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ORIGINAL INVESTIGATION

Content analysis of Reddit posts about coadministration of selective serotonin reuptake inhibitors and psilocybin mushrooms

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Abstract

Rationale Treatments with the serotonergic psychedelic psilocybin are being investigated for multiple neuropsychiatric disorders. Because many patients with these disorders use selective serotonin reuptake inhibitors (SSRIs), understanding interactions between psilocybin and SSRIs is critical for evaluating the safety, efficacy, and scalability of psilocybin-based treatments. Current knowledge about these interactions is limited, as most clinical psilocybin research has prohibited concomitant SSRI use.

Objectives We aimed to explore potential interactions between psilocybin and SSRIs by characterizing peoples' real-world experiences using psilocybin mushrooms and SSRIs together.

Methods We conducted a systematic search of Reddit for posts describing psilocybin mushroom and SSRI coadministration. We identified 443 eligible posts and applied qualitative content analysis to each.

Results 8% of posts reported negative physical or psychological effects resulting from coadministration. These included 13 reports that may reflect serotonin toxicity, and 1 concerning for a psychotic/manic episode. 54% of posts described reduced intensity of the acute psilocybin experience, but 39% reported unchanged intensity with SSRI coadministration.

Conclusions Psilocybin's interactions with SSRIs are likely complex and may depend on multiple factors. Prospective studies are needed to evaluate whether psilocybin treatments are reliably safe and effective in the setting of SSRI use.

Keywords Psilocybin · Serotonin · Antidepressant · Drug-drug interactions

Introduction

Accumulating evidence suggests that treatment with the psychedelic drug psilocybin may lead to robust and persistent symptom improvement among people with a variety of neuropsychiatric illnesses, including depressive and anxiety disorders (Anderson et al. 2020; Carhart-Harris et al. 2016; Davis et al. 2020; Griffiths et al. 2016; Moreno et al. 2006), headache disorders (Schindler 2022; Schindler et al. 2021), and substance use disorders (Bogenschutz et al. 2015; Johnson et al. 2014). Though psilocybin mushrooms have been used as part of traditional health and wellness practices for centuries, decades of prohibition on psychedelic research mean that we have limited data on the safety, efficacy, and parameter space of psilocybin-based treatments (Nichols and Walter 2021). One critical issue is our lack of knowledge about psilocybin's interactions with existing pharmacologic agents used to target neuropsychiatric symptoms. This is an

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essential gap to address, as drug-drug interactions (DDI) may impact the implementation of novel psilocybin-based treatments. Specifically, if the safety and/or efficacy of psilocybin administration is reduced when combined with certain medications, patients may need to discontinue those medications before trialing a psilocybin-based treatment. This could have implications for scalability, as stopping a medication regimen can put patients at risk for relapse (Renoir 2013; Tamam and Ozpoyraz 2002).

Potential DDI between psilocybin and selective serotonin reuptake inhibitors (SSRIs) is a particularly relevant issue, as these medications are a first-line treatment for multiple common conditions including depression, anxiety, obsessive-compulsive disorder, and post-traumatic stress disorder. Among people using pharmacologic treatments for depression, for example, approximately 65% are prescribed an SSRI (Lou 2020). Moreover, discontinuing these medications even temporarily can precipitate withdrawal symptoms (Cosci and Chouinard 2020; Fornaro et al. 2023). Concern about DDI stems from the fact that psilocin, the active metabolite of psilocybin, shares a core structure with serotonin (5-HT). Psilocin produces its characteristic dose-dependent effects, which range from mild sympathomimetic activation to dramatic alterations in perception and consciousness (Griffiths et al. 2006; Studerus et al. 2010), primarily via its high binding affinity for the 5-hydroxytriptamine-2A (5-HT_{2A}) receptor (Madsen et al. 2019; Nichols 2016; Vollenweider et al. 1998). Though 5-HT_{2A} receptor partial agonism is necessary for the altered state of mind associated with psilocybin ingestion (Madsen et al. 2019; Stenbæk et al. 2021), psilocin modulates the serotonin system via other mechanisms as well, binding to multiple 5-HT receptor subtypes (Pokorny et al. 2016), weakly inhibiting the serotonin transporter (SERT; Blough et al. 2014; Rickli et al. 2016), and causing competitive inhibition of monoamine oxidase (Freedman et al. 1970). SSRIs also modulate serotonin signaling through multiple mechanisms, potently inhibiting SERT (Meyer et al. 2004) and, with repeated administration, decreasing the functional sensitivity of 5-HT_{1A} autoreceptors to increase availability of serotonin in the synapse (Artigas et al. 1996; Stahl 1998). Little is known about how the complex effects of SSRIs and psilocin on monoamine neurotransmission combine to impact patients' clinical status.

Given their mechanisms of action, one concern about combining psilocybin with SSRIs is the risk of serotonin toxicity (ST). This toxidrome stems from excessive serotonergic activity at central and peripheral nervous system synapses and leads to the triad of mental status changes, autonomic instability, and neuromuscular hyperactivity (Boyer and Shannon 2005). While the term "serotonin syndrome" is often used, serotonergic overactivity is better thought of as a spectrum of toxicity rather than a defined syndrome (Dunkley et al. 2003; Gillman 2004). Although monotherapy with serotonergic agents can precipitate toxicity (Abadie et al. 2015; Culbertson et al. 2018; Prakash et al. 2021), psilocybin on its own does not appear to confer a large risk of clinically significant ST. The common adverse effects associated with psilocybin administration (e.g., anxiety, tachycardia, nausea) may reflect the mild end of the ST spectrum, but reports of psilocybin mushroom ingestion causing ST severe enough to alert poison control centers are notably rare given reported rates of use in the community (Malcolm and Thomas 2021). To our knowledge, there are three published cases of ST meeting criteria for serotonin syndrome after ingestion of psilocybin mushrooms (Suzuki 2016) and one case of a psilocybin-induced arrhythmia and myocardial infarction (Borowiak et al. 1998). The small number of cases in the literature suggests that instances where psilocybin mushrooms have been associated with life-threatening ST (e.g., cardiac events, seizures) are likely extremely uncommon (Leonard et al. 2018). It is important to highlight that there are other reports of serious adverse outcomes (see Bickel et al. 2005; Blond and Schindler 2023; Carbonaro et al. 2016; Tiscione and Miller 2006) after psilocybin mushroom use, but that ST specifically has not been implicated and/or these cases have also involved confounding factors such as underlying medical conditions, use of other substances, or physical trauma which may independently increase risk of ST (Leonard et al. 2018). Clinical trials of psilocybin therapy, which have administered synthetic formulations of the drug at dosages ranging 0.14–0.36 mg/kg, also have not observed cases of clinically significant ST (dos Santos and Hallak 2020; Galvão-Coelho et al. 2021; Romeo et al. 2020). While these data are reassuring, nearly all trials have prohibited concomittant use of SSRIs (Galvão-Coelho et al. 2021), and patients are thought to be at greatest risk of ST when drugs with complementary serotonergic mechanisms of action are combined. Two recent studies have shed light on the issue of ST with psilocybin and SSRI coadministration. First, a psilocybin trial enrolled 19 people on SSRI therapy (Goodwin et al. 2022) and found that the overall rate of adverse events was not elevated relative to trials prohibiting SSRI use. However, two of the participants experienced severe blood pressure increases leading to administration of an antihypertensive agent; whether these autonomic changes reflected ST is not clear. Second, a recent survey study of people who had ingested psilocybin mushrooms while using SSRIs found that 55 of 1942 (2.8%) respondents believed they had developed serotonin syndrome (Gukasyan et al. 2023). These findings point to the need for additional study to understand which patients may be vulnerable to ST, particularly as clinical research expands to include patients with medical comorbidities that may raise their risk.

Another concern often cited in the clinical community is that concomittant SSRI use attenuates the subjective acute experience of psilocybin (ref: personal communications with individual health care providers and materials from organizations offering therapy with psilocybin mushrooms e.g., www.essence.nl/drug-interaction). This is relevant given that some studies have found a relationship between the quality of the acute experience and subsequent clinical benefit (Griffiths et al. 2011; Johnson et al. 2008; Kopra et al. 2023). Research directly addressing this issue is scarce. In the survey study referenced above, roughly half of respondents who reported current or recent SSRI use endorsed a weaker than expected subjective experience after taking psilocybin mushrooms (Gukasyan et al. 2023). Another study interviewed 32 people who had used a similar serotonergic psychedelic, lysergic acid diethylamide (LSD), both in the presence and absence of SSRI treatment; 28 described a diminished acute subjective response to the drug with SSRIs (Bonson et al. 1996). Studies have also underscored the need to consider acute versus chronic effects of SSRIs. For example, acute administration of fluoxetine has been shown to potentiate the effects of LSD in rats (Fiorella et al. 1996). Further, a case report described exacerbation of LSD "flashbacks" immediately after starting an SSRI (Markel et al. 1994), and in the study by (Bonson et al. 1996), the one participant on SSRI treatment for only one week reported an increased response to LSD. Importantly, LSD and psilocin differ in their serotonin receptor interaction profiles (Dinis-Oliveira 2017; Nichols 2004); interactions between psilocybin and SSRIs thus may be distinct. To our knowledge, only one prospective study has evaluated whether SSRI use modulates the subjective effects of psilocybin. (Becker et al. 2022) randomized 23 healthy people to receive a 25 mg dose of psilocybin following 2 weeks of pretreatment with escitalopram or placebo. They found no detectable differences in pharmacokinetics or overall intensity, though escitalopram reduced negative subjective effects. These results provide important insights about interactions between SSRIs and psilocybin, however, 2 weeks of SSRI administration in healthy people may not mimic the neuroadaptations produced by chronic treatment in the setting of a neuropsychiatric disorder (Bahri et al. 2014; de Montigny et al. 1990). Taken together, these studies indicate that we have far more to learn about how SSRI treatment impacts the subjective experience of psilocybin.

Social media platforms are increasingly used to investigate a broad array of health-related behaviors (Chary et al. 2017; Rhidenour et al. 2022; Safarishahrbijari and Osgood 2018) and can help to address this knowledge gap by offering a window into peoples' real-world experiences with psilocybin and SSRIs. Reddit, which has over 430 million monthly users (Dean 2021) facilitates anonymous online discussion in topic-specific forums (sub-reddits), making it particularly well-suited for research on sensitive topics such as illicit substance use (Graves et al. 2022). Indeed, Reddit has previously been leveraged to investigate potential interactions between serotonergic psychedelics and anticonvulsants (Nayak et al. 2021). Building on this work, we systematically collected and analyzed written entries (posts) by Reddit community members (redditors) discussing their experiences using SSRIs and psilocybin mushrooms concurrently. We focused on psilocybin given that it is the most-studied serotonergic psychedelic in clinical research and commonly used in the community (Yockey and King 2021). Our goal was to characterize the content of these posts both quantitatively and qualitatively.

Methods

Data collection and determination of eligible posts

Between January 18, 2021 and April 28, 2021, we systematically searched Reddit using its embedded search feature and a combination of two keywords: a psilocybin term and an SSRI medication name (3 psilocybin keywords: "mushrooms", "shrooms", and "psilocybin" paired with 18 SSRI keywords: "sertraline" ("Zoloft"), "escitalopram" ("Lexapro"), "fluoxetine" ("Prozac"), "citalopram" ("Celexa"), "paroxetine" ("Paxil"), "vortioxetine" ("Trintellix"),[1] "fluvoxamine" ("Luvox"), "vilazodone" ("Viibryd"), and "SSRI" for a total of 54 searches). See Fig. 1 for posts and comments (we refer to all such content as "posts") describing an experience of someone who had taken psilocybin mushrooms while simultaneously taking an SSRI. We included all search results from 2005 (the year Reddit was founded) to January 18, 2021, excluding the contents of private or locked subreddits. We reviewed the first 60 most relevant results as determined by Reddit's search algorithm in their entirety for each search (though note that the terms "vortioxetine", "Trintellix", "fluvoxamine", "Luvox", "vilazodone", and "Viibryd" produced less than 60 search results). This limit was chosen to maximize feasibility and prevent bias towards medications that are more commonly prescribed. To maintain anonymity and due to the impracticality of contacting redditors, we did not obtain informed consent from individuals. We received approval to conduct this study from the University of California San Francisco Institutional Review Board.

We included posts that involved: (1) a first- or second-person experience of taking psilocybin mushrooms, and (2)

[1] Vortioxetine has multimodal actions and is not technically considered an SSRI (Alvarez et al. 2014). We included it because of its similar SERT-inhibiting activity and affinity for multiple serotonin receptor subtypes.

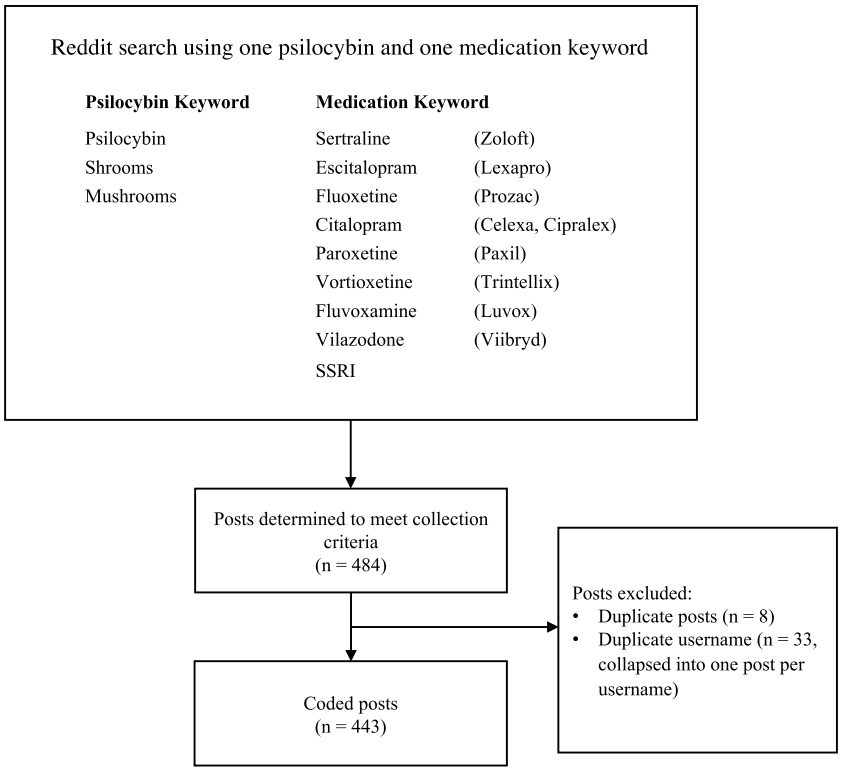

Fig. 1 CONSORT flow diagram

explicit or implied use of an SSRI concurrently, and (3) any description of their experience. Second-person experiences had to come from an identified person (e.g., "my girlfriend" or "my friend"); we excluded non-specific cases (e.g., "I heard" or "they say"). We excluded posts referring only to microdosing experiences (i.e., ingesting small enough quantities of psilocybin that there are no discernable subjective effects) as microdosing was not the focus of this project. We also coded the presence of any non-SSRI medications that were mentioned.

Qualitative data analysis

We applied qualitative content analysis, which generates a descriptive account of patterns across data (Vaismoradi et al. 2016), on the text of all eligible Reddit posts. First, we selected two domains of interest a priori: (1) physical and psychological negative effects and (2) intensity of the acute experience associated with consumption of psilocybin mushrooms in the setting of SSRI use. Next, authors JZ, GA, and KS conducted a preliminary review of a random selection of eligible posts to identify potential coding frameworks. These authors created the final coding framework for both domains through discussion in line with a directed content analysis approach (Hsieh and Shannon 2005). Then, we used deductive coding to apply these predefined codes to eligible posts.

Briefly, we subdivided each domain into mutually exclusive categories, dividing Domain 1 (negative effects) into psychological (e.g., anxiety, depression, paranoia), physical (e.g., nausea, vomiting, headache), or not mentioned. We divided Domain 2 (intensity of experience) into decreased, increased, no change, or not mentioned. We also coded mention of any non-SSRI medications. Due to the nature of Reddit posts, demographic information, psychiatric diagnoses, and other information pertaining to dose of medication or psilocybin was limited and inconsistent. We did not include these variables in our coding framework. See Table S1 for a complete description of the coding framework.

Three authors (VM, AF, and MF) initially coded a random selection of 45 eligible posts to determine interrater reliability (IRR) of the coding framework. We computed Fleiss' kappa (Fleiss 1971) for each coder pair, then averaged to obtain a single index of IRR. We found substantial agreement ($\kappa = 0.79$). All remaining posts were then divided evenly between the three authors VM, AF, and MF (n ~ 133 each). Authors (VM, AF, MF, JZ, GA, and KS) met frequently to resolve discrepancies in coding through discussion. After finalizing codes, we summarized the frequency of various experiences and used illustrative, verbatim quotes (edited for anonymity, clarity, and grammar) to characterize participants' experiences.

Table 1 Reported negative effects (Domain 1)

	n	Psychological	Physical	Not mentioned
Escitalopram	114	7 (6%)	3 (3%)	104 (91%)
Sertraline	112	5 (4%)	4 (4%)	103 (92%)
Fluoxetine	57	2 (4%)	2 (4%)	53 (93%)
Citalopram	43	1 (2%)	4 (9%)	38 (88%)
Paroxetine	27	1 (4%)	1 (4%)	25 (93%)
Vortioxetine	6	0	0	6 (100%)
Fluvoxamine	6	0	0	6 (100%)
Vilazodone	3	2 (67%)	0	1 (33%)
Multiple SSRIs	3	0	0	3 (100%)
SSRI not specified	72	4 (6%)	1 (1%)	67 (93%)
Total	443	22 (5%)	15 (3%)	406 (92%)

Results

Sample

We collected 484 posts from Reddit. We filtered these for duplicates, removing 8 identical posts under the same usernames. 26 usernames were each associated with 2 posts and 3 other usernames were each associated with 3 or more posts. We combined contents from posts from the same username into a single post per username rather than choosing a single post and discarding the others. Note that usernames marked as "[deleted]" (indicating a deleted Reddit profile) could not be filtered; we retained these as individual posts. This left 443 eligible posts for coding. Three posts mentioned someone taking more than one SSRI simultaneously, these posts were included in their own SSRI category. 37 posts reported also taking non-SSRI medications concurrently (see Table S2). Specific SSRIs were not evenly represented– either escitalopram or sertraline was mentioned in over 50% of posts.

Domain 1: Negative effects

Negative effects were reported in 37 (8%) of posts (see Table 1). Psychological negative effects were most common, reported in 22 (5%) of posts. Physical effects were reported in 15 (3%) posts. The majority of the posts (n = 406, 92%) did not mention a negative effect.

The following are key excerpts from the 22 posts that mentioned psychological negative effects. The most concerning was a single post describing psychotic symptoms leading to a psychiatric hospitalization:

> "...I took some shrooms. I have taken LSD and mushrooms before with no side effects but this trip … lasted for longer than a week. I was so gone that I was institutionalized twice the second time not taking anything beforehand but I did get flashes of delusions and hallucinations that were definitely left over from that nightmarish trip. Long story short I am entirely convinced that this all happened because of my medication… It was a drug called [citalopram]..."

One post explicitly mentioned paranoia:

> "...I took a whole 8th [of an ounce of psilocybin mushrooms] one night about 2 years ago. I was on [escitalopram] …I can say it ruined it for good for me never went back…just extremely strong emotions that went from happy and fun to sad and extremely paranoid…"

One post described memory loss and confusion:

> "I'm on 50 mg of sertraline and 150 mg of wellbutrin xl. i took shrooms last night, about 1 g dry. It was my 3rd time taking shrooms but this time I experienced complete confusion. like i forgot who i was and who everyone was around me. I'm still feeling weird about it…"

Of the 15 posts that mentioned physical negative effects, 2 (< 1% of total posts) reports were suggestive of possible severe ST, reporting symptoms that included seizure and muscle rigidity:

> "I had a seizure on [paroxetine] and mushrooms."
> "...One of my friends was on [fluoxetine]...during the come up he was shaking a lot and couldn't even hold his hand still for a cigarette…Later after the come up he says that he didn't know if he was having a stroke or not, cause he said his arm went numb and clenched up to his chest and couldn't move it at all…"

Other negative physical effects that may represent mild ST (headache, nausea, and vomiting) were reported in the majority of these posts, with 9 (2% of total posts) reporting headache, 2 (< 1%) reporting nausea, and 2 (< 1%) reporting vomiting:

> "I've been taking citalopram for a while now and…I get headaches and nauseous to the point where I can't move if I mix my medication and shrooms. Always ends up with me puking and having a bad trip."
> "...I'm on [sertraline] as well (only 75 mg however). The first time I ever took shrooms I hadn't been on the medication yet, everything went good. The second time I took them I was on the [sertraline] too and I projectile vomited multiple times. Same dosage of shrooms each time…"

Table 2 Change in subjective experience (Domain 2)

	n	Decreased	No change	Increased	Not mentioned
Escitalopram	114	55 (48%)	50 (44%)	1 (1%)	8 (7%)
Sertraline	112	66 (59%)	37 (33%)	2 (2%)	7 (6%)
Fluoxetine	57	22 (39%)	30 (53%)	0	5 (9%)
Citalopram	43	23 (53%)	19 (44%)	0	1 (2%)
Paroxetine	27	18 (67%)	7 (26%)	1 (4%)	1 (4%)
Vortioxetine	6	2 (33%)	4 (67%)	0	0
Fluvoxamine	6	4 (67%)	2 (33%)	0	0
Vilazodone	3	1 (33%)	1 (33%)	1 (33%)	0
Multiple SSRIs	3	0	3 (100%)	0	0
SSRI not specified	72	47 (65%)	22 (31%)	0	3 (4%)
Total	443	238 (54%)	175 (39%)	5 (1%)	25 (6%)

Domain 2: Change in subjective experience

Reduced intensity of the experience when psilocybin was combined with an SSRI was the most common report, observed in 238 (54%) of posts, though 175 (39%) reported no change in intensity (see Table 2). Five reports (1%) described experiencing greater intensity.

The following are excerpts from the 238 (54%) posts that described reduced intensity of the psilocybin experience:

> "...I take 20 mg of [escitalopram] and took 7.5 grams of shrooms (a lot!) and nothing really happened. The shrooms were legit too as a friend took half that and was tripping all day"

42 of these posts (9.5% of total posts) reported no subjective effects:

> "I [am taking sertraline and] ate shrooms (3.5g) for the very first time yesterday... and felt absolutely nothing. A few people took some from the same batch and tripped, so I know they were magic mushrooms."

29 (6.5%) specifically described a complete lack or reduction in visual perceptual disturbances or hallucinations:

> "...On 10 mg of [escitalopram], constantly only experience about half of what my friends do on the same dose. On a recent 5 gram trip, I had no visuals or anything like that…"
> "I ate roughly an eighth [of an ounce] while on my sertraline and honestly I got very little from them. I mostly just felt the body load and very few visuals…"

In contrast, many redditors (175 posts, %) reported no change in the intensity of their psilocybin experience while also taking an SSRI:

> "...I've taken both shrooms…on 30 mg [citalopram] and didn't notice much of a difference with or without the SSRIs."
> "Honestly I'm on SSRIs and I don't feel a difference on my psychedelic trips. I guess I must depend on the molecule you're taking. I lemon teked 1.5g last weekend had a crazy trip with an amazing afterglow…I'm on 10mg of escitalopram"

Finally, 5 (1%) posts described an increased psychedelic experience while on SSRIs:

> "One week I took [sertraline] and Psilocybin together, but I feel a bit [too] much effect"

However, many people describe making adjustments to their SSRI use or using other methods to modulate the subjective effects of psilocybin mushrooms. 38 (8.6% of total posts) described reducing or stopping their SSRIs for a period of time prior to taking psilocybin mushrooms.

> "Dosage: 3 grams. Escitalopram 20mg/day, stopped two days before. ---> normal/positive trip."
> "I was on fluoxetine for a couple weeks took a 3 day break and had a trip of the same intensity as to when I was on it prior…."

4 (< 1% of total posts) also mentioned "lemon tekking" mushrooms, i.e., soaking them in lemon juice, in order to overcome reduced intensity in the setting of SSRI use with mixed results

> "I take [escitalopram, off right now, but it definitely] kills your trips. lemon tek was the only thing that worked"
> "[I] take an SSRI and… I have eaten up to 5g of dry cubes at once (10g over the course of an afternoon) and still only felt a mild effect (didn't have a full trip).... I've tried Lemon Tek and no difference…"

Table 3 Reported negative effects by change in subjective experience

Negative effects (Domain 1)	n	Change in subjective experience (Domain 2)			
		Decreased	No change	Increased	Not Mentioned
Psychological	22	11 (50%)	3 (14%)	3 (14%)	5 (23%)[a]
Physical	15	7 (47%)	5 (33%)[c]	0	3 (20%)[b]
Not Mentioned	406	220 (54%)	167 (41%)	2 (1%)	17 (4%)
Total	443	238 (54%)	175(39%)	5(1%)	25(6%)

[a]One psychosis/mania with hospitalization, [b]One seizure, [c]One possible case of severe serotonin toxicity

Cross referencing Domains 1 and 2 did not reveal an obvious relationship between reports of negative effects and reports of changes in psychedelic experience (see Table 3). Additionally, 37 posts mentioned concurrently taking non-SSRI medications in addition to the SSRIs (see Table S2).

Discussion

We identified and analyzed 443 Reddit posts discussing psilocybin mushroom ingestion in the setting of SSRI use. Negative effects, described in 8% of reports, spanned psychological and physical domains. Psychological effects ranged from mood dysfunction to cognitive and perceptual changes, with one case severe enough to result in psychiatric hospitalization. Physical effects included multiple symptoms that could reflect ST, including one report of a seizure. A majority (54%) of posts reported a decrease in the intensity of psilocybin effects with SSRI use, but a significant proportion (39%) reported no change. Only a handful of posts 5 (1%) described increased intensity. Taken together, these findings suggest potentially complex interactions between SSRIs and psilocybin.

Risk of ST

Several of the negative effects reported by Redditors are similar to those reported in published clinical trials of psilocybin therapy. Headache and nausea (reported by 2.3% of our sample) are some of the most frequently reported negative effects in psilocybin clinical trials (Ko et al. 2023; Santos et al. 2018) and may reflect some degree of serotonin toxicity (Boyer and Shannon 2005; Prakash et al. 2014). In the largest trial to date, which enrolled participants with treatment resistant depression and excluded SSRI use, rates were notably higher than what we observed (headache: 15% of those who received 10 mg and 24% of those who received 25 mg; nausea: 7% and 22%; (Goodwin et al. 2022). Our findings could suggest lack of increased risk of ST with concomittant SSRIs, consistent with the psilocybin trial that enrolled 19 people on SSRI therapy and did not report cases of ST (Goodwin et al. 2023). However, (Goodwin et al. 2023) did observe severe blood pressure changes among 2 participants, and we found 2 posts describing tremor, rigidity, or seizure. Complicating the interpretation of these data is the fact that a key feature of ST, altered mental status manifesting as agitation or delirium, is difficult to assess in the setting of psychedelic drug intoxication (Leonard et al. 2018). This may compound the challenge of diagnosing mild to moderate cases of ST, which can go undetected (Francescangeli et al. 2019). We must consider the possibility that use of an SSRI could have increased the risk of serious negative effects experienced by some Redditors, and that similar outcomes could emerge in future clinical trials that allow concomittant serotonergic medications.

However, it is also important to note that the majority of posts did not mention any effects concerning for ST, which could suggest that concomittant psilocybin and SSRI use does not increase the risk of toxicity. There are at least two reasons for this. First, both psilocybin and SSRIs inhibit reuptake rather than causing acute release of serotonin; their combined action may not increase extracellular serotonin to a level that overwhelms reuptake by SERT and metabolism by MAO (see Fig. 2). In vitro work in human HEK293 cells shows that psilocin increases extracellular serotonin levels comparably to citalopram, but only half as much as MDMA (Rickli et al. 2016). Similarly, in rats, psilocin-induced increases in serotonin levels in the frontal cortex are comparable to increases observed following ketamine, which is not associated with ST (Wojtas et al. 2022). Further, though SSRIs typically block ~ 80% of SERT activity at therapeutic doses, preclinical data suggest that psilocin appears to exhibit low-moderate binding affinity at SERT (Malcolm and Thomas 2021)–the combined effect of psilocin and an SSRI may not lead to significant further activity reduction. Second, psilocin's functional selectivity and partial agonism at the 5-HT_{2A}R, coupled with its competition with serotonin at the 5-HT_{2A}R, may prevent excessive signaling even in the setting of elevated extracellular serotonin levels (see Fig. 2b, c). While serotonin binds ~ 4 times as potently as psilocin at the 5-HT_{2A}R, standard doses of psilocin exhibit receptor occupancies in humans of up to ~ 72%, confirming competition and a substantial displacement of serotonin (Kozell et al. 2023; Madsen et al. 2019). The 5-HT_{2A}R and other G protein coupled receptors (GPCRs) activate numerous signal transduction pathways, and the relative activation of these pathways is ligand and system-dependent (i.e., they demonstrate functional selectivity). For example, serotonin binding to the 5-HT_{2A}R activates the IP3-Ca^{2+} releasing pathway and the phospholipase A

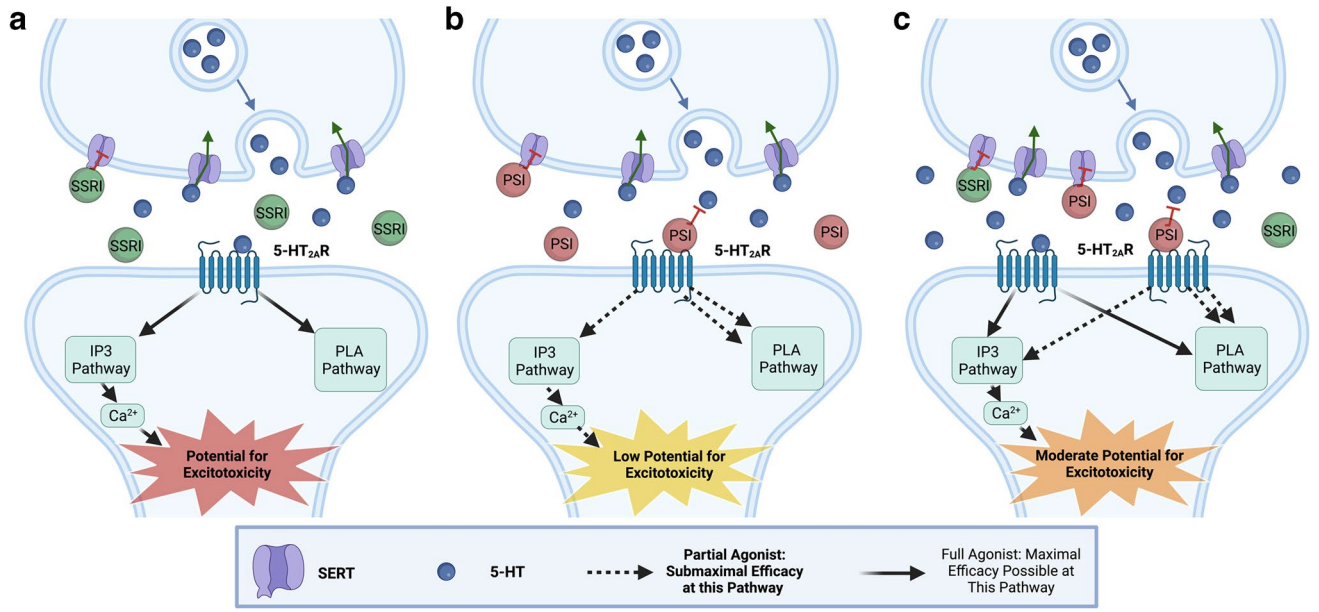

Fig. 2 Simplified synapse with SSRI, psilocin (PSI), or psilocin + SSRI and two signal transduction pathways activated by 5-HT_{2A}R to illustrate biased activation by psilocin, but not serotonin. The 5-HT_{2A}R activates many other signal transduction pathways, but only inositol trisphosphate (IP3) and phospholipase A (PLA) are illustrated here for simplicity. Other 5-HTRs also contribute (not shown). **a**. SSRIs bind to the serotonin transporter (SERT), block reuptake, and acutely increase 5-HT in the synaptic cleft, leading to increased 5-HT_{2A}R activation. 5-HT is a full unbiased agonist: activates signal transduction pathways fully and equally. IP3 increases intracellular Ca^{2+} levels, contributing to serotonin toxicity. **b**. Psilocin inhibits SERT, increasing extracellular 5-HT levels similarly to an SSRI. Psilocin competes with 5-HT at 5-HT_{2A}R, reducing the frequency of serotonin binding. Psilocin is a biased agonist for 5-HT_{2A}R, preferentially activating PLA and other signal transduction pathways vs IP3-Ca^{2+}, reducing the risk of serotonin toxicity. **c**. SSRIs + Psilocin bind to SERT, likely increasing 5-HT levels more than either drug alone, which is illustrated in the figure by more 5-HT in the synaptic cleft. Increased 5-HT_{2A}R binding by 5-HT leads to increased IP3-Ca^{2+}, but psilocin competes with 5-HT at 5-HT_{2A}R, reducing maximal Ca^{2+} release and reducing the risk of serotonin toxicity. Publication and licensing rights obtained from BioRender

(PLA) pathway to produce arachidonic acid with similar potency. Psilocin, however, activates the PLA pathway much more potently than the IP3-Ca^{2+} releasing pathway (Gumpper et al. 2022; Kolb et al. 2022; Nichols 2016; Zhou and Bohn 2014). Thus, relative to serotonin, psilocin likely leads to lower intracellular Ca^{2+} levels and, consequently, a lower risk of toxicity (Mody and MacDonald 1995). In addition, psilocin is only a partial agonist at both of these pathways (Rickli et al. 2016) which may also limit Ca^{2+} release. These characteristics raise the possibility that while the combination of psilocin and an SSRI may increase extracellular serotonin levels more than either drug alone, competition at 5-HT_{2A}R could lead to less intracellular Ca^{2+} release as a result of reduced serotonin binding. If Ca^{2+} release is limited, the risk of hyperexcitability and subsequent ST may be mitigated. Lastly, it is important to note that while the hyperthermia and hypertonicity that occur in severe cases of ST has been predominantly linked to 5-HT_{2A} R agonism (Francescangeli et al. 2019; Haberzettl et al. 2014; Mazzola-Pomietto et al. 1995; Nisijima et al. 2001), direct and indirect activation of other serotonin receptors (e.g., 5-$HT_{2B,}$ 5-HT_{1A}, 5-HT_{7}) may also mediate toxicity (Diaz and Maroteaux 2011; Erkizia-Santamaría et al. 2022; Nikiforuk 2015). Clarifying the mechanisms by which DDI with psilocybin lead to ST requires further examination in prospective studies.

Risk of psychotic and manic symptoms

One post described the effects of psilocybin ingestion in the setting of SSRI treatment lasting over a week, with visual disturbances and delusional thinking that led to hospitalization. Persistently altered perceptual and cognitive effects like this have not been reported in published clinical trials. Multiple factors may have contributed to this Redditor's experience. First, their symptoms may have been entirely attributable to psilocybin. Psilocybin and other serotonergic psychedelics have psychotomimetic properties that are leveraged to model psychotic illness in preclinical research (González-Maeso and Sealfon 2009). Despite the lack of empirical data in humans, there has been long-standing concern that psychedelic use could precipitate psychosis (Friesen 2022). Persistent, spontaneous visual perceptual disturbances reminiscent of acute psychedelic intoxication in particular are suggestive of hallucinogen persisting perceptual disorder (HPPD; Hermle et al. 2012), a syndrome with

unknown prevalence. Its etiology is also unclear; hypothesized mechanisms include damage to γ-aminobutyric acid (GABA) -releasing inhibitory cortical interneurons and an imbalance between the inhibitory and excitatory input in low-level visual processing (Litjens et al. 2014). The details of this Redditor's experience cannot be determined, though their mention of delusions does raise the possibility of disturbances not limited to visual perception. Delusional thinking is more suggestive of a psychosis, or mania with psychotic features. Though SSRI use can be associated with the onset of manic symptoms (Tohen et al. 2009), the risk of serotonergic psychedelics–alone or in combination with SSRIs–precipitating mania is unknown (Gard et al. 2021; Morton et al. 2022). To our knowledge, only one published case report has described new-onset mania and psychosis that developed following ingestion of psilocybin mushrooms with concomittant use of a serotonergic antidepressant, venlafaxine (Barber et al. 2022). Other possible explanations for this Redditor's experience include those unrelated to the psilocybin-SSRI combination, including another underlying neuropsychiatric illness, use of other substances, acute infection, inflammatory dysregulation, or metabolic disturbance–all of which can lead to profoundly altered mental states including psychosis.

Modulation of the acute subjective psilocybin experience

Roughly half of the posts described a reduced acute subjective psychedelic experience with concomittant use of an SSRI. This is consistent with recent findings from the survey study of people who had used psilocybin mushrooms and antidepressants by (Gukasyan et al. 2023), and may be explained by at least three (non-mutually exclusive) mechanisms. First, SSRI-induced increases in serotonin levels may over time lead to downregulation of somatodendritic autoreceptors in the raphe nuclei, thereby elevating serotonin levels (Gardier et al. 1996). As proposed above, serotonin may then compete with psilocin at the 5-HT_{2A}R and reduce its binding. Second, chronically increased serotonin levels may lead to downregulation of 5-HT_{2A}R and 5-HT_{1A}R receptors themselves, also resulting in decreased frequency of psilocin binding (Beasley et al. 1992; Klimek et al. 1994; Massou et al. 1997; Meyer et al. 2001; Nelson et al. 1989). In line with this hypothesis, a positron emission tomography study in 19 people with depression demonstrated that treatment with paroxetine for over six weeks was associated with down-regulation of cortical 5-HT_{2A} receptors (Meyer et al. 2001). Third, molecular and biochemical alterations to the signal transduction pathways downstream of 5-HT_{2A}R and 5-HT_{1A}R in response to chronically elevated serotonin levels could also alter psilocin's effects (Bymaster et al. 2002; Kitaichi et al. 2010; Stahl 1998). Whether the reduced subjective experience described by redditors is related to the often-described phenomenon of SSRI-induced emotional blunting (Barnhart et al. 2004; Marazziti et al. 2019; Price et al. 2009) is also interesting to consider. One study found that ~ 26 days of escitalopram administration in healthy individuals was associated with reduced reward sensitivity during a reinforcement learning task, which could underlie this blunting effect (Langley et al. 2023). Further work is needed to characterize the modulations of serotonin signaling and behavior that may occur with SSRI use and how they may impact the psilocybin experience.

Multiple redditors described attempts to compensate for a reduced subjective experience by "lemon tekking" mushrooms, a process that involves soaking them in a citric acid solution. The low pH is thought to (1) extract psilocybin from the chitin and other non-psychoactive material in the mushroom, (2) facilitate dephosphorylation of psilocybin into the active compound, psilocin, and (3) prevent breakdown of psilocin due to oxidation (Casale 1985; Gold 1991). Lemon tekking may reduce the time required for gut absorption and enhance the concentration of psilocin consumed, potentially leading to higher peak plasma concentrations of psilocin than is possible with consumption of whole mushrooms. Redditors reported mixed experiences in terms of achieving a desired subjective experience. Whether SSRI-induced reductions in the subjective psychedelic experience can be overcome by administering higher effective dosages of psilocybin, and the safety of this approach, is an important question for future study.

A significant proportion of posts (39%) described no change in intensity in the setting of SSRI use, with 54% reporting blunting and 1% reporting intensification. These results are only partially consistent with the two-week escitalopram pretreatment study discussed above (Becker et al. 2022), highlighting multiple issues for consideration. First, duration of SSRI treatment may be a critical variable. Redditors in our sample likely vary in this regard, with some on treatment much longer than two weeks, and may consequently have differential alterations in serotonergic signaling (Artigas et al. 1996; Meyer et al. 2004; Stahl 1998). Related, participants in the study by Becker et al. (2022) were medically and psychiatrically healthy; it is likely that redditors describing SSRI treatment have been diagnosed with neuropsychiatric illnesses that may involve baseline alterations in the serotonin as well as other neurotransmitter systems. People with depression, for example, can demonstrate abnormal 5-HT_{2A} receptor availability (Bhagwagar et al. 2006; Shelton et al. 2009; Steinberg et al. 2019) that may normalize with remission of symptoms (Messa et al. 2003; Steinberg et al. 2019). Lastly, age is another potentially impactful moderator of the subjective psilocybin experience. Participants in the study by Becker et al. (2022) had an average age of 34 (± 10), whereas people ages 18–29 are

significantly more likely to use reddit than adults 50+ (Auxier and Anderson 2021). Older age has been associated with altered serotonin system function (Kakiuchi et al. 2001) including decreased 5-HT_{2A} receptor availability (Moses-Kolko et al. 2011; Radhakrishnan et al. 2018; Versijpt et al. 2003), decreased ability of SSRIs to alter 5-HT_{2A} receptor availability (Meyer et al. 2001), and decreased intensity of psychedelic effects (Aday et al. 2021). Together, these variables may underlie divergent findings, suggesting that the often-held belief that SSRIs attenuate acute psychedelic effects may be an oversimplification that requires further investigation.

A challenge of interpreting our findings is the fact that we do not yet understand the impact that modulating the acute psychedelic experience has on clinical outcomes. Evidence regarding the relationship between intensity and quality of the experience and subsequent benefit is mixed (Anderson et al. 2020; Griffiths et al. 2006, 2016; Olson 2020; Rotz et al. 2023). Recent preclinical work has raised the possibility that psilocybin's therapeutic effects may not depend on the acute subjective experience (Hibicke et al. 2020) or 5-HT_{2A} receptor mechanisms (Hesselgrave et al. 2021; Moliner et al. 2023; Shao et al. 2021). Enhanced synaptic plasticity (Ly et al. 2018; Shao et al. 2021), changes in functional neural connectivity (Preller et al. 2020), reopening of the social reward learning critical period (Nardou et al. 2023), and anti-inflammatory effects (Flanagan and Nichols 2018) have all been proposed as potential mechanisms of action. In one of the few clinical trials that has permitted concomittant SSRI therapy (Carhart-Harris et al. 2018), at least one participant (patient 2) taking an SSRI had a relatively reduced acute experience but a large antidepressant effect (Fig S1 in Carhart-Harris et al. (2018) and personal communication with Robin Carhart-Harris). Studies investigating the role of the psychedelic experience in therapeutic effects are underway (see NCT04842045, for example).

Limitations of this study

There are several limitations that are important to highlight. First, lack of standardization, verification, and selection biases are challenges to social media research in general. Redditors may be more likely to post about notable experiences, which could lead to overrepresentation of posts regarding negative effects or altered intensity, relative to no changes. On the other hand, experiences resulting in severe illness or mortality may prevent users from sharing posts online, leading to underrepresentation of debilitating or life-threatening negative effects. Second, we lack consistent information about influential pharmacologic factors including the dosages and potencies of the psilocybin mushrooms as well as the SSRI dosages and duration of therapy. Third, we cannot account for the extra-pharmacologic factors that are relevant for understanding responses to a psychedelic, including personality traits (Studerus et al. 2012), expectancy (Aday et al. 2022), and interpersonal support during the acute experience (Breeksema et al. 2020). Fourth, the use of other substances cannot be ruled out and may impact psilocybin effects (Bogenschutz et al. 2022). Fifth, to increase homogeneity, we did not search for medication names used outside the United States, and only focused on SSRIs–additional serotonergic and other medications likely interact with psilocybin in clinically relevant ways. Although we did code mentions of non-SSRI medications also used concomitantly with the SSRI and psilocybin mushrooms, the small number of these mentions and the range of medications mentioned do not allow for assessment of potential interactions with additional classes. Sixth, it is possible that there are meaningful differences between the synthetic psilocybin used in research settings and the psilocybin mushrooms accessible in the community–few data are available regarding other psychoactive compounds found in mushrooms (Dinis-Oliveira 2017). Lastly, we must keep in mind that posts typically described single instances of psilocybin mushroom ingestion, but we do not know whether Redditors used repeatedly/frequently and how this may have influenced their experiences. Psilocybin administration leads to rapid tachyphylaxis with repeated dosing over hours to days, likely due to downregulation of the 5-HT_{2A} receptor (de la Fuente Revenga et al. 2022). Although nearly all clinical trials thus far have investigated the effects of a single dose of psilocybin, protocols involving multiple administrations will likely be explored in the future (Leger and Unterwald 2022). Additional work will be needed to understand the potentially different interactions between SSRI treatment and repeated psilocybin administration.

Conclusions

Although psilocybin is considered to have a strong tolerability profile based on preclinical (Rickli et al. 2016) and clinical trial data (Ko et al. 2023; Santos et al. 2018), our findings based on reports from the community suggest that additional work is needed to understand its potentially complex interactions with SSRIs. Currently, there are over 100 registered active or planned trials of psilocybin therapy (see Table S3); it is unclear how concomittant SSRI therapy will be managed in most of these. Of registered studies, 4 explicitly state that SSRIs are allowed or required, 35 do not mention SSRI medications, and 84 either exclude SSRIs specifically or exclude all psychotropic medications. Systematic evaluation of adverse events, including signs and symptoms of ST, as well as thorough documentation of subjective characteristics of the psilocybin experience will be critical to improve our understanding of these interactions

and minimize risks to patients as psychedelic treatments are developed.

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Declarations

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