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The role of illicit drugs in developing medication related osteonecrosis (MRONJ): a systematic review

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Abstract

Background: Medication-related osteonecrosis of the jaw (MRONJ) is a very challenging condition to treat. MRONJ has primarily been associated with anti-resorptive and anti-angiogenic drugs, which are increasingly being used to prevent adverse skeletally related complications in patients with cancer and bone pathologies. Although these medications have been proven to cause osteonecrosis of the jaws (ONJ) there are also a number of other drugs that could potentially cause this condition. The aim of this systematic review is to ascertain whether there is an associated risk of osteonecrosis of the jaw (ONJ) in recreational drug users (RDU).

Material and Methods: Three authors independently searched PubMed, MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials for published reports of osteonecrosis of the jaw (ONJ) in recreational drug users (RDU) or illicit drug users (IDU) who had no history of treatment with anti-angiogenic or anti-resorptive agents.

Results: Only 30 studies were eligible for analysis, and all were independently assessed for risk of bias. There was a total of 101 patients with ONJ attributed solely to illicit drug consumption. The most common site of ONJ was the maxilla (n = 54). The most common illicit drug related to ONJ was desmorphine, known as "Krokodil", this was followed by cocaine, methamphetamine, anabolic steroids and

hydrocodone/acetaminophen. In n=52 of the cases the ONJ resolved following treatment however, n=8 showed a recurrence.

Conclusion: Although all the studies were judged to be at a high risk of bias, the limited data suggests that some patients are at risk of developing ONJ as a result of illicit drug usage. Studies of higher quality are needed to establish the relative risk of ONJ in this patient group.

Keywords: osteonecrosis of the jaw, ONJ, recreational drugs, illicit drugs, drug abuse.

1. Introduction

The term 'osteonecrosis of the jaws' (ONJ) refers to a potentially serious complication due to treatment with drugs, such as anti-angiogenic or anti-resorptive agents.[1,2] Recently, a new injectable street drug has become available, which is used as a cheap substitute for heroin. This drug, known as "Krokodil", was first identified in Russia and Ukraine. It is obtained by synthesising desomorphone from codeine tablets and has been linked to severe side effects, including ONJ.[3]

Illicit drugs (ID) are a group of drugs which are used for non-medical purposes and are illegal due to the high risk of addiction and undesirable side-effects. They can be separated into two categories: those which are illegal to possess, consume and sell and those which are used outside of the conditions in which they were prescribed. They include plant-based drugs such as heroin, cocaine, and cannabis, synthetic drugs such as amphetamines, and pharmaceutical synthetic drugs such as opioids (Table I).[4]

Drug misuse is one of the major social, legal, and public-health challenges in the modern world, contributing to substantial morbidity and mortality.[6]The health risks of illicit drug consumption are known to increase with the frequency and quantity of drugs used. The International Classification of Diseases define drug dependence as the presence of three or more indicators of dependence for at least a month within the previous year.[5] These indicators consist of: a strong desire to take the substance, a withdrawal syndrome on ceasing or reducing use, tolerance to the effects of the drug, the need for larger doses to achieve the desired psychological effect and a disproportionate amount of time spent by the user obtaining, using, and recovering from drug use; and persistence of drug taking; and impaired control over use despite

the problems that occur.

The incidence of illicit drug dependence is thought to be increasing in developed countries however, no global estimates have been made to date and accurate estimates are challenging to obtain, due to the illegality of the drugs and the surrounding stigma of addiction.[4,5]. The most accurate data comes from developed countries in Europe, North America, and Australasia. [6,7] There is evidence to show that all four drug classes (opioids, amphetamines, cocaine, and cannabis) are used in most countries, but quantitative estimates of their use are scarce. The 2011 world drug report by the UN Office on Drugs and Crime (UNODC) highlights this uncertainty by providing a range of prevalence estimates of prevalence for countries and regions. UNODC estimated that 149–271 million people aged between 15–64 years had used an illicit drug at least once in 2009.[8] A systematic review showed that in 2007, the prevalence of injecting drug users worldwide, was 11–21 million people.[9] Recent research has shown an increase of 30.2% in the global use of illicit drugs between 1990 and 2015.[10]

ONJ related to bisphosphonate drugs has been well documented in the literature over the past few decades.[11] However, new evidence has shown that along with bisphosphonates (BPs), other bone targeting agents (BTAs) can also cause osteonecrosis of the jaw bones. In addition, monoclonal antibodies able to bind and selectively inhibit vascular endothelial growth factor-A (VEGF-A), specifically mammalian target of rapamycin (mTOR) inhibitors, can also cause similar effects. [12-14] For this reason, the term medication related osteonecrosis of the jaw (MRONJ) was adopted as terminology in the 2014 position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS).[15]

Following a tooth extraction in cancer patients exposed to intravenous BPs, ONJ incidence has been estimated to range from 1.6 to 14.8%. The incidence of MRONJ in patients with cancer receiving denosumab was 1.3- 15.6%.[16-19] If the illicit drug user has the same risk of developing ONJ as oncology and osteoporotic patients then this poses a significant concern.

When patients present with clinically exposed and/or radiographic findings similar to classic ONJ, it is essential to identify the key risk factors and the population groups who may be affected. This information then allows for appropriate preventative

measures to be implemented. The aim of this systematic review is to analyse all available evidence and evaluate the reported outcome regarding ONJ associated with recreational drug users (RDU) with no history of anti-angiogenic agents or anti-resorptive treatment. No previous systematic reviews have been published on this topic.

2. Material and Methods

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20]

The following databases were used for the review: PubMed, MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL). A three-stage screening approach was used to ensure the precision and quality of the search. The screening of titles and abstracts was carried out independently by three authors (RS, RB and EB) to eliminate any irrelevant materials (i.e. reviews, animal studies, non-clinical studies and studies that reported patients on anti-angiogenic agents and anti-resorptive therapies). Conflicting opinions were resolved by discussion until a consensus was reached.

A data screening and abstraction form was used to:

- Verify the study eligibility derived from the inclusion/exclusion criteria.
- Carry out the methodological quality assessment.
- Extract data on study characteristics and outcomes for the included studies. (Figure 1).

The authors of any studies eligible for inclusion in the review, unless without sufficient information, were contacted directly.

3. Criteria for Inclusion in this Review

3.1 Types of Studies

The types of studies included in the research were published or unpublished randomised control trials, case-controlled trials, case series, retrospective studies and case reports. Papers were obtained from January 1950 to December 2019. Animal studies, reviews and studies including patients with previous history of radiation therapy to the head and neck regions and patients on, or with a history of, anti-angiogenic and anti-resorptive therapies, were excluded. No language restrictions were imposed on the search.

3.2. Types of Participants

The review considered studies involving patients who developed ONJ after illicit drug usage. No restriction of age, gender, or ethnic origin was applied. There was no restriction on the minimum number of patients included in the studies.

3.3 Objectives

The objectives of this study were to assess the risk of developing ONJ in the RDU population.

4. Types of Outcome Measures

4.2 Primary outcomes

To identify the category of recreational drug substance most frequently associated with ONJ. To assess the type of cause-event associated with developing ONJ in RDU subjects. To identify the most common sites for the occurrence of ONJ.

4.2 Secondary outcomes

To identify the ONJ time- to- event. To identify the ONJ preferred treatment (surgical or conservative) with the relative success rate. To identify the rate of complications and side effects related to ONJ intervention.

5. Data Extracted

Data extracted from the studies included: number of patients, patient's sex and age, risk factors (eg. steroid therapy, diabetes, infective disease), ONJ trigger cause, site of ONJ, type of illicit drug used and cumulative dose, type of ONJ intervention, post-operative complications and follow-up time. All selected papers were carefully read to identify: author(s), year of publication, study design, population and treatment characteristics.

In case of missing information, the authors were contacted and were given 6 weeks to reply. If the information was still missing the missing data was indicated as 'Not Reported (NR)' in the text and tables.

6. Review Quality Assessment Data

Two review authors (RS, RB) appraised the risk of bias in the included studies by using a tool recommended by the 'Cochrane Handbook for Systematic Reviews of Interventions' for randomised control trials (RCTs) and 'Risk Of Bias In Non-randomised Studies of Interventions' (ROBINS-I) tool for case-control studies. [21,22] Moreover, the authors used the CARE checklist for case reports and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for the case series/longitudinal studies. [23, 24] Any disagreements in risk of bias assessments were referred to another author of the review team (OA) and resolved through discussion.

7. Results

A total of 30 articles were included in this review. The types of articles included in this research were case reports (n = 21), case series (n = 7) and retrospective studies (n = 2) (Table II).[25-54] Of these, 20 articles reported patients with cocaine addiction, 7 articles reported patients with desomorphine "Krokodil" addiction, 1 article reported a patient with methamphetamine addiction, 1 article included a patient treated with anabolic steroids and 1 article reported a patient addicted to a hydrocodone/acetaminophen preparation. The published data described patients affected by ONJ from 1989 to 2019.

The total number of patients included in this systematic review was n=101, of which n=80 were male and n=21 were female. The site for ONJ was predominantly in the maxilla, n=54 patients, followed by the mandible, n=31 patients, and was present in both jaws in n=16 patients (Table III).

The most common illicit drug associated with ONJ was desomorphine "Krokodil" which accounted for n=68 of the n=101 patients. This was followed by n=30 patients addicted to cocaine, n=1 patient addicted to methamphetamine, n=1 patient on anabolic steroids and n=1 patient addicted to hydrocodone/acetaminophen.

Overall, only n=8 patients developed a recurrence after surgical management and this only occured in the patients addicted to desmorphine "Krokodil".

The results are shown by the category of addiction and as descriptive statistics because of significant heterogeneity in the published data (Table IV and V).

7.1 List of Excluded Studies

37 studies were originally considered to be potentially eligible for inclusion, but, after inspection of the full papers, 7 were excluded for not meeting the inclusion criteria for this review (Table VI). [55-61]

7.2 Desomorphine "Krokodil" Patient Analysis

N=68 patients out of the n=101 developed ONJ because of desomorphine "Krokodil" abuse. The mean weighted age was 41.1 ± 4.8. ONJ was seen predominantly in men (n=67). The ONJ localization was predominantly in the mandible (n=31), followed by the maxilla (n=22). In only n=15 patients was the ONJ found to be affecting both jaws. The time of drug exposure varied from 5 months to 72 months. However, in 3 out 7 articles the time of drug exposure was unclear or not reported.

The ONJ reported was primarily following dento-alveolar surgery, which accounted for n=45 of the cases. In all but one case (n=67), the ONJ was treated surgically (i.e sequestrectomy, jaw resection) successfully in n=42 cases. Only n=8 of the cases treated surgically developed a recurrence of ONJ.

7.3 Cocaine Patient Analysis

N=30 patients out of n=101 developed ONJ alongside cocaine abuse. The mean age of these patients was 38.3 ± 8.9. Of these patients n=20 were female and n=10 were male. In all patients the ONJ was manifested by erosion of the hard palate with an associated oro-nasal communication. The time of drug exposure varied from 24 to 120 months. However, in 12 out of 18 articles, the time of drug exposure was either not mentioned or unclear. In all the cases of cocaine addicted patients, the ONJ was spontaneous.

Among the n=30 patients affected by ONJ with permanent oral-nasal communication, n=14 were treated surgically, whilst n=13 patients were treated conservatively (i.e antibiotics, obturator). No recurrence of ONJ was observed in any of the studies however, the oro-nasal fistula worsened in n=5 of the cases.

7.4 Methamphetamine Patient Analysis

N=1 patient out of the n=101 developed ONJ concurrent with methamphetamine addiction. A 44 year old man was found to have developed ONJ in the maxilla although the cause was unclear. The patient subsequently admitted to using methamphetamine

for 240 months. The ONJ was treated surgically and showed complete resolution.

7.5 Anabolic Steroid Patient Analysis

N=1 patient out of n=101 developed ONJ due to usage of testosterone and anastrozole. This 55 year old man developed pain and subsequent ONJ in both jaws after 6 months of drug administration. The patient was found to have previously undiagnosed factor V Leiden heterozygosity. The ONJ resolved completely following conservative management (drug holiday).

7.6 Hydrocodone/acetaminophen Patient Analysis

N=1 patient out of n=101 developed ONJ following snorting a hydrocodone/acetaminophen preparation. This 31 year old man developed speech impairment associated with a perforated palate following use of a hydrocodone/acetaminophen preparation. Surgical repair of the oro-nasal communication had previously been attempted unsuccessfully. The ONJ was treated conservatively (acrylic obturator) with no worsening of the oro-nasal communication reported.

8. Risk of Bias and Review Quality Assessment

All the case report studies, contained a lack of clarity in many of the domains of the CARE Checklist and had incomplete data. The lack of clarity was predominantly related to the time of drug exposure, follow-up and diagnostic procedures. Therefore, the level of bias for all the included case reports can be concluded to be high. There was a consistent lack of clarity in some of the domains of the STROBE checklist in the case series and the retrospective studies. These were predominantly regarding the outcome measurement methods as well as diagnostic procedures, thus the possibility of a high level of bias for all these studies must be accepted.

Discussion

MRONJ is a well-known adverse effect of anti-resorptive and anti-angiogenic medications particularly when used for primary or metastatic bone cancer. [15, 17]
Indeed, this risk seems to be greater in patients who require intravenous drug therapy and for those who have had a prolonged period of exposure. [62, 63] Moreover, the literature has reported that steroid therapy, systemic factors, and genetic factors can

predispose a patient to developing MRONJ. Studies suggest a wide-ranging MRONJ incidence from 0 to 27.5% in individuals exposed to intravenous BPs, with a mean incidence of 7%. With oral administration however, the incidence ranges only from 0.1% to 0.06%.[15, 64] Other drugs also have the potential to cause ONJ.[65, 66]

Currently, no systematic analysis has been performed to link the usage of recreational drugs to ONJ. This systematic review has highlighted the potential relationship between several types of illicit drugs with this severe condition.

It is well known that cocaine, apart from causing intense vasoconstriction, acts as a dopamine (DA), serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor, leading to deregulation of these neurotransmitters. These three neurotransmitters are present in the central nervous system but have different regulatory functions in the body. Serotonin has been studied and linked to the control of bone mass and morphology.[67] Katsuragawa[68] reported that the acoustic properties of cancellous bone can be used as an indicator of bone strength and the propogation of speed was significantly lower in METH abusers. Other investigators, using dual energy X-ray absorptiometry, observed that the bone mineral density (BMD) in the lumbar spine was lower in METH abusers compared to non-users.[69]

Desomorphine was first synthesized in the USA in 1932. [70] and is reported to be the main component of “Krokodil”, however, there is no information about the other constituents present in the injectable solution. Mosettig et al [71] described the synthesis of desomorphine from codeine using an acetic acid solution, and a-chlorocodide as an intermediary. The first step is transformation of codeine into a-chlorocodide using thionyl chloride. There is then a subsequent reduction to produce desocodeine and finally, a desmethylation to produce desomorphine.

The process of “Krokodil” synthesis is almost identical to that of methamphetamine synthesis from ephedrine, 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. [72, 73]

Specifically, red phosphorus is the reagent of the formation of the hydriodic acid, which is the responsible for the reaction to form desomorphine. However, large amounts of phosphorus are used and it is not completely utilised during the reaction. This ineffective purification process means that phosphorus is likely to be present in the final product. It has been suggested that red phosphorus can induce permanent deformities in the facial bone structures. [44]

Anastrozole (a non-steroidal aromatase inhibitor) markedly suppresses estrogen levels and is becoming increasingly important as an adjuvant hormonal therapy. However, in a 2-year drug trial analysis, it was reported that anastrozole treatment was associated with increased bone turnover and significant bone mineral density (BMD) loss. [74]

The purpose of this systematic review was to analyse current evidence and assess the risk of developing ONJ in subjects exposed to illicit drugs. Our findings indicate that there is a correlation between an individual exposed to particular types of recreational drugs and ONJ.

Despite the included studies consisting of low-quality evidence with a high risk of bias, there is some evidence to show successful resolution of ONJ in the majority of this group of patients, with a very low incidence of recurrence only in n=8 cases in the short, medium and long term.

Several omissions were found across all studies and this has had an impact on the quality of the research. Indeed, in some studies, time of drug exposure was not reported; also, in most of the studies only short term follow-ups were reported.

Due to the limited data available on the topic of this review, it is difficult to draw a definitive conclusion regarding the use of recreational drugs and the development of ONJ. However, as per the authors analysis, there is some correlation between specific addictive drugs and ONJ. Drugs such as cocaine and “Krokodil” have been shown to lead to an increased risk of osteonecrosis.

The authors believe that additional high level evidence studies, such as multi-centre studies, case-controlled studies (prospective and retrospective) are essential to understand how to effectively manage these patients.

The authors advocate that the following rules should be applied for research protocols:

- Diagnosis and staging of the disease should be assessed with standardized, reproducable scales and calibrated amongst clinicians involved in the study (e.g. pathology and microbiology assessment are required in order to confirm the aetiology of the disease).
- Common, quantifiable and clinically relevant endpoints (time to complete wound healing, pain, specific investigations, treatment acceptability and participant satisfaction) should be described in a sufficiently detailed manner.

- A long follow-up period of at least 18 months is essential for patients where ONJ has been established.

Conclusion

MRONJ is known to be an iatrogenic complication for patients undergoing anti-resorptive and anti-angiogenic drug therapy. However, there are other medications that can cause such severe adverse side effects. This is the first systematic review reporting the correlation between ONJ and recreational drug users (RDU) but also highlighting the absence of high-level evidence in the literature on this topic. However, the available data does suggest that further well-designed clinical studies could lead to a better understanding on how to improve the management for this cohort of patients.

Conflicts of Interest

This study was not supported by any company and all the authors have not conflicts of interest.

Authors' Contributions

All the authors of this manuscript have substantial contributions to the conception or design of the work; to the acquisition, analysis, or interpretation of data for the work; to draft of the paper and revising it critically and finally approved the version to be published.

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Ethics statement/confirmation of patient permission

This study is a review. Hence no ethical approval or patient permission is required

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Figure 1: Study flow diagram

Recreational drugs	Street name	Commercial name	Common ways of taken	Possible health effects	
				Short-term	Long-term
Cocaine	Blow, Bump, C, Candy, Charlie, Coke, Crack, Flake, Rock, Snow, Toot	Cocaine hydrochloride topical solution (anaesthetic rarely used in medical procedures)	Snorted, smoked, injected	Narrowed blood vessels; enlarged pupils; increased body temperature, heart rate, and blood pressure; headache; abdominal pain and nausea; euphoria; increased energy, alertness; insomnia, restlessness; anxiety; erratic and violent behavior, panic attacks, paranoia, psychosis; heart rhythm problems, heart attack; stroke; seizure, coma.	Loss of sense of smell, nosebleeds, nasal damage and trouble swallowing resulting from snorting; infection and death of bowel tissue from decreased blood flow; poor nutrition and weight loss; lung damage.
Heroin	Brown sugar, China White, Dope, H, Horse, Junk, Skag, Skunk, Smack, White Horse	No commercial uses	Snorted, smoked, injected	Euphoria; dry mouth; itching; nausea; vomiting; miosis; analgesia; slowed breathing and heart rate.	Collapsed veins; skin abscesses; endocarditis; constipation and stomach cramps; liver or kidney disease.
LSD	Acid, Blotter, Blue Heaven, Cubes, Microdot, Yellow Sunshine	No commercial uses	Swallowed, absorbed via mouth tissues (paper squares)	Rapid emotional swings; distortion of a person's ability to recognize reality, think rationally, or communicate with others; raised blood pressure, heart rate, body temperature; dizziness; loss of appetite; tremors; miosis.	Hallucinogen; Persisting Perception Disorder (HPPD); ongoing visual disturbances, disorganized thinking, paranois and mood swings.
Marijuana	Blunt, Bud, Dope, Ganja, Grass, Green, Herb, Joint, Mary Jane, Pot, Reefer, Sinsemilla, Skunk, Smoke, Trees, Weed Hashish: Boom, Gangster, Hash, Hemp	-	Smoked, ingested (mixed in food or brewed as tea	Enhanced sensory perception and euphoria followed by drowsiness/relaxation; slowed reaction time; problems with balance and coordination; increased heart rate and appetite; problems with learning and memory; anxiety	Mental health problems, chronic cough, frequent respiratory infections. In rare cases, risk of recurrent episodes of severe nausea and vomiting

MDMA	Adam, Clarity, Eve, Lover's Speed, Peace, Uppers	No commercial uses	Snorted, swallowed	Lowered inhibition; enhanced sensory perception; increased heart rate and blood pressure; muscle tension; nausea; faintness; chills or sweating; sharp rise in body temperature leading to kidney failure or death.	Long-lasting confusion, depression, problems with attention, memory, and sleep; increased anxiety, Impulsiveness, decreased. libido
Methamphetamine	Crank, Chalk, Crystal, Fire, Glass, Go Fast, Ice, Meth, Speed	Desoxyn®	Snorted, smoked, injected, swallowed	Increased wakefulness and physical activity; decreased appetite; increased breathing, heart rate, blood pressure, temperature; irregular heartbeat	Anxiety, confusion, insomnia, mood problems, violent behavior, paranoia, hallucinations, delusions, weight loss, severe dental problems ("meth mouth"), intense itching leading to skin sores
PCP	Angel Dust, Boat, Hog, Love Boat, Peace Pill	No commercial uses	Snorted, smoked, injected, swallowed	Delusions, hallucinations, paranoia, problems in thinking, anxiety. Low doses: slight increase in breathing rate; increased blood pressure and heart rate; shallow breathing; rush and sweating; numbness of body extremity; problems with coordination. High doses: nausea; vomiting; flicking up and down of the eyes; drooling; loss of balance; dizziness; violence; seizures, coma, and death.	Memory loss, problems with speech and thinking, loss of appetite, anxiety.
Synthetic cannabinoids	K2, Spice, Black Mamba, Bliss, Bombay Blue, Fake Weed, Fire, Genie, Moon Rocks, Skunk, Smacked, Yucatan, Zohai	No commercial uses	Smoked, swallowed (brewed as tea)	Increased heart rate; vomiting; agitation; confusion; hallucinations, anxiety, paranoia; increased blood pressure.	Unknown
Synthetic cathinones "baths salts"	Bloom, Cloud Nine, Cosmic Blast, Flakka, Ivory Wave, Lunar Wave, Scarface, Vanilla Sky, White Lightning	No commercial uses	Snorted, injected, swallowed	Increased heart rate and blood pressure; euphoria; increased sociability and libido; paranoia, agitation, and hallucinations; violent behavior; sweating; nausea, vomiting; insomnia; irritability; dizziness; depression; panic attacks; reduced motor control; cloudy thinking	Death
Desomorphine "Krokodil"	"Krokodil" and "Crocodil"	Permonid	Injected	Skin present as greenish damaged blood vessels, thrombosis and damaged soft tissues surrounding the injection sites	Death
Ketamine	"K" or "Special K." Other street names include Cat Valium, Super Acid, Special La Coke, Purple, Jet	Ketalar	Snorted, injected, swallowed	Hallucinations; vomiting and nausea; altered hearing; delirium; impaired judgment, attention and memory; involuntary eye movement; high blood pressure; increase of the heart beat; excessive salivation; dysphasia	Incontinence; decreased bladder volume, blood in the urine; memory loss

	and Vitamin K.				
PCP drug	Angel Dust, Boat, Hog, Love Boat, Peace Pill	No commercial uses	Snorted, injected, swallowed, smoked	Hallucinations, paranoia, anxiety; increased breathing rate; increased blood pressure and heart rate; numbness of the hands or feet; nausea, vomiting; loss of balance, dizziness; violence; seizures, coma and death.	Memory loss; problems with speech and thinking; loss of appetite; anxiety
Anabolic steroids	Roids, steroid, juice	Testosterone (Axiron, Androgel, Fortesta, Testopel, Striant, Delatestryl, Testim, Androderm) Androstenedione. Stanozolol (Winstrol) Nandrolone (Deca-Durabolin) Methandrosteolone (Dianabol)	Injected, swallowed	Acne, Mood swings; fatigue; restlessness/ agitation; decreased appetite; difficulty sleeping; decreased sperm count; Impotence	Anger and aggression; paranoia, delusions; heart attack; stroke; kidney failure; liver cancer.

Table I: Commonly abused drugs

Author(s	Type of study	Patients number	Level of Evidence
Armstrong & Shikani 1996 [25]	CR	1	Level 5
Bianchi et al 2014 [26]	CR	1	Level 5
Blanco & Martinez 2017 [27]	CR	1	Level 5
Coletti et al 2014 [28]	CS	4	Level 4
Gendeh et al 1998 [29]	CR	1	Level 5
Goodger et al 2005 [30]	CR	1	Level 5
Hakobyan & Poghosyan 2017a [31]	CR	1	Level 5
Hakobyan & Poghosyan 2017b [32]	CR	1	Level 5
Hakobyan & Poghosyan 2019 [33]	CS	2	Level 4
Hakobyan et al 2017 [34]	RS	17	Level 3
Hakobyan et al 2018 [35]	RS	6	Level 3
Helie & Fournier 1997 [36]	CR	1	Level 5
Jewers et al 2005 [37]	CR	1	Level 5
Kuriloff & Kimmelman 1989 [38]	CS	1	Level 5*
Lancaster et al 2000 [39]	CR	1	Level 5
Mattson-Gates et al 1991 [40]	CR	1	Level 5
Molteni et al 2016 [41]	CR	1	Level 5
Nastro Siniscalchi et al 2012 [42]	CR	1	Level 5
Pandit & Glueck 2014 [43]	CR	1	Level 5
Poghosyan et al 2014 [44]	CS	40	Level 4
Rustemeyer et al 2014 [45]	CR	1	Level 5

Sastry et al 1997 [46]	CR	1	Level 5
Sergent et al 2019 [47]	CR	1	Level 5
Serrano-Sánchez et al 2010 [48]	CS	5	Level 4
Seyer et al 2002 [49]	CR	1	Level 5
Simsek et al 2006 [50]	CS	2	Level 4
Sittel & Eckel 1998 [51]	CR	1	Level 5
Teng & Steinbacher 2013 [52]	CR	1	Level 5
Trimarchi et al 2003 [53]	CS	3	Level 4
Villa 1999 [54]	CR	1	Level 5

Tables II: Studies included in the systematic review, including number of patients and evidence level. Retrospective study (RS), Case series (CS) and case report (CR); Levels of Evidence for Prognostic Studies Adapted from the American Society of Plastic Surgeons (https://www.plasticsurgery.org/Documents/medical-professionals/health-policy/ evidence-practice/ASPS-Rating-Scale-March-2011.pdf).

Study	**Age/Sex**	**Trigging cause**	**Site of the necrosis**	**Clinical Presentation**	**MRONJ Stage**
Armstrong & Shikani 1996 [25]	31 F	Spontaneous	Hard Palate	Oro-nasal fistula	N/A
Bianchi et al 2014 [26]	31 F	Spontaneous	Hard Palate	Oro-nasal fistula	NR
Blanco & Martinez 2017 [27]	42 F	Spontaneous	Hard Palate	Oro-nasal fistula	NR
Coletti et al 2014 [28]	43 M; 36-46 F;	Spontaneous	Hard Palate	Oro-nasal fistula	NR
Gendeh et al 1998 [29]	44 F	Spontaneous	Hard Palate	Oro-nasal fistula	N/A
Goodger et al 2005 [30]	43 F	Spontaneous	Hard Palate	Oro-nasal fistula	NR
Hakobyan & Poghosyan 2017a [31]	48 M	Dental extraction	Both jaws	Exposed bone	Stage III
Hakobyan & Poghosyan 2017b [32]	40 M	Dental extraction	Maxilla	Exposed bone	Stage III
Hakobyan & Poghosyan 2019 [33]	38 M; 50 M	Dental extraction	Maxilla	Exposed bone	Stage III x 3
Hakobyan et al 2017 [34]	25-56 M	NR	Mandible x 10 Maxilla x 1 Both jaws x 6	NR	NR
Hakobyan et al 2018 [35]	36 – 52 M	NR	Maxilla 6	Bone exposure x 6	Stage III x 6
Helie & Fournier 1997 [36]	46 F	Spontaneous	Hard Palate	Oro-nasal fistula	N/A
Jewers et al 2005 [37]	31 M	Spontaneous	Hard Palate	Oro-nasal fistula	NR
Kuriloff & Kimmelman 1989 [38]	29 F	Spontaneous	Hard Palate	Oro-nasal fistula	N/A
Lancaster et al 2000 [39]	33 F	Spontaneous	Hard Palate	Oro-nasal fistula	N/A
Mattson-Gates et al 1991 [40]	28 F	Spontaneous	Hard Palate	Oro-nasal fistula	N/A
Molteni et al 2016 [41]	38 F	Spontaneous	Hard Palate	Oro-nasal fistula	NR
Nastro Siniscalchi et al 2012 [42]	42 M	Spontaneous	Hard Palate	Oro-nasal fistula	NR

Pandit & Glueck 2014 [43]	55 M	Spontaneous	Both jaws	NR	NR
Poghosyan et al 2014 [44]	26-54 39 x M 1 x F	Dental extraction	Mandible x 21 Maxilla x 11 Both jaws x 8	Exposed bone x 40	Unclear
Rustemeyer et al 2014 [45]	44 M	Unclear	Maxilla	Exposed bone	Stage III
Sastry et al 1997 [46]	37 F	Spontaneous	Maxilla	Oro-nasal fistula	N/A
Sergent et al 2019 [47]	36 M	Dental extraction	Maxilla	Exposed bone	Stage III
Serrano-Sánchez et al 2010 [48]	32 -50 F 30 – 50 M	Spontaneous x 5	Maxilla x 5	Oro-nasal fistula x 5	NR
Seyer et al 2002 [49]	50 F	Spontaneous	Maxilla	Oro-nasal fistula	N/A
Simsek et al 2006 [50]	30-34 M	Spontaneous x 2	Maxilla x 2	Oro-nasal fistula x 2	N/A
Sittel & Eckel 1998 [51]	35 M	Spontaneous	Maxilla	Oro-nasal fistula	N/A
Teng & Steinbacher 2013 [52]	31 F	Spontaneous	Hard Palate	Oro-nasal fistula	NR
Trimarchi et al 2003 [53]	25 F; 40-66 M;	Spontaneous x 3	Maxilla x 3	Oro-nasal fistula x 3	N/A
Villa 1999 [54]	38 M	Spontaneous	Maxilla	Oro-nasal fistula	N/A

Tables III: Preoperative epidemiologic analysis (age, sex, predisposing factors and site of the necrosis involved). M: male; F: female; not reported (NR) and not applicable (NA).

Study	**Type of drug**	**Route of administration**	**Other relevant medical conditions**	**Microbiology investigation**	**Time of drug exposure - months**
Armstrong & Shikani 1996 [25]	Cocaine	Snorted	Nil	Proteus mirabilis, Enterobacter aerogenes, Coagulase-negative Staphylococcus, Light Enterococcus faecalis and Candida albicans.	Unclear/not mentioned
Bianchi et al 2014 [26]	Cocaine	Snorted	Nil	Enterococcus faecalis and Staphylococcus aureus.	60 months
Blanco & Martinez 2017 [27]	Cocaine	Snorted	NR	Enterococcus faecalis and Staphylococcus aureus.	15 months
Coletti et al 2014 [28]	Cocaine	Snorted	NR	NR	60-120 months (4 cases)
Gendeh et al 1998 [29]	Cocaine	Snorted	NR	Staphylococcus	Unclear
Goodger et al 2005 [30]	Cocaine	Snorted	NR	Nil	60 months
Hakobyan & Poghosyan 2017a [31]	Desomorphine - “Krokodil”	Intravenous	HCV	NR	18 months
Hakobyan & Poghosyan 2017b [32]	Desomorphine - “Krokodil”	Intravenous	HCV	NR	18 moths

Hakobyan & Poghosyan 2019 [33]	Desomorphine - "Krokodil"	Intravenous	HCV	NR	12-36 months (2 cases)
Hakobyan et al 2017 [34]	Desomorphine - "Krokodil"	Intravenous	NR	NR	5-72 months. (17 cases)
Hakobyan et al 2018 [35]	Desomorphine - "Krokodil"	Intravenous	HCV	NR	6-18 months (6 cases)
Helie & Fournier 1997 [36]	Hydrocodone/acetaminophen	Snorted	Schizophrenia	Candida organisms	NR
Jewers et al 2005 [37]	Cocaine	Snorted	NR	NR	NR
Kuriloff & Kimmelman 1989 [38]	Cocaine	Snorted	Nil	Group A Streptococcus	24 months
Lancaster et al 2000 [39]	Cocaine	Snorted	Nil	Staphylococcus aureus	Unclear
Mattson-Gates et al 1991 [40]	Cocaine	Snorted	NR	NR	4 years
Molteni et al 2016 [41]	Cocaine	Snorted	Unclear	Staphylococcus aureus	NR
Nastro Siniscalchi et al 2012 [42]	Cocaine	Snorted	Nil	NR	120 months
Pandit & Glueck 2014 [43]	Testosterone & Anastrozole	Oral	Factor V Leiden heterozygosity (previously undiagnosed); 4 myocardial infractions with multiple stents ; On testosterone, androgel 50mg/day, to try to improve impaired sexual performance. After 6 months anastrozole (1 mg/day) due to high serum E2	NR	6 months (anastrozole and testosterone)
Poghosyan et al 2014 [44]	Desomorphine - "Krokodil"	Intravenous	37x HCV; 2x HBV, 1x HIV	NR	NR
Rustemeyer et al 2014 [45]	Methamphetamine	NR	Liver Cirrhosis HBV, HCV Alcohol abuse and smokers	NR	20 years
Sastry et al 1997 [46]	Cocaine	Snorted	-	NR	Unclear
Sergent et al 2019 [47]	Desomorphine – "Krokodil"	Intravenous	HCV, depression, smoker 20/day	NR	Unclear – "several years"
Serrano-Sánchez et al 2010 [48]	Cocaine	Snorted	1/5 pts smokers and regular alcohol use	NR	NR
			Nil	Nil	Unclear – "years"

Seyer et al 2002 [49]	Cocaine	Snorted			
Simsek et al 2006 [50]	Cocaine	Snorted	Unclear	Staphylococcus aureus	Unclear
Sittel & Eckel 1998 [51]	Cocaine	Snorted	NR	NR	Unclear
Teng & Steinbacher 2013 [52]	Cocaine	Snorted	Smoking	NR	NR
Trimarchi et al 2003 [53]	Cocaine	Snorted	Unclear	Staphylococcus aureus	NR
Villa 1999 [54]	Cocaine	Snorted	Smoking	NR	Unclear – "years"

Tables IV: Type of drugs, comorbidity and time of drug exposure in the articles included in the research. Not Reported (NR), myocardial infarction (MI), Hepatitis C (HCV), Hepatitis B (HBV),

Study	Type of MRONJ management	Follow-up time - months	Outcome of the study
Armstrong & Shikani 1996 [25]	AB - intravenous cefuroxime. On day three LD of the nasal cavity, paranasal sinuses and palate. Discharged on a one-week course of AB (oral ciprofloxacin, trimethoprim) sulfamethoxisole and St (a prednisolone taper)	Unclear	Unchanged
Bianchi et al 2014 [26]	2 stage surgery (1st stage bilateral buccal fat pad flap and forearm free flap, 2nd stage costal cartilage graft)	12	Resolved
Blanco & Martinez 2017 [27]	Obturator	NR	NR
Coletti et al 2014 [28]	3 x partially deepithelialized radial fascio-cutaneous free flap 1 x LD + planning reconstruction	1 x 24 months 1 x 15 months 1 x 13 months 1 x Unclear	3 x Resolved 1 x Stable
Gendeh et al 1998 [29]	Conservative management	12	Worsening of the oro-nasal fistula
Goodger et al 2005 [30]	LD + anterior based lateral tongue flap	Drop out	Lost on follow up
Hakobyan & Poghosyan 2017a [31]	Sequestrectomy + LD	36 months	Resolved
Hakobyan & Poghosyan 2017b [32]	Sequestrectomy + LD	2 months	Resolved
Hakobyan & Poghosyan 2019 [33]	Surgical resection	7 months 8 months	
Hakobyan et al 2017 [34]	Sequestrectomy + LD	NR	NR
Hakobyan et al 2018 [35]	Removal of necrotic bone and closure of formed maxillary sinus floor defects with buccal fat pad and local mucoperiosteal flaps. (Sequestrectomy + LD) AB (Clindamycin, Metronidazole), oral cavity rinses with antiseptics, and nasal vaso- constrictors.	Unclear	Resolved - free of symptoms: no signs of recurrence or of oro-antral communication
Helie & Fournier 1997 [36]	Acrylic palatal obturator	Unclear	Stable
Jewers et al 2005 [37]	Attempted repair with bilateral palatal faps.	NR	Failed due to continued cocaine usage
Kuriloff & Kimmelman 1989 [38]	Oral AB, SSI, emolliants, upper denture to obturate fistula	NR	NR
Lancaster et al 2000 [39]	SSI, oral AB and cocaine cessation	NR	No further extension of necrosis
	Stage 1 – unilateral pedicle flap		Speech improved – pt described as "normal"

Mattson-Gates et al 1991 [40]	Stage 2 (7 weeks later)– reconstruction using rib and cartilage graft technique	Pt failed to attend follow up after 1 week	Satisfactory cosmetic result
Molteni et al 2016 [41]	AB infusion (Metronidazole 500 mg QDS, Ceftazidime 2 g TDS and Vancomycin 500 mg QDS for 10 days) + Acrylic palatal obturator	Unclear	Unclear
Nastro Siniscalchi et al 2012 [42]	Local bilateral palatal flaps + AB	12 months	Resolved
Pandit & Glueck 2014 [43]	Testosterone and anastrozole were stopped	NR	Within 3 months, pt's jaw pain was significantly reduced Resolved within 6 months.
Poghosyan et al 2014 [44]	Perforation < 1 cm - hypertrophic mucosa of maxillary sinus floor not removed and wound closed tightly. Perforation > 1 cm - pathological mucosa of maxillary sinus removed, packed with iodoform gauze and end of gauze taken out from ostium in the inferior nasal meatus. The wound in oral cavity closed tightly. Mandible - marginal or segmental resections (+/- TMJ exarticulation). If after marginal resection the height of the remaining bone was < 0.5 cm →segmental resection Sequestrum on the mandible - intraoral wound closed partly and bone wound was left to heal by secondary intention using iodoform gauze. Both jaws - intraoral wounds closed tightly, local flaps without tension. Post-operative conservative treatment or treatment if Krokodil cessation <1 month 1. Oral hygiene 2. Removal of mobile parts of necrotisized bone 3. Abscess and inflammatory mass surgery 4. Detoxication therapy (isotonic saline solution, 5% glucose solution, Ringer's solution, Lasix) 5. AB and antifungal therapy in case of necrotic bone suppuration 6. Treatment in drug addiction clinic	NR	Recurrence in mandible 23% (5/21 marginal resection recurrences, 3/14 segmental resection recurrences) No cases of recurrence were seen after surgery on the maxilla. 2 cases of total resection of alveolar process with hard palate and partial resection of zygomatic bone were performed in the maxilla. In other cases partial resection of the alveolar process, hard palate and zygomatic bone was done. In 8 (38%) cases from 21 lesions in the maxilla an oro-antral communication was formed. In 13 (23%) sequestra were found: 8 in the maxilla, 5 in the mandible.
Rustemeyer et al 2014 [45]	IV AB and 2 stage surgery 1st – resection of necrotic area 2nd – reconstruction of maxilla using vascularized osteo-myocutaeneous fibula flap	Pt failed to attend follow up	NR
Sastry et al 1997 [46]	NR	Unclear	Progression
Sergent et al 2019 [47]	NR	NR	NR
Serrano-Sánchez et al 2010 [48]	1/5 pts – pedicle flap 4/5 pts – non-surgical management (1 x palatal obturator, 3 x NR)	NR	NR
Seyer et al 2002 [49]	Pt did not return for treatment	Pt failed to attend follow up	NR
Simsek et al 2006 [50]	1 x pt Sulphametoxazole, Trimethoprim and oral corticosteroids + palatal obturator 1 x pt – Sulphametoxazole and trimethoprim	Unclear	Unclear
Sittel & Eckel 1998 [51]	Staged nasal and maxillofacial reconstruction	NR	NR
Teng & Steinbacher 2013 [52]	Z-plasty standard Bipedicled mucoperiosteal flaps	6 months	Resolved

Trimarchi et al 2003 [53]	1 x pt – AB, SSI, St, Cy, Az 2 x pts – AB, SSI, LD	1x 6 months 1 x 48 months 1x 96 months	1 x pt no progression 2 x pts progression of the oro-nasal fistula
Villa 1999 [54]	Removable obturator	NR	For re-evaluation for possible surgical closure of oro-nasal fistula at a later date

Tables V: MRONJ management and outcome during the follow up period. (pt); Computed tomography (CT), magnetic resonance imaging (MRI), cone beam computer tomography (CBCT), Not Reported (NR), Antibiotics (AB), Saline Solution Irrigations (SSI), Local Debridement (LD), Cyclophosphamide (Cy), Azathioprine (Az), Steroids (St),

Study	**Type of study**	**Patients number**	**Reason of exclusion**
Alexander et al 2012 [55]	Retrospective analysis	9	Met the inclusion criteria but not enough information provided according to the outcomes of this systematic review
Arshad & Leader 2018 [56]	Abstract	1	Did not meet the inclusion criteria
Braverman et al 1999 [57]	CR	1	Did not meet the inclusion criteria
Qari et al 2017 [58]	Abstract	5	Did not meet the inclusion criteria
Rauso et al 2018 [59]	Letter to the editor	-	Did not meet the inclusion criteria
Shibli et al 2005 [60]	CR	1	Did not meet the inclusion criteria
Sloan & Klimkina 2009 [61]	CR	1	Did not meet the inclusion criteria

TableVI: List of excluded studies. Case report (CR)