

Correlations of Kratom (*Mitragyna speciosa* Korth.) Use Behavior and Psychiatric Conditions from a cross-sectional survey

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TITLE

Correlations of Kratom (*Mitragyna speciosa* Korth.) Use Behavior and Psychiatric Conditions
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Running title

Kratom Use in Psychiatric Conditions

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Oliver Grundmann declares that he is a member of the Advisory board for the American Kratom Vendors Association.

Ethics Approval

The questionnaire and methodology for this study was approved by the Institutional Review Board of the University of Florida (IRB #2019-01121).

Consent

Informed consent was obtained from all individual participants included in the study before the survey started.

Author contributions

Conceptualization: Oliver Grundmann, Kirsten E. Smith, Charles A. Veltri; *Methodology:* Oliver Grundmann, Kirsten E. Smith, Charles A. Veltri, Ornella Corazza, Giovanni Martinotti, Marc T. Swogger; *Formal analysis and investigation:* Oliver Grundmann, Sara Morcos; *Writing - original draft preparation:* Oliver Grundmann, Sara Morcos, Charles A. Veltri; *Writing - review and editing:* Oliver Grundmann, Charles A. Veltri, Sara Morcos, Kirsten E. Smith, Darshan Singh, Ornella Corazza, Eduardo Cinosi, Giovanni Martinotti, Zach Walsh, Marc T. Swogger

ABSTRACT

Kratom (*Mitragyna speciosa* Korth.) use has increased substantially over the past decade outside of its indigenous regions, especially for the self-treatment of psychiatric conditions. An anonymous, cross-sectional, online survey was completed by 4,945 people who use kratom (PWUK) between July 2019 and July 2020. A total of 2,296 respondents completed an extended survey utilizing clinical scales for attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), depressive and anxiety disorders.

PWUK and met criteria for ADHD, PTSD, depressive or anxiety disorders were primarily middle-aged (31-50 years), employed, more likely to have college-level education (81.3% vs. 80.0%), and reported increased concurrent or prior use of kratom with cannabis products, cannabidiol, and benzodiazepines. In all psychiatric conditions, PWUK reported less depressive and anxious moods. Self-reported quality of life was worse in psychiatric conditions whereas current pain was more severe. Based on this observational study, further clinical studies are warranted for kratom.

Keywords: Kratom; ADHD; PTSD; depression; anxiety

INTRODUCTION

Kratom, also known as *Mitragyna speciosa* Korth., is a Southeast Asian plant with a wide variety of traditional uses. Its complex pharmacology produces various reported effects, including analgesia, stimulation and mood enhancement, and mitigation of withdrawal from classical opioids and other unwanted substances, such as alcohol (Babu et al., 2008; Smith, Dunn, et al., 2021; Smith, Rogers, et al., 2022; Swogger & Walsh, 2018). Kratom's popularity outside of Southeast Asia has grown considerably over the past decade. The main pharmacological active ingredients studied are mitragynine (MG) and 7-hydroxy mitragynine (7-OHMG), which bind to the mu-opioid receptor as partial agonists (Hemby et al., 2019). While the potency of MG is relatively lower compared to morphine, 7-OHMG presents with a higher potency, at least as evaluated in cell-based assays and animal experiments (Obeng et al., 2021). Both have been identified to be biased G-protein coupled receptor (GPCR) partial agonists without beta-arrestin recruitment, which is potentially associated with less respiratory depression (Kruegel & Grundmann, 2017). It has been reported that Kratom has some health benefits in pain management, fever reduction, diarrhea, and mitigation of withdrawal symptoms from other substances and can create a euphoric high in combination with cough syrup, caffeinated beverages, and other ingredients among Southeast Asian youth (Singh et al., 2016). The Kratom leaves' consumption method depends on the region and the preference of the individuals taking it; it ranges from smoking, chewing, and brewing a tea from the fresh leaves or consuming its dried powder form in food/drinks, etc. (Singh et al., 2016). The extent of the effect relies on the amount/dose that the individual consumes; lower doses are associated with stimulant effects, while higher doses are associated with sedative and opioid-like effects (Singh et al., 2016). Although Kratom has been used to mitigate withdrawal symptoms from other substances

(opioids, amphetamine, marijuana, barbiturates, nicotine, etc.), some reports indicate that regular Kratom use, particularly at higher doses, can lead to tolerance, dependence development, and subsequent withdrawal symptoms if used for an extended period and at higher doses (Agapoff & Kilaru, 2019; Smith, Dunn, et al., 2022; Smith, Rogers, et al., 2022).

Studies, across Western and Eastern cultures, demonstrate that people use kratom as an alternative to, or harm reduction strategy for, opioids (Swogger & Walsh, 2018). It is also used because it is easy to obtain through internet sources and in local shops, following a specific trend that has been common for novel psychoactive substances in the last two decades (Schifano et al., 2005). Countries have different regulations for Kratom use. Kratom is currently scheduled as a controlled substance in several countries including Malaysia, Australia, and the UK and it is hence considered illegal to use. While in the United States the Kratom legalization is controversial and varies across states. Presently kratom is banned in Indiana, Arkansas, Alabama, Rhode Island, Vermont, and Wisconsin. Although the US Drug Enforcement Administration (DEA) proposed Kratom classification to Schedule I in August 2016 this decision was reversed after 45 days because of petitions by Kratom users (Swogger & Walsh, 2018). To date, Kratom is not regulated by the US Food and Drug Administration (FDA) and can be legally purchased in different forms, including capsules, powders, or flavored tea and concentrated extracts. Surveys have found a trend of kratom use to be popular amongst early adult and middle-aged individuals (31-50 years old on average) who have a median income of \$35,000 and above, as a self-treatment for pain, anxiety, mood disorders, and other conditions (Bath et al., 2020; Garcia-Romeu et al., 2020; Grundmann, 2017; Smith, Rogers, et al., 2021).

Although there is ongoing research nationally and internationally to investigate the pharmacology of kratom, new data is emerging that indicates its use as an antipsychotic and antidepressant (Johnson et al., 2020). In one study, researchers examined pre-clinical data from several well-established models of depressive disorders where kratom alkaloids demonstrated its anti-depressant activity (Idayu et al., 2011). Though kratom has well-established affinity for opioid receptors, some findings suggest it also has affinity for serotonin and dopamine receptors, which may help explain why kratom has been so widely used for self-treating mood and anxiety. Taken together, self-report from regular users and preclinical findings indicate its possible future medical utility in treating depression and other psychological conditions.

Epidemiological data suggests that high lifetime prevalence rates, refractory rates and limited treatment options for serious mental illness or conditions such as post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), and depressive and anxiety disorders might explain high rates of kratom use among individuals who are diagnosed with these disorders, but possibly un- or under-treated (Smith, Rogers, et al., 2021). Co-morbidities among kratom-using people are now well documented. The lifetime PTSD prevalence of diagnostic interview ascertained PTSD has been reported to range from 14.5% to 48.8% in an international meta-analysis (Spottswood et al., 2017). Also, a cross-national comparison of major depression from 10 population-based surveys reported lifetime prevalence of Major Depressive Disorder (MDD) in the United States as 16.9% (Kessler & Bromet, 2013). In a different study, the authors reported an estimate of 9.0% lifetime prevalence of generalized anxiety disorder (GAD) (Kessler et al., 2012). Lifetime prevalence of ADHD was reported as 8.1% across all age groups in a US national comorbidity survey replication (Kessler et al., 2005).

Given the considerable public health burden of psychological conditions, the associations between kratom use and these conditions, and kratom users' reported benefits from kratom for addressing psychological disorder symptoms, we aimed to further investigate the perceived benefits of kratom use for mental health conditions. In our cross-sectional survey, we focused on assessing the relationship between responders' demographics, general health status, overall psychosocial health, validated psychometric scales for ADHD, PTSD, depressive, and anxiety disorders, and kratom use experience. Additionally, we assessed health-related reasons for kratom use, including use to address drug dependency or use as a form of harm-reduction substitution for illicit drugs. Analyses were conducted among respondents who completed the validated questionnaires, demographic section, and met the inclusion criteria for a diagnosis of the following mental health disorders: depression, anxiety, PTSD, ADHD. The primary aim was to analyze the demographics and use patterns in those who were assessed as having met clinical cut-off points indicating the presence of anxiety, depression, PTSD, and ADHD.

METHODS

Survey setting, approval, and data collection

This online, anonymous, self-selected survey was conducted between July 2019 and July 2020. The Qualtrics (Qualtrics, Provo, UT) survey platform was used to collect responses from current PWUK (Snow & Mann, 2013). The demographic and substance co-use data have been published earlier (Grundmann, Veltri, Morcos, Knightes III, Smith, Singh, et al., 2022). A snowballing technique was used for the distribution of the survey in North America, Europe, and Southeast Asia via social media channels and kratom-related online communities, including

Facebook, Reddit, and other forum groups. Kratom distributors and vendors also distributed survey information as did the American Kratom Association (<https://www.amerikankratom.org/>) who shared study information to its primarily US-based members. No incentives were provided for survey participation. Inclusion criteria were attestation of being ≥ 18 years and acknowledgment of the consent statement. Anonymity was ensured and repeated responding prevented by intermittently storing internet protocol addresses that were deleted once a respondent completed the survey or remained inactive for 48 hours. All study procedures were approved by the Institutional Review Board at the University of XXX (IRB #2019-01121).

Survey instrument

A locally developed kratom survey instrument was designed using the consensus input and expertise of the study team. The complete survey is attached as supplementary material.

Here, we focused on the following survey domains:

Demographics: country of residence, age, gender, marital status, ethnicity, employment status, and education.

General health status was measured using the 5-level EQ-5D (Oppe et al., 2014).

Overall health was measured by asking participants to rate their overall health using a visual analogue scale, VAS (Gudex et al., 1996). Participants were also asked to provide reasons for healthcare provider visits, self-rated pain level (VAS), and diagnosed health conditions (“Have you been told by a physician or medical professional that you have any of the conditions listed below? (select all that apply)”).

Kratom use experience was measured by asking participants to respond to questions pertaining to aspects that comprise kratom use in the greater context of their health.

Extended survey questions on psychiatric conditions included the Adult ADHD Self-Report Scale v 1.1 (Hines et al., 2012), the Primary Care PTSD Screen for DSM-5 (Prins et al., 2016), and the Symptom Checklist-90-Revised (SCL-90) for depressive and anxiety disorders (Morgan et al., 1998). For a respondent to meet criteria for each scale, the evaluation criteria had to be met. For ADHD, respondents had to select “often” or more frequently on four out of six questions in part A to meet criteria. For PTSD, at least three out of five questions had to be answered with “yes” to meet criteria. For the depression and anxiety dimensions of the SCL-90, a respondent had to select a three or four (“quite a bit” or “extremely”) in seven out of thirteen questions for the depression dimension and six out of ten for the anxiety dimension. Since no psychiatrist confirmed the diagnosis, the results are based on a respondent meeting the criteria which makes them a likely candidate for the respective psychiatric condition.

Data analysis

Data were analyzed in GNU PSPP (<http://www.gnu.org/software/pspp/>, version 0.10.4-g50f7b7) and SPSS Statistics (version 26, IBM, Armonk, NY). Correlational analysis was conducted using either a chi-square or logistic regression analysis. Chi-square analysis was performed for nominal and ordinal variables against expected values for goodness of fit. Odds ratios were calculated using binomial logistic regression with one level set as the comparator with a 95% confidence interval. Logistic regression models included all pertinent independent variables in the same model comparing all levels against each other (Bonferroni adjustment for comparisons among levels, post-survey power calculation resulted in at least 85% power and 93% confidence for all models).

RESULTS

A total of 7,381 responses were collected. Only respondents that completed at least 80% of the survey including the demographics section were considered valid responses (5,152; 69.8%) and included in the analyses. Of the completed surveys 2,296 (44.6%) respondents answered the extended survey questions assessing psychiatric conditions.

Demographics

A majority of respondents were male (50.91%) between the ages of 31-60 years (65.52%), married (44.18%), white non-Hispanics (83.53%), employed for wages (43.50%) and had at least some college education (73.02%). Anxiety (53.89%), depression (31.98%), PTSD (13.41%) and ADHD (16.43%) were the most commonly self-reported psychiatric conditions diagnosed by a healthcare provider.

Distinct demographic patterns associated with psychiatric conditions

For respondents who met criteria for ADHD, most were between age 31-50 (50.50%), male (51.90%), married (41.65%), white non-Hispanic (90.60%), employed for wages (39.00%) and had at least some college education (80.30%). Of those who met PTSD criteria, according to the adult PTSD screening scale, most respondents were between age 31-50 (56.80%), female (57.70%), married (41.15%), white non-Hispanic (94.10%), employed for wages (46.10%) and had at least some college education (84.40%). Demographic variables among most participants who met criteria for a depressive disorder were of age 31-50 years (51.6%), male (53.40%), married (41.73%), white non-Hispanic (92.40%), employed for wages (44.50%), and had at least some college education (80.00%). For those meeting criteria for an anxiety disorder, most respondents were of age 31-50 (53.4%), equally affecting male (50.30%) and female (49.40%) participants, married (42.84%), white non-Hispanic (92.60%), employed for wages (45.40%) and had at least some college education (80.60%).

Prior or concomitant use of other substances with kratom in psychiatric conditions

It was found that individuals who reported a psychiatric condition (ADHD, anxiety, depression, and PTSD) and used kratom were more likely to use benzodiazepines (ADHD, 7.51% vs. 4.43%, OR: 1.75, CI: 1.14-2.68, $p=0.013$; anxiety, 8.28% vs. 2.21%, OR: 3.99, CI: 2.3-6.93, $p<0.01$; depression, 7.72%, OR: 3.49, CI: 2.29-5.33, $p<0.01$) and cannabis. In respondents reporting ADHD and depressive disorders, individuals are more likely to use CBD oil (ADHD, 15.50%, OR: 1.54, CI: 1.14-2.09, $p=0.07$; depression, 14.95%, OR: 2.17, CI: 1.67-2.82, $p<0.01$). In respondents reporting depressive disorders, the individual was more likely to use kava or cocaine concomitantly with kratom (3.78%, OR: 1.91, CI: 1.17-3.12, $p=0.008$).

Self-reported beneficial effects of kratom use in psychiatric conditions

The most self-reported beneficial effects of kratom use in all four psychiatric conditions evaluated were fewer depressive symptoms (ADHD, 79.9%, OR: 2.02, CI: 1.56-2.61, $p<0.01$; PTSD, 86.89%, OR: 3.25, CI 2.22-4.76, $p<0.01$; Depression, 79.8%, OR: 2.86, CI: 2.39-3.42, $p<0.01$; Anxiety, 78.13%, OR: 2.32, CI: 1.89-2.85, $p<0.01$), less symptoms of anxiety (ADHD, 79.18%, OR: 1.99, CI: 1.54-2.57, $p<0.01$; PTSD, 86.07%, OR: 3.13, CI: 2.16-4.55, $p<0.01$; Depression, 76.45%, OR: 2.2, CI: 1.85-2.62, $p<0.01$; Anxiety, 78.63%, OR: 2.57, CI 2.09-3.16, $p<0.01$), and less PTSD symptoms (ADHD, 27.60%, OR: 2.08, CI: 1.62-2.67, $p<0.01$; PTSD, 52.46%, OR: 6.69, CI: 5.06-8.85, $p<0.01$; depression, 24.04%, OR: 2.41, CI: 1.94-2.99, $p<0.01$; anxiety, 25.34%, OR: 3.15, CI: 2.36-4.19, $p<0.01$). Individuals who were diagnosed with ADHD and are kratom users were more likely to report sleep improvement (47.94%, OR: 0.73, CI 0.59-0.9, $p=0.004$), decreased pain (ADHD, 14.89%, OR: 0.68, CI: 0.51-0.91, $p=0.012$; PTSD 9.32%, OR: 1.68, CI: 1.06-2.68, $p=0.019$; anxiety, 56.44%, OR: 1.4, CI: 1.06-1.85, $p=0.018$), and experience an elevated mood, euphoria or feeling “high” (ADHD,

33.17%, OR: 1.47, CI: 1.17-1.86, $p=0.001$). Sleep improvement, (61.48%, OR: 1.42, CI: 1.08-1.86, $p=0.011$), sexual enhancement (18.44%, OR: 1.69, CI: 1.19-2.39, $p=0.005$), and increased focus (6.61%, OR: 1.32, CI: 1-1.74, $p=0.047$) were more commonly experienced by those meeting PTSD inclusion criteria. In subjects reporting depression and anxiety, reducing or stopping the use of other drugs (depression, 18.2%, OR: 1.41, CI: 1.14-1.76, $p=0.002$; anxiety, 18.58%, OR: 1.35, CI: 1.04-1.75, $p=0.021$) and experiencing an increase in empathy (depression, 21.95%, OR: 1.32, CI: 1.09-1.62, $p=0.005$; anxiety, 23.06%, OR: 1.42, CI: 1.12-1.81, $p=0.004$) were all more likely to be reported.

Self-reported detrimental effects of kratom use in psychiatric conditions

Overall, gastrointestinal symptoms (nausea and vomiting) (ADHD, 40.67%, PTSD, 32.79%, Depression, 30.87%, Anxiety, 31.33%) as well as irritability/agitation (ADHD, 10.65%, OR: 3.26, CI: 2.19-4.84, $p<0.01$; PTSD, 7.79%, OR: 1.89, CI: 1.13-3.15, $p=0.022$; Depression, 6.43% OR: 2.3, CI: 1.54-3.43, $p<0.01$; Anxiety, 6.59%, OR: 2.1, CI: 1.3-3.41, $p<0.01$) were common issues that arose when self-reporting detrimental effects of the use of kratom in psychiatric conditions. Respondents reporting symptoms of anxiety experienced heart palpitations (depression, 1.64%, OR: 2.92, CI: 1.36-6.25, $p=0.003$; anxiety 2.20%, OR: 2.51, CI: 1.03-6.14, $p=0.028$), shortness of breath (ADHD, 2.18%, OR: 5.26, CI: 2.02-13.72, $p=0.001$; depression, 1.29%, OR: 8.06, CI: 1.85-35.12, $p<0.01$; anxiety, 1.27%, OR: 4.34, CI: 0.99-19.02, $p=0.021$), diarrhea (anxiety, 1.52%, OR: 3.47, CI: 1.02-11.84, $p=0.023$), and constipation (ADHD, 28.1%, OR: 2.13, CI: 1.66-2.73, $p<0.01$; depression, 22.5%, OR: 2.11, CI: 1.7-2.62, $p<0.01$; anxiety, 22.3%, OR: 1.78, CI: 1.38-2.31, $p<0.01$) at a higher rate. Both populations of respondents reporting depression and anxiety showed to have sleep problems (insomnia, sleep too much, etc.) (depression 4.02%, OR: 1.81, CI: 1.13-2.9, $p=0.011$; anxiety 3.80%, OR: 1.87,

CI: 1.02-3.44, $p=0.034$), reduced appetite (depression, 4.18%, OR: 1.82, CI: 1.15-2.8, $p=0.009$; anxiety, 4.90%, OR: 2.86, CI: 1.52-5.36, $p=0.034$), reduced concentration (depression, 2.25%, OR: 3.15, CI: 1.48-6.7, $p=0.001$; anxiety, 2.36%, OR: 4.08, CI: 1.43-11.69, $p<0.01$), and specifically higher anger, hostility, or aggression (depression, 1.85%, OR: 2.9, CI: 1.29-6.51, $p=0.006$; anxiety, 1.86%, OR: 2.55, CI: 0.96-6.76, $p=0.002$). In addition, hair loss (4.18%, OR: 2.53, CI: 1.51-4.23) and hyperpigmentation of skin (0.59%, OR: 5.01, CI: 1.1-22.92, $p=0.016$) was commonly reported in respondents reporting depressive disorders. Sexual problems such as erectile dysfunction, reduced libido/pleasure (ADHD, 6.05%, OR: 2.12, CI: 1.31-3.44, $p=0.004$; depression, 5.31%, OR: 2.96, CI: 1.83-4.7, $p<0.01$; anxiety, 3.28%, OR: 2.25, CI: 1.29-3.93, $p=0.002$) were significant across all conditions except PTSD. No other self-reported symptoms were significantly different from those not reporting psychiatric symptoms.

Quality of Life and current pain is significantly worse in psychiatric conditions

Those with PTSD, ADHD, depression, and anxiety symptoms overall presented with lower quality of life as evaluated by a visual analogue scale (Figure 1), with users meeting PTSD criteria with the lowest quality of life (6.82 vs. 7.93, $p<0.01$).

Those with psychiatric conditions presented with greater self-reported current pain compared to those who did not meet diagnostic criteria (Figure 2). Those who met PTSD criteria ranked their pain the highest and presented with worse average pain (5.61) on the VAS than other conditions (depression: 5.09, ADHD: 4.93, anxiety: 5.14) or users not meeting any criteria for these mental health conditions (average: 4.80).

DISCUSSION

Psychiatric conditions are more commonly diagnosed among those with a substance use disorder as well as among those with chronic somatic health conditions (Neumann et al., 2013). Given the increasing popularity of kratom for self-treatment of various health conditions, the congruence of self-reported health conditions and kratom use, the extent of psychiatric symptoms reported in this survey was unsurprising. The demographic variables (age distribution, marital and employment status, education) of those reporting psychiatric symptoms was similar to who users who did not experience psychiatric disorder. There are, however, some distinct differences that align with prior literature.

Psychiatric conditions more common among young and single kratom users

All four psychiatric conditions examined were more common among younger (18-40 years) kratom users who were single. For PTSD, about two-thirds of diagnosed patients in primary care settings are female which aligns with this survey's findings (Spottswood et al., 2017). Mood disorders, and particularly depressive disorders, are more prevalent among younger patients that are single and have a history of SUD which impacts their ability to work compared to older adults (Serafini et al., 2018). For this survey, findings indicate that younger and single kratom users are more likely to report psychiatric symptoms.

Higher substance co-use among kratom users with psychiatric conditions

Several substances were used either concomitantly or prior to kratom initiation either in a healthcare provider setting or for self-treatment through licit or illicit means. Both CBD and cannabis products were more commonly taken by respondents reporting ADHD or depressive symptoms than by those who did not report such symptoms. The role of cannabinoids in ADHD and PTSD is still controversial, and detrimental effects are reported for mood and anxiety disorders. The use of kratom with cannabinoids can lead to unpredictable effects and need to be

investigated in future studies. Benzodiazepines were also commonly used by kratom users reporting psychiatric symptoms. In a small patient cohort using high-dose benzodiazepines, those with ADHD performed worse in cognitive function and indicated lower quality of life (Federico et al., 2021). Kratom, especially in lower doses (Warner et al., 2016), may be used as a stimulant to mitigate ADHD symptoms and benzodiazepine adverse effects.

The prior or concomitant use of benzodiazepines with kratom, similar to ADHD, may suggest a counterbalancing of adverse effects to provide less sedation. Depressive disorders can present with a range of symptoms, such as insomnia, irritability, or pain that can be treated with benzodiazepines (Kolacz et al., 2022). Theoretically, some of the benzodiazepine effects may be additive to kratom (potentiating sedation, muscle relaxation) while others are counteracting (stimulant). Because benzodiazepines play a central role in the treatment of anxiety disorders, it is unsurprising to find an increased use of this drug class in those subjects reporting depression and anxiety. A study among kratom users in Malaysia who also recreationally used benzodiazepines indicates that the combined use can serve multiple purposes such as increasing euphoria, reducing dependence on methamphetamine and withdrawal symptoms, promoting sleep, and decreasing cravings for kratom (Singh et al., 2020). This would indicate that at least some kratom users utilize benzodiazepines to mitigate adverse and withdrawal effects from their kratom use. The temporal relation between kratom use and other substances was not evaluated in this study hence making a conclusion of how benzodiazepines are utilized difficult.

The only lowered risk of kratom use and an anxiety disorder concerned the use of cocaine (Sareen et al., 2006). In general, those with an anxiety disorder are more likely to use cocaine but at least among kratom users, there appears to be a benefit of taking kratom to reduce the risk of cocaine exposure. This mirrors the use of kratom in amphetamine users that report a reduction in

amphetamine and methamphetamine use and withdrawal symptoms following kratom initiation (Saref et al., 2020). This data could be of relevance in reason of future strategies involving the use of kratom in stimulant use disorders.

Beneficial and detrimental symptoms of kratom use centered on psychological effects

For those reporting psychiatric symptoms, the primary beneficial effects of kratom use were less depressive and anxious symptoms which was significantly increased in all four psychiatric conditions. This may indicate that pre-clinical trials reporting an antidepressant and antipsychotic effect of kratom may have the capacity to eventually translate to human use and eventual therapeutics development (Johnson et al., 2020). Animal trials also indicate changes in neuronal circuitry related to depression, anxiety, and analgesia following chronic administration of kratom (Buckhalter et al., 2021). Similarly, those reporting anxiety and depressive symptoms also were more likely to experience decreased pain with kratom use whereas ADHD respondents were less likely to do so. Although few trials have investigated a relationship between pain sensitivity and ADHD, one study indicates that increased pain sensitivity in adolescent ADHD patients is associated with more severe emotional dysregulation (Bruton et al., 2022). Those with ADHD may therefore be more sensitive to pain and kratom may not benefit them to the same degree as others.

Detrimental effects of kratom use primarily focused on increased irritability or agitation and increased anger, hostility, or aggression. Irritability, agitation, or emotional outbursts are not uncommon among many psychiatric conditions and a recent validated questionnaire indicated strong correlations with depressive and anxiety disorders as well as ADHD and PTSD (Palm et al., 2021). Kratom does not appear to alleviate these psychiatric symptoms although it is not clear whether or to what degree kratom may play a role in impacting them. Nausea and vomiting

have been commonly associated with kratom consumption and may depend on the amount consumed per dose or frequency of consumption (Grundmann, 2017). While average kratom dose and frequency were not higher in those with a psychiatric condition other than a SUD (Grundmann, Veltri, Morcos, Knightes III, Smith, Singh, et al., 2022), it is unclear how kratom may interact with other medications taken among people with those conditions. Because of the potential for drug interactions, kratom consumption may lead to a higher incidence of adverse effects in patients taking a range of prescription medicines, especially medications metabolized by CYP 2D6, CYP 3A, and CYP 2C9 (Hanapi et al., 2021). Inhibition of these enzymes may increase the blood concentration of several antidepressant and anxiolytic medications that are used concomitantly with kratom in the treatment of psychiatric disorders. Common adverse effects of antidepressants that appear to be increased in several of the investigated disorders are vomiting, nausea, dry mouth, sexual problems, and constipation. Of concern is the increased self-reported rate of heart palpitations which may require careful evaluation of kratom use.

LIMITATIONS

Despite the subjective possible benefit of kratom use evidenced from this survey and by recent reports regarding different psychiatric conditions (Johnson et al., 2020), controlled trials and large studies are lacking. Moreover, in our survey the quality of life for respondents affected by a psychiatric condition was lower than in those without, for PTSD by more than one point on a ten-point visual analogue scale (6.82 vs. 7.93, $p < 0.01$). This relative discrepancy is even more stark when compared to healthy participants who completed the EQ-5D-5L scoring an average of 9.56 on the scale as the COVID-19 pandemic began in 2020 (Grundmann, Veltri, Morcos, Knightes III, Smith, Singh, et al., 2022). This indicates that the benefit of kratom may be limited,

need to be confirmed in randomized controlled trials, and depend on the product consumed as well as its subjectively perceived effects.

A prior publication does not indicate that kratom availability was affected by the COVID-19 pandemic overall, but it cannot be excluded for all respondents (Grundmann, Veltri, Morcos, Knightes III, Smith, & Rogers, 2022). The survey did include responses from various countries, but most responses (96.43%) were collected from the US and Canada (Grundmann, Veltri, Morcos, Knightes III, Smith, Singh, et al., 2022) and the applicability of the findings should therefore be limited to these two countries. Because of the inherent nature and bias of self-reported survey data, the results should be interpreted with caution and may be skewed towards a positive perception of kratom. Moreover, the psychiatric evaluation has not been performed by a psychiatrist and is based on self-reported scales and/or previous healthcare evaluation reported by the respondents. A possible further bias could be represented by a possible exclusion of subjects reporting early detrimental effects after the use of kratom: these subjects are probably not included in those categories reached by the snowball sampling of this survey: kratom users' communities and participants of blog and social/on-line platforms concerning kratom. The use of the Internet for data collection and only providing the survey in English may skew towards a younger, urban and sub-urban population with internet access and English-language proficiency. These limitations are offset by the overall size of the sample and the inclusion of validated instruments not previously used in kratom survey studies.

CONCLUSIONS

The utilization of kratom products in the self-treatment of psychiatric conditions remains a strong motivator. For all conditions investigated, kratom was used by a younger population that

was more likely to be single. In general, kratom was either used concomitantly or following cessation of cannabis products, CBD, or benzodiazepines. While cannabis and CBD products may be sold in the same environment (local stores, shops, or over the internet), benzodiazepines are either used as prescription drugs or as diverted medications for recreational purposes. Here kratom was reported as improving depressive and anxious mood in those with a psychiatric condition, indicating its perceived benefits for self-treatment. However, its concomitant use with prescription medications may also aggravate adverse effects. The role of kratom in reducing the use of stimulants is of potential interest, specifically in those subjects reporting psychiatric symptoms. Substance and alcohol use can be considered as a self-medication strategy in psychiatric respondents: the use of kratom could represent a strategy not associated with a possible detrimental effect, as in the case of comorbid psychiatric disorders and alcohol/substance use. However, a possible protective effect of kratom needs to be confirmed in future studies, with randomized controlled trials. More studies on the effect of kratom in psychiatric conditions as well as its potential to interfere with medication use is warranted. Kratom use should be disclosed to respective healthcare professionals and its use carefully monitored, especially in users with existing psychiatric conditions.

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Figure legends

Figure 1: Quality of Life (QoL) visual analogue scale (VAS) scores for each psychiatric condition and the average score of participants not meeting inclusion criteria. A lower score indicates a lower QoL. All psychiatric conditions present with a lower QoL compared to the average negative score.

Figure 2: Current pain visual analogue scale (VAS) scores for each psychiatric condition and the average score of participants not meeting inclusion criteria. A higher number indicates more severe self-reported pain. Participants meeting post-traumatic stress disorder (PTSD) inclusion criteria present with more severe pain compared to the average negative and other psychiatric conditions.

TITLE

Correlations of Kratom (*Mitragyna speciosa* Korth.) Use Behavior and Psychiatric Conditions from a cross-sectional survey

Declarations

Conflict of interest

The Authors declare that there is no conflict of interest.

Financial interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. ± This work was supported in part by the Intramural Research Program of the National Institutes of Health, NIDA.

Non-financial interests

Oliver Grundmann declares that he is a member of the Advisory board for the American Kratom Vendors Association.

Ethics Approval

The questionnaire and methodology for this study was approved by the Institutional Review Board of the University of Florida (IRB #2019-01121).

Consent

Informed consent was obtained from all individual participants included in the study before the survey started.

Author contributions

Conceptualization: Oliver Grundmann, Kirsten E. Smith, Charles A. Veltri; *Methodology:* Oliver Grundmann, Kirsten E. Smith, Charles A. Veltri, Ornella Corazza, Giovanni Martinotti, Marc T. Swogger; *Formal analysis and investigation:* Oliver Grundmann, Sara Morcos; *Writing - original draft preparation:* Oliver Grundmann, Sara Morcos, Charles A. Veltri; *Writing - review and editing:* Oliver Grundmann, Charles A. Veltri, Sara Morcos, Kirsten E. Smith, Darshan Singh, Ornella Corazza, Eduardo Cinosi, Giovanni Martinotti, Zach Walsh, Marc T. Swogger

Table 1: Demographics and self-reported health diagnoses of people who use kratom and met the inclusion criteria for ADHD, PTSD, anxiety disorders, or depressive disorders. NA: not applicable. VAS score: visual analogue score only applies to the diagnosed health condition and the change in condition after initiation of kratom use on a 0-10 scale, with 5 being no change, >5 to 10 being improvement, and 0 to <5 being worsening of the condition. The mean VAS score is given for each condition.

	Frequency	Percent	VAS score	Chi-square
Age				
18-20 years	33	1.33%	NA	p<0.0001
21-30 years	277	11.16%		
31-40 years	636	25.61%		
41-50 years	564	22.71%		
51-60 years	427	17.20%		
61 years and older	359	14.46%		
Sex				
Female	1021	41.12%	NA	p<0.0001
Male	1264	50.91%		
Transgender	7	0.28%		
Marital status				
Single/never married	495	19.94	NA	p<0.0001
Married	1097	44.18		
Partnered	272	10.95		
Divorced	358	14.42		
Widowed	52	2.09		
Race/Ethnicity				
Black or African-American	11	0.44%	NA	p<0.0001
Asian	47	1.89%		
Hispanic or Latino/a	49	1.97%		
White (Non-Hispanic)	2074	83.53%		
American Indian or Alaska Native	22	0.89%		
Other	48	1.93%		
Employment status				
Employed for wages	1080	43.50%	NA	p<0.0001
Self employed	358	14.42%		
Out of work for 1 year or more	56	2.26%		
Out of work for less than 1 year	49	1.97%		
Homemaker	124	4.99%		

Student	67	2.70%		
Retired	230	9.26%		
Unable to work	264	10.63%		
Employed – currently off sick	17	0.68%		
<i>Education</i>				
Did not complete High school	54	2.17%	NA	p<0.0001
High School graduate or equivalent	393	15.83%		
Some college (e.g. AA, AS, or no degree)	1028	41.40%		
Bachelor's degree (e.g. BA, BS, AB)	537	21.63%		
Advanced degree (e.g. MBA, MS, PhD, JD, MD)	248	9.99%		
<i>Have you been told by a physician or medical professional that you have any of the conditions listed below (select all that apply)? Due to multiple selection of conditions, percentages do not add up to 100%.</i>				
Anxiety	1338	53.89%	8.96	NA
Back pain	1295	52.15%	8.90	
Chronic pain	1269	51.11%	8.84	
Depression	794	31.98%	8.92	
Acute pain	543	21.87%	8.89	
Other	406	16.35%	NA	
ADHD/ADD (Attention Deficit Hyperactivity Disorder/Attention Deficit Disorder)	408	16.43%	9.00	
Fibromyalgia	389	15.67%	8.76	
PTSD (Post-Traumatic Stress Disorder)	333	13.41%	9.02	
Rheumatoid arthritis	265	10.67%	8.98	
Substance use disorder (alcohol, prescription drugs, illicit drugs)	191	7.69%	9.20	
Bipolar disorder	200	8.05%	9.12	
Personality disorder	81	3.26%	9.10	
Schizophrenia or other psychotic disorder	22	0.89%	8.80	

Table 2: Percentages of demographic variables by psychiatric conditions compared to average kratom users not meeting inclusion criteria for a psychiatric condition.

Variable	N	Average Negative	ADHD Positive	PTSD Positive	Depression Positive	Anxiety Positive
<i>Age</i>						
18-20 years	61	1.15%	2.60%	2.30%	1.90%	1.80%
21-30 years	640	10.18%	20.30%	14.50%	14.00%	14.20%
31-40 years	1407	27.75%	27.20%	35.00%	27.30%	28.80%
41-50 years	1209	25.10%	23.30%	21.80%	24.30%	24.60%
51-60 years	918	19.43%	17.40%	18.60%	18.20%	17.30%
61 years and older	710	15.65%	1.70%	7.70%	7.70%	13.40%
<i>Sex</i>						
Female	2265	43.25%	48.10%	57.70%	46.30%	49.40%
Male	2650	56.38%	51.90%	42.30%	53.40%	50.30%
<i>Marital status</i>						
Single/Never married	1085	19.7%	28.53%	22.57%	26.65%	25.02%
Married	2418	51.85%	41.65%	41.15%	41.73%	42.84%
Partnered	544	11.40%	12.85%	14.16%	12.39%	13.37%
Divorced	733	15.12%	14.40%	19.03%	16.63%	16.62%
Widowed	122	1.94%	2.57%	3.10%	2.61%	2.14%
<i>Race/Ethnicity</i>						
Black or African-American	29	0.43%	0.80%	0.90%	0.40%	0.40%
American Indian or Alaska Native	40	1.13%	0.80%	0.50%	1.00%	1.00%
Asian	111	2.18%	1.00%	1.40%	1.50%	1.10%
Hispanic or Latino/a	113	2.18%	3.40%	0.90%	2.30%	2.40%
White (Non-Hispanic)	4446	92.0%	90.60%	94.10%	92.40%	92.60%
Other	110	2.13%	3.40%	2.30%	2.40%	2.40%
<i>Employment status</i>						
Employed for wages	2401	50.00%	39.00%	46.10%	44.50%	45.40%
Self employed	731	17.28%	13.10%	8.80%	14.00%	14.20%
Out of work for 1 year or more	105	1.80%	5.00%	4.10%	3.60%	3.50%

Out of work for less than 1 year	83	1.65%	3.70%	0.90%	3.20%	3.30%
Homemaker	298	5.28%	6.50%	6.90%	6.00%	6.60%
Student	150	2.38%	5.80%	2.80%	3.60%	3.60%
Unable to work	463	10.15%	19.10%	20.70%	14.70%	14.00%
Retired	581	10.95%	6.50%	7.40%	9.40%	8.60%
Employed – currently off sick	33	0.53%	1.30%	2.30%	1.00%	0.90%
<i>Education</i>						
Did not complete High school (reference)	109	2.43%	1.80%	1.80%	2.70%	2.00%
High school graduate or equivalent	863	17.55%	18.00%	13.70%	17.30%	17.40%
Some college (e.g. AA, AS, or no degree)	2254	45.35%	49.50%	50.70%	46.30%	47.30%
Bachelor's degree (e.g. BA, BS, BA)	1127	23.40%	21.20%	23.70%	23.30%	23.30%
Advanced degree (e.g. MBA, MS, PhD, JD, MD)	520	11.28%	9.60%	10.00%	10.40%	10.00%

Table 3: Prior or concomitant use of other substances with kratom in psychiatric conditions.

	ADHD				PTSD				Depression				Anxiety			
	N (%)	OR	95% CI	p-value	N (%)	OR	95% CI	p-value	N (%)	OR	95% CI	p-value	N (%)	OR	95% CI	p-value
<i>If yes, which of the following drug(s)/substance(s) have/are you taking Kratom with (select all that apply)?</i>																
CBD (Cannabidiol) oil	64 (15.50)	1.54	1.14-2.09	0.007	33 (13.52)	1.29	0.87-1.91	0.211	186 (14.95)	2.17	1.67-2.82	<0.01	157 (13.26)	1.21	0.9-1.62	0.195
Ketamine or other anesthetic/dissociative drugs	4 (0.97)	2.31	0.6-7.71	0.198	0		NA		8 (0.64)	1.6	0.52-4.9	0.406	9 (0.76)	2.59	0.56-12.02	0.184
Benzodiazepines	31 (7.51)	1.75	1.14-2.68	0.013	21 (8.61)	1.97	1.21-3.22	0.011	96 (7.72)	3.49	2.29-5.33	<0.01	98 (8.28)	3.99	2.3-6.93	<0.01
Amphetamine	13 (3.15)	1.63	0.86-3.1	0.149	9 (3.69)	1.92	0.9-3.992	0.103	36 (2.89)	2.28	1.26-4.13	0.005	40 (3.38)	3.92	1.65-9.29	<0.01
Cannabis (marijuana, hashish)	80 (19.37)	1.87	1.41-2.48	<0.01	46 (18.85)	1.72	1.22-2.44	0.003	209 (16.80)	2.23	1.73-2.86	<0.01	186 (15.71)	1.41	1.07-1.87	0.015
Fentanyl or other synthetic opioids	9 (2.18)	1.22	0.58-2.57	0.605	4 (1.64)	0.95	0.34-2.69	0.924	27 (2.17)	1.7	0.91-3.16	0.091	24 (2.03)	1.15	0.57-2.31	0.696
Heroin	0		NA		2 (0.82)	5.91	0.98-35.54	0.08	2 (0.82)	1.5	0.25-8.96	0.657	3 (0.24)	1.72	0.18-16.57	0.625
Tryptamines	3 (0.73)	1.98	0.51-7.68	0.349	0		NA		6 (0.48)	1.2	0.36-3.93	0.767	5 (0.42)	0.95	0.23-4.01	0.949
Synthetic cannabinoids	0		NA		0		NA		0		NA		0		NA	
Methadone or other prescribed medications to treat opioid/heroin dependence	1 (0.24)	0.92	0.11-7.89	0.938	2 (0.82)	3.54	0.68-18.36	0.175	4 (0.32)	1	0.25-3.99	0.995	3 (0.25)	0.57	0.12-2.84	0.497
Mephedrone or any other synthetic cathinones	0		NA		0		NA		0		NA		0		NA	
Phenylethylamines (e.g. 2C-E, AL-LAD, 4-HO-MiPT)	2 (0.48)	1.53	0.31-7.63	0.614	0		NA		7 (0.56)	3.5	0.73-16.88	0.087	6 (0.51)	3.45	0.41-28.7	0.19
Kava	18 (4.36)	1.62	0.94-2.8	0.097	11 (4.51)	1.7	0.8-3.298	0.135	47 (3.78)	1.91	1.17-3.12	0.008	47 (3.97)	1.71	0.96-3.04	0.058
Cocaine	1 (0.24)	0.46	0.06-3.59	0.409	2 (0.82)	1.96	0.4-9.142	0.424	10 (0.80)	10.03	1.28-78.49	0.003	10 (0.84)	0.63	0.61-0.66	0.003
Hallucinogenic mushrooms	5 (0.22)	1.28	0.47-3.47	0.635	3 (1.23)	1.39	0.41-4.75	0.609	15 (1.21)	1.67	0.73-3.83	0.22	16 (1.35)	1.31	0.54-3.21	0.544
Others (please specify):	44 (10.65)	1.25	0.88-1.78	0.217	24 (9.84)	1.14	0.73-1.79	0.561	137 (11.01)	1.68	1.27-2.23	<0.01	128 (10.81)	1.18	0.86-1.63	0.296

Table 4: Self-reported beneficial and detrimental effects of kratom use in psychiatric conditions.

	ADHD				PTSD				Depression				Anxiety			
	N (%)	OR	95% CI	p-value	N (%)	OR	95% CI	p-value	N (%)	OR	95% CI	p-value	N (%)	OR	95% CI	p-value
<i>Which positive or beneficial effects have you experienced when using Kratom? (select all that apply)</i>																
Increased energy	328 (79.42)	1.14	0.88-1.49	0.309	194 (79.51)	1.08	0.78-1.5	0.628	956 (38.50)	0.86	0.71-1.04	0.121	936 (50.27)	1.18	0.95-1.48	0.141
Decreased pain	344 (14.89)	0.68	0.51-0.91	0.012	223 (9.32)	1.68	1.06-2.68	0.019	1095 (44.10)	1.22	0.96-1.54	0.1	1051 (56.44)	1.4	1.06-1.85	0.018
Increased focus	249 (10.77)	1.1	0.88-1.37	0.393	158 (6.61)	1.32	1-1.74	0.047	738 (29.72)	1.05	0.9-1.24	0.513	718 (38.56)	1.18	0.97-1.43	0.091
Less depressive mood	330 (79.90)	2.02	1.56-2.61	<0.01	212 (86.89)	3.25	2.22-4.76	<0.01	993 (79.82)	2.86	2.39-3.42	<0.01	993 (78.13)	2.32	1.89-2.85	<0.01
Less anxious mood	327 (79.18)	1.99	1.54-2.57	<0.01	210 (86.07)	3.13	2.16-4.55	<0.01	951 (76.45)	2.2	1.85-2.62	<0.01	951 (78.63)	2.57	2.09-3.16	<0.01
Reduced or stopped use of opioid painkillers	189 (45.76)	0.92	0.74-1.14	0.432	127 (52.05)	1.21	0.93-1.58	0.16	594 (47.75)	0.99	0.84-1.15	0.86	578 (48.82)	1.09	0.9-1.32	0.358
Reduced PTSD symptoms	114 (27.60)	2.08	1.62-2.67	<0.01	128 (52.46)	6.69	5.06-8.85	<0.01	299 (24.04)	2.41	1.94-2.99	<0.01	300 (25.34)	3.15	2.36-4.19	<0.01
Elevated mood, euphoria or feeling "high"	137 (33.17)	1.47	1.17-1.86	<0.01	71 (2.97)	1.14	0.85-1.53	0.378	396 (31.81)	1.74	1.45-2.09	<0.01	373 (20.03)	1.48	1.19-1.83	<0.01
Other (please specify)	56 (13.56)	1.46	1.06-2.01	0.024	28 (11.48)	1.2	0.79-1.82	0.41	128 (5.16)	1.01	0.78-1.31	0.921	131 (11.06)	1.03	0.76-1.4	0.843
No positive or beneficial effects from Kratom use	0		NA		0		NA		2 (0.08)	1	0.14-7.08	0.997	2 (0.11)	1.15	0.1-12.66	0.911
Reduced or stopped the use of other drugs (e.g. heroin, cocaine, ketamine, cannabis)	75 (18.16)	1.21	0.92-1.6	0.185	48 (19.67)	1.31	0.93-1.83	0.127	227 (18.25)	1.41	1.14-1.76	0.002	220 (18.58)	1.35	1.04-1.75	0.021
Increased empathy	94 (22.76)	1.23	0.95-1.59	0.113	57 (23.36)	1.26	0.92-1.73	0.155	273 (21.95)	1.32	1.09-1.62	0.005	273 (23.06)	1.42	1.12-1.81	0.004
Sexual enhancement	56 (13.56)	1.17	0.85-1.6	0.343	45 (18.44)	1.69	1.19-2.39	0.005	153 (12.30)	1	0.79-1.27	0.981	158 (13.34)	1.18	0.89-1.58	0.248
Sleep improvement	198 (47.94)	0.73	0.59-0.9	0.004	150 (61.48)	1.42	1.08-1.86	0.011	672 (54.02)	1.01	0.86-1.18	0.926	659 (35.39)	1.13	0.93-1.36	0.211
<i>Which negative effect(s) did you experience with the use of Kratom? (select all that apply)</i>																
Nausea	119 (28.81)	2.37	1.85-3.04	<0.01	52 (21.31)	1.34	0.96-1.85	0.089	274 (22.03)	2.04	1.64-2.53	<0.01	267 (22.55)	1.88	1.45-2.43	<0.01
Vomiting	49 (11.86)	2.4	1.67-3.43	<0.01	28 (11.48)	2.03	1.32-3.13	0.003	110 (8.84)	2.31	1.64-3.25	<0.01	104 (8.78)	2.16	1.41-3.29	<0.01
Diarrhea	7 (1.69)	1.91	0.79-4.63	0.174	4 (1.64)	1.69	0.57-4.96	0.369	17 (1.37)	1.89	0.84-4.26	0.114	18 (1.52)	3.47	1.02-11.84	0.023
Heart palpitations (rapid heart beat, tachycardia)	11 (2.66)	2.57	1.22-5.4	0.019	4 (1.54)	1.31	0.45-3.77	0.629	4 (1.64)	2.92	1.36-6.25	0.003	26 (2.20)	2.51	1.03-6.14	0.028

Shortness of breath	9 (2.18)	5.26	2.02-13.72	<0.01	4 (1.64)	2.54	0.83-7.78	0.136	16 (1.29)	8.06	1.85-35.12	<0.01	15 (1.27)	4.34	0.99-19.02	0.021
Constipation	116 (28.09)	2.13	1.66-2.73	<0.01	47 (19.26)	1.16	0.83-1.63	0.39	280 (22.51)	2.11	1.7-2.62	<0.01	264 (22.30)	1.78	1.38-2.31	<0.01
Pain	1 (0.24)	0.51	0.06-4.03	0.485	3 (1.23)	2.42	0.67-8.73	0.217	7 (0.56)	1	0.35-2.85	0.994	6 (0.51)	1.72	0.35-8.55	0.489
Stomach upset	49 (11.86)	2.01	1.42-2.86	<0.01	25 (10.25)	1.5	0.96-2.34	0.087	25 (10.25)	2.4	1.73-3.34	<0.01	118 (9.97)	2.03	1.38-3	<0.01
Dizziness or drowsiness	46 (11.14)	1.59	1.12-2.26	0.013	22 (9.02)	1.13	0.71-1.8	0.608	138 (11.09)	2.37	1.74-3.23	<0.01	143 (12.08)	2.77	1.87-4.12	<0.01
Fainting	0	NA			0	NA			0	NA			0	NA		
Irritability or agitation	44 (10.65)	3.26	2.19-4.84	<0.01	19 (7.79)	1.89	1.13-3.15	0.022	80 (6.43)	2.3	1.54-3.43	<0.01	78 (6.59)	2.1	1.3-3.41	<0.01
High blood pressure (hypertension)	5 (1.21)	2.9	0.94-8.9	0.08	2 (0.82)	1.61	0.35-7.29	0.561	12 (0.96)	4.01	1.13-14.26	0.016	11 (0.93)	3.17	0.7-14.34	0.091
Other (please specify)	40 (0.69)	1.47	1.01-.213	0.048	16 (9.30)	0.9	0.53-1.53	0.682	109 (8.76)	1.63	1.1-2.239	0.002	105 (8.84)	1.55	1.0-2.266	0.019
No negative effects from Kratom use	1 (0.24)	1.53	0.16-14.78	0.722	1 (0.41)	2.94	0.3-28.4	0.398	3 (0.24)	2.99	0.31-28.81	0.308	0	NA		
Dry mouth	31 (7.51)	2.18	1.41-3.39	<0.01	16 (6.56)	1.7	0.98-2.96	0.073	68	1.73	1.16-2.58	<0.01	70 (5.91)	2.3	1.36-3.9	0.001
Problems urinating	20 (4.84)	3.06	1.73-5.43	<0.01	6 (2.46)	1.21	0.51-2.86	0.678	37 (2.97)	2.5	1.37-4.58	<0.01	33 (2.79)	1.92	0.94-3.91	0.061
Aching of muscles/bones	6 (1.45)	1.73	0.67-4.46	0.274	3 (1.23)	1.26	0.37-4.26	0.717	15 (1.21)	1.67	0.73-3.83	0.22	14 (1.18)	2.02	0.66-6.15	0.192
Hyperpigmentation of your skin (darker patches observed on your skin)	0	NA			0	NA			7 (0.59)	5.01	1.1-22.92	0.016	10 (0.80)	1.34	0.34-5.19	0.668
Hair loss	15 (3.63)	1.36	0.76-2.45	0.311	6 (2.46)	0.8	0.34-1.85	0.585	52 (4.18)	2.53	1.51-4.23	<0.01	44 (3.72)	1.71	0.94-3.09	0.067
Sleep problems (insomnia, sleep too much)	18 (4.36)	1.5	0.87-2.58	0.157	13 (5.33)	1.83	0.99-3.38	0.068	50 (4.02)	1.81	1.13-2.9	0.011	45 (3.80)	1.87	1.02-3.44	0.034
Reduced appetite, weight loss	20 (4.84)	1.67	0.99-2.82	0.063	7 (2.87)	0.88	0.4-1.93	0.74	52 (4.18)	1.82	1.15-2.89	0.009	58 (4.90)	2.86	1.52-5.36	0.034
Reduced concentration	9 (2.18)	1.6	0.75-3.45	0.245	3 (1.23)	0.85	0.26-2.8	0.785	28 (2.25)	3.15	1.48-6.7	0.001	28 (2.36)	4.08	1.43-11.69	<0.01
Anger, hostility, aggression	16 (3.87)	5.42	2.63-11.2	<0.01	3 (1.23)	1.02	0.31-3.38	0.979	23 (1.85)	2.9	1.29-6.51	0.006	22 (1.86)	2.55	0.96-6.76	0.002
Seizures	0	NA			0	NA			0	NA			0	NA		
Involuntary (unwanted) movements of the limbs/tremors	9 (2.18)	1.44	0.67-3.06	0.363	4 (1.64)	1.1	0.39-3.14	0.857	25 (2.01)	1.67	0.88-3.19	0.112	25 (2.11)	2.42	0.99-5.92	0.037
Psychotic symptoms (e.g. hallucinations, paranoia, delusions)	2 (0.48)	4.61	0.65-32.85	0.144	1 (0.41)	2.21	0.25-19.81	0.515	0	NA			0	NA		
Sexual problems (e.g. erectile dysfunction, reduced libido/pleasure)	25 (6.05)	2.12	1.31-3.44	0.004	10 (4.10)	1.2	0.61-2.35	0.607	66 (5.31)	2.96	1.83-4.79	<0.01	61 (3.28)	2.25	1.29-3.93	0.002
Liver problems (e.g. elevated liver enzymes in blood tests)	1 (0.24)	1.53	0.16-14.78	0.722	0	NA			3 (0.24)	2.99	0.31-28.81	0.308	0	NA		

Figure 1

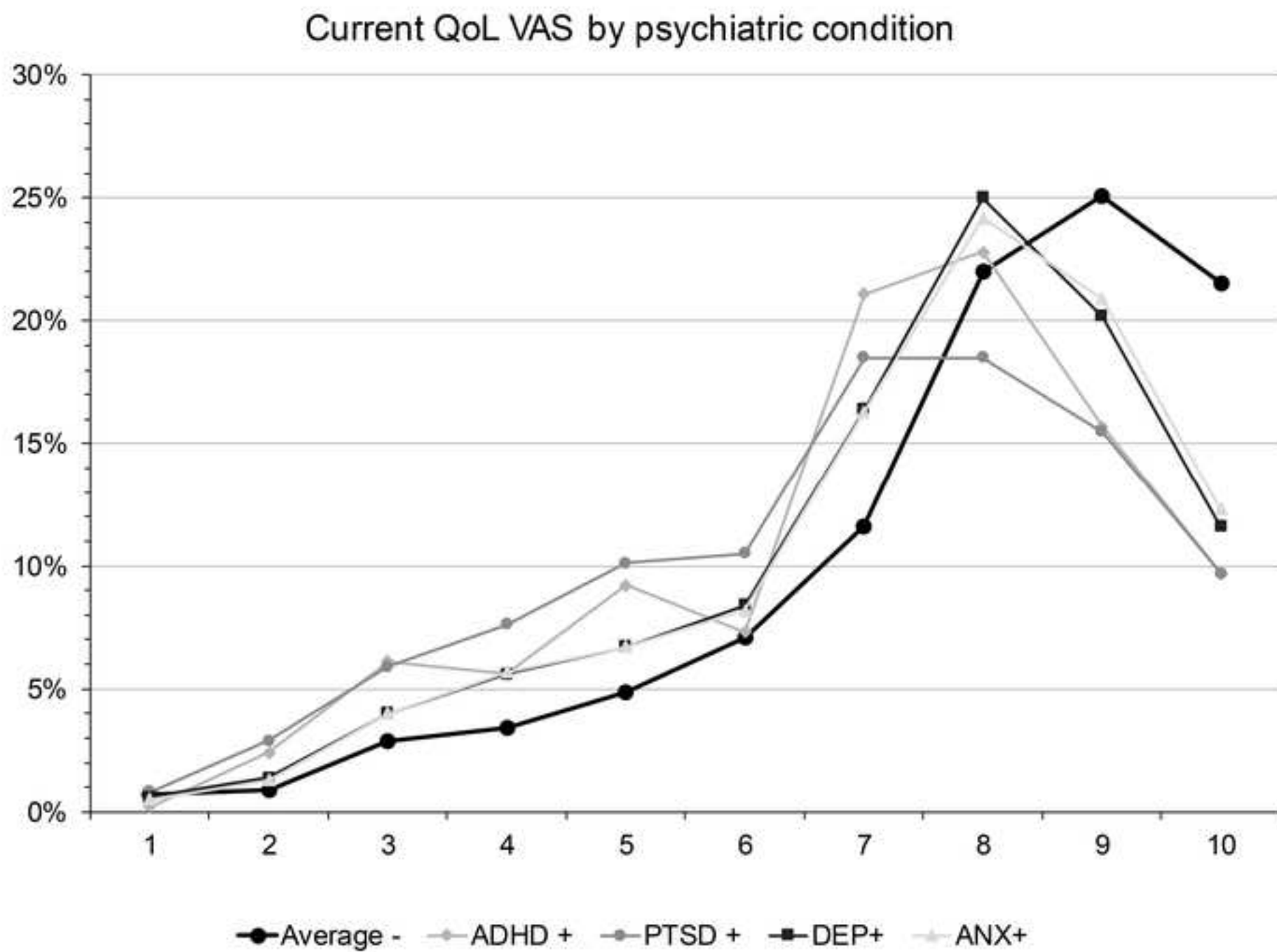


Figure 2

