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Adverse Events Related to Kratom Discontinuation and the Utilization of Prescribed Medications During Hospitalization: A 4-year Retrospective Study in Thanyarak Songkhla Hospital, Thailand

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Abstract:

Objective: The purpose of this study was to investigate adverse events related to kratom cessation and the utilization of prescribed medications during hospitalization.

Material and Methods: This retrospective study was conducted in Thanyarak Songkhla Hospital, Thailand. The study included patients aged 15 years and above who had a history of kratom consumption prior to hospitalization. Adverse events after kratom discontinuation during the patient's hospital admission were documented. The prescribed drug regimens during hospitalization were recorded.

Results: During the 4-year study period, 81 patients were enrolled. Fifty-four patients (67%) developed adverse events. The majority of enrolled patients were males between the ages of 15 and 34 years. The popular 4x100 kratom cocktail was commonly consumed prior to admission. Musculoskeletal pain (28%) and psychological disorders such as insomnia,

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agitation, and anxiety were observed as major adverse events. Patients with adverse events received more medications than those without adverse events (p-value=0.02). Typical antipsychotics were commonly prescribed for patients with adverse events related to kratom discontinuation (p-value<0.01).

Conclusion: In hospitalized patients who had consumed kratom previously, 67% experienced adverse events. The most common adverse events were musculoskeletal pain and psychological disorders. In patients with adverse events, antipsychotics were commonly prescribed. A history of kratom consumption should be asked during hospitalization for all admitted patients to assess the possibility of an adverse event and provide appropriate management.

Keywords: addiction, adverse events, kratom, kratom-related illness, mitragynine

Introduction

Kratom (*Mitragyna speciosa* (Korth.) Havil.; Rubiaceae Family) is a native plant distributed in southern Thailand which contains a variety of indole alkaloids. It is a unique source of mitragynine and 7-hydroxymitragynine, well-known psychoactive substances[1-3]. Kratom leaves have been traditionally used as a stimulant by chewing fresh leaves, brewed as tea, and smoking. In Thailand, kratom leaves have been decriminalized since August 2021 based on the advantages of its pharmacological activities[4]. The production and consumption of kratom cocktails with other psychoactive substances is still illegal. The native people of southern Thailand hold a positive attitude towards kratom, accepting it as a medicinal plant that enhances work productivity and health[5,6]. The 2021 legislative reform led to an increased utilization of the kratom tree and traditional recipes. Nevertheless, it is essential to bear in mind that the use of this substance also carries potential health risks, including psychotic symptoms and addictive/withdrawal symptoms[6].

Adverse events related to kratom consumption is an area in which very limited research has been done, particularly within a clinical setting. Negative consequences linked to kratom consumption such as neurological, psychiatric, gastrointestinal, pulmonary, electrolyte, and renal issues were reported in a recent review[7]. A retrospective study from the Ramathibodi Poison Center (RPC), Thailand, found that kratom poisoning and withdrawal had been found in patients who consumed kratom. Palpitations and myalgia are common kratom poisoning and withdrawal symptoms[8]. The intensity of kratom withdrawal is predicted by factors such as the duration of kratom use, frequency of use, and the daily amount of kratom consumed[9].

Kratom leaves have psychoactive properties that can lead to health issues when abused. Nevertheless, kratom leaves are generally regarded as safer when compared to other narcotic substances like methamphetamine, heroin, and morphine. Solely using kratom does not harm the health. However, combining kratom with other psychoactive drugs can potentially result in fatal consequences. Furthermore, it is necessary to take into account the potential for product contamination, which can include the presence of harmful substances like microbes and toxic metals[3,7]. Analyses of kratom exposure cases in both Thailand and the United States have revealed that when kratom is concurrently used with other substances, the effects tend to be more severe compared to single-substance use[10]. The RPC reported '4×100 fatal cocktail' that caused a 21-year-old man's death. An autopsy examination found mitragynine, alprazolam, tramadol, nortriptyline, methadone, methamphetamine, and caffeine in his blood[11]. A cytochrome P450-mediated drug interaction of

kratom alkaloids was suggested as a possible mechanism. Mitragynine is extensively metabolized by CYP450 enzymes (CYP34A, 2D6, and 2C9) and is a potent inhibitor of CYP2D6 (major), CYP2C19, and CYP3A4, as well as being involved with glucuronidation[3,12,13]. Concurrent use of kratom with certain other drugs, which act as a substrate for those liver enzymes, has the potential to cause drug toxicity and adverse events. Multidrug users usually consume kratom leaves in a potentially fatal cocktail. The southern border provinces of Thailand have many cases of fatal kratom cocktail users many of whom are teenagers. This situation has given rise to various challenges concerning individuals involved in criminal activities and drug addicts[10,14].

Thanyarak Songkhla Hospital, Songkhla, Thailand, is a government hospital responsible for treating drug addicts in southern Thailand. There has been a noticeable rise in new cases of patients admitted with a history of kratom consumption after kratom was legalized. The retrospective survey in this study was performed for the years 2015–2018 from the medical records of hospitalized patients. Evidence of adverse events related to kratom discontinuation in kratom users was recorded and the medication utilization during hospitalization was collected.

Material and Methods

Study design and setting

All medical records of hospitalized patients at Thanyarak Songkhla Hospital from January 2015–December 2018 were reviewed. The study protocol was approved by the Ethics Committee of the Princess Mother National Institute on Drug Abuse Treatment, Ministry of Public Health, Thailand (EC number: 028/2562, date of approval: February 27, 2019).

Participants and outcomes

Eligible patients were above 15 years of age and had a self–reported history of kratom consumption or kratom–containing product use before hospitalization. Patients with psychological disorders, concurrent use of kratom with other psychoactive substances, and those with incomplete medical records were excluded. The demographic data including age and sex, hospital length of stay (LOS), and pattern of kratom use were collected. Adverse events following kratom discontinuation as reported in previous studies (e.g., musculoskeletal pain, neuropsychiatric disorders, and rhinorrhea/lacrimation) were reviewed and documented[8,15]. Participants were categorized into two groups based on whether or not they experienced adverse events related to the cessation of kratom usage. The prescribed drug regimens during hospitalization were also collected.

Data analysis

Descriptive statistics were used to describe the results of the study. Where appropriate, categorical variables were compared with Pearson's chi–square, and continuous variables were analyzed by student t–test or Wilcoxon rank sum test. All statistical analyses were performed using the STATA program, version 17.0, Stata Corporation, Texas, USA.

Results

A total of 137 patients underwent screening (Figure 1). Eighty–one hospitalized patients with a history of kratom consumption were enrolled in this study. Fifty–four out of the total participants (66.7%) reported experiencing adverse events. Table 1 shows the information regarding the patient's demographics, kratom consumption history, and length of hospital stay. Male patients 77/80 (95.1%) were the majority in the study. The population with adverse events distributed between 15 and 34 years old. During the review of kratom–related products, the majority of patients consumed kratom cocktails instead of chewing kratom leaves. Fifty percent of the subjects who experienced adverse events had

consumed kratom with the last kratom use occurring less than one day prior to admission. The median hospital LOS was 14 days in both groups.

Among the 54 patients who experienced adverse events, a total of 127 adverse events were identified (Figure 2). The top five adverse events were muscle and joint pain (27.6%), followed by insomnia (21.3%), fatigue (15.7%), agitation (8.7%), and hallucination (7.9%).

Table 2 shows the prescribed medications during admission of patients with history of kratom consumption. The median and interquartile range (IQR) of prescribed medications during hospitalization was 4.5 (1.0, 4.0) items per patient for those who experienced adverse events, and 3.0 (3.0, 5.0) items per patient for those who did not have adverse events (p-value=0.019). Multivitamins, vitamin B complex, benzodiazepines (BDZs), atypical antipsychotics, and serotonin reuptake inhibitors (SSRIs) were comparably prescribed in both groups. Typical antipsychotics were found to be prescribed at a significantly higher rate to patients who experienced adverse events compared to those who did not exhibit any adverse events (p-value<0.01). Nonsteroidal anti-inflammatory drugs (NSAIDs) and skeletal muscle relaxants were commonly given for patients with adverse events. However, the study did not find a statistically significant difference between the two treatment groups regarding the number of prescribed NSIADs and skeletal muscle relaxants (p-value=0.190).

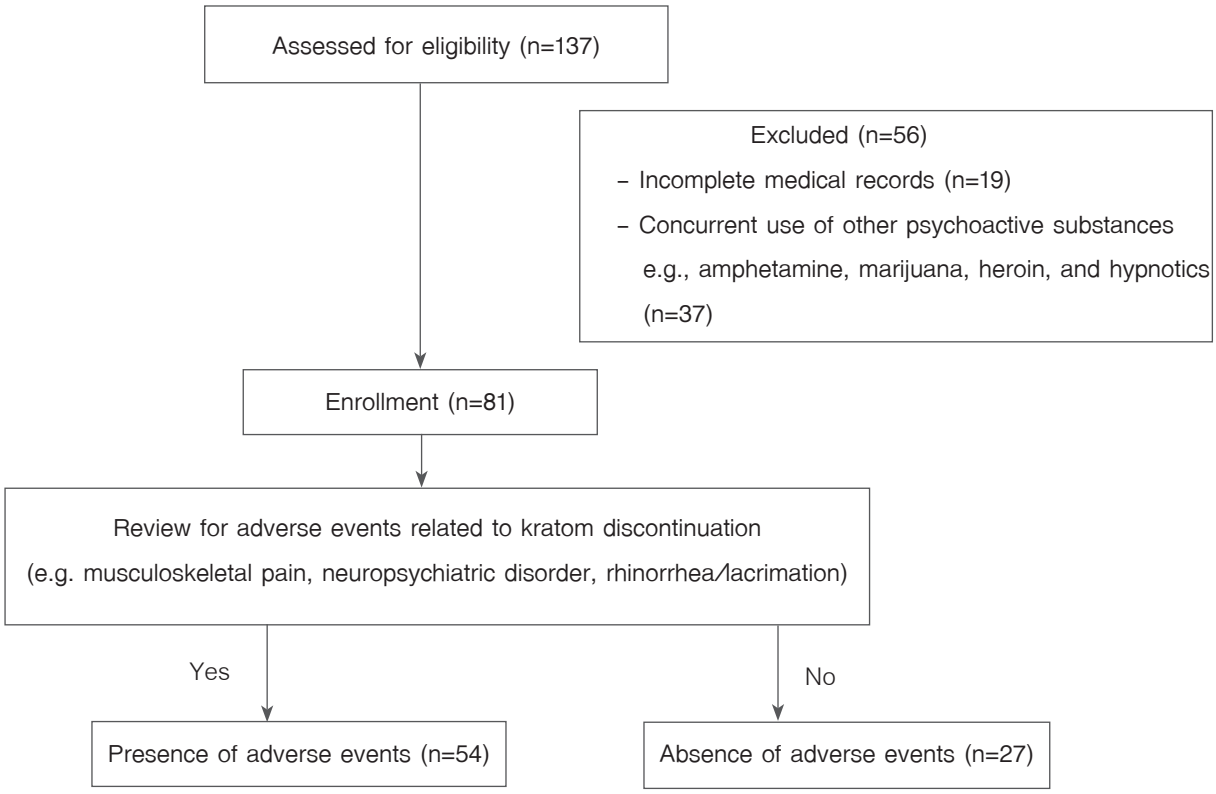

Figure 1 Flow diagram of the study

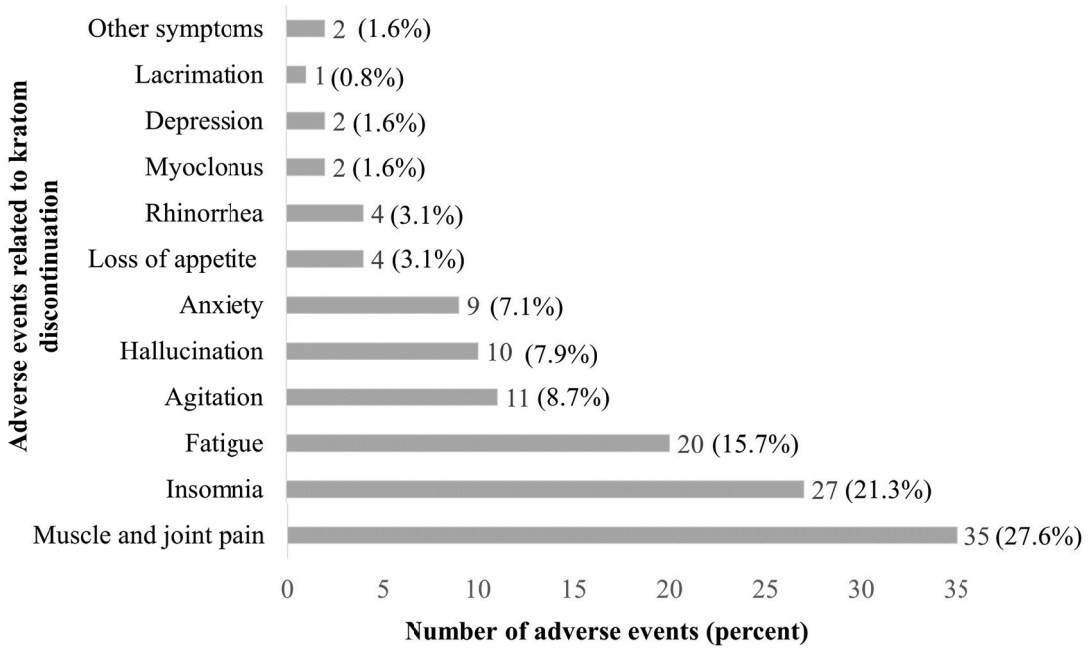

Figure 2 The frequency of kratom-associated adverse events after hospitalization

Table 1 Demographics, kratom consumption history, and hospital length of stay

	Overall (n=81)	Presence of adverse events (n=54)	Absence of adverse events (n=27)	p-value
Gender				
Male	77 (95.1)	51 (94.4)	26 (96.3)	0.717[a]
Female	4 (4.9)	3 (5.6)	1 (3.7)	
Age range (%)				0.350[a]
15–24 years	41 (50.6)	30 (55.5)	11 (40.7)	
25–34 years	36 (44.4)	22 (40.7)	14 (51.8)	
35–44 years	3 (3.7)	2 (3.7)	1 (3.7)	
45–54 years	0 (0.0)	0 (0.0)	0 (0.0)	
≥55 years	1 (1.2)	0 (0.0)	1 (3.7)	
Kratom product (%)				1.000[a]
Kratom leaf	9 (11.1)	6 (11.1)	3 (11.1)	
Kratom cocktail	72 (88.8)	48 (88.8)	24 (88.8)	
Last kratom consumption before hospitalization (%)				0.122[a]
<1 day	37 (45.7)	27 (50.0)	10 (37.0)	
1–2 days	10 (12.3)	5 (9.3)	5 (18.5)	
2–7 days	17 (21.0)	13 (24.1)	4 (14.8)	
>7 days	10 (12.3)	4 (7.4)	6 (22.2)	
No data	7 (8.6)	5 (9.3)	2 (7.4)	
Hospital LOS, median (IQR)	14.0 (7.0, 21.0)	14.0 (7.0, 21.0)	14 (8.5, 25.0)	0.515[b]

IQR=interquartile range, LOS=length of stay
[a]Pearson's chi-square
[b]Wilcoxon rank-sum test

Table 2 Prescribed medications during admission of patients with history of kratom consumption

	Overall (n=81)		Presence of adverse events (n=54)		Absence of adverse events (n=27)		p-value
Overall prescribed medications (items)		346		245		101	
Median number of prescribed medications per person (IQR)	4.0	(3.0, 5.0)	4.5	(1.0, 4.0)	3.0	(3.0, 5.0)	0.019[a]
MTV	73	(90.1%)	47	(87.0%)	26	(96.3%)	0.188[b]
Vitamin B complex	72	(88.9%)	46	(85.2%)	26	(96.3%)	0.134[b]
BDZs (clonazepam and clorazepate)	63	(77.8%)	43	(79.6%)	20	(74.1%)	0.571[b]
Muscle relaxants (orphenadrine/paracetamol)	35	(43.2%)	27	(50.0%)	8	(29.6%)	0.081[b]
NSAIDs (ibuprofen, naproxen, and diclofenac)	27	(33.3%)	21	(38.9%)	6	(22.2%)	0.190[b]
Typical antipsychotics (chlorpromazine, haloperidol, and perphenazine)	22	(27.2%)	21	(38.9%)	1	(3.7%)	0.000[c]
Atypical antipsychotics (risperidone)	8	(9.9%)	6	(11.1%)	2	(7.4%)	0.712[c]
Anti-parkinsonism agents (trihexyphenidyl)	18	(22.2%)	15	(27.8%)	3	(11.1%)	0.155[c]
SSRIs (fluoxetine, sertraline, and trazodone)	13	(16.0%)	9	(16.7%)	4	(14.8%)	1.000[c]
PPIs (omeprazole)	5	(6.2%)	3	(5.6%)	2	(7.4%)	
AEDs (valproic acid)	4	(4.9%)	3	(5.6%)	1	(3.7%)	
Antihistamines (loratadine)	3	(3.7%)	1	(1.9%)	2	(7.4%)	
Other (domperidone and oral rehydration solution)	3	(3.7%)	3	(5.6%)	0	(0.0%)	

AEDs=antiepileptic drugs, BDZs=benzodiazepines, MTV=multivitamins, NSAIDs=nonsteroidal anti-inflammatory drugs, SSRIs=serotonin reuptake inhibitors, PPIs=proton pump inhibitors
[a]Wilcoxon rank-sum test
[b]Pearson's chi-square
[c]Fisher's exact test

Discussion

The current work presents a four-year retrospective cross-sectional study of adverse events and prescribed medications among kratom users admitted to Thanyarak Songkhla Hospital, Thailand. More than half of the participants developed adverse events after abruptly discontinuing their kratom-related products during hospitalization. Musculoskeletal pain and psychological disorders such as insomnia, agitation, and anxiety were observed as major adverse events. These findings were consistent with a previous report of kratom withdrawal symptoms[8,16,17]. Kratom withdrawal symptoms are also an opioid abstinence syndrome which is first noted 12–24 hours from last use and can last up to seven days[8,15]. Symptoms associated with kratom cessation can involve both physiological and psychological elements. Physiological symptoms may include nausea, sweating, chills, muscle and body aches, tremors, twitches, diarrhea, rhinorrhea, and lacrimation. Psychological symptoms can encompass insomnia, restlessness, irritability/hostility, fatigue, anxiety, mood disturbances, and, in some cases, hallucinations[8,15]. Currently, practice guidelines for the management of adverse events after kratom cessation are quite limited. This study found that that patients with a history of kratom use prior to hospital admission were treated based on their adverse events. Drug therapies such as NSAIDs and muscle relaxants were prescribed for musculoskeletal pain, antipsychotics for psychiatric disorders, and BDZs for insomnia Typical antipsychotics were commonly prescribed for patients with adverse events, and they received considerably more medications during hospitalization than patients with no adverse events.

The demographic data showed that more than 88% of the patients enrolled in the study had drank kratom cocktails before hospitalization. The well-known kratom cocktail, or 4×100 cocktail, is commonly composed of a water extract of kratom leaves, caffeine, codeine, and/or BDZs, tramadol, and chlorpheniramine[11]. While this study specifically excluded patients who reported using psychoactive substances concurrently with kratom, we note that patients with drug addiction, e.g. to amphetamine, methamphetamine, ecstasy, or other narcotic substances, were still included in the study, as some patients may choose to conceal this information.

Davidson et al. (2021) summarized the fatal cases in the United States related to kratom consumption[10]. Severe adverse events were mostly found when kratom was taken with opioids such as oxycodone, hydromorphone, morphine, or heroin[10]. Kratom leaves and kratom tea contain mitragynine, which is a μ- and δ-opioid receptor agonist and has an effect on the nervous system. Mitragynine is metabolized via hepatic cytochrome P450 (CYP) enzymes and acts as an inhibitor in certain CYPs such as CYP2D6, CYP3A4, and CYP2C9[3,12]. Kratom, therefore, should be a concern when administered with drugs that are metabolized by those enzymes. In the present study, 346 prescribed medications for 81 patients were recorded. Consideration of the prescribed drug based on its being a substrate for CYP 2D6 enzymes concluded that haloperidol, perphenazine, and risperidone should be avoided in patients being treated for psychotic disorders in kratom users[18]. The predicted toxicity caused by consumption of drugs with kratom or kratom products is summarized in Supplementary Table A.

In this retrospective study, adverse events following the discontinuation of kratom consumption were assessed, along with the evaluation of prescription information. Based on the results of our study, it cannot be definitively concluded that the adverse reactions observed were solely caused by the discontinuation of kratom. Other factors and potential confounding variables may have contributed to the occurrence of adverse events in these cases, i.e., the observed adverse events could potentially be attributed to herb-drug interactions resulting from the concurrent use of multiple medications. The lack of information about narcotics in the medical records limited a more thorough assessment of the reasons for the adverse event outcomes. On the other hand, the examination of the blood or urine of these patients during hospitalization along with a questionnaire may disclose the remaining substances in the patients' bodies in reality. The results obtained from Thanyarak Songkhla Hospital suggested that the management of adverse events after discontinuing kratom or kratom-related products should be carefully based on symptomatic evidence. It should be noted that treatment outcome data were not collected as part of this study. Therefore, the study does not provide information regarding the outcomes or effectiveness of the treatments administered to the patients. The recent legalization of this substance has contributed to the increasing rate of kratom consumption, and the consequences of its addiction are likely to increase. Therefore, the results of the newly implemented kratom policy in terms of clinical and economic outcomes should be closely monitored in Thailand and other countries where it is currently available for consumption.

Conclusion

Kratom adverse events were observed in 67% of hospitalized patients with a history of kratom consumption, and these patients received more medications than those without symptoms. Musculoskeletal pain and psychological disorders were the major adverse events. Typical antipsychotics were commonly prescribed in patients with adverse events. To assess the potential for adverse effects and ensure appropriate management, it is

advisable to inquire about a history of kratom consumption during hospitalization of every patient. This information can aid healthcare providers in understanding any possible associations between kratom use and the patient's current condition, allowing for more targeted and effective care.

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Conflict of interest

All authors declare no conflicts of interest.

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Supplementary Table A The prescribed drugs during hospitalization and predicted toxicity caused by consumption of drugs with kratom or kratom products.

Prescribed drug during hospitalization	Substrate of the P450 liver enzyme	Prediction of drug interactions with kratom*	Toxicity prediction from drug interactions with kratom
Clonazepam	CYP3A4 (major)	Yes (minor)	Sedative-hypnotic effects → CNS and respiratory depression
Clorazepate	CYP3A4 (minor)	Yes (minor)	Sedative-hypnotic effects → CNS and respiratory depression
Orphenadrine	CYP1A2 (minor), CYP2B6 (minor), CYP2D6 (minor), CYP3A4 (minor)	Yes (minor)	Anticholinergic toxicity, seizures, cardiac conduction abnormalities, and ventricular dysrhythmias
paracetamol	CYP1A2 (minor), CYP2A6 (minor), CYP2C9 (minor), CYP2D6 (minor), CYP2E1 (major), CYP3A4 (minor),	Yes (minor)	Hepatotoxicity
Ibuprofen	CYP2C19 (minor), CYP2C9 (minor)	Yes (minor)	Abdominal pain, nausea, vomiting, CNS depression, lethargy, and confusion
Naproxen	CYP1A2 (minor), CYP2C9 (minor)	No data	No data
Diclofenac	CYP1A2 (minor), CYP2B6 (minor), CYP2C19 (minor), CYP2C8 (minor), CYP2C9 (major), CYP2D6 (minor), CYP3A4 (minor)	Yes (minor)	Abdominal pain, nausea, vomiting, CNS depression, lethargy, and confusion
Chlorpromazine	CYP1A2 (minor), CYP2D6 (minor), CYP3A4 (minor)	Yes (minor)	CNS depression (ranging from somnolence to coma), hypotension, and sinus tachycardia. Respiratory depression and seizure activity. Ventricular arrhythmias (e.g., QTc prolongation, QRS widening, torsades de pointes)
Haloperidol	CYP1A2 (minor), CYP2D6 (major), CYP3A4 (major)	Yes (major)	CNS depression (ranging from somnolence to coma), hypotension, and sinus tachycardia. Respiratory depression and seizure activity. Ventricular arrhythmias (e.g., QTc prolongation, QRS widening, torsades de pointes)
Perphenazine	YP1A2 (minor), CYP2C19 (minor), CYP2C9 (minor), CYP2D6 (major), CYP3A4 (minor)	Yes (major)	CNS depression (ranging from somnolence to coma), hypotension, and sinus tachycardia. Respiratory depression and seizure activity. Ventricular arrhythmias (e.g., QTc prolongation, QRS widening, torsades de pointes)
Risperidone	CYP2D6 (major), CYP3A4 (major)	Yes (major)	CNS depression, sinus tachycardia, and hypotension
Trihexyphenidyl	None known	None known	Anticholinergic toxicity may include tachycardia, mydriasis, urinary retention, hyperthermia, decreased bowel sounds, constipation, dry mucous membranes, disorientation, senselessness, and repetitive picking at something or grabbing at non-existent objects (e.g., hallucinations)
Fluoxetine	CYP1A2 (minor), CYP2B6 (minor), CYP2C19 (minor), CYP2C9 (minor), CYP2D6 (minor), CYP2E1 (minor), CYP3A4 (minor)	Yes (minor)	Nausea, vomiting, CNS depression, drowsiness, dizziness, hypertension, sinus tachycardia, tremor, and blurred vision. Rare, but potentially life-threatening: seizures, QTc prolongation, decreased consciousness, and serotonin syndrome.
Sertraline	CYP2B6 (minor), CYP2C19 (minor), CYP2C9 (minor), CYP2D6 (minor), CYP3A4 (major)	Yes (minor)	Nausea, vomiting, CNS depression, drowsiness, dizziness, hypertension, sinus tachycardia, tremor, and blurred vision. Rare, but potentially life-threatening: seizures, QTc prolongation, decreased consciousness, and serotonin syndrome.
Trazodone	CYP2D6 (minor), CYP3A4 (major)	Yes (minor)	No data

Supplementary Table A continuous

Prescribed drug during hospitalization	Substrate of the P450 liver enzyme	Prediction of drug interactions with kratom*	Toxicity prediction from drug interactions with kratom
Omeprazole	CYP2A6 (minor), CYP2C19 (major), CYP2C9 (minor), CYP2D6 (minor), CYP3A4 (minor)	Yes (minor)	No data
Valproic acid	CYP2A6 (minor), CYP2B6 (minor), CYP2C19 (minor), CYP2C9 (minor), CYP2E1 (minor)	Yes (minor)	Central nervous system depression and hepatotoxicity
Loratadine	CYP2D6 (minor), CYP3A4 (minor)	Yes (minor)	Mild CNS depression and/or agitation
Domperidone	CYP1A2 (minor), CYP2B6 (minor), CYP2C8 (minor), CYP2D6 (minor), CYP3A4 (major)	Yes (minor)	Acute dystonic reactions, drowsiness, fatigue, lassitude, and restlessness, diarrhea, dry mouth, and headache

CNS=central nervous system, CYP=cytochrome P450, QRS=Q-, R- and S-wave on electrocardiogram, QTc=corrected QT interval
*Kratom leaves and kratom products contain mitragynine, which is a potent cytochrome P450 inhibitors of CYP2D6 (major), CYP2C19 (minor), and CYP3A4 (minor). If a prescribed medication during hospitalization is majorly metabolized by CYP2D6, the herb-drug interaction will classify to be major. Otherwise, the interaction will classify to be minor herb-drug interaction.
Reference: Lexicomp Online, Lexi-Drugs Multinational. Waltham, MA: UpToDate, Inc. https://online.lexi.com. Accessed February 23, 2023.