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REVIEW ARTICLE

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Fungal Infections in People Who Use Drugs

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Illicit drug use in the United States continues to rise, alongside an increasing number of severe infections associated with drug use. Surveillance studies report that 28%–34% of candidemia cases are linked to intravenous drug use, with *Candida albicans* being the most commonly isolated species, followed by *Candida parapsilosis* and *Candida glabrata*. Marijuana use is associated with lung infections caused by *Aspergillus* and the *Mucorales*, showing a 3.5-fold increased risk of mold infections and a 2.2-fold increased risk for other fungal infections. Intravenous drug use also presents a recognized risk factor for *Aspergillus* and *Mucorales* infections. Additionally, substances like cannabis, methamphetamines, and opioids share metabolic pathways with triazoles, a class of antifungal, and terbinafine through the CYP enzyme system. These antifungal drugs strongly inhibit CYP3A4 and CYP2D6, leading to potential drug interactions, adverse effects, overdose risks, and even death.

Keywords. comprehensive review; drug interactions; invasive fungal infections; invasive mycosis; people who use drugs.

Worldwide, 292 million people used drugs in 2022, according to the 2024 World Drug Report by the United Nations Office on Drugs and Crime, marking a 10% increase over the past decade. Of these, 228 million people used cannabis, followed by 60 million using opioids, 30 million using amphetamines, 23.5 million using cocaine, and 20 million using ecstasy. Injection drug use was reported in 13.9 million people [1].

In the United States, the latest National Survey on Drug Use and Health by the Substance Abuse and Mental Health Services Administration for 2023 showed that the number of people who reported using illicit drugs in the month before being surveyed increased from 40 million (14.3%) in 2021 to 46.6 million (16.5%) in 2022 and to 47.7 million (16.8%) in 2023 [2–4].

Opioids have the largest contribution to the burden of disease among controlled substance users worldwide [5]. In the United States, opioid-related death rates have increased from 1 to 10.4/100 000 people (age-adjusted), an increase of 1040% from 2013 to 2019 [6].

The COVID-19 pandemic saw an increase in the number of drug overdoses according, to estimates from the Centers for Disease Control and Prevention. An estimated 107 622 drug overdose deaths were reported in the United States in 2021, an increase of nearly 15% compared to 2020. Overdose deaths involving opioids rose from an estimated 70 029 in 2020 to 80 816 in 2021 [7]. Following a decline during the pandemic years, the use of stimulants, such as cocaine and ecstasy, has increased in the postpandemic years [1].

The disease burden attributed to substance use was estimated to be 1.5% of the global disease burden, according to the Global Burden of Disease, Injuries and Risk Factors 2016 study [8]. Bloodborne viral pathogens, such as hepatitis C and HIV, have been linked to intravenous drug use (IDU) [9]. Bacterial and fungal infectious syndromes also present concern in people who use drugs. The proportion of invasive infections caused by *Candida* species has increased in recent years [10], and the number of hospital admissions related to invasive fungal infections has risen [11]. However, the exact number of these infections is unknown [12], this may be in part because the current European Organization for Research and Treatment of Cancer and the Mycosis Study Group Education and Research Consortium criteria [13] do not include illicit drug use in their definitions.

This article will review the literature and epidemiologic data on fungal infections in people who use drugs (PWUD), focusing on the most common fungal infections associated with commonly used illicit drugs, including cannabis, opioids, cocaine, and ecstasy.

INVASIVE CANDIDIASIS

Invasive candidiasis refers to infections caused by yeast of the *Candida* species and is one of the most common opportunistic

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fungal infections worldwide [14]. The spectrum of invasive candidiasis ranges from bloodstream infections (candidemia) to osteomyelitis, arthritis, endophthalmitis, and intraabdominal infections, with candidemia being the most frequent presentation [15].

Candidemia is one of the most common causes of bloodstream infections in the United States [16], with an estimated 23 000 cases occurring each year [17]. The *Candida* species most commonly responsible for candidemia, accounting for 9% of cases, are *C albicans*, *Nakaseomyces glabratus* (formerly *C glabrata*), *C parapsilosis*, *C tropicalis*, and *Pichia kudriavzevii* (formerly *C krusei*), in order of frequency [18]. However, a 2018 study by Poowanawittayakom et al. reported a higher incidence of non-*C albicans* species among intravenous drug users compared to nonintravenous drug users in their cohort [10].

The gastrointestinal tract is considered the most common source of infection in candidemia, with the skin being a less frequent source [19]. Risk factors associated with invasive candidiasis include critical illness, prolonged admission to an intensive care unit, abdominal surgery, acute necrotizing pancreatitis, hematologic malignancies, solid organ transplantation, solid organ tumors, use of broad-spectrum antibiotics, presence of central vascular catheters, total parenteral nutrition, hemodialysis, glucocorticoid use, chemotherapy-induced mucositis, and multifocal *Candida* colonization [20]. Intravenous drug use is recognized as an important risk factor for candidemia, especially in community-acquired cases among patients aged 19 to 44 years who lack the previously mentioned risk factors [21].

Population-based active surveillance studies across multiple US states report that 14% to 34.6% of candidemia cases were related to intravenous drug use [21–23], with the latter specifically referring to the age group between 19 and 44 years of age. In the study by Zhang et al, 10% of the cohort with candidemia reported recent intravenous drug use; more importantly, this number increased to 34% in the 19–44 year age group [22]. The median age of candidemia in intravenous drug users is 35 years of age, compared to ∼63 in the non-IDU candidemia [21, 23].

Intravenous drug use–associated candidemia presents as community onset in 60% of cases, and as disseminated disease in up to one third of patients, leading to endophthalmitis, septic arthritis, osteomyelitis, and endocarditis [23, 24]. A higher frequency of endocarditis, embolization, osteomyelitis, and central nervous system (CNS) involvement have been reported in IDU-related candidemia compared to non–IDU-related candidemia; however, only endocarditis and osteomyelitis reached statistical significance in a study by Poowanawittayakom et al [10, 23]. Morbidity and mortality associated with end-organ disease are high, with mortality from candidemia in people who inject drugs (PWID) ranging between 8% and 21%, compared to 25%–34% in non-IDU users [10, 23]. The lower mortality rate among PWID is thought to be related to the younger age, and fewer comorbidities found in this patient cohort.

The identification of *Candida* to the species level is important in cases of invasive candidiasis due to the high diversity of *Candida* species and the acquired or intrinsic resistance of certain species [15]. Early diagnosis and appropriate empiric antifungal therapy with an echinocandin are crucial and have been associated with decreased mortality [25, 26]. Deescalation to an azole following the susceptibility profile is a strategy that yields favorable results and decreases the financial burden on patients and healthcare facilities by reducing hospital costs and shortening the length of stay. Other agents, such as amphotericin B formulations or azoles, may primarily be preferred in cases of CNS infections or endophthalmitis, where echinocandins have limited penetration [15]. Except for isolated chorioretinitis, the concomitant administration of intravitreal therapy is usually advised [27, 28]. The recommended duration of treatment for uncomplicated candidemia is at least 14 days after the eradication of *Candida* spp. from the blood and the resolution of symptoms. This duration can extend from 6 to 12 weeks to several months in cases of deep-seated infections [28].

The shift toward a predominance of non-albicans *Candida* spp. has brought challenges regarding antifungal resistance. Fluconazole resistance rates have been reported at 11%–13% for *N glabrata*, 2%–6% of *C parapsilosis*, and 4%–9% of *C tropicalis* isolate [29, 30]. However, Jenkins et al. published resistance rates as high as 29% for *N glabrata* [31]. These findings underscore the importance of susceptibility testing for non-albicans isolates but also highlight the issue of prolonged parenteral therapy in PWUD. Treatment options for azole-resistant *Candida* isolates are limited to echinocandins, a class of antifungals available only for intravenous administration. Peripherally inserted central catheters are required for outpatient parenteral antimicrobial therapy (OPAT); however, this presents a challenge in this patient population, often resulting in prolonged hospitalizations with an increased risk of hospital-acquired infections, withdrawal symptoms, and patient-directed discharges [32, 33]. Ethical considerations, such as respecting patient autonomy, and avoiding stigmatization of drug abuse, must also be taken into account. Current Infectious Diseases Society of America practice guidelines on OPAT neither recommend nor oppose OPAT-based therapy for PWID but express concern about the potential misuse of vascular devices [34]. A comprehensive review of OPAT in PWUD is beyond the scope of the current article.

INVASIVE ASPERGILLOSIS

Invasive aspergillosis is an opportunistic infection with an attributable mortality rate as high as 80% [35], usually affecting immunocompromised hosts. It most frequently affects the respiratory tract, CNS, and eyes. Risk factors most commonly associated with invasive aspergillosis include periods of neutropenia, solid organ transplantation, hematological malignancy,

hematopoietic stem cell transplantation, and prolonged use of steroids or other immunosuppressive agents [36].

Cannabis was categorized as a Schedule 1 controlled substance in 1970 by the United States Controlled Substances Act [37]. Despite this, cannabis remains the most used illicit drug in the United States, according to the most recent Substance Abuse and Mental Health Services Administration report [4]. In recent years, some states have decriminalized and/or regulated the recreational and medicinal use of cannabis.

Aspergillus spores and hyphal fragments are widespread and exposure is universal. Tobacco and marijuana are commonly contaminated with fungi. Unlike tobacco, marijuana is often smoked without a filter and down to a smaller butt. Cannabis smokers also hold their breath and maintain a Valsalva maneuver, which increases exposure to *Aspergillus* as well as other fungi such as *Fusarium, Rhizopus,* and *Scedosporium species* [38, 39]. Fungal spores in marijuana do not appear to be inactivated during combustion [40].

Although the exact incidence is unknown, *Aspergillus* and other fungal pathogens can cause serious and often fatal infections in immunocompromised hosts, such as those with cancer, transplant recipients, and people with HIV. People who use cannabis are 3.5 times more likely to have mold infections and 2.2 times more likely to have other fungal infections than people who do not use cannabis [41].

It has been postulated that smoking induces structural and immunological lung damage that confers increased susceptibility to infection [41–43]. However, a 2018 publication focusing on transplant recipients also reported an increase in the number of invasive fungal infections in patients who vaped or consumed cannabis edibles [44]; however, no causal relation could be made due to the nature of the study. Additionally, cannabis oil has also been found to yield mold growth when cultured [45].

Invasive fungal sinusitis is a severe infection, with a mortality rate between 20% and 100% [46–49] depending on underlying comorbidities, with higher rates observed in severely immunocompromised individuals or the presence of CNS involvement. Additional risk factors include diabetes [50, 51], trauma [49], alcoholism [51], living in hot and dry climates [49], farming [52], maxillary tooth extraction [53, 54], marijuana use [52], and intranasal cocaine use [55, 56]. Aspergillus fumigatus is the most common species associated with invasive sinus disease, while *A flavus* is less common a more severe disease presentation because of toxin production is possible based on prior observations and data from animal models [50, 57]. Symptoms such as facial pain, nasal congestion and/or drainage, and epistaxis [58] usually precede significant radiologic findings, and nasal cultures are often negative [59]. Histopathologic examination of tissue is frequently required to make the diagnosis [49]. Treatment includes thorough surgical debridement and systemic antifungal therapy with voriconazole [60].

Aspergillus endophthalmitis has been reported in the literature, with *Aspergillus flavus*, *A fumigatus*, *A terreus*, and *A glaucus* being implicated [40]. Hematogenous dissemination of *Aspergillus* spores, directly inoculated from contaminated drugs or paraphernalia, is thought to be the mechanism involved in the development of endophthalmitis [61]. Patients typically report acute to subacute unilateral vision loss and ocular pain. Findings on physical examination include conjunctival injection, anterior uveitis, vitritis, and chorioretinitis. Unlike *Candida* spp, cutaneous and costochondral involvement is rarely seen in *Aspergillus* endophthalmitis cases. Blood cultures have a poor yield in these cases, whereas vitreous cultures demonstrate better performance [40]. Treatment involves a combination of local and systemic antifungal therapy [60].

Although rare, *Aspergillus* species have also been implicated in cases of endocarditis, with only a few cases reported in the literature [36, 40]. Diagnosis becomes challenging in these cases, as *Aspergillus* spp. are rarely isolated from blood cultures. Patients tend to present with large vegetations and septic emboli (60%), likely related to late diagnoses [40]. *Aspergillus fumigatus*, *A flavus*, and *A niger* were most frequently isolated [36, 40]. Management requires systemic antifungals and valvular surgery [36, 60]. Mortality, from case reports, was 100% [36, 40].

Osteomyelitis involving the ribs, sternum, and vertebrae caused by *Aspergillus* spp. has also been described in PWID, with management involving systemic therapy and surgical debridement. Renal involvement, presenting as fungal bezoars, has also been reported in PWID. Treatment in these cases includes systemic and bladder irrigation with amphotericin B [40].

CNS disease resulting from Aspergillus is rare in PWID, but a few publications (5) have reported on this entity. Unlike cases in immunocompromised hosts, who mainly present with parenchymal abscesses and cerebrospinal fluid (CSF) analysis showing little to no pleocytosis and negative cultures, PWID frequently have meningeal or ventricular involvement, with CSF profiles showing pleocytosis, low glucose, and isolation of *Aspergillus* spp. from CSF culture in 75% of cases. Mortality is high, with only 2 of 5 subjects surviving the disease, a 60% mortality rate [40].

Unlike cases of endophthalmitis, endocarditis, and osteomyelitis, no cases of pulmonary *Aspergillosis* directly related to intravenous drug use have been reported [40].

MUCORMYCOSIS

Mucormycosis is caused by fungi of the order Mucorales, which are ubiquitous in the environment. Mucormycosis can present as rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and isolated cerebral disease, with each form having different predisposing conditions and prognoses [62]. Known risk factors for developing cutaneous mucormycosis include uncontrolled diabetes, ketoacidosis, hematologic malignancies,

organ transplantation, deferoxamine therapy, injection drug use, HIV, malnutrition, trauma, burns, steroid use, and aplastic anemia [63–65]

Primary cutaneous mucormycosis is primarily acquired through direct inoculation and has been described in case reports associated with intravenous drug use [66]. Between 40% and 50% of mucormycosis cases occur in patients without predisposing underlying conditions [67]. It may appear as a single, painful erythematous lesion that can progress to necrosis and ulceration [68] at the inoculation site. Tissue biopsy for histopathology and culture is required for diagnosis, though patients are often treated presumptively. Surgical debridement and systemic antifungals are the mainstays of therapy, with liposomal amphotericin B recommended as the first-line agent [68].

Isolated cerebral mucormycosis presents with disease localized to the CNS (cerebral hemispheres, cerebellum, and brainstem) without extension to the sinuses, cranial bones, or other organ systems. It is commonly due to hematogenous seeding following direct inoculation via the intravenous route. The vast majority of cases have been reported in immunocompetent patients with a history of intravenous drug use. The most frequently reported symptoms are headache, fever, focal weakness, and altered mental status. In a large case series, intravenous drug use was reported in 92% of cases, with most patients having basal ganglia involvement (85.5%). The imaging modality of choice is brain magnetic resonance imaging. Diagnosis requires tissue biopsy for histopathology and culture, although molecular-based methods such as polymerase chain reaction and sequencing have also been reported and used in clinical practice. The treatment of choice is liposomal amphotericin B [62, 69]. The role of combination therapy with other azoles active against Mucorales is still controversial, with no demonstrated benefit in other patient populations [70].

Pulmonary mucormycosis has been described in cannabis smokers with underlying immunosuppressing conditions, such as hematologic malignancy or poorly controlled diabetes mellitus. Marijuana is known to harbor multiple fungal spores, including Mucor, which may survive the drying and curing process [71]. According to a 2017 analysis, medical marijuana samples from 20 dispensaries in California were tested for fungal and bacterial pathogens using 16S, internal spacer gene sequence analysis, and metagenomics; *Aspergillus*, *Cryptococcus*, and *Mucor* were identified, along with several bacterial pathogens [72]. Definitive diagnosis requires tissue biopsy for histopathologic evaluation and culture. Liposomal amphotericin B is the treatment of choice, with aggressive and early surgical intervention if feasible, as this approach has been shown to reduce mortality [73].

Renal involvement in disseminated disease has been described in up to 20% of case [74], but isolated renal disease is limited to case reports. Intravenous inoculation of spores is thought to be responsible for isolated renal disease. HIV, intravenous drug use, and diabetes mellitus are recognized risk factors. Patients present with a pyelonephritis-like syndrome, including flank pain, fever, pyuria, and hematuria. Unilateral involvement is more common, with bilateral involvement associated with a worse prognosis [75, 76]. Evaluation includes urinalysis, urine culture, renal ultrasound, and computed tomography imaging. Imaging findings include an enlarged kidney with loss of normal structure, hypodense regions representing areas of infarction and abscess formation, and perinephric collections [77, 78]. Although imaging can suggest the diagnosis, tissue is required for a definitive diagnosis, with samples sent for histopathologic evaluation and culture. Treatment involves surgical debridement, which may include nephrectomy in some cases, and systemic therapy with amphotericin B.

CRYPTOCOCCOSIS

Risk factors for cryptococcal disease include HIV, organ transplantation, corticosteroid use, hematological malignancies, sarcoidosis, chronic liver disease, and immune modulators such as anti–tumor necrosis factor therapies and other drugs targeting T cells [79, 80].

Cryptococcal meningitis caused by *Cryptococcus neoformans* in a nonimmunocompromised patient with heavy daily cannabis smoking has been reported, with cannabis suspected by the authors as the source of her exposure to *Cryptococcus*. The authors analyzed samples from the type of cannabis the patient preferred to buy from her usual dispensary in California and found a small amount of 6 different *Cryptococcus* species, with 3 of the 9 samples containing *C neoformans* [81].

Intravenous injection of heroin, fentanyl, and methamphetamines have been associated with immunosuppression and increased pathogenicity of *C neoformans* [82–85]. Multiple reports of cryptococcal meningitis associated with intravenous administration of illicit drugs have been published [80, 86, 87].

Management of cryptococcal meningitis includes an induction phase with liposomal amphotericin B at 3–4 mg/kg daily plus flucytosine at 25 mg/kg 4 times per day for a minimum of 2 weeks, followed by consolidation with fluconazole at 400–800 mg daily for 8 weeks, and maintenance with fluconazole at 200 mg daily for 12 months [79].

HISTOPLASMOSIS

Histoplasmosis cases in patients with a history of illicit drug use are mainly limited to case reports from Spain, in patients with concomitant diagnoses of HIV and AIDS. Exposure to endemic areas is the most common risk factor in these reports; however, inhalation of cocaine coming from endemic areas, or the practice of sharing needles (between people exposed to endemic regions and people without exposure) for the administration of intravenous illicit drugs have been postulated as other potential routes of exposure for patients living in nonendemic areas

[88–91]. In the United States, an outbreak of histoplasmosis related to the uprooting of cannabis plants in a cannabis field by police officers has been reported [92].

OTHER INVASIVE MYCOSES

To the knowledge of the authors, no cases of blastomycosis, or coccidioidomycosis have been reported in association with the use of illicit drugs. In vitro studies have shown that methamphetamines can affect the phagocytic function of macrophages and cytokine production in mouse lungs, impairing their ability to control histoplasmosis. Mice exposed to methamphetamines showed an increased fungal burden, heightened pulmonary inflammation, and decreased survival [93].

DRUG–DRUG INTERACTIONS INVOLVING ILLICIT DRUGS

Data are limited regarding interactions between illicit drugs and commonly prescribed medications, including antifungals.

The term "cannabinoid" refers to a diverse group of chemical compounds that, regardless of their origin (natural, synthetic, or endogenous), exert effects by binding to cannabinoid receptors in the human body [94]. Potential sites of action for cannabinoids include CB1, CB2, opioid, muscarinic, nicotinic, serotonin, calcium, potassium, sodium, and peroxisome proliferator-activated receptors, among others, explaining their broad clinical effects [95, 96]. Tetrahydrocannabinol is primarily metabolized by CYP 2C9 and 3A4 enzymes, whereas cannabidiol is primarily metabolized by CYP 2C19 and 3A4. Coadministration of ketoconazole has been shown to increase the maximum concentration and area under the curve of tetrahydrocannabinol by 1.2- and 1.8-fold, respectively, while increasing maximum concentration and area under the curve 2-fold for cannabidiol, supporting a drug interaction involving the CYP 3A4 pathway [97].

Studies have shown that CYP isoenzymes 1A2, 2D1/6, 3A2/4, and 2D6 are involved in various steps of the metabolism of amphetamines and their derivatives [98]. Similarly, the metabolism of opioids primarily involves CYP isoenzymes 3A4 and 2D6 [99]. Antifungals are also metabolized through the CYP system, with isoenzyme 3A4 playing a major role in the metabolism of triazoles and terbinafine [100]. Triazole antifungals are strong inhibitors of CYP 3A4 [99], whereas terbinafine inhibits CYP 2D6 [101].

Studies on pharmacokinetics and drug–drug interactions involving illicit drugs and prescription medications are limited by ethical considerations. Given the common metabolic pathways employed by illicit drugs and some antifungals, inhibition of these pathways by triazoles could lead to increased levels of drugs like methamphetamines and opioids, potentially resulting in undesired effects and overdose.

CONCLUSIONS

As the number of people who use drugs increases in the United States and worldwide, so does the number of infectious complications related to drug use, including fungal infections. Injection drug use now accounts for about one third of candidemia cases, with non–*C albicans* species making up more than half of cases. Fungal spores from various fungal species have been identified in cannabis, putting consumers of these products at increased risk for invasive fungal disease due to *Aspergillus* spp, *Cryptococcus*, and *Mucorales*. Intravenous drug use has also been linked to fungal infections such as candidemia, mucormycosis, aspergillosis, and histoplasmosis. Many illicit drugs and antifungals are metabolized through the CYP 3A4 pathway, creating the potential for drug interactions, adverse effects, overdose risks, and even death.

Notes

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