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## Khat use and occurrence of psychotic symptoms in the general male population in Southwestern Ethiopia: evidence for sensitization by traumatic experiences

Khat trees are native to East Africa and the Arabian peninsula. Their leaves contain amphetamine-like alkaloids such as cathinone, cathine and norephedrine, and are chewed for their stimulating and euphorogenic effects<sup>1</sup>. Khat use varies by season: in the dry season, there is limited availability and market prices are high; in the rainy season, the opposite is true. Excessive use is associated with dependence and khat-induced psychosis<sup>2</sup>.

In collaboration with the Gilgel Gibe Field Research Center of Jimma University, in Southwestern Ethiopia, we studied khat use and khat-induced psychotic symptoms in 1,100 men aged 18 to 40 years (mean 28.4 ± 6.6), randomly selected from the center's population registry.

Trained raters interviewed participants at two subsequent time points, i.e. during the dry season (T1; N=853) and during the rainy season, nine months later (T2; N=695). They explored khat use during the past 7 days using the Timeline Followback Method Assessment. Psychotic symptoms experienced during the past 6 months were assessed by four items from the Composite International Diagnostic Interview (CIDI) selected on the basis of previous studies<sup>3</sup>. Khat-induced psychotic symptoms were defined as being present during or up to 6 hours after consumption and assessed with supplementary questions<sup>3</sup>. Potentially traumatic experiences (e.g., assault or life-threatening injury) during the period up to T1 or since T1 were explored by an adapted version of the Life Events Checklist for DSM-5 (LEC-5)<sup>4</sup>. A cut-off of four experiences was fixed by median split. Urine samples were collected to analyze khat alkaloids through immunoassay tests for amphetamine.

Khat use in the past 7 days was reported by 599 individuals (70.2%) at T1, and 565 (81.3%) at T2. The 6-month prevalence of khat-induced psychotic symptoms was 7.9% at T1 and 12.8% at T2.

At T2, we found 225 individuals with a positive immunoassay test. In these subjects, the rate of khat-induced psychotic symptoms was 26.6% among those with a history of four or more past traumatic experiences (N=124) and 14.0% among those with a history of less than four of those experiences (N=121) (p=0.015). This result could not be explained by higher khat use among the high trauma group (p>0.081 for all use indicators in the last 7 days among people with high vs. low trauma load).

We also observed that recent trauma exposure was associated with elevated presence of khat-induced psychotic symptoms in individuals with low trauma exposure during the period up to T1 (with recent trauma: 28%; without recent trauma: 12%; p=0.009). Among individuals with high trauma exposure during that period, additional recent trauma did not have this effect (with recent trauma: 25%; without recent trauma: 26%; p=0.933).

Our findings suggest that, in the general male population of an African country, traumatic experiences can sensitize to the effects of a psychomimetic substance. This is in line with the behavioral sensitization paradigm, which suggests that repeated administration of amphetamines or exposure to stress can cause sensitization of dopamine neurons and consequently a higher dopamine release in response to subsequent stress or amphetamine, which facilitates the development of psychotic symptoms<sup>5-7</sup>.

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