

Chronischer Khatkonsum und psychotische Störungen: ein Literaturüberblick und Ausblick

Schlüsselwörter

Khat, Qat, Psychose, Schizophrenie, Überblick

Zusammenfassung

Fragestellung: *Khatblätter, die das amphetaminähnliche Kathinon enthalten, werden traditionell in afrikanischen und arabischen Ländern gekaut. In den letzten Jahrzehnten veränderte sich das Konsummuster tiefgreifend. Darauf Bezug nehmend wird hier ein Überblick über den Zusammenhang von Khatkonsum und Psychosen gegeben. Ergebnisse:* *Mehrere Falldarstellungen aber nur wenige Gruppen- und Populationsstudien behandeln das Thema. Sie sind insgesamt inkonsistent, haben methodische Probleme, berichten oft nur qualitative Ergebnisse und behandeln wichtige Fragen nicht. Schlussfolgerungen:* *Obwohl Khatkonsum häufig mit Psychosen in Zusammenhang gebracht wird, gibt es nur wenige fundierte Studien. Gesicherte Erkenntnisse sind z. B., dass exzessiver Khatgenuss zu kurzdauernden Psychosen führen kann und dass vulnerablen Personen vom Khatkonsum abgeraten werden sollte. Unklar bleibt die Richtung des Zusammenhangs zwischen Khatkonsum und unspezifischer Psychopathologie. Quantitative, kontrollierte Längsschnittstudien sind erforderlich, um psychiatrische Konsequenzen zu verstehen, und inwieweit Khat mit der Entwicklung von langdauernden Psychosen und ihrem Verlauf zusammenhängt.*

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Chronic khat use and psychotic disorders: A review of the literature and future prospects

Key words

Khat, qat, psychosis, schizophrenia, review

Abstract

Aims: In recent decades, the traditional habit of chewing the khat leaves, which contain the amphetamine-like cathinone, has undergone profound changes in African and Arab countries, from a socially regulated use pattern to uncontrolled consumption. This is of special public mental-health concern. In this article, a review of the scientific literature on the relationship between khat use and psychosis is provided. **Results:** Several case studies, but only a few group and community-based studies, have addressed this topic. The studies show inconsistent results, have methodological problems, and fail to report quantitative results. Many important questions remain unaddressed. **Conclusions:** The frequently stated association between khat use and psychosis contrasts with the small number of sound studies. Currently, only a few conclusions can be drawn, that excessive khat use can cause brief psychotic disorders and that people with a preexisting vulnerability should be discouraged to use it. The direction of causality between general psychopathology and khat use remains unclear. This review confirms the need for quantitative, controlled, and longitudinal studies, which can help deepen the understanding of the mental-health effects and its link to the development and course of long-lasting psychosis.

Introduction

Khat (*Catha edulis Forsk*) is an ever-green shrub of the *Celastraceae* family, normally reaching 6 m in height, but in an equatorial climate it might grow to 25 m (UNODC, 1956). Khat can be found in the Abyssinian highlands, the Horn of Africa, Eastern and Southern Africa, the Arab peninsula, and Afghanistan (Krikorian, 1983). The first historical reference to it is found in a medieval Arab manuscript from the first half of the thirteenth century (UNODC, 1956). The first botanical description goes back to the naturalist Peter Forsskål (1732–1763; Meampel, 1992). For a complete botanical description, see Nordal (1980). For commercial purposes, it is grown in altitudes of 1,500 to 2,500 m above sea level, mostly pruned to 2–7 m (Kennedy, 1987; Lemessa, 2001).

In Ethiopia, Yemen, Somalia, and Kenya, the fresh young leaves and tender stems are traditionally consumed for their stimulating properties (Halbach, 1972). The freshness of the plant material is considered crucial, because 48 hours after its harvest the desired properties will have largely dimin-

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ished. Khat was traditionally used during Muslim religious ceremonies and when studying the Koran, for recreational purposes, as a natural plant remedy with medicinal properties, and for reducing physical fatigue while traveling or working. The leaves are mostly chewed, and an egg-sized bolus is kept in the cheek for several hours before it is spit out; the extracted juice is swallowed. Especially among Somali consumers, the whole plant material might be swallowed (personal communication, P. Hansen). However, it is also used as tea (Abyssinian, Arabic or Bushman's tea), paste, or as dried powder. The most common traditional setting for consumption is the »khat party« (Baasher, 1980; Kennedy, 1987; Weir, 1985), which is known to have taken place for centuries among the higher classes (Schopen, 1979). Men usually gather on weekends after lunch in specially prepared rooms in private houses (»mafrish«, »mafrij«) and chew khat until the early evening. Nowadays, khat parties also take place in public teashops or cafes, where sodas, sweet tea, water, chewing gum, and cigarettes are often being consumed at the same time. Women are said to chew less frequently, and mixed-gender khat parties seem to be rare. A detailed description of the khat party is provided elsewhere (Al-Motarreb, Baker, & Broadley, 2002; Baasher, 1980; Kennedy, 1987). These gatherings were and still are an important social institution, because political, business and social affairs are settled during khat chewing, and khat is also an integral part of other rites and celebrations, e.g. weddings and rites of passage (Al-Motarreb et al., 2002; Carrier, 2005). The lower classes and inhabitants of rural areas, e.g. farmers, traditionally used khat throughout the day during heavy work, for fighting physical fatigue, or the suppression of hunger (Gebissa, 2004; Luqman & Danowski, 1976; Schopen, 1979). The cultural, social, and national importance of khat chewing has been emphasized by many researchers (Gebissa, 2004; Kennedy, 1987; Weir, 1985).

Chemical agents, pharmacology, and neurophysiological effects

Since the 19th century, pharmacologists have tried to isolate the agents that are responsible for the stimulating effect of the khat leaves (Halbach, 1972). Today it is known that the unstable alkaloid S-(-)-cathinone (S(-)-alpha-aminopropiophenone) is the main psychoactive agent (Szendrei, 1980). In addition, cathine (S,S-(+)-norpseudoephedrine), other alkaloids and tannins have been identified (Al-Hebshi & Skaug, 2005).

Cathinone content depends on the origin and freshness of the plant material, and these factors are correlated with the estimated quality and market price (Al-Motarreb et al., 2002; Geissshusler & Brenneisen, 1987). By chewing the khat leaves, cathinone is effectively extracted into the saliva and directly absorbed through the oral mucosa and in the stomach (Toennes, Harder, Schramm, Niess & Kauert, 2003). For cathinone, maximal plasma concentrations are reached 2 to 2.5 hours after the start of a session; for cathine, after 2.6 hours. Cathinone has a mean terminal elimination half-life of 1.5–4.5 hours; for cathine it is approximately 5 hours (Toennes et al., 2003; Widler, Mathys, Brenneisen, Kalix & Fisch, 1994). In different experimental khat sessions, after the ingestion of 0.6 and 0.8 g of khat leaves per kg of body weight, the maximum concentrations of cathinone in plasma have been 58.9 ± 18.8 ng/ml and 127 ± 53 ng/ml; for cathine, they have been 71.2 ± 13.9 ng/ml and 89 ± 49 ng/ml (Toennes et al., 2003; Widler et al., 1994). After ingestion, S-(-)-cathinone is reduced to its main metabolites R,S-(-)-norephedrine and S,S-(+)-norpseudoephedrine (Brenneisen, Geissshusler & Schorno, 1986; Toennes et al., 2003).

Numerous laboratory studies have confirmed that cathinone resembles amphetamine in chemical structure and that it affects the central and peripheral nervous system (Kalix, 1990) and behaviour (Woolverton & Johanson, 1984; Zelger, Schorno & Carlini, 1980) similarly (for a review see Kalix,

1991; Nencini & Ahmed, 1989). In the CNS, cathinone provokes the release of catecholamines, especially dopamine, at the presynaptic storage sites, and is about half as potent as amphetamine (Pehek, Schechter & Yamamoto, 1990); it inhibits re-uptake and can produce depletion of central dopamine (Schechter, 1990a, 1990b). Cathine has a much smaller effect in the release of central catecholamines. Peripherally, cathinone and cathine are equipotent in the release of noradrenaline at the presynaptic storage sites; thus, both have sympathicomimetic effects. The short-term physiological effects of khat reflect the sympathicomimetic and central dopaminergic activity, e.g. increased heart rate and elevated diastolic and systolic blood pressure (Brenneisen, Fisch, Koelbing, Geissshusler & Kalix, 1990; Hassan et al., 2000; Toennes et al., 2003; Widler et al., 1994). The immediate emotional effects in experimental human settings are euphoria (Brenneisen et al., 1990; Widler et al., 1994) and a subsequent depressive reaction (Hassan, Gunaid, El-Khally & Murray-Lyon, 2002). Thus, it has been argued that the depressive phase after the end of the khat session motivates the user to continue to chew (Griffiths, 1998).

Kalix (1991) postulated a higher potential to induce dependence than amphetamine because: (1) cathinone has a more rapid onset of action in discrimination experiments (Johanson & Schuster, 1981; Woolverton & Johanson, 1984), (2) tolerance to cathinone's anorectic effects develops faster and is more pronounced, (3) in conditioning experiments, cathinone is less aversive than amphetamine (Goudie & Newton, 1985), and (4) in self-administration experiments, response rates are higher to cathinone than those maintained by amphetamine (Johanson & Schuster, 1981; Yanagita, 1986).

Economics of consumption

For centuries khat has probably been used only among the production and neighbouring regions; long-distance transport was not feasible be-

cause of the short-lived nature of khat's stimulating properties (Gebissa, 2004). During the past decades, the economic importance and consumption of khat leaves have increased dramatically, from a custom practiced only by certain social or ethnic groups in parts of Africa and the Arabian Peninsula, to a widespread habit in the general population of these countries (Alem, Kebede & Kullgren, 1999; Belew, Kebede, Kassaye & Enquosselassie, 2000; Kebede et al., 2005; Sellassie & Gebre, 1996) and among immigrant communities all around the world (Nencini, Grassi, Botan, Asseyr & Paroli, 1989; Patel, Wright & Gammampila, 2005). One decade ago it was estimated that on a world-wide scale, there were 5 to 10 million consumers each day (Balint, Ghebrekidan & Balint, 1991; Kalix, 1996). Today, the main producing countries are Ethiopia, Yemen, and Kenya, where the production, trade, and use of khat are not legally restricted. Ethiopia is considered to be the world's largest producer, with khat being the country's second largest export product in 1999 (FAO, 2001). In Yemen, the area under khat production has expanded dramatically, and the khat sector now produces 10% of the national GDP (Ward, 2000; Worldbank, 2005). Also in Kenya, the economic importance of khat is considered great, with remarkable monopoly-like trading structures linked to Somalia, its main export destination (Maitai, 1996). The khat sector today feeds millions of farmers and people involved in its trade. Due to its high and stable market prices and its resistance against drought and frost, farmers have a more secure and higher income from khat than from other crops (Feyisa & Aune, 2003; Gebissa, 2004; Kennedy, 1987; Seyoum, Kidane & Gebru, 1986). Thus, khat growing communities have been found to be more prosperous than others (McKee, 1987; Seyoum et al., 1986). However, the khat boom has also caused marked changes in traditional agriculture and land-use systems (Feyisa & Aune, 2003) as well as ecological problems, e.g.

through the exploitation of scarce water resources for irrigation farming (Worldbank, 1999).

There is evidence that khat-chewing habits have changed qualitatively during the last decades. What was previously a formalized and strongly regulated social habit, now has features of excessiveness, informality, and decoupling from normative control, at least in some user groups (Nabuzoka & Badhadhe, 2000). This is apparent in individuals' consumption of higher quantities of the drug (Dhadphale, Mengech & Chege, 1981; Griffiths, 1998; Nabuzoka & Badhadhe, 2000; Odenwald, Hinkel et al., submitted; Patel et al., 2005), longer continuous consumption time (Nabuzoka & Badhadhe, 2000; Odenwald, Lingenfelder et al., submitted), and parallel use of other drugs, e.g. benzodiazepines or alcohol (Nabuzoka & Badhadhe, 2000; Odenwald, Hinkel et al., submitted; Omolo & Dhadphale, 1987; Sellassie & Gebre, 1996; Zein, 1988).

Although previously khat chewers were traditionally »initiated« at about 20 years of age, nowadays they start using the drug earlier, and especially in Kenya consumption has become part of the youth culture (Carrier, 2005; Nabuzoka & Badhadhe, 2000; Patel et al., 2005). Furthermore, the formerly male habit is now practiced more and more by women (Alem et al., 1999; Griffiths, 1998; Nabuzoka & Badhadhe, 2000; Patel et al., 2005) and, alarmingly, also during pregnancy and lactation (Belew et al., 2000; Eriksson, Ghani & Kristiansson, 1991). Cathine has been identified in human breastmilk (4 of 7 samples tested positive, 2–4 hours following chewing; positive samples ranged between 90 ng/ml and 140 ng/ml) and in infant urine (one sample that was taken 12 hours following chewing was found to have 200 ng/ml; Kristiansson, Abdul Ghani, Eriksson, Garle & Qirbi, 1987).

New patterns of use, which were not previously described in the academic literature, have been observed in Somalia and Ethiopia: »ijabane« or »igabana« (»eye opener«). This consump-

tion during early morning hours was previously known only among khat farmers (Gebissa, 2004). Today, during morning hours, crowds of khat chewers gather in the proximity of khat markets. They chew together and share with one another, in order to chase away the typical khat-induced »qaadiro« (»hangover«; personal observation, confirmed by P. Hansen, personal communication). Some researchers highlight the special function of khat chewing in immigrant communities in western countries, where it apparently serves an identity-defining role (Ahmed & Salib, 1998; Griffiths, 1998; Patel et al., 2005).

Controversy surrounding khat and medical knowledge of its consequences

The benefits of and harm from khat use has long been debated. Since colonial times, there have been descriptions of adverse behavioural reactions and negative health effects from khat use (Carothers, 1945). Its use has been linked to economic problems, general unproductivity, underdevelopment, and disease (WHO, 1983; for a review, see Gebissa, 2004). Thus, attempts to ban khat have been undertaken, for example, in 1957 in the territories under British control and in 1983 in Somalia (Elmi, Ahmed & Samatar, 1987; Gebissa, 2004; Luqman & Danowski, 1976). After World War II, the WHO and other UN organizations became active (UNODC, 1956) and initiated basic research on khat (Szendrei, 1980), which eventually led to its placement under the International Convention on Psychotropic Substances (United Nations, 1971) in 1986.

Another line of argument was introduced by Islamic scholars, who considered khat to be »haram« and forbidden by the Holy Koran (Al-Ghdaian, 1983), leading to its ban by the »World Islamic Conference for the Campaign Against Alcohol and Drugs«, in Medina in 1982 (El-Kader, 1983) and in some Islamic countries, especially Saudi Arabia.

During the last two decades, there

has been an increase in scientific research on the health effects of khat use beyond the question of addiction, and recently several scholars have written extensive reviews of the literature (ACMD, 2005; Al-Habori, 2005; Al-Hebshi & Skaug, 2005; Al-Motarreb et al., 2002). The following consequences of khat chewing on physical health have been confirmed: (a) Some evidence has accumulated for a link between khat chewing and myocardial infarction, although confounding factors, such as smoking, should be studied further; (b) certain gastro-intestinal problems, such as constipation, and lesions of the oral mucosa are clear consequences of khat chewing; (c) khat chewing appears to be associated with the development of oral cancers; however, the mechanisms involved are not clearly understood; the evidence for other forms of cancer and for duodenal ulcers is less clear; (d) there is some evidence that khat has cytotoxic effects and causes histopathological changes, e.g. in liver tissue; (e) acute effects on reproductive functions, e.g. spermatorrhoea and changed libido, might occur and chronic use might have negative effects on male semen parameters; (f) lower birth weights of babies born to khat-chewing mothers have frequently been found.

Currently there is no comprehensive review on khat and psychopathology. However, several observations were noted above: (a) khat causes psychological but not physical dependence, and tolerance does not develop; (b) khat-induced psychotic disorders are thought to be rare. The authors acknowledge the lack of conclusive data, especially those regarding the effects of khat on mental health.

The goal of this review is to systematically analyse the available scientific literature on the association between psychotic symptoms and disorders and chronic khat use. This relationship has often been suggested because of the similarities between cathinone and amphetamine. Emphasis is placed on methodological aspects of the published literature.

Method

A literature search was conducted using PubMed and PsychInfo with the search terms »khat« or »qat« and »psychosis« or »psychopathology«. Literature cited in articles or books that was not listed in the databases was also used. Because of the limited number of published works, articles with methodological problems were included. In total, there were 46 articles or reports that provided original quantitative or qualitative data on khat chewing and psychotic symptoms.

Psychopathological effects of chronic khat consumption

Early medical researchers visiting Yemen claimed that khat use could have behavioural effects that could be distinguished from schizophrenia only by their transient nature and that schizophrenic patients were frequent chewers of khat (Luqman & Danowski, 1976). According to the currently prevailing opinion, khat-induced psychotic disorders are a rare phenomenon because of the bulky nature of the drug (Halbach, 1972; Kalix, 1987). However, others have stated that khat-induced psychopathology might not have been detected because caretakers habitually lock or chain psychotic patients inside their homes due to the lack of treatment facilities. This practice has been documented in Yemen (Luqman & Danowski, 1976), Ethiopia (Alem & Shibre, 1997) and Somalia (Odenwald et al., 2005). Psychiatrists from Africa have noted that patients with khat-induced psychosis had been seen on their units (Dhadphale & Mengech, 1987), and they speculated that there were many undetected cases in the communities (Alem & Shibre, 1997). According to the World Drug Report 2004, in Ethiopia khat was the main drug of abuse among 75.6% of all patients who were treated for drug-related problems; in Kenya the figure was 14.3% (UNODC, 2004).

Khat and psychosis: Theoretical background

Amphetamines and some of its de-

rivatives have been shown to induce psychotic symptoms in experiments in humans (Bell, 1973) and animals (Robinson & Becker, 1986), and they have been known to exacerbate psychotic states in psychiatric patients (Angrist, Rotrosen & Gershon, 1980; Janowsky & Davis, 1976). However, the scientific debate about amphetamine-induced psychosis is ongoing, and it remains unclear whether the use of amphetamine-like substances can actually *cause* a psychotic disorder in an otherwise healthy individual, or whether it *triggers* the onset of schizophrenia in an individual with high vulnerability to the disease (Phillips & Johnson, 2001; Poole & Brabbins, 1996). Increased drug use among psychotic patients may also result from their attempt to counteract nonspecific physical symptoms or side effects of neuroleptics (Mueser, Drake & Wallach, 1998).

In animal models of dopamine-related psychopathology, the effects of cathinone and khat extract have been addressed. Behavioral responses to single high doses of amphetamine have been proposed as an animal model for stimulant-induced psychosis (Robinson & Becker, 1986). Much like amphetamine, single cathinone or cathine administrations have been shown to elicit dose-dependent locomotor activity or stereotyped behaviours, e.g. sniffing in rodents, with higher doses eliciting a greater behavioural response (Calcagnetti & Schechter, 1992; Zelger et al., 1980). The behavioural sensitization paradigm is another model of stimulant-induced psychotic behaviour (Robinson & Becker, 1986). One study has shown that cathinone and khat extract have similar effects in this paradigm as amphetamines (Banjaw, Miczek & Schmidt, 2005).

Khat consumption might be related to the development of psychosis in various ways. If psychosis is considered to result from genetic and acquired vulnerability and additional stress factors or other triggers (Nuechterlein et al., 1992; Zubin, Magaziner & Steinhauer, 1983), the repeated or early-life expo-

sure to the chemical agents in khat might increase an individual's vulnerability (Sato, Numachi & Hamamura, 1992). At a later stage in life, khat use might trigger the onset of psychotic disorders in individuals who have a genetically determined or acquired vulnerability for it. Moreover, khat consumption may affect the course of a psychotic disorder.

In the context of khat use and its psychiatric sequelae in human beings, four questions are important or have been addressed by researchers: (a) Is there an association between khat chewing and general psychopathology? (b) Can khat induce short-lived psychotic reactions that are clinically relevant and are distinct from schizophrenia-spectrum disorders? (c) Can khat trigger psychotic disorders in vulnerable individuals or exacerbate symptoms in psychotic patients? (d) Can khat use increase the vulnerability for developing a schizophrenia-spectrum disorder?

(a) Is there an association between khat chewing and general psychopathology?

This question raises a number of related issues: *First*, is psychopathology among khat chewers different than among non-chewers? *Second*, is the prevalence of khat chewing among psychiatric patients different than among other groups? *Third*, is there a causal link between khat chewing and psychopathology?

Psychopathology among chewers and non-chewers: Some studies have addressed the question of whether khat users show nonspecific signs of psychopathology, anxiety, depression, or suicidal tendencies more frequently than nonchewers. Five such studies were undertaken in African and Arab countries.

Between 1974 and 1976, an American research project (Kennedy, Teague, Rokaw & Cooney, 1983) recruited 706 respondents from three major urban centres of the Yemen Arab Republic, selecting quotas for khat use (non-users, light-to-moderate users, heavy

users), gender, age, and socio-economic status. Local Yemeni staff interviewed the respondents about their khat habits and invited them to a hospital where a physician who was »blind« to their khat use carried out a medical examination and assessed the medical history without using a structured interview. The diagnosis of current psychiatric problems did not reveal clear relationships; unfortunately, the authors did not report the related statistics. However, among male participants, the lifetime prevalence of a psychiatric or psychosomatic problem was associated with khat chewing: 29.8% of non-users, 45.9% of light-to-moderate users, and 61.9% of heavy users had a life-time history of such a problem ($Chi^2 = 22.14, p < .001$; $OR = 2.29$). Women had a higher prevalence of psychiatric and psychosomatic problems than men (about 75%) regardless of their khat use.

Dhadphale and Omolo (1988) randomly selected 100 persons (50 men and 50 women) from a hospital waiting list in a khat-growing region of Kenya, and assessed khat use and psychiatric symptoms with the Self Report Questionnaire (SRQ; Harding et al., 1980). Whereas moderate users ($N = 23$) were not different from nonusers ($71; t = .32, p > .05$), heavy users ($N = 6$) had a higher SRQ total score than the other groups (heavy versus moderate: $t = 2.59, p < .02$; heavy versus non-users: $t = 2.96, p < .02$).

In a cross-sectional household survey conducted in 1994 and 1995, Alem and colleagues (1999) assessed the prevalence (current and life-time) and frequency of khat use in a representative sample of 10,468 respondents from a traditional khat-growing rural community in Ethiopia (response rate = 85%). Psychiatric cases were identified with the SRQ. The authors reported the results only for the variable »current daily khat use«. Among the daily chewers ($n = 911, 8.7\%$ of the total sample), 17.0% (155) were identified as psychiatric cases, compared to 17.5% (1,671) of other types of users ($Chi^2 = 3.10, n.s.$). The authors as-

sumed that khat chewers in the sample were using the drug moderately according to the local tradition. However, they did not quantify the amount of khat intake, and did not control for the impact of other factors, e.g. stressful life events. In 1997, the same Ethiopian research group (Belew et al., 2000) interviewed 1,028 randomly selected persons above the age of 15 from a cross-sectional household survey (response rate = 86.6%) in another rural district of Ethiopia, where khat was not traditionally produced; they used the SRQ and additional ad-hoc items to measure psychiatric symptoms. They reported that current khat chewers (31.7% of the sample) were more likely than non-chewers to score above the SRQ cut-off ($OR = 8.3, CI (95\%) = 5.20-13.31$) and that they more frequently had sleep problems ($OR = 3.75, CI (95\%) = 2.63-5.37$). They reported the same effect for frequency and duration of khat use (frequency: $OR = 8.20, CI (95\%) = 4.88-13.85$; duration: $OR = 8.14, CI (95\%) = 5.06-13.17$). The authors attributed the differences between the two studies to the different composition of the two samples: 83% of the respondents in the first study were members of the Guarge ethnic group. In the second study, the majority (68%) of the sample were members of the Oromo ethnic group, who also had the highest prevalence of khat chewing (36%). This explanation is supported by the finding that among the Oromos, the widespread habit of khat chewing was probably adopted only in recent decades (Gebissa, 2004), and, thus, the traditional knowledge about the dangers of the drug and the related social-control mechanisms might not have developed.

In a cross-sectional household survey in urban and rural areas of Yemen (Numan, 2004), 792 participants were recruited using random selection procedure, 538 of whom were khat users (187 of them every-day users). They were assessed with the Symptom Checklist 90 (SCL-90; Derogatis, 1977). There were no differences between khat chewers and non-chewers, except

that substantial anxiety symptoms were more common among the non-khat chewers. The means of the SCL-90 subscales and the relationship between frequency of khat intake and the measures of psychopathology were not reported. There are some concerns that the sample was not representative, even though it was described as representative, because the author indicated that he did not find any case of manifest mental or physical illness or even a history of mental illness in the sample. Furthermore, there are doubts about the validity of the data, because khat users were interviewed during group khat-use sessions. Presumably, the intoxication and the group situation affected the responses.

Four controlled studies are available with immigrant groups in Western countries. Litman, Levav, Saltz-Rennert & Maoz's (1986) study drew a random sample of 136 persons between 15 and 65 years of age from two Yemenite agricultural villages inhabited by immigrants who had resettled in Israel after 1948. Using the Psychiatric Epidemiology Research Interview (PERI, Dohrenwend, Shrout, Egri & Mendelsohn, 1980), the authors identified respondents who were likely to have a psychiatric disorder. In the more traditional village, they found more such cases among khat chewers than among non-chewers: 8 of 11 heavy chewers (72.7%), 13 of 33 infrequent chewers (39.4%) and 10 of 36 non-chewers (27.8%; $Chi^2 = 7.182$, $df = 2$, $p < .05$). They did not report sufficient information from the multivariate analysis that they ran, or give the sociodemographic characteristics of the cases and non-cases.

Using the General Health Questionnaire (GHQ; Goldberg & Hillier, 1979), Ahmed and Salib (1998) compared 27 khat users with 25 non-users, all of whom were male and recruited from the Somali community in Liverpool. A Somali social worker conducted the interview in a community setting. Although the authors identified a relatively large number of individuals above the cut-off point, there was no

group difference (chewers: 41%; non-chewers: 36%, $p = .72$). Khat use was not quantified, and confounding variables were not controlled.

Bhui and colleagues (Bhui et al., 2003; Bhui, Audini, Singh, Duffett & Bhugra, 2006) conducted two studies among Somalis living in London. In the first study, they interviewed 180 randomly selected adults from a Somali community panel from Greenwich. They assessed symptoms of depression and anxiety using the Hopkins Symptom Checklist (HSCL; Derogatis & Melisaratos, 1983), suicidal ideation using the Beck Depression Inventory (BDI; Beck & Steer, 1987), prevalence of substance abuse (no quantitative information), traumatic experiences with the Harvard Trauma Questionnaire (HTQ; Mollica et al., 1992) and immigration-related stressful experiences. They trained their non-professional interviewers to probe for selected psychotic symptoms (grandiose delusions, hallucinations, unusual thought content) from the Brief Psychiatric Rating Scale (BPRS; Overall & Goreham, 1962). The authors identified respondents as »cases« from the distribution of HSCL scores (upper quartile), when they had a score of one or higher on the BDI suicide item or when at least one psychotic symptom was judged to be present. Among the 72 khat users, the cases with suicidal ideation were more frequent than among the non-users (66.1% vs. 33.9%, $p < .001$), a result which confirmed previous qualitative reports (CVS Consultants & Migrant and Refugee Communities Forum, 1999). The frequency of cases with a critical load on anxiety/depression symptoms or of psychotic cases did not differ between the khat chewers (21.7% and 16.1%) and non-chewers (26.0% and 20.4%). This study reported neither quantitative results nor a detailed analysis of confounding variables, e.g. traumatic experiences. In the second study (Bhui et al., 2006), the researchers interviewed 143 Somalis randomly recruited from GP registers and community sites; they used a

Somali version of the MINI-International Neuropsychiatric Interview (Sheehan et al., 1998) and also assessed respondents' khat intake. The prevalence of »common mental disorders« (CMD, anxiety and depression) was 34%; PTSD was 14%; and suicidal ideation was 9.1%. In a logistic regression model, khat use was a highly significant predictor ($OR = 10.47$, $CI 95\% 1.11-98.25$) of any mental disorder diagnosed with the MINI. However, quantitative measures of khat chewing were not obtained, and results on symptom levels were not reported.

Prevalence of khat use among psychiatric patients: Few studies have addressed the question of whether khat chewing is different among psychiatric patients than other groups. Most group and community-based studies on the psychiatric effects of khat have excluded participants with severe psychiatric illnesses (Alem et al., 1999; Belew et al., 2000; Bhui et al., 2003). Some anecdotal reports have mentioned that khat use is common among psychiatric inpatients at the Horn of Africa (Alem et al., 1999). In a study that we conducted in Hargeisa, Somaliland (Odenwald et al., 2005), all except one of 38 male psychotic cases had used khat, in contrast to 25 of the 38 matched controls ($p < 0.001$). In the week before the interview, 54% (i.e. 20 of 37) of the male patients who were lifetime khat users and 36% (i.e. 9 of 25) of the control group had chewed it ($p = 0.162$).

Underlying mechanisms: In the currently available literature, the underlying mechanisms – how khat use and psychopathology are associated – are not specifically studied. Many authors have implicitly tested the hypothesis that khat chewing causes psychopathology (Belew et al., 2000; Numan, 2004). In contrast, several researchers have espoused the hypothesis that increased khat use and the subsequent development of dependence are a response to psychological problems related to stressful or traumatic life events (e.g. »self-medication«; ACMD, 2005; Fountain et al., 2004; Nabuzoka

& Badhadhe, 2000; Yousef, Huq & Lambert, 1995). In a study in Somalia, we found among 64 ex-combatants that those with Posttraumatic Stress Disorder (PTSD, $n = 14$) spent on average two hours per day more than others chewing khat (Odenwald, Lingenfelder, et al., submitted). In another study, we found a positive association between the number of traumatic events experienced and the quantity of khat used (Odenwald et al., 2005). These results show that several hypotheses about how khat use and psychopathology are related should be tested; based on the current literature, no definitive statements can be made.

In summary, there are only few studies that have ever assessed whether khat use is related to general psychopathology; furthermore, the studies have many methodological problems, and important information was not reported. Of general concern are the types of instruments used to measure nonspecific symptoms of psychopathology, which usually include a large number of items referring to psychiatric patients' typical somatic complaints. However, these complaints (e.g. digestion problems) can also be direct consequences of khat use, making it difficult to disentangle cause and effect. A recent study in Yemen (Date, Tanida & Hobara, 2004) reported more chronic health complaints among chewers who habitually used pesticide-polluted khat than users from an area where no pesticides were used. Furthermore, the effects of khat chewing cannot be studied without assessing traumatic experiences or stressful life events as confounding variables. These factors alone might have a significant impact on the mental health of respondents and on their drug use, for example, as means of »self-medication«. Thus, the reported symptoms among chewers can be attributed to various factors, which are not necessarily related to or caused by khat chewing. Another important methodological issue is interviewers' level of training. In the two controlled studies that employed poorly trained inter-

viewers (Ahmed & Salib, 1998; Alem et al., 1999), no association was found between khat use and respondents' mental health. In all controlled studies in which well-trained interviewers were used, at least one association between khat use and a psychiatric symptom was found (Belew et al., 2000; Bhui et al., 2003; Bhui et al., 2006; Dhadphale & Omolo, 1988; Kennedy et al., 1983; Litman et al., 1986). One study was not included because of serious methodological problems (Nunan, 2004).

It is not possible to draw a definitive conclusion about the association between khat chewing and general psychopathology, although there is tentative evidence that the two are related, at least under certain circumstances. We might speculate that this association occurs especially among heavy users, in groups that have only recently acquired the habit of khat chewing (Belew et al., 2000), in individuals who use khat outside the traditional regulative mechanisms (Nabuzoka & Badhadhe, 2000) or among immigrants with a high load on stressful and traumatic life experiences (Bhui et al., 2003).

Future studies of psychopathology among khat chewers should always assess khat use quantitatively, because excessive use rather than khat use per se might be related to psychopathology. In order to disentangle cause and effect, both specific and nonspecific psychiatric measures should be used, and research methods and designs should be used that allow confounding variables to be controlled, for example, by using appropriate control groups. Persons who are severely psychiatrically disturbed should not be excluded from future studies, because the negative consequences of khat use might be strongest among them. Studies should aim to minimize the influence of situational variables on the results that are reported. Finally, longitudinal assessments are required for identifying causal relationships between khat chewing and psychopathology.

(b) Can khat induce clinically relevant, short-lived psychotic reactions that are distinct from schizophrenia-spectrum disorders?

In Griffiths and colleagues' study (Griffiths, 1998; Griffiths et al., 1997), trained Somali interviewers used an ad-hoc structured interview to ask 207 Somalis living in London about khat intake and associated symptoms. Among khat users ($n = 161$), 19% reported paranoia (acute paranoia: 4%) and 14% reported hallucinations (2%) after khat chewing at any time in their lives. Patel et al.'s (2005) report of 602 Somalis (324 male, 278 female) in four cities in the UK used the same methods. Among recent khat users, approximately 20% reported paranoid symptoms (acute paranoia < 5%), and approximately 15% reported hallucinations (< 5%). The authors also found a higher frequency of khat use among those participants who reported lifetime hallucinations after chewing khat (4.1 days per week versus 2.7 days per week). However, the assessment of psychopathology was by way of self-reports, leaving it unclear whether the reports were clinically meaningful. Neither of the studies systematically compared khat users and non-users. They also did not analyse khat use quantitatively, nor did they assess the influence of confounding variables.

A better source of information is the 20 up-to-date descriptions of cases of khat-induced brief psychotic episodes that are available in the medical literature (Alem & Shibre, 1997; Carothers, 1945; Critchlow & Seifert, 1987; Dhadphale et al., 1981; Giannini & Castellani, 1982; Gough & Cookson, 1984; Jager & Sireling, 1994; McLaren, 1987; Nielen, van der Heijden, Tuinier & Verhoeven, 2004; Pantelis, Hindler & Taylor, 1989; Yousef et al., 1995). All except one of the patients in these studies were male. All were natives of countries in which khat has been traditionally used: 12 were of Somali origin, four were Yemenite, and four were Kenyan. Most of the cases were detected in Western countries to which the patients had immigrated: eleven in

Great Britain, two in the Netherlands and one in the United States; five were seen in Kenya and one in Ethiopia. Seventeen cases reported excessive khat use before the onset of psychotic symptoms. In 11 cases, violent behaviour was reported during the development of acute psychiatric symptoms. All of the cases had completely remitted after six months and 17 after four weeks; the median time for complete remission was two weeks. Seven of the cases were not treated with any medication and remitted only upon cessation of khat use. In eleven cases, more than one episode was reported. An average of 2.1 episodes (range = 1 to 6) occurred across all the cases. A frequently reported pattern of khat use among these cases was solitary use, in contrast to the traditional social use. Pantelis et al. (1989) reviewed 12 of these cases and identified three types with different symptom clusters: (1) The most common type was a paranoid psychotic state, often associated with auditory hallucinations and clear consciousness. (2) Others showed manic symptoms associated with grandiose delusions. (3) Less common was a depressive syndrome, possibly related to cessation after a period of excessive use. From the evidence accumulated through these case reports and the information on similarities between cathinone and amphetamine and the laboratory research on cathinone, it can be concluded that khat has the capacity to elicit short-lived psychotic states, which usually develop after excessive chewing and remit completely usually within four weeks, in many cases without neuroleptic medication. The prevalence of such clinically relevant psychotic states in immigrant populations and in the countries where khat use reaches highest levels is not known, especially because these individuals might not be referred to medical services (Luqman & Danowski, 1976) or they might be misdiagnosed due to the lack of specific knowledge about khat (Granek, Shalev & Weingarten, 1988). Currently also unclear are the risk and resilience factors, e.g.

sensitization through prior episodes, co-morbid psychiatric or somatic disorders, and traumatic experiences.

In the descriptions of such cases, the following information should be included: the quantification of khat-intake prior to the current episode (e.g. units per week), duration of the last intoxication, when the person first started to use khat, number of previous episodes and their relationship to khat use.

(c) Can khat trigger psychotic disorders in vulnerable individuals or exacerbate symptoms (e.g. aggressive outbreaks) in psychotic patients?

Very few studies have addressed this topic. Two case reports describe the exacerbation of psychotic symptoms in patients with pre-existing psychotic disorders (Granek et al., 1988; Mion, Ruttimann, Oberti & Aversenq, 1997); one of them had used only a small amount of khat.

We found in our study with psychotic patients in Somaliland (Odenwald et al., 2005) in which we used a retrospective assessment that the onset of lifetime khat use preceded the first psychotic episode in 31 of 38 male patients. Furthermore, in the weeks preceding the onset of psychotic symptoms, patients had chewed an average of 2.5 ± 2.0 bundles/day, compared to 0.5 ± 0.6 bundles/day for controls ($p < 0.001$). Excessive khat intake (> 2 bundles/day) during this period was found in 78% (i.e. 29 of 37) of the male patients who were chewers but in only 4% (i.e. 1 of 25) of chewers in the control group ($p < 0.001$). At the time of the interview, khat chewing did not differ between psychotic patients and matched controls; psychotic patients used an average of 1.5 ± 1.0 bundles/day, whereas controls used an average of 0.9 ± 0.7 ($p = 0.172$). However, the amount of khat that was used during the week before the interview was correlated with scores on the Positive and Negative Syndrome Scale (PANSS, Kay, 1991) Anergia subscale ($r = -0.35$, $p = 0.029$, $N = 38$).

In respect to aggressive behaviours induced by khat intake, the only clinical data available are from the 20 published cases with a brief khat-induced psychotic disorder. From them, eleven showed aggressive behaviours. Additionally, one recent laboratory study showed that cathinone and khat extract increase isolation-induced baseline aggression (Banjaw et al., 2005), an animal model of serotonin-related psychopathology.

Despite the scarcity of data, based on the similarities between khat and amphetamine and the animal models of psychosis, it can be expected that khat might indeed exacerbate pre-existing psychiatric disorders or trigger long-lasting psychotic disorders in vulnerable individuals. Khat's relationship to aggressive behaviours, however, remains unclear. The empirical evidence is scarce, and all of these questions need to be further addressed. It is unclear whether moderate use or only excessive, chronic or prolonged chewing might have the adverse effects. Of special importance in this context is the question of whether sensitization to the effects of khat is associated with relapses or deterioration of symptoms (Yui et al., 2002). The longitudinal assessment of patient data (e.g. in hospitals) or systematic retrospective assessment of the number of previous episodes and their relationship to khat intake remains an important task for future studies.

(d) Can khat use increase vulnerability to a schizophrenia spectrum disorder?

In this section, the evidence on whether or not khat use can directly increase lifetime vulnerability is discussed. No study has directly addressed this topic, but the results of a few studies encourage further research on this issue.

From longitudinal research on cannabis and psychosis, there is growing evidence that excessive cannabis use early in life enhances the vulnerability to later schizophrenia (for a review see Arseneault, Cannon, Witton & Mur-

ray, 2004). Other studies have shown that in contrast to healthy controls, among schizophrenic patients drug use had started in early adolescence (Hambrecht & Hafner, 1996). Among the above reviewed case studies we find the onset of khat use as early as with 12 years of age (McLaren, 1987). In the study with psychotic patients in Somalia cited above (Odenwald et al., 2005), the average age of onset of khat intake was found to be about four years earlier among psychotic cases (16.6 ± 4.8 years) than among matched healthy controls (20.7 ± 7.0 years, $p = 0.010$). The time between first khat use and the onset of positive symptoms was on mean 8.6 ± 6.6 years (median = 7 years); therefore, it seems likely that the onset of khat chewing occurs prior to the prodromal phase in a substantial proportion of schizophrenia patients.

Furthermore, international epidemiological studies of schizophrenia have shown that its prevalence is evenly distributed between males and females (Jablensky et al., 1992). However, because khat chewing in Somalia is a predominantly male habit, a higher prevalence of male schizophrenia patients would be consistent with the hypothesis that khat chewing increases vulnerability. In our Somali sample (Odenwald et al., 2005) that was randomly selected among a representative group of psychiatric patients from a large household survey, there was a higher than expected prevalence of male psychotic cases (38 of 43).

Finally, it is known that brain damage during the pre- and perinatal period and infancy increases the vulnerability to the development of schizophrenia (for a review see Weinberger & Marceno, 2003). In animal models, brain damage induced by poisonous substances in rodents during pregnancy causes a higher vulnerability to the effects of CNS stimulants in animal models of psychosis (Lipska, Halim, Segal & Weinberger, 2002; for a review see Thompson, Pogue-Geile & Grace, 2004). In a study with guinea pigs, prenatal exposure to khat caused EEG changes that were measured in the

neonatal period (Thordstein, Jansson & Kristiansson, 1991). Additionally, from laboratory studies, evidence for the neuro-toxic effects of khat is growing (for a review see Carvalho, 2003). This evidence warrants special attention because some studies have reported khat use by pregnant women and breast-feeding mothers (Alem et al., 1999; Eriksson et al., 1991) and because cathine has been found in breast milk of khat chewing mothers and in the urine of their infants (Kristiansson et al., 1987).

To date, very little evidence has been accumulated that khat use increases the vulnerability to a schizophrenia spectrum disorder; this is not surprising because no studies have ever specifically address this topic. There are, however, findings that would justify further research on this topic, as discussed above. For the public health of countries at the Horn of Africa this question is of high importance. Longitudinal assessments but also cross-sectional studies would provide valuable information. Another important step would be the improvement of treatment and documentation standards in psychiatric hospitals. In Somali hospitals, client charts are often poorly completed or are non-existent (Alkan & Ali, 2001). Clinicians should try to assess retrospectively the development of psychotic symptoms by using standardized methods, for example the Inventory for the Retrospective Assessment of Schizophrenia (IRAOS, Hafner et al., 1992).

Discussion: Current situation and future prospects

The current knowledge base concerning its effects on mental health, thirty years after the detection and isolation of the »natural amphetamine« (Kalix, 1992) cathinone, is very thin. Although its economic importance and use are growing, and profound changes in the traditional use patterns are occurring, the research on mental-health consequences falls short. Most studies have used a weak methodology, have not referred to insights gained

from schizophrenia research, e.g. on vulnerability-enhancing factors, and have reported only qualitative data. The research on the topic of khat and mental health often seems to implicitly test the hypothesis that khat chewing *per se* is detrimental to mental health, and the research designs and methodologies are consistent with this reasoning. The current review shows that the relationship is not so simple – khat use and mental problems are related to each other in various, probably multiple, ways. Specific patterns of khat use, not khat chewing *per se* should be the focus of scientific studies. This implies that completely different research strategies should be used. Important questions for the public health in the countries at the Horn of Africa and Eastern Africa and among immigrant groups in Western countries remain unanswered.

Concerning the long-lasting effects of khat chewing, Kalix (1990) stated more than 15 years ago: »With regard to the chronic effects of khat use, it is difficult to make definite statements, mainly because the literature tends to either overindict the habit because it is strange and obvious, or to minimize its consequences in the view of its longstanding tradition and ethnological interest« (p. 411). This view also depicts the current situation and its pitfalls for research, the controversy surrounding khat research remains emotional. This situation might explain why both the focus and the quality of the research often seem to be inadequate.

A number of important questions urgently need to be addressed as discussed above, for example the prevalence of khat chewing among psychiatric patients, the effects of khat chewing on pre-existing mental disorders, the development of sensitization in human khat chewers, the direction of the association between khat use and psychopathology and the consequences of khat use during pregnancy and lactation on children's health. Because khat use has changed qualitatively and quantitatively during the last decades, there might be an undetected

and silently growing public-health problem in the countries around the Horn of Africa.

Researchers, clinicians and decision makers should be aware that khat use is part of a long-standing tradition and that it is an important economic factor that cannot simply be eliminated by laws, as is the case with other drugs. On the other hand, many users are not aware of the dangers related to khat use. Thus, public health measures are needed to raise awareness for its potential dangers, and governments need to better monitor and influence its production, trade and consumption. But in order to find sustainable solutions, multi-disciplinary research is needed, from economics to anthropology, medicine and pharmacology. The researchers from these different backgrounds need to work together in joint projects. An interdisciplinary platform for scientific discussions and exchange is urgently needed.

Conclusions

- Current knowledge on the impact of khat use on mental health has a thin evidence base. With the most urgent questions unanswered, an important public health threat at the Horn of Africa might remain unrecognized.
- Heavy khat use can induce short-lived psychotic states, which remit upon cessation within several weeks.
- Khat use by vulnerable individuals should be discouraged, because it might exacerbate pre-existing schizophrenia-spectrum disorders or trigger them.
- The existing knowledge base shows the need to study whether khat use can increase the vulnerability to schizophrenia spectrum disorders, especially when infants, children and adolescents are exposed to the toxic agents of the khat leaves.
- Under certain conditions, khat

chewing might be associated with other co-morbid psychopathology, e.g. anxiety or suicidal ideation, although the direction of causality remains unclear. These conditions might include the absence of regulating social norms and traditional knowledge on the dangers of khat, e.g. in groups having acquired the habit only recently, or a high load on stressful or traumatic life events, e.g. among immigrants or in post-conflict regions.

- Public health measures are needed to raise awareness about the potential dangers of khat use.

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