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Effects of Kratom (Mitragyna speciosa) and Mitragynine in Humans

Introduction

Kratom (*Mitragyna speciosa*) is a tropical tree native to Southeast Asia whose leaves have been used traditionally for their psychoactive and medicinal properties [1]. Preparations of kratom (such as chewed fresh leaves, dried leaf powder, capsules, or brewed teas) contain multiple alkaloids, chiefly **mitragynine** and a potent minor alkaloid **7-hydroxymitragynine** [2]. At lower doses, kratom produces stimulant-like effects (increased energy, alertness and sociability), whereas higher doses have sedative and opioid-like analgesic effects [2] [3]. These dose-dependent effects underpin kratom's growing use as a natural remedy for pain, mood disorders, and as a self-treatment for opioid withdrawal [4] [1]. In recent years, kratom use has spread to Western countries; for example, an estimated 1.7 million Americans used kratom in 2021 [5]. Despite its perceived benefits, kratom remains controversial due to concerns about safety, addiction potential, and lack of regulatory oversight. This report reviews human-based evidence on kratom's acute and chronic effects on the **physiological**, **neurological**, and **psychological** domains, evaluates its therapeutic potential in pain, mood, and opioid withdrawal contexts, and discusses risks of dependence and adverse outcomes, along with regulatory and public health considerations. All findings are drawn from recent peer-reviewed human studies and authoritative sources.

Physiological Effects of Kratom

Acute Physiological Effects: In controlled studies with human volunteers, kratom (and isolated mitragynine) has shown relatively mild acute effects on basic vital signs. For example, single doses of pure mitragynine up to 40 mg produced no clinically significant changes in heart rate, blood pressure, respiratory rate, or body temperature in healthy adults [6] [7]. Minor decreases in blood pressure and breathing rate were noted at some higher doses, but values remained within normal ranges [7]. Kratom's stimulant properties are apparent at low doses – users often report increased alertness, energy, and reduced fatigue shortly after consumption [8] [9]. A recent placebo-controlled trial found that a low 5 mg mitragynine dose increased subjective **arousal** and improved performance on attention tasks, consistent with a mild stimulant effect [8]. In contrast, higher doses acutely produce more opioid-like physiological effects. High doses can cause noticeable **miosis** (pupil constriction) and subtle motor incoordination; in one observational study of regular users, an average 5.16 g dose of kratom powder led to a significant reduction in pupil diameter for over 2 hours post-dose [10]. High-dose mitragynine (40 mg) in a lab trial caused participants to feel sedated and physically fatigued, though without dangerous cardiorespiratory depression [8] [11]. Consistent with opioid-like activity, kratom dose-dependently **relieves pain** – acute administration of a kratom tea was shown to significantly increase pain tolerance in human volunteers (cold pressor test tolerance doubled 1 hour after a kratom dose vs. placebo) [12] [13]. Additionally, kratom can acutely suppress symptoms of opioid withdrawal; in regular users with mild withdrawal at baseline, taking their typical morning dose of kratom quickly reduced subjective withdrawal scores and produced mild euphoria without major physiological side effects [10] [14].

Chronic Physiological Effects: With long-term use, the body develops **tolerance** to many of kratom's effects, often prompting escalating dosages to achieve the same results [4]. Regular users typically consume 3–6 doses per day (for example, Southeast Asian users might drink 3–6 glasses of kratom decoction daily, estimated to total 200–400 mg mitragynine) [15] [16]. Despite high alkaloid intake, chronic kratom consumers in surveys and clinical studies generally appear to maintain normal physiological function. One study in Malaysia found that long-term daily kratom users (mean 6 years use) had **no significant abnormalities in clinical labs** – their hematological, liver enzyme, kidney function, and endocrine profiles (including testosterone levels) were within normal ranges, indistinguishable from non-users [17] [18]. Cognitive and motor tests likewise show that heavy kratom use (over 3 glasses of tea per day) does not broadly impair coordination or muscle function (no deficits in fine motor or balance tasks compared to controls) [19] [20]. Many chronic users even report improved work stamina and reduced fatigue as reasons for continued use [21] [22]. Nevertheless, long-term consumption can have some physical downsides. Gastrointestinal effects like **constipation** are commonly reported – about one-third of users in a large survey noted mild constipation or upset stomach as a side effect of regular kratom use [23] [24]. Anecdotal reports and case studies link heavy prolonged use to weight loss, dehydration, and darkened skin pigmentation, though systematic data are limited. **Hepatotoxicity** (liver injury) from kratom appears to be rare but serious when it occurs. Isolated case reports have documented acute cholestatic hepatitis and even liver failure requiring transplant in a handful of individuals taking high-dose kratom products [25] [26]. In most reported cases, liver enzymes normalized after kratom cessation, indicating an idiosyncratic drug-induced liver injury. Similarly, **seizures** or **cardiac issues** have been reported in some kratom-related medical emergencies, but these almost always involve extremely high doses or co-ingestion of other drugs (e.g. other opioids or stimulants) [27] [28]. Overall, human evidence to date suggests that kratom, when used in moderation and without adulterants, has relatively few severe chronic physiological effects – **typical long-term users often show no clinically significant organ damage or health problems** [17] [18]. However, tolerance and physical dependence can develop with daily use, and heavy use carries risks of gastrointestinal distress, mild nutritional or hormonal effects, and in rare cases organ toxicity.

Neurological Effects and Pharmacology

Mechanisms of Action: Mitragynine and 7-hydroxymitragynine act on multiple receptor systems in the brain, which explains kratom's complex neurological profile. They are partial agonists at **mu-opioid receptors**, accounting for kratom's analgesic and euphoric effects without the full respiratory depression of classic opioids [29]. Interestingly, they also exhibit antagonist or agonist activity at other receptors, including alpha-adrenergic receptors, serotonin (5-HT_{2A} and 5-HT_{1A}), dopamine D₁, and even kappa-opioid receptors [30]. The opioid receptor activation is G-protein biased, thought to result in strong pain relief with reduced beta-arrestin recruitment (hence potentially less respiratory suppression) [31]. These diverse interactions likely contribute to kratom's stimulant effects at low doses (e.g. adrenergic and dopaminergic activation) versus sedative effects at higher doses (mu-opioid agonism predominates). Notably, mitragynine's metabolic conversion to 7-hydroxymitragynine (a more potent mu agonist) in the body may enhance opioid-like effects in vivo [32] [33]. Overall, kratom's neuropharmacology is complex and not yet fully mapped in humans; however, its primary action on opioid receptors is central to understanding its neurological and psychological impact.

Acute Neurological Effects: Shortly after consumption, low-dose kratom can produce mild **psychostimulant** effects on the central nervous system. In a placebo-controlled trial, a 5–10 mg mitragynine dose improved measures of **sustained attention and alertness**, and even reduced lapses in a vigilance task, indicating enhanced attentional capacity [8] [34]. Users often describe feeling more focused and motivated under low doses of kratom, akin to a caffeine-like boost (without jitteriness at moderate amounts). In the same study, low doses also increased scores on the Addiction Research

Center Inventory (ARCI) Amphetamine scale, reflecting stimulant-type subjective effects [35] [36]. By contrast, high doses shift the neurobehavioral effects toward **CNS depression**. A 40 mg dose of mitragynine in naive subjects led to significant increases in an ARCI scale associated with sedation and **amnesia**, and provoked mild dissociative symptoms (e.g. feeling foggy or detached) on a clinical scale [37] [11]. Participants at this high dose reported difficulty concentrating and some memory impairment for the period of intoxication [37] [11]. Motor coordination and reflexes, however, were only minimally affected acutely. Objective neurocognitive testing showed no major deficits in reaction time or executive function even at the highest dose, aside from a slight increase in impulsive errors on a response-inhibition task at 5 mg (possibly due to over-arousal) [34] [38]. Real-world studies align with these findings: regular kratom consumers performing simulated driving have shown **no significant impairment** in psychomotor performance or decision-making at their usual doses [39] [40]. In essence, acute kratom use in moderate amounts produces a unique combination of mental stimulation and analgesia with relatively preserved cognitive function, whereas very high doses can cause transient drowsiness, confusion, or dizziness.

Chronic Neurological Effects: Remarkably, long-term kratom use does not appear to cause gross neurological deficits in humans according to current evidence. A neurocognitive study compared 70 long-term kratom users (average >2 years of near-daily use) to non-user controls and found **no significant differences** in overall cognitive functioning [19] [20]. Regular users performing a battery of tests showed normal memory, learning, and executive function, even those consuming more than 3 glasses of kratom tea per day (estimated ~73–75 mg mitragynine daily) [41] [20]. Only a subtle deficit in one specific memory task (visual episodic memory) was noted in the heaviest users, while other domains (motor skills, attention span, working memory, and decision-making) were intact [41] [42]. There is also *no clinical evidence of kratom causing chronic neurodegenerative changes or neuropathy*. Unlike alcohol or methamphetamine abuse, kratom use has not been linked to conditions like peripheral neuropathy or brain atrophy in observational studies. Importantly, **seizure risk** with chronic kratom alone appears low – seizure cases typically involve polydrug exposure or adulterated products [27] [28]. Additionally, concerns about kratom-induced **psychosis** or other psychiatric sequelae have not been borne out in population studies; a Malaysian cohort of long-term users showed no increased incidence of psychosis or other severe psychiatric disorders attributable to kratom [43] [44]. Some neurological adaptation does occur: chronic exposure leads to tolerance at the receptor level (necessitating higher doses for the same effect) and **dependence** characterized by neuronal changes similar to those seen in mild opioid dependence [31] [45]. Upon cessation after prolonged use, neurochemical rebound can precipitate withdrawal symptoms (e.g. hyper-excitability of locus coeruleus neurons, etc.), manifesting as agitation and irritability. Overall, however, available human research suggests **no major long-term cognitive impairment or irreversible neurological damage** from kratom alone [19] [20] – a finding that differentiates it from many other psychoactive substances. It should be noted that this conclusion may be specific to unadulterated kratom products; contaminants or co-used drugs could introduce neurological risks beyond those of kratom's alkaloids.

Psychological Effects and Mood Impact

Acute Psychological Effects: Kratom's immediate psychoactive effects can range from mild euphoria and anxiety relief to sedation or dysphoria, depending on dosage and individual response. Many users report a **positive mood lift** and calming effect within 30–60 minutes of a typical dose. In survey data, about 22% of users specifically take kratom for relief of **anxiety, stress, or depression** and often endorse improved mood and relaxation shortly after dosing [46] [47]. Laboratory findings corroborate these subjective reports: low doses of mitragynine (5–10 mg) produced small but significant increases on the ARCI **"Morphine-Benzedrine Group" (MBG)** scale, which is an index of euphoria/well-being [35] [36]. In one trial, 5 mg mitragynine slightly elevated participants' self-rated feelings of contentment and friendliness (consistent with the stimulant-euphoric profile), without causing any hallucinations or

severe alterations in perception [35] [48]. Kratom's anxiolytic and antidepressant-like effects have not been formally tested in clinical trials, but anecdotal evidence is strong: users frequently describe acute kratom use as reducing racing thoughts, easing social anxiety, and providing a general sense of well-being or motivation. Physiologically, this may relate to kratom's agonism of adrenergic and serotonergic pathways, which can dampen stress responses. **Higher doses**, on the other hand, can produce **sedation, cognitive clouding, and negative mood** in the short term. Inexperienced users who ingest large amounts (e.g. >8–10 g leaf or equivalent) sometimes report feeling **dysphoric** or overly lethargic, with symptoms like nausea, dizziness, and irritability. The controlled study of 40 mg mitragynine noted that volunteers had increased scores on a measure of **psychopathological symptoms**, particularly obsessive or intrusive thoughts, during the acute high-dose period [49] [50]. Some also experienced transient anxiety and mild confusion (one subject described it as "momentary panic or gloominess") at the peak of the high dose. Notably, **hallucinations or paranoia are extremely uncommon** with kratom alone at any dose – such effects, when reported, often involve adulterated products or mixing kratom with other substances [27] [51]. In summary, acutely kratom tends to have *mood-brightening and anxiolytic effects in moderate doses*, whereas very high doses can paradoxically cause discomfort, anxiety, or sedation that may be perceived as a negative psychological state. The acute **side effect profile** on the mind is generally mild: about 13% of users have ever experienced "bad" reactions (e.g. nervousness, irritability, or emotional blunting), and these incidents are overwhelmingly self-limited and manageable without medical intervention [52] [53].

Chronic Psychological Effects: The longer-term impact of habitual kratom use on mental health is complex and can be both beneficial and adverse. On the positive side, many chronic users utilize kratom as a form of **self-medication for mood disorders**. In a Johns Hopkins survey of nearly 2,800 kratom consumers, 67% reported using kratom to alleviate **anxiety** and 65% to alleviate **depression**, often with notable success [54] [55]. A significant number of participants stated that regular kratom use allowed them to reduce or discontinue prescription psychiatric medications [56] [57]. Users commonly describe that a routine morning dose of kratom helps them feel "normal" – providing mental energy and positivity that counteracts depressive symptoms – without causing intoxication or impairment in daily functioning [58] [59]. In this sense, some researchers have likened **daily kratom use** to heavy caffeine use, insofar as both can become needed to achieve one's optimal functioning and stave off fatigue or low mood [60] [61]. Crucially, chronic kratom use generally does *not* appear to cause **personality changes, cognitive decline, or social withdrawal** in the way that many illicit drugs can. Long-term users in Southeast Asia are often employed, married, and socially integrated, with no obvious psychological deterioration noted by observers [62] [63]. Unlike alcohol or stimulants, kratom is rarely associated with violent behavior or severe impulsivity. However, the **dependence** that can develop introduces a psychological component: users may feel they *need* kratom to face daily stresses or to feel "normal," which can lead to psychological attachment and craving (discussed more under *Dependence* below). When chronically high doses are taken, some subtle negative psychological effects have been reported. For instance, a subset of heavy users have described increased **nervousness, restlessness, or irritability** when on kratom, especially if exceeding their usual dose or using a very potent extract [64] [65]. This likely relates to overstimulation of adrenergic receptors. Additionally, if kratom is used in escalating amounts over time, users may experience **anhedonia or depressed mood** when not using (a mild withdrawal phenomenon). *Severe psychiatric complications* from long-term kratom alone are very rare – e.g., cases of psychosis with hallucinations or delusions have been occasionally documented but nearly always involve either extremely high intake or other co-occurring substance use or psychiatric illness [27] [51]. One notable risk in chronic use, especially for women of childbearing age, is **neonatal abstinence syndrome** if kratom is used during pregnancy. The FDA has reported cases of infants born to kratom-using mothers exhibiting withdrawal symptoms (jitteriness, crying, muscle stiffness) after birth [66]. This indicates that kratom's psychological and physical dependence aspects can extend to the fetus and newborn, raising concerns about use in pregnancy. In summary, most long-term kratom users do not suffer worsening of psychological health – in fact, many

perceive an improvement in mood stability and stress management – but dependence can subtly shift the psychological role of kratom from optional enhancer to perceived *necessity*, and abrupt removal of kratom after long-term use can unmask or exacerbate underlying anxiety or depressive tendencies.

Therapeutic Potential of Kratom

Despite being unapproved for any medical indication, kratom has drawn significant interest for its **potential therapeutic applications**. Human reports have spurred investigations into several key areas where kratom's unique effects might offer benefits: **pain management**, **mental health (mood/anxiety)**, and **opioid withdrawal support**. Below we evaluate the evidence in each domain:

Pain Management

One of kratom's primary traditional uses is as an **analgesic** for both acute and chronic pain. The mu-opioid receptor activity of mitragynine and 7-hydroxymitragynine suggests an opioid-like painkilling action, which has been confirmed in animal models and is supported by human anecdotal data [32] [67]. Importantly, a controlled human trial provided objective evidence of kratom's analgesic efficacy: in a double-blind study, 26 experienced kratom users were given either a kratom leaf decoction or placebo after a brief abstinence. **Pain tolerance** (measured by cold pressor test) increased dramatically from ~11 seconds to ~25 seconds (more than double) one hour after consuming kratom, whereas no improvement occurred with placebo [12] [68]. Participants reported significant pain relief without serious side effects in this trial. This finding aligns with extensive survey data. In a 2019 online survey, **91% of respondents** who used kratom for pain self-reported that it was effective in relieving their pain, and over 90% said it helped them cut down on or replace opioid analgesics [47] [69]. Many users specifically use kratom to manage chronic musculoskeletal pain (back, joint, or injury-related pain) and report sustained benefit with regular dosing [54] [55]. Unlike typical opioids, kratom's analgesia may come with a lower incidence of respiratory depression and constipation (though constipation can still occur). Some individuals with chronic pain conditions (such as fibromyalgia or arthritis) have been able to reduce or discontinue prescription opioids by switching to kratom, citing comparable pain control with fewer cognitive side effects [47] [53]. However, formal clinical trials in pain patients are lacking, so these outcomes are based on self-reported use. It's also worth noting that kratom's analgesic effects are dose-dependent and there is a ceiling to pain relief; extremely high doses will not necessarily yield better analgesia and may instead cause sedation or toxicity. Still, the **therapeutic potential for pain** is one of kratom's most promising attributes. Experts have suggested that, with proper regulation and research, kratom or its alkaloids might be developed into a pain treatment that could serve as a **lower-risk alternative to classical opioids** [4] [70]. More studies are needed to compare kratom's pain-relieving power and safety head-to-head with standard analgesics. But existing human evidence (both experimental and observational) indicates that kratom can provide meaningful analgesia for acute pain (e.g. enhancing tolerance to painful stimuli) and for chronic pain (reducing daily pain levels), meriting further exploration in pain management contexts.

Mood Enhancement and Mental Health

Kratom also shows potential as a **mood regulator and antidepressant/anxiolytic**, though data here come mostly from user surveys and case reports rather than trials. A large proportion of kratom consumers use it to self-treat mood disorders: in one survey, 67% used kratom for **anxiety** relief and 65% for **depression**, with many indicating that it was helpful [54] [55]. Users often report that small daily doses improve their overall mood, increase motivation, and reduce anxiety without the emotional blunting that some pharmaceutical drugs produce. **Stress reduction** is a commonly cited benefit – laborers in Southeast Asia have long chewed kratom leaves to alleviate fatigue and the stresses of manual work [21] [22]. Modern-day users similarly claim kratom helps them feel more "calm and

optimistic" during daily activities. There is some neurobiological rationale for these effects: kratom's alkaloids may interact with adrenergic and serotonergic pathways to produce mild **antidepressant** effects (preclinical studies have noted increased synaptic serotonin and anti-inflammatory activity, which are linked to antidepressant action). Additionally, anecdotal evidence suggests kratom can have an **anxiolytic effect** akin to low-dose benzodiazepines or certain herbal anxiolytics – users with social anxiety or PTSD have reported using kratom before anxiety-provoking situations (like social gatherings) to feel more at ease [46]. Unlike traditional anxiolytics, kratom does not typically impair cognition or motor skills at anxiolytic doses, which could be an advantage if confirmed. It's important to stress, however, that no rigorous clinical trials have yet evaluated kratom for any psychiatric condition. All evidence of efficacy is from uncontrolled use. Nonetheless, the consistency of positive reports (coupled with relatively low incidence of severe psychiatric side effects) points to a potential **therapeutic role for kratom in mood regulation**. It might be particularly useful for individuals who have not tolerated conventional antidepressants or anxiolytics, or as an adjunct for those with partial relief. Caution is warranted, since reliance on kratom can itself lead to dependency that might complicate one's mental health in the long run (needing the substance to fend off dysphoria). Some researchers call for controlled studies to formally test kratom or isolated mitragynine in conditions like generalized anxiety disorder or mild depression [71] [72]. Until then, any use of kratom for mood disorders remains an **off-label, self-directed practice**, albeit one that many people swear by. The generally low rate of serious adverse events in these users (few report exacerbation of anxiety or emergence of suicidality – in fact many report the opposite) suggests a therapeutic potential that deserves further investigation.

Opioid Withdrawal and Addiction Treatment

Perhaps the most publicized potential use of kratom is as a tool for managing **opioid withdrawal** and as a harm-reduction agent for opioid dependence. Kratom has a long history in Southeast Asia of being used to transition people off opiates; for decades, individuals addicted to opium or heroin in Thailand and Malaysia have consumed kratom to reduce withdrawal sickness and cravings [73]. Renewed interest in this traditional practice has arisen amid the opioid epidemic in Western countries. Surveys show a substantial subset of kratom users are people with opioid use disorder (OUD) or chronic opioid prescriptions who turned to kratom as a substitute. In one survey of U.S. kratom consumers, **41% reported using kratom to help quit or reduce opioids**, and among those, 87% said it was effective in alleviating opioid withdrawal symptoms [74] [75]. Remarkably, 35% of these individuals indicated they had been able to remain off opioids for over a year thanks to kratom [54] [76]. Kratom's partial opioid agonism can ease classic withdrawal symptoms like muscle aches, insomnia, diarrhea, and anxiety, without producing the intense high (and respiratory depression) of stronger opioids. A recent direct-observation study showed quantitatively that a typical kratom dose in dependent users **suppressed withdrawal**: before dosing, participants had mild opioid withdrawal scores, and within an hour of taking kratom their withdrawal scores dropped significantly (by ~4 points on a standardized scale) [10] [77]. Participants also reported feeling moderate relief and only mild euphoria (many rated euphoria as only "mild" on a morphine-effect scale) [14] [78]. These findings suggest kratom can indeed act as a gentler replacement for opioids, mitigating withdrawal while producing less impairment. Importantly, unlike methadone or buprenorphine, kratom is not a licensed opioid treatment, so individuals are dosing themselves without medical supervision. This has drawbacks (variable product potency, no guidance on tapering) but also speaks to kratom's **accessibility** as an over-the-counter aid for those who cannot access formal treatment. Some addiction medicine specialists have cautiously noted that **kratom might serve as a harm-reduction agent** for people who refuse or do not have access to FDA-approved medications [79] [80]. Early case series have reported individuals successfully using kratom to self-taper off heroin or prescription opioids, experiencing a far milder withdrawal than expected [73]. However, evidence is not unanimous: a minority of users report that kratom did not fully prevent their withdrawals or that they became dependent on kratom itself in the process (essentially swapping one dependence for another, albeit a less dangerous one). Overall, the **therapeutic promise** here is that

kratom could be developed into a medication to aid in opioid detoxification or maintenance, potentially offering a treatment with low respiratory depression risk and greater patient acceptability (since it provides some stimulant effects and is plant-derived, which some patients prefer) [4]. The FDA has not approved kratom for this purpose and warns against it, but calls for research are growing. Given the magnitude of the opioid crisis, even anecdotal 91% success rates in reducing opioid use with kratom are notable [47] [81]. Rigorous trials would be needed to establish dosing protocols, efficacy, and safety in comparison to standard of care (buprenorphine/methadone). In summary, **human experience strongly suggests kratom can alleviate opioid withdrawal symptoms and help some individuals transition away from more dangerous opioids**. This positions kratom as a potential therapeutic ally in treating OUD, though one that requires careful consideration of its own dependency risk and the need for medical oversight.

Risks: Dependence, Tolerance, and Adverse Outcomes

While kratom may have potential benefits, it also carries **significant risks** that must be acknowledged. Chief among these are the development of dependence and tolerance, and the occurrence of adverse health effects with heavy or improper use.

Dependence and Withdrawal: Kratom can cause **physical and psychological dependence** with regular use. Repeated daily consumption leads to neuroadaptation at opioid receptors (and other pathways), resulting in **tolerance** – users needing progressively higher doses to achieve the same effect [31]. Many long-term users describe escalating their intake over months or years. In one survey, about 50–60% of daily users met criteria for kratom use disorder (KUD) or at least experienced difficulty cutting down, indicating a high rate of dependence among frequent users [82] [83]. The DSM-5 diagnostic criteria most commonly met in these cases were tolerance, withdrawal, using more/longer than intended, and craving [84] [61]. Notably, **severe impairment from kratom addiction is relatively uncommon** – fewer than 3% of users in a large survey met criteria for a *moderate or severe* substance use disorder related to kratom [85] [86]. Most who develop dependence have what might be considered a mild dependency (characterized by needing kratom to feel normal and avoid withdrawal, but without major social or occupational dysfunction) [58] [61]. When a dependent user stops kratom abruptly, a **withdrawal syndrome** will likely ensue within 12–48 hours. Kratom withdrawal is broadly analogous to a scaled-down opioid withdrawal. Documented symptoms include: **irritability, anxiety, dysphoric mood, yawning, rhinorrhea (runny nose), muscle aches, joint pain, insomnia, tremors, sweating, goosebumps, diarrhea, and cravings for kratom or other opioids** [45] [87]. Many users also report a rebound in anxiety and depression temporarily during withdrawal. In interviews, long-term users described the kratom withdrawal experience as similar to having the flu combined with heightened anxiety or restless legs. The duration of withdrawal is usually shorter than that of heroin – acute symptoms peak around 2–3 days and resolve within a week in most cases, although psychological cravings may persist longer [45] [87]. A systematic review of case reports found that heavy users (consuming >15 g/day) can have more severe withdrawal, occasionally requiring medical management with opioids or sedatives [88] [89]. However, most cases of kratom withdrawal have been managed outpatient with supportive care. One encouraging data point: a lab study in Malaysia observed **no significant withdrawal distress** during a 10–20 hour kratom abstinence in daily users who were then given placebo, aside from mild symptoms – they did not exhibit dangerous blood pressure spikes or vomiting, etc., as might be seen in opioid withdrawal [90] [91]. This suggests kratom withdrawal, while unpleasant, is typically **manageable and not life-threatening**. Nonetheless, dependence risk is real – the FDA has documented cases of infants born with neonatal withdrawal (from maternal kratom use), underlining that kratom can produce classic opioid-type dependence even in utero [66]. Users should be aware that regular kratom use can lead to a habit that is hard to break; gradual tapering is often recommended to minimize withdrawal symptoms. In summary, **tolerance and dependence are common outcomes of chronic kratom use**, and withdrawal symptoms, though generally milder than

those of potent opioids, do occur and can be a barrier to quitting. This risk tempers kratom's appeal as a "no-addiction" alternative – it is not free from addiction potential, contrary to some anecdotal claims.

Adverse Health Effects: Beyond dependence, kratom poses other health risks, especially when misused or used in combination with other substances. One major concern is the risk of **overdose toxicity**. Pure kratom overdose (i.e. taking an exceedingly high dose of kratom alone) is uncommon to result in fatality, because mitragynine is a partial agonist and appears to have a ceiling on respiratory depression. Epidemiological data suggest far fewer kratom-involved deaths than opioid deaths; e.g., fewer than 100 kratom-related deaths were reported over a period when tens of thousands of opioid fatalities occurred [92] [93]. Crucially, most kratom-linked deaths **involved polydrug use** – medical examiner reports often find other central nervous system depressants (such as opioids, benzodiazepines, or alcohol) present alongside kratom [28] [94]. The contribution of kratom in these cases is unclear, but likely synergistic effects (for example, combining kratom with opioids can compound respiratory depression). That said, at very high doses, kratom *can* cause serious toxic effects: extreme sedation, **seizures**, **delirium**, and coma have been seen in overdose situations (usually involving extracts or concentrates). Poison control center data from the U.S. show that of thousands of kratom exposure calls, a minority (~9%) had **severe outcomes** (like seizures or hallucinations), and there have been reports of fatal outcomes in some cases [95] [28]. Again, most severe cases featured other substances or adulterants. **Liver toxicity**, though rare, is a documented risk. Cases of **drug-induced liver injury (DILI)** from kratom typically present as cholestatic jaundice a few weeks after starting regular use. Patients develop yellow eyes, itching, and elevated liver enzymes. Most recover after discontinuation, but there have been a couple of life-threatening liver failures linked to kratom requiring transplants [96] [97]. The mechanism isn't fully understood – it could be an idiosyncratic immune reaction or contamination by other hepatotoxins. **Kidney problems** are less reported, but dehydration from heavy use could theoretically cause renal issues. There have also been scattered reports of **high blood pressure**, **tachycardia**, or **arrhythmias** in some users, particularly when kratom is combined with stimulants or has high norepinephrine activity (certain strains). From a public health perspective, one of the biggest risks comes not from kratom's intrinsic toxicity but from the **unregulated nature of kratom products**. Analyses have found some commercial kratom powders and capsules are contaminated with **heavy metals** (like lead, arsenic, and nickel) at concerning levels [98] [99]. The FDA tested 30 products and found many exceeded safe exposure limits for lead and nickel, such that a person consuming large daily doses could accumulate toxic levels [100]. Chronic heavy-metal exposure from kratom could lead to insidious problems like lead poisoning (anemia, neurological deficits) if unchecked [101] [102]. Another issue has been microbial contamination; for example, a Salmonella outbreak in 2018 was traced to contaminated kratom, sickening over 100 people [51]. Furthermore, some unscrupulous vendors have **adulterated** kratom products with actual pharmaceuticals to enhance effects – a notable case was "Krypton" kratom in Sweden, laced with O-desmethyltramadol (an opioid), which led to several overdose deaths [103] [103]. Users taking only labeled "kratom" might unwittingly ingest other potent drugs. For these reasons, the safety of kratom products on the market can be highly variable. Common **side effects** of kratom, even with pure products, include: gastrointestinal upset (nausea, constipation), dry mouth, increased urination, mild itching, loss of appetite, and in some cases mild **sedation or dizziness** [104] [105]. These side effects are typically dose-related and manageable. Chronic high-dose use has been associated with skin hyperpigmentation and **hypogonadism** in older literature, but as noted earlier, a clinical study did *not* find reduced testosterone in long-term users [17] [18]. On the mental health side, heavy use can cause **apathy, brain fog, or irritability**, sometimes described as a "kratom hangover" the next day if dosing was high. Importantly, **driving under the influence of kratom** might pose risks at higher doses; while regular users showed little impairment at usual doses [39], new users or those who take an excessive dose could have slowed reaction time or nodding off, which is dangerous when operating vehicles. In summation, **adverse outcomes from kratom are real but largely preventable**: the substance itself has relatively low acute toxicity in isolation, but dependence, withdrawal, contamination, and polydrug use can create serious

health issues. Public education on safe dosing, avoiding mixes, and sourcing tested products is critical to minimize these risks.

Regulatory and Public Health Considerations

The rise of kratom use has prompted vigorous debate among regulators and health authorities, resulting in a patchwork of legal statuses and public health responses around the world. **Currently, kratom is not scheduled as a controlled substance at the federal level in the United States**, but it is considered a "Drug of Concern" by the DEA [106] [107]. In 2016, the U.S. Drug Enforcement Administration announced intent to place kratom's main alkaloids in Schedule I (the strictest category), citing concerns about abuse and 36 reported deaths, but this move was halted after public outcry and lobbying by kratom consumer groups [27] [108]. As a result, kratom remains legal federally, yet **several U.S. states and municipalities have banned or restricted kratom** (including Alabama, Arkansas, Indiana, Wisconsin, Vermont, and Rhode Island, among others). Other states have passed "Kratom Consumer Protection Acts" instead, which impose age limits and purity labeling requirements rather than outright bans. The U.S. Food and Drug Administration (FDA) has taken a firm stance against kratom's marketing. The FDA has ruled that kratom is **not a permitted dietary supplement** (classifying it as an adulterating ingredient due to safety concerns) and has blocked imports of kratom products [109] [110]. No kratom-based product is approved for any medical use, and the FDA continues to warn consumers not to use kratom, highlighting risks of addiction, seizures, and liver damage [28] [111]. The agency has also issued alerts when kratom products were found contaminated with Salmonella or heavy metals [112]. From a public health perspective, U.S. agencies are walking a fine line – they acknowledge the lack of clinical trials proving safety or efficacy, yet they face pressure from advocates who argue kratom should remain available as a safer alternative to opioids. Researchers from Johns Hopkins have even suggested that an outright ban could cause public health harm by removing an opioid substitute and possibly driving users to more dangerous drugs [56] [57]. They urge regulation and quality control rather than prohibition [71] [72].

Internationally, kratom's legality varies widely. **Kratom is illegal or controlled in many countries** – for example, it is a prohibited narcotic in Malaysia and Myanmar, banned in Australia and many European countries (e.g. Denmark, Poland), and regulated as a controlled substance in Canada (not allowed for human consumption). Until recently, Thailand had outlawed kratom, but in 2021 Thailand removed kratom from its list of banned narcotics, recognizing its medicinal use and allowing regulated domestic use (a landmark reversal in a country that once criminalized kratom severely). The World Health Organization (WHO) reviewed kratom's status in late 2021 and, while stopping short of recommending international scheduling, it designated kratom for **continued monitoring** due to rising global usage and abuse potential [113] [103]. Notably, kratom is **explicitly not controlled under UN drug treaties at this time** [113]. In some regions, kratom exists in a gray zone – for instance, in the UK and Germany it's not approved for sale but not a scheduled drug either, so online imports occur. This regulatory patchwork creates challenges: inconsistent quality control, varying public knowledge, and difficulties in tracking usage patterns.

Public health officials express concern that increasing kratom use could have unintended consequences. Poison control data indicate a sharp rise in kratom-related calls over the past decade [114], reflecting its growing popularity. Emergency departments have seen more cases of kratom intoxication or withdrawal, though still relatively few compared to other substances. A public health focus has been on educating consumers: for example, not to mix kratom with other depressants, and to be cautious of driving or performing risky tasks until they know how kratom affects them. Another concern is **adolescent use** – as kratom is easy to purchase online, there is worry that teens might experiment with it, potentially leading to dependence. On the flip side, some public health experts consider kratom's availability as potentially **mitigating opioid overdose deaths**, if opioid-dependent

individuals switch to kratom. This harm reduction aspect is still debated, as kratom itself carries risks (and at higher doses could still cause unconsciousness or injury). Regulatory bodies like the FDA are actively monitoring scientific data; the FDA has even funded research (including human pharmacokinetic studies and surveys) to better understand kratom's risk-benefit profile [115].

In summary, **regulation of kratom is in flux**, balancing potential public health benefits against risks. Authorities agree on the need for quality standards – for instance, testing for heavy metals and accurate alkaloid labeling – to protect consumers [116] [117]. Until kratom's legal status is resolved through more research and policy-making, it remains a substance that individuals must approach cautiously. Health agencies continue to emphasize that people should consult healthcare providers about kratom use, and not assume it is harmless simply because it is "natural." The current regulatory trend appears to be toward more oversight (short of bans) in many jurisdictions, aiming to ensure **consumer safety, prevent adulteration, restrict sales to minors, and provide education** about the risks of dependence and adverse effects. Public health messaging is evolving from outright fear-based warnings to more nuanced harm reduction guidance as more becomes known about kratom's real-world impact.

Conclusion

Kratom and its primary alkaloid mitragynine have complex effects that span the stimulant and opioid spectrum, making it a unique psychoactive agent. Human studies and surveys indicate that **acutely, kratom can increase energy, focus, and alleviate pain or opioid withdrawal, whereas higher doses provide sedation and analgesia at the cost of some cognitive and mood side effects**. Chronically, many users have successfully harnessed kratom's effects for self-managing pain and mood disorders or tapering off opioids, reporting improved quality of life. There is emerging evidence of genuine therapeutic potential – kratom can significantly increase pain tolerance [12] and users testify to relief from anxiety, depression, and drug cravings that might otherwise require more harmful medications [47] [54]. However, this must be weighed against the **clear risks**. Kratom is **not a risk-free herb**: it can lead to dependence with a withdrawal syndrome, and uncontrolled use (especially with adulterated products or in combination with other substances) has resulted in serious adverse outcomes, including organ injury and deaths [28]. Fortunately, typical use in the absence of other drugs appears to carry relatively low risk of life-threatening effects [92] [28], and most side effects are mild and reversible [53] [24]. The public health challenge is to maximize any benefits of kratom (for those who choose it as an alternative therapy) while minimizing harm through education, research, and sensible regulation. Given the current evidence, kratom occupies a **controversial middle ground** – neither the benign herbal panacea its proponents sometimes claim, nor the deadly narcotic that some early critics feared. **Recent human research underscores a need for balanced understanding**: kratom may offer a novel approach to pain and opioid withdrawal management [31] [52], but its use must be approached with caution due to the potential for addiction and other health risks [31] [28]. Moving forward, rigorous clinical studies are warranted to formally evaluate kratom's efficacy and safety in therapeutic contexts, and to determine how it can be used (if at all) responsibly in medicine. Meanwhile, regulators and health professionals should continue monitoring kratom's impact, ensuring consumers are informed about both its promising effects and its perils. The story of kratom is still unfolding, guided by scientific findings that will help distinguish legitimate medicinal value from hype, and guide appropriate public health strategies.

Sources: Recent peer-reviewed studies and reviews on kratom's pharmacology, human effects, and public health impact [4] [54] [28] [12], as cited throughout this report.

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