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Heroin Adulteration

Additives Are Associated with An Increase in Overdose Deaths

By Matthew Feldhammer, PhD, and James C. Ritchie, PhD

The number of deaths from heroin overdoses in the United States has increased markedly in recent years. Between 1999 and 2014, heroin-related deaths increased 439%, according to the National Center on Health Statistics (Figure 1) (1).

The many factors driving this trend include the decreased cost and increased availability of the drug, which probably contributed to an increase in the number of heroin users. Many people who became addicted to prescription opioids over the past two decades have turned to heroin in response to crackdowns by law enforcement on their opioids. In addition, there has been a substantial increase in drug potency and the use of toxic additives such as fentanyl (2).

Many patients being prescribed opioids for chronic pain have signed pain management contracts that mandate submission to routine drug testing. Such screening has allowed clinicians to detect prescription diversion or patient noncompliance with increasing frequency and accuracy.

Tests for drugs of abuse have historically been carried out by hospitals and specialized toxicology laboratories using commercially available immunoassays. However, widespread adoption of clinical mass spectrometry (MS) for confirmatory testing in recent years has permitted the detection of not only drugs and their metabolites but also specific additives and adulterants. MS analysis also allows forensics professionals to identify the source of the illicit production by determining which impurities are present in the drug. Indeed, many toxicology laboratories have seen sharp increases in the number and diversity of adulterants in patients' specimens.

In addition to the additives used by clandestine narcotics producers, drug abusers have also turned to complex methods of sample adulteration to avoid detection by drug screens. To combat this trend, many toxicology professionals use MS to detect some of the most common commercially available additives and adulterants.

This review focuses mainly on the geographic differences in heroin batches, the various additives placed by clandestine drug manufacturers, and the impact of additives on drug users.

Geographic Origin

The production and sale of heroin is estimated to be a $60 billion a year industry spanning the globe. The Golden Triangle, encompassing Thailand, Laos, and Myanmar (Burma), was the world's leading opium producer in the 1970s and 1980s. During the 1990s, Latin America became the primary supplier of heroin to the U.S. (Figure 2). There was a striking geographical divide, with the eastern U.S. being supplied primarily from Columbia, the western U.S. supplied from Mexico, and the middle supplied by a combination of the two (4).

In the past decade, heroin production has shifted to southwest Asia's Golden Crescent, particularly Afghanistan, which in 2010 accounted for nearly 80% of the world's opium, according to U.N. estimates. According to Canadian law enforcement agencies, the Golden Crescent is the major source of Canadian heroin, although little of it finds its way into the U.S.

The U.S. Drug Enforcement Administration (DEA) estimates that heroin purity in the U.S. ranges

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from 10–40%, with a median of 31% (Figure 3) (3).

The purity of heroin, as well as the adulterants and impurities, vary by geographic origin. Knowledge about drug purity, as well as the presence and nature of common artifacts, diluents, and adulterants, can provide actionable information for clinicians and laboratories trying to understand patients who present with overdoses or unexpected side effects (5).

The terms cutting, lacing, and adulterating are often used interchangeably in the context of narcotics manufacturing. Both clandestine manufacturers and lower echelon distributors use these processes to maximize yields and profits while maintaining a level of purity their users rely upon. The compounds that end up being consumed by users can be grouped into three general categories:

- artifacts from the manufacturing process, such as compounds that occur naturally in the opium plant, compounds that are co-extracted during production, and impurities from the manufacturing process itself (such as solvents and opium alkaloids);
- diluents or cutting agents, which are pharmacologically inert substances added post-manufacturing to increase product yields (such as sugar, talc, and flour); and
- pharmacologically active adulterants (such as caffeine, diazepam, fentanyl, and phenobarbital).

Artifacts from Manufacturing

The impurities that result from the manufacturing process of heroin can provide valuable insight into the country of origin and even the specific laboratory where production occurred (6). Most of these compounds are either acidic or neutral and result from the reaction of acetic anhydride with morphine, codeine, thebaine, papaverine, noscapine, norlaudanosine, reticuline, narceine, and other alkaloids present in opium (7). Characterization of these compounds has historically required tedious, labor-intensive, and low-throughput processes.

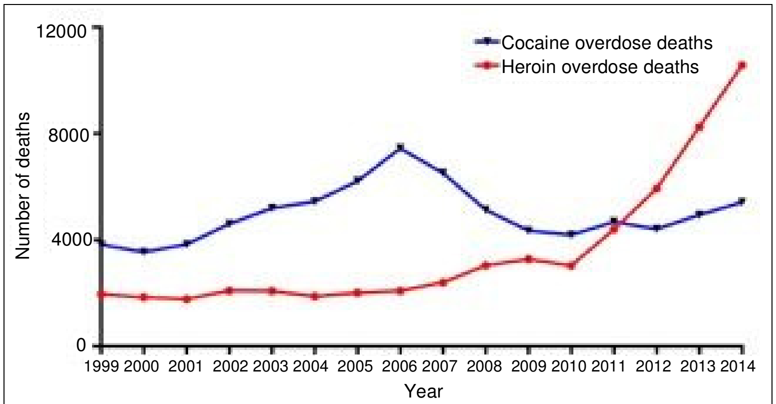

Figure 1. U.S. Heroin and Cocaine Overdose Deaths from 1999–2014. Adapted from (3).

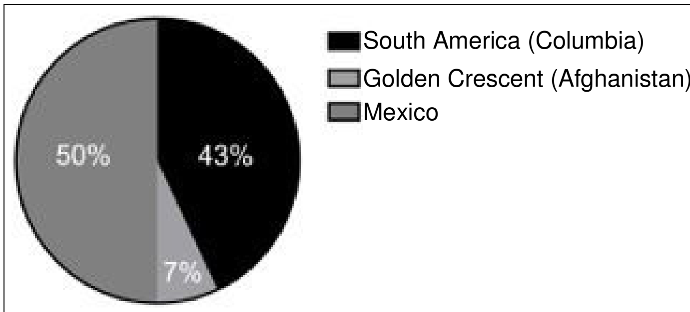

Figure 2. Primary Suppliers of U.S. Heroin as Determined by the DEA Heroin Signature Program. Data obtained from (15).

The DEA's Special Testing and Research Laboratory is the primary body tasked with identifying the source of unknown drug specimens in the U.S. It employs three analytical methods in this regard:

- capillary electrophoresis for the quantification of heroin and major production impurities such as acetylcodeine, O6-monoacetylmorphine, O3-monoacetylmorphine, and others mentioned above;
- static headspace gas chromatography-mass spectrometry for the quantification of trace solvents in the matrix material of the heroin; and
- programmed temperature vaporizing injector-gas chromatography-mass spectrometry for the measurement of trace acidic and neutral impurities such as triacetylnormorphine, diacetylnorcodeine, substituted phenanthrenes, and *N*-acetylnornarceine-like impurities that are direct results of the acetic anhydride reaction (7).

This complex analysis can identify the precise chemical barcode that is specific for each manufacturing process and each region in the global heroin trade. The Mexican-manufactured heroin seized in the western U.S. contains a large amount of sugars. Mexican "black tar" heroin is characterized by the presence of stilbene compounds (a by-product of tetrahydrobenzylisoquinoline breakdown), which are identified in almost 100% of samples. This signature is significantly different from that of heroin from Afghanistan or Myanmar, which is predominantly characterized by the presence of both the stilbene compounds and C-1 acetate impurities (8).

Technological advances in chromatographic separation and the sensitivity of mass spectrometry have been proposed as ways to alleviate some of the cumbersome analysis inherent in the identification of these compounds (9). Recently, Liu et al. described a

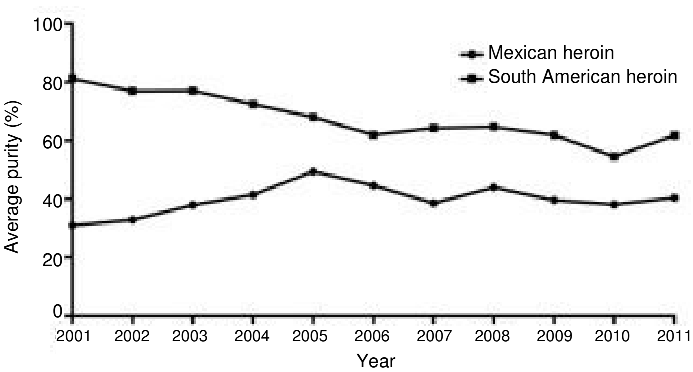

Figure 3. Average Purity of Mexican and South American Heroin Determined from Samples Seized in the U.S., 2001–2011. Data obtained from (15).

method using ultra performance liquid chromatography coupled to quadrupole-time of flight mass spectrometry. Using these techniques, they were able to identify 19 unique acidic and neutral impurities, which were sufficient to identify the country of origin with 97% accuracy compared with the more time-consuming and labor-intensive classical analysis (6). This study was conducted primarily on samples from the Golden Crescent or Golden Triangle, so its utility for analysis of heroin seized in the U.S. will have to be validated before it can be widely adopted.

Diluents, Bulking, and Cutting Agents

Chemically inert cutting agents are added at any level in the narcotics supply chain from manufacturer to street dealer to increase profit by enhancing volume. Commonly used agents include sugars, talc, baking soda, and flour. A key characteristic of most of them is that they are cheap and legal. In contrast to common perceptions, several European studies have found that heroin seized during import was similar in purity to that seized on the street, suggesting that very little bulking occurs after the production stage and after importation (10).

Broseus et al. analyzed heroin and cocaine seized in Switzerland over the past decade for the presence of cutting compounds. Echoing similar findings in the U.S. literature, they found the cutting agents for heroin did not change much over time. In contrast, they found significant shifts in the bulking agents added to cocaine. The main cutting agents they identified in heroin samples were caffeine plus acetaminophen; sugars (glucose, lactose, sucrose, and mannitol); and carbonates (5). In light of these findings, the detection of cutting agents is of limited utility in determining the manufacturing source of heroin but plays an important role in determining its purity.

Pharmacologically Active Adulterants

As with cutting agents, the adulteration of heroin samples with pharmacologically active substances can occur at any point in the supply chain. There is little evidence to support the popular notion that illicit drugs are adulterated with rat poison, ground glass, brick dust, and household cleaning products (11). It is plausible that these myths persist among drug users and the general public to explain overdose-related fatalities, but it is important to realize that drug dealers build their business on repeat customers. It is not in their interest to provide a product that would eliminate their client base.

There is strong evidence, however, that certain adulterants are routinely added to heroin in the U.S. Most samples seized have detectable levels of caffeine and acetaminophen, with reports of some heroin containing procaine, phenobarbital, quinine, xylazine, clenbuterol, and scopolamine. As previously mentioned, these adulterants often serve to enhance or facilitate the consumption of the drug. For instance, procaine, a local anesthetic, is likely added to facilitate injection of the drug. Caffeine can lower the vapor pressure of the drug, making smoking it easier. Acetaminophen mimics some of the analgesic effects of the drug. Cole et al. present a comprehensive list of the most common heroin adulterants and the potential reasons they are being used (10).

Acetyl Fentanyl Adulteration

Recently, the DEA has warned of acetyl fentanyl adulteration of heroin samples. In particular, these cases have been reported in the eastern and northeastern U.S. Fentanyl and acetyl fentanyl are directly contributing to the dramatic rise in heroin-related overdose deaths. The Centers for Disease Control and Prevention estimates that pharmaceutical-grade fentanyl is 80 times more potent than morphine and hundreds of times more potent than heroin. Its illicit counterpart, acetyl fentanyl, while likely not as potent, is still much more potent than heroin and can induce overdose even in experienced users (12). According to the DEA, illicitly produced acetyl fentanyl—and not diverted prescription fentanyl—has been detected more often in samples and patients presenting with heroin overdoses.

Emergency departments do not routinely test for acetyl fentanyl in heroin-related in overdoses, which can lead to confusion in determining the drugs present. Several case reports from the Rhode Island State Laboratories highlighted this fact: Initial immunoassay toxicology screens of blood specimens from 10 suspected overdose deaths tested positive for fentanyl. However, GC-MS confirmatory testing was negative for fentanyl. Further investigation revealed the presence of acetyl fentanyl, thanks to astute analysis by the toxicologists working to determine the cause of the positive immunoassays. This example illustrates the need to include ion-specific testing for acetyl fentanyl as part of the confirmatory process for initial positive immunoassay screens (13).

The Rise in Overdoses

As noted earlier, the U.S. is currently seeing a dramatic rise in the number of heroin-related overdose deaths. The reported numbers likely underrepresent the actual number because 6-monoacetyl morphine is quickly metabolized to morphine and most medical examiners are reluctant to attribute an overdose death to heroin when this metabolite is absent. In addition, many medical examiners do not consider whether an overdose was caused by heroin alone or heroin adulterated with acetyl fentanyl because the possibility requires an elevated level of suspicion by the physician or the toxicologist.

A further complication is that patients overdosing on acetyl fentanyl or heroin present with almost identical symptoms, commonly including severe obtundation, coma, respiratory arrest, hypotension, and cardiac arrhythmia. Without intervention, these symptoms can quickly result in death. On the other hand, early intervention can dramatically increase a patient's chances of survival.

Naloxone (Narcan) is a common and effective therapeutic intervention for both heroin and acetyl fentanyl overdoses. It works by acting as a competitive antagonist for the opioid receptor and reversing its activation.

In response to the recent rise in overdose-related mortalities, the U.S. Food and Drug Administration recently granted fast-track approval for a nasal spray version of naloxone. The government has incentivized its widespread distribution, especially among first responders. It is therefore critical that hospital and laboratory staff in areas with elevated incidences of acetyl fentanyl-related overdoses adopt protocols to identify its presence as part of their routine toxicological testing.

Obstacles to Diagnosis

An additional obstacle to determining the contribution of heroin adulterants to overdoses is the fact that heroin users often abuse multiple drugs. This tendency often muddies the waters because the presence of multiple substances in an overdose victim's specimens makes it impossible to attribute the cause to either adulterated heroin or the other drugs present. It is essential, then, that governmental organizations and toxicology labs continue to analyze seized samples in order to inform the clinical community which adulterants may be present in patients presenting with overdose symptoms.

To address this point, Ohio's Miami Valley Regional Crime Lab reported that the drugs in a seized shipment included illicit fentanyl only; illicit fentanyl and heroin; illicit fentanyl and cocaine; and illicit fentanyl, heroin, and cocaine (14). The authors describe 90 cases of acetyl fentanyl-related deaths seen by the county coroner's office between 2013 and 2014. In 19 of these cases, the fentanyl was accompanied by heroin or by both heroin and cocaine. In the cases in which only acetyl fentanyl was detected, almost all decedents had a history of heroin use, with needles often found at the scene of death.

It has also been reported that drug dealers are selling acetyl fentanyl disguised as heroin, which could be the cause of cases in which only acetyl fentanyl is detected. These cases highlight the continuing threat heroin adulteration poses and should alert toxicologists, medical examiners, and emergency room doctors to the increasing prevalence of acetyl fentanyl adulteration in patients presenting with heroin overdose symptoms.

Krokodil: An Emerging Threat?

Krokodil (desomorphine) is a popular and cheap alternative to heroin in Russia and Ukraine. It has received significant attention because of a series of media reports detailing the necrotizing skin lesions that users may develop after only a few instances of use.

Despite many media warnings of the impending arrival of this new drug, there has been only one unconfirmed case report from the U.S. in the medical literature. In 2013, a group from St. Louis claimed to document the first U.S. case of krokodil use, which further fanned the media flames. However, several comments were quickly published questioning the validity of the authors' claims by pointing out the lack of laboratory confirmation of the presence of desomorphine. This case report was based almost entirely on the claims of the patient that she had used krokodil without any outside or confirmatory evidence. There have been no other case reports from the U.S. or Canada.

Although the drug does pose a serious public health problem in Russia and Ukraine, it is highly unlikely it will make its way to the U.S. Russia and Ukraine have cracked down on the availability of heroin, dramatically driving up costs and limiting supply, but heroin remains readily and cheaply available in the U.S. despite law enforcements efforts. Moreover, codeine, the main ingredient in krokodil, requires a prescription in the U.S., but until recently was available over the counter in Russia. Therefore, despite the widespread media attention, krokodil likely represents a hyperbolic threat that can be put on the backburner until a substantiated case report emerges.

Conclusion

The recent media and political attention paid to the issue of opioid abuse in the U.S. underscores the need for more effective strategies to deal with this public health problem. The past decade has seen an unprecedented rise in opioid-related overdose deaths that is a valid cause for public concern. The old adage that heroin abuse is primarily a problem of poverty and the inner city is being thrown out the window by the frequency of case reports from suburban and affluent areas. This trend is highly complex and multifactorial in nature, but likely hinges on the increased rates of prescription opioid abuse among the public.

Recent trends in the adulteration of heroin with highly potent acetyl fentanyl have undoubtedly contributed to the increase in overdoses. The true contribution of heroin adulteration to the opioid overdose epidemic, however, is likely to remain uncertain until we can develop a standardized system for reporting drug-related deaths that can be used to coordinate the toxicological analysis with state and federal evidence relating to the adulterants identified in drug seizures.

Learning Objectives

After reading this article, the reader will be able to list the different categories of adulterants detected in heroin compounds and briefly describe their nature. The reader will also be able to describe the association between heroin, acetyl fentanyl, and the rise in overdose-related deaths in the U.S.

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Herbal Medicine Adulteration

Labs Play Key Role in Identifying Pharmaceuticals Added to Herbs

By Angela M. Ferguson, PhD, and Uttam Garg, PhD

Many herbal medicines derived from plants and plant extracts have been used for medicinal purposes for thousands of years. Recently, herbal remedies have gained popularity in developed countries and become widely used. Because of their natural origin, many users perceive them to be safe and harmless compared with conventional drugs. Patients may also take them along with conventional drugs with the idea that the combination will be more beneficial.

Less Regulation

The U.S. Food and Drug Administration (FDA) regulates dietary supplements under a different set of regulations from conventional medicines. The Dietary Supplement Health and Education Act of 1994 allows the sale of herbal remedies without the proof of their safety and therapeutic efficacy required of pharmaceuticals. The FDA can take action against an adulterated or misbranded dietary supplement only after it reaches the market. Because the FDA does not oversee their manufacture to the extent that it does conventional drugs, the herbal remedies found in the U.S. and many other countries have contamination and adulteration problems (1–3).

Drugs Found as Adulterants

Case reports and direct analysis of herbal remedies provide many examples of adulteration of these products by conventional drugs or their analogs (2–4). The major categories of adulterants are analgesics and nonsteroidal anti-inflammatory drugs, hypoglycemic agents, erectile dysfunction drugs, psychotropic drugs, steroids, and stimulants.

Adulterants that have been reported through case studies include acetaminophen, aminopyrine, dexamethasone, diazepam, diclofenac, fenfluramine, glibenclamide, hydrochlorothiazide, hydrocortisone, ibuprofen, indomethacin, mefenamic acid, phenylbutazone, phenytoin, prednisolone, propofol, sibutramine, and trimethadione (4). Conventional drugs that have been found through direct analysis of herbal products include acetildenafil, amoxicillin, betamethasone, caffeine, captopril, chlormethiazole, chlorpheniramine, chlorzoxazone, codeine, corticosteroids, dexamethasone, dextromethorphan, diazepam, diclofenac, diphenhydramine, dipyrone, ephedrine, ethoxybenzamide, famotidine, fenfluramine, furosemide, glibenclamide, gliclazide, glimepiride, homosildenafil, hydrochlorothiazide, hydroxyhomosildenafil, ibuprofen, indomethacin, methyltestosterone, metformin, N-didesmethylsibutramine, nifepidine, norephedrine, phenacetin, phenformin, phentermine, phenylbutazone, prednisolone, prednisone, promethazine, sibutramine, sildenafil, triamterene, tadalafil, and testosterone (2–4). Due to space limitations, only a few major categories of herbal remedies are discussed below.

Examples of Adulterated Herbal Remedies

There are a number of herbal remedies available for the treatment of diabetes, and patients are drawn to them because of the proven legitimacy of some herbal medicines. However, the literature contains many reports that these herbs are frequently adulterated with modern diabetes drugs (4). In a recent report from Hong Kong, 27 cases of adulterated diabetes herbal remedies were identified between 2005 and 2010 at one medical center (5). Seventeen patients reported adverse events, including hypoglycemia and lactic acidosis. Four of the patients were taking prescription medication for diabetes concurrently. Of the 29 products tested, glibenclamide was the most frequently identified adulterant, found in 22 products. Other oral diabetes medications found included phenformin, metformin, rosiglitazone, gliclazide, glimepiride, nateglinide, and repaglinide.

Erectile dysfunction (ED) is the focus of a thriving market for natural remedies and supplements that claim to aid sexual performance. Many patients feel reluctant or embarrassed to discuss this problem with their healthcare provider, and these products can be purchased anonymously over the counter or online. A well-known and serious usage warning for the most commonly prescribed conventional drugs for erectile dysfunction—phosphodiesterase type 5 (PDE5) inhibitors—is that they should not be used in conjunction with nitrates or nitrites because the combination can lead to a decrease in blood pressure that can result in decreased coronary perfusion and myocardial infarction. Diabetes, hypertension, and cardiovascular disease are often associated with ED, but patients with these conditions frequently use nitrates, so should not be prescribed PDE5 inhibitors. These patients may look for herbal products as an alternative.

A survey of 91 samples from 58 products claiming to naturally enhance sexual performance found that 74 of the samples (81%) contained one or more active ingredients or analogs of synthetic PDE5 inhibitors, including tadalafil or sildenafil (6). Alarmingly, the concentration of added pharmaceuticals exceeded the highest approved drug concentration and few of the product labels warned against concomitant nitrate use.

Obesity Products

Another area where use of herbal remedies has increased is in combating obesity, a major chronic problem in developed nations. Given the social impact, it is not surprising that obese patients are interested in weight-loss products, including herbal remedies that may be adulterated with conventional weight-reduction drugs.

Khazan et al. examined eight herbal weight-loss supplements sold in Iran for five synthetic adulterants that are frequently added to natural remedies (7). The researchers screened for the presence of sibutramine, phenolphthalein, and phenytoin using gas chromatography-mass spectrometry (GC-MS) as well as rimonabant and bumetanide using liquid chromatography-MS. Seven of the eight supplements tested positive for the presence of at least one of the adulterants, and five of these contained two or more adulterants. Sibutramine was the most common adulterant found, being present in six of the eight supplements, followed by bumetanide, phenolphthalein, and phenytoin, which were present in five, three, and two remedies, respectively. Rimonabant was not identified in any of the supplements.

Laboratory Role in Identifying Adulteration

With the widespread use of herbal products and their adulteration with conventional drugs and other contaminants, the users of these products frequently need medical attention due to their detrimental effects. The laboratory plays a vital role in the identification of the adulterants to provide this care.

Chromatographic techniques linked to mass spectrometry are the preferred methods to detect these adulterants because they are specific and can provide structural information (1). GC-MS has been frequently used for the analysis and identification of drugs. Because many drugs are not volatile and are heat-labile, liquid chromatography-tandem mass spectrometry has been gaining popularity and has become the technique of choice (3,4).

Vaclavik et al. recently described the use of an ultra-high performance liquid chromatography-quadrupole-orbital ion trap mass spectrometry method that could identify and quantify 96 pharmaceuticals, plant toxins, and other secondary metabolites in herbal dietary supplements (3).

In summary, many herbal remedies used for thousands of years by other cultures have gained popularity in the western world in recent years. The reasons for this surge include the legitimate effectiveness of certain herbal remedies, affordability, and the belief that herbal products are safe and harmless. Due to poor regulation and a huge market, these products are often adulterated with conventional drugs or their analogs. Laboratories play an important role in the detection of adulterants in these products. Healthcare providers and consumers should recognize the potential risk posed by herbal remedies adulterated with conventional drugs.

Learning Objectives

After reading this article, the reader will recognize the global problem of adulteration of herbal remedies and understand the role of the clinical laboratory in identifying the pharmaceuticals and other adulterants added to herbal remedies.

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Kratom

Herb Gains Popularity as a Gentler Opiate Substitute

By James Ritchie, PhD

A Southeast Asian herb is gaining popularity among addicted heroin and prescription opiate users, pain sufferers, and hipsters looking for a nice buzz, and it's legal in most places—at least for now.

Kratom (also known as ketum and kratumum) is a botanical extract derived from the leaves of a tropical evergreen tree, *Mitragyna speciosa.* The tree belongs to the coffee family and is indigenous to Thailand, Myanmar, and Malaysia. It has long been used in these areas as an herbal medication to treat chronic pain, to increase energy and stamina, to treat diarrhea, as a substitute for opium, and for opium withdrawal (1). Despite growing there naturally, it has been outlawed in Thailand since 1943.

Traditionally, fresh or dried kratom leaves are chewed or made into tea; they are seldom smoked. At a low dose, kratom has stimulant effects and is used by laborers to combat fatigue during long working hours. At higher dosages, however, it can have sedative-narcotic effects.

The phytochemicals isolated from various parts of the tree include more than 40 structurally related alkaloids, as well as several flavonoids, terpenoid saponins, polyphenols, and glycosides. The main psychoactive components in the leaves are mitragynine and 7-hydroxymitragynine, which is thought to be the primary active compound (Figures 1 and 2). Of note, both compounds have been found only in *M. speciosa* (2,3).

Kratom products are usually supplied as crushed or powdered dried leaves that are light to dark green

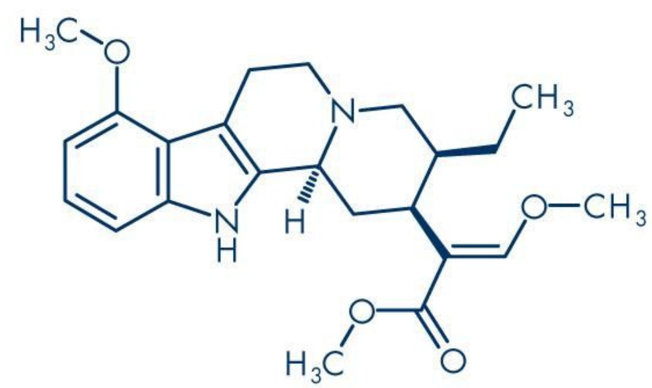

Figure 1. Mitragynine
Molecular formula: $C_{23}H_{30}N_2O_4$
Molecular weight: 398.50 g/mol
Mitragynine is the most abundant alkaloid in kratom leaves. It was first isolated in 1921 and its chemical structure was fully elucidated in 1964. The systematic (Chemical Abstract) name is (αE,2S,3S,12bS)-3-ethyl-1,2,3,4,6,7,12,12b-octahydro-8-methoxy-α-(methoxymethylene)-indolo[2,3-a]quinolizine-2-acetic acid methyl ester (CAS Registry Number: 4098-40-2). Other names: (E)-16,17-didehydro-9,17-dimethoxy-17,18-seco-20α-yohimban-16-carboxylic acid methyl ester, 9-methoxycorynantheidine, and SK&F 12711. Source is (9).

Figure 2. 7-Hydroxymitragynine
Molecular formula: $C_{23}H_{30}N_2O_5$
Molecular weight: 414.50 g/mol
7-Hydroxymitragynine is present only in very small amounts in kratom leaves and was identified in 1993. Its systematic (Chemical Abstract) name is (αE,2S,3S,7aS,12bS)-3-ethyl-1,2,3,4,6,7,7a,12b-octahydro-7a-hydroxy-8-methoxy-α-(methoxymethylene)-indolo[2,3-a]quinolizine-2-acetic acid methyl ester (CAS Registry Number: 174418-82-7).
Source is (9).

in color. Preparations fortified with extracts from other plants and herbs are also available, and are generally powdery and greenish or beige-brown. In addition, paste-like extracts and dark brown kratom resin can be made by partially or fully distilling the liquid from aqueous kratom leaf suspensions. Finally, tinctures and capsules, filled with powdered kratom, are also available.

Legal Status

Kratom is now widely available on the Internet. A recent Google search returned 852,000 entries, of which approximately half were offers for the sale of kratom leaves, bulk powders, or powder-filled capsules. In the United States, kratom is classed as an herbal supplement and is defined as having no medical use. Noting its potential for abuse, the Drug Enforcement Administration has listed it as a drug of concern, but has not yet moved to criminalize it. Four states have made possession of kratom illegal (Indiana, Tennessee, Vermont, and Wyoming). Similar laws have been proposed in Florida and New Jersey.

In 2015, the Food and Drug Administration issued an import alert to seize herbal products containing kratom entering the country on the grounds that the agency considers it to be a new dietary supplement without the history of safe use required for it to be marketed in the U.S. (4).

There are limited studies of its pharmacokinetics in humans. One study of chronic kratom users found peak mitragynine concentrations 50 minutes after an oral dose (tea), with a terminal half-life of approximately 23.2 ± 16.1 hours and a volume of distribution of 38 liters (5).

Laboratory Tests

Randox Toxicology recently developed an enzyme-linked immunosorbent assay (ELISA) that can detect mitragynine and its metabolites (9-O-desmethylmitragynine, 7-alpha-hydroxymitragynine, and 7-alpha-acetoxymitragynine) in urine and blood specimens. Currently this is the only immunoassay available for screening.

Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays have been described by several researchers (6,7,8). The ultraviolet (UV) spectrum of a methanol solution of mitragynine shows a maximum at 225 nm with shoulders at 247, 285, and 293 nm. Significant fragments in the electron impact ionization mass spectrum are (m/z): 398 (M+), 383, 366, 269, 214, 200, and 186. The UV spectrum of an ethanol solution of 7-hydroxy-mitragynine shows a maximum at 220 nm with shoulders at 245 and 305 nm. Significant fragments in the electron impact ionization mass spectrum are (m/z): 414(M+), 397, 383, and 367 (9).

The parent alkaloids and their metabolites can be quantified in urine at >100 ng/mL by GC-MS, at >25 ng/mL by high performance liquid chromatograph-UV, and at >0.02 ng/mL by LC-MS/MS. The concentration of mitragynine in a forensic urine sample of a regular kratom user was 167 ng/mL (LC-MS/MS). In a poisoning case, the blood serum concentration of mitragynine two weeks after cessation of regular oral ingestion of large doses (14–21 grams daily) of dried kratom leaves was 0.020 ng/mL (LC-MS/MS) (9).

To date, the literature contains only a few case reports in which kratom has been identified. This may be an underestimation because most labs do not yet test for this drug. The limited number of deaths where kratom was implicated include poly-drug use or suicide by a user who was also being treated for depression. Direct kratom overdoses resulting in life-threatening respiratory depression, which usually occurs in traditional opioid overdoses, have not been reported.

Addiction and dependence have been reported but the clinical manifestations, much like the kratom high itself, appear to be mild compared with opioids such as heroin and morphine.

Of course, so far the only source of kratom available is the natural unrefined herb. It is difficult to predict what the effects would be of a purified or concentrated form of mitragynine or its many metabolites. More investigation into the effects and risks of kratom are needed but current evidence indicates that kratom acts similarly to other natural opiates—by occupying the mu receptor—but with milder effects. Thus, kratom may someday find use in the treatment of patients with an opioid dependency. Regardless of the future potential benefits or risks posed by this drug, laboratories should be aware of its potential for use and abuse and increase their drug screening menus accordingly.

Learning Objectives

After reading this article, the reader will understand the mechanism of action of kratom as well as its legal status in the U.S. The reader will also gain insight into the methods of measurement of this new opioid.

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