# Khat and synthetic cathinones: Emerging drugs of abuse with dental implications

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The rising global availability of the stimulant and euphoric substances, khat and synthetic cathinones, has become a cause for concern in many countries, including the United States. Both substances are illegal in United States, although this has not deterred their use. Besides central nervous system effects, these drugs also cause sympathomimetic and orodental adverse effects, similar to those of amphetamine. Although synthetic cathinones are stronger than khat in most cases, the latter additionally contains tannins, which have astringent effects on tissues components, including those in the oral cavity. Recognizing the use prevalence and reported orodental adverse effects of khat and synthetic cathinones, dental practitioners should be more familiar with these substances to optimally treat and educate their patients abusing them. This paper reviews the pharmacology and adverse effects of khat and synthetic cathinones, along with the extent of their use in United States, with particular emphasis on dental implications. (Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:140–146)

Khat is an evergreen shrub widely grown in parts of Eastern Africa and southwestern Arabian Peninsula.[1-5] Its fresh leaves are typically chewed for their stimulant and euphoric effects, and the habit of chewing khat in these regions is regarded a deep-rooted practice, especially among members of the Muslim community.[1-3] The majority of khat chewers are adult males, who usually participate in khat group sessions almost every day for a number of years.[1-3]

There has been an increase in regional khat consumption during the past several decades, and the availability of khat has also expanded to many other places.[1-5] The World Health Organization and others have estimated that more than 20 million people chew khat on a regular basis worldwide.[6-8] This new development has been facilitated by increased number of immigrants from khat-producing areas and by improved methods of khat transportation and distribution.[1,9,10]

It has been determined that khat leaves contain more than 40 different compounds; contain 3 phenylalkylamine alkaloids (identified as cathinone, cathine and norephedrine); and have stimulant, euphoric, and sympathomimetic effects, among others.[11,12] Of these, cathinone is the most efficacious, contributing to nearly all of the central nervous system (CNS) effects of khat, for which it is primarily consumed. Unrelated to the alkaloids, khat leaves also contain another group of bioactive compounds known as *tannins*, which possess astringent effects.[8,13] Both the alkaloid and tannin components have been reported to contribute to the orodental adverse effects associated with khat chewing.

On the basis of the structure of khat's cathinone, analogues have been synthesized since the 1920s, following the lead of Europe.[14-20] These are a group of recreational drugs that only came to the attention of U.S. authorities in 2010 under the popular name "bath salts."[14-16,18-23] Because of strict regulations, these products are largely synthesized in underground laboratories and made available to users on illicit markets. Apart from having similar actions as the natural cathinone, these drugs also share most of the pharmacologic/toxicologic properties of amphetamine and related compounds. To date, more than 40 different chemicals have been identified as synthetic cathinones in the United States, and many of them are used as cheap substitutes for other more widely abused and tightly regulated stimulants. In addition to CNS stimulation and euphoria, synthetic cathinones also induce multiple additional effects, including sympathomimetic and orodental adverse reactions.[14,15,19,20,22-24]

Among the synthetic cathinones identified so far, some are more commonly used than others, and these include mephedrone, methylone, methcathinone, 3,4-methylenedioxypyrovalerone, naphyrone, butylone, pentedrone, 4-fluoromethcathitone, pyrovalerone, and methedrone.[14,15,21] These drugs are synthesized in the form of a white or brown crystal-like powder and sold to consumers usually in small plastic or foil packages of 200 to 500 mg, labeled as "bath salt" accompanied by the phrase "not for human use."[18,19,23] In some cases, products sold are concealed with some other deceptive labels, such as "plant food," 'jewelry cleaner," "insect repellant," and "phone screen cleaner," together with appealing brand names to make them even more attractive. Besides the powder form, products are also available in other

## Statement of Clinical Relevance

Khat and synthetic cathinones are emerging drugs of abuse that cause multiple central and peripheral adverse effects with considerable dental implications of which oral health care professionals need to be aware.

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formulations, such tablets and capsules. With improved synthesis and marketing efficiencies, there appears to be a recent trend toward a rapid increase in availability of synthetic cathinones in many parts of the world, including in North America, Europe, and Asia.[18,19,21,23]

Given the potential health risks associated with the abuse of khat and synthetic cathinones, the increasing availability of these substances has become a cause for growing concern. This paper reviews the pharmacology and adverse effects of khat and synthetic cathinones, with particular emphasis on dental implications, along with the legality and extent of their abuse in the United States. Because previous reviews on khat and synthetic cathinones in relation to oral health were very limited in both quantity and scope, the current work was intended to provide a more comprehensive and updated information based on the literature from credible sources.

## PHARMACOLOGY AND ADVERSE EFFECTS OF KHAT AND SYNTHETIC CATHINONES

Among the 3 types of psychoactive alkaloids in khat, cathinone has been reported to be the most active as a stimulant, euphoric, and sympathomimetic substance, acting like amphetamine, although to a lesser extent.[6,18,21,24] Its mechanisms of action as a stimulant and a euphoric compound are mainly related to enhancement of neuronal release of dopamine and norepinephrine, and inhibition of the metabolizing enzyme, monoamine oxidase.[5,6,25-27] Through both mechanisms, synaptic concentrations of the monoamines are increased, resulting in enhanced activity. There are also reports indicating augmented release of serotonin by cathinone, but the significance of this is not clear. Apart from these effects, norepinephrine accumulation in peripheral adrenergic synapses causes increased responses of different target tissues, more notably the cardiovascular system.[5,6,25-27]

It has been reported that largely on the basis of the above mechanisms, khat/cathinone causes both acute (short-term) and chronic (long-term) central, peripheral, and oral adverse effects, depending on the amount used and the duration of use. These effects are a reflection of augmented CNS and sympathomimetic responses linked to levels of synaptic neurotransmitters.

Tannins present in khat leaves are a group of polyphenolic biomolecules that form complexes with different macromolecules, especially proteins, potentially affecting functions of tissues that they come in contact with.[13,28,29] Therefore, besides the effects of the phenylalkylamine alkaloids, khat chewing produces additional adverse effects on tissues in the oral cavity, the gastrointestinal (GI) system, and the liver as a result of the release of tannins.[13,28,30,31]

The specific effects manifested in different parts of the body as a consequence of khat chewing are summarized in Table I. It is evident that at least part of the actions of khat mediated via CNS stimulation, peripheral sympathetic activation and the astringent effects of tannins contribute to the development of the orodental conditions listed.[5,12,13,24,27,28,31,32] Furthermore, it has been reported that the physical impact of forceful and persistent khat chewing, per se, can be an additional factor contributing to orodental disorders.[6,14,31] As mentioned earlier and reported previously, it is predictable that the magnitude and/or nature of the orodental effects induced can vary with the amount of khat chewed and the duration of the chewing habit.[12,13,26,28,30-34] The different orodental effects of khat chewing reported include dry mouth/xerostomia, bruxism, caries, periodontal diseases, tooth/occlusal wear,

**Table I.** Reported orodental and systemic effects of khat chewing*

| *Orodental manifestations of khat chewing*[13,26,28,30-32] | *Systemic effects of khat chewing, some with potential influences on dental management*[2,5,6,8,11,12,14,25-27,33-37] | |
|---|---|---|
| | *Short-term/intermediate effects* | *Long-term effects* |
| • Dry mouth/xerostomia<br>• Caries<br>• Periodontal disease/lesions and gingival recession at site of chewing<br>• Mucosal white lesions and/or dark pigmentation<br>• Oral trauma, ulcers and burning sensation<br>• Bruxism<br>• Occlusal wear<br>• Difficulty in opening mouth/trismus<br>• Difficulty in swallowing<br>• Temporomandibular joint dislocation<br>• Oral mucosal keratosis, cancer | • Mild euphoria and excitement<br>• Alertness and relief of fatigue<br>• Insomnia<br>• Improved ability to communicate and talkativeness<br>• Dizziness, lethargy, depression, headache (migraine)<br>• Fine tremor post khat session<br>• Psychotic reactions at high doses<br>• Irritability<br>• Hallucinations, mostly at end of khat session<br>• Inability to concentrate<br>• Anorexia<br>• Tachycardia, vasoconstriction, increased blood pressure<br>• Hyperthermia, perspiration, tachypnea, polydipsia<br>• Impotence, libido change (mostly in men)<br>• Mydriasis, blurred vision<br>• Constipation<br>• Hyperglycemia (inconsistent) | • Gastrointestinal disorders, including stomach ulcers, inflammation, constipation, increased risk of upper gastrointestinal tumors, hemorrhoids<br>• Malnutrition and weight loss<br>• Psychosis, depressive reactions, impaired cognitive functioning<br>• Increased cardiovascular disorders, myocardial infarction, heart attack, cerebral hemorrhage<br>• Liver cirrhosis, fibrosis<br>• Pulmonary edema, bronchitis<br>• Impaired male sexual function, impotence |

*The nature and intensity of effects can vary with amount and duration of khat chewed.

oral ulcers, truisms, difficulty in swallowing, keratosis, and oral cancer, among others (Table I). These khat-related conditions are further discussed in connection with their implications for dental treatments.

By comparison to khat, it is not that clear how the different synthetic cathinones produce their effects. However, from their structural resemblance to the natural cathinone and amphetamine, it is expected that they exert similar pharmacologic/toxicologic effects. Supporting this contention, the literature generally suggests that the synthetic cathinones that have been investigated induce CNS stimulation, euphoria, and sympathomimetic effects, among other effects, which are related to increased synaptic concentrations of the monoamines dopamine, norepinephrine and serotonin.[14,18,21,23,33,38] Increased release of the monoamines and inhibition of their neural reuptake by these drugs have been shown to be the underlying mechanism. The fact that different synthetic cathinones display varying abilities of increasing extracellular neurotransmitter levels may account for the different mood-altering effects, toxicities and addiction potentials associated with the individual drugs. As confirmed experimentally, the addiction liability reported for synthetic cathinones is more specifically linked to their ability to elevate dopamine in specific areas of the brain known to be involved in this behavior.[14,18,21,23,33,38]

It should be noted that most of the current understanding of the pharmacology and adverse effects of synthetic cathinones in humans is largely based on case reports, data from poison control centers, emergence medicine department reports, and drug abuser survey studies.[6,14,18,20,21,23,24,26,33,35] Thus, in the absence of well-planned systematic investigations, inherent flaws are likely to exist at least in some of the results reported. Compounded with this are also the limited ability to test accurately for the diverse synthetic cathinones, the obscure identity/composition of the products in a given package, and the way the drugs are used by abusers.[14,16-18,33] The literature also indicates that with synthetic cathinones, substitution of ingredients or incorrect labeling of products is a common practice, further compounding the problem.

Despite the above limitations, however, there is a consensus that synthetic cathinones produce consistent short-term (acute) and long-term (chronic) effects in the CNS as well as peripherally, including in the oral cavity. Relative to the effects of the natural cathinone, these drugs are more than 10 times as strong in their actions or toxicities.[16,18,19,35] The central and peripheral effects of these emerging drugs are summarized in Table II, along with the associated orodental effects. As shown in Table II, it is clear that at least a portion of the adverse effects described are related to stimulation of the CNS and the peripheral sympathetic pathway, and these may include the orodental disorders listed. There is a possibility that these drugs may inflict more direct effects on the oral cavity as well as on other organs, such as the liver. The orodental effects reported in relation to the abuse of synthetic cathinones include dry mouth/xerostomia, bruxism, caries, periodontal diseases, and tooth wear, among several others. These effects are further discussed in connection to their implications for dental treatments. It should be noted that as with khat (or the natural of cathinone), the intensity and/or the nature of the effects

**Table II.** Reported orodental and systemic effects of synthetic cathinone use*[,14-21,23,24,33,36]

| *Orodental manifestations of synthetic cathinone use* | *Systemic effects of synthetic cathinone use, some with potential influences on dental management* | |
|---|---|---|
| | *Short-term/intermediate effects* | *Long-term effects* |
| • Dry mouth/xerostomia<br>• Caries<br>• Tongue disorder<br>• Bruxism<br>• Increased muscle tension, jaw clinching<br>• Tooth wear<br>• Periodontal lesions<br>• Oral mucosal ulcers | • Overall sympathetic hyperactivity<br>• Euphoria, increased alertness, increased sociability<br>• Insomnia<br>• Anxiety, psychosis, paranoia, agitation, aggression, violet behavior (mostly with mephedrone)<br>• Hallucinations, delusional behavior, confusion<br>• Dizziness, depression, headache, suicide thoughts<br>• Seizures<br>• Increased heart rate, increased blood pressure, chest pain<br>• Nosebleeds<br>• Anorexia, nausea, vomiting<br>• Hyperthermia<br>• Tremor of extremities<br>• Mydriasis<br>• Increased sex drive<br>• Acute renal failure<br>• Disseminated intravascular coagulation<br>• Metabolic acidosis (mostly with methylone)<br>• Death resulting from acute overdose and suicide | • Overall sympathetic hyperactivity<br>• Severe aggression, paranoia, violence<br>• Malnutrition and weight loss<br>• Hyponatremia<br>• Rhabdomyolysis<br>• Renal failure<br>• Hepatic failure<br>• Parkinsonism (mostly with methcathinone)<br>• Serotonin neurotoxicity (mostly with methylone, mephedrone)<br>• Blood and circulatory disorders<br>• Hypertension<br>• Muscle spasms<br>• Loss of bowel control<br>• Sharp increase in body temperature<br>• Infectious diseases from shared needles used for IV injection of drugs<br>• More frequent deaths from complications |

*The nature and intensity of effects can vary with amount and duration of synthetic cathinone used.

of synthetic cathinones may vary with the amounts of the compounds consumed and the duration of the habit, in addition to the types of compounds used. Associated with the intravenous administered of synthetic cathinones by abusers, greater risks for contracting human immunodeficiency virus (HIV) infection, hepatitis, and other infectious diseases have also been reported.[18,21,29,33]

## DEPENDENCE AND WITHDRAWAL ASSOCIATED WITH KHAT AND SYNTHETIC CATHINONES

Khat contains cathinone as a major psychoactive ingredient that causes increased synaptic concentration of dopamine and other neurotransmitters. The activation of dopaminergic pathways in specific areas of the brain (e.g., mesolimbic) is linked to the euphoric effects of khat.[2,33,35] However, because the cathinone released from khat during chewing is low and susceptible to rapid degradation, its effect is relatively short-lived. Therefore, under normal circumstances, khat causes mostly moderate psychological dependence, with no clear physical dependence or addiction.[2,10] Accordingly, most khat consumers show the signs of psychological dependence without well-defined physical dependence or addiction. However, physical dependence can be an important factor if there is an underlying metal disorder or susceptibility. Following discontinuation of khat chewing after prolonged consumption, signs of withdrawal are commonly observed, and these include occasional lethargy, mild depression, nightmares, slight tremor, and social isolation, among others.[2,6,10] Coupled with psychological dependence, the withdrawal effects may contribute to continued consumption of khat. However, there seems to be no hard evidence indicating the development of tolerance with the use of khat. In contrast to amphetamine, the psychopharmacologic effects of khat described are much less intense.

As mentioned earlier, use of synthetic cathinones leads to CNS stimulation and euphoria, and the role of dopamine as a trigger for euphoria is well established.[14,18,21,23,33,38] Relative to khat/cathinone, this is more so, given the more efficacious effects of these synthetic drugs. Consistent with this, available records also indicate that the use of synthetic cathinones leads to a much higher abuse or addictive liability.[14,18,21,23,33] In this regard, animal studies involving self-administration patterns have demonstrated that synthetic cathinones escalate drug intake nearly identical to that of methamphetamine. Human users of synthetic cathinones have reported that these drugs trigger intense cravings or uncontrolled urges for repeated use, suggesting strong addictive effects.[14,18,21,23,33] It has also been shown in other studies that repeated use the drugs produce tolerance, psychological and physical dependence, and severe withdrawal syndromes. The reported withdrawal syndromes include depression, anxiety, tremors, sleeping problems, and paranoia. These abuse characteristics of synthetic cathinones lend the drugs to be more challenging than cathinone or khat itself.[14,18,21,23,33]

## REPORTED DRUG INTERACTIONS WITH KHAT RELEVANT TO DENTISTRY

There are limited evidence-based reports demonstrating the interactions between khat and drugs of dental relevance. GI absorption of the antibiotics amoxicillin and ampicillin has been reported to be reduced by khat ingestion, with the possibility of decreasing the bioavailability and effectiveness of the antibiotics.[34] This effect of khat on the GI system is likely to be related to the astringent action of tannins found in khat leaves.[34] Therefore, concomitant oral administration of these antibiotics for treatment may not produce anticipated therapeutic results. From this observation, it is also prudent to be cautious when using other orally administered antibiotics, at least from the same drug category. However, taking these drugs orally 2 hours after khat consumption does not appear to alter their effectiveness.[34] Nonetheless, using these antibiotics while chewing khat is opted for, appropriate routes other than the oral route should be considered.

Other than the above interaction report, there is no data-based information in the literature regarding the interactions of drugs with either khat or synthetic cathinones. However, various drug interactions with these stimulant drugs have been proposed, largely on the basis of theoretical grounds and observations of interactions involving other closely related drugs.[23,33,38] This issue is given further considerations in connection to the discussion on the dental implications of the uses of khat and synthetic cathinones.[5]

## LEGAL STATUS AND EXTENT OF USE OF KHAT AND SYNTHETIC CATHINONES IN THE UNITED STATES

Cathinone and cathine of khat are controlled substances in the United States, under the Controlled Substances Act (CSA).[9,33] Cathinone is a Schedule I stimulant drug, and cathine is a Schedule IV drug. Because of the presence of cathinone, khat is banned in the United States, although, as a plant, it is not controlled.[8,9]

According to the Drug Enforcement Agency (DEA), the abuse of khat in the United States is most prevalent among immigrants from East Africa and Arabian Peninsula, more notably those from Yemen and Somalia.[8,9] The extent of abuse is relatively high in cities with a large number of immigrants from these counties. These cities include Washington DC, New York City, Boston, Columbus, Detroit, Dallas, Los Angeles, Kansas City, Minneapolis, Pittsburgh, Oakland and Nashville.[9] Khat is smuggled into the United States illegally from the

regions of primary cultivation and/or through third parties located in Europe. From seizure data, it has become evident that the availability of khat in the United States has steadily increased in recent years. There are also reports that besides the immigrant population, some non-immigrant groups, including white Americans, have begun abusing khat, further raising the level of concern about the expanding popularity of the stimulant plant.[9]

As noted earlier, similar to many other countries, recreational synthetic cathinones in the United States (commonly known as "bath salts"), are among the new largely unregulated psychoactive substances available on the illicit market.[14,15,17,23] Currently, all the identified synthetic cathinones in the United States are listed as Schedule I drugs. There is also a suspicion that some other products that have evaded the control mechanism show up on the illicit market. As stimulant and euphoric agents, these drugs are much stronger than khat, and they are often marketed as cheap substitutes for the more popular illegal stimulants, such as methamphetamine, cocaine, and ecstasy.[6,14-18,20,21,24] They are available online and in drug paraphernalia stores under a variety of brand names, including Bloom, Flakka, Cloud Nine, Lunar Wave, Scarface, Vanilla Sky, and White Sky. Despite the limitations of large-scale prevalence studies, available evidence collectively indicates that these drugs are among the rapidly proliferating group of substances in the United States.[6,14-18,20,21,24] For instance, the number of calls received by poison control centers across the United States regarding bath salt has been reported to have increased from 304 incidents in 2010 to 6138 in 2011, indicating a more than 20-fold increase.[14,18,20,21,23,24] Nonetheless, in view of the existing acute shortage of information, particularly with respect to the rapidly changing scenario, there is an urgent need for more research on these emerging group of potentially harmful drugs.

## DENTAL IMPLICATIONS OF USE OF KHAT AND SYNTHETIC CATHINONES

A wide range of acute and chronic orodental and systemic effects have been reported as consequences of khat chewing and use of synthetic cathinones.[2,6,14,15,33] The intensity and/or nature of the effects depend on various factors, including the type and amount of substances used, the duration of consumption, the presence of other interacting substances and the condition of the consumer, among others. Dentists should be familiar with these harmful drugs and the effects they produce to provide optimal dental care and to educate their patients taking these substances. In view of the rising consumption of these drugs by the general population, dentists are more likely to see more of such patients in their clinics. Although the orodental effects inflicted by these stimulants are of direct dental relevance, the systemic effects described can have indirect influence, such as through the need for modification of dental treatments.

As shown in Tables I and II, both khat and synthetic cathinones, in most cases, cause multiple identical oral effects. These effects are related, among others, to a reduction in saliva production, development of caries, bruxism, tooth/occlusal wear and periodontal disease, although there may be some overlap among some of these factors. Bruxism and facial tics that usually follow prolonged abuse of these drugs are identified as contributory to the incidence of traumatized tongue and worn teeth.[33,38] The role of these stimulant drugs in periodontal disease is partly explained by the fact that both drug types impair circulation in the periodontal structures, although there may be some other factors playing an additional role.[11,33,34] The American Dental Association practical guide reference, published in 2015, recommends the application of topical fluorides, management of xerostomia, use of occlusal guards, and provision of periodontal treatment for such orodental conditions, where appropriate.[33] It is also important to realize that certain differences exist in the oral effects of khat and synthetic cathinones, which require careful diagnosis and treatment.

Additionally, because of the presence tannins in khat leaves and the physical effect of forceful and prolonged chewing, chronic khat consumption is associated with multiple other orodental abnormalities, including mucosal white lesions, dark mucosal pigmentations, periodontal lesions at chewing sites, temporomandibular joint dislocations, difficulty in swallowing, and oral keratosis, and cancer, all of which should be given diligent attention for diagnosis and treatment.[6,13,14,25-28,30-32,34,39] Considering only the orodental effects of cathinone of khat and synthetic cathinones, it is highly likely that the latter may produce more intense adverse effects for a comparable duration of use, consistent with reports in the literature.[6,14,15,18,19,21,24]

Because most abusers of khat and synthetic cathinones concomitantly consume other potentially harmful substances, such as large quantities of sugary carbonated/acidic beverages, and smoke tobacco, clinicians should incorporate in their treatment a plan of action for addressing these problems, too.[1,11,33] Nutritional deficiencies resulting from prolonged anorexia, GI disorders, and hepatic effects caused by khat chewing and/or synthetic cathinone use can lead to immune suppression, potentially exacerbating existing infections with added risks for dental adverse consequences.[5,6,8,14,16,18-20,24-27,34,36] In this case, caution should be exercised in prescribing opioid analgesics to these patients, as chronic use of these drugs is known to inhibit the immune system.[33,38]

Cardiovascular disorders are among the different systemic effects caused by khat and synthetic cathinone. These disorders include tachycardia, cardiac dysrhythmias, myocardial infarction, increased blood pressure/

hypertension, heart attack and cerebrovascular accidents/hemorrhages.[23,33,36] Most of these effects increasingly become more severe with the duration of abuse of the drugs, particularly in individuals with enhanced susceptibility. Practitioners are expected to be cognizant of these adverse events when dealing with patients engaged in drug abuse but seek appropriate treatment and consultative measures. Because anxiety and a stressful environment (as usually experienced in dental office) are likely contraindications with certain cardiovascular abnormalities, efforts should also be made by clinicians to minimize stress in these patients. In view of the increased sympathomimetic responses to the abuse of khat and synthetic cathinone, it is recommended that the simultaneous administration of vasoconstrictors (e.g., epinephrine) with local anesthetics and their use in gingival retraction cords be minimized or avoided. Such uses of vasoconstrictors have the potential to enhance the cardiac (e.g., tachycardia) and vascular (e.g., elevated blood pressure) effects that are usually associated with the consumption of either khat or synthetic cathinones.[33,38]

The GI effects of khat should also be of a concern to dentists because at least the tannin components are well known to reduce the oral absorption and bioavailability of certain drugs, such as oral amoxicillin and ampicillin, as mentioned earlier.[33,34] In such cases, alternative approaches should be sought, as suggested previously. Moreover, tannins in khat can cause malabsorption of nutrients, potentially contributing to the risk of nutritional deficiencies commonly seen in chronic khat chewers.[13,28] Both khat and synthetic cathinones have been reported to induce hepatic adverse events, which, in turn, can impair the metabolism and/or utilization of drugs and nutrients, with consequential potentially harmful effects. Studies have also shown that synthetic cathinones are metabolized by liver cytochrome $P_{450}$, and on the basis of this finding, interactions between certain drugs and synthetic cathinones have been hypothesized to occur at the level of hepatic drug metabolism.[18-21] As many drugs taken by dental patients are metabolized by liver cytochrome $P_{450}$, practitioners should make every effort to minimize or avoid such interactions in patients who abuse synthetic cathinones.

Dentists should not only be concerned about the physical effects of khat and synthetic cathinones, but they should also be concerned about aspects of behavioral issues related to substance use/abuse that might interfere with the delivery of dental care. Excessive and prolonged use of the stimulant substances may cause reduced responses to at least some anxiolytics, sedative–hypnotics, analgesics, and anesthetics, necessitating the utilization of increased doses of these medications or rescheduling of treatment appointments.[33,38] Increased sensory and motor activity elicited by high doses of CNS stimulants can cause nervousness, hyperexcitability, hyperreactivity, irritability, restlessness, tremor, and muscle twitches, among others, which may physically interfere with dental management.[33,38] In some cases, excessive stimulation by abused drugs may be followed by depression, which, in turn, can result in undesirable outcomes for dental treatments. The development of tolerance to and dependence on synthetic cathinones and, in some cases, to khat may intervene with the proper use of psychoactive stimulant medications by patients, requiring the administration of increased doses or use of alternative approaches.[33,38] Drug-induced self-neglect and poor oral hygiene in patients are also relevant issues about which the dentist needs to be more vigilant. Being conscious of the use prevalence and legal control of khat and synthetic cathinones and the appreciation of the cultural background of khat users are of benefit to dental practitioners to better understand, treat, and educate patients who abuse these drugs.

## CONCLUSIONS

During the past several decades, the use of khat and synthetic cathinones has increased in various places worldwide, including the United States. Both substances are banned in the United States because of their abuse potential, although this has not deterred their availability. Besides inducing CNS stimulation and euphoria, these substances also cause, among others, sympathomimetic and orodental adverse effects, mostly resembling the effects of amphetamine. Although most of the effects produced by synthetic cathinones are greater than those induced by khat, the latter additionally contains tannins, with astringent effects on tissues, including those in the oral cavity. As the availability of khat and synthetic cathinones continues to increase, in of recognition of the orodental adverse effects they produce, dental practitioners should be more familiar with them to optimally treat and educate their patients abusing these substances. This review serves as a step toward this direction by way of providing relevant information, with specific recommendations, whenever feasible, from credible literature sources. The review also attempts to identify limitations of the available literature, further emphasizing the need for additional research on the topic.

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