Oral Manifestations Related To Drug Abuse: A Systematic Review

Manifestasi Oral Terkait Penyalahgunaan Narkoba: Tinjauan Sistematis

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Abstract

Drug abuse influences the pathological of oral diseases. There are scarce evidence-based data on the oral manifestations related to drug abuse. This systematic review aim to assess the oral manifestations related to drug abuse. Electronic databases were searched using keywords include oral manifestations, drug abuse and systematic review. Observational studies published until September 2018 with the outcome of oral manifestations related to drug abuse were included. Data were extracted as percentage included drug type, route of administration, and oral manifestations. Study quality was assessed using the quartile score of Scopus index. The systematic review of 17 studies revealed that methamphetamine (53%), heroin (41%), cannabis (35%), and cocaine (35%) were the most frequent abused drugs from 10139 samples. The routes of administration include smoking (58%), inhalation (35%), injection (35%), and oral route (17%), with duration of use ranged from one year to forty years. The most significant of oral manifestations reported were periodontal diseases (76%), dental caries (76%), and xerostomia (41%). Adverse drug reaction in oral cavity may cause, directly or indirectly, immune suppression, susceptibility to infections, and oral pathologies due to chemical composition and mechanism of action specifically to drug type related with duration of use and route of administration.

Keywords: Drug abuse, oral manifestations, systematic review

Abstrak

Penyalahgunaan narkoba mempengaruhi patologis penyakit mulut. Data tentang manifestasi oral yang terkait dengan penyalahgunaan narkoba berdasarkan bukti masih jarang. Tinjauan sistematis ini bertujuan untuk menilai manifestasi oral yang terkait dengan penyalahgunaan narkoba. Pencarian pada database elektronik menggunakan kata kunci yaitu manifestasi oral, penyalahgunaan narkoba dan tinjauan sistematis. Studi observasional yang diterbitkan hingga September 2018 dengan hasil manifestasi oral yang terkait dengan penyalahgunaan narkoba dimasukkan. Data diekstraksi sebagai persentase termasuk jenis obat, rute pemberian, dan manifestasi oral. Kualitas studi dinilai menggunakan skor kuartil dari indeks Scopus. Tinjauan sistematis dari 17 studi mengungkapkan bahwa metamfetamin (53%), heroin (41%), ganja (35%), dan kokain (35%) adalah obat yang paling sering disalahgunakan dari 1.0139 sampel. Cara penggunaan meliputi merokok (58%), inhalasi (35%), injeksi (35%), dan rute oral (17%), dengan durasi penggunaan berkisar dari satu tahun hingga empat puluh tahun. Manifestasi oral yang paling signifikan yang dilaporkan adalah penyakit periodontal (76%), karies gigi (76%), dan xerostomia (41%). Reaksi obat yang merugikan dalam rongga mulut dapat secara langsung maupun tidak langsung menyebabkan, imunosupresi, kerentanan terhadap infeksi, dan patologi oral dikarenakan komposisi kimia dan mekanisme kerja khusus untuk setiap jenis obat dan yang terkait dengan durasi penggunaan dan rute penggunaan.

Kata kunci: Penyalahgunaan narkoba, manifestasi oral, tinjauan sistematis

INTRODUCTION

Drug abuse or drug use disorder is the use of a substance for a purpose not consistent with legal or medical guidelines, as in the non-medical use of prescription medications.[1] The World Drug Report 2018 by the UN Office on Drugs and Crime (UNODC) estimated that 5,6% people aged 15-64 years had used an illicit drug at least once in 2016.[2] The type and frequency of drugs used

worldwide varied substantially across region including cannabis (182 million), opioids (34 million), methamphetamine (34 million), ecstasy (21 million) and cocaine (19 million).[2] In Indonesia, based on the 2017 national survey on substance abuse by the Badan Narkotika Nasional (BNN) reported that 3.3 million people aged 10-59 years (1.77%) had used illicit drugs. However, the prevalence showed that there was significant decreesed from 2014 (2.18%).[3]

Drug abuse contribute to the global burden of disease through the adverse effects of its use including the acute toxic effects, the acute effects of intoxication, development of dependence, and risk factors for chronic disease due to repeated exposure. Strong evidence supports that drug-induced psychotic and drug dependence are the acute and chronic consequences of substance abuse.[4] Drug abuse is chemical substances that alter the functioning of the central nervous system (CNS) directly or indirectly, which may lead to changes in the basal activity of the brain. The brain reward system is stimulated by the drugs, causing the release of the neurotransmitter dopamine (DA) into the nucleus accumbens (Nacc) and promoting the feeling of pleasure, which makes the body perceive this eliciting stimuli as more salient.[5] The substance abuse have both neuronal and central immune signalling modulation properties that combine to create the rewarding and dependence behaviours, modulate the immune function via immuno suppressive effects and increase susceptibility to infections.[6]

Epidemiologic research reveals that illicit drug use influences the pathological of oral diseases. Oral diseases are among the most frequently reported health problems among drug abusers.[7] Patients with substance use disorders have greater and more severe dental caries and periodontal disease than the general population, but are less likely to have received dental care.[8] Furthermore, longer duration of exposure to illicit drugs leads to higher prevalence of xerostomia, orofacial pain, and oral mucosal diseases.[7] However, there are scarce evidence-based data on the oral manifestations, particularly oral mucosal diseases, related to illicit drug use. In the present study, we conducted a systematic review on the oral manifestations related to drug abuse.

METHODOLOGY

We followed the guidelines developed and recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIS MA).[9] This study outcome was the oral manifestations related to drug abuse with no restrictions on the age and gender of samples, assessment methods, route and duration of use. Substances used include cannabis, cocaine, heroin, methamphetamine, and opioids. We included observational or descriptive studies (cross-sectional, cohort, and case-control) that reported the oral manifestations related to drug abuse and only papers written in Bahasa and English with the availability of full text. We excluded publications other than original research studies (reviews, editorials, case reports, and case series) and papers focusing on animal studies, purely alcohol or tobacco abuse.

We searched relevant papers through online database sources include PubMed, and Google Scholar published until September 2018 using Medical Subject Headings (MeSH) terms as appropriate: oral manifestations, drug abuse, drug addiction, cannabis, cocaine, heroin, methamphetamine, and opioids. We used Boolean method with the word AND / OR for the combination of previously mentioned keywords. Articles found were scanned and filtered by relevance using the PRISMA flowchart.

For all of the included studies, the following structured information was recorded using contingency table: study characteristics (first author, year of publication, country, and study design), population characteristics (number of samples, age, and gender), intervention characteristics (assessments method) and outcome characteristics (oral manifestations, drug type, route of administration, and duration of use were presented as percentage).

The quality of the articles was assessed by the two authors using the quartile score of Scopus index. The included studies were considered high quality when it possesses the Q1-Q3 quality.[10]

RESULT

Articles found were scanned and filtered by relevance using the PRISMA flowchart as shown in figure 1. In total, 132 studies were found, but only 18 studies met the eligibility criteria for systematic review.

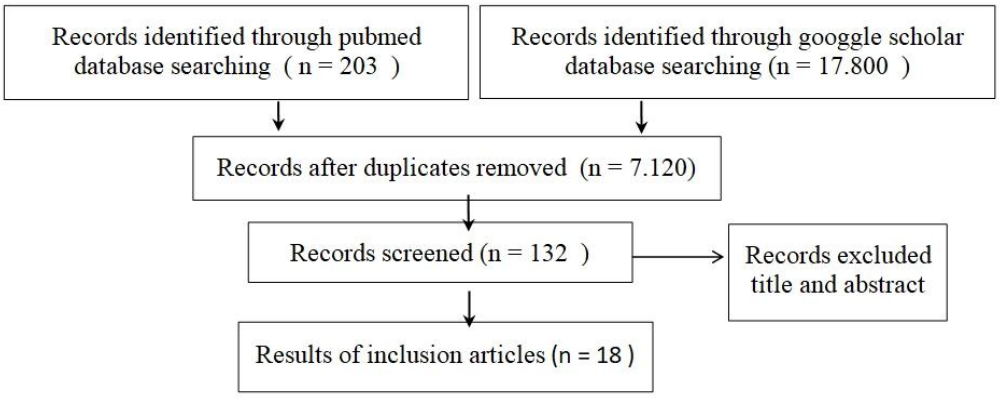

Figure 1. PRISMA flowchart of the included studies

All included studies were published between 2008 and 2018. Of the 18 included studies, 12 were cross-sectional studies,[14,15,16,18,19,20,22,24,25,26,27] 4 were cohort studies,[11,12,13,17] and 2 were case-control studies.[21,23] The total samples from all included studies were 10389, which 4449 were male and 3868 were female. 6 studies did not specify the gender of the samples.[11,12,13,14,17,19] 3 studies included male-only samples.[18,25,26] The subjects age were ranged between 13-75 years. The characteristics of included studies were recorded on table 1.

Table 1. Characteristics of included studies

Study: Author, year (Country)[reference]	Study design	Samples (n)	Gender (f:m)	Age: mean or range (year)	Assessments	Study quality	Duration of use (year)
Thomson 2008 (New Zealand)[11]	Cohort	1015	Na	18-32	Clinical	Q1	14
Robbins 2010 (USA)[12]	Cohort	340	Na	18	Interview, clinical	Q1	22
Shetty 2010 (USA)[13]	Cohort	301	Na	36-79	Clinical	Q1	na
Brown 2012 (USA)[14]	Cross-sectional	58	Na	18-36	Questionnaire, clinical	Q1	na
He Ma 2012 (China)[15]	Cross-sectional	445	218:317	20-59	Clinical	Q2	1-32
Protrka 2013 (Croatia)[16]	Cross-sectional	200	94:106	30	Clinical	Q3	na
Moreno 2013 (Spain)[17]	Cohort	70	Na	30-56	Clinical	Q2	17-40 6-30 8-30
Kayyal 2014 (Saudi Arabia)[18]	Cross-sectional	57	Male-only	16-64	Clinical	Q3	> 5
Smit 2015 (South Africa)[19]	Cross-sectional	308	Na	28	Questionnaire, clinical	Q2	4, 8, 12, > 12
Shetty 2015 (USA)[20]	Cross-sectional	571	111:460	> 30	Clinical	Q1	na
Rommel 2016 (Germany)[21]	Case-control	100	17:83	29	Clinical	Q1	> 1
Antoniazz 2016 (Brazil)[22]	Cross-sectional	121	54:158	13-46	Clinical	Q1	> 1
Trimarchi 2017 (Italy)[23]	Case-control	10	2:8	28-60	Clinical, radiography	Q2	2-30
Mohammadii 2017 (Iran)[24]	Cross-sectional	5900	3238:2662	15-75	Interview, questionnaire, clinical	Q3	Na 7, 13

Sordi 2017 (Brazil)[25]	Cross-sectional	70	24:46	> 18	questionnaire, clinical	Q2	
Cury 2018 (Brazil)[26]	Cross-sectional	161	Male-only	18-60	Clinical	Q2	14
Tao Ye 2018 (China)[27]	Cross-sectional	162	Male-only	19-50	Questionnnaire, clinical	Q1	> 4
Kalbassi 2018 (Iran)[28]	Cross-sectional	500	110-390	18-60	Clinical	Q3	na

f: female; m: male; na: not available

The most frequent psychotropic drugs used were methamphetamine (MA) (50%)[12,13,14,18,19,20,21,26,27], cocaine (44%)[12,17,18,22,23,25,26,28], heroin (38%)[12,14,15,16,17,18,27], cannabis (38%)[11,12,17,18,22,27], opium (11%)[24,27]. 6 studies were using polydrug abusers as samples.[12,14,17,18,22,27] The respective percentages were recorded on figure 2. The route of administration for this substance abuse include smoking (61%), inhalation (44%), injection (38%), and oral route (17%) as shown on figure 3. The duration of drug use ranged from 1 year to 41 years (Table 1).

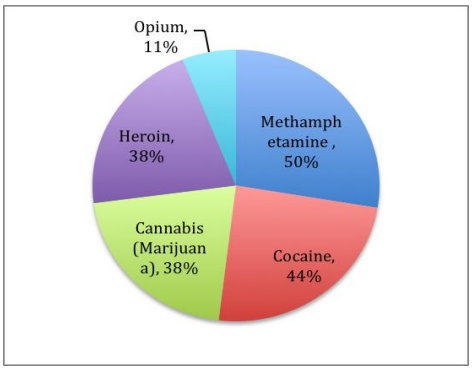

Figure 2. Drug Type

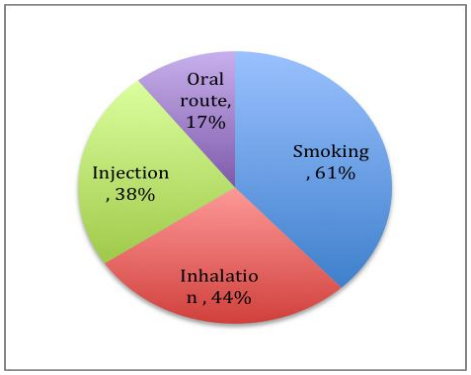

Figure 3. Route of administration

The most significant of oral manifestations reported from included studies were periodontal diseases (78%), dental caries (78%), xerostomia (44%), and bruxism (17%). The oral mucosal lesions found were stomatitis (17%), palatal perforation, traumatic ulcer, leukoplakia, and melanotic nevus (11%). Actinic cheilitis, leukoedema, fistula, lichenoid lesions, Angular cheilitis, mucisitis, papiloma, burn mouth, frictional keratosis, candidiasi and tongue depapilasi were also found (6%). The respective percentage of oral manifestations related to drug abuse was shown on figure 4.

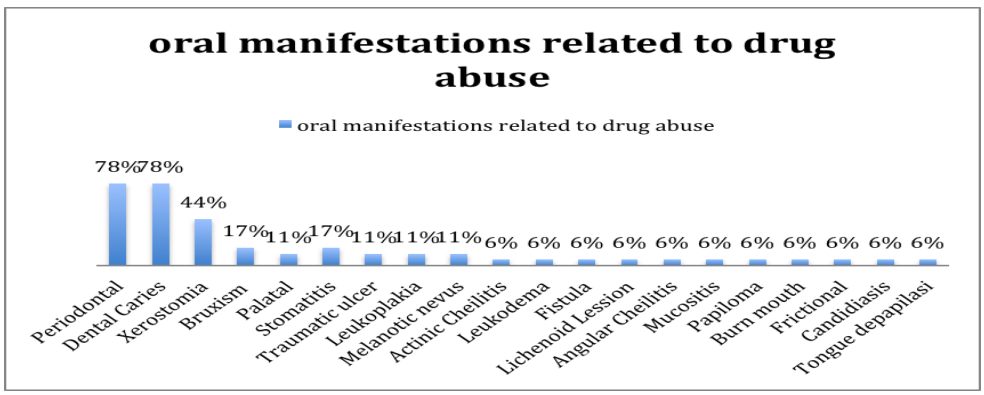

Figure 4. Oral manifestations related to drug abuse

Study qualitative Of the 18 reviewed papers, 8 studies were Q1[11,13,14,20,22,22,27], 6 were Q2[15,17,19,23,25,26], and 4 were Q3.[16,18,24,28] According to Scopus index, all of the included studies were considered as high quality.

DISCUSSION

Drug abuse involves many psychosocial components which strongly affects each other including cultural factors (race/ethnicity and religious aspects), social factors (job-related), and clinical factors (somatic symptoms).[4] But it is important to realize that drug addiction is neither a weakness in character nor a moral issue. Most addictive drugs directly or indirectly activate the brain's reward system by markedly increasing the release of dopamine which is a neurotransmitter regulating emotion, cognition, movement, motivation, and pleasure. The overstimulation of the brain reward pathway with dopamine produces intense euphoric effects. The chronic exposure to a class of drugs may alter the biochemistry of the addictive brain, changing the relative levels of the neurotransmitters, such as γ-aminobutyric acid, dopamine, and serotonin.[4] Substance abuse and addiction are not limited to a specific age group.[1] Our review revealed that the age of drug abusers from included studies were ranged between 13-75 years. We found female to male ratio of drug abusers approximately 3844:4184. Globally It's estimated that men are more likely to have a drug addiction than women.[1]

MA, Cocaine, Cannabis, and Heroin have among the highest global burden of disease among illicit drugs.[5] Our review found that in descending prevalence of this drug type were: MA, cannabis, heroin, cocaine, and opium, while six studies reported using polydrug use.[12,14,17,18,22,28] Polydrug use proved to be closely associated with higher levels of dependence and with the risk of overdose.[29] In terms of routes of administration, our study revealed that in descending frequency of the most patterns of use were: smoking, inhalation, injection, and oral route. The duration of drug use ranged from one year to forty years. Frequency and duration of use are likely moderators of harms associated with routes of administration. Injectors are at higher risk of transmission of drug-related infectious diseases and death.[29]

There are substantial negative effects of illicit drugs on oral health. Longer duration of exposure to illicit drugs leads to higher prevalence of poor oral hygiene, oral mucosal disease, dysfunction of stomatognatic system, even poor nutrition and speech impediments.[7] Our review revealed that periodontal diseases, dental caries, xerostomia, and bruxism were the most significant of oral manifestations related to drug abuse. The results are in accordance with a meta-analysis by Baghaie et al. (2017) which concluded that people with substance abuse disorders have increased rates of both dental and periodontal disease.[8]

Drug abuse (opioids, cannabis, MA) or drug works on nervous system (morphine) has been implicated in drug-induced xerostomia. However, despite the sympathomimetic effects of cocaine, there appear to be no data suggesting a relationship between cocaine use and xerostomia.[30] The possible etiology of drug abuse-induced xerostomia is that certain illicit drugs as sympathomimetic amines can stimulate the sympathetic nervous system and α2-adrenoreceptors within the salivary gland vasculature, causing vasoconstriction and reduction of salivary flow which leads to xerostomia.[7]

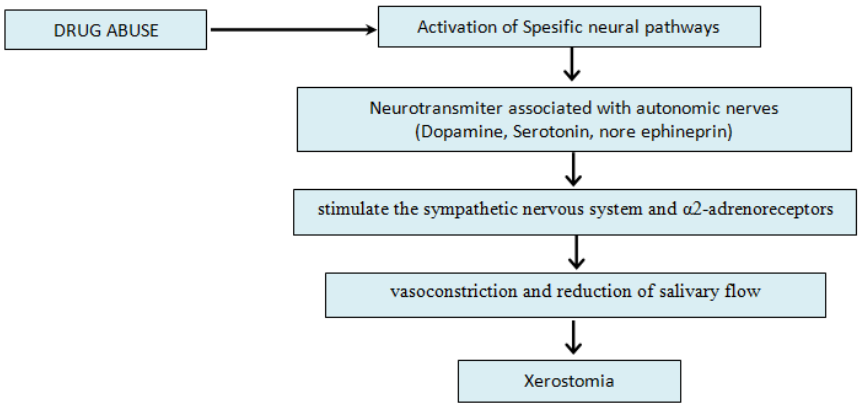

Figure 5. Mechanism of drug abuse caused Xerostomia[5,7]

It is suggested that the higher prevalence of caries in drug abusers has a close relationship with xerostomia, high carbohydrate diet, and poor oral hygiene. In the periodontal disease, immuno suppression and endocrine dysfunction are the two more possible etiological factors in addition with

those factors previously mentioned.[7] A recent scoping review by Mederos et al. (2018) conclude that the specific mechanism by which cannabis acts in the gingival tissues is unknown, but its consumption seems to make periodontal disease worse.[31] MA can trigger xerostomia and severe dental caries. The chronic MA uses are more likely to have gingivitis, bruxism, excessive tooth wear and cracked teeth. The mucosal lesions may appear on the lips and the gingival tissue may have recession.[31]

The oral mucosal lesions found in our review were palatal perforation, stomatitis, traumatic ulcer, leukoplakia, actinic cheilitis, leukoedema, and lichenoid lesions. The prolonged used of illicit drugs cause damage directly to the oral mucosa (ulceration) due to the chemical composition.[7] A systematic review by Silvestre et al. (2010) reporting the hard palate perforation in cocaine abusers concluded that the direct contact of inhaled (snorted) cocaine with the nasal and palatine mucosa can produce direct irritation and ischemia due to vasoconstrictive and caustic effect, leading over the long term to create an oronasal perforation secondary to maxillary bone destructtion.[32] Although based on the limited data, oral health care providers should be aware of cannabis-associated oral side effects, such as xerostomia, leukoedema and increased prevalence and density of *Candida albicans*.[33]

In general, adverse drug reaction (ADR) or adverse drug events (ADE) may have a variety of clinical presentations in the oral cavity include xerostomia, lichenoid reactions, aphthous-like and non-aphthous-like ulcers, bullous disorders, pigmentation, keratosis, fibrovascular hyperplasia, dysesthesias, and osteonecrosis of the jaws.[32] Moreover, there is a relationship between addictive drugs, such as opiates, cocaine, and marijuana, and increased susceptibility to infections. Researches also have shown that immuno modulation induced by these drugs is mainly receptor-mediated. All opioids, especially morphine, are known to alter or suppress the functionality of the various cell types of both innate and adaptive immunity.[34]

We realized that our review is a broad topic and using keywords with language-based limitations and full text availability applied may have resulted in regional and reporting bias and the possible exclusion of key studies published in other languages or unpublished and non-peer-reviewed studies. Bias may occur because inclusion is only the journal for the last 10 years. Researcher bias was addressed through the use of Scopus index to validate the quality of included studies as it may not appropriate to assess the risk of bias in systematic review of observational studies. Our review should be interpreted with caution since all the included studies using different methodologies.

For most illicit drugs, it is difficult to indicate the association between the use and the diseases caused by them due to polydrug use and frequently combined with tobacco and alcohol. In particular, the extent to which and how the illicit drugs are used in the past, is hardly known. This knowledge is necessary to link disease to the use of various drugs. The authors recommend that future research with well design study (e.g. standardized assessments), especially related to a specific entity of oral mucosal lesion as an outcome, be conducted, since there is still limited data on non-polydrug abusers.

The data provided in the present review strongly suggest that the difference in the prevalence of oral lesions is mainly associated with drug type (polydrug and non-polydrug abuse), duration of use, route of administration, and research methodlogies.

Most of included studies confirmed the possible association between drug abuse and oral manifestations, especially oral mucosal lesions. But, the specific mechanism on how each drug acts in oral mucosal lesions is still need to elucidate.

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