



Review article

The harmful chemistry behind krokodil (desomorphine) synthesis and mechanisms of toxicity



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ABSTRACT

“Krokodil” is the street name for the homemade injectable mixture that has been used as a cheap substitute for heroin. Its use begun in Russia and Ukraine and nowadays is being spread over several other countries. Desomorphine is the semi-synthetic opioid claimed to be the main component of krokodil and considered to be responsible for its psychoactive characteristics. The starting materials for desomorphine synthesis are codeine tablets, alkali solutions, organic solvent, acidified water, iodine and red phosphorus, all of which are easily available in retail outlets, such as supermarkets, drugstores, etc. The resulting product is a light brown liquid that is called krokodil. People who inject krokodil present a great variety of serious signs and symptoms, including thrombophlebitis, ulcerations, gangrene, and necrosis, quickly evolving to limb amputation and death. These effects are thought to result from the toxic components produced as byproducts during the homemade drug synthesis.

In this work, we reviewed several aspects of krokodil use, including its epidemiology, pharmacology and the chemical properties of the main active ingredient (desomorphine). To enhance our understanding of the clinical and toxic effects and to support the implementation of harm reduction measures, we also describe the “bathtub chemistry” of krokodil and the content of the final solution.

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1. Introduction

“Krokodil” is the street name for an injectable drug mixture, which is used as a cheap substitute for heroin and was first observed in Russia and Ukraine around 2002/3. Krokodil is obtained from codeine tablets in a simple bootleg process aimed to synthesize desomorphine. Media reports suggest that krokodil is about five times cheaper than heroin [1,2]. In Russia, krokodil is also known as “Russian magic”, “croc” or “krok” [2,3]. The name krokodil is derived from the typical scaly green colored skin injuries associated with continued use, resembling a crocodile (krokodil in Russian) skin [3–5]. Russia, Ukraine and Georgia seem to be the countries most affected by krokodil use.

Because of its recent emergence, and, in particular, the dramatic consequences associated with this drug concoction, it is important to understand the epidemiology of krokodil use, the pharmacology of the main active substance (desomorphine) and the synthesis method of krokodil. Such information is highly relevant for the implementation of preventive measures for reducing krokodil use and the reported toxic effects. The present review highlights these different aspects of this harmful drug. To achieve our goals, articles written in English, French and Germany were searched in the National Library of Medicine’s PubMed MedLine database and Web of Knowledge using key words such as “croc”, krokodil, “home-made drug”, “flesh eating drug” and “desomorphine”. Web sites and YouTube videos related to krokodil use were also reviewed.

2. Epidemiology of krokodil use

According to the European Drug Report [6], 0.41% of the European population is addicted to opioids, mainly heroin. In Asia, this prevalence is not so different, especially in Asian parts of Russia, Laos, Afghanistan and Myanmar [7]. Russia, Ukraine and all other former Soviet Republics share a long history of injectable drug use [2]. In Russia, 2.3% of the population is injecting drugs, especially opioid derivatives. This percentage reflects the proximity to Afghanistan, the major world opium producer. The Russian government recognizes that it is very difficult to control all the borders due to their extension. Afghan heroin usually crosses the Russian borders inside trucks passing through cities and smaller communities; finally the drug is sold in clandestine street markets.

Heroin is not easily available in Ukraine and therefore home drug production remains a common source for injectable opioids [8]. In Eastern Europe countries, especially Georgia and Ukraine, drug users switched to homemade drugs such as krokodil, due to the cost of heroin. Indeed, media reports suggest that 5% or more of Russian drug users may be injecting krokodil [2]. The homemade krokodil is prepared almost the same way as methamphetamine [2] making this transition not unexpected once methamphetamine seems to be spreading through Russia Federation and Poland [7].

The first case of krokodil use was reported on the North-East of European part of Russia in 2002, and since then it spread over Russia and some of the neighboring former Soviet Republics. Krokodil appeared in the Russian drug market in 2003, associated with the decreased availability of Afghan heroin in local drug markets [2,9]. In 2012, it was estimated that around 100,000 people used krokodil in Russia and around 20,000 in Ukraine [2]. At this time point, Russia and Ukraine seem to be the most affected countries by the use of this drug, but several cases were also

reported in Georgia [10] and Kazakhstan [11]. Russia banned over-the-counter codeine sales on June 1, 2012 and that legislative document sharply reduced the use of krokodil, but codeine has been reportedly moved onto the black market [12].

Krokodil was firstly described in USA (Chicago) in 2011 [13]. According to the physician responsible for the case, patients were not aware of being using krokodil. Thekkemuriyi et al. [5] reported a case of a 30-year-old heroin addicted man was treated in a hospital in St. Louis for a painful necrotic ulcer and auto-imputed fingers after 6–7 months of krokodil use. He admitted a unique exposure because he had not enough money to buy his regular diary dose of heroin. A possible case was described in German in 2011 by Gahr et al. [3]. Dermatological lesions, typical for krokodil use, were observed in four heroin users. It was assumed that they were using heroin contaminated with krokodil. Lemon [14] described the first UK case, when a girl from Romania was hospitalized with krokodil symptoms. It is believed that the use of krokodil spread to Poland, Czech Republic, France, Belgium, Sweden, Norway and other European countries with Russian immigration [15].

3. Chemical properties of desomorphine

The main active substance of krokodil is referred to be a semi-synthetic opioid derivative from morphine, called desomorphine ($C_{17}H_{21}NO_2$, dihydrodesoxymorphine) (Fig. 1). Chemically, desomorphine is a white to light beige solid at room temperature, with a molecular weight of 271.35 g/mol and a melting point of 189 °C. It is a stable powder when stored under adequate conditions and an organic base, like other opioids. The protonated form has a pKa value of 9.69 and it is therefore ionized in a biological environment. Desomorphine is only partly soluble in water (1.425 g/L at 25 °C) as a free base, while in salt form, is highly water soluble [16]. Desomorphine was first synthesized in the USA in 1932 by Small et al. [17] as a demonstration of a process of catalytic hydrogenation of halogenocodides to obtain morphine derivatives [3]. Desomorphine may be synthesized from codeine and it differs from morphine only by the lack of a hydroxy group and a double bond (Fig. 1). This structural difference allows an increased activity of desomorphine when compared to codeine and even morphine [18,19]. The elimination of the alcoholic hydroxyl group gives desomorphine the same toxicity and increased analgesic action compared to morphine [17].

4. Synthesis of krokodil

The process of krokodil synthesis is almost identical to that of methamphetamine synthesis from ephedrine [20,21] consisting of a simple extraction and reduction to obtain the opioid derivative. This reduction process is known as the Nagai route and is based on a reduction method using hydriodic acid (HI) and red phosphorus as reagents [21]. This synthetic route is preferred in the Asian and South Asian regions and in Australia in commercial illicit methamphetamine production [21–23]. Krokodil is obtained using codeine as a starting material, which is usually sold in the pharmaceutical market in the form of tablets, mixed with other substances such as paracetamol, acetylsalicylic acid and, in some cases, caffeine. The process needs very little equipment and involves two steps (Fig. 2):

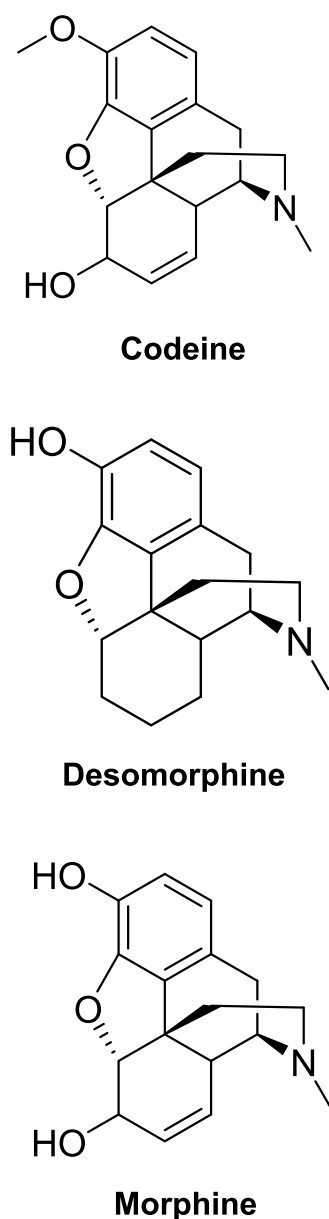


Fig. 1. Chemical structures of codeine, morphine and desomorphine.

a) *Extraction of codeine from the tablets*: Commercial codeine is a salt, usually a phosphate salt. About 10 codeine tablets (about 80–400 mg of codeine) are pulverized and mixed with a strong base solution, most commonly sodium hydroxide to obtain codeine free base, which is then extracted to the organic layer. The water soluble compounds associated with codeine in the tablets are washed away in this step. Codeine is then back-extracted to the aqueous layer as a hydrochloride salt after the organic extract is vigorously mixed with acidified (HCl) water. In the laboratory, this extraction is a straightforward process, but people who inject drugs (PWID) use low cost compounds available in supermarkets and hardware stores. The strong base used is usually a commercial product for cleaning drains and sewer pipes containing strong alkalis such as sodium hydroxide (Krot™, Drano™). The organic solvent is usually gasoline, although some users reported to use paint thinner [2]. The acidic solution is usually hydrochloric acid obtained from batteries or from industrial products. The aqueous solution containing codeine may be directly used in the subsequent step or codeine may be extracted or dried using acetone or heating.

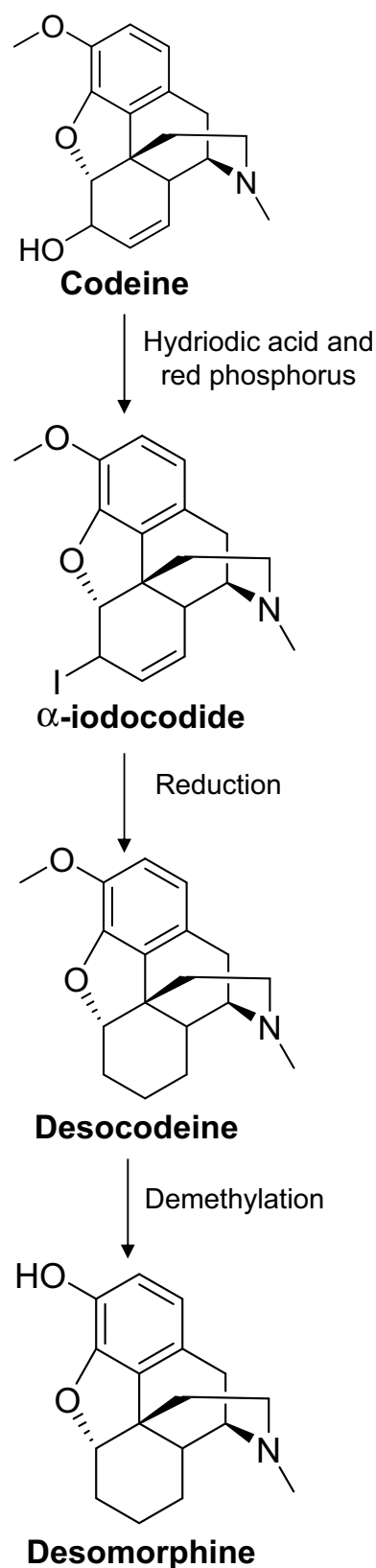


Fig. 2. Synthetic pathway for the production of desomorphine from codeine tablets.

b) *Reduction of codeine to desomorphine*: Codeine is mixed with iodine, water and red phosphorous in a glass or other container and the resulting mixture is heated, producing hydriodic acid, a very strong acid that has been used to reduce carbonyl groups,

nitriles, halides, and alcohols for more than 100 years [20,23,24]. The reduction process occurs using hydriodic acid alone or iodine and red phosphorus that form hydriodic acid *in situ*. The role of phosphorus is to convert back the molecular iodine formed during the reaction to hydriodic acid [23]. The reduction involves a cyclic oxidation of the iodide anion to iodine and reduction of iodine back to the iodide by red phosphorus that is converted to phosphorous or phosphoric acid [24]. This step allows the cleavage of the methoxy group of codeine to form a hydroxyl group because when ethers are treated with a strong acid in the presence of a nucleophile, they can be cleaved to give alcohols and alkyl halides. Hydriodic acid is also capable to introduce an iodide molecule in the codeine ring, forming an alkyl halide that should be reduced after this step. This is not difficult because iodide is a large leaving group and a very stable anion. The raw materials employed are also easily recovered from household products. Iodine is extracted from medical solutions or used as crystals and red phosphorous is usually obtained from matchboxes.

According to krokodil cooks, the drug is ready to be injected after approximately 45 min, when the mixture has changed color (from an opaque purple to a transparent brown to light yellow) and odor. Darker brown colors are probably the result of remnants of iodide ions [24], but there are some users claim to obtain clear solutions.

The resulting krokodil mixture has a strong acidic pH. Some users report the use of cigarette ashes or sodium bicarbonate to increase the pH value of the mixture, but this may not be enough to increase it above 3 [2].

5. Quantification of desomorphine

Although there is scarce pharmacokinetics data, after krokodil administration, desomorphine may be detected in blood samples for couple of hours and in urine for 2–3 days [25]. Desomorphine may be detected using GC/MS and derivatization after an extraction step such as the SPE methodology.

Savchuk et al. [26] quantified codeine and synthetic analogs of codeine, including desomorphine, in biological samples, by gas chromatography–mass spectrometry (GC/MS), using different derivatization reagents such as trifluoroacetic anhydride (TFAA), *N,O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) and *N*-methyl-bis trifluoroacetamide (MBTFA); mass spectra were obtained for all derivatives. The derivatives were also determined by liquid chromatography with ultraviolet detection (HPLC–UV) or thin-layer chromatography (TLC) techniques. Srimurugan et al. [27] reported a simple method of desomorphine synthesis and their respective deuterium-labeled analog, using GC/MS as a confirmatory technique. Recently, Su et al. [28] developed a solid-phase dynamic extraction–gas chromatography–mass spectrometry (SPDE–GC–MS) method using sol–gel titanium film coated needles for the detection and determination of desocodeine and desomorphine at trace levels in urine samples. This sensitive method showed a low limit of quantification and a wide linear range [28].

6. A mixture of alkaloids

Whether the “bootleg” chemistry described above effectively produces desomorphine and the actual content of the krokodil mixture remain important questions. Few scientific reports on the chemical composition and contaminants of krokodil have been published.

Although desomorphine is said to be the main component of krokodil, there is no information about the other compounds

present in the injectable solution. Mosettig et al. [29] described the synthesis of desomorphine from codeine using an acetic acid solution, and α -chlorocodide as an intermediary. The first step is transformation of codeine into α -chlorocodide using thionyl chloride and subsequent reduction to produce desocodeine and, finally, a desmethylation to produce desomorphine (Fig. 2) [29]. Srimurugan et al. [27] described desomorphine synthesis from codeine using tosylation and mesylation with high yield and purity without posterior purification. Savchuk et al. [26] analyzed washouts from cotton wool tampons obtained after a krokodil purification, and washouts from used syringes, liquid residues from syringes and urine samples from krokodil users. The authors reported the presence of methyl-desomorphine, dihydromorphine-3,6-dideoxy, morphinan-4,5-epoxy-3-ol and dihydrodesomorphine, four synthetic analogs of desomorphine, codeine and other compounds. These results suggest that krokodil actually contains desomorphine, along with other synthesis intermediates, depending on the skills of the manufacturer and the starting materials available. Codeine is always associated with other compounds in the available raw materials and the influence of these compounds upon the chemical reactions that produce desomorphine is not known.

7. Pharmacology and toxicology of desomorphine

The pharmacological action of desomorphine was first reported in 1934 [30]. Being an opioid, it has central analgesic properties as a μ opioid agonist [31], produces pain relief, respiratory depression [32], emesis, constipation, physical dependence and sedation [18] and is a powerful muscle relaxant; it is also capable to cause euphoria and sedation. The analgesic effect of desomorphine is approximately 8–10 times greater than that of morphine [18]. The drug has a short onset of action and its effects are not prolonged with dose increases [33]. The effects last only 2 or 3 h and thus last significantly shorter than morphine or heroin. Dependence and tolerance are also phenomenon that occurs with a continuous desomorphine use. The ability to produce tolerance has relation with the ability of opioids to induce the internalization of the opioid receptor (μ). Receptor μ internalization is stimulated by phosphorylation of the receptor's carboxyl-terminal cytoplasmic domain, especially in a cluster of three serine and threonine residues within the cytoplasmic tail of the receptor [34]. This phosphorylation occurs in multiple sites and has different profiles to different opioids. Multi-site phosphorylation can effectively sharpen drug-dependent differences in regulated endocytosis of receptors and may explain the differences between drug actions of different opioids and their capacity to cause dependence and tolerance [34].

Desomorphine was used for pain relief in Switzerland under the trademark Permonid[®] between 1940 and 1952, when, due to its addictive potential and high risk of respiratory depression, it was banned from the Swiss market [3].

Interestingly, Wright and Sabine [35] reported desomorphine as a potent cholinesterase inhibitor when they compared the cholinesterase inactivation of morphine, dilaudid, codeine and desomorphine. Desomorphine was the most effective inhibitor of both plasma and brain human cholinesterase suggesting the binding site to be a preserved region of the protein [35].

The LD₅₀ for intravenous injections of desomorphine in rats has been reported to be 27 mg/kg, compared to 22 mg/kg for heroin, 300 mg/kg for codeine and 226–318 mg/kg for morphine. The chemical, physical, and toxicological properties of desomorphine have not been thoroughly investigated [36], nor have their interactions with (homemade) synthetic stimulants, which are often combined with opioids.

8. Signs and symptoms of krokodil exposure

Krokodil is mostly injected intravenously and, in an effort to avoid arrest or stigma [2,37], often in veins in less overt locations, such as the armpit or femoral artery [38]. The clinical manifestations presented by the krokodil consumers are reportedly devastating. The first (visible) physical signs of krokodil related harms concern skin and venous damage, including ulcers and phlebitis at and around the injection sites. The skin may become iridescent and discoloration may occur, followed by desquamation. Repeated or regular use may turn the skin around the injection site scaly and rough, like a crocodile skin [31], while gangrene and limb amputations may occur with continued use (Fig. 3A–D) [2,5,13,16,39]. In the maxillofacial area, jaw osteonecrosis was recently reported (Fig. 3E) [40]. This is characterized by pain, exposure of the alveolar process of the jaws (92.2% of cases) [41], swelling of the surrounding soft tissues and intra- and extra-oral fistulas in the affected area [40,42,43]. Table 1 summarizes the most common effects of signs and symptoms presented by krokodil users. Some authors have also reported neurological damage, such as speech impediments, motor skill impairments and reduced memory and concentration [2]. Neurological harms may be present without or before the occurrence of obvious physical damage [12].

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection rates among PWID in the countries with the longest histories of krokodil use are extremely high. In Russia PWID were approximately 75% of the more than 650,000 HIV infections in 2011 [44]. The reported number of cases of HIV

Table 1

Toxic effects related to krokodil exposure [3,5,39,46,56].

Local toxic effects

Abscesses, gangrene, thrombophlebitis, limb ulceration and amputations, jaw osteonecrosis, skin discoloration, black and open ulcers, necrosis, skin and soft tissue infection, necrosis, bleeding, rotting gums and ears, scabs, popped skin lesions

Systemic toxic effects

Blood vessel, muscle, cartilage and bone damages, multiple organ failure, hypothyroidism, liver and kidney inflammation, pain, swelling, endocarditis, pneumonia, meningitis, pale skin, low blood pressure and heart beats, swollen hands, death

Neurotoxicity

Loss of cognitive functions, speech difficulty and changes of personality, loss of memory, hallucinations

among adults age 15–49 by the end of 2007 in Ukraine was estimated to be somewhere between 230,000 and 573,000, which yields an overall prevalence of 1.63%. HCV has a great prevalence between PWID in Ukraine with ranges from 62 to 88% in the same period [45]. These viruses may cause the systemic damage, especially HIV since it affects the immune system [2,46,47]. In Georgia, in 2011, 9 of 10 PWID interviewed at harm reduction facilities reported use of krokodil, compared to none the year before. The incidence of HCV is also very high, but HIV prevalence is significantly lower. Reports from Georgia on krokodil related harms have yet to appear [10,48], and suggests an interaction with HIV.



Fig. 3. Clinical effects of krokodil. Black ulcers (A), viridescent and discolored skin (B), necrosis and gangrene (C), limb amputation (D) and jaw osteonecrosis (E). Reproduced with permission from (A) [5], (B) [57], (C) [58], (D) [59] and (E) [60].

9. Bad chemistry hurts: use of harmful reagents

Hydriodic acid and red phosphorous are known to be very corrosive and dangerous substances, especially when administered intravenously. The formation of white phosphorus is perhaps another plausible explanation for the observed tissue damage. Nevertheless, the production of white phosphorus from red allotropic modification in an acidic and warm media in the presence of hydriodic acid and red phosphorous must still be confirmed. Moreover, a different crystal form of phosphorous (dark red needles) is obtained when red phosphorous is submitted to iodine recrystallization at low temperatures [49]. This indicates that some modifications may occur on the red phosphorous molecules during krokodil preparation. Red phosphorous is the reagent of the formation of the hydriodic acid, which is the main responsible for the reaction to form desomorphine. However, large amounts of phosphorous are used and it is not totally consumed during the reaction. This is an ineffective purification process and therefore phosphorous is expected to be part of the final product. This is an ineffective purification process, therefore it is expected to have phosphorous in the krokodil. Moreover, red phosphorous have been suggested to induce permanent deformities in the facial skull such as the appearance of jaw osteonecrosis [40]. The exact mechanism is unknown but apoptosis of osteoclasts, disturbance of osteoclast progenitor cell differentiation, disturbance of osteoclast enzyme activity, destruction of bone microstructure caused by phosphorous deposition and anti-neovascularization have been suggested [50]. Although there are available phosphorous coatings from matchbox strikers (i.e. “safe matches”) without oxidizers, they are more expensive and not commonly used for “krokodil” synthesis.

Besides the reported toxic effects for users, those that only produce “krokodil” are also at risk due to gas iodine production during the heating process of the synthesis. Indeed, iodine excess is associated with damage to the endocrine system and muscles [31].

Finally, chronic exposure to remnants of the solvents such as gasoline (including lead and/or other additives) or paint thinner and the alkaline drain cleaner used in codeine extraction may cause encephalopathy and neurological damage [51]. Lead exposure induces neurologic and hematological dysfunctions (due its capacity to inhibit zinc-containing enzymes), renal and hepatic damage as well as reproductive disorders in the human body [52]. The neurologic action of lead damages cells in the hippocampus, a part of the brain involved in memory and interferes with the release of neurotransmitters, especially glutamate, which is the responsible for many functions including learning [53,54].

10. Pharmacology and social context

Despite clear and advanced morbidity many users reportedly refrain from timely seeking medical assistance and continue injecting the drug [2,37,55]. It may be that pain from these injuries is subdued by the analgesic effect of the injected krokodil, which is about 10 times that of morphine [18]. The cholinesterase inhibition by desomorphine may also result in neurological symptoms [35]. However, the combination of neurological symptoms and desomorphine analgesic properties is unlikely to offer a complete explanation for ignoring the extreme symptoms that are associated with the injection of krokodil and failing timely seek help. The dependence potential of desomorphine, aside from variations in half-life, behaves pharmacologically quite alike other short acting opioids. While the short half-life of desomorphine may induce binge patterns and sleep deprivation [2], Georgian krokodil users suggested that self-detoxification from krokodil was less hardship than from heroin. Medical stigma and mal-treatment and, conversely, distrust of medical providers, as well as links between

the medical establishment and drug enforcement (going back to the Soviet era) are reportedly important barriers to accessing treatment, which may also be beyond the financial reach of those affected [2].

Krokodil use is associated with various other medical and social ailments in impoverished communities. More affluent drug consumers labeled krokodil as a drug for losers or kids [2]. Thus, while heroin may be a drug of choice, krokodil is definitively a drug of need and despair. The rise of krokodil in Russia, Ukraine or Georgia cannot be understood without considering the extremely harsh drug policies in these countries. The users in Georgia explained that, in order to prevent arrest, they avoid (heavily policed) illicit drug markets and go to the pharmacy instead [2,10].

11. Concluding remarks

There is no doubt that krokodil is an extremely dangerous mixture of compounds, believed to contain desomorphine as its main psychoactive ingredient. The use of harmful substances in the synthesis and the absence of proper purification methods before the drug is consumed results in the formation of a very damaging mixture. The potent analgesic effect of desomorphine may well contribute to postponing seeking medical assistance. But medical mal-treatment, stigma and discrimination of PWID are reportedly common among medical providers, while the relatively few harm reduction projects are ill-equipped to deal with such extreme harms.

Until 2011 the use of this drug seemed largely confined to Russia and Ukraine. Yet, that same year krokodil rapidly emerged in Georgia and, more recently, case reports of suspected krokodil use have emerged from various locations in Europe, the USA and elsewhere [15], although few of these case reports have been confirmed.

Difficulties in obtaining heroin, repressive drug policies to consumers and economic austerity may drive PWID toward krokodil. The risks of serious bodily harm and premature death are evident, as we showed in this review, but at this point the extent of these harms remains uncharted, as are the potential interactions with other health risks associated with drug injecting, HIV infection in particular.

Chemical content analysis of krokodil should provide needed information about its active ingredients and contaminants and on the actual chemical processes in its home production. These findings should contribute to preventive measures for reducing the harmful toxic effects of this drug concoction. Sensationalist media reports, citing Russian narcologists, claimed that, once initiated into krokodil use, the life expectancy of people who inject the drug is reduced to about 2–3 years [31], but local harm reduction providers mentioned clients that have consumed krokodil for many years. Both consumers and service providers suggest that skilled “cooks” can prepare a clean krokodil solution that can be injected without resulting in the excessive harms discussed here. Indeed, bad chemistry hurts, and kills, but repressive drug policies are equally part of krokodil hurtful recipe.

Conflict of interest

The authors declare no conflict of interest, particularly no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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