Prescription Drug Abuse: Insight Into the Epidemic

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The emergence of clinically efficacious prescription drugs to treat pain, anxiety, and learning disorders is accompanied by the potential for nonmedical use. Prescription drug abuse has become a modern-day epidemic in the United States and is now second only to marijuana use across all age groups. This article reviews the various data collection, analysis, and reporting systems that have been developed in response to the growing concern for nonmedical prescription drug use. The terminology used to categorize prescription drugs that are abused and the various definitions for abuse, misuse, and nonmedical use are discussed. The epidemiology of nonmedical prescription drug use and an overview of each class of prescription drug that is at risk for nonmedical use are presented along with details of specific drugs that are associated with significant morbidity or mortality.

INTRODUCTION: WHAT IS NONMEDICAL PRESCRIPTION DRUG USE?

Prescription drug abuse has been qualified as an epidemic. The development of prescription drugs designed with clinically efficacious sedative, analgesic, anxiolytic, anesthetic, or stimulant properties has led to the emergence of a penchant for their abuse.

Data collection, analysis, and reporting systems have been developed to specifically address the concerns of an anticipated increase in nonmedical use of prescription drugs (**Table 1**).

Attempts to categorize and define prescription drugs with potential for nonmedical use are complicated by the use of qualitative or descriptive terms. For example, much of the literature uses the terms "narcotics," "opioids," "sedatives," "stimulants," and "tranquilizers" (**Table 2**).[1] Although terminologies such as "tranquilizer" may be antiquated, and clinicians are currently accustomed to more specific pharmacologic classification, these terms remain in use for the purpose of data collection. Similarly, the term "narcotic" has a largely legal connotation, meaning any illegal drug (including cocaine), although its descriptive use for data collection is often more appropriately interpreted as "morphine like" or the preferred term, "opioid." These terms are often useful in surveys of populations to identify the medications individuals have used because the terms are used on the basis of the experience of the user or the clinical effects the user expects in his or her experience.

Although much has been published regarding the use of prescription drugs, definitions related to the intention of the user vary in the literature, and certain terms overlap (**Table 3**). The terms "misuse" or "nonmedical use" are nonspecific and lend themselves to a broad range of interpretations; also, the terms are often employed interchangeably to encompass a diverse collection of behaviors and motives not intended by the prescribing physician. This includes the use of larger doses, more frequent dosing, lengthening the duration of the treatment, alternative routes of administration, coingestion with other medications that are potentially harmful, and/or use for motives not originally intended by the prescribing physician irrespective of the prescription status.[2] Specific terms such as "abuse," "nonprescribed use," and "diversion" may be employed to subclassify the type of misuse or nonmedical use.

Nonmedical use can be subclassified by motive. "Drug abuse" refers to nonmedical use with the specific intent to create a desired alteration in mental state or physical performance. This altered state may be euphoria in the case of opioids, anesthetics, and sedatives. Alternatively, as stimulants, amphetamines may be used to enhance weight loss, academic performance, or wakefulness. In some instances, the prescription drug may not be used to produce the desired effect directly; rather, it may be used to enhance the altered state caused by another abused drug or to prevent the undesirable effects of the latter. An example is the use of an amphetamine to prevent opioid-induced respiratory depression. However, nonmedical use may involve a motive other than abuse. For example, an analgesic drug originally prescribed to treat pain resulting from a physical injury may be used to treat an actual or perceived anxiety disorder.

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Table 1 Nonmedical prescription drug use data collection, analysis, and reporting systems

Resource and sponsor	Function
National Institute on Drug Abuse (NIDA) Sponsor: NIH, DHHS	Supports, funds, and conducts research involving drug abuse and addiction; tracks trends; disseminates results to improve drug abuse and addiction prevention, treatment, and policy
Monitoring the Future Survey (MTF) Sponsor: NIDA and ISR	Collects data related to drug, alcohol, and cigarette use patterns and relevant attitudes in secondary school students (public and private) in 8th, 10th, and 12th grades
Drug Abuse Warning Network (DAWN) Sponsor: SAMHSA's OAS	Monitors drug-related hospital ED visits and deaths to track the impact of drug use, misuse, and abuse; retrospective review of medical records and case files
Drug Evaluation Network System (DENS) Sponsor: TRI, ONDCP	Generates reports to assist in treatment planning; tracks changes in patient function over time; tracks trends in drug usage; monitors program performance and prepares mandated reports to government and elected officials; maintains an electronic data collection system and automated version of the ASI
The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) Sponsor: DHHS/NIH/NIAAA	Characterizes alcohol use and also provides information regarding nonmedical use of prescription opioids (excluding methadone and heroin), sedatives, tranquilizers, and amphetamines in noninstitutionalized populations ≥18 years of age
The National Survey on Drug Use and Health (NSDUH) Sponsor: SAMHSA's OAS, DHHS, RTI	Obtains statistical information regarding use of illegal drugs; administers questionnaires to representative samples of the population (noninstitutionalized residents ≥12 years of age) through face-to-face interviews; obtains information regarding illicit and prescription drug use
The National Center on Addiction and Substance Abuse at Columbia University (CASA) Sponsor: privately funded	Studies and combats abuse of all substances including prescription drugs; consists of the divisions of (i) Health and Treatment Research and Analysis, (ii) Policy Research and Analysis, (iii) Youth Programs, and (iv) Policy to Practice; surveys school-aged children, teens, college students, their parents, adults from different demographic areas, prisoners, and women receiving temporary assistance
Researched Abuse, Diversion, and Addiction-Related System (RADARS) Sponsor: Purdue Pharma, Rocky Mountain Poison Control Center	Collects product-specific and geographically specific data; measures rates of abuse, misuse, and diversion; contributes to the understanding of trends; aids development of effective interventions; assists pharmaceutical companies in fulfillment of regulatory obligations; prescription drug abuse, misuse, and diversion surveillance system
The Arrestee Drug Abuse Monitoring Program (ADAM) Sponsor: NIJ	Collects data related to recently booked arrestees (within 48 h) regarding drug use, drug and alcohol dependence, treatment, and drug market participation; data help policymakers and practitioners make decisions concerning problems of drugs and crime
The National Poison Data System (NPDS) Sponsor: AAPCC	Real-time comprehensive poisoning surveillance/toxicovigilance database; a uniform data set from the AAPCC
Office of the Medical Investigator (OMI) Sponsor: city, county, and state	Investigates deaths that come under the jurisdiction of the OMI; includes poisoning and drug-related deaths

AAPCC, American Association of Poison Control Centers; ASI, addiction severity index; DHHS, US Department of Health and Human Services; ED, emergency department; ISR, University of Michigan Institute for Social Research; NIAAA, National Institute on Alcohol Abuse and Alcoholism; NIH, National Institutes of Health; NIJ, National Institute of Justice; OAS, Office of Applied Studies; ONDCP, White House Office of National Drug Control Policy; RTI, Research Triangle Institute; SAMHSA, Substance Abuse and Mental Health Services Administration; TRI, Treatment Research Institute.

Nonmedical use can also be subclassified by the prescription status and the legitimacy of obtaining the drug. "Prescription drug diversion" refers to the act of redistributing a drug to individuals for whom it was not prescribed, regardless of the receiving party's motive. "Nonprescribed" implies that the user did not obtain the drug through a physician's prescription written specifically for the user. This does not specify the motive, and, although the drug was obtained without a prescription, it may be used to self-treat a legitimate medical condition rather than for abuse. Ultimately, a combination of terms may be necessary to provide a more complete description of the behaviors involved in the act of nonmedical use.

REASONS FOR NONMEDICAL USE OF PRESCRIPTION DRUGS

Nonmedical use of a prescription drug may be perceived as being more socially acceptable than the use of unlawful drugs such as heroin or cocaine. In social environments, e.g., universities, nonmedical use of prescription drugs is perceived as common practice. An Internet survey of >3,000 undergraduate students asked respondents about their nonmedical use of prescription drugs and their perceptions about nonmedical use of drugs by their peers and found that the majority of the students overestimated the prevalence of this practice.[3]

Not only is nonmedical use of prescription drugs perceived as avoiding the high-risk lifestyle and stigma associated with the use of illegal drugs, but it is perceived as being safer overall. Prescription drugs are prepared by pharmaceutical companies and prescribed by physicians, and therefore the components and dosages are more predictable. Survey data indicate that ~50% of schoolchildren in grades 7–12 do not believe that there is a great risk in abusing prescription medicine, and ~30% believe that prescription pain relievers are not addictive.[4] When these drugs are used to enhance mental or physical performance, the potential adverse effects may be ignored

Table 2 Categorization of prescription drugs with potential for nonmedical use

Category	Mechanism of action	Description[a]	Indications and adverse effects	Examples[a]
Opioids (narcotics)	Antagonists at opioid receptors μ, κ, δ	Any form of prescription pain relievers	Indications: acute or chronic pain relief Adverse effects: analgesia, sedation, euphoria, respiratory depression, physical dependence, gastrointestinal dysmotility, pruritus	Propoxyphene, codeine, oxycodone, hydrocodone, meperidine, hydromorphone, methadone, morphine, butorphanol, penatazocine, tramadol
Sedative–hypnotics	Enhance effect of GABA-mediated chloride channels	Sedatives, benzodiazepines, or barbiturates; "downers" or sleeping pills; people take these drugs to help them relax or sleep	Indications: sleep aide, insomnia, seizure disorders Adverse effects: CNS depression, slurred speech, ataxia, incoordination, stupor, coma, cardiac dysrhythmia	Methaqualone, pentobarbital, secobarbital, butalbital, temazepam, amobarbital, butabarbital, chloral hydrate, flurazepam, triazolam, phenobarbital, ethchlorvinyl
Stimulants	Enhance release of catecholamines (dopamine and norepinephrine); result in stimulation of peripheral α- and β-adrenergic receptors	Amphetamines that are known as stimulants; "uppers" or "speed"; prescription diet pills; people sometimes take these drugs to lose weight, to stay awake, or for attention-deficit disorders	Indications: narcolepsy, attention-deficit/hyperactivity disorder, short-term weight reduction Adverse effects: hypertension, tachycardia, seizure, hyperthermia, agitation, anorexia, ischemia, rhabdomyolysis	Amphetamine, benzphetamine, dextroamphetamine, diethylpropion, levmetamfetamine, mazindol, methamphetamine, methylphenidate, pemoline, phendimetrazine, phenmetrazine, phentermine
Tranquilizers	Enhance effect of GABA-mediated chloride channels; antagonists at central dopamine receptor	Anxiolytic benzodiazepines; muscle relaxants; drugs prescribed to relax people, to calm people down, to relieve anxiety, or to relax muscle spasms	Indications: anxiety and panic disorders Adverse effects: CNS depression (but less compromise in mental status than with sedative–hypnotics), slurred speech, ataxia, incoordination, stupor, coma, cardiac dysrhythmia	Alaprazolam, buspirone, carisoprodol, chlordiazepoxide, clonazepam, clorazepate dipotassium, cyclobenzaprine, diazepam, flunitrazepam, hydroxyzine, lorazepam, meprobamate, oxazepam

CNS, central nervous system; GABA, γ-aminobutyric acid; NSDUH, National Survey on Drug Use and Health.

[a]According to the NSDUH survey.

Table 3 Terminology used to describe nonmedical prescription drug use

Resource	Terminology and definition
Monitoring the Future Survey (MTF)	Misuse: "on your own, that is, without a doctor telling you to take them"
Drug Abuse Warning Network (DAWN)	Abuse or misuse: meets criteria for case types classified as overmedication, malicious poisoning, and other
The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	Nonmedical use: "without a prescription, in greater amounts, more often, longer than prescribed or for a reason other than a doctor said you should use them"
The National Survey on Drug Use and Health (NSDUH)	Abuse: "without a prescription of the individual's own or simply for the experience or feeling the drugs caused"
The National Center on Addiction and Substance Abuse at Columbia University (CASA)	Abuse: "was not prescribed for you or was taken only for the experience or feeling it caused"
Researched Abuse, Diversion, and Addiction-Related System (RADARS)	Abuse: (i) use to get high or (ii) use in combination with other drugs to get high, or (iii) use as a substitute for other drugs of abuse
The National Poison Data System (NPDS)	Abuse: "intentional improper or incorrect use of a substance, likely attempting to gain a high, euphoric effect, or some other psychotropic effect"
Office of Chief Medical Examiner (OCME)	Death from abuse: "accidental"; death was not the intended outcome of the behavior: "unnatural"; death from complications of chronic abuse: "natural"

by the user. For example, nonmedical use of stimulant drugs such as methylphenidate may be legitimized as a study aid, but adverse effects similar to those associated with cocaine use can occur.[5,6]

For individuals in most demographic groups, prescription drugs are easier to obtain than illicit drugs. A survey in Canada compared the characteristics of persons abusing prescription drugs with those who abused heroin. The former were more likely to have both physical health problems and better access to private physicians.[7] According to the National Survey on Drug Use and Health (NSDUH) (2007–2008), among persons of ages 12 years and older who admitted to nonmedical use of analgesics at any time during the previous 12 months, nearly 20% obtained their most recent medication with a physician's prescription.[8] For persons who are inexperienced or uncomfortable with the risks of obtaining illicit drugs from a drug dealer, prescription drugs may be accessed through safer means.[9] For instance, in the same survey, 55.9% of those admitting nonmedical use of

analgesics had obtained the drug on the most recent occasion from a friend or relative. Another 18.0% reported that they had obtained the drug each time from a single doctor, 0.4% bought the drugs through the Internet, and only 4.3% bought the drugs from a drug dealer or other stranger.[8]

Prescription drugs are preferred by persons living in areas in which inexpensive illicit drugs are unavailable. A national survey performed during 2002–2004 found that in the United States prescription drug abuse is concentrated in rural, suburban, and small to medium-sized urban areas. They also found little abuse of prescription drugs in large metropolitan areas in which heroin use in endemic.[10]

Many prescription drugs have chemical structural characteristics that make them difficult to detect by means of a standard urine drug screening. For example, a standard urine immunoassay for opioid drugs of abuse entails an antibody directed against morphine. A common screening immunoassay for drugs of abuse will give positive results for opiates at the threshold morphine concentration of 2,000 ng/ml, depending on the assay and its intent (e.g., medical and occupational). Semisynthetic opioids that are not metabolized to morphine (e.g., hydrocodone, hydromorphone, and oxycodone) demonstrate variable detectability and will generally not test positive at conventional doses, whereas those that are metabolized to morphine (e.g., codeine and heroin) will be readily identified. Synthetic opioids, such as fentanyl, methadone, meperidine, tramadol, and propoxyphene have minimal to nil crossreactivity.[11] Separate testing must be performed in order to provide conclusive evidence that any of these drugs was consumed.[12]

EPIDEMIOLOGY: WHAT IMPACT DOES NONMEDICAL USE OF PRESCRIPTION DRUGS HAVE ON SOCIETY?

Nonmedical use of prescription drugs is an economic, societal, and personal burden, especially if the motive is abuse. According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), substance abuse is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one or more of the following, occurring within a 12-month period:[13]

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home.
2. Recurrent substance use in situations in which it is physically hazardous.
3. Recurrent substance-related legal problems.
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.

In reviewing these criteria, it is evident how prescription drug abuse can lead to problems in health, domestic life, the workplace, and even with the law. National surveys have produced alarming data regarding the increasing nonmedical use of prescription drugs. Separate NSDUH surveys suggest that ~5.2 million individuals reported nonmedical use of prescription

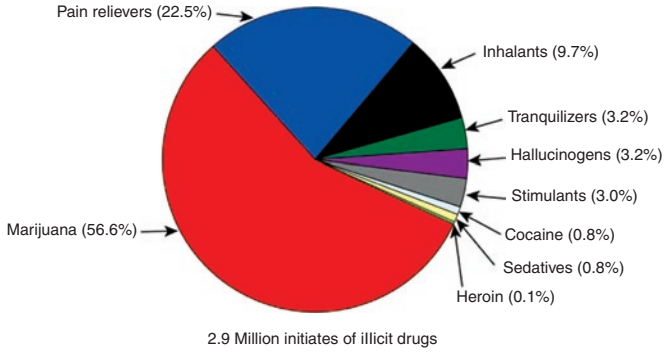

Figure 1 Specific drug used in the initiation of illicit drug use among past-year initiates of illicit drugs aged 12 or older: 2008 (ref. 8). (The percentages do not add to 100% because of rounding or because a small number of respondents initiated multiple drugs on the same day.)

analgesics during the previous month[14] and that abuse of prescription drugs is second only to marijuana use across all age groups (**Figure 1**).[8]

The monetary burden to society of nonmedical use of prescription opioids in the United States was estimated at $9.5 billion for 2005 (ref. 15). The nonmedical use of prescription drugs by individuals can lead to their being arrested for legal offenses, thereby resulting in legal and adjudication costs, correctional facility expenditures, and the use of police resources; it can also lead to increased rates of morbidity and death among workers or incarceration in prison, resulting in decreased productivity and consequent economic loss. In addition, opioid abusers use more medical services and prescription drugs as compared with nonabusers. They are also more likely to be diagnosed as having abused other nonopiod substances and more likely to have episodes of poisoning with such nonopiod substances. In addition, these individuals are more likely to be diagnosed as having related comorbidities (e.g., hepatitis, pancreatitis, and psychiatric conditions).[16]

According to data from the Drug Abuse Warning Network, in 2006, hospitals in the United States received a total of 113 million emergency department (ED) visits, and it is estimated that 1.7 million (1.5%) of these were associated with nonmedical drug use (**Table 4**).[17] A pharmaceutical drug was the sole agent in 28% of the visits, 10% involved alcohol along with pharmaceuticals, 8% involved illicit drugs with pharmaceuticals, and 3% involved illicit drugs with pharmaceuticals and alcohol. According to the Drug Abuse Warning Network, the total number of ED visits attributable to nonmedical use of pharmaceuticals alone increased by 44% from 2004 to 2006; pharmaceuticals used in combination with illicit drug(s) increased by 36% from 2004 to 2006; and pharmaceuticals used in combination with alcohol increased by 22% from 2005 to 2006 (**Table 5**).[17]

In addition to morbidity, mortality is a significant consequence of nonmedical use of prescription drugs. During 1999–2006, the number of deaths due to poisoning in the United States nearly doubled, from ~20,000 to ~37,000. This increase was largely accounted for by deaths involving prescription opioid analgesics, among which those involving methadone accounted for most of the increase. This increase coincided with

Table 4 Drug misuse and abuse in emergency department (ED) visits in the United States, by type of drug involvement: 2006 (ref. 17)

Drug involvement[a]	Estimated visits[b]	Percent of visits (%)	Relative SE (RSE)	95% Confidence interval	
				Lower bound	Upper bound
All types of drug misuse/abuse	1,742,887	100	8.5	1,451,086	2,034,688
Illicit drugs only	536,554	31	18.3	343,920	729,189
Alcohol only (age <21)	126,704	7	12.5	95,766	157,642
Pharmaceuticals only	486,276	28	5.8	430,721	541,832
Combinations					
Illicit drugs with alcohol[c]	219,521	13	13.5	161,230	277,812
Illicit drugs with pharmaceuticals	142,535	8	10.4	113,561	171,510
Alcohol with pharmaceuticals	171,743	10	5.8	152,240	191,246
Illicit drugs with alcohol and pharmaceuticals	59,553	3	9.8	48,079	71,028

[a]The classification of drugs used in Drug Abuse Warning Network (DAWN) is derived from the Multum Lexicon, ©2007, Multum Information Services, Inc. The classification was modified to meet the unique requirements of DAWN. The Multum Licensing Agreement governing use of the lexicon can be found on the Internet at http://www.multum.com. [b]These are estimates of ED visits based on a representative sample of nonfederal, short-stay hospitals with 24-h EDs in the United States. [c]DAWN excludes alcohol-only visits for adults. Alcohol, when present with other drugs, is included for all ages.

Source: Office of Applied Studies, DAWN, Substance Abuse and Mental Health Services Administration, 2006 (March 2008 update).

Table 5 Drug misuse and abuse in emergency department (ED) visits in the United States, by type of drug involvement: 2004, 2005, and 2006 (ref. 17)

Drug involvement[a]	Estimated visits[b]			Percent change[c]	
	2004	2005	2006	2004, 2006	2005, 2006
All types of drug misuse/abuse	**1,619,054**	**1,616,311**	**1,742,887**		
Illicit drugs only	502,136	517,558	536,554		
Alcohol only (age < 21)	150,988	110,599	126,704		
Pharmaceuticals only	336,987	444,309	486,276	44%	
Combinations					
Illicit drugs with alcohol	338,638	221,823	219,521		
Illicit drugs with pharmaceuticals	105,017	127,245	142,535	36%	
Alcohol with pharmaceuticals	139,716	140,275	171,743		22%
Illicit drugs with alcohol and pharmaceuticals	45,571	54,500	59,553		

[a]The classification of drugs used in Drug Abuse Warning Network (DAWN) is derived from the Multum Lexicon, ©2007, Multum Informations Services, Inc. The classification was modified to meet the unique requirements of DAWN. The Multum Licensing Agreement governing use of the lexicon can be found on the Internet at http://www.multum.com. [b]These are estimates of ED visits based on a representative sample of nonfederal, short-stay hospitals with 24-h EDs in the United States. [c]This column includes statistically significant ($P < 0.05$) increases or decreases between estimates for the periods shown.

Source: Office of Applied Studies, DAWN, Substance Abuse and Mental Health Services Administration, 2006 (3/2008 update).

a nearly fourfold increase in the use of prescription opioids nationally.[18,19]

OBSTACLES TO UNDERSTANDING THE MAGNITUDE OF THE CRISIS

There are obstacles that limit our understanding of the magnitude of the prescription drug abuse crisis. For example, the lack of consensus on definitions produces surveys that use incompatible terms to assess nonmedical use of prescription drugs (**Table 3**).[2,20] Detailed data collection focusing on the means by which a prescription drug is obtained, the motive for obtaining it, dosing, duration of regimen, coingestion of other substances, route of administration, and diversion is necessary to identify nonmedical use. This must be put into perspective and compared with the details of the original prescription and the physician's initial intention in making the prescription. On the basis of documentation in medical records alone, it is almost impossible to distinguish whether these drugs were obtained by filling legitimate prescriptions to treat medical conditions or for nonmedical use with the specific intent to abuse.

The true number of deaths caused by nonmedical use of prescription drug is not known with certainty. The cause of death in poisoning-related fatalities is difficult to determine, and agreement between experts, such as medical examiners and medical toxicologists, is often less than ideal, especially in cases of chronic toxicity.[21] Although a death can be associated with the use of prescription drugs, a conclusive delineation of the prescription drug as the causal agent is complicated by drug tolerance, concomitant exposures, and the difficulty in interpreting postmortem concentrations in isolation.

OVERVIEW OF THE USE OF NONMEDICAL PRESCRIPTION DRUGS AS CATEGORIZED BY DRUG CLASS

Opioids

Opioids are the class of drugs that are most frequently used for nonmedical purposes.[22] Prescription opioids have surpassed marijuana as the most common drug for individuals initiating drug abuse,[14] and they account for 33% of ED visits for problems related to nonmedical drug use. Nonmedical use of hydrocodone and hydrocodone combinations accounted for 57,550 ED visits, oxycodone and oxycodone combinations for 64,888 visits, and methadone for 45,130 ED visits in 2006 (ref. 17).

According to data from medical examiners and the records of Prescription Drug Monitoring Programs (PDMPs) and opioid treatment programs, the majority of drug overdose–related deaths in West Virginia in 2006 were associated with nonmedical use and diversion of prescription opioid analgesics.[23] The high prevalence of a substance abuse history in decedents and their lack of an appropriate prescription suggest that most of these deaths were related to nonmedical use of prescription drugs.[24]

The term "opiate" refers to a drug derived from opium poppy, such as morphine and codeine. "Opioid" is a much broader term, encompassing opiates and other agents capable of binding to the μ-opioid receptor and producing morphine-like clinical effects. Semisynthetic opioids, such as oxycodone, are derived by modification of an opiate. Synthetic opioids, such as fentanyl and methadone, are not derived from an opiate but also bind to and are agonists at the μ-opioid receptor. Prescription opioids available in the United States include morphine, methadone, codeine, hydrocodone, oxycodone, propoxyphene, fentanyl, tramadol, and hydromorphone.

The potential of an opioid to produce euphoria is related to the efficiency with which it penetrates the blood–brain barrier and its binding characteristics at the μ-opioid receptor. Distribution into the central nervous system is facilitated by organic functional groups that enhance lipid solubility. For this reason, heroin and methadone rapidly attain higher concentrations in the central nervous system than morphine does. By binding to the μ-opioid receptors, opioid agonists enable release of dopamine in the mesolimbic system to produce euphoria.[25,26] The link between pleasurable effects and the potential to produce addiction, and therefore toxicity, is well described, whereas analgesic potency alone may not accurately reflect abuse liability.[27]

Hydrocodone (dihydrocodeinone) is a semisynthetic opioid receptor agonist. Although hydrocodone itself is listed under Schedule II, it is approved by the US Food and Drug Administration only for use in combination formulations with acetaminophen, ibuprofen, and aspirin, all of which are listed under Schedule III. Hydrocodone-acetaminophen has been by far the most commonly prescribed analgesic of any category in the United States over the past 5 years.[28] In 2008, it was the top-selling generic drug, generating 1.8 billion retail dollars in gross sales.[29] This is a 2.7% increase from 2007, in addition to a 6.9% increase from 2006 (ref. 30). Although a survey of schoolchildren in grades 8, 10, and 12 in the United States reported stable or declining rates for the use of most illicit drugs, nonmedical use of hydrocodone-acetaminophen showed a rise in two out of three. In the survey, nearly 10% of all the twelfth-graders were found to have used hydrocodone-acetaminophen nonmedically.[31]

Only enteral forms (i.e., pills) of hydrocodone and many other opioids are available. Ingestion of hydrocodone is a sufficient route for most abusers. However, insufflation is preferred by some, who report a shorter onset time for euphoria, although the effect is for a shorter duration. Insufflation of hydrocodone has been reported to result in nasal obstruction, fungal infections, and palatal and septal perforation.[32,33]

Intravenous injection of crushed or dissolved pills in order to increase the pleasurable effect is associated with significant adverse effects. These are caused by inactive excipients that are harmless when ingested but dangerous when injected directly into the bloodstream. Prescription drug abusers who inject these medications intravenously may experience declining pulmonary function, pulmonary hypertension, micronodular pulmonary disease, and death secondary to the embolization of the insoluble excipient.[34–36]

Other measures utilized to enhance the euphoria associated with the use of hydrocodone include coadministration with grapefruit juice. Hydrocodone undergoes oxidative metabolism mediated by hepatic cytochrome P450 (CYP) 2D6 to hydromorphone and by hepatic CYP3A4 to norhydrocodone.[37] Hydromorphone has a μ-receptor binding affinity that is 30-fold that of the parent compound, whereas the norhydrocodone metabolite is inactive.[38] Therefore, inhibition of CYP3A4 with grapefruit juice may result in preferential increase in CYP2D6-mediated metabolism to hydromorphone.

The potential to abuse hydrocodone is limited by the fact that it is available only in combination formulations. Some abusers attempt to isolate the hydrocodone component through a process known as cold-water extraction. In this process, the pill is pulverized and dissolved in warm water, which is then rapidly cooled. This precipitates the acetaminophen, ibuprofen, or aspirin component of the pill because these components are insoluble in cold water. The solute is then filtered out and discarded, and the dissolved hydrocodone is ingested or injected intravenously.

Oxycodone is another Schedule II semisynthetic μ-opioid agonist. The widespread abuse of oxycodone in rural America has caused the media to term it "hillbilly heroin"; the epidemic use of oxycodone in those areas was accompanied by a rise in opioid-related deaths.[19,39] Oxycodone is also metabolized by CYP3A4 and CYP2D6 to noroxycodone and oxymorphone, respectively.[40] Although the oxymorphone metabolite has a μ-receptor agonist activity that is 14-fold that of the oxycodone parent compound, it is the parent oxycodone that is primarily responsible for the analgesic effects.[41]

Oxycodone is available only in oral formulation, both alone and in combination with nonopioid analgesics. A controlled-release oxycodone formulation is designed to improve compliance and convenience. However, individual tablets of controlled-release oxycodone contain larger amounts of oxycodone than the immediate-release formulation, and the crushing of controlled-release oxycodone tablets results in the rapid release of absorbable oxycodone. Intravenous injection of

crushed and solubilized oxycodone results in a mean normalized area under the concentration–time curve that is twice that for a similar quantity of oral oxycodone.[42,43] The abuse of crushed and solubilized oxycodone as rectal enemas may result in variable avoidance of first-pass hepatic metabolism; however, the bioavailability is essentially the same.[44]

Lawsuits that have been settled suggest that controlled-release oxycodone was misrepresented and misleadingly promoted as having reduced abuse liability. The label for controlled-release oxycodone (OxyContin) now includes a black-box warning of the potentially lethal consequences of crushing the controlled-release tablets and injecting or snorting the contents.[45,46]

Methadone. Methadone is a synthetic long-acting Schedule II opioid. It is generally manufactured as a racemic mixture of (R)- and (S)-methadone; (R)-methadone accounts for most, if not all, of the opioid effects. The primary metabolism of methadone is *N*-demethylation to 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium, which is further *N*-demethylated to 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline.[47] Demethylation is catalyzed predominantly by CYP3A4.[48] Serum concentrations of methadone can be increased or decreased by inhibitors or inducers of CYP3A4, respectively. In addition, there is evidence for varied levels of participation of other CYPs (2B6, 2C8, 2C9, 2C19, and 2D6) in the metabolism of methadone.[49,50]

Methadone is utilized medically not only as an analgesic but also in opioid detoxification and maintenance programs. Methadone reduces criminal behavior and mortality associated with heroin use and decreases disease transmission related to intravenous drug use, notably hepatitis and HIV. However, diversion of methadone from maintenance programs occurs, and participants report that illicit diverted methadone is readily available at low cost. Nonmedical use of methadone may surpass that of oxycodone in some US states. (The remaining references for this article may be found in the **Supplementary References** online.)

As with all opioids, methadone overdose carries the risk of respiratory depression. In addition, it is associated with life-threatening dysrhythmias such as torsade de pointes. The (S)-methadone enantiomer inhibits the cardiac voltage-gated potassium channel, which can cause prolongation of the QT interval. Given that these are dose-dependent effects, methadone abusers are at greatest risk of morbidity and mortality.

The majority of methadone-related deaths occur in persons who are not enrolled in methadone treatment programs.[24] Methadone-related deaths among patients who are legitimately enrolled in methadone maintenance programs occur mostly within the first 30 days of treatment initiation. This may be attributable to the long delay in attaining steady-state tissue concentrations in combination with therapeutically escalating doses.[24] In addition, increases in episodes of methadone-related deaths may be disproportionately high in comparison with the increase in patients enrolled in methadone maintenance programs or the amount of methadone retailed to opioid treatment programs during that period. This suggests that many patients obtain methadone from sources other than opioid treatment programs, including illicit sources.

The estimate of deaths that can truly be attributed to methadone use is difficult to determine. Postmortem identification of methadone and/or its metabolite may be an incidental finding because concentration values alone cannot be interpreted in isolation. Knowledge of the subject's prior opioid use (e.g., opioid tolerance), concomitant exposures, and medical history is also required.

Fentanyl. Fentanyl is a highly potent, synthetic, Schedule II μ-opioid receptor agonist. It is metabolized primarily by CYP3A4 through oxidative dealkylation to norfentanyl. Concomitant administration of a CYP3A4 inhibitor along with fentanyl may increase plasma fentanyl concentrations and increase the risk for adverse effects. Fentanyl is commercially available in parenteral, transmucosal (patch), buccal (lozenge), and inhalational delivery formulations. The lozenge formulations are intended to be absorbed transmucosally. Fentanyl is not intended to be swallowed because the slow gastrointestinal absorption and high first-pass metabolism would render it inefficient in providing analgesia.

For the treatment of patients with chronic pain, a transdermal fentanyl device (patch) is available. The reservoir skin patch was introduced initially, followed by a matrix delivery system that has since become more popular. The reservoir skin patch consists of four functional layers. The first (outermost) layer is an impermeable one, to protect the patch from the environment, and the second is the drug reservoir containing fentanyl and a small amount of ethanol (to act as a permeation enhancer) combined with hydroxycellulose gel. The third layer regulates the rate of delivery of the fentanyl ethanol mixture to the skin. The fourth layer, closest to the skin, is a silicone skin adhesive that secures the transdermal delivery device to the skin surface. In the matrix delivery system, the fentanyl is incorporated into the adhesive itself, and the rate-limiting membrane is omitted. The pharmacokinetic profiles of the two formulations are reportedly similar, but the matrix formulation may be more comfortable to wear. There may be greater variability in the rate of fentanyl absorption from the matrix, which can result in highly variable plasma fentanyl concentrations. Even after use, the reservoir and the matrix will still contain a significant amount of fentanyl that can be exploited for abuse.

Fentanyl patches have been manipulated for abuse in many ways. Application to a mucous membrane (e.g., the oral, rectal, and vaginal mucosa), excessive application, or chewing the patch are reported. The fentanyl-containing gel can be extracted from the reservoir and injected intravenously. The patch can also be pyrolyzed and "smoked" or steeped much like a tea bag. Abuse of fentanyl patches may lead to life-threatening adverse events and fatality.

Nonmedical use of fentanyl, alone or in combination with other products, accounted for ~16,012 ED visits in 2006. The corresponding figures for 2004 and 2005 were 9,823 and 11,211, respectively, showing a steady year-on-year increase.[17] There have also been an increasing number of reports of fentanyl-related deaths, almost all of them associated with abuse of the transdermal patch. Consequently, in July 2005, the US Food and Drug Administration issued a strongly worded public health

advisory listing specific concerns with the use of transdermal fentanyl.

Sedatives and tranquilizers

Benzodiazepines. Benzodiazepines are used primarily as sedatives or anxiolytics, although they have other uses, including as hypnotics and anticonvulsants. Benzodiazepines achieve their effect by enhancing the function of the neuronal γ-aminobutyric acid–mediated chloride channels. However, unlike other sedative–hypnotics, benzodiazepines do not open the γ-aminobutyric acid–chloride channels independently of this neurotransmitter, providing them with a unique safety margin even with overdose. They are not known to cause any specific organ-system injury even with long-term use.

Benzodiazepine abuse contributes significantly to prescription drug abuse. ED visits involving nonmedical use of benzodiazepines increased 36% from 2004 to 2006 (ref. 17).

Abuse of benzodiazepines tends to occur in conjunction with abuse of other medications. Death from benzodiazepine overdose alone is a rare event; most often, a combination of benzodiazepine with other sedative–hypnotics and/or ethanol is found to be the cause. Opioid-dependent patients are known to abuse benzodiazepines for complementary psychoactive effects. Most benzodiazepine abusers are young, male, and likely to abuse other drugs as well.

Alprazolam. Alprazolam is a Schedule IV triazolobenzodiazepine prescribed for the treatment of anxiety and panic disorders. It ranked 25th in the list of top 200 generic drugs with respect to gross retail sales revenue ($467,609,000) in 2008. The extensive prescription of alprazolam may contribute to the ease of obtaining it for the purpose of abuse.[29] It has been suggested that alprazolam may be relatively more toxic in overdose than other benzodiazepines and associated with longer durations of intoxication and higher admission rates in intensive care units. Alprazolam abuse and dependence are most common among individuals who abuse other substances such as cocaine and methadone. In a pilot survey, most of the 46 youths attending an inpatient drug treatment program perceived the use of alprazolam as being associated with extensive social reinforcement. In this study, a majority stated that medical professionals (doctors and pharmacists) were the greatest facilitators in obtaining alprazolam. In an interview of benzodiazepine abusers among methadone maintenance program patients in Baltimore, New York City, and Philadelphia, alprazolam was ranked among the top three benzodiazepines in terms of the "high" produced. However, overall, the literature does not consistently support the view that the potential for alprazolam abuse is greater than for abuse of other benzodiazepines.

Clonazepam. Clonazepam is a Schedule IV benzodiazepine used as monotherapy for the short-term treatment of panic disorder. It may have a role, in association with selective serotonin reuptake inhibitors, in the treatment of depression or bipolar disease. Unlike other benzodiazepines, clonazepam has serotonergic properties, which may contribute to its psychotropic and antimyoclonic effects.

A study in France to assess the magnitude of clonazepam abuse observed an increase of 82% in clonazepam users between 2001 and 2006. An increasing proportion of these users (0.86–1.38%) had multiple prescribing physicians, different pharmacies, and higher benzodiazepine dosage.

Stimulants

"Stimulants" refers to medications that enhance alertness by increasing circulating catecholamines, particularly dopamine, norepinephrine, and, at higher doses, serotonin. Stimulants may induce the release of catecholamines and may block their reuptake by competitive inhibition. Illicit stimulants include cocaine, methylenedioxymethamphetamine, and methamphetamine. Amphetamines are Schedule II prescription stimulant medications and carry a similar potential for abuse (**Table 2**). The most commonly abused prescription stimulants include amphetamine/dextroamphetamine and methylphenidate. There are few medical indications for amphetamines: these include narcolepsy, short-term weight loss, and treatment of attention-deficit/hyperactivity disorder. Nonmedical use of these medications produces anorectic effects when misused for weight loss, a heightened sense of attention, and wakefulness when misused for academic performance enhancement, and hallucinations, euphoria, and altered perception when abused.

The abuse of prescription stimulants has become common among students ever since these drugs were introduced for the treatment of attention-deficit/hyperactivity disorder. The conceptualization of this condition as a lifelong disorder has increased the duration of treatment with methylphenidate and also increased the number of prescriptions in circulation. The Drug Enforcement Agency reported a 600% increase in methylphenidate prescriptions from 1990 to 1995. Nonmedical use of stimulant medication is most common among college-aged students (18–24 years). A survey of students taking methylphenidate for attention-deficit/hyperactivity disorder found that 16% of the respondents had been asked by other students to trade, sell, or give them their stimulant medication. In a survey of university students, 3% of survey respondents anonymously reported nonmedical use of methylphenidate within the past year. Among this population, the most common motive for nonmedical use of prescription stimulants was to increase their focus and concentration in order to enhance academic performance.

Like other prescription drugs, not only can methylphenidate be abused orally but it can also be crushed and insufflated intranasally or dissolved for injection. Delivery of the drug to the central nervous system is rapid when abused intranasally or intravenously, and therefore these routes are preferred by those abusing stimulants for their euphorigenic effects. The oral route is preferred by those misusing the stimulant to enhance wakefulness and maintain alertness.

The adverse effects of stimulant abuse can resemble those associated with cocaine and include cardiovascular effects such as hypertension, tachycardia, vasospasm, and dysrhythmia. In addition, neurologic and psychiatric disturbances may

occur, such as headaches, seizures, tics, tremor, hyperthermia, serotonin syndrome, hallucinations, anxiety, and paranoia.[6]

Anesthetics

Anesthetics induce reversible changes in the perception of and reaction to pain and reversible loss of responsive reflexes. When the anesthetic effects wear away, there is amnesia to events in the immediate past. Anesthetics encompass inhalational, intravenous, subcutaneous, intramuscular, topical, and oral agents. They may be used in combinations at varying doses to produce the desired psychoactive effects along a continuum of sedation and analgesia. The effects of anesthetics range from general anesthesia, rendering the patient unconscious, unarousable to painful stimuli, and unable to maintain an airway independently; to minimal sedation (anxiolysis), with normal response to verbal commands but impairment of concentration, memory, and coordination. Anesthetics interact with many neuronal proteins to induce these effects, and numerous ion channels contribute to their mechanisms of action.

Although abuse of anesthetic agents does occur, it contributes to a very small portion of prescription drug abuse. Although they are available by prescription, many of these agents are administered through intravenous or inhalational routes and generally require the presence of a physician for monitoring and administration. The indication for prescribing an anesthetic agent would be rare. Abuse of anesthetic drugs is more likely to be identified among the health-care professionals who have access to anesthetics in their daily clinical practice. Reports of anesthetic abuse usually relate to anesthesiologists, in whom the rate of substance abuse disorders is thought to be higher than in other physicians. A survey of 126 academic anesthesiology training programs carried out in 2008 reported that 22% of the departments had recorded at least one incident of inhalational anesthetic abuse. However, opioids rather than anesthetics remain the drug of choice among anesthesiologists who abuse medications.

Ketamine. Ketamine is a dissociative anesthetic that produces catalepsy, catatonia, and amnesia, but not necessarily complete unconsciousness. It is a Schedule III, highly controlled pharmaceutical substance that is widely utilized in hospitals and veterinary clinics. Abusers obtain it through diversion from legitimate suppliers of the drug rather than through prescriptions in circulation. Ketamine induces altered perception of auditory, visual, and pain stimuli, resulting in a general lack of responsive awareness. It is thought to produce most of its effects through antagonism at *N*-methyl-D-aspartate receptors. It is a white powder that is soluble in water and alcohol and can be snorted, injected, applied on smokable materials, or consumed in drinks. At low doses, the sympathomimetic properties predominate, resulting in enhancement of catecholamine (particularly dopamine) activity. At higher doses, the psychedelic properties predominate, producing altered perception of surroundings, color, sound, time, and body distortion. This may include a sensation of feeling light or an out-of-body experience called a "K-hole." These effects may contribute to its preferential abuse in dance clubs, which have loud music and flashing lights. The potential adverse effects observed with acute intoxication are depression of the central nervous system, severe psychomotor agitation, rhabdomyolysis, abdominal pain, and lower urinary tract symptoms. The potential adverse effects with chronic use include psychosis, psychomotor and cognitive impairment, and, ultimately, dependence.

Propofol. Propofol (Diprivan) is utilized for sedation before medical or surgical procedures and as an anesthetic induction agent for surgery. It is ideal for procedures in which rapid awakening is desirable. Diprivan is currently not a controlled substance and is unscheduled. The potency and narrow therapeutic index of propofol leave little margin for error, and an overdose can produce unconsciousness and apnea. Like benzodiazepines and alcohol, propofol alters the γ-aminobutyric acid–activated opening of chloride channels, resulting in hyperpolarization of cell membranes. This results in euphoria, sedation, and ventilatory depression.

Reports of patients experiencing addiction after treatment with propofol are very limited. Although reports are emerging regarding propofol abuse for recreational purposes by medical professionals and deaths resulting from such abuse, these are rare and mostly among anesthesiologists. A 2007 e-mail survey of 126 academic anesthesiology training programs noted an incidence of propofol abuse of 10/10,000 anesthesia providers per decade. In June of 2009, the report of celebrity Michael Jackson's death involving Diprivan raised concerns regarding propofol abuse, but the details are not readily available to the public.

WHAT IS BEING DONE TO ADDRESS NONMEDICAL USE OF PRESCRIPTION DRUGS

The Diversion Control Program of the Drug Enforcement Administration oversees and regulates the legal manufacture and distribution of controlled pharmaceuticals. Per the 2006 testimony of the deputy assistant administrator of the Office of Diversion Control, increased resources and manpower were dedicated to investigating the diversion of controlled pharmaceuticals.

In 2005, the National All Schedules Prescription Electronic Reporting (NASPER) Act was passed and signed into law. This act authorized the use of $US60 million for fiscal years 2006–2010 to create federal grants at the US Department of Health and Human Services to establish and improve PDMPs. PDMPs were developed for the purpose of identifying and preventing prescription drug diversion. As of 2006, 38 states in the United States had PDMPs. They serve to provide information regarding illicit use and abuse to physicians, pharmacists, and the public. However, the design of these programs varies from state to state, and most are limited in the extent to which they can provide timely access to information so that physicians can proactively reduce or prevent nonmedical use of prescription drugs, including diversion.

Multiple federal, state, and local organizations (**Table 1**) actively collect and publish data that serve to educate authorities, physicians, pharmacists, and the public regarding trends and demographics related to the nonmedical use of prescription drugs. Some studies, such as the Monitoring the Future Survey (MTF) of the Substance Abuse and Mental Health Services

Administration, collect data about narrow populations such as school-aged children, whereas others, such as the Drug Abuse Warning Network, have large catchments.

The properties of a drug, such as time to onset of effects, the method of administration, and maximum plasma concentrations after administration, may all contribute to its abuse. Pharmaceutical technology can help to combat prescription drug abuse by synthesizing tamper-resistant formulations that will enable the drug to be used for the therapeutic indication while making it difficult to manipulate or modify for abuse purposes. An example is the creation of an abuse-deterrent formulation of long-acting oxycodone. This formulation cannot be readily extracted, broken, chewed, or crushed. Another example is the addition of naloxone/naltrexone or opioid receptor antagonists to oral buprenorphine or morphine, respectively, to deter abuse.

PSEUDOADDICTION

The campaigns against prescription drug abuse are paralleled by the arguments for addressing the reality that pain is currently undertreated. The rise in the number of opioid analgesic prescriptions is caused not only by more drugs being diverted for abuse but also by a rise in the number of legitimate prescriptions for the treatment of pain. Undertreatment of pain is considered by many to be a health problem in the United States and has led to the development of initiatives to address the multiple barriers to adequate pain control. Several patient advocacy groups and professional organizations are focusing on improving the management of pain. Consequently, numerous clinical guidelines have also been developed, including those adopted by the Federation of State Medical Boards.

CONCLUSION

Health-care professionals are continuously challenged with the dilemma of adequately treating legitimate pain while trying not to contribute to nonmedical use of prescription drugs. Understanding that nonmedical use of prescription drugs encompasses behaviors other than abuse may further aid in its identification and deterrence. Publications and reports from various data collection sources can inform health-care professionals about the current status of nonmedical prescription drug use in their communities. Nonetheless, the limitations in obtaining detailed data, the lack of consensus definitions, and the fact that surveys often employ incompatible terms should be taken into account when interpreting the data. Information regarding the prescription drugs that are highly abused, the ways in which they are abused, and the consequences of such abuse may help health-care professionals identify and treat prescription drug abusers. Physicians and clinical pharmacologists should be familiar with their state's PDMPs and be able to report and access information regarding nonmedical prescription drug use in the population they serve. Further development of abuse-deterrent formulations may help to lower the incidence of nonmedical use of prescription drugs. Prescription drug abuse is a crisis that affects not only clinical pharmacologists and physicians but also law-enforcement agencies, government legislation and funding, pharmaceutical technology, domestic life, and the workplace. Ultimately, the efforts of health-care professionals alone cannot adequately address the crisis; a collaborative effort by all the stakeholders is required.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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