Psychotropic Drugs Used in Anesthesia Practice

Abuse Liability and Epidemiology of Abuse
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ANESTHESIOLOGISTS administer many drugs that alter mood in patients during the perioperative period. These drugs include inhaled general anesthetic agents, barbiturates, benzodiazepines, opioids, α₂-adrenergic agents, local anesthetic agents, antihistamines, and anticholinergic agents. This article discusses abuse liability and the estimated prevalence of abuse of these drugs. Because the practice of anesthesiology involves manipulation of consciousness via psychotropic agents, an understanding of the abuse potential of these consciousness-altering agents may be helpful.

Testing Methods for Abuse Liability

Abuse liability is defined as the potential or likelihood that a drug will be used for nonmedical (recreational) purposes. The most commonly used testing methods for abuse liability assess the reinforcing (or rewarding) effects of a drug, its subjective effects, and its discriminative stimulus effects.

Three methods are used by psychopharmacologists to assess the reinforcing or rewarding effects of drugs: self-administration, preference, and conditioned place preference. With self-administration, the test animal (or human) is given access to a drug and a nondrug (placebo) so that consumption of each can be compared. In animal studies, the animal presses a lever for access to a drug or its vehicle (usually saline), which is typically delivered from an infusion pump to an intravenous catheter. If the response rate when the drug is available is higher than the response rate when the vehicle is available, the drug is said to function as a reinforcer. Although most studies of drug self-administration involve animals as subjects, numerous studies of self-administration have been conducted with humans. The concordance in results between self-administration studies using animals and humans is high, validating the use of animals to estimate the potential for a drug’s abuse in humans.1-5

The preference or choice procedure is similar to a self-administration procedure, except that the testee may have more options: drug versus placebo, drug versus drug, or drug versus a nondrug reinforcer (such as food or saccharin). The first option measures whether a drug is a reinforcer, and the second and third options measure the relative reinforcing efficacy of one drug compared with another or with a nondrug substance.

There are several variants to the conditioned place preference procedure. In one variant, an animal is placed in a two-compartment chamber. Each compartment is distinguishable from the other by one or more features (e.g., color of the walls, texture of the floors). When the animal has habituated to the chamber, the conditioning process begins. In a series of alternating trials, the animal is injected with a drug and placed in the drug compartment or injected with saline and placed in the other compartment, so that the effects of the drug...
become associated with one of the compartments. After the conditioning trials, the drug-free animal is placed in a neutral area of the chamber, and the relative amount of time spent in the drug compartment is measured. If the animal spends more time in the drug compartment than in the nondrug compartment, the drug is said to have rewarding effects.

To measure subjective effects in humans, a drug or placebo is administered, and the person is asked periodically to report subjective feelings. The medium of self-report varies and includes visual analog scales, adjective rating checklists, and standardized questionnaires to measure mood or specific drug-induced changes in subjective effects. Three questionnaires frequently used by psychopharmacologists include the Profile of Mood States (POMS), the Addiction Research Center Inventory (ARCI), and the Single Dose Questionnaire (SDQ). A shortened version of the original ARCI 550-item inventory consists of 49 items grouped into five different subscales representing subjective effects associated with different drugs: the Pentobarbital-Chlorpromazine Alcohol Group for sedation; the Amphetamine scale and the Benzodrine Group scale for intellectual efficiency and psychomotor stimulation; the Morphine-Benzedrine Group scale for euphoria; and the Lysergic Acid Diethylamide Scale indicative of dysphoria or psychotomimetic effects.

The discriminative stimulus effects of a drug are internal, or interoceptive, cues produced by the drug that are presumably mediated by the same neurochemical substrate(s) that mediate the subjective effects of a drug in humans. To measure drug discrimination in animals, the animal is trained to emit a certain behavioral response after receiving drug X and another response after receiving drug Y. One of the drugs is typically the placebo and represents the nondrug response. For example, when an animal is given drug X (called the training drug), it is trained to press one of two levers (e.g., the left lever) in a test chamber. When the animal is given drug Y (e.g., placebo), it is trained to press the right lever in the chamber. A correct response (responding on the left lever when drug X is given and responding on the right lever when drug Y is given) is reinforced (usually with food pellets), whereas inaccurate responses (e.g., responding on the left lever when drug Y is given) during the discrimination training phase are not reinforced. The key stage of the drug discrimination procedure is the testing phase, which involves giving a drug other than drug X. If the animal responds on the left lever, the test drug is said to substitute for drug X and to have similar discriminative stimulus effects to those of drug X. If the animal presses the right lever, the test drug does not have similar discriminative stimulus effects to that of drug X. The drug discrimination procedure is highly specific; typically only those drugs with pharmacologic similarities to the training drug result in drug-appropriate responses, and drugs with pharmacologic dissimilarities result in nondrug or placebo-appropriate responses. Drug discrimination is a valid screening tool for abuse liability in that a drug that has similar discriminative stimulus effects to that of a training drug with abuse potential (e.g., heroin) is also likely to have abuse potential.

Testing Anesthetic Drugs for Abuse Liability

In general, those drugs that are reinforcing, that have a pleasant spectrum of subjective effects, or that share discriminative stimulus effects with known drugs of abuse are said to have abuse liability. Those drugs that do not have these effects are said to have negligible or minimal abuse liability. There is no system universally agreed on by psychopharmacologists to rank the degree of abuse liability of a drug. The degree of abuse liability depends on many factors, including the doses tested, the route of administration, the species tested, and the test method used (self-administration testing vs. subjective effects testing). When enough scientific data have been collected on a drug using several different assays and species, however, it is generally possible to place a drug into one of three abuse liability categories: substantial, minimal, or equivocal. A drug with substantial abuse liability is one for which there is concordance across studies, assays, and species that indicates abuse liability. Conversely, a drug with minimal abuse liability is one for which there is concordance across studies, assays, and species that indicates negligible abuse liability. A drug with equivocal abuse liability is a drug in which the degree of abuse liability is not clear. It may be that one procedure indicates substantial abuse liability and another procedure suggests minimal abuse liability, or it may be that even using the same species and assay there are disagreements among studies, with some suggesting substantial abuse liability and others suggesting something less than substantial. Finally, a drug with equivocal abuse liability may show less than substantial effects but greater than minimal in a given procedure. For example, using subjective effects testing, a drug may produce a spectrum of pleasant and dysphoric effects. Or, in a
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self-administration procedure, the drug may generate responses at a slightly higher rate than that generated by presentation of the drug vehicle; by definition the drug functions as a reinforcer, but its efficacy may be weak. These drugs can be classified as having equivocal abuse liability.

**μ-Agonist Opioids**

Fentanyl and its analogs, alfentanil, sufentanil, and more recently remifentanil, have been tested for abuse liability. Fentanyl and sufentanil produced a conditioned place preference in rats, and fentanyl is self-administered by rats and primates, indicating that these drugs are reinforcers. Fentanyl and sufentanil share discriminative stimulus effects with other μ opioids that are abused, including morphine and heroin. When fentanyl (dose range, 0.4-1.6 mg/70 kg) was administered to non-physically dependent opioid abusers, they reported increased euphoria scores on the ARCI, identified the drug as “dope,” and reported on the SDQ that they liked the drug effects. In another study that assessed fentanyl (0.125 and 0.250 mg/70 kg) and alfentanil (1 and 2 mg/70 kg, intravenously) in nondependent opioid abusers, a similar spectrum of pleasant subjective effects was found with both drugs. Remifentanil, at several subanesthetic doses, was compared with fentanyl in nondependent opioid abusers in an abuse liability study. The drugs had similar euphoric effects, although the duration of effect was longer with fentanyl, which is consistent with its pharmacokinetic profile. The investigators concluded that a drug abuser seeking a longer-lasting drug effect might select fentanyl over remifentanil, but these data do not rule out remifentanil abuse when briefer or repeated effects are desired.

Abuse liability studies can and do include non-drug-abusing humans. Such studies give important information regarding the overall abuse liability in the general population, most of whom are not drug abusers. There is evidence that fentanyl has abuse liability in non-drug abusers. In two studies in human subjects, participants reported liking fentanyl, but in another study some participants liked its effects, some found the effects to be neutral, and others disliked its effects. In a self-administration study, non-drug abusers were more likely to choose fentanyl than saline in the presence of a painful stimulus. Again, there was intersubject variability on the measure of reinforcing effects, with some choosing fentanyl over placebo even in the absence of pain.

Therefore, fentanyl appears to have abuse potential in some non-drug abusers.

Morphine and heroin (3,6-diacetylmorphine) also have been assessed for abuse liability. Although heroin, the most commonly abused opioid in the world, is not available for clinical use in the United States, it is in medical use in some countries, including the United Kingdom. In laboratory self-administration studies performed with animals, morphine and heroin are readily self-administered and function as rewards in conditioned place preference procedures. Both drugs substitute for each other in drug discrimination studies and also share discriminative stimulus effects with other full μ agonists. The reinforcing effects of heroin and morphine have been established in nondependent opioid abusers. After administration of morphine or heroin, opioid abusers increased scores for euphoria on the ARCI, identified the drugs as “dope,” and reported liking them on the SDQ. Non-drug-abusing volunteers, however, reported dislike of the drug effects. In other studies, the unpleasant effects of morphine, such as heaviness, lethargy, and drowsiness, were reported more frequently than euphoria. Thus, morphine and heroin have substantial abuse liability in opioid abusers and minimal abuse liability in non-drug abusers.

Meperidine (pethidine) has the same abuse liability profile as that of morphine and heroin; in animals, it is self-administered and has discriminative stimulus effects in common with other full μ agonists. In opioid abusers, it increased euphoria scores on the ARCI and drug-liking ratings and was identified as “dope” on the SDQ. The drug’s profile of subjective effects differs from that of morphine. Meperidine increased sedation scores on the ARCI and “sleepy” ratings on the SDQ, and some study participants identified the drug as a barbiturate. The increased feelings of sedation may be attributable to the putative anticholinergic effects of meperidine. In non-drug abusers, meperidine also produced higher sedation ratings than did morphine. It is noteworthy that meperidine tended to produce more consistent liking ratings among healthy volunteers than did morphine.

Hydromorphone, in both dependent and nondependent opioid abusers, resembles morphine in its effects, and its abuse potential is considered to be the same as that of morphine. Animal and human abuse liability tests have established that codeine, hydrocodone, and propoxyphene have an abuse potential similar to that of other μ opioid agonists. Codeine and
Three opioids, buprenorphine, dezocine, and tramadol, are partial µ agonists. In physically dependent humans, buprenorphine and dezocine are thought to have low abuse liability because these drugs precipitate a mild withdrawal syndrome. In non-physically dependent animals and humans with a history of opioid abuse, however, the drugs function as reinforcers, and have a positive subjective effects profile. Tramadol also has substantial noradrenergic and serotonergic activity. The abuse potential of this drug has not been studied as thoroughly as that of other opioids. Tramadol is self-administered in rhesus monkeys. In nondependent opioid abusers, the drug has minimal subjective effects but is identified as “dope”, in dependent opioid users it has no subjective, behavioral, or physiologic effects.

Abuse of Opioids

The abuse liability of full µ agonists in animals and humans is high. The actual abuse of opioids is low in the United States population but still affects hundreds of thousands of people, has remained relatively constant over the last 30 yr, and poses a significant public health problem. All of the full µ opioids, including the opioid/acetaminophen or opioid/paracetamol preparations, are abused. The lifetime, past-year, and past-month incidence figures of nonmedical use of heroin reported by people ≥12 yr surveyed by the National Household Survey on Drug Abuse (NHSDA) were 1.2%, 0.2%, and 0.1%, respectively. Why full µ opioids such as morphine and meperidine are not abused to any great extent by opioid abusers is unknown. One potential reason may be that these drugs are not easily diverted from pharmaceutical supply houses and hospitals, given their scheduling status, and therefore they are not readily available in the drug-abusing community. Differences in metabolic pathways may account for the differential abuse; meperidine has an active metabolite, normeperidine, which with chronic high doses can cause excitation and toxicity in the central nervous system, including tremors and convulsions. Heroin, in contrast, does not have toxic metabolites. Another factor to consider is pharmacokinetic properties; the “rush” with morphine is not as immediate as with heroin because morphine crosses the blood-brain barrier more slowly. Drugs with a more rapid onset of effect tend to be more reinforcing, and abused, than drugs with a slower onset of effect.
ABUSE LIABILITY OF ANESTHETIC DRUGS

Abuse of fentanyl is associated with high morbidity and mortality.\textsuperscript{74–77} One subgroup in the general population likely to abuse fentanyl and sufentanil is anesthesia personnel,\textsuperscript{78} possibly because they have ready access to these drugs. Other potential difficulties include the difficulty in detecting abuse of fentanyl/sufentanil with urine toxicology screening (i.e., many clinical laboratories do not test for fentanyl and its analogs because fentanyl does not cross-react with commercially available opioid immunosays, and concentrations of fentanyl in fluids and tissues in fatal intoxications are near the lower limit of detection for even the most sensitive analytical techniques because of its potency\textsuperscript{79}); the rapid onset of effects (the “rush”) with fentanyl; its calming and euphoric effects; and the relative ease of titrating effect and duration of effect, given the short-acting nature of the drugs. Abuse of fentanyl might increase in the coming years with the advent of new formulations in which injection will no longer be necessary (oral transmucosal fentanyl citrate, transdermal fentanyl patch). Although there are no confirmed cases of abuse of oral transmucosal fentanyl citrate to date, there is a case report of a person inhaling fentanyl from a patch.\textsuperscript{80} Whether remifentanil will pose a serious threat as an abused drug among anesthesia personnel is unknown. It is possible that the short-lived effects of remifentanil, unless prolonged by a continuous infusion, would deter abuse. If remifentanil supplants fentanyl for medical procedures, however, its greater availability may increase illicit use. Remifentanil, unlike other fentanyl-related agents, requires dilution and can be diverted for personal use more easily during the diluting process. Finally, because remifentanil is relatively new, the amount needed for each patient are not easily determined from the small scientific literature base currently available. A larger amount may be prepared for a case than is actually needed, again making diversion easier.

In laboratory animals, the mixed opioid agonist-antagonist drugs have high abuse liability, but in opioid abusers they tend to produce sedation and dysphoria, indicating a lower probability of abuse. Only a few case reports of abuse exist.\textsuperscript{81–84} In drug abusers who depend physically on opioids, withdrawal symptoms would probably be precipitated by use of these drugs. The partial agonist, buprenorphine, has a profile of high abuse liability in animals and in abusers who are not physically dependent on opioids. Abuse of buprenorphine by dependent and nondependent opioid abusers has been reported in several countries, including the United Kingdom, New Zealand, and India\textsuperscript{85–89}

Benzodiazepines

Midazolam and diazepam have been assessed for abuse liability. Rodents and primates self-administer midazolam, and it induces conditioned place preference, demonstrating reinforcing effects.\textsuperscript{90–92} In drug discrimination studies with animals, midazolam shares similar discriminative stimulus characteristics with other benzodiazepines and also, in rodents, with the barbiturates.\textsuperscript{93,94} No studies with humans have assessed the abuse liability of midazolam systematically. Before midazolam was developed, diazepam was used preemptively and for conscious sedation procedures because of its amnestic effects. The popularity of diazepam has declined, possibly because its carrier, propylene glycol, is painful and because midazolam is an available alternative. As with midazolam, diazepam functions as a reinforcer in animals.\textsuperscript{91,95} Diazepam shares discriminative stimulus effects with other benzodiazepines and some barbiturates.\textsuperscript{96,97} Several studies have characterized the abuse liability of diazepam in sedative abusers and non-drug-abusing volunteers.\textsuperscript{98,99} In sedative abusers, diazepam was chosen over placebo in choice tests. Relative to placebo, it increased euphoria scores on the ARCI and drug-taking ratings.\textsuperscript{100} In nonanxious volunteers who characterized their alcohol consumption as light, diazepam did not function as a reinforcer and did not generate positive subjective effects.\textsuperscript{101} In nonanxious moderate drinkers, however, the drug functioned as a reinforcer and increased drug-taking ratings and mood scores for friendliness and elation on the POMS.\textsuperscript{101,102} Thus, quantity of alcohol normally consumed can modulate the reinforcing effects of benzodiazepines. Finally, in volunteers with anxiety disorders, diazepam functioned as a reinforcer in two studies\textsuperscript{103,104} but not in two others.\textsuperscript{105,106}

Other benzodiazepines used in anesthetic practice include lorazepam, alprazolam, triazolam, flunitrazepam, and temazepam. Flunitrazepam is not available for clinical use in the United States but is available elsewhere. These drugs have relatively short durations of action, which make them suitable for premedication, and they are used as hypnotic, anxiolytic, and sedative agents.\textsuperscript{107–111} Several preclinical and human studies (testing subjective and reinforcing effects) have established that alprazolam, lorazepam, triazolam, and flunitrazepam have abuse potential.\textsuperscript{112–119} The amount of information on the abuse liability of temazepam is limited,\textsuperscript{120,121} although there are reports of its abuse.\textsuperscript{122,123} Diazepam and other short-acting benzodiazepines
function as reinforcers in animals, in sedative-abusing humans, in moderate drinkers, and perhaps in anxious individuals. Humans who find benzodiazepines to be reinforcing also report a profile of positive subjective effects (i.e., liking of drug effects). More testing of abuse liability must be conducted in sedative abusers and non-drug-abusing volunteers with midazolam and temazepam.

Abuse of Benzodiazepines

The epidemiology of benzodiazepine abuse is difficult to assess. The NHSDA provides only aggregate data regarding nonmedical use of benzodiazepines and barbiturates. The lifetime, past-year, and past-month incidence of nonmedical use of sedatives and tranquilizers reported by people ≥12 yr surveyed were 6.6%, 1.3%, and 0.6%, respectively. The decreasing use of barbiturates suggests that most people abusing sedative-hypnotic agents abuse benzodiazepines instead. Benzodiazepines likely to be abused are shorter acting and have a rapid onset, including all of those discussed in the previous section.

The people most likely to abuse benzodiazepines are those who also abuse other substances, i.e., polydrug abusers. Some patients on methadone maintenance ingest a benzodiazepine after their methadone dose, reportedly to achieve a “high” state that is unachievable with either drug alone. People who abuse opioids or who are undergoing opioid withdrawal also self-medicate with benzodiazepines to prevent or ameliorate some signs and symptoms of withdrawal (e.g., difficulty in sleeping, anxiety). The relationship between alcoholism and abuse of benzodiazepines is far from clear. There is some evidence of greater use of benzodiazepines by this subgroup compared with the general population. Strong evidence that the benzodiazepines are abused by this subgroup is lacking, although anxious alcoholics may take the drug for anxiolysis.

Finally, there has been some concern about the overprescription of benzodiazepines for anxiety and sleep disorders. Most people who have prescriptions for benzodiazepines for anxiety or sleep disorders take them for ≤1 month. Although a significant minority of patients take benzodiazepines for ≥1 yr (e.g., two patient surveys presented ≥12-month use rates of 15% and 25%, their use patterns (e.g., lack of dose escalation) indicate that they are taking the drug for the prescribed reason, anxiolysis or insomnia. Several reviews of whether benzodiazepines are overprescribed and abused in the general population have concluded that there is little evidence for either.

Intravenously Administered Anesthetic Agents

Barbiturates

Thiopental and methohexital are the two barbiturates most frequently used in anesthesia practice. Primates self-administer methohexital, demonstrating that it has reinforcing effects. Thiopental has not been tested for its reinforcing efficacy. In drug discrimination procedures, barbiturates share discriminative stimulus effects with each other and with benzodiazepines. The abuse liability of thiopental and methohexital has not been studied in humans. Sedative abusers preferred pentobarbital, another shorter-acting barbiturate, to placebo.

Pentobarbital increased drug-liking and euphoria scores on the ARCI. Non-drug-abusing volunteers, however, did not prefer pentobarbital to placebo; further, the drug did not generate positive subjective effects in them.

Although information on the abuse liability of thiopental and methohexital is limited, the information that has been presented shows that short-acting barbiturates have abuse potential. The abuse potential is greater in sedative abusers than in non-drug-abusing volunteers. The actual incidence of barbiturate abuse is difficult to quantify. In the 1970s the incidence of barbiturate abuse was appreciable, but epidemiologic surveys in various countries indicate that barbiturate abuse has since declined.

For example, in the Monitoring of the Future survey, sponsored by the National Institute on Drug Abuse, the percent of 12th grade students who reported barbiturate use in the past month decreased by 64%, from 4.7% in 1975 to 1.7% in 1994. This decline in barbiturate abuse appears to track the decline in prescription use of barbiturates, as newer and safer sedative-hypnotic agents have become available over the past two decades.

Propofol

Little research has been done on the abuse liability of propofol or its effects relative to other drug classes. In two animal studies, subanesthetic and anesthetic doses of propofol induced a conditioned place preference; thus, propofol and its after-effects (recovery) had
rewarding properties. No studies have examined the effects of propofol in drug abusers. Several studies with non-drug-abusing patients and healthy volunteers have yielded mixed results. One study showed no measurable subjective effects from propofol, in several other studies, patients experienced positive mood states. There was considerable intersubject variability in the volunteer studies, with some participants showing a positive response, others a neutral response, and others a negative response to the drug. In a study that assessed the reinforcing effects of propofol (0.6 mg/kg, intravenously) with a preference procedure, 50% of the participants consistently chose the drug and reported liking it, whereas the other 50% consistently chose the placebo and reported either unpleasant acute or residual effects from propofol. The investigators concluded that in some non-drug-abusing volunteers, propofol functions as a reinforcer.

It is difficult to categorize the abuse liability of propofol broadly in the absence of crucial studies that examine its reinforcing and discriminative stimulus effects in sedative abusers. Such studies are needed, given the positive profile of effects propofol produces in animals and in non-drug-abusing volunteers and patients. Of the two published case reports regarding abuse of propofol, one involved an anesthesiologist. Several factors mitigate against its use: its evanescent effect (unless the drug is delivered by an infusion pump) and the possibility of thrombophlebitis and pain on injection from its lipid carrier.

Ketamine
Ketamine, a dissociative anesthetic agent, is a noncompetitive antagonist at the N-methyl-D-aspartate receptor. Rodents and primates self-administer ketamine. A compound closely related to ketamine, phenylcyclohexane, was preferred in a conditioned place preference procedure in one study, but in another study it produced a place aversion. Ketamine shares discriminative stimulus effects with phencyclidine and other excitatory amino acid antagonists. Ketamine has not been studied in drug abusers for its abuse liability, which is noteworthy, given the similarity of its pharmacologic profile with phencyclidine and hallucinogens. The subjective effects of ketamine have been studied in healthy volunteers and somewhat less systematically in patients, with consistent results. Reported effects include derealization, the perception that the environment around oneself is unreal; depersonalization, the belief that one no longer exists or exists outside of one’s body; thought disorders; acute or residual visual hallucinations; and pleasant or unpleasant dreams. Some individuals report flashback-like effects weeks or months after receiving ketamine.

Ketamine appears to have abuse liability based on its reinforcing and discriminative stimulus effects in animals. There were case reports of ketamine abuse in the 1980s and, more recently, reports of ketamine use during all-night dancing or “rave” parties. The incidence of ketamine abuse is low but may be increasing. Hallucinogen use, including use of the noncompetitive N-methyl-D-aspartate antagonist phencyclidine, increased from 1994 to 1995.

Inhaled Anesthetic Agents
The volatile inhaled anesthetic agents, isoflurane, enflurane, halothane, desflurane, and sevoflurane, have not been tested for their reinforcing effects. Ether, however, functioned as a reinforcer in macaque monkeys. In two drug discrimination studies in mice, halothane shared discriminative stimulus effects with the training drugs, ethanol and pentobarbital. This substitution suggests that at least some of the subjective effects of halothane, ethanol, and pentobarbital are mediated by the same neurochemical pathway. The subjective effects of subanesthetic concentrations of isoflurane have been studied in non-drug-abusing volunteers. Isoflurane produced sedative-like effects, with substantial intersubject variability on drug liking.

Nitrous oxide, at concentrations ranging from 15–70%, functions as a reinforcer in primates. In the studies that demonstrated reinforcement, different concentrations of nitrous oxide or oxygen (placebo) were delivered contingent on pressing a lever. The lever was pressed more when nitrous oxide was available than when oxygen (placebo) was available. In the only drug discrimination study involving nitrous oxide, it substituted for the training drug, ethylketocyclazocine, a selective κ opioid agonist, but not for morphine. The investigators concluded that the discriminative stimulus effects of nitrous oxide are more κ-like than μ-like. This conclusion is consistent with that from some studies of nitrous oxide in humans, which reported dysphoric effects such as hallucinations, unpleasant memories, and confusion. In other studies with the same subject population, however, pleasant effects were reported, effects that are atypical of κ agonists in humans. The reinforcing effects of nitrous oxide in concentrations used in dental procedures (20–40%) have been

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studied in non-drug-abusing volunteers. Nitrous oxide did not function as a reinforcer in most individuals tested.\textsuperscript{191-193} Nitrous oxide functioned as a reinforcer in moderate alcohol drinkers, however.\textsuperscript{191} As with the benzodiazepine diazepam, the effects of nitrous oxide were more reinforcing in non-drug-abusing moderate drinkers than in lighter drinkers.\textsuperscript{101,102}

Abuse of Inhaled Anesthetic Agents

The primary population that abuses volatile inhaled anesthetic agents includes people who work in medical settings.\textsuperscript{195} Accidental deaths have been documented with enflurane and halothane, and evidence indicated that the anesthetic agent was used for intoxication rather than life-saving purposes.\textsuperscript{196-198} Causes of death have included airway obstruction, cardiac arrhythmias, and hepatitis.\textsuperscript{199} An interesting case of abuse of isoflurane was reported during the war between the United States and Iraq in 1990 and 1991. Most of the United States troops were stationed in Saudi Arabia, where alcohol was not allowed because of Muslim conventions. An Air Force pharmacist was convicted in 1991 of not only distributing sleeping pills and amphetamines to enlisted men but also “committing conduct unbecoming an officer” by sniffing isoflurane in the presence of an enlisted man. He stated during the court-martial trial that isoflurane became a common substitute for beer. During the war, one soldier died from a myocardial infarction, apparently after having used isoflurane.\textsuperscript{1} During “normal” conditions, a drug such as isoflurane may not be abused because other more familiar drugs are available. If the familiar drugs are no longer available, however, a drug that produces similar subjective effects may be substituted in its place. The most recent NHSDA estimated lifetime recreational use of volatile anesthetic agents to be 0.3% of the population aged 12 yr and older.\textsuperscript{70}

Nitrous oxide, although readily accessible in the operating room and the dental office, does not appear to be abused to any great extent by medical and dental personnel.\textsuperscript{200} The drug is used recreationally \textit{via} small cylindrical cartridges used to make whipping cream or by the procurement of large gas cylinders from a medical setting or industrial supply store. The gas is placed in balloons and people achieve a transient state of intoxication by breathing and rebreathing from the balloon.

The most recent NHSDA estimated lifetime recreational use of nitrous oxide to be 2.2% of the population aged 12 yr and older.\textsuperscript{20}

Local Anesthetic Agents

Cocaine is used in intranasal surgery to provide anesthesia and, because of its vasoconstrictive effects, to decrease bleeding and shrink congested mucous membranes.\textsuperscript{201} The abuse potential of cocaine has received as much, if not more, attention than opioids in the past decade. Cocaine functions as a reinforcer, as demonstrated in drug self-administration studies in rats and rhesus monkeys.\textsuperscript{202} The drug is thought to be a very strong reinforcer in that animals expend a tremendous amount of energy to “earn” cocaine.\textsuperscript{203} and, in certain situations, forgo food to the point of starvation.\textsuperscript{204} Conditioned place preference procedures mirror the results of self-administration studies; cocaine consistently has rewarding properties.\textsuperscript{205} Cocaine has discriminative stimulus effects in common with a number of other psychomotor stimulants and dopaminergic agonists, including \textit{d}-amphetamine, methamphetamine, and apomorphine.\textsuperscript{206,207} The reinforcing and subjective effects of cocaine have been studied in cocaine abusers. Intranasal, smoked, and intravenous cocaine are self-administered at a rate higher than placebo.\textsuperscript{208,209} Subjective effects include increased euphoria scores on the ARCI and increased ratings for “good drug effects.”\textsuperscript{210}

Procaine and the other commonly used ester local anesthetic agents chloroprocaine and tetracaine bear a structural similarity to cocaine and are used frequently for topical and regional anesthesia. Procaine and chloroprocaine were positive reinforcers when delivered intravenously to rhesus monkeys.\textsuperscript{211,212} Tetracaine was self-administered only occasionally and appears to be a marginal reinforcer.\textsuperscript{213} Procaine also serves as a discriminative stimulus in rats, and cocaine has partially or fully substituted for procaine.\textsuperscript{214,215} The similarity of discriminative stimulus effects with procaine and cocaine and their reinforcing effects in animals suggest that procaine has abuse potential in humans. In the only study to assess the abuse liability of procaine in cocaine abusers, some of the subjective effects of procaine were similar and others were dissimilar to those produced by cocaine. Procaine did not differ from placebo on ARCI or POMS scores, but three of four individuals identified procaine doses of 48 and 96 mg as cocaine.\textsuperscript{216}

Lidocaine, an amide local anesthetic drug, is used as a
topical and regional agent and intravenously as an antiarrhythmic agent. An intranasal formulation is used to treat migraine headaches. Intravenously administered lidocaine did not function as a reinforcer in primates. In drug discrimination studies with rats, lidocaine shared discriminative stimulus effects with procaine, indicating that lidocaine might have some abuse potential. In one study, intranasally administered lidocaine produced subjective responses similar to those produced by cocaine in stimulant abusers, but the study has been criticized because it assessed only one subjective measure, that of “high.” In another study, neither euphoria scores from the ARCI nor liking ratings increased after intravenous administration of lidocaine in humans with histories of cocaine abuse. Studies with lidocaine suggest that other local anesthetic agents from the amide class that are used for regional anesthesia, including bupivacaine and mepivacaine, may have low abuse liability.

Abuse of Local Anesthetic Agents

Cocaine, regardless of route of administration, has clear abuse liability as measured in animal and human studies. The actual epidemiology of cocaine abuse mirrors its abuse liability. The lifetime, past-year, and past-month incidence of nonmedical use of cocaine reported by people aged 12 yr and older by the NHSDA were 10.3%, 1.7%, and 0.7%, respectively. Clearly, there continues to be a significant public health problem with cocaine use in this country. The abuse of cocaine among medical personnel, however, appears to be no higher than in the general population. Its common formulation as a cocaine suspension in medical settings and its limited availability decreases the likelihood of intrahospital abuse of this drug. Based on studies in animals, procaine and the other drugs of the ester class have a high abuse potential in theory, although actual abuse of these local anesthetic agents is low. One reason for the lack of procaine abuse may be its relatively short elimination half-life (7.7 min vs. 40 min for cocaine); a procaine abuser would have to administer the drug frequently to maintain an intoxicated state.

α₂-Adrenergic Agonists

Clonidine has been studied for its reinforcing and discriminative stimulus effects. Primates pressed a lever to obtain clonidine at a higher rate than for saline. In rats, clonidine had rewarding effects in conditioned place preference trials and substituted for morphine in a drug discrimination study. Yet the reinforcing efficacy of clonidine was not confirmed in opioid abusers who were undergoing methadone detoxification. In oral form, clonidine is used to ameliorate withdrawal symptoms during heroin detoxification. There have been only a few case reports of abuse of clonidine in the literature. Patients in methadone maintenance programs reportedly used clonidine to boost the euphoric effects of diazepam, which is sometimes prescribed for symptoms of opioid withdrawal. Clonidine also may be used in times of illicit opioid scarcity. One high-risk group identified as likely to abuse clonidine is opioid-dependent women who also use cocaine.

Dexametadomidine, another α₂ selective agonist being evaluated as an adjuvant to general anesthesia, has not been tested for abuse liability in animals or humans. Healthy volunteers and patients reported sedative effects from the drug. The patients also reported anxiety.

Anticholinergic Agents

Several animal studies have tested anticholinergic agents for their abuse liability. Intravenously administered scopolamine functions as a reinforcer in rats. Atropine and scopolamine substitute for one another in drug discrimination studies, but typically do not substitute for drugs from other classes, such as morphine, imipramine, amphetamine, and pentobarbital. Numerous studies have characterized the subjective effects of anticholinergic drugs in healthy volunteers. In general, scopolamine tends to have more marked effects on mood than does atropine, most likely because of the greater penetration by scopolamine of the blood-brain barrier. Supratherapeutic doses of atropine produce subjective effects, however. At lower doses, anticholinergic agents produce sedation, dizziness, dry mouth, and bradycardia; decreased arousal and energy; and blurred vision (because of dilation of the eye). At higher doses, a central anticholinergic syndrome, which includes psychotomimetic effects (delirium, hallucinations, confusion, and restlessness), can occur. There have been some case reports of anticholinergic abuse, primarily among patients taking antipsychotic medication. Anticholinergic agents such as trihexyphenidyl and benztropine are prescribed for amelioration of
certain side effects of antipsychotic and antiparkinsonian agents (e.g., extrapyramidal side effects). Patients took supratherapeutic doses, presumably for the psychotomimetic and euphoric effects.\textsuperscript{233-235} There are also case reports of people co-abusing anticholinergic agents with other drugs (including alcohol) to enhance the psychoactive effects of these substances.\textsuperscript{236}

**Antihistamines**

Intravenous self-administration of H\textsubscript{1} antagonists, including diphenhydramine, has been demonstrated in monkeys,\textsuperscript{237} indicating that H\textsubscript{1} antihistamines have reinforcing effects in primates. In a drug discrimination study, diphenhydramine substituted for cocaine in three of four pigeons.\textsuperscript{238} Abuse liability of H\textsubscript{1} antihistamines has not been shown in humans. In humans who abused sedatives, oral diphenhydramine in doses up to 400 mg did not increase drug-like ratings or euphoria scores on the ARCI, relative to placebo. In contrast, ARCI scores for sedation and dysphoria were increased, and some self-reported side effects were restlessness, agitation, irritability, and vomiting.\textsuperscript{239} In a sample of non-drug-abusing volunteers, 25 and 50 mg of orally administered tripeplenamine were not chosen more often than placebo, indicating a lack of reinforcing effects. Study participants reported disliking its sedative effects.\textsuperscript{240} There is one study of opioid abusers who reported euphoria after parenterally administered tripeplenamine,\textsuperscript{251} but there are only a few case reports in the medical literature on antihistamine abuse.\textsuperscript{252-255} In the 1970s in several regions of the United States, tripeplenamine was injected concurrently with pentazocine ("Ts" and "blues") to produce a heroin/cocaine-like high.\textsuperscript{254} The abuse of "Ts" and "blues" declined precipitously when the manufacturer of oral pentazocine added naloxone to the formulation.\textsuperscript{254,255} In nondependent opioid abusers, this new formulation antagonized the effects of pentazocine, and in dependent opioid abusers, it precipitated opioid withdrawal. Were tripeplenamine functioning as a reinforcer, as suggested by Lange and Jasinski,\textsuperscript{251} abuse of tripeplenamine alone should have continued in opioid abusers. It apparently has not. In summary, although animal studies suggest an abuse liability of antihistamines, studies in humans suggest, at best, equivocal abuse potential, and the epidemiologic data concerning actual abuse of antihistamines are more concordant with the human studies.

**Ephedrine**

In baboons, ephedrine was self-administered, but in an unstable and erratic pattern.\textsuperscript{256} In rats, ephedrine shared discriminative stimulus effects with amphetamine, methamphetamine, and cocaine.\textsuperscript{257,258} In opioid abusers, subcutaneous ephedrine increased euphoria scores on the ARCI and drug-like ratings, in the same manner as amphetamine and methamphetamine.\textsuperscript{7} The reinforcing properties of ephedrine have been examined via a choice procedure in non-drug-abusing volunteers.\textsuperscript{259} Choice of ephedrine did not exceed chance levels. The profile of subjective effects predicted a low abuse potential for this drug in this subpopulation; it included increased visual analog scale ratings of "high," "stimulated," and "anxious" without increasing drug-like ratings. Consistent with the abuse liability of this drug among opioid abusers, however, there are reports of ephedrine abuse in the literature. In Japan, over-the-counter cough syrup containing ephedrine is abused.\textsuperscript{260} Some over-the-counter stimulants include ephedrine, and these drugs are abused by truck drivers and athletes, presumably for their stimulant effects.\textsuperscript{261,262} The abuse of methamphetamine, which is synthesized in clandestine laboratories from ephedrine,\textsuperscript{263} is increasing in the United States.\textsuperscript{264,265}

**Antiemetic Agents**

Droperidol and metoclopramide are dopamine antagonists. The primary side effects of droperidol include anxiogenesis, restlessness, and dizziness;\textsuperscript{266} those of metoclopramide include restlessness, dry mouth, and drowsiness.\textsuperscript{267} No abuse liability testing has been conducted on these older generation antiemetic agents, and there are no published cases of abuse of these drugs. The newer generation 5-hydroxytryptamine\textsubscript{3} antagonist, ondansetron induced neither a preference nor an aversion for the side of the chamber paired with the drug in the conditioned place preference paradigm.\textsuperscript{268} The drug appears to be devoid of subjective effects at therapeutic and supratherapeutic doses.\textsuperscript{269} No cases of ondansetron abuse have been published. Several studies in animals\textsuperscript{270-273} and humans\textsuperscript{274-276} have examined ondansetron and other 5-hydroxytryptamine\textsubscript{3} antagonists as potential treatments of opioid, alcohol, and stimulant abuse with mixed results. The amount of interest in the past several years directed at 5-hydroxytryptamine\textsubscript{3} compounds for disorders ranging from drug abuse to generalized anxiety disorder suggests that these compounds
ABUSE LIABILITY OF ANESTHETIC DRUGS

Table 1. Putative Abuse Liability of Anesthetic Drugs

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Animals</th>
<th>Drug-abusing Humans</th>
<th>Non-Drug-abusing Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full (\mu) agonists</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Mixed action</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Propofol</td>
<td>?</td>
<td>NT</td>
<td>+</td>
</tr>
<tr>
<td>Ketamine</td>
<td>+</td>
<td>NT</td>
<td>-</td>
</tr>
<tr>
<td>Inhaled general anesthetics</td>
<td>++</td>
<td>NT</td>
<td>²</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esters (cocaïne)</td>
<td>++</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Amides (lidocaine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\alpha)-Agonists</td>
<td>++</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>?</td>
<td>NT</td>
<td>-</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>++</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>?</td>
<td>NT</td>
<td>-</td>
</tr>
<tr>
<td>Antimetetics</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(ondansetron only)

++ = substantial abuse liability; + = equivocal abuse liability; - = minimal abuse liability; ? = in non-drug-abusing volunteers who consume alcohol, has abuse potential in moderate drinkers and minimal abuse liability in lighter drinkers; ? = abuse liability cannot be designated from the limited number of studies; NT = not tested.

will continue to be studied for their therapeutic efficacy for some time.²⁷⁷

Summary

Table 1 categorizes the different anesthetic drugs based on their putative abuse liability. Full \(\mu\) opioid agonists, benzodiazepines, and cocaine clearly have abuse potential and are abused. Other drugs such as mixed agonist-antagonist opioids and antihistamines have equivocal abuse potential, and epidemiologic data indicate a low incidence of abuse of these drugs. Finally, there are gaps in the literature in which the abuse potential of drugs such as ketamine, inhaled general anesthetic agents, and propofol would be worthy of testing, especially in drug abusers.

Clinical Ramifications

There are several issues remaining that are pertinent to testing of abuse liability and the epidemiology of abuse of anesthetic drugs. We raise these issues in question form. We believe such questions have clinical relevance to the anesthesia profession and deserve attention.

1. **Why do some anesthetic drugs have abuse potential and others do not, i.e., what characteristics do abused drugs have that are missing from drugs that are rarely abused?**

Abused drugs tend to induce a state of euphoria or extreme well-being. This euphoria is thought to be intimately related to the abuse potential of a drug.²⁷⁸-²⁸¹ Researchers have attempted to unravel the neurochemical underpinnings of the euphorigenic effects of such diverse drugs as cocaine, heroin, and diazepam. One theory is that these drugs, through different mechanisms of action, stimulate the mesolimbic dopamine system,²⁸²,²⁸³ considered to be the reward center of the brain.²⁸⁴ Drugs that are used recreationally by humans, including alcohol and tobacco, tend to stimulate this system. Lesioning this system decreases self-administration of drugs such as nicotine, cocaine, and heroin.²⁸⁵,²⁸⁶ Another important reward mechanism appears to be activation of the endogenous opioid system. When this system is deactivated by opiate receptor antagonists, self-administration of opioids and other drugs (e.g., alcohol) can be decreased, suggesting that the reinforcing effects of some drugs are mediated by activation of opiate receptors.²⁸⁷-²⁹¹

2. **Why does abuse potential of a drug not necessarily predict its abuse?**

Morphine has high abuse potential but is not abused to a large extent within or outside the medical community. Barbiturates have abuse potential, but the incidence of their abuse has decreased over the past 20 yr. There are many reasons for the less-than-expected abuse of a drug. The abuse of drugs is not linked only to pharmacology but to a number of other factors.²⁹² One key factor is availability. The manufacture of barbiturates by pharmaceutical companies has decreased over the past 20 yr because of the decrease in prescription use of this drug class. Therefore, even though barbiturates may be diverted for nonprescribed uses, the drugs are scarce, creating less opportunity for abuse. Another factor is relative availability. Morphine, which has the potential for abuse, is not abused to a great extent because heroin is readily available and is preferred to morphine. If availability of heroin were to decrease markedly, it is likely that abuse of other full \(\mu\) agonists such as morphine would increase greatly. Finally, such factors as drug pricing and fads are often involved in the apparent dissociation between the abuse liability of a drug and its actual abuse.²⁹³

3. **Why do patients who receive "drugs of abuse" peri- and post-operatively not subsequently seek out these...**

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drugs, i.e., why isn’t there a greater incidence of iatro-
genic addiction (drug seeking prompted by exposure to a
drug for a medically valid reason)?

We speculate about the answer to this question. Drug
abuse is “caused” by a number of variables, such as
familial problems, peer pressure, mental and physical
stressors, economic distress, personality disorders, ge-
etic predisposition, and psychiatric morbidity.\textsuperscript{294,295}
Exposure to a drug is certainly a necessary precursor to
drug abuse, but exposure alone is seldom sufficient. In
almost all cases of drug abuse, other predisposing factors
contribute to the abuse. In addition to not having these
predisposing factors, most patients would have difficulty
procuring opioids and barbiturates for illicit purposes.
Finally, there is the issue of whether patients who re-
ceive psychotropic abusable drugs during or after sur-
gery experience pleasant subjective effects. In a sterile
medical setting or in the presence of the stress of pain
during drug administration, it may not be possible to
experience euphoric effects. In a recent laboratory
study, pain decreased the intensity of the subjective
effects of morphine in volunteers.\textsuperscript{296} Pain also may an-
tagonize pleasant effects of drugs given during the peri-
and postoperative period in much the same way that
pain antagonizes the respiratory depressant effects of
opioids.\textsuperscript{297} We contend, however, that patients with
a history of drug abuse could be at increased risk for drug
relapse by exposure to drugs of abuse perioperatively.
Although definitive clinical studies have not been con-
ducted in this area, our speculation is based on animal
and human studies showing that passive administration
of a drug, after the self-administration of that drug
ceased, can “reinstate” responding to that drug.\textsuperscript{298,299}
Thus, a patient who had abused opioids in the past but
is currently abstinent may crave or abuse opioids after
receiving them during perioperative care.\textsuperscript{300} Further re-
search, retrospective and prospective, is needed on this
interesting and clinically important issue.

4. Because drugs used in anesthesia practice can rein-
state drug craving and perhaps drug seeking, should the perioperative drug treatment of patients
who are active or recovering alcoholics and drug abusers differ from treatment for non-drug abusers?

Some procedures can be performed with regional an-
esthesia, obviating the need for sedation or analgesia
with benzodiazepines, opioids, or inhaled and intrave-
nous anesthetic agents. The advent of many different
kinds of nonsteroidal antiinflammatory drugs also makes
it possible to choose a nonopioid analgesic regimen with
no known abuse potential. The first consideration of an
anesthesiologist in choosing an analgesic, however,
should be achieving an optimal degree of pain relief. If
opioids are indicated, the drugs should be used in effect-
ive doses, because underdosing can lead to drug craving,
increased anxiety, and, most obviously, pain.\textsuperscript{301} The
interested reader is referred to other articles that address
the special needs of drug abusers during the periopera-
tive period.\textsuperscript{301–308}

5. Why is drug abuse not epidemic among anesthes-
iology personnel who work daily with drugs with
substantial abuse liability?

In most instances, mere availability of a drug is not
in itself sufficient to lead to abuse of a drug. Other
factors, including genetic predisposition, comorbidity,
deprivation of other reinforcers, and stressors, are
usually necessary. One could argue, however, that
mere availability might play a role in drug abuse
among anesthesiologists in that the percentage of an-
esthesiologists in drug abuse programs for physicians
is greater than the percentage of physicians who are
anesthesiologists (12.1% vs. 3.9%, respectively, in one
study\textsuperscript{309}). This statistic suggests a greater propensity
for drug abuse by anesthesiologists than by physicians
in other medical subspecialties. The percentage of
anesthesiologists who are drug (or alcohol) abusers
has not been estimated, however, nor has the area of
how incidence of drug abuse among anesthesiologists
comparing with that in the general population.

6. Should storage/accountability practices be
changed for anesthetic drugs?

In many hospitals, drug accountability procedures have
become more sophisticated (e.g., satellite pharmacies
within an operating room) so that drug diversion for
personal use is more difficult. The question is whether storage
and accountability should be changed for the so-called
benign drugs. We have some concerns about ketamine
because it has rewarding effects in animals\textsuperscript{162–164}, shares
discriminative stimulus effects with another drug of abuse,
phencyclidine\textsuperscript{167,168}; and is known to be abused.\textsuperscript{174–176}
We also have some concerns about propofol, which has
rewarding effects in animals\textsuperscript{92,152} Some non-drug-abusing
volunteers chose it over placebo in a laboratory study,\textsuperscript{159}
and there have been cases of abuse of propofol, albeit
isolated.\textsuperscript{160,161} Aside from ketamine and propofol, however,
there is little evidence of substantial abuse of antihis-
tamines, anticholinergic agents, or lidocaine. The drugs
that have substantial potential for abuse (e.g., opioids and
cocaine) are stored, accounted for, and used appropriately
in most hospitals.
Conclusion

The purpose of this article was to discuss the abuse liability and abuse of drugs that anesthesiologists use in their practice. One major point to be gleaned from this article is that the abuse liability and abuse of drugs used in anesthesia practice vary within and across drug classes. A second point is that the pharmacology (mechanism of action) of a drug is only one determinant of its abuse; other factors include characteristics of the person and the environment. Finally, several issues were raised to serve as catalysts for further collaborative research between the disciplines of anesthesiology and psychopharmacology.

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