Effects of Psilocybin and Select Pharmaceutical Interactions

Jordan McDowell, Jada K. Middleton, Alanna C. Bluett, Alisa Kozachenko, Bayan Attar, Yuvraj Saini, Jennifer Burke, Cayden E. McPhee, Mutahera Mutahera, Talya Ahmed, Nabila Ibrahim, Gilbert Atukwatsibwe, Sulabha Adhikari, Mohammad Esmaili, Jean-Vital Yambayamba

Abstract

In Canada, the use of both prescription medications and psychedelics has become increasingly prevalent. As of 2022, approximately 16.5% of Canadians—about 6.3 million individuals—were prescribed at least one antidepressant, with fluoxetine remaining one of the most commonly used options (IQVIA, 2023). Benzodiazepine use, including drugs like alprazolam, ranges between 5% to 10% nationwide, with notably higher usage (15–20%) among older adults aged 65 and over (Davies et al., 2017). Psilocybin use, while less common, has shown steady presence in the population; in 2019, years hallucinogens such as psilocybin, LSD, and PCP were used by approximately 2% of Canadians—equating to roughly 587,000 people— and by approximately 6% of young adults aged 20 to 24 (Health Canada, 2023). Based on the statistical overlap between antidepressant and psychedelic users, it is estimated that over 126,000 Canadians may be experiencing interactions between these drug classes, a number that is expected to grow as both psychedelic therapy and recreational use become more culturally accepted. We investigated the chemical, physical, and psychological effects of psilocybin, fluoxetine, and alprazolam and their interactions with each other. In clinical contexts, benzodiazepines like midazolam are sometimes used to manage overwhelming psychedelic experiences, offering a pharmacological baseline for understanding how sedatives may interact with psilocybin. When taken concurrently, fluoxetine appears to attenuate the mind-altering effects typically induced by psilocybin, likely due to its modulation of serotonin receptor activity. This dampening effect suggests a pharmacological counteraction between the two substances. There is little direct research on the interaction between psilocybin and alprazolam, but from what is indicated, they may exhibit small interactive effects. Understanding these interactions may provide insight into more accurate harm-reduction strategies and clinical decision-making.

Introduction

This study investigates the interaction between psilocybin and common pharmaceuticals, specifically fluoxetine and alprazolam. The intersection of neuroscience, pharmacology, and psychopharmacology provides a critical framework for evaluating these interactions, particularly in the context of increasing public interest and therapeutic application. By analyzing how these substances interact on a biochemical level, this research aims to explore their combined effects on cognition, emotion, and therapeutic safety. Specifically focuses on psilocybin interacting with fluoxetine or alprazolam at a biochemical level and their potential impact on medical and psychological treatments. This has significant implications in neuropharmacology, therapeutic applications, and drug safety. To contextualize these interactions, the following literature review summarizes prior research on psilocybin's effects and its interactions with common

Vol. 10(1) | DOI: https://doi.org/10.31542/bcek6t76
MacEwan University Student eJournal | © 2026 under CC BY-NC | ISSN 2369-5617

pharmaceuticals. A set of primary research articles provided the foundational biochemical and pharmacological context for evaluating the specific substances in question, including their mechanisms of action, chemical structures, and interaction profiles. These sources were critical in shaping the study's approach to psilocybin's interactions with fluoxetine and alprazolam.

The study conducted by Gukasyan et al. (2023) aimed to address the extent to which antidepressants influence the effects of psilocybin during both concurrent and postdiscontinuation use. Their findings indicated that selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIS) diminish psilocybin's drug effects, whereas non-serotonergic antidepressants do not. This dampening of effects may persist for up to three months following antidepressant discontinuation. These results are directly relevant to the present research, as they provide empirical insight into the interaction between psilocybin and serotonergic antidepressants, including the classification of medications involved and the duration of altered responses. While Gukasyan et al. (2023) provide evidence on specific antidepressant interactions, broader methodological issues in psychedelic studies have also been noted.

Literature Review

A 2024 systematic review by Soliman et al. (2024) highlighted the methodological inconsistencies across psychedelic-assisted therapy trials, emphasizing the lack of control for pharmaceutical variables, particularly antidepressants. This supports the need for targeted studies that focus on specific drug combinations. Additionally, Barbut Siva et al. (2024) conducted a survey examining the effects of serotonergic antidepressants like fluoxetine on the subjective intensity of psychedelic experiences. They found that SSRIs and SNRIs appear to weaken or "blunt" psilocybin's characteristic effects, including altered perception, emotional intensity, and visual hallucinations, by dampening serotonin receptor activity. Beyond antidepressants, benzodiazepines may also interact with psilocybin, as explored by Nicholas et al. (2024), who explored the co-administration of midazolam, a benzodiazepine closely related to alprazolam, with psilocybin. While participants still reported intense psychedelic experiences, their memory of the session was significantly impaired. These findings collectively reinforce the rationale for studying psilocybin's interaction with common pharmaceutical agents and their effect on therapeutic outcomes.

As the use of psychedelics and other hallucinogenic substances (such as LSD, psilocybin, and MDMA) becomes more prevalent, both therapeutically and recreationally, it is essential to understand the interactions and effects between psychedelics and other common pharmaceuticals that are prescribed. Understanding the effects of these drug interactions informs harm-reduction strategies by identifying when adverse effects or reduced efficacy may occur, especially in populations concurrently using prescription medications like antidepressants (e.g., fluoxetine) or benzodiazepines (e.g., alprazolam) (George & Tripp, 2023). It broadens the knowledge base about drug-pharmaceutical interactions and how these effects are physically and psychologically present in people. To better understand these interactions, we next examine the pharmacological and physiological profiles of psilocybin, fluoxetine, and alprazolam.

Substance Profiles

Psilocybin

Psilocybin is a substance found in the Psilocybe genus of mushrooms that is known to induce psychedelic effects—such as visual hallucinations, altered perception of time, and ego dissolution—primarily mediated by serotonin 2A receptor agonism. These differ significantly from substances like OxyContin, which is an opioid and primarily causes sedation and pain relief rather than perceptual changes in users when consumed. Psilocybe cubensis is the most widespread species across multiple continents (Lowe et al., 2021). Psilocybin is administered orally and undergoes rapid dephosphorylation in the gastrointestinal tract and liver, converting into psilocin, the primary active compound responsible for its psychoactive effects. Psilocin reaches peak plasma concentrations roughly two hours post-ingestion and has a half-life of approximately 163 minutes (Brown et al., 2017). Thomann and researchers observed that psilocin is predominantly metabolized via glucuronidation into psilocin-O-glucuronide, which is then excreted in urine (Thomann et al., 2024). Although various metabolic enzymes are involved—including MAO, ALDH, and ADH—psilocybin metabolism primarily occurs through dephosphorylation and hepatic glucuronidation, involving glucuronosyl transferase enzymes, which facilitate excretion. Notably, only trace amounts of unmetabolized psilocybin are excreted, suggesting significant metabolic transformation. However, the specific routes of elimination and involvement of alternative pathways, such as N-oxide formation, remain areas of ongoing study. The active ingredient psilocin interacts antagonistically with the type 2A receptors in the brain (Lowe et al., 2021). Once in the brain, psilocin can exhibit antidepressant effects; additionally, psilocybin treatment has been shown to increase reactivity to positive stimuli in the amygdala (Lowe et al., 2021).

Fluoxetine

Fluoxetine is a Selective Serotonin Reuptake Inhibitor (SSRI), which is commonly prescribed for major depressive disorder (MDD), obsessive-compulsive disorder, bulimia nervosa, and panic disorders. It increases serotonin levels in the brain, enhancing mood and emotional stability (Altamura et al., 1994). It is absorbed primarily through oral intake with a bioavailability of approximately 72% (Altamura et al., 1994). The cytochrome P450 enzyme system primarily metabolizes it in the liver, specifically CYP2D6 (Altamura et al., 1994).

Norfluoxetine, an active metabolite (Altamura et al., 1994), is produced through metabolization. Fluoxetine has an elimination half-life of approximately 1 to 4 days, while its active metabolite, norfluoxetine, remains in the system much longer, with a half-life ranging from 7 to 15 days (Altamura et al., 1994). This extended half-life contributes to fluoxetine's delayed therapeutic onset but also its lasting pharmacological impact and increased risk for prolonged drug-drug interactions, even weeks after cessation. Both fluoxetine and norfluoxetine are potent inhibitors of CYP2D6, which can lead to drug-drug interactions by affecting the metabolism of other medications processed by this enzyme (Deodhar et al., 2021). Fluoxetine undergoes metabolism primarily through the cytochrome P450 (CYP) enzyme system—particularly CYP2D6—distinct from the enzymatic pathways previously discussed (Deodhar et al., 2021). Its chemical action includes increasing serotonin levels in the synaptic cleft by inhibiting reuptake

into the presynaptic neuron (Bergstrom et al., 1988). Psychologically, it is associated with reduced anxiety and improved mood, although users may initially experience heightened anxiety or insomnia. Physical side effects commonly include sexual dysfunction and gastrointestinal issues (Bergstrom et al., 1988).

Alprazolam

Alprazolam is a benzodiazepine used primarily to manage anxiety disorders, panic disorders, and occasionally insomnia (Verster & Volkerts, 2004). It is an inhibitory neurotransmitter that enhances the effect of GABA–gamma-aminobutyric acid, creating anxiolytic, sedative, and relaxing effects (Verster & Volkerts, 2004). Alprazolam is primarily metabolized in the liver by the cytochrome P450 enzyme system, especially CYP3A4 (Greenblatt et al., 1993). Notably, CYP3A4 is involved in the metabolism of a wide range of substances, making it a highly promiscuous enzyme. When one drug, such as alprazolam, heavily utilizes this pathway, it can reduce the metabolic efficiency for other substances processed by the same enzyme, potentially leading to altered plasma levels, prolonged effects, or unexpected side effects. This is particularly relevant in polypharmacy or recreational co-use contexts. The chemical effects enhance GABA transmission by binding to the benzodiazepine site on the receptor, which then increases chloride ion influx(Verster & Volkerts, 2004). This causes the neurons in the brain to hyperpolarize, slowing down brain functions/neural activity (Verster & Volkerts, 2004). Psychological effects primarily include reduced anxiety (Verster & Volkerts, 2004). As for the physical effects, it can be used for sedation, muscle relaxation, and anticonvulsant effects; however, alprazolam can have physical side effects, including drowsiness, dizziness, and coordination impairment (Verster & Volkerts, 2004). It's important to note that due to the nature of benzodiazepines, alprazolam has the potential to create dependency and exhibit withdrawal symptoms once the medication is stopped (Verster & Volkerts, 2004). Having established each substance's pharmacology, we now explore how these drugs interact when used concurrently.

Interactions

Psilocybin and Fluoxetine

The interaction between psilocybin and fluoxetine has been the subject of growing interest due to the widespread prescription of SSRIs. Research by Barbut Siva et al. (2024) demonstrated that individuals who had been using SSRIs for multiple weeks reported a reduced intensity of psychedelic effects, supporting earlier studies by Strassman (1992) that found similar outcomes with LSD. This is believed to be due to downregulation or desensitization of 5-HT_2A receptors, which are the primary targets of Psilocin. However, other studies have shown that concurrent administration does not eliminate psilocybin's therapeutic benefits. Becker et al. (2022) found that while escitalopram pre-treatment reduced the physiological intensity and adverse effects of psilocybin, the positive psychological effects remained. Goodwin and researchers further showed that in patients with treatment-resistant depression, psilocybin still produced therapeutic outcomes even while patients remained on SSRIs (Goodwin et al., 2023). These findings suggest that fluoxetine may diminish the subjective experience but does not entirely block the antidepressant potential of psilocybin.

Psilocybin and Alprazolam

While no clinical studies have directly examined the interaction between psilocybin and alprazolam, findings from a similar benzodiazepine, midazolam, provide useful insight. Nicholas et al. (2024) reported that midazolam's co-administration with psilocybin was shown to impair memory recall while preserving the subjective psychedelic experience. This supports the idea that benzodiazepines may not blunt the immediate psychological effects of psychedelics, but can interfere with essential therapeutic processes like integration and reflection. Because alprazolam shares a comparable pharmacological profile, it's reasonable to expect a similar dynamic. This insight is central to our analysis, as it emphasizes the need for careful evaluation of pharmacological combinations in psychedelic-assisted therapy. These observed and inferred interactions inform the broader implications of concurrent psilocybin and pharmaceutical use, which we discuss below.

Discussion

As certain substances and drugs become more widespread through recreational or medicinal use, it is essential to understand and recognize that they interact with common pharmaceuticals. It would be beneficial for future studies to focus on specific drug-to-drug interactions so that safe consumption practices can be further implemented. Some substance interactions have little to no research, like psilocybin and alprazolam; there was a lack of primary sources on this interaction, which gave minimal insight as to the psychological effects of this interaction.

Our findings indicate that fluoxetine, a commonly prescribed SSRI, appears to reduce the intensity of psilocybin's psychedelic effects by downregulating or desensitizing 5-HT_2A serotonin receptors, which are the primary targets of psilocybin. While this interaction may dampen the subjective experience, studies have shown that it does not necessarily negate psilocybin's therapeutic benefits, especially in treating depression (Goodwin et al., 2023). However, it may be inferred based on evidence from midazolam—a benzodiazepine with similar pharmacologic profile—that while the psychedelic experience remains subjectively intense, memory recall and post-session integration may be significantly impaired (Nicholas et al., 2024). This implies that while SSRIs dampen the experience, benzodiazepines may interfere with the long-term psychological processing of the session, highlighting different but significant considerations in co-administration.

These interactions may reduce therapeutic efficacy or introduce complications, particularly when benzodiazepines like alprazolam are involved, which have been shown to impair memory integration during psychedelic experiences (Nicholas et al., 2024). From a sociocultural perspective, the increasing normalization of both mental health treatment and psychedelic use highlights the urgent need for accessible, evidence-based education. Without this, individuals may unknowingly compromise their treatment outcomes or face risks such as serotonin syndrome or diminished post-session insight (Brown et al., 2017; Thomas, 2021). As psychedelics move closer to mainstream therapeutic settings, ongoing research will be critical in informing safe guidelines, clinical protocols, and public awareness initiatives. As substance intake increases in society, the psychological impacts of these pairings also increase. The lack

of current knowledge is something that researchers could fill in as the occurrence of these interactions becomes increasingly common.

References

Altamura, A. C., Moro, A. R., & Percudani, M. (1994). Clinical pharmacokinetics of fluoxetine. *Clinical Pharmacokinetics, 26*(3), 201–214. https://doi.org/10.2165/00003088-199426030-00004

Barbut Siva, J., Barba, T., Kettner, H., Kuc, J., Nutt, D. J., Carhart-Harris, R., & Erritzoe, D. (2024). Interactions between classic psychedelics and serotonergic antidepressants: Effects on the acute psychedelic subjective experience, well-being and depressive symptoms from a prospective survey study. *Journal of Psychopharmacology*, *38*(2), 145–155. https://doi.org/10.1177/02698811231224217

Becker, A. M., Holze, F., Grandinetti, T., Klaiber, A., Toedtli, V. E., Kolaczynska, K. E., Duthaler, U., Varghese, N., Eckert, A., Grunblatt, E., & Liechti, M. E. (2022). Acute effects of psilocybin after escitalopram or placebo pretreatment in a randomized, doubleblind, placebo-controlled, crossover study in healthy subjects. *Clinical Pharmacology & Therapeutics, 111*(4), 886–895. https://doi.org/10.1002/cpt.2487

Bergstrom, R. F., Lemberger, L., Farid, N. A., & Wolen, R. L. (1988). Clinical pharmacology and pharmacokinetics of fluoxetine: A review. *British Journal of Psychiatry*, *153*(S3), 47–50. https://doi.org/10.1192/S0007125000297286

Brown, R. T., Nicholas, C. R., Cozzi, N. V., Gassman, M. C., Cooper, K. M., Muller, D., Thomas, C. D., Hetzel, S. J., Henriquez, K. M., Ribaudo, A. S., & Hutson, P. R. (2017). Pharmacokinetics of escalating doses of oral psilocybin in healthy adults. *Clinical Pharmacokinetics*, *56*(12), 1543–1554. https://doi.org/10.1007/s40262-017-0540-6

Davies, S. J. C., Jacob, B., Rudoler, D., Zaheer, J., De Oliveira, C., & Kurdyak, P. (2017). Benzodiazepine prescription in Ontario residents aged 65 and over: A population-based study from 1998 to 2013. *Therapeutic Advances in Psychopharmacology*, *8*(3), 99–114. https://doi.org/10.1177/2045125317743651

Deodhar, M., Rihani, S. B. A., Darakjian, L., Turgeon, J., & Michaud, V. (2021). Assessing the mechanism of fluoxetine-mediated CYP2D6 inhibition. *Pharmaceutics*, *13*(2), 148. https://doi.org/10.3390/pharmaceutics13020148

George, T. T., & Tripp, J. (2023). Alprazolam. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK538165/

Goodwin, G. M., Croal, M., Feifel, D., Kelly, J. R., Marwood, L., Mistry, S., O'Keane, V., Peck, S. K., Simmons, H., Sisa, C., Stansfield, S. C., Tsai, J., Williams, S., & Malievskaia, E. (2023). Psilocybin for treatment resistant depression in patients taking a concomitant SSRI medication. *Neuropsychopharmacology*, *48*(10), 1492–1499. https://doi.org/10.1038/s41386-023-01648-7

Greenblatt, D. J., & Wright, C. E. (1993). Clinical pharmacokinetics of alprazolam: Therapeutic implications. *Clinical Pharmacokinetics*, *24*(6), 453–471. https://doi.org/10.2165/00003088-199324060-00003

Gukasyan, N., Griffiths, R. R., Yaden, D. B., Antoine, D. G., & Nayak, S. M. (2023). Attenuation of psilocybin mushroom effects during and after SSRI/SNRI antidepressant use. *Journal of Psychopharmacology*, *37*(7), 707–716. https://doi.org/10.1177/02698811231179910

Health Canada. (2023). *Canadian Alcohol and Drugs Survey (CADS): Summary of results for 2019*.https://www.canada.ca/en/health-canada/services/canadian-alcohol-drugs-survey/2019-summary.html

IQVIA. (2023). *Prevalence and treatment of mental health disorders in Canada (2019–2022).* https://www.iqvia.com/-/media/iqvia/pdfs/canada/fact-sheets/iqvia_2023_snapshot_antidepressants_2019-2022.pdf

Lowe, H., Toyang, N., Steele, B., Valentine, H., Grant, J., Ali, A., Ngwa, W., & Gordon, L. (2021). The therapeutic potential of psilocybin. *Molecules*, *26*(10), Article 2948. https://doi.org/10.3390/molecules26102948

Nicholas, C. R., Banks, M. I., Lennertz, R. C., Wenthur, C. J., Krause, B. M., Riedner, B. A., Smith, R. F., Hutson, P. R., Sauder, C. J., Dunne, J. D., Roseman, L., & Raison, C. L. (2024). Co-administration of midazolam and psilocybin: Differential effects on subjective quality versus memory of the psychedelic experience. *Translational Psychiatry*, *14*(1), Article 372. https://doi.org/10.1038/s41398-024-03059-8

Soliman, P. S., Curley, D. E., Capone, C., Eaton, E., & Haass-Koffler, C. L. (2024). In the new era of psychedelic assisted therapy: A systematic review of study methodology in randomized controlled trials. *Psychopharmacology*, *241*(6), 1101–1110. https://doi.org/10.1007/s00213-024-06598-6

Strassman, R. J. (1992). Human hallucinogen interactions with drugs affecting serotonergic neurotransmission. *Neuropsychopharmacology*, *7*(3), 241–243. https://pubmed.ncbi.nlm.nih.gov/1388647/

Thomann, J., Kolaczynska, K. E., Stoeckmann, O. V., Rudin, D., Vizeli, P., Hoener, M. C., Pryce, C. R., Vollenweider, F. X., Liechti, M. E., & Duthaler, U. (2024). In vitro and in vivo metabolism of psilocybin's active metabolite psilocin. *Frontiers in Pharmacology*, *15*, Article 1391689. https://doi.org/10.3389/fphar.2024.1391689

Thomas, K. (2021, October 20). Assessing risk for serotonin syndrome when treating patients on antidepressants with psychedelic medicine. *Pharmacy Times*. https://www.pharmacytimes.com/view/assessing-risk-for-serotonin-syndrome-when-treating-patients-on-antidepressants-with-psychedelic-medicine

Verster, J. C., & Volkerts, E. R. (2004). Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: A review of the literature. *CNS Drug Reviews*, *10*(1), 45–76. https://doi.org/10.1111/j.1527-3458.2004.tb00003.x