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REVIEW ARTICLE

Mucocutaneous Manifestations of Recreational Drug Use

Carolina V. Alexander-Savino[1,2] · Ginat W. Mirowski[3,4] · Donna A. Culton[2]

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Abstract
Recreational drug use is increasingly common in the dermatology patient population and is often associated with both general and specific mucocutaneous manifestations. Signs of substance use disorder may include changes to general appearance, skin, and mucosal findings associated with particular routes of drug administration (injection, insufflation, or inhalation) or findings specific to a particular drug. In this review article, we provide an overview of the mucocutaneous manifestations of illicit drug use including cocaine, methamphetamine, heroin, hallucinogens, marijuana, and common adulterants to facilitate the identification and improved care of these patients with the goal being to connect this patient population with appropriate resources for treatment.

Key Points

Recreational drug use is increasing within the dermatology patient population.

Dermatologists can recognize mucocutaneous signs of recreational drug use to allow for a broader differential diagnosis for some common dermatologic findings.

Rare and life-threatening mucocutaneous manifestations in patients using recreational drugs should be recognized quickly for appropriate treatment.

✉ Donna A. Culton
donna_culton@med.unc.edu

1 State University of New York Upstate Medical University, Syracuse, NY, USA

2 Department of Dermatology, University of North Carolina at Chapel Hill, 410 Market Street, Suite 400, Chapel Hill, NC 27516, USA

3 Department of Dermatology, Indiana University School of Medicine, Indianapolis, IN, USA

4 Department of Oral Pathology, Medicine, Radiology, Indiana University School of Dentistry, Indianapolis, IN, USA

1 Introduction

According to the National Survey on Drug Use and Health in 2021, over 61.2 million (21.9%) of Americans over the age of 12 years used recreational drugs within the past year. While the majority (86% of adults) misused marijuana, 15% (9.2 million) misused opioids. These numbers are based on the criteria for Diagnosing and Classifying Substance Use Disorders as defined by the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders [1]. Recreational drug use is more common in those aged 18–25 years, with 40% of this age group having used recreational drugs in the past year in the USA [2]. The rising rate of recreational substance use comes at a great cost, both financially and in terms of human lives. Financially, the cost of illicit drug use in the USA is estimated to be around $193 billion [3]. More importantly, drug overdoses have killed close to a million Americans since 1999, with over 96,700 deaths in 2021 and comprising about a third of deaths in the USA [4]. Nearly 85% of these deaths involved illicitly manufactured fentanyl, heroin, cocaine, or methamphetamine [5]. At least half of deaths due to overdose were in persons using multiple drugs [6]. Unfortunately, 60% of individuals who died from a drug overdose had an identified opportunity for linkage to care or life-saving actions [5].

Recognizing the signs of substance use disorder is imperative and potentially lifesaving. As dermatologists, we have the opportunity to identify mucocutaneous manifestations of drug use in the clinical setting and educate healthcare providers on these signs. In this review article, we provide an

overview of the mucocutaneous manifestations of illicit drug use including cocaine, methamphetamine, heroin, hallucinogens, marijuana, and common adulterants. The intent of this article is to facilitate the identification and improved care of these patients with the goal being to connect this patient population with appropriate resources. Thus, we have presented the information separated by general findings, findings by route of administration, and by drug type. Though this categorization creates some overlap, we aim to provide a comprehensive and cross-referenced overview that can be easily utilized in the outpatient setting by the busy clinician.

2 Non-Specific Mucocutaneous Findings

2.1 General Appearance

Illicit drug use can cause many changes to the general appearance of an individual. Patients may have a drunk or disoriented appearance, and inattentiveness. The nature of being under the influence of drugs can cause concern about the stigma associated with drug use while others may self-neglect. Self-neglect can lead to poor overall hygiene and oral hygiene, regardless of the method of administration or particular drug [7]. Some patients will attempt to hide signs of illicit drug use (such as track marks or petechiae, bruising, and post-inflammatory hyperpigmentation from tourniquets) by wearing inappropriate clothing such hoodies and long-sleeved shirts in very hot weather. Pupil dilation or conjunctival injection from drug use may be masked by wearing sunglasses indoors [8]. Some individuals will have tattoos over track marks and soot tattoos [9, 10]. In the case of inhalant use, patients may emit a chemical odor, have paint or solvent marks on clothing, or carry spray paints and/or chemical-soaked rags [11, 12]. Patients may appear older, as some drugs may cause non-specific findings of accelerated aging [13]. Hair can prematurely gray in a more generalized manner across the scalp with temporal graying more significantly related to the duration of the drug used, particularly for amphetamines and heroin [14]. Some may experience alopecia due to toxicity of the drug, stress, general neglect, and malnutrition while stimulants can cause anxiety and trigger trichotillomania [15, 16]. Xerosis and cheilitis are commonly found in this patient population and are due to vasoconstrictive effects on the skin and mucosa [17]. Thermal burns can be a clue to drug addiction as well, as patients are more prone to have burns because of smoking while being under the influence of drugs or also preparing their drugs for administration. For example, madarosis (loss of the eyebrows and eyelashes) may be seen in heroin users due to thermal injury to follicles while preparing heroin for injection [9].

2.2 Pruritus and Formication

Pruritus is a common finding associated with the use of numerous illicit drugs including cocaine, amphetamines, and opioids [18, 19]. Patients present with generalized pruritus and subsequent excoriations, prurigo nodules, and ulcers. Formication is the tactile sensation of bugs crawling on or under the skin and is a common side effect of cocaine and methamphetamine use, which can lead to signs of skin picking. Patients with formication may also exhibit excoriations, prurigo nodules, or ulcers as above, but often deny pruritus [20]. Formication may be associated with concurrent visual hallucinations [21].

2.3 General Oral Mucosa Findings

Common oral manifestations in patients who use recreational drugs include accelerated tooth decay, periodontal disease, xerostomia, halitosis, and candidiasis (both *albicans* and non-*albicans* species, particularly *Candida dubliensis*) [7, 22]. In some cases, systemic candidemia may occur and is often due to *Candida albicans* though there is an overrepresentation of *Candida parapsilosis* in intravenous (IV) drug users. Oral manifestations of nutritional deficiencies may be noted as well due to a poor diet [22–27].

3 Mucocutaneous Findings by Patterns Associated with Routes of Administration

3.1 Injection

Appreciating how illicit drugs are prepared for injection can lead to a better understanding of some of the reactions and side effects experienced by people who inject drugs (PWID). Street drugs may be injected intravenously (‘mainlining’ and ‘fixing’), subcutaneously (‘skin popping’), intramuscularly, and even intra-arterially. By the time street drugs reach the user, they have often been diluted with cutting agents or adulterants to increase profits, boost or mimic the effect of the drug, and/or facilitate drug delivery [28]. Cutting agents and adulterants include commonplace products, such as flour, baking soda, sugars, caffeine, and paracetamol, or prescription drugs, such as hydroxyzine, diltiazem, phenacetin, and lidocaine. Toxic chemicals may be added, such as levamisole and xylazine. Cutting agents may introduce bacterial contaminants such as those found in soil and dust including anthrax and clostridium [29–32]. Powders, crystals, and, in some cases, tablets containing fillers such as starch, silicates, cellulose, salts, and sugars are added. The drug is then pulverized or crushed and dissolved in water, lemon juice, a

vitamin C solution, or another solvent depending on the drug being used. Once in solution, these drugs are then heated (or "cooked") with a flame to further dissolve the drug, predisposing individuals to a thermal injury from steam or burns. Once fully dissolved, the drugs are passed through filters such as cotton wool, cigarette filters, and rayon before being placed in a syringe [28]. This method of filtering drugs may further introduce insoluble particles into the bloodstream upon injection [33–38]. Finally, PWID commonly do so in the company of others and may re-use and share needles and other equipment, increasing the risk of bloodborne pathogens such as HIV and hepatitis C [39]. Moreover, many of those who use drugs often experience homelessness or have other social factors that limit their access to clean supplies and equipment [40, 41]. Not surprisingly, given all the steps outlined above, the risk of infection is great. In fact, active injecting is one the strongest risk factors for drug-related mortality. Unfortunately, PWID are 13 times more likely to die prematurely than their peers [42, 43].

3.1.1 Skin and Soft-Tissue Infections

As mentioned above, PWID are at high risk for skin and soft-tissue infections (SSTIs). In fact, SSTIs are the primary reason a PWID will visit a healthcare provider presenting as abscesses, cellulitis, and necrotizing infections [44]. A meta-analysis of injection-related injuries and infection found that the current/past month prevalence of abscesses in PWID ranges between 6.1% (95% confidence interval [CI] 4.65–7.9) and 32.0% (95% CI 25.0–39.6) [45]. Another study reported over two thirds of PWID had a an SSTI over the course of 1 year [46].

The estimated prevalence of abscesses in PWID over the course of 6–12 months is 6.1% (95% CI 4.6–9.8) and 37.3% (95% CI 34.1–40.6) [45]. Thus, it is estimated that there are around 155,000–540,000 SSTIs in the USA annually among PWID [47]. Abscesses take about 1–2 weeks to evolve and typically present as painful, erythematous, and fluctuant nodules that may be associated with fevers; first-line treatment is incision and drainage. Clinicians must also consider a pseudoaneurysm, which can be confused with an abscess in a PWID but would be pulsatile and result from an intra-arterial injection [48, 49]. Abscesses and pseudoaneurysms can easily be differentiated on an ultrasound. Pseudoaneurysms will have a pulsative flow causing turbulent forward and backward flow that can be detected with color Dopplers and contain a neck structure connecting the vessel with the aneurysmal sac [50]. Abscesses are localized fluid collections presenting as heterogenic, anechoic, or hypoechoic spherical masses with poorly defined borders. Compression of abscesses causes "swirling" of purulent contents but there is no pulsatile flow in abscesses [51].

Pathogens associated with abscesses include *Staphylococcus aureus*, although an increased incidence of oral pathogens may be seen in those who lick their needles prior to injecting [52]. *Clostridium* may occur in the skin due to germination of spores with heating of drugs prior to injection when drugs are cut with soil. People who inject drugs also have an increased risk of developing tetanus or even anthrax infections [53–58]. Some abscesses may also be sterile, and these are due to the injection of oil-based, not fully absorbed drugs that can become firm dermal or subcutaneous nodules once they heal [52].

Several risk factors have been attributed to the development of SSTIs including the use of non-sterile needles and intradermal injection ("skin popping") [55]. Skin popping is associated with a five-fold increased risk of SSTIs compared with IV administration [59]. While many abscesses can be managed in an outpatient basis, these can be a source of significant morbidity and mortality and can cause sepsis, gangrene, amputation, and even death [43, 60].

People who inject drugs are also at an increased risk of developing cellulitis. Cellulitis is an infection of the deep dermis and subcutaneous tissue and diagnosed primarily via a physical examination. The signs of cellulitis include the cardinal signs of inflammation: erythema, pain, warmth, and swelling [61]. Vesicles, bullae, ecchymoses, and petechiae may also be seen. Erythema in darker skin tones can present as violaceous, deep red/brown, or black plaques [62]. Purulence may or may not be present. Cellulitis will often have a growing ill-defined border and be asymmetric [63, 64]. Patients may experience the signs and symptoms of systemic infection, such as fevers, chills, and malaise before the onset of cellulitis.

People who inject drugs are also prone to necrotizing infections [65]. Necrotizing soft-tissue infections can involve multiple layers of the skin as well the subcutaneous tissue, fascia, and muscles [66]. Patients typically have rapidly spreading, ill-defined erythema that may look more dusky gray than red, with edema that extends peripherally and pain out of proportion to what is seen on a physical examination [42, 43]. Exudates, when present, are usually malodorous and often without purulent drainage resembling dirty dish water. Bullae and/or crepitus can also be present. Any of these signs should prompt an emergent evaluation for surgical debridement [66–68].

3.1.2 Intravenous Drug Injection

3.1.2.1 Track Marks Initially, injection sites may appear similar to the site of a blood draw, with bruising, hematoma, and/or a pinpoint hemorrhagic crust where the needle penetrated the skin. However, as many drugs can cause inflammation and infection, these areas can also appear as painful erythematous macules and papules at the injec-

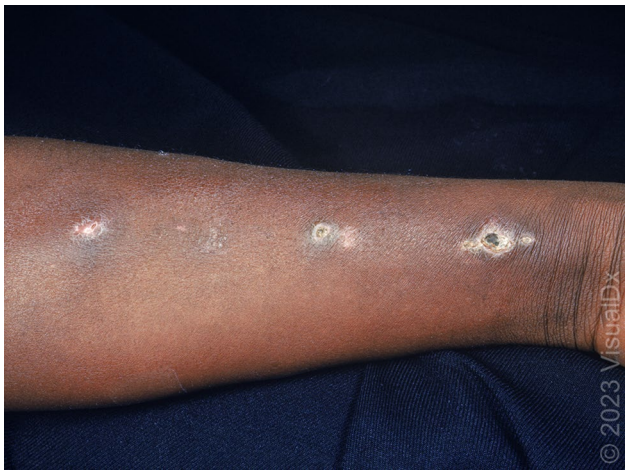

Fig. 1 Track marks. Linear fibrotic hyperpigmented plaques over veins frequently accessed for intravenous injection that are commonly seen over the antecubital fossae. Image with permission from VisualDx

tion site. Over time, these sites develop linear erythema and hyperpigmentation, eventually followed by skin and venous fibrosis and scarring from repeat injection into the same vein (Fig. 1) [69]. Thrombophlebitis may occur presenting as pain, induration, and a "cord-like" sensation on palpation of the vein involved. In septic thrombophlebitis, microorganisms invade the venous wall, producing inflammation, thrombosis, and bacteremia [70]. Track marks are ultimately a consequence of both skin and venous damage due to repeated injections, blunt and/or dirty needle use, and chemical irritation from insoluble particles in the substance being injected or irritant properties of the drug itself [71, 72]. For example, heroin is more likely to cause track marks than cocaine given increased irritant properties [73]. Track marks often are found in the antecubital fossa (usually of the non-dominant side) but can also be in the upper arms and forearms, hands, legs, dorsal feet, and less commonly the neck and groin. Patients will often inject in new areas after the initial areas of injection have collapsed, become fibrotic and painful (time-dependent progression), and/or to find new areas associated with less social stigma [74]. Some PWID resort to subcutaneous ("skin popping") injection once they have lost venous access [75, 76]. Areas of injection may also be visible after heating if a needle was sterilized with a flame, leaving a soot tattoo behind [77].

3.1.2.2 Tourniquet Hyperpigmentation Tourniquet hyperpigmentation refers to circumferential purpura, petechiae, or post-inflammatory hyperpigmentation due to tourniquets (such as belts, ties, and shoelaces) used to increase venous access during injections [9, 78]. Tourniquet hyperpigmentation is often found near track marks.

3.1.2.3 Puffy Hand Syndrome Non-pitting, edematous, erythematous hands and feet may be seen with an IV drug injection (Fig. 2A). The edema may spare the fingers and toes. Initially intermittent, edema can become chronic and unresolving with postural changes or cessation of the substance being used. The dorsum of the hands are affected to a

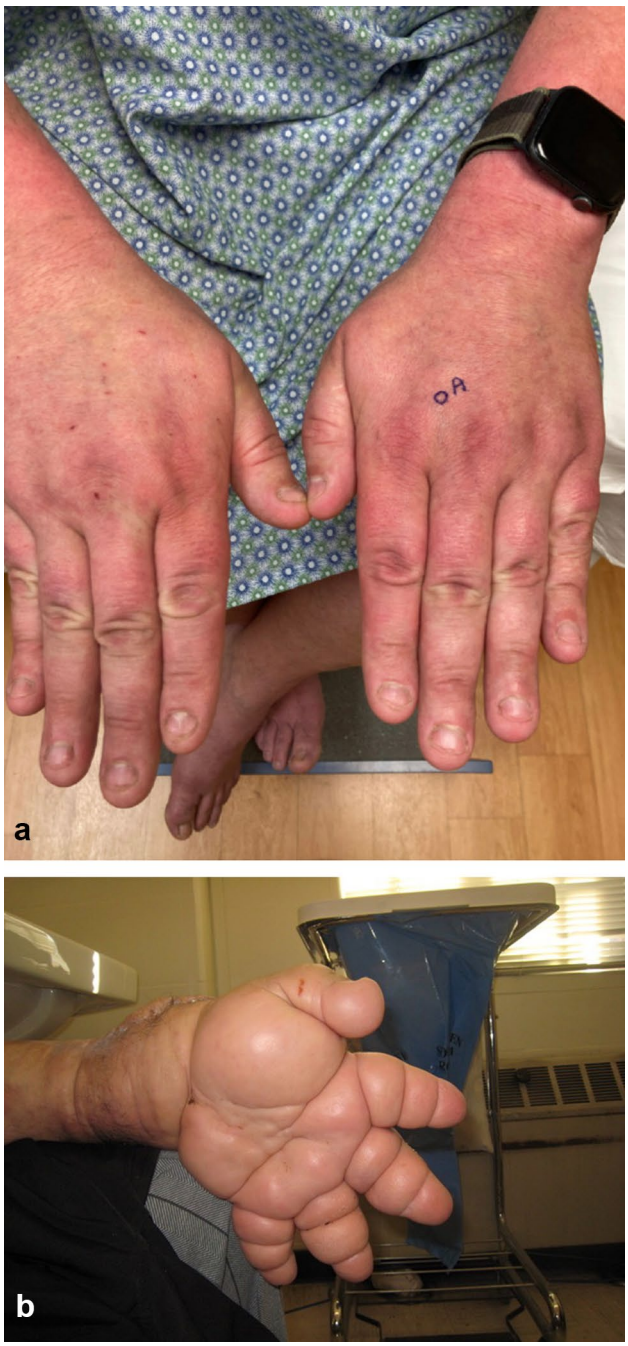

Fig. 2 Puffy hand syndrome. **A** Early phase of puffy hand syndrome with chronic edematous hands. Images provided by Daniel Nedelman, MD and Julie E. Mervak, MD. **B** Late phase of puffy hand syndrome with severely edematous hands secondary to lymphedema. Images provided by Toby Maurer

greater extent, as these are commonly injected [79]. Severe disease may involve the palmar surface as well (Fig. 2B).

The clinical findings are caused by lymphedema secondary to damage to the lymphatics due to the sclerosing properties of injected drugs or adulterants [80, 81]. Risk factors include damage to lymphatic vessels and veins, skin ulcers, thrombosis, cellulitis, and injecting drugs with adulterants that are known to cause sclerosing of the veins [80]. Being female and not using tourniquets can also increase the risk of this syndrome [82, 83]. Fibrosis of the subcutaneous tissue leading to fibrosing of the lymphatic system can be seen on a biopsy and lymphangiograms [84].

3.1.2.4 Endocarditis People who inject drugs are prone to right-sided endocarditis caused by bacterial contamination during an injection or when an injected substance contains insoluble materials [85]. While seeding of the mitral valve can occur, this is more rare. Septic microemboli can cause irregular non-tender hemorrhagic macules found on the palms and soles (Janeway lesions) or small brown lines within nails (splinter hemorrhages), as well as petechiae and painful red-purple nodules with a pale center that suddenly appear on the finger or toe pads, indicative of a vasculitis (Osler nodes) [86].

3.1.3 Intradermal or Subcutaneous Drug Injection (Skin Popping)

Skin popping is a term that is used to describe intradermal or subcutaneous administration of drugs such as cocaine, opioids, and barbiturates. This route of administration occurs accidentally if the vein is missed during an attempted IV injection or as a preferred route of administration particularly after venous access has been lost [87]. This route of administration also reduces the chances of overdosing and enhances drug effects because of a slower release into the bloodstream [28, 75]. Skin popping is associated with a five-fold increased risk of SSTIs compared with IV administration and is the greatest risk factor for SSTIs in PWID [44, 88]. Recurrent skin infections may also increase the risk of amyloid A amyloidosis in this patient population, who will present with features consistent of nephrotic syndrome [89–91]. There are no characteristic skin lesions in amyloid A amyloidosis [92]. Even when skin popping does not cause infection, the local inflammatory response can result in necrosis, ulceration, and fibrosis [93, 94]. Cutaneous signs of chronic skin popping include hyperpigmented fibrotic lesions or depressed atrophic round scars, often found in the extremities (Fig. 3) [75, 95]. Keloidal changes may be seen [96]. Skin popping sites can become ulcerated and may be used as a "shooters patch". These ulcers are characterized by a purple-tinged hue with a fibrotic texture on an otherwise healthy-appearing bed of granulation tissue.

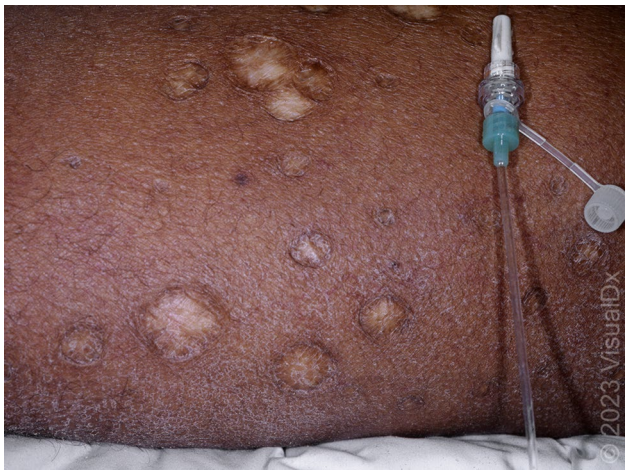

Fig. 3 Skin popping scars. Atrophic circular plaques at sites of intradermal or subcutaneous injection points, commonly seen on the extremities. Image with permission from VisualDx

Patients may lose sensation in these areas but still complain of pain for secondary gains [94, 97]. Shooters patches are often found in the upper extremities, usually in an otherwise young healthy patient. Patients may not immediately seek medical care [97].

3.1.4 Intra-Arterial Injection

Intra-arterial injection may occur intentionally or accidentally while attempting an IV or intradermal injection. Pseudoaneurysms may develop and can mimic abscesses but are pulsatile [48, 49]. Cases of IV drug injections into major arteries have also been reported [98–100]. If injected into small arteries during an attempted intradermal injection, some drugs such as cocaine can cause vasospasms and induce necrosis of digits and of the areas injected [75]. Pseudoaneurysms can be diagnosed with an ultrasound as these will have a pulsative flow causing turbulent forward and backward flow that can be detected with color Dopplers and contain a neck structure connecting the vessel with the aneurysmal sac [50].

3.2 Insufflation (Snorting)

Insufflation or snorting of substances can cause chemical irritation and inflammation of the nasal mucosa, which can manifest as chronic rhinitis or sinusitis, edema, facial and temporomandibular joint pain, dysphonia, dysphagia, anosmia, foreign body sensation, and ulceration of the nasal passages [12, 101]. Patients may present with a hyperemic nasal mucosa and recurrent epistaxis, and thus have hemorrhagic crusting along the border of the nostrils [12]. Nostrils may also become asymmetric as the chronic inflammation will

erode tissues [102]. Prolonged use can cause nasal septal and palatal perforations and may even erode the midline pyramidal bones (manifesting as a saddle nose deformity), the lateral nasal walls, and maxillary and ethmoidal sinuses. A case of erosion of the occipital bone due to cocaine has been reported [101]. Verrucae in the nasal mucosa can be an indication of insufflation and because of sharing of snorting papers or dollar bills predisposing individuals to human papillomavirus infection, although this is more of an incidental finding and usually secondary to nose picking [103]. Sharing of other utensils, such as straws, can increase the risk for other viruses, such as hepatitis C [104]. Other general signs of drug insufflation can be a white powder over the nose, or a long fifth digit fingernail, used to scoop cocaine from small bags and snort from [105].

3.3 Inhalation

Inhalants are chemicals that are often found in commonly used legal products such as glues, paints, fuels, and sprays and contain volatile agents that are intentionally inhaled for psychoactive effects [106]. Per the National Survey on Drug Use and Health, adolescents account for the largest number of inhalant users, with approximately 1.8 million aged 12 years and older having used inhalants [107]. Inhalant use can also be specific to other patient populations, such as adults with occupational access to volatile solvents, propellants, or anesthetics [108] or men who have sex with men (as the use of nitrates causes sphincter relaxation facilitating anal intercourse) [109]. Signs of inhalant use include patients having a chemical smell on the breath and/or clothes, paint or oil stains on clothing, nose, mouth, and nails, and carrying sprays, and/or chemical-soaked rags in paper or plastic bags. Inhalant use effects are short lived, but if under the influence, patients may have inattentiveness, a drunk-like behavior, gait, and speech, and display irritability, anxiety, or violence. However, presentation is most often subtle and may present as chronic headaches or a decline in academic or work performance [110]. Mucocutaneous findings associated with inhalant use include chemical-induced irritation of the ocular and oral mucosa manifesting as conjunctival injection and hyperemic nasal and buccal mucosa, rhinorrhea, cheilitis, and oral sores. Nails may also have stains from solvents used [106]. These patients may also experience chemical burns, periorificial dermatitis, and allergic contact dermatitis. Inhalant toxicity to multiple organs such as the brain, heart, lungs, kidneys, and liver can have severe consequences, including death [106, 111, 112].

The inhalation of drug vapors (smoking) is a common method of administration of recreational drugs such as methamphetamines, crack cocaine (crystalline rocks of cocaine), black tar heroin, phencyclidine (angel dust), cannabis, and *N*,*N*-dimethyltryptamine [113]. Smoking allows a faster absorption into the bloodstream through the pulmonary alveolar capillaries but may also have shorter lasting effects. Paraphernalia associated with smoking drugs include pipes, tin foil, and glass stems [113]. Incisor abrasions, periodontitis, cavities, and premature aging have also been associated with inhalation of drugs, particularly crack cocaine [12]. Additionally, crack cocaine can cause blisters, sores, and cuts on the mucosal surfaces that can increase the risk of transmission of infections, such as herpes simplex virus and HIV [114]. Blackened hyperkeratotic linear or circular lesions on the palmar aspects of the fingers and palms due to repeated burns from holding a hot glass pipe when smoking crack cocaine have been reported [115]. Other non-specific signs of smoking drugs include thermal burns on the thumb pads and second and third digits [105, 116] or in the oral cavity as erythematous ulcers and vesicle formation along the affected mucosa. Drug users can also develop madarosis or loss of the eyebrows and eyelashes due to a follicular injury from hot fumes being released during smoking [117].

4 Mucocutaneous Manifestations by Drug

Below is a summary of the mucocutaneous manifestations of recreational drug use as organized by drug. A summary of the information presented can be found in Table 1.

4.1 Cocaine (Coke, Snow, White, Flake, Blow, Crack, Bump)

Cocaine is a fine white powder that can be snorted, consumed through the oral route, or mixed with water for injection. It is also available in a more potent and addictive free-base form (crack), which comes as solid blocks or crystals that are smoked with systemic affects in seconds (compared with minutes for snorted cocaine). Cocaine can have many mucocutaneous manifestations that have been carefully summarized and reviewed [12, 18, 102] and are also summarized in Table 1. Mucocutaneous manifestations of cocaine use depend on the route of administration. These include thermal burns and madarosis. "Crack hands" refers to hyperpigmentation and hyperkeratosis of the hands due to pipe burns. Open wounds are a ground of infection, particularly for human papillomavirus, predisposing to verrucae formation [115]. Track marks, thrombophlebitis, skin abscesses, pseudoaneurysms, cellulitis, puffy hand syndrome, and neurotic excoriations can also be seen (see Sect. 3). Nail and hair changes have also been reported with cocaine use. Premature aging is common with drug use, and generalized graying and alopecia has been reported. Alopecia can be associated with malnutrition [14]. Additionally, stimulants can induce anxiety that may trigger trichotillomania in some patients [15]. Perniosis, pulp atrophy, and parrot-beaked nails should clue

Table 1 Mucocutaneous manifestations of illicit drug use by route of administration[a]

Manifestation	Description	Drugs associated with (predominant mode of administration, if known)
Cracked hands	Hyperpigmentation and hyperkeratosis of the hands due to pipe burns. Open wounds are an entry for HPV infection and verrucae formation	Cocaine (inhalation)
Thermal burns	Vesicles and ulcers in the oral mucosa Burns on the thumb pads and second and third digits, usually in the non-dominant hand Madarosis	Cocaine (inhalation, injection) Heroin (inhalation, injection)
Track marks	Erythematous hyperpigmented discoloration and fibrosis over veins	Cocaine (intravenous) Heroin (intravenous) Methamphetamines (intravenous)
Thrombophlebitis	Painful indurated, cord-like changes to veins upon palpation	Cocaine (intravenous) Heroin (intravenous) Methamphetamines (intravenous)
Skin abscesses	Painful, round, fluctuant, erythematous subcutaneous nodules	Cocaine (injection) Heroin (injection) Methamphetamines (injection)
Pseudoaneurysms	Similar to skin abscesses but may pulsate. Often differentiated from an abscess with an ultrasound	Cocaine (intra-arterial) Heroin (intra-arterial) Methamphetamines (intra-arterial)
Cellulitis	Usually asymmetric, ill-defined, painful, warm, erythematous, edematous expanding plaques. May have vesicles, bullae, ecchymoses	Cocaine (injection) Heroin (injection) Methamphetamines (injection)
Puffy hand syndrome	Edematous hands that persist despite elevation and drug discontinuation	Cocaine (injection) Heroin (injection) Methamphetamines (injection)
Neurotic excoriations	Erythematous papules with a hemorrhagic crust and excoriations, most likely secondary to formication	Stimulants such as cocaine and amphetamines
Cocaine-induced midline destruction	Erythema, erosions, and ulceration of the nasal mucosal membranes, which may necrose and form fistulas in the oropharynx, orbits, nasolacrimal ducts, and even base of the skull	Cocaine (insufflation)
Raynaud's phenomenon	Characterized by white discoloration of the digits, then turning blue as the tissue becomes ischemic, and then red as blood flow returns to the areas involved	Cocaine Cannabis
Buerger's like disease	Severe vasoconstriction will cause ulceration and atrophy of the pads of the digits	Cocaine Methamphetamines Cannabis
Peripheral arterial disease	Ischemia caused by severe vasospasm inducing pain and necrosis of digits and extremities	Cocaine Cannabis
Retiform purpura	Purpuric retiform plaques with surrounding erythema usually affecting the ears, nose, other facial regions, abdomen, and limbs	Cocaine with levamisole (injection)
ANCA-vasculitis	Appears 24–96 hours after exposure. Usually p-ANCA with pr3 positivity	Cocaine with levamisole (injection)
Perniosis, pulp atrophy, and parrot-beaked clawing of the nails	While it is not specific to crack cocaine use, this triad should alert the clinician of prolonged use	Cocaine
Long digit fingernail	For insufflation	Cocaine
Meth mouth	Gingival inflammation, caries on buccal and lingual surfaces, and enamel erosions at the gingival margins	Methamphetamines General drug use
Skin picking sores	Prurigo nodules, erythematous erosions and ulcers, some with a hemorrhagic crust or secondary infection distributed throughout the body, including the face	Stimulants such as cocaine and amphetamines
Skin popping scars	Hyperpigmented fibrotic lesions or depressed atrophic round scars, often found in the extremities	Cocaine(intradermal and subcutaneous) Opioids (intradermal and subcutaneous) Barbiturates (intradermal and subcutaneous)

Table 1 (continued)

Manifestation	Description	Drugs associated with (predominant mode of administration, if known)
Urticarial lesions	With predilection to the face and genitals	Heroin
Velvety hyperpigmented patches on axillae and neck	May be confused with acanthosis nigricans	Heroin
Fixed drug eruptions	Violaceous erythematous patch/plaque that will present in the same location after exposure to the drug	Heroin Cocaine
Necrolytic migratory erythema	Erythematous painful eczematous or psoriasiform erythematous papules that will coalesce to form arcuate plaques with a scalloped border. Not associated with glucagonomas	Heroin
Angular cheilitis	Cracking and irritation of the mouth corners	Cocaine (inhalation) Hallucinogens (inhalation) Other inhalants
Perioral dermatitis	Diffuse facial papules and pustules in perioral distribution without comedones	Hallucinogens Other inhalants
Conjunctival injection	Redness in the conjunctiva	Cannabis
Arteritis and vaso-occlusive changes	Peripheral necrosis of the peripheral appendages	Cocaine Cannabis
Erythema with periodontal disease	Predilection for gingivitis and gingival hypertrophy increased caries increased risk of candidiasis Broken teeth (such as incisors in cocaine)	Cocaine (inhalation) Cannabis (inhalation)
Retiform purpura	Reticular purpuric plaques with necrosis on the ears, face (particularly nasal tip) and abdomen though extremities are often involved as well	Levamisole (injection)
Pyoderma gangrenosum-like lesions	A pustule appears that then ulcerates and becomes necrotic with a dusky violaceous border. Predilection to the face, ears, and trunk	Levamisole (injection)
Xylazine-induced skin changes	Progressive large, necrotic ulcers that may be raw and erythematous or have dark brown eschars May be in sites distant from injection ANCA negative	Xylazine (injection)

HPV human papillomavirus

[a]For references, please refer to the text

the physician on prolonged use of crack cocaine, although not specific for cocaine use [118]. Last, some patients may have a long digit fingernail that can be used for insufflation of cocaine [18].

Raynaud's phenomenon, Buerger's-like disease, and peripheral artery disease have also been reported [12, 102]. These are likely due to the vasoconstrictive effects of cocaine. Similarly, cocaine can induce midline destruction (Fig. 4). This can present as erythema, erosions, and ulceration of the nasal mucosal membranes, which may necrose and form fistulas in the oropharynx, orbits, nasolacrimal ducts, and even the base of the skull [101]. Cocaine is also often adulterated with substances such as levamisole, which can cause classic retiform purpuric plaques with surrounding erythema that usually affect the ears, nose, other facial regions, abdomen, and limbs (see Sect. 5). p-ANCA vasculitis double positive for anti-myeloperoxidase and anti-proteinase 3 can be seen in the setting of cocaine use that has been adulterated with levamisole and rarely seen in other settings [119]. Importantly, anti-myeloperoxidase titers can also be several fold higher than those with idiopathic vasculitis and are associated with leukopenia. Clinical presentations can be varied, but the most common clinical manifestation is pain in the large joints with systemic symptoms such as fever, sweats, and malaise. Cutaneous lesions can range from necrotic and purpuric plaques to abscesses to ecchymotic bullous lesions [119, 120]. Patients present with rhinorrhea and/or midline destruction could have a necrotizing and crescenteric glomerulonephritis as well as a pulmonary hemorrhage, suggesting granulomatosis with polyangiitis [119–121]. However, those with granulomatosis with polyangiitis will have more pronounced constitutional symptoms and a more marked elevation of markers of chronic disease than those who have cocaine-induced midline destruction [119]. Scleroderma and systemic sclerosis has also been associated with cocaine use. Patients can present with a predominantly vascular

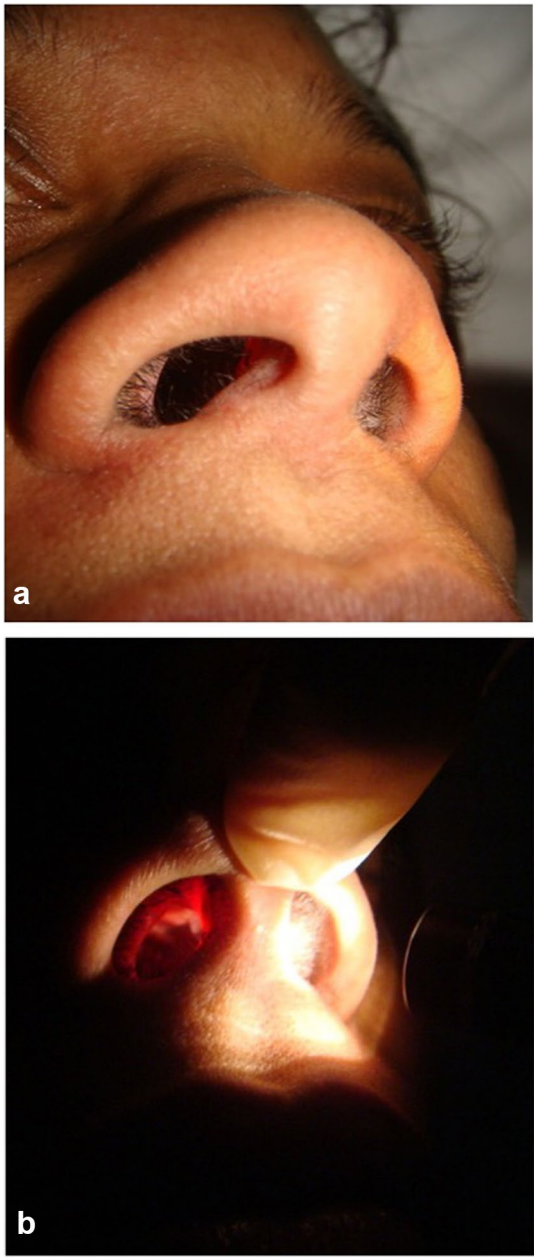

Fig. 4 Cocaine-induced midline destruction of nasal septum. **A** Septal perforation without back light. **B** Septal perforation with back light in opposite nostril to better visualize the septal perforation. Images provided by Ginat W Mirowski, DMD, MD

involvement, such as with Raynaud's phenomenon but mild or absent esophageal or lung involvement. Anticentromere antibodies or anti-Scl70 antibodies may or may not be present but a renal biopsy aids in diagnosis. The pathogenesis of the association between sclerosis and cocaine use and whether this could also be caused by levamisole contamination remain uncertain [122].

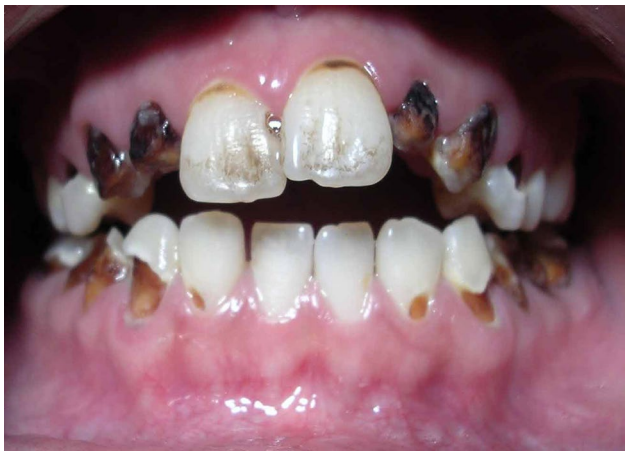

Fig. 5 "Meth Mouth" characterized by gingival inflammation, excessive cavities, and enamel erosions and the gingival margins. Image by Dozenist (assumed), "Suspected meth mouth 09-19-05" distributed under CC BY-SA 3.0

4.2 Methamphetamine (Meth, Speed, Chalk, Ice, Crystal Meth, Crank, Glass)

Methamphetamine is a stimulant that leads to euphoria and alertness, but also anxiety, psychosis, and hallucination. It is the third most commonly used drug worldwide second to cannabis and opioids [123]. In addition to the toxic effects of the drug itself, production of methamphetamine from readily available precursor materials includes toxic and flammable processes, leading to thermal and chemical burns often in clandestine home laboratories (though patients presenting with such burns will typically attribute burns to accidents with cooking of food) [124, 125]. Methamphetamine comes as a powder, tablet, or crystals and can be ingested via smoking, insufflation (snorting), injection, swallowing, or via anal or vaginal suppositories. Common general findings include premature aging, xerosis, pruritus with associated prurigo nodules, and hyperhidrosis. Formication leading to skin-picking behaviors, particularly over the face, can be seen and may be associated with hallucinations that there are bugs under the skin [126]. Given the frequent use of the IV route of administration, methamphetamine is associated with SSTIs including cellulitis and abscesses [127].

A classic mucosal finding among methamphetamine users is "meth mouth," which presents with gingival inflammation, caries of the buccal and lingual surfaces (a four-fold increase above the general population), and enamel erosions at the gingival margins (Fig. 5) [128, 129]. This pattern of caries and enamel erosions is atypical in adults and may be the reason these patients ultimately seek medical or dental care [130]. Pabst et al. have reviewed the clinical presentation of meth mouth and jaw necrosis [131]. Meth mouth is thought to be caused by decreased saliva production and output

resulting in xerostomia, as well as bruxism (teeth-grinding) that leads to increased wear patterns and cracked teeth, increased consumption of sugary beverages and snacks, and overall poor dental hygiene [132, 133]. Tooth loss correlates with the number of years of methamphetamine use [134]. Interestingly, no one particular route of administration is more associated with meth mouth [132]. It should be noted that the common features of meth mouth are not necessarily specific to methamphetamine use and may be seen with the use of other illicit drugs [23].

4.3 Heroin (Smack, H, Ska, Skag, Junk, Brownstone)

Heroin is an opioid that is made from morphine. It comes in a fine white powder, or a sticky substance called "black tar". It can be insufflated (snorted), smoked, or dissolved in water and heated for injection and can cause several cutaneous findings [135]. As discussed previously, PWID may develop abscesses and soft-tissue infections, track marks, puffy hand syndrome, pseudoaneurysms, cutaneous findings of skin popping, and shooters patches [28, 43, 48, 49, 60, 75, 78, 79, 94, 97]. Granulomas may also form because of additives and impurities in the substance being injected [136]. About 4% of heroin users will also experience a "high itch" associated with urticarial lesions that can last several days and that have a predilection for the face and genitals [96]. Itch can cause neurotic excoriations and ulcers.

Some patients may present with velvety hyperpigmented patches on the axillae and neck, often confused with acanthosis nigricans [78]. Others have reported cases of fixed drug eruptions due to heroin use, which presents with a violaceous erythematous or hyperpigmented patch/plaques that will present in the same location after exposure to the drug [78, 137]. Similar cases have been reported for ecstasy [138] and cocaine [139]. Heroin can also cause toxic epidermal necrosis, which presents with sloughing of the mucosa around the mouth and necrosis of the skin, and a necrolytic migratory erythema that is not associated with glucagonomas [96]. In necrolytic migratory erythema, subjects will present with erythematous, painful, eczematous or psoriasiform erythematous papules that will coalesce to form arcuate plaques with a scalloped border [140].

4.4 Hallucinogens

Non-specific findings in those who use hallucinogens include angular cheilitis secondary to xerostomia caused by these drugs and/or jaundice and icteric sclera due to hepatotoxicity [17, 141]. Use of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy, Molly) has been reported to cause a perioral dermatitis presenting as diffuse facial papules and pustules in perioral distribution without comedones [142]. Persons using MDMA may experience bruxism and trismus potentially related to serotonin; reports of wearing candy necklaces and pacifiers to mitigate jaw clenching have been described [143–146].

4.5 Cannabis (Marijuana, Pot, Weed, Grass, Ganja, Mary Jane)

Cannabis is the most commonly used recreational drug resulting in euphoria followed by drowsiness, slow reaction time, and an increased appetite [2]. Recreational and medicinal use has grown with legalization in some states over the past years and reports of potential benefits in dermatologic conditions [147], though federal laws continue to define marijuana as illegal. The dried leaves are typically smoked in cigarettes, pipes, or cigars (joints, bongs, and blunts, respectively), but may be cut or mixed with other drugs. Edible forms are also available. General mucocutaneous findings include xerostomia and dry eyes [148]. Rare cutaneous manifestations include arteritis and vaso-occlusive changes with peripheral necrosis of lower limbs due to vasoconstrictive effects. Similar findings can also present in the hands with Raynaud's phenomenon and/or ulcer formation with digital necrosis [149]. Diagnostically, a duplex ultrasound can differentiate between cannabis arteritis and atherosclerosis [150]. Treatment consists of cannabis cessation and daily aspirin 81 mg, which can lead to resolution [151]. Mucosal findings include xerostomia and/or erythema with periodontal disease including gingivitis and gingival hypertrophy, increased caries, and increased risk of candidiasis similar to what is seen with other illicit drugs [26, 152].

5 Mucocutaneous Manifestations of Impurities, Cutting Agents, and Adulterants

Illicit drugs often lack purity and contain other substances owing to processing, cutting agents (typically inert substances used to add bulk to the product), or adulterants (psychoactive agents added to enhance effect or delivery). Cutting agents are additional substances often added to illicit drugs to increase volume and reduce the cost, added intentionally during processing. These agents are often inert substances with similar visual properties to the drug itself to camouflage their presence (same color or texture) [153]. Cutting agents include a variety of common substances such as sugar, flour, talc, dirt, and magnesium salts among others. While some (sugars, for example) have little clinical toxicity, others can cause foreign body granulomas (talc) or infections (dirt) after injecting drugs cut with these substances.

The term adulterant typically refers to a substance that is pharmacologically active. Adulterants are added to illicit drugs intentionally to enhance drug effect or delivery.

Examples of adulterants are numerous and include quinine, lidocaine, amphetamine, caffeine, heroin, scopolamine, hydroxyzine, diphenhydramine levamisole, and xylazine. Levamisole and xylazine are increasingly common adulterants with a growing recognition of severe cutaneous manifestations.

5.1 Levamisole

Levamisole is an antiparasitic medication typically used in livestock. While previously used in humans for oncologic and autoimmune conditions, levamisole caused neutropenia, agranulocytosis, and vasculitis and was ultimately withdrawn from the US market in 1999 [154, 155]. Levamisole is being increasingly added to cocaine and was detected in 70% of seized cocaine in 2009 compared with 30% in 2008 [156, 157]. The first reports of retiform purpura and vasculitis/vasculopathy with levamisole tainted cocaine were published in 2003; these cutaneous findings are now a well-recognized phenomenon with a fairly distinct cutaneous presentation of retiform purpura with necrosis on the ears, face (particularly nasal tip), and abdomen, though extremities are often involved as well (Fig. 6) [158–160]. A biopsy of such lesions showed combined features of vasculitis and thrombotic vasculopathy with occlusion of vessels and immunofluorescence showing deposition of IgG, IgA, and C3 in vessels of the superficial dermis [161, 162]. A laboratory evaluation is significant for positive anti-nuclear antibodies, antiphospholipid (lupus anticoagulant), and ANCAs. Among cases complicated by cutaneous findings, ANCAs were positive in nearly 80% of cases (most often p-ANCA) [159]. Cutaneous and laboratory findings typically resolve within 2–3 weeks of cessation in the absence of re-exposure. Additional cutaneous manifestations of levamisole tainted cocaine such as pyoderma gangrenosum-like lesions have been reported alone or in combination with the more classic retiform purpuric lesions [163, 164]. Pyoderma gangrenosum-like presentations present most commonly on the extremities and may also be associated with p-ANCA [164]. A high index of suspicion is necessary as the short half-life of levamisole makes it difficult to capture on testing.

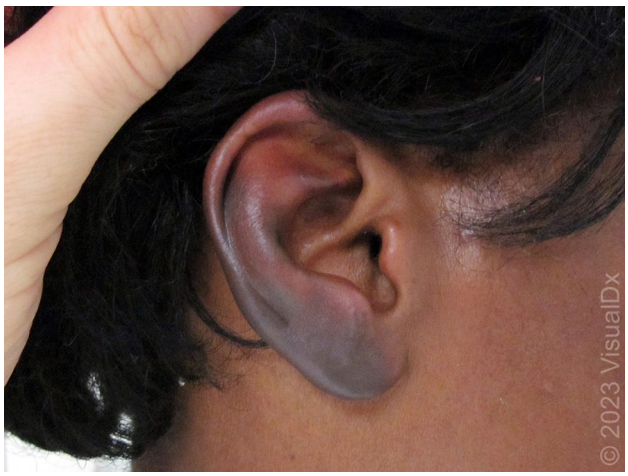

Fig. 6 Levamisole-induced retiform purpura. Retiform purpuric plaques associated with levamisole-tainted drugs (most frequently cocaine) commonly seen on the bilateral helices, nasal tip, face, and extremities. Image with permission from VisualDx

5.2 Xylazine (Tranq)

Xylazine is an alpha-adrenergic receptor agonist with vasoconstrictive properties used as a sedative (or tranquilizer) and pain reliever in veterinary medicine. Although having similar effects to opioids, it is not an opioid and effects are not reversed by naloxone; there is no known antidote [165]. Symptoms include coma, apnea, bradycardia, and hypotension. Xylazine tainted fentanyl and heroin ("Tranq Dope") is being increasingly detected in the illicitly manufactured fentanyl supplies across the USA after early identification in hotspots including Puerto Rico (2001) and Philadelphia (2006) where up to 90% of fentanyl is contaminated with xylazine [166, 167]. There is also an increase in deaths due to an opioid overdose when xylazine is detected [168]. While initially added as a bulking agent, xylazine is thought to enhance and prolong the effect of opioids. Xylazine can also be added to cocaine ("speedball"), which is more common in Puerto Rico [169, 170]. Numerous cutaneous manifestations of xylazine have been reported that range from ulcers (Fig. 7A) to necrotic

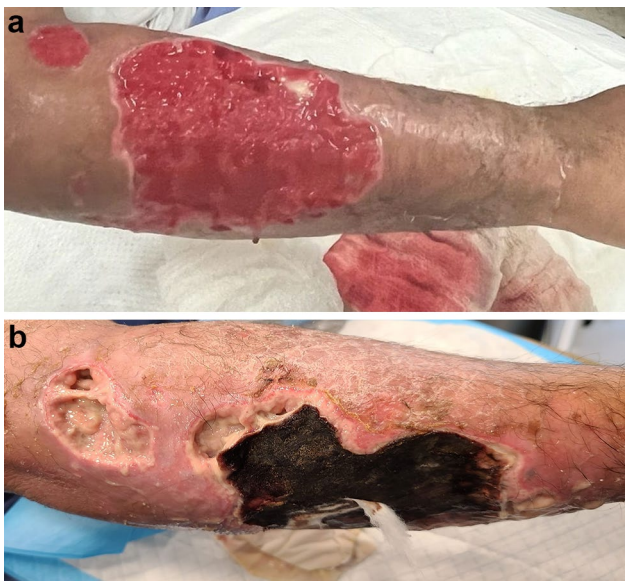

Fig. 7 Xylazine-induced ulcers. Wide, large, erythematous, non-healing ulcer (**A**) or erythematous ulcer with necrotic eschar (**B**). Images provided by David Lehmann, MD and Jeana Marraffa, MD

eschars (Fig. 7B), sometimes in a background of retiform purpura at the sites of injection but also remote to the site of injection [166, 171–173]. These cutaneous findings are likely a result of the vasoconstrictive effects of xylazine. Biopsies do not typically show vasculitis with mixed reports of thrombi/vasculopathy. Antiphospholipid and ANCAs are typically negative [171]. Xylazine is not detected on toxicology screens and is rapidly eliminated from the body, making it difficult to detect even with specialty testing [165].

The clinical consideration and management of xylazine overdoses have been addressed elsewhere [174]. Briefly, because of the overlap in presentation between xylazine and opioids, naloxone should be administered. Patients who do not respond or are partially responsive to naloxone should prompt consideration of xylazine intoxication or a mixed overdose. Respiratory rate and miosis improve, but if the mental status remains unimproved, then supportive care should be initiated. With regard to wound care, it is imperative that patients stop injecting the drug for healing. As expected, there is a risk of superinfection and thus the wound must be kept clean, moist, and covered at all times.

6 Resources for Substance Use Disorder in the USA

There are many resources within the USA that can help those with substance use disorder. These include hotlines, support groups, treatment centers, therapists, community-based organizations, educational programs, recovery coaches, and sober companions and even online recovery applications.

A national, 24/7, free confidential hotline that can assist families and individuals with substance use disorder to connect with local treatment facilities, support groups, and community organizations is provided by the Substance Abuse and Mental Health Services Administration (SAMHSA) [175]. The hotline's number is 1-800-662-HELP (4357).

Some hospitals may have addiction services for their patients or psychiatrists and therapists trained in helping those with drug use disorders. Some licensed healthcare providers may be able to even prescribe medication that can aid drug use disorders, such as methadone, suboxone, and naltrexone. Treatment centers can provide detoxification services and counseling, as well as support. Some organizations offer virtual and physical meetings held in different languages and cultures all around the world, such as Narcotics Anonymous [176]. Insurance companies and Medicaid could provide coverage for drug addiction services and programs. Employee assistance programs are also available to provide referrals and counseling for patients with substance use.

7 Conclusions

Mucocutaneous manifestations of illicit drug use may be non-specific or uniquely characteristic depending on the route of administration, specific drug, or adulterant. Improved recognition of these mucocutaneous manifestations can lead to better identification and treatment of this patient population and allow physicians to connect these patients to appropriate resources for addiction and dependency.

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Consent to Participate Not applicable.

Consent for Publication Not applicable.

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Authors' Contributions CVA, GWM, and DAC contributed to the literature review and writing of the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for the work as presented.

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