



## The many faces of psilocybin-related psychosis: A case series

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### ABSTRACT

**Background:** Psilocybin use has been increasingly popular in the United States, and its use as a novel therapeutic treatment for psychiatric conditions has led to greater public acceptance as a recreational substance. Consequently, clinicians are faced with managing complications and adverse effects associated with psilocybin use.

**Basic Procedures/Main Findings:** We present three cases seen in a dual diagnosis inpatient psychiatry unit during a four-week period in 2023: Case 1: the case of intermittent psilocybin use associated with a particularly prolonged psychosis requiring treatment with higher doses and a longer course of neuroleptic medication; Case 2: the case of a short period of frequent psilocybin use culminating into increasing paranoia and a medically serious suicide attempt treated with neuroleptics; and Case 3: the case of long-term “microdosing” followed by mania-like symptoms including grandiosity, irritability, and physical aggression towards others, but with resolution of symptoms after discontinuing psilocybin use.

**Conclusions:** Amidst psilocybin’s increasing prevalence and acceptance, clinicians are faced with managing the complications and adverse effects of psilocybin use with minimal guidelines or evidence. This case series aims to highlight varied presentations, management strategies, and treatment responses to contribute some insight into this unknown territory.

### Introduction

Psilocybin, the active compound in hallucinogenic mushrooms, has been increasing in popularity as a novel therapeutic treatment and as a recreational substance. While Colorado and Oregon are the only states where the therapeutic use of psilocybin is legal at the time of this writing, in recent years, psilocybin use has been decriminalized in at least fifteen U.S. cities including Denver, Colorado; Oakland, California; and Washington, D.C. with many other jurisdictions considering legality (Barber et al., 2022). The reported therapeutic uses of psilocybin are incredibly broad and include treatment-resistant depression, OCD, some substance use disorders, and cluster headaches (Tyls et al., Mar. 2014). Recreational use is also common. A cohort representative of the U.S. adult population in 2010 found that 17 % of participants had lifetime recreational psychedelic use including LSD, psilocybin, mescaline, and peyote (Krebs and Johansen, 2013). An estimated 21 million U.S. residents reported lifetime use of psilocybin specifically (Krebs and Johansen, 2013). According to the 2021 U.S. Youth Risk Behavior

Survey, 6.5 % of high school aged youth reported ever using hallucinogenic drugs such as LSD, PCP, mescaline, or psilocybin (“United States, High School Youth Risk Behavior Survey, 2021 2024”). Individuals in younger age groups, those with previous psychedelic experiences, and those without moral or religious objections towards psychedelic use are more likely to view psilocybin favorably, possibly suggesting these populations are more vulnerable to psilocybin use leading to adverse outcomes (Corrigan et al., 2022). Reported adverse outcomes of psilocybin include non-serious effects such as headache or anxiety, and serious effects such as suicidal ideation and behavior, or non-suicidal self-injury (Hinkle et al., Sep. 2024).

A group of scientists from Switzerland found that the mechanism of psilocybin-induced psychosis is largely anchored in serotonin-2A receptor activation, independently of dopamine stimulation (Vollenweider et al., Dec. 1998). On a survey of individuals with experience using five substances (cannabis, psilocybin, amphetamine, ketamine, and alcohol), out of these substances, psilocybin was the best drug model of positive psychotic symptoms such as delusions, hallucinations,

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and disorganization (Carhart-Harris et al., 2013). However, its effects were not particularly reliable with only 13 % of respondents reporting often or always experiencing these types of symptoms after psilocybin. These effects were not described as psychotic, were not sustained, and were managed without pharmacologic intervention. Based on this, the authors concluded that administering moderate doses of psilocybin to healthy, high-functioning, and well-prepared individuals under careful monitoring poses an acceptable level of risk. Because we are seeing increases in psilocybin use in individuals who are not screened to be well-prepared, high functioning, nor had monitored use, a re-evaluation of the risk in naturalistic settings, including in the context of other substance use, is warranted.

Psilocybin's increasing prevalence and public acceptance as part of the recent "psychedelic hype bubble" phenomenon means that psychiatrists must be prepared to manage patients needing help after a difficult psychedelic experience (Yaden et al., Oct. 2022). However, it is currently unknown what the risk of negative outcomes is and how to best treat patients with prolonged psychosis or other severe reactions to psilocybin. The purpose of this case series is to describe three patients seen in the dual diagnosis inpatient psychiatry unit of a major academic hospital during one four-week medical student rotation in 2023. All three patients recreationally used psilocybin prior to the onset of psychiatric symptoms severe enough to warrant hospitalization. However, each patient reported a different pattern of use, and each resulted in unique psychiatric outcomes.

## Methods

Written consent was obtained from all three subjects highlighted in this case series.

## Case presentations

### Case 1

A 25-year-old woman presented with abrupt disorganized speech, paranoia, grandiose delusions, and lack of sleep for 48 h. Upon admission, she believed that she was involved in the secret plots of world leaders and the treatment team was experimenting on her and exposing her to diseases. First rank psychotic symptoms included thought insertion and perceiving outside forces controlling her body. She denied hallucinations but appeared anxiously preoccupied. She disclosed consuming psychedelic mushrooms at a music festival the weekend prior. She had tried psilocybin before, but this time had consumed a three-fourth ounce, triple her usual amount. She also reported vaping cannabis daily. Her first episode of psychosis occurred four years ago, when she was hospitalized for two months after experimenting with LSD for the first time. Since then, she had three similar presentations, all in the setting of substance use including hallucinogens, stimulants, and cannabis. In other settings, she had been diagnosed with Bipolar Affective Disorder. Family reported periods of depression and hypomania, with unclear relation to substance use. However, she only had mania warranting hospitalization with the use of psychomimetic drugs. Other considered diagnoses were substance-induced psychosis or a primary schizophrenia.

She was treated with olanzapine (Zyprexa) 25 mg daily (10 mg each morning and 15 mg at night). For two weeks, she had waxing and waning improvement in her symptoms until finally having sustained improvement in her thought process (increased linearity, decreased paranoia, more insight into delusions not being real) over the last week before discharge. Given her continued improvement, on discharge the olanzapine (Zyprexa) was consolidated to 20 mg nightly.

Given the atypical features of her psychosis and the extended period before treatment response, extensive medical workup for psychosis was performed (Skikic and Arriola, 2020). The following tests had results within normal limits: C-reactive protein, erythrocyte sedimentation rate,

anti-NMDA antibody, anti-streptolysin O antibody, treponema pallidum antibody, toxoplasma IgG, HIV antibody, thyroid stimulating hormone, parathyroid hormone, serum calcium, magnesium, phosphorus, ceruloplasmin, vitamin A, vitamin B3, vitamin B12, folate, homocysteine, methylmalonic acid, arsenic, lead, mercury, total urine porphyrins, and hemoglobin A1C. Test results were notable for a low vitamin B1 level of 75 nmol/L (reference range 78–185) and a low vitamin D 25-hydroxy level of 23 ng/mL (30–100). Anti-nuclear antibodies (ANA) were present with a nuclear speckled pattern at a titer of 1:80. Random urine fractionated porphyrins were positive for elevated coproporphyrin III at 100.5 mg/g creat (4.8–88.6), but this was thought to be medication-related. Urine toxicology screen on admission was unconfirmed positive for cannabinoids. She declined brain imaging studies.

The patient was seen in outpatient psychiatry clinic two months later for follow-up. She had not been taking olanzapine (Zyprexa) for the past week due to running out. She reported sleeping well, denied any hallucinations or delusions, but a mild grandiosity and abstractness to her speech was noted by her outpatient psychiatrist. She was stable with fair insight into her psychiatric conditions. She denied any substance use in the interim and stated she is "allergic" to cannabis and psilocybin referring to her recent hospitalization; however, she was not confident she would never use substances in the future. Since discharging from the hospital, she had re-enrolled in community college and applied for part-time jobs.

### Case 2

A 30-year-old man with history of self-diagnosed "depression and anxiety" but no prior psychiatric treatment and no family psychiatric history, presented after a serious suicide attempt by hanging and cutting his neck and wrists in the setting of paranoia and psychosis. He was discovered by a family member who aborted the attempt and brought him to the hospital. Per family, he had been increasingly paranoid for two months, which peaked in severity three days prior to the attempt. He had been smoking cannabis regularly and had started "microdosing" psilocybin biweekly 6 months prior to admission. He disclosed that he was attempting to self-medicate for chronic gastrointestinal symptoms with cannabis and psilocybin. He last ingested psilocybin, at a larger dose, ten days prior to the suicide attempt but was still experiencing paranoia up until the attempt. He reported drinking alcohol twice weekly, at most 6 drinks per sitting. He had also tried MDMA and cocaine several times recently before the attempt.

Urine toxicology screen on admission was unconfirmed positive for cannabinoids and fentanyl (after receiving fentanyl in the emergency department). Serum alcohol level was <10. Laboratory testing did not indicate any infectious or metabolic abnormalities that could explain the symptoms. The following tests yielded results within normal limits: ANA, treponema pallidum antibody, HIV antibody, thyroid stimulating hormone, folate, ceruloplasmin, methylmalonic acid, and hemoglobin A1C. A brain MRI with and without contrast four days into admission which showed no abnormalities that would explain his psychosis.

Mental status exam on admission was notable for disorganized thought process, paranoia, ideas of reference, decreased concentration, and challenges initiating speech. He was initially diagnosed with substance-induced psychosis given the substance use history. He did mention that he was worried he had schizophrenia. He was treated with 7.5 mg of olanzapine (Zyprexa) daily divided into 2.5 mg during the day and 5 mg at bedtime. Over time on this regimen, the patient's thought process and speech became more organized, and he became less paranoid, so the olanzapine (Zyprexa) was tapered to only 5 mg nightly. By discharge a week later, he was no longer paranoid, his thoughts were organized, and he and his family felt he was completely back to his baseline. He was discharged to a partial hospitalization program to continue treatment. In addition to substance-induced psychosis that appeared improved after a substance-free period, it could not be ruled out that this was a first episode psychosis in the setting of new

schizophrenia responsive to olanzapine (Zyprexa). Future recommendations to the patient's new outpatient psychiatry team advised slowly tapering the remaining olanzapine (Zyprexa) 5 mg in the setting of abstaining from substance use, to determine his need for continued antipsychotics and therefore his likelihood for endogenous psychotic disorder beyond the drug reaction.

### Case 3

A 35-year-old man with no history of psychiatric admission, but who as a child was diagnosed with ADHD, PTSD, and GAD by an outpatient therapist, presented with increasing irritability and impulsivity. He also experienced increasing separation from reality with paranoia and grandiose delusions. This culminated into his involvement in a physical altercation and arrest for assault with a knife prior to admission. Initially, he was observed to have pressured speech, elevated mood, labile affect, grandiose delusions about his dreams predicting the future, flight of ideas, and a circumferential thought process. Urine toxicology screen was unconfirmed positive for benzodiazepines, cocaine, and cannabinoids. Serum alcohol level was <10. A CT scan of the head without contrast was also performed given the recent assault, which was negative for any acute intracranial abnormalities.

The patient shared he had been "microdosing" psilocybin, as well as his own homemade formulation of saline and ketamine. He had tried psilocybin in the form of raw hallucinogenic mushrooms a few times previously but started taking them regularly three weeks prior to admission after obtaining a bag of psilocybin-containing gummies. He reported ingesting the entire four-gram bag over seven days. His ketamine use started one year prior to admission; he typically would insufflate one gram of his homemade "esketamine" over two days, then stop ketamine for the next two months. This practice recurred every two months; he last used ketamine two months prior to admission. He also had a significant cannabis use history starting as a teenager, and prior to admission he was smoking an eighth of cannabis and one gram of hash daily. Despite his urine toxicology screen also being positive for cocaine, he denied knowingly using cocaine. His family shared that since the patient started "microdosing" on psilocybin and ketamine, his behavior had become increasingly labile and grandiose.

Since the presentation was most convincing for a substance-induced mood and psychotic disorder, no psychotropic medications were started. His symptoms improved gradually over his week-long admission without any medications. His thought process became more linear, his speech was less pressured, and his affect was more stable. He was discharged and transferred directly to an inpatient substance rehabilitation center, where he completed treatment.

Six months after hospitalization, he provided updates in a follow-up call. He reported feeling overall well and denied any mood or psychiatric symptoms aside from occasional insomnia. He denied any new hospitalizations or ED presentations for psychiatric concerns since discharge. During the call, he was observed to have a significantly more linear thought process. His speech was not at all hyperverbal or pressured. No delusions or hallucinations were elicited. He had resumed regular cannabis use to alleviate chronic nerve pain but denied any psilocybin or ketamine use since discharge. He noted that abstaining from alcohol use, increased physical activity, and a healthy diet have also helped him stay well.

### Discussion

This case series addresses a need for more clinical information for treating patients with psilocybin-induced psychosis. Between LSD and psilocybin, there are fewer case reports of prolonged psychiatric symptoms after psilocybin use compared to LSD use (Krebs and Johansen, 2013). A strength of this series is that all three patients were evaluated and managed by the same treatment team and within the same inpatient unit, leaving room for fewer environmental variables between the

hospitalizations. This contrasts with a retrospective case series of thirteen patients with hallucinogen persisting perception disorder who were evaluated by four neuro-ophthalmologists across five Australian health care sites (Ford et al., 2022).

The patient in Case 1 reported ingesting triple her previous doses of psilocybin prior to presentation. A review combining data from eight studies conducted between 1999 and 2008 found that psilocybin dose-dependently induced changes in mood, perception, thought, and self-experience (Studerus et al., 2011). Adverse reactions such as strong dysphoria and/or anxiety/panic, occurred only at the two highest doses in a relatively small proportion of subjects. This dose-dependency would support the psilocybin use patterns and resulting symptoms seen in this patient. This contrasts with the individual in Case 2, who had begun microdosing earlier, but did not exhibit a strong adverse effect until the dose became larger. Furthermore, in almost all instances of this patient experimenting with psychoactive substances, she became psychotic resulting in multiple hospitalizations. This could be an effect of her baseline history of having Bipolar Affective Disorder (BPAD), which may confer an increased susceptibility to psychedelic effects. A recent case report from Alabama highlighted a patient with unmedicated Bipolar II Disorder who developed his first full manic episode in the context of ingesting psilocybin along with other illicit substances (Halim et al., 2023). Patients with BPAD are more likely to engage in risky behaviors such as substance use, and given psilocybin's effect on serotonergic receptors, they are even more likely to experience psychiatric symptoms following psilocybin use. This risk is further compounded by the uncertainty presented by the fact that BPAD is an exclusion criterion in most clinical studies of psilocybin largely due to the theoretical concern of activating mania (Gard et al., 2021). Therefore, very little is known about the effects of psilocybin in patients with BPAD, highlighting the need for additional research and vigilance when addressing possible psilocybin use in this vulnerable patient population. For these reasons, individuals with endogenous risks such as BPAD should avoid using psychomimetics, especially in uncontrolled environments.

The patient in Case 2 presented after an alarming suicide attempt, warranting a discussion of the relationship between psilocybin use and suicidality. Researchers found that lifetime psilocybin use was associated with lower levels of psychological distress and suicidality using data from the National Survey on Drug Use and Health (NSDUH) (Hendricks et al., Sep. 2015). Perhaps our patient's paradoxical increase in suicidality could be explained in part by the fact that his psilocybin use occurred outside of a monitored, clinical setting. To discuss psychedelics more broadly, researchers from Canada performed a literature review of studies examining the relationship between classic psychedelic use (i.e. psilocybin, LSD, and ayahuasca) and suicidality (Zeifman et al., Apr. 2021). They found that psychedelic use in controlled, clinical settings may be associated with reduced suicidality possibly due to decreases in experiential avoidance and the serotonergic mechanism of action decreasing depression severity. However, they also noted that in unmonitored settings, psychedelic use was occasionally found to lead to suicide, possibly due to impaired executive functioning or emotionally challenging experiences, or due to psychosis. Additionally, our patient identified as African American. Another study utilizing data from the NSDUH specifically examined the association of racial identity and effects of psychedelics (MDMA and psilocybin) on mental health (Jones and Nock, Oct. 2022). They found that people who identify as African American who used psychedelics had no significant odds of improvement in suicidality and psychological distress. They speculated that this could be attributed to baseline disparities such as socioeconomic differences and education levels. Furthermore, due to deeply rooted racism and prejudice in America, African Americans are more likely to be arrested for illegal substance use, which could lead to a difference in the initial mindset of the individual prior to using psychedelics, which could negatively affect the overall experience.

The patient in Case 3 is the only patient in our series who displayed aggressive behavior towards other as a part of his substance-induced

psychosis. His substance use history is complicated, but he was able to report a clear timeline. Given that his cannabis use had been ongoing long-term without any changes, he had reportedly not used ketamine for over two months, and he denied cocaine use, it appears that the larger than usual amount of psilocybin used in the month prior to admission may have most significantly affected the aggressive presentation. In a survey of two thousand respondents, 10.7 % reported putting themselves or others at risk of physical harm, and 2.6 % reported behavior in a physically aggressive or violent manner during their single worst “bad trip” on psilocybin (Carbonaro et al., Dec. 2016). Another study reviewed serotonergic psychedelics in patients with autism spectrum disorder and found that studies showed an increase in aggressive behavior and dissociative and psychotic states after psychedelic use in these patients (Markopoulos et al., 2021). This could possibly explain our patient’s physically violent behavior leading to his arrest prior to admission, in the setting of having ingested a larger than usual amount of psilocybin. The literature on the relationship between psilocybin and aggressive behavior is sparse, and more research is needed to better understand psilocybin’s potential to cause serious consequences including physical harm to self and others, and incarceration.

### Limitations

This case series is not without limitations. We were compelled to compile these cases as they all shared the relatively novel commonality of psilocybin; however, the presence of other substances introduces a degree of ambiguity, a common occurrence in real-life scenarios. With this increase in psilocybin use, clinicians are most likely to continue to see it appear as an added factor in polysubstance use, as we have seen here. Additionally, conclusions drawn from a case series are inherently limited due to the lack of control groups and the potential for bias, making it difficult to establish causality or generalize findings to broader populations compared to more rigorous study designs. Additionally, all three cases reported regular cannabis use, which likely confounded their psychotic presentations (Kuepper et al., Mar. 2011; Hall and Degenhardt, Jun. 2008). However, based on history obtained, they all experienced functional decline or debilitating psychosis only when other drugs were started, including psilocybin. Moreover, psilocybin, unlike other substances like alcohol or cannabinoids, does not have a readily available clinical test that can objectively assess how much of the substance was ingested, or if it was actually used at all. We relied on our patients and their family members to provide this information from memory, days to weeks after they had taken the psilocybin. However, we are grateful for our patients’ willingness to share openly about their substance use and other sensitive matters, not only to benefit their own treatment, but to allow us to write this case series with their permission.

### Brief recommendations for clinicians

Clinical trials have suggested psilocybin treatment can result in a 25–50 % remission rate in depression, depending on the study (Tabaac et al., Mar. 2024). However, it’s important to keep in mind most patients who use psilocybin are not thoroughly screened participants using in a controlled setting. They often have other comorbid psychiatric history and concurrent substance use. Therefore, it is essential to educate patients about the risks of psilocybin, especially in unstudied “real-world” situations. Clinicians managing patients who use psilocybin should gather detailed past medical and psychiatric history. A thorough substance use history including a timeline if multiple substances were introduced at different times provides important context. If antipsychotics are prescribed to treat prolonged psychosis or mania related to psilocybin use, gradual tapering should be considered once stability is achieved, and long-term follow-up appointments are crucial for monitoring symptoms and substance use patterns.

### Conclusion

In summary, these cases illustrate three unique presentations of acute psychosis in the context of non-clinical psilocybin use. One patient had a history of BPAD which may have contributed to her prolonged psychotic symptoms, given BPAD patients’ theoretical heightened sensitivity to psilocybin and lack of clinical trials in this patient population. The second patient presented with severe suicidality as part of his psilocybin-induced psychosis, which adds to the existing mixed literature of psilocybin both increasing and decreasing suicidality. Both of these patients’ psychiatric symptoms improved on the dopamine antagonist olanzapine (Zyprexa), although the first patient’s course was waxing and waning compared to the second patient’s. The third patient presented with aggression as part of his psychosis and demonstrated improvement of his symptoms over time without medications. This case series highlights the need for further research to guide psychiatrists in addressing psilocybin’s surging popularity in American society, especially with the current mixed messages of its utility and risks for treatment of mental health disorder.

### Patient consent statement

The three patients in these case presentations directly provided written consent to be included in this publication. Additionally, personally identifiable details have been removed from the submission whenever possible.

### Ethical publication statement

This submission adheres to all relevant ethical guidelines. Per our institution’s IRB guidelines, a case series involving three or fewer patients does not produce generalizable knowledge, nor is it an investigation of an FDA-regulated product. Therefore, IRB review and approval were not required for this activity at our institution.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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