Journal of Addictive Diseases
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/wjad20

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Maximilian Gahr MD [a], Roland W. Freudenmann MD [a], Christoph Hiemke PhD [b], Ingo M. Gunst [a], Bernhard J. Connemann MD [a] & Carlos Schönfeldt-Lecuona MD [a]

[a] Department of Psychiatry and Psychotherapy III, University Hospital of Ulm, Leimgrubenweg, Ulm, Germany

[b] Department of Psychiatry and Psychotherapy, University Medical Center of Mainz, Untere Zahlbacher, Mainz, Germany

Accepted author version posted online: 08 Oct 2012.Version of record first published: 17 Dec 2012.

To cite this article: Maximilian Gahr MD , Roland W. Freudenmann MD , Christoph Hiemke PhD , Ingo M. Gunst , Bernhard J. Connemann MD & Carlos Schönfeldt-Lecuona MD (2012): Desomorphine Goes "Crocodile", Journal of Addictive Diseases, 31:4, 407-412

To link to this article: http://dx.doi.org/10.1080/10550887.2012.735570

Journal of Addictive Diseases, 31:407–412, 2012

ISSN: 1055-0887 print / 1545-0848 online
DOI: 10.1080/10550887.2012.735570

Routledge
Taylor & Francis Group

DESOMORPHINE GOES "CROCODILE"

Maximilian Gahr, MD[1], Roland W. Freudenmann, MD[1], Christoph Hiemke, PhD[2], Ingo M. Gunst[1], Bernhard J. Connemann, MD[1], Carlos Schönfeldt-Lecuona, MD[1]

[1]Department of Psychiatry and Psychotherapy III, University Hospital of Ulm, Leimgrubenweg, Ulm, Germany
[2]Department of Psychiatry and Psychotherapy, University Medical Center of Mainz, Untere Zahlbacher, Mainz, Germany

A systematic review was conducted to identify the available data for the term *Krokodil,* which is a jargon expression for an allegedly new drug. Krokodil seems to be a mixture of several substances and was first used in Russia in 2003, with a tremendous increase in the number of addicted individuals since then. The psychoactive core agent of Krokodil is desomorphine, an opioid-analogon that can be manufactured by boiling tablets containing codeine and other ingredients. The procedure results in a suspension that is used intravenously and regularly causes complications such as abscess, thrombophlebitis, and gangrene.

KEYWORDS. Desomorphine, drugs, heroin, morphine, substance dependence

INTRODUCTION

Since the beginning of 2011, a dramatic increase has been observed in the number of reports on the use of Krokodil (also known as Crocodile, Krok, or Croc) in print or screen media and throughout the World Wide Web. In the context of investigative journalism, most articles use the term *Krokodil* to describe a presumedly new drug that originated in Russia and has already arrived in Germany but not in other European countries. According to such reports, Krokodil is the "... drug that eats junkies"[1] and it is "... Russia's deadly designer drug,"[2] but no scientific commentary on this phenomenon appears to be available. This article attempts to elucidate the phenomenon of Krokodil from a critical point of view using the available evidence to provide information regarding the underlying psychoactive substance, its history of production and use, its epidemiologic aspects, its associated risks, and the current situation of its use in Germany.

METHODS

A literature search in December 2011 of the Embase, PubMed, and Scopus databases using the search terms *Krokodil*, *Crocodile*, *Krok,* and *Croc* did not reveal any articles that effectively dealt with the mentioned drug Krokodil, reflecting a lack of scientific examination of this phenomenon. The search term *desomorphine* resulted in only 2 articles, neither of which was related to Krokodil. All articles found on the Internet using the same search terms in a Google search engine originated from non-scientific sources (e.g., *Pravda*, *The Independent*, *Time*).[1–9] The latter articles invariably claim the psychoactive core agent of Krokodil to be desomorphine, even if qualitative analyses of substances availabe to drug abusers under the name Krokodil do not appear to exist. From this, we derive that the current knowledge concerning Krokodil is based mostly on non-scientific contributions.

The authors thank Dr. Alexander L. Bieri, Curator of the Roche Historical Collection and Archive, Basel, for the valuable informations.
Address correspondence to Maximilian Gahr, MD, Department of Psychiatry and Psychotherapy III, University Hospital of Ulm, Leimgrubenweg 12-14, 89075, Ulm, Germany. E-mail: maximilian.gahr@uni-ulm.de

RESULTS

Krokodil: Epidemiology and Current Situation in Europe

The Russian Internet news page NOVOSTI (Russian News & Information Agency) reported that desomorphine first emerged in the Russian drug scene around 2003 under the term *Krokodil*.[10] Thereafter, an epidemic increase in the number of addicted individuals was observed.[10] As hypothesized by Russian media, the reason for the rapid increase seems to be the unproblematic availability of Krokodil resulting from a simple production process that can be accomplished at home for little cost. Due to these circumstances, almost all current desomorphine users are claimed to be former heroin users who switched to Krokodil.[10]

In the first quarter of 2011, 65 millions doses of desomorphine were seized in Russia.[11] Currently, 100,000 of 2.5 million individuals in Russia with substance dependence seem to have desomorphine addiction.[12] However, the actual number could be higher than reported.[13] Due to this dramatic development, it was concluded that in Russia, effective June 1, 2012, codeine-containing tablets, which are the chemical basis for the home production of desomorphine, were to only be available in pharmacies.[12]

In October 2011, the first possible cases of Krokodil use in Germany were reported.[3] Devastating dermatological lesions, typical for Krokodil use, were observed in 4 heroin dependants in Bochum, located in Northwest Germany.[4] It was assumed that they were using heroin contaminated with Krokodil. The nonscientific journal *Spiegel Online* reported that Krokodil has already been offered on the black market in Frankfurt am Main.[3] Two other possible cases were reported in November 2011 in Bremerhaven, located in Northern Germany.[7] A qualitative chemical analysis of the substances found in the 4 cases from Bochum was announced,[14] but desomorphine has not yet been officially confirmed. However, communications from Russia assume desomorphine, a well-known synthetic opioid-analogon that can be easily and cheaply manufactured as described above, to be the core component of Krokodil.[10] To the best of our knowledge, there are no reports regarding Krokodil use in European countries other than Germany.

Desomorphine: History, Pharmacological and Chemical Classification, and Use in Medicine

Desomorphine ($C_{17}H_{21}NO_2$, dihydrodesoxymorphine, or according to the International Union of Pure and Applied Chemistry 4,5-α-Epoxy-17-methylmorphinan-3-ol) is an opioid analogon that was first synthesized and patented in the United States in 1932.[15,16] Desomorphine chemically differs from morphine with regard to the absent secondary hydroxy group and the saturated double bond (Figure 1).[17,18] It was originally synthesized with the intention to create an alternative to morphine in terms of tolerance and addiction properties and improve the side effect profile (e.g., narcotic properties, nausea, and respiratory depression).[18] However, desomorphine fell short of these expectations. On the contrary, desomorphine even showed an increased dependence potential compared with morphine.[19–21] Like other opioids, desomorphine features analgesic, muscle-relaxing, sedating, and euphorizing properties.[19–22] Compared with morphine, the analgetic potency of desomorphine is 8 to 10 times higher and it shows a faster onset of action and a shorter elimination half-life.[20–22] Especially the latter properties may account for the increased addictive potential of desomorphine compared with morphine.

Desomorphine was used in Switzerland and introduced to the Swiss market in 1940 by the company Hoffman-La Roche, under the registered trade name of Permonid. Permonid was available in the form of ampulla and suppository. It was used predominantly for postoperative pain due to its fast onset of action and reduced tendency to cause respiratory depression and nausea.[17,18] Toward the end of 1952, Permonid was withdrawn from the market. Notably, the production of Permonid was continued in Switzerland until 1981 due to the idiosyncratic analgesic needs of a single patient in Bern, Switzerland, who suffered from a rare

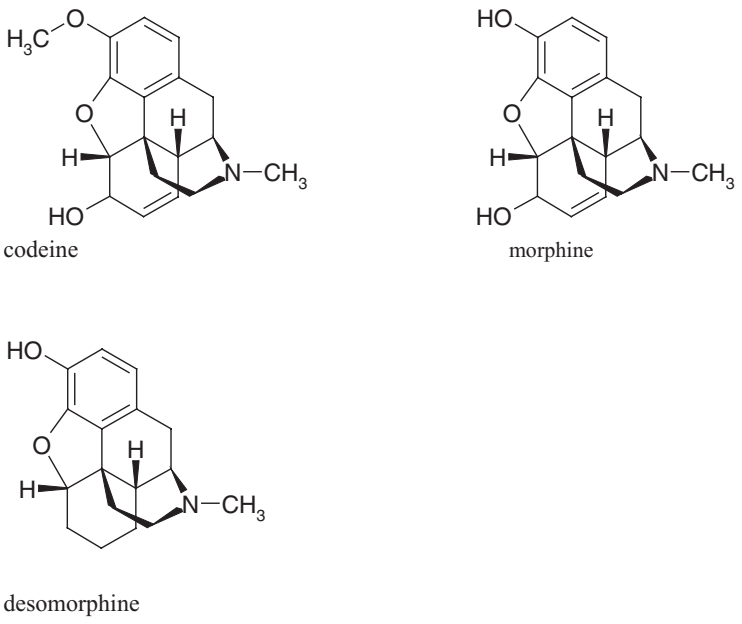

FIGURE 1. Chemical structures of codeine, morphine and desomorphine.

disease. This particular patient received a daily dose of 0.16 g (about 80 ampoules) from her attending physician, allegedly without developing somatic side effects (Dr. Alexander L. Bieri, Curator of The Roche Historical Collection and Archive, Basel, personal communication). As a consequence of its high dependence potential, desomorphine belongs to the group of non-marketable drugs in Germany and Austria.[23,24]

Krokodil: Manufacture

Krokodil can be manufactured easily and relatively quickly from tablets containing codeine (most frequent in Russia are Codelac® [Pharmstandard-Leksredstva, Russia], and Terpincod® [Pharmstandard-Leksredstva, Russia]). These tablets are available in Russia as inexpensive over-the-counter drugs.[13] As shown by a recent study, desomorphine can be synthesized in the kitchen laboratory from codeine, iodine, and red phosphorus.[25] (See Figure 1 for the chemical structure of codeine, morphine, and desomorphine.) Typically, 5 to 10 tablets containing codeine (costs approximately 300 rubles, equivalent to 9 USD) are boiled with a diluting agent (mostly paint thinner that may contain lead, zinc, ferric or ferrous agents, and antimony) and lighter fuel (gasoline), hydrochloric acid, iodine, and red phosphorous (as a phosphate source), which is being scraped from the striking pads of matchboxes.[13] In this process, desomorphine is generated from codeine (3-methylmorphine) via 2 intermediate steps (α-chlorocodide and desocodeine).[13,18,26]

Chemical Composition and Way of Use

The final product of this self-production process is called Crocodile or Krokodil and is a suspension that contains desomorphine as its psychoactive core agent and all other agents involved in the production process, such as iodine, phosphorus, and several heavy metal compounds.[1,2] Unfortunately, based on the results of our literature search, no scientific qualitative chemical analysis of the suspension Krokodil currently exists. This circumstance complicates the assessment of the actual components of Krokodil. Thus, currently available statements regarding the chemical components or contaminants of Krokodil are largely theoretical and can only be derived on the basis of the identified parent compounds that are used for the self-production process. However, due to the various possible primary substrates that can be used for the manufacture of Krokodil, it is most likely that—depending on the available

basic substrates—the chemical composition of Krokodil varies between users, especially regarding the spectrum and concentration of toxic byproducts. In most cases, the suspension is being applied intravenously without using any type of filter, what accounts for the tremendous risk profile of Krokodil.[13] Due to the short elimination half-life of desomorphine, patients with desomorphine dependence perform more applications compared with those with heroin dependence. This is particularly problematic against the background of the injection-associated risks of Krokodil use.

Krokodil: Risk Profile

Due to its high degree of contamination with various toxic byproducts, the application of Krokodil regularly induces immediate damage to blood vessels, muscles, and bone and can induce multiple organ failure.[1,2,13] Furthermore, the variety of substances injected with Krokodil leads to thyroid and muscle damage (via iodine), damage of cartilage tissue (via phosphorus), inflammatory reactions of liver and kidneys, deterioration of cognitive functions, and electrolyte metabolization by the heavy metal ingredients during chronic use. Quickly developing abscesses, thrombophlebitis, gangrene, and large-scaled necrosis are pathophysiological aspects that frequently make extensive amputation the only way to preserve the patients' lives.[2]

In view of the outlined drastic complications that are caused by the toxic byproducts rather than by the desomorphine itself, the designation Krokodil becomes comprehensible. On the one hand, the expression displays the hazards resulting from the substance; on the other hand, the viridescent-livid discoloration and gross desquamation from gangrenous imflammation at the injection site has been said to resemble the scales of a crocodile.[2] The pharmakokinetic properties of desomorphine (fast onset of action, short duration of action, and markedly increased potency compared with morphine, all resulting in rapid development of tolerance) plausibly explain the increased addictive potential of Krokodil compared with heroin (diacetylmorphine or diamorphine) as described in the contributions of the scientific journals. The use of a psychoactive substance with a high dependence potential accompanied by various toxic byproducts leads to a mean survival time of 2 years after the first Krokodil use according to reports from the media.[2,13]

DISCUSSION

The active principle of Krokodil is less a new drug rather than self-produced desomorphine accompanied by various toxic agents that emerge during the self-production process. The synthetic opioid-analogon desomorphine was invented in 1932. It is well-suited as an addictive substance due to its pharmacodynamic and -kinetic properties and can easily be manufactured from codeine, which is an over-the-counter drug in Russia. Since 2003, the prevalence of Krokodil use in Russia has been increasing rapidly, presumably as a consequence of its low cost and its high dependence potential. Because Krokodil is a suspension and is highly impure due to contamination with multiple toxic ingredients, the intravenous application is associated with a high risk for the development of local and systemic tissue damage regularly leading to death within few years. In October 2011, the first reports of suspicious cases of Krokodil use emerged in Germany, but official confirmation has not been made yet. Codeine is available only through prescription in most European countries, but the possibility of a developing, spreading phenomenon exists, particularly because Krokodil use implies the knowledge of how to produce a drug similar to heroin rather than a new drug that could only be acquired on the black market. Furthermore, heroin is more expensive, and the low financial effort of Krokodil in comparison with heroin might be reason enough for many individuals with heroin dependence to switch to Krokodil. Recent reports of Krokodil use in a European country should prompt physicians and psychiatrists to pay particular attention in their professional context to all cases that might be related to this drug. Possible cases should be investigated promptly, and individuals with heroin dependence should be informed

about the devastating and irreversible and regularly fatal consequences of Krokodil use to prevent substance switch. All governmental and non-governmental authorities involved in drug surveillance, monitoring, and preventing programs should be aware of this new phenomenon.

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