary aims were to quantify (1) the effects of current antidepressant use on subjective drug intensity, and (2) potential residual changes in subjective drug intensity that are present after antidepressant discontinuation. We also collected data on reports of serotonin syndrome.

Methods

The survey was deemed exempt from review by the Johns Hopkins University School of Medicine Institutional Review Board. Anonymous responses were collected between September 2020 and November 2021 via the Qualtrics web-based survey platform. Advertisements for the survey were posted on forums, subreddits, and social media pertaining to psychedelic drugs and/or individuals who struggle with mood, anxiety, or other mental health conditions. The survey landing page led to an informed consent document detailing the survey purpose, as well as potential risks and benefits of participation. To proceed, participants were required to agree that they met the major inclusion criteria including: (1) understanding written English, (2) being over the age of 18, and (3) having used a moderate or high dose of psilocybin while being treated with an antidepressant, or within 2 years after stopping treatment. No incentives were provided for participants.

After providing demographic information and diagnostic history, participants were asked whether they had taken psilocybin (1) "BEFORE ever having been on an antidepressant," (2) "WHILE taking an antidepressant," or (3) "AFTER discontinuing an antidepressant." Participants could select one or more options. Those who had taken psilocybin while taking an antidepressant (option 2) and those who had taken psilocybin after stopping an antidepressant (option 3) received two separate sub-surveys (called Survey 1 and Survey 2 below, but note that these terms refer to distinct survey streams on the same overall survey). Thus, a participant may have answered either "Survey 1: Psilocybin while on antidepressants," "Survey 2: Psilocybin after discontinuation of antidepressants," or both. Below, measures and statistical analyses are reported separately for these two surveys.

Responses from duplicate IP addresses and from individuals who indicated that their responses should be discarded due to poor quality responses were excluded from analysis.

Survey 1: Psilocybin while on antidepressants

Measures in Survey 1: Psilocybin while on antidepressants

Participants who had taken psilocybin while on an antidepressant were asked questions about *individual episodes* of taking

psilocybin while on an antidepressant as well as several *general questions* about their psilocybin experiences while on antidepressants.

Participants were asked how many times they had taken a moderate to large dose of psilocybin while on an antidepressant. If they reported having one or two experiences of psilocybin on an antidepressant, they were asked to report specifically on those episodes. If they reported having more than two such episodes they were asked to report, separately, on the most and least intense ones. For the analysis of individual episodes, only reports of participants who had one or two episodes of psilocybin on an antidepressant (and were thus able to report on every lifetime instance of this) were used.

For each episode, participants were asked what antidepressant they took from a drop-down menu that included all commonly prescribed SSRIs, SNRIs, as well as bupropion (a norepinephrine dopamine reuptake inhibitor, NDRI), and mirtazapine. Participants who selected an SSRI, SNRI, or NDRI from the drop-down menu were assigned the appropriate drug class. There was an option to select "other" and write free text for antidepressants that were not listed, such as tricyclics and MAOIs. Drug class was specified as tricyclic or MAOI by manually inspecting free-text responses.

Participants were asked to describe the effect in relation to their expectation for the dose: "No effect at all," "Weaker than expected," "About the same as expected," or "Stronger than expected." Participants were also asked (1) whether they had previously taken a similar dose of mushrooms before starting an antidepressant, and (2) whether someone who was not taking an antidepressant had taken a similar dose at the same time as them.

Duration of antidepressant use at the time of the psilocybin experience was assessed with the following categories: Less than 1 week, 1–2 weeks, 4–6 months, 2–4 weeks, 2–4 months, more than 1 year, 1–2 months, and 6–12 months. Participants also indicated what other medications they were taking, what form of psilocybin, and an estimated dose they took (free text), whether they took the same psilocybin dose prior to starting the antidepressant, and whether others around them not on antidepressants took the same dose at the same time. They were also asked how long they had been taking their antidepressant medication, whether they had taken a "drug holiday" (skipping doses of their antidepressant prior to psilocybin use for the purpose of mitigating unwanted drug interactions), and if so, for how long.

In addition, all participants who had taken psilocybin both on an antidepressant and off an antidepressant were asked several general questions. These participants were identified as those who endorsed taking psilocybin while on an antidepressant (option 2 above), and had taken psilocybin either before (option 1 above) or after (option 3 above) being on an antidepressant. The following questions were asked: "In general, how are the effects of psilocybin when taking an antidepressant compared to not taking an antidepressant," with the following response options: "Less intense," "About the same intensity," and "More intense." Those who reported less intensity were also asked whether they had ever taken a drug holiday. Those who reported lower intensity were also asked whether they have "been able to overcome the diminished effect by taking a larger dose?"

All participants were asked whether they had believed they experienced an adverse event from combining psilocybin and an antidepressant. These participants were also asked whether they believed that they developed serotonin syndrome after taking this combination after reading the following description: "Serotonin syndrome is a life-threatening condition that usually requires emergency medical treatment (that is, if you had ever had this condition you almost certainly would have gone to the hospital for treatment). It can happen shortly after ingestion of drugs that affect levels of serotonin in the brain. Symptoms can include restlessness, confusion, fast heart rate, elevated blood pressure, muscle rigidity, fever, and seizures."

Statistical analyses of Survey 1: Psilocybin while on antidepressants

All analyses were completed using R Statistical Software Version 4.1.2. To investigate the effect of antidepressants during individual episodes of a psilocybin experience, only those who endorsed one or two such psilocybin experiences were analyzed. Thus, participants reported every psilocybin episode on an antidepressant they had had. In addition, only reports that met at least one of the following criteria were used: (1) had used the same dose of the same form of psilocybin prior to starting their antidepressant or (2) took psilocybin with others not on antidepressants who took the same dose.

In addition, the analysis of individual episodes was also restricted to those who took psilocybin in the form of dried mushrooms, were able to report the effect of the psilocybin experience, reported an intelligible dose in grams or milligrams, were taking an SSRI, SNRI, or NDRI (the most commonly prescribed drug classes), and were not taking other psychoactive medications.

Free-text responses of dried psilocybin mushroom dose were manually examined and converted to grams. "1/8th" or "one eighth" was assumed to refer to an eighth of an ounce, and therefore 3.5 g. Dose ranges, such as "3–5 g" were averaged (e.g., 4 g). Doses that were not resolvable to grams (e.g., "3 small mushrooms," or "4 caps") were not included in the analysis of individual episodes. Doses in pounds were discarded for being improbable, as were nonsensical responses such as "Abt 2 h." One participant reporting a dose of 23 g was removed for being improbable.

A logistic regression model was performed using reported weaker psychedelic effect as the outcome variable and age, sex, antidepressant class, psilocybin dose, and length of time on antidepressant, and whether they had taken a drug holiday as predictor variables. This outcome variable of weaker psychedelic effect combined "No effect at all" into "Weaker than expected." Antidepressant dose was not included in these models as potencies varied very widely across drugs. Statistical significance of main effects was assessed using Type II Wald chi-square tests with the ANOVA function from the R package car (Fox and Weisberg, 2019). Logistic regression coefficients were exponentiated into odds ratios and then converted to probabilities of weaker effect for ease of interpretation.

A sensitivity analysis removing all cases that include other (non-prescribed) psychoactive drugs was also performed.

In order to investigate possible potentiation of psilocybin effects by tricyclic antidepressants (Bonson and Murphy, 1995), the proportions of reported effects among those individuals who endorsed taking psilocybin concurrently with a tricyclic antidepressant were counted.

Statistical analysis of general (not episode specific) questions concerning the combination of psilocybin with antidepressants, including on drug holidays, adverse events including serotonin syndrome, and overcoming of dampened effects was performed with basic descriptive statistics.

Survey 2: Psilocybin after discontinuation of antidepressants

Measures in Survey 2: Psilocybin after discontinuation of antidepressants

Respondents who ever used psilocybin after discontinuing an antidepressant were asked to specify how long after discontinuing their medication they had used the drug from the following options: (1) within 1 week, (2) 1 week to 1 month, (3) 1 to 3 months, (4) 3–6 months, (5) 6–12 months, or (6) ⩾12 months after discontinuation of their medication. If there was more than one episode of use during a selected timeframe, respondents were asked to answer questions about the first episode of use that occurred in that window. The survey was designed to limit respondents to describing two episodes, but due to an error in survey flow, some participants provided responses for more than two episodes. For each index episode, respondents indicated their age at the time of psilocybin use, which medication(s) they had been on prior to the episode, their approximate doses, and the duration of antidepressant use prior to discontinuation. Respondents either selected from a drop-down list of common antidepressants or were able to enter a free-text response if their selected medication was not shown. Free-text responses for primary antidepressant were parsed for generic and trade names of the drugs listed in the drop-down menu. If respondents indicated in their free-text response an antidepressant that was on the primary list of common SSRI or SNRIs, their responses were included in the analysis. They were also asked to indicate whether they were on any other psychotropic medications alongside their primary antidepressant drug using free-text entry.

Concurrent use of other drugs at the time of psilocybin use was also queried using a checklist of common drugs. They also indicated the form (dried vs. fresh mushrooms, truffles, or other) and approximate dose used. Participants were also asked to report on the anticipated intensity of their dose, and the actual intensity of the dose relative to the anticipated intensity (Mild, Moderate, Strong, or Extreme). Respondents also indicated whether they took multiple doses of psilocybin during that particular episode due to not feeling strong enough effects from the initial dose.

Statistical analyses of Survey 2

Responses indicating "weaker than expected" effects or "no effect at all" were collapsed into a reduced subjective effects variable due to the low number of responses indicating no effect at all. A logistic regression model was conducted using the outcome of reduced subjective effects and predictor variables including sex, age at time of use, time since antidepressant discontinuation, duration of antidepressant treatment prior to discontinuation, anticipated intensity of psilocybin effects, use of other drug together with psilocybin, and use of other medication with antidepressant prior to discontinuation. As in Survey 1, regression coefficients were exponentiated into odds ratios and then converted to probabilities of weaker effect for ease of interpretation.

Sensitivity analysis was performed by separately analyzing respondents who did and did not indicate that their primary antidepressant was fluoxetine, which has a significantly longer half-life than most other antidepressants (approximately 6 days, with the active metabolite norfluoxetine having a half-life of up to 2 weeks in chronic users) (van Harten, 1993).

Results

Participant characteristics

Of the 8724 participants who arrived at the survey landing page, 387 were removed for responding from a duplicate IP address, 4781 did not take psilocybin during or after an antidepressant, and therefore did not meet inclusion criteria, and 931 did not complete the survey. Ultimately 2625 participants completed the survey and were not excluded. Demographics are shown in Table S1. The sample was mostly white (91%), male (55%), located in the United States (72%), and had completed at least a bachelor's degree (54%). Surveys were collected from September 16, 2020 to November 1, 2021.

Results of Survey 1: Psilocybin while on antidepressants

Of the 2625 participants who completed the survey and were not initially removed, some were excluded for a variety of reasons in order to arrive at a sample of participants who had psilocybin experiences while on an antidepressant: 1942 (74.0%) reported taking a moderate to high dose of psilocybin while on an antidepressant; 559 (28.8%) endorsed a single such episode; 445 (22.9%) endorsed two such episodes, and the remaining 938 (48.3%) endorsed more than two such episodes.

In the analysis of individual episodes, we were interested in only participants who were able to report on every lifetime instance of taking psilocybin on antidepressant, we retained the 1004 participants who endorsed only one or two episodes of this (which totaled 1449 episodes). Of these, 590 participants (totaling 671 episodes) had the experience with friends taking a similar dose and not on antidepressants, and 433 participants (totaling 499 episodes) reported taking a similar psilocybin dose before taking antidepressants. These were not mutually exclusive categories, and 711 participants (totaling 950 episodes) met at least one of these criteria. Of these 950 episodes, reports were removed in sequence for the following reasons: 135 reports used forms other than dried mushrooms and were removed from analysis; 9 were removed for being unable to report the effect of the psilocybin experience, 69 were removed for reporting psilocybin doses that could not be quantified in grams (e.g., a number of mushrooms, or very unlikely values such as pounds); 39 were removed for using an antidepressant outside of one of the large drug classes (SSRI, SNRI, or NDRI), leaving 698 episodes in 533 participants. Of the 39 episodes not involving an SSRI, SNRI, or NDRI, 13 episodes involved mirtazapine, 6 episodes involved a tricyclic antidepressant (5 amitriptyline and 1 imipramine), and 4 involved an MAOI (2 moclobemide, 1 phenelzine, and 1 tranylcypromine). Eighty-seven (12.5%) episodes involved the use of multiple prescribed psychoactive medication and were removed from the analysis. This category included antidepressants, antipsychotics, and mood stabilizers. The three most common such drugs were bupropion ($n=30$), followed by aripiprazole ($n=14$),

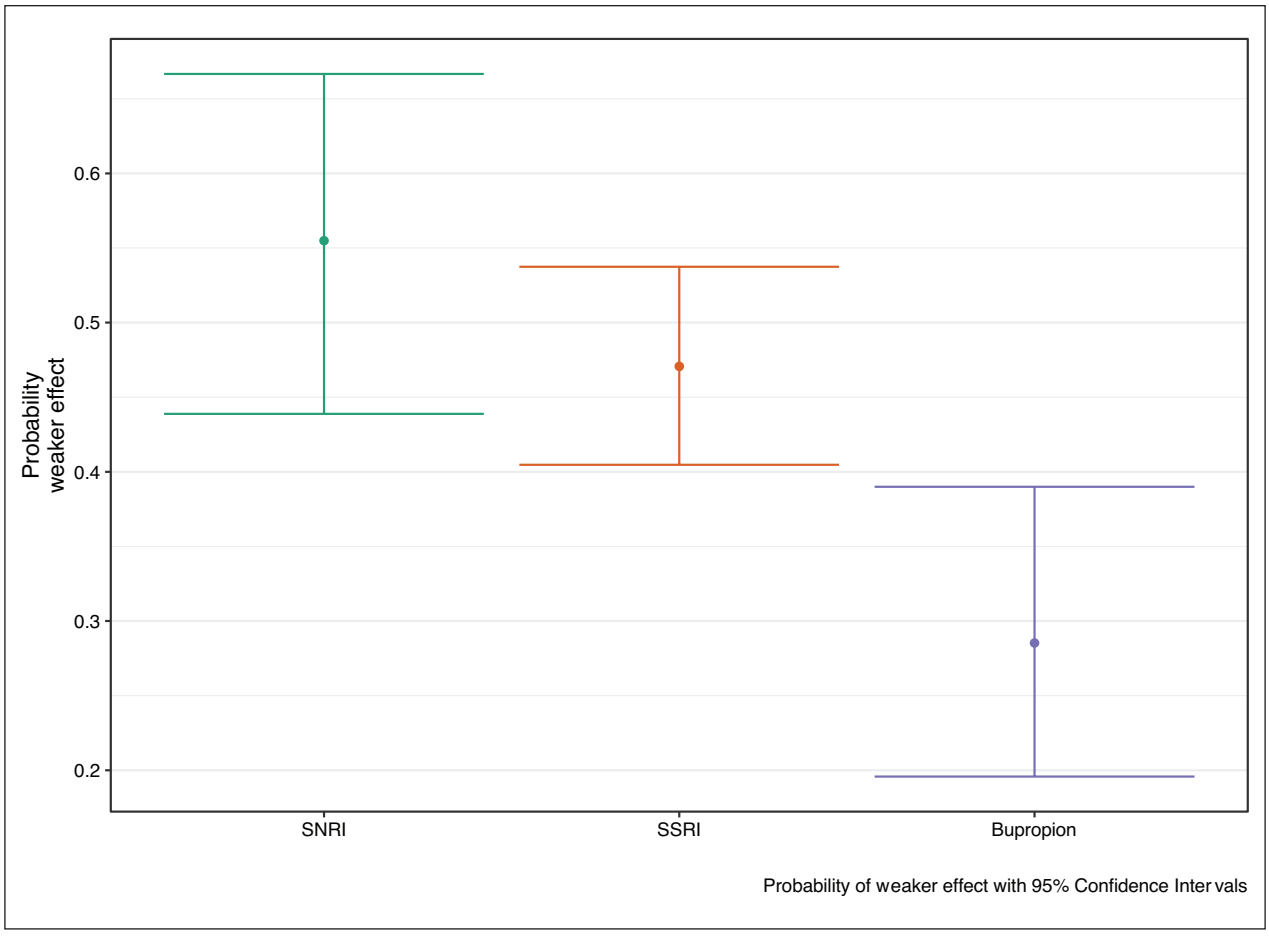

Figure 1. Adjusted probability of weaker than expected effects of psilocybin with concurrent use of three classes of antidepressants (SSRI, SNRI, and bupropion; $n = 611$ episodes).

and quetiapine ($n = 12$). These exclusions resulted in a total of 611 reports for the analysis among 468 participants. See figure S1 for a flowchart detailing the exclusions leading to the final sample. The total number of responses by antidepressant is shown in Table S4.

Of the 611 reports in the sample, some reported using multiple substances and so were subjected to a sensitivity analysis. Specifically, 362 (59.2%) episodes involved use of another psychoactive drug during the experience. These were primarily cannabis ($n = 287$), followed by alcohol ($n = 87$), amphetamine ($n = 21$), other psychedelics ($n = 12$), benzodiazepines ($n = 8$), and opioids ($n = 3$). These were retained in the main analysis and removed as a sensitivity analysis. Main effects of antidepressant drug class ($p < 0.001$) were statistically significant. Sex, age, psilocybin dose, duration of time on antidepressant (whether treated as an ordinal or continuous variable), and antidepressant drug holiday were not statistically significant. After removing the 362 (59.2%) participants who reported using another psychoactive drug, the main effect of drug class remained statistically significant with similar mean effects ($p = 0.03$), so it was deemed justifiable to use the full sample ($N = 611$).

The probabilities of weaker psychedelic effects were adjusted for age, sex, psilocybin dose, duration of antidepressant use, and whether a drug holiday was taken 0.47, 95% CI [0.40, 0.54] after SSRIs, 0.55, 95% CI [0.44, 0.67] after SNRIs, and 0.29, 95% CI [0.2, 0.39] after bupropion. These are shown in Figure 1.

Two additional analyses restricted to the two antidepressants with the largest numbers of respondents, escitalopram ($n = 156$) and sertraline ($n = 133$), were conducted and included antidepressant dose and an antidepressant dose × duration interaction as predictors found no statistically significant effects of antidepressant dose, time, or their interaction. This provided further justification to use the full sample ($N = 611$).

Of the six episodes involving psilocybin taken with a tricyclic antidepressant, only one reported stronger effects than expected. Of the 13 episodes involving mirtazapine, 5 (38.4%) were reported as weaker than expected, 4 (30.8%) were about the same as expected, and 4 (30.8%) were stronger.

Overcoming dampened effects

All participants who endorsed taking psilocybin before and in combination with an antidepressant, or in combination with an antidepressant and after ($n = 1062$; this includes individuals excluded in the above analysis of individual episodes: all drug classes of antidepressant, those who had more than two instances of taking psilocybin with an antidepressant, those taking different

forms of psilocybin) were asked, "In general, how are the effects of psilocybin when taking an antidepressant compared to not taking an antidepressant?" The majority, 549 (51.7%) reported reduced intensity of psilocybin when on antidepressants, 72 (6.8%) reported more, 313 (29.5%) reported about the same intensity, and the remaining 128 (12.1%) reported that they were not sure.

Of the 549 who reported reduced intensity of psilocybin effects, 284 (51.7%) attempted to overcome this with a higher dose of psilocybin. Of these 284, 129 (45.4%) reported they were able to overcome weakened effects with a higher dose, and 155 (54.6%) reported they could not.

Drug holiday

In the analysis of individual episodes, there was no statistically significant effect of taking a drug holiday. Of 611 individual episodes, 78 (12.8%) involved an antidepressant drug holiday. In descending order, 1 day off was taken in 22 episodes, 3 days off were taken in 15 episodes, 2 days off were taken in episodes 13, with the remaining 28 episodes involving more time off than this. Only eight episodes endorsed taking 10 days off or more their antidepressant prior to taking psilocybin.

Adverse events and serotonin syndrome

Only 110 (5.7%) indicated they believed they experienced an adverse event from combining psilocybin and an antidepressant. Examination of associated free-text responses by one of the researchers suggested that of these, 33 (30%) respondents did not experience an adverse event (e.g., "I'm sure the SSRI weakens the effect of psilocybin" and "Using psilocybin made me genuinely happy, more happier than antidepressants made me."). Removing these, only 4.0% of all participants indicated experiencing an adverse event.

Fifty-five (2.8%) participants believed they had developed serotonin syndrome after reading the description provided above in Methods; however, of these, only eight participants also indicated they believed they experienced an adverse event as a result of taking psilocybin concurrently with an antidepressant. We did not collect free-text responses specifically about serotonin syndrome and have no way of confirming whether these participants did in fact visit a hospital or were otherwise diagnosed with serotonin syndrome by a healthcare provider.

Results of Survey 2: Psilocybin after antidepressant discontinuation

Given the significant effects of serotonergic medications (SSRIs and SNRIs) relative to the NDRI class on intensity of psilocybin effects identified in Survey 1, analysis of Survey 2 focused on the residual effects of the major classes of serotonergic antidepressants exclusively.

Of 2625 completers, 1354 participants reported using psilocybin sometime after discontinuing an antidepressant in a total of 1955 episodes. Participants were excluded ($n=262$) sequentially for the following reasons: could not report an effect of the psilocybin experience ($n=21$); were not taking an antidepressant ($n=28$); were not taking an SSRI or SNRI ($n=213$), leaving a total of 1092 participants for analysis of individual episodes of serotonergic antidepressant use. In terms of individual episodes, the following exclusions ($n=169$) were made in sequence: could not report an effect of the psilocybin experience ($n=28$); were not taking an antidepressant ($n=48$); were not taking an SSRI or SNRI ($n=337$), leaving a total of 1542 episodes of psilocybin after antidepressant discontinuation in 1092 participants. Each respondent provided information on a mean of 1.41 ± 0.9 SD episodes. By drug class, respondents reported on episodes following an SSRI ($n=1{,}276$) and SNRI ($n=266$). See figure S1 for a flowchart detailing the exclusions leading to the final sample.

Absolute prevalence of weaker than expected psilocybin effects by time after SSRI or SNRI discontinuation are shown in Figure 2. Weaker than expected effects were present in $32.7\% \pm$ SE 4.6 of reports within 1 week of discontinuation, $25.9\% \pm$ SE 2.7 at 1 week to 1 month, $23.3\% \pm$ SE 2.3 at 1–3 months, $15.7\% \pm$ SE 2.3 at 3–6 months, $18.8\% \pm$ SE 2.4 at 6–12 months, and $15.6\% \pm$ SE 2.1 at 12+ months. Results of the model for reduced effects are shown in Figure 2 and Table S2. Following antidepressant discontinuation, odds of reduced psilocybin effects are significantly lower beginning at 3–6 months (probability = 0.3, 95% CI [0.20–0.42], $p=0.001$) and on. Older age was associated with higher likelihood of reduced effects after discontinuation (probability = 0.503 per year over mean, [0.50–0.51], $p=0.012$). SNRI was not significantly associated with odds of reduced effects relative to SSRI. Use of multiple psychiatric medications prior to discontinuation was significantly associated with higher likelihood of reduced effects (probability = 0.58, [0.52–0.65], $p=0.014$). Contrary to what was expected, duration of antidepressant treatment >12 months was associated with lower probability of reduced effects (probability = 0.35, [0.23–0.49], $p=0.033$) relative to the shortest duration of antidepressant treatment (<1 month). Anticipated drug intensity characterized as moderate or strong was also associated with lower odds of reduced effects relative to milder doses.

To determine whether fluoxetine, which has a longer than average half-life, was driving some of the reduced effects at timepoints beyond 1 week of discontinuation, we examined the model separately with subsets of the sample that used fluoxetine versus any other SSR or SNRI. After dropping fluoxetine cases ($n=320$), the model remained significant at the same timepoints as the primary model described above (see Table S3).

Discussion

Our results indicated that concurrent SSRI/SNRI use may be associated with weaker acute psilocybin effects, although this occurred in only about half of participants. This is substantially lower than previously reported rates of reduced drug effects from LSD (88%) after chronic SSRI use (Bonson et al., 1996). This difference may be due to our significantly larger sample, or perhaps a real difference between LSD and psilocybin effects in antidepressant users. There were very few reports of adverse events resulting from the combination of psilocybin and an antidepressant. In clinical trials, psilocybin is generally not administered to participants who are taking a serotonergic antidepressant. Doing so has been thought to impact both efficacy (the combination may diminish psilocybin's effects) and safety (the combination may cause serotonin syndrome or another adverse interaction).

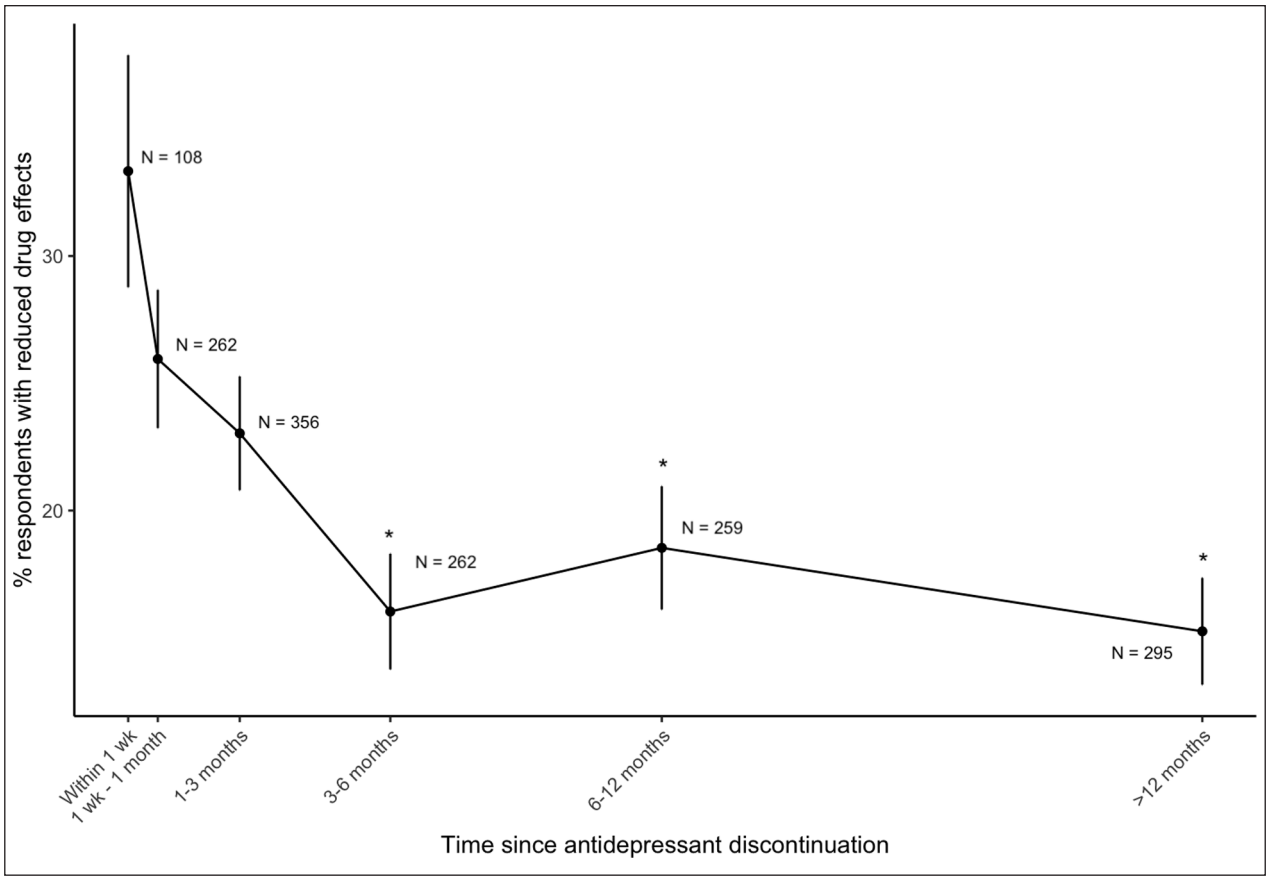

Figure 2. Percentage of respondents reporting weaker than expected effects of psilocybin (mean ± SE) following SSRI or SNRI discontinuation by time since medication discontinuation. *N* indicates the number of responses analyzed per timepoint. Asterisks indicate significant difference from the "within 1 week" timepoint in the adjusted model (see Table S2).

We did not find evidence that higher doses of SSRI/SNRI, or longer duration of time on the drugs, lead to greater reduction in psilocybin effects. We also did not find clear evidence that the majority of those who experience weakened psilocybin effects are able to overcome this weakened effect with a greater psilocybin dose. Drug holidays did not appear to reliably increase the effect of psilocybin. Future larger surveys and controlled dosing studies will be important to confirming these observations. Also surveys of participants in legal psilocybin retreats in which psilocybin dosing during or after discontinuation of antidepressants could provide important additional data.

After SSRI/SNRI discontinuation, the likelihood of reduced effects decreases over time but may be significant as long as 1–3 months after discontinuation. Sensitivity analysis suggested that this finding was not driven by cases involving fluoxetine, an SSRI with a particularly long half-life. As most SSRI/SNRIs have half-lives of about 1 day, this suggests these effects are driven by slower, longer-term changes in the brain. Our results were congruent with a recent finding in a controlled trial indicating that participants who had been recently tapered off of antidepressants had significantly less therapeutic efficacy with psilocybin (RL Carhart-Harris et al., 2021b) Notably, this finding was not reproduced in a larger study with high rates of recent antidepressant use, though this study found lower rates of treatment response overall, with less durability of antidepressant effects (Goodwin et al., 2022). This may suggest a difference inherent to treatment-resistant populations, and we unfortunately did not assess history of treatment resistance in our study. The model for Survey 2 showed that those with 12+ months of antidepressant use prior to discontinuation were *less* likely to have reduced effects relative to those who had used antidepressants for less than 1 month. This countered expectation, since longer amounts of time on an antidepressant would be thought to be associated with more pronounced 5-HT_{2A} receptor downregulation. This finding may have been due to sampling bias, as the number of respondents with <1 month of antidepressant use was relatively small ($N=69$ for <1 month, vs. $N=703$ for 12+ months of antidepressant use). However, changing the referent group to those with 12+ months of antidepressant use resulted in similar findings, with only the <1 month group being significantly different in the previously identified direction.

Many pressing practical questions remain: what is the *magnitude* of weakened psilocybin effects on an antidepressant, can this be overcome with a higher psilocybin dose, should patients wait longer than five half-lives after antidepressant discontinuation before using psilocybin, and, perhaps most importantly, is tapering even necessary at all? Even if reduced subjective effects are observed in more controlled studies, it is not clear that this

necessarily leads to reductions in therapeutic efficacy. While previous studies suggest that higher ratings of subjective drug effects are generally well correlated with long-term improvements in well-being in both healthy and depressed participants, this relationship was not found between measures of subjective effects like the MEQ, and reductions in mood symptoms in patients with depression (Griffiths et al., 2008; Gukasyan et al., 2022; Sloshower et al., 2023). A recent case report also highlighted a clinical trial participant who experienced an absence of psilocybin effects due to ongoing use of trazodone, but reportedly went on to experience a rapid and substantial decrease in depression symptoms (Rosenblat et al., 2023). A final note on this topic is that we did not analyze differences in specific aspects of the drug experience, for example, differences in perceptual versus psychological or somatic effects.

The mechanism of decreased psilocybin effects is likely to be $5HT_{2A}$ receptor downregulation. Subjective effects of psilocybin are known to be correlated with $5HT_{2A}$ receptor occupancy (Madsen et al., 2019). Six weeks of citalopram treatment in dogs decreases cortical $5HT_{2A}$ binding consistent with receptor downregulation (Peremans et al., 2005). In humans, 6 weeks of treatment with the SSRI paroxetine lead to downregulation of $5HT_{2A}$ receptors (Meyer et al., 2001), while a single dose of paroxetine does not (Meyer et al., 1999). It is important to note, however, that the data are not entirely convergent, with some studies finding increased $5\text{-}HT_2$ binding after treatment in depressed patients (Moresco et al., 2000; Zanardi et al., 2001). Although a study of healthy individuals dosed with 25 mg psilocybin after 2 weeks of escitalopram (SSRI) pretreatment did not show reduced psilocybin effects, we believe this is not likely to generalize to more chronic use of SSRIs typical in clinical practice (Becker et al., 2022). We suspect a similar study conducted 2 months after discontinuation of escitalopram would show reduced psilocybin effects. We also hypothesize that this would correlate with the degree of $5HT_{2A}$ receptor downregulation. Curiously, however, the model in Survey 2 found that the greatest duration of antidepressant use prior to discontinuation (12 or more months) was associated with significantly *lower* likelihood of reduced effects. This is contrary to what we would expect with the above explanation.

Adverse events and serotonin toxicity

Reported adverse events attributed to combining psilocybin with an antidepressant were very low in this sample, as were reports of serotonin syndrome. Serotonin syndrome is perhaps better called "serotonin toxicity," as it refers to a dose-dependent phenomena of excess intrasynaptic serotonin, rather than an idiosyncratic phenomenon (Gillman, 2006). It should be noted however that although $5HT_{2A}$ appears primarily responsible for the pathophysiology of serotonin toxicity, even massive overdoses of classic psychedelics do not seem to reliably cause serotonin toxicity (Malcolm and Thomas, 2021). This may be because commonly used tryptamines and ergolines do not activate the full second messenger cascade of the $5HT_{2A}$ receptor that endogenous serotonin does (Malcolm and Thomas, 2021; Nichols, 2004). Moreover, psilocin, DMT, and LSD are *partial* agonists that bind to the receptor with greater affinity than endogenous serotonin (Rickli et al., 2016). Serotonin toxicity is rare and the majority of cases occur when an MAOI is combined with a serotonin reuptake inhibitor or a serotonin-releasing agent (Malcolm and Thomas, 2021). However, it is noteworthy that DMT is commonly administered with reversible MAOIs in the form of ayahuasca. Even administered with MAOIs, psilocybin is unlikely to cause serotonin toxicity, and this risk is likely to be lower with serotonin reuptake inhibitors (Malcolm and Thomas, 2021). Indeed, only eight individuals endorsed a belief they had experienced serotonin syndrome and also stated they experienced an adverse reaction to the combination of psilocybin and an antidepressant, amounting to 0.4% of individuals who had combined the two.

Clinical and ethical implications

Antidepressant discontinuation is associated with relapse and withdrawal phenomena that may put patients at risk of serious harm (Gemma et al., 2021; Hengartner et al., 2020). Therefore, it is important clinically and ethically to understand whether discontinuation of antidepressants is necessary. In psychedelic research settings, antidepressant discontinuation may aid in drawing firmer scientific inferences about the extent of psychedelic effects. However, it is possible that through stratified randomization practices, antidepressant discontinuation could be reduced or avoided. It could be of considerable clinical importance to have a more precise understanding of the extent to which psychedelic effects are reduced. This can help clinicians decide whether to discontinue antidepressants, to increase the dose of psilocybin to offset the dampening effect of these medications, and consider the risks related to withdrawal as well as potential reductions in psychedelic treatment efficacy. Longer tapering periods may also be considered, as they would allow for sufficient time for serotonin receptor density to adjust (Horowitz and Taylor, 2019).

Limitations

This study has multiple limitations. Data were collected via an anonymous online survey, which may have affected the quality of responses. The findings are based on retrospective self-report data, which may be affected by recall and other biases. We were unable to confirm self-report of serotonin syndrome by reviewing medical records, for example. Additionally, we are unable to express the effect size of weakened effects—participants categorically reported whether they experienced weakened effects. It is also possible that some domains of psychedelic drug effects may have been affected more than others (e.g., perceptual vs. emotional or somatic effects). This may be significant in that some aspects of drug effects tend to be more correlated with outcomes in clinical studies than others (Roseman et al., 2018). Some baseline level of weaker than expected effects is likely among naturalistic use in general given variability of psilocybin/psilocin content in mushrooms. We also have limited ability to interpret effect of dose in Survey 1 for this reason. Nonetheless, by restricting analysis to individuals who reported taking the same dose prior to being on the antidepressant or the same dose not on an antidepressant, we are able to examine effects with a plausible comparator. Furthermore, this analysis only included cases in which participants had combined an antidepressant with psilocybin once or twice, and were thus able to report on every lifetime instance of this. We did not collect data on contextual

factors (e.g., music, presence of supportive individuals), which may have affected self-reported differences in drug effects. Finally, there may be some effects of specific mental health diagnoses that are independent of medication use, though we did not include diagnosis in our analyses due to the very broad range of responses for this variable.

Results of cross-sectional survey studies of psychedelics may be inadvertently distorted by enthusiasm of participants to convey positive experiences thus biasing results via selective enrollment and recall of experiences. However, the results found here—that SSRI/SNRI's tend to weaken psilocybin's effects during and sometime after use, seems unlikely to be the result of demand effects or social desirability bias.

Conclusions

We found evidence that psilocybin's effects were reduced with concurrent SSRI/SNRI use more than the NDRI bupropion, and that significantly weaker than expected effects after SSRI/SNRIs may last up to 1–3 months after discontinuation even with drugs that have relatively short half-lives. Nonetheless, nearly half of participants taking a concurrent SSRI/SNRI did not endorse reduced psilocybin effects. There were few reported adverse events from combining antidepressants and psilocybin. Given the high rate of SSRI/SNRI prescription and ongoing investigation of psilocybin's antidepressant activity, more studies of concurrent psilocybin and these medications are needed to guide current research practices as well as the possible future medical use. Additionally, detailed data collection on patterns of pre-study antidepressant use may be useful to determine optimal duration of medication washout periods.

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Supplemental material

Supplemental material for this article is available online.

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