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The Burden of the Nonmedical Use of Prescription Opioid Analgesics

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ABSTRACT

An increase in the prescribing of opioids over the past several years often has been perceived as the primary reason for the increase in the nonmedical use of prescription opioids. Determining the prevalence of this illicit use has been difficult, because of varied methodologies and terminologies that are used to estimate the number of people directly contributing to or affected by this burden. Despite these discrepancies, the findings from several nationally recognized surveys have demonstrated that the prevalence of nonmedical prescription opioid use is indeed significant and has been increasing in recent years. The considerable burden on society imposed by misuse and abuse of these drugs is largely due to the monetary costs associated with nonmedical use (e.g., strategies implemented to prevent or deter abuse, treatment programs for misusers, etc.), decreased economic productivity, and the indirect effect on access to appropriate health care. However, using various nonpharmacologic and pharmacologic approaches to treat patients who use prescription opioids illicitly can decrease its overall prevalence and associated impact, with the development of novel opioid formulations designed to reduce nonmedical use providing valuable clinical tools as part of an overall risk management program. In addition, prescription monitoring programs are a prevalent drug control system designed to identify and address abuse and diversion of prescription medications, including opioids. Such resources, along with an accurate understanding of the problem, extend greater hope that the public health challenge of nonmedical prescription opioid use can be effectively mitigated.

Key Words. Abuse; Addiction; Nonmedical; Pharmacoeconomic; Opioid; Prescription

Introduction

The nonmedical use of prescription opioid analgesics is an ongoing challenge [1]. Its overall burden to society has been difficult to quantify, though it manifests itself in several ways, including the physical and psychological consequences of addiction and the effect of illicit use on physicians' prescribing habits [2]. The financial burden associated with such misuse and abuse is significant, especially when such factors as associated health care and workplace costs and the cost of treatment for patients with opioid addiction are considered [3]. Understanding the magnitude of nonmedical prescription opioid use is necessary when attempting to define its burden, but is compromised by inconsistent use and operationalization of terminology associated with addiction-related concepts. Nevertheless, such information can facilitate exploration of the different motives for and mechanisms of nonmedical opioid use and help come to terms with its varied pharmacoeconomic costs. A concerted accumulation of data based on similar conceptualization and quantification of nonmedical use of prescription opioids also

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can play a role in better utilizing available pharmacologic and nonpharmacologic treatment options, as well as state drug control strategies, designed to reduce or prevent this public health problem.

Defining the Burden of Nonmedical Prescription Opioid Use

National Surveys of Nonmedical Prescription Opioid Use

A number of national surveys attempt to estimate the prevalence of the nonmedical use of both illicit and prescription drugs—including opioid analgesics—in the general population. The surveys tend to be methodologically dissimilar and use inconsistent language to describe and measure nonmedical drug use, which can make it difficult to reach firm conclusions about the incidence, prevalence, and consequences of this public health problem. A difficulty quantifying the phenomenon can hinder the development of effective interventions to minimize illicit drug use (discussed in more detail later). Several of these surveys are described below.

National Survey of Drug Use and Health

The National Survey of Drug Use and Health (NSDUH) (previously called the National Household Survey on Drug Abuse), begun in 1971, is currently sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) and is the federal government's primary source of national data on the use of alcohol, tobacco, and illicit substances [4]. The NSDUH annually obtains questionnaire-based interviews from nearly 68,000 individuals in three age groups: youths (12–17 years), young adults (18–25 years), and adults (26 years or older) [4]. Samples from these age populations for each state and the District of Columbia are used to generate individual, state, and national estimates of drug use. Illicit use of prescription pain relievers is assessed by the following question: "How long has it been since you last used any prescription pain reliever that was not prescribed for you, or that you took only for the experience or feeling it caused?" [4]. Although intended to provide an indication principally of abuse, this question also can capture those who use others' prescription pain relievers for medical reasons (medical misuse); although unlawful, this behavior is conceptually distinct from "abuse" and should be addressed through other means. As a result, it is not possible to draw a straightforward interpretation of this metric, which includes both people seeking a "high" as well as those seeking pain relief, albeit through inappropriate methods. It should be noted that the category of "pain relievers" comprises approximately 30 separate medications, including scheduled opioid analgesics (e.g., fentanyl, hydrocodone-combination products, methadone, morphine, oxycodone and oxycodone-combination products, and propoxyphene) and federally nonscheduled drugs such as tramadol [4].

Important methodological changes in the NSDUH—including the decision to provide incentives to participants and an increased adherence to study protocol through monitoring and retraining of interviewers—have occurred over time, so results obtained since 2002 cannot be compared with earlier survey findings [5]. Evaluating NSDUH results from 2002 to 2007, the latest available, shows a significant rise in the number of people reporting nonmedical use of pain relievers during the past month [4]. Throughout this period, past-month nonmedical use increased from 4.4 million to 5.2 million individuals [4].

Monitoring the Future

The Monitoring the Future (MTF) survey, begun in 1975, is conducted by the University of Michigan Institute for Social Research and is funded by the National Institutes of Health's National Institute on Drug Abuse [6,7]. The annual MTF survey is specifically designed to measure reported use of both licit and illicit substances by adolescents and young adults. The MTF assesses changes over time in response to questionnaires from representative samples of secondary school students (in grades 8, 10, and 12), college students, and adults younger than 45 years of age. The survey uses a sequential-cohort design, meaning that college students and adults who complete the questionnaires are from previous high school samples that have been tracked over time [7].

In 2007, 48,025 students from 403 public and private secondary schools, as well as approximately 15,000 college students and adults, were surveyed [6,7]. Like the NSDUH, the MTF essentially measures nonmedical use of prescription medications, asking surveyed individuals how many times they had used different classes of drugs "without a doctor telling you to take them." One of the drug classes measured is "narcotics other than heroin," which includes the ability to specify prescription opioids such as

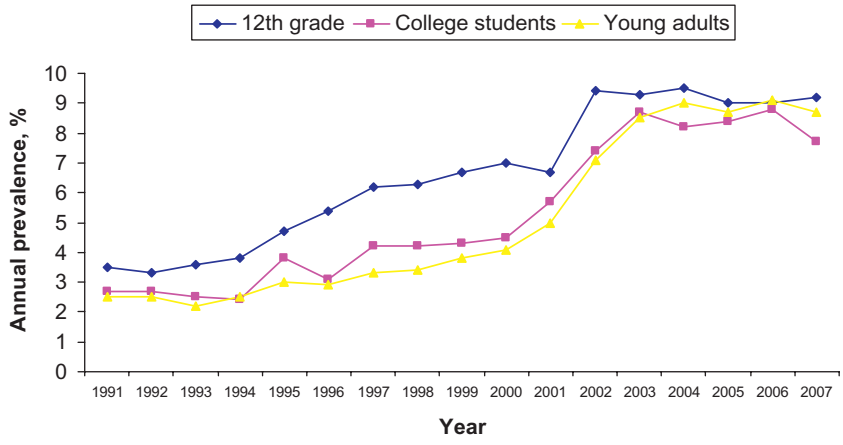

Figure 1 Annual prevalence of nonmedical non-heroin narcotic use: 1991–2007. *Source:* Johnston et al. [7].

OxyContin (oxycodone HCl controlled release; Purdue Pharma L.P., Stamford, CT), Percocet (oxycodone HCl/acetaminophen; Endo Pharmaceuticals, Inc., Chadds Ford, PA), and Vicodin (hydrocodone/acetaminophen; Abbott Laboratories, Chicago, IL), as well as illicit compounds such as opium [6]. Like the NSDUH, this survey combines abuse with self-initiated, but nevertheless unlawful, medical use.

As shown in Figure 1, the annual prevalence of nonmedical non-heroin narcotic use among 12th graders increased by 263% from 1991 (3.5%) to 2007 (9.2%) and has been historically higher than that reported by both college student and young adult respondents [6]. Even larger percentage increases over the same period were noted in college students (up 285%) and young adults (up 348%) [7]. In recent years there has been a near convergence among the three age categories, as the steady rise in the nonmedical use of non-heroin narcotics among 12th grade students seems to have leveled off since 2001. However, this dramatic increase in the nonmedical use of non-heroin narcotics remains unique, with no class of illicit drug demonstrating increases at a comparable level; indeed, several types of illicit substances, including inhalants (glue, solvents, butane, and aerosols, etc.), lysergic acid diethylamide, and phencyclidine, showed declining use over the same period [7]. It must be noted that an updating of the list of examples in the questionnaire assessing use of non-heroin narcotics in 2002 may have contributed to the increase in prevalence. The list of examples of non-heroin narcotics other than heroin replaced Talwin (pentazocine; Sterling Drug Company, Rensselaer, NY), laudanum, and paregoric—all of which had negligible rates of use by 2001—with Vicodin, OxyContin, and Percocet [6].

Unlike the NSDUH, the MTF survey also provides information regarding the frequency of use by the respondents. For instance, in 2007, half of the 12th graders who reported using non-heroin narcotics nonmedically in the past month (3.8% of all those surveyed) used them one to two times during that period [6]. Fewer than 0.6% of respondents reported using non-heroin narcotics 10 or more times in the previous month [6]. This suggests that non-heroin narcotic use in teenagers is prevalent at a population level but infrequent for many on a personal level, perhaps indicative of periodic experimental or recreational use.

Drug Abuse Warning Network

Initiated in 1972, the Drug Abuse Warning Network (DAWN) is now operated by SAMHSA [8,9]. The DAWN is a public health surveillance system using a probability sample and statistical weighting methodology to estimate the number of emergency department (ED) visits related to substance use, misuse, and abuse, as well as the drugs involved in these visits [9]. However, the relationship between a visit and drug use is not necessarily causal, because the drug may or may not have caused the event generating the ED visit [9]. Also, the reason for a drug's identification during an ED visit is not specified because the motivation for using each drug is not assessed [9]. The DAWN system defines its outcome measure broadly, encompassing any use that is considered to be "nonmedical," including suicide attempt, adverse reaction, overmedication, malicious poisoning, and accidental ingestion [9]. Thus, for example, ED patients who have been found to take prescribed medication in a manner other than directed for management of suboptimally treated pain are indistinguishable from those who took the drug to obtain a euphoric effect. As a result, as

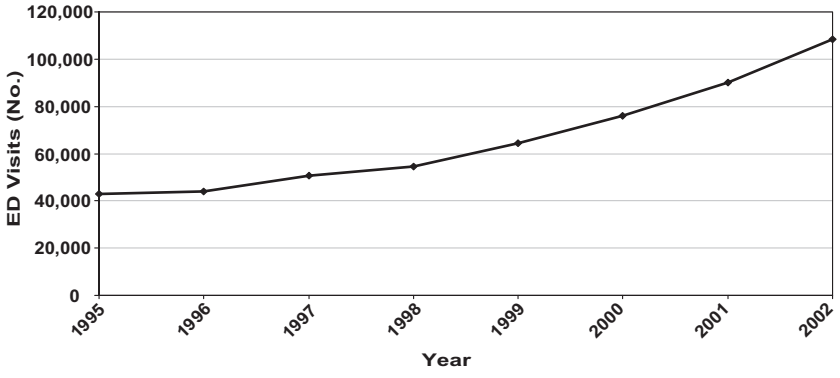

Figure 2 Drug abuse-related ED visits involving narcotic analgesics: 1995–2002. *Source:* Substance Abuse and Mental Health Services Administration and Office of Applied Studies [10]. ED = emergency department.

with the NSDUH and the MTF surveys, the DAWN findings should not be interpreted as directly measuring the prevalence of prescription opioid abuse. The DAWN methodology underwent substantial change in 2003, resulting in an inability to compare new data to those collected prior to the transition. However, it is enlightening to compare trend data from both the previous and improved DAWN designs.

The DAWN trend data from 1995 to 2002 showed a more than twofold increase (per 100,000 population) in the rate of opioid analgesic-related ED visits for all age groups over 17 years (Figure 2) and accounted for an increase of 153% in the number of such ED visits during this time period [10]. The greatest increases in ED visits during this period occurred for products containing oxycodone (512%), methadone (176%), hydrocodone (159%), and morphine (116%) [10].

The DAWN trend data from 2004 to 2006 showed a 43% increase in ED visits related to the nonmedical use of prescription narcotic analgesics, from 172,726 to 247,669 (Table 1) [9]. Use of oxycodone/combinations led to the greatest number of ED visits in 2006 (64,888, up from 41,701 in 2004). Buprenorphine/combination-related ED visits demonstrated the largest percent increase for this 3-year time frame (from around 30 visits in 2004 to 4,440 visits in 2006).

The National Center on Addiction and Substance Abuse

As an important adjunct to national prevalence surveys, the National Center on Addiction and Substance Abuse (CASA) has been surveying teens and parents for 13 years to measure their attitudes toward substance abuse [11]. In so doing, the CASA attempts to identify parental attitudes or behaviors that influence whether their children will engage in substance abuse. Although the survey does not address attitudes toward specific drugs, it does assess the perceived availability of prescription opioids by teens. For years, the CASA has asked, "Which is easiest for someone your age to buy: cigarettes, beer, marijuana, or prescription drugs such as OxyContin, Percocet, Vicodin or Ritalin (methylphenidate) without a prescription?" The most recent survey found for the first time that teens perceive prescription drugs as easier to buy than beer [11]. Additionally, when asked,

Table 1 Nonmedical prescription narcotic analgesic use coincident with ED visits: 2004–2006

Narcotic Analgesics	2004	2005	2006
Buprenorphine/combinations	(Under 30)	(Under 30)	4,440
Codeine/combinations	7,171	6,180	6,928
Fentanyl/combinations	9,823	11,211	16,012
Hydrocodone/combinations	39,844	47,192	57,550
Hydromorphone/combinations	3,385	4,714	6,780
Meperidine/combinations	782	383	1,440
Methadone	36,806	42,684	45,130
Morphine/combinations	13,966	15,762	20,416
Oxycodone/combinations	41,701	52,943	64,888
Propoxyphene/combinations	6,744	7,648	6,220

Note: Information for buprenorphine/combinations was represented in the DAWN report by three dots (. . .), indicating an estimate with a relative standard error greater than 50% or an estimate less than 30. The estimate values were used in this table to provide comparisons to 2006 data.
Source: Substance Abuse and Mental Health Services Administration and Office of Applied Studies [9].
DAWN = Drug Abuse Warning Network; ED = emergency department.

"Which types of prescription drugs seem to be the most popular with teens your age: painkillers such as OxyContin, Percocet, and Vicodin, or stimulants such as Ritalin and Adderall?", 46% of teens answered "painkillers." [11]. The CASA classifies prescription opioids together with other prescription medications subject to abuse, such as psychostimulants [11]. Based on the results of other surveys described here, however, it seems likely that opioid medications comprise a notable portion of the prescription drugs illicitly available to and used nonmedically by teens.

Although findings from these different surveys cannot be directly compared, due to inconsistent metrics and methodologies, they all confirm the increasing nonmedical use of prescription opioids in recent years. Typically, less has been known about the geographic distribution of prescription opioid abuse. Zip code data from the Researched Abuse, Diversion and Addiction-Related Surveillance® system suggest that while prescription drug abuse is prevalent throughout the country, certain areas of the United States, including the suburban and rural northeast, Appalachia, and the upper northwest, show higher prevalence [12]. A retrospective chart review from patients seeking treatment for substance abuse addiction from October 2000 to March 2002 at a Lexington, Kentucky, addiction treatment center illustrates the extent of the problem in one of these regions [13]. The study found that more than half of the admissions (51.3%) were for opioid abuse or addiction; more than half of this group (62.8%) sought help for OxyContin addiction [13].

Addiction-Related Terminology Concerning the Nonmedical Use of Prescription Opioids

Foremost, it is difficult to accurately conceptualize the burden of nonmedical prescription opioid use if inconsistent or misunderstood terminology is employed to characterize its elements. For example, a significant clinical burden relates to the prevalent perception that patients who are legitimately prescribed treatment for pain will become addicted to opioids. One survey of family physicians' attitudes (using 267 of 2,750, for a 10% response rate) toward prescribing long-acting opioids to patients with moderate to severe chronic nonmalignant pain showed that 51% believed that doing so would lead to addiction [14]. This concern has prompted many physicians to refrain from prescribing opioids, even when opioids may prove the most beneficial treatment option [2]. In many ways, such perceptions are exacerbated by erroneous beliefs about what constitutes addiction, misuse, and abuse (Table 2) [15–18].

Recent empirical evidence suggests that a noteworthy minority of health care professionals (12% of Wisconsin pharmacists [19] and 23% of Wisconsin physicians [20]) believe that addiction is characterized solely by physiological phenomena such as physical dependence or tolerance. In addition, in a 2004 national survey of state medical board members, 18% of respondents reported addiction as synonymous with physical dependence or tolerance [21]. This misconception has potentially profound clinical implications, given that these views are held by members of the boards that determine physicians' breaches of profes-

Table 2 Terminology

Misuse	The intentional or unintentional use of a prescribed medication in a manner that is contrary to directions, regardless of whether a harmful outcome occurs [17].
Nonmedical use	Intentional or unintentional use of a legitimately prescribed medication in an unprescribed manner. Such behaviors include using the medication for its psychic effect (either for experimentation or recreationally), deciding to increase the dose on one's own, unknowingly taking a larger dose than directed, engaging in a suicidal attempt or gesture, and inadvertent poisoning [18].
Substance abuse	An intentional, maladaptive pattern of use of a medication (whether legitimately prescribed or not) leading to significant impairment or distress—such as repeated failure to fulfill role obligations, recurrent use in situations in which it is physically hazardous, multiple legal problems, and recurrent social and interpersonal problems—occurring over a 12-month period [16].
Addiction	A primary, chronic, neurobiologic disease, with genetic, psychologic, and environmental factors influencing its development and manifestations. Addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving [15].
Physical dependence	A state of adaptation manifested by a drug class-specific withdrawal syndrome that occurs by abrupt cessation of a drug, rapid dose reduction, decreasing levels of the drug in the blood, and/or administration of an antagonist [15].
Tolerance	A state of adaptation in which exposure to a given dose of a drug induces changes that result in diminution of one or more of the drug's effects over time [15].

sional conduct. Clinical and regulatory confusion about the concept of addiction, which can enhance the perceived risk of iatrogenic addiction among patients with pain being treated with opioids, can be expected to persist and create an additional and often overlooked societal burden by perpetuating the undertreatment of pain.

Such misperceptions are prevalent despite the availability of accurate nosological terminology. Health care professionals' diagnostic practices are largely guided by classification systems represented by the American Psychiatric Association's Diagnostic and Statistical Manual, 4th edition (DSM-IV) [15] and the World Health Organization's International Classification of Diseases, 10th edition (ICD-10) [22]. These current authoritative sources make it clear that the concept of "addiction" (termed *substance dependence* in the DSM-IV and *dependence syndrome* in the ICD-10) cannot be satisfied solely by physical dependence or analgesic tolerance. Of course, tolerance or physical dependence can be and often are present in a person diagnosed with addiction, but the essential elements of the diagnosis relate to compulsive use and continued use despite harm to the individual [15,23]. A new edition of the DSM (DSM-V), likely to be published in 2012, may again redefine concepts and change terms related to *substance abuse* and *substance dependence* [24].

The varying definitions, as outlined in Table 2, have numerous clinical implications but also must be viewed in the context of addiction terminology contained in legislative standards. In addition to common diagnostic or consensus classifications is applied within the health care community, the U.S. Public Health and Welfare Act [25] and laws in 16 states contain inaccurate definitions related to addiction that govern health care practice and patient care [26]. These definitions were created in the early 1970s and do not conform to the current medical and scientific understanding of addiction. The following definition, from Pennsylvania law, is typical of legislative language from several states:

> "Drug-dependent person" means a person who is using a drug, controlled substance or alcohol, and who is in a state of psychic or physical dependence, or both, arising from administration of that drug, controlled substance or alcohol on a continuous basis. Such dependence is characterized by behavioral and other responses which include a strong compulsion to take the drug, controlled substance or alcohol on a continuous basis in order to experience its psychic effects, or to avoid the discomfort of its absence [27].

Based on this definition, a patient using opioids on a long-term basis solely for analgesic purposes could be legally considered a drug-dependent person. Such inaccuracies of terminology in legislation and regulations that govern health care practice can affect decision making and patient treatment. Although these laws are necessary to prosecute illegal behavior related to the nonmedical use of prescription opioids, the use of poorly defined and antiquated definitions poses obstacles for clinicians and patients. Consequently, without a clear and consistent set of definitions for use among legal, regulatory, and health care agencies, as well as for groups sponsoring the national surveys discussed above, addiction-related terminology will continue to have a negative impact on patient care and on society.

Classifying Nonmedical Prescription Opioid Use

The previously discussed national surveys, while sources of valuable information regarding the nonmedical use of prescription opioids, generally do not distinguish among the different motives for and mechanisms of drug use and abuse. Within clinical practice, an appropriate differential diagnosis must be performed to determine whether behaviors that may appear to represent abuse are truly indicative of frank abuse, the disease of addiction, diversion, or some other phenomenon (e.g., pseudoaddiction, physical dependence, or tolerance) [28]. Determining how likely a person is to abuse prescription opioids may be difficult, but there are several biological, psychological, and social factors that can assist in this assessment. Biological factors associated with increased risk for prescription opioid abuse include age less than 41 years, male gender, and a family history of prescription drug or alcohol abuse [29]. Psychological factors demonstrated to be associated with an increased risk of abuse include a history of personal substance use disorder or other psychiatric comorbidity (e.g., personality, anxiety, depressive, or bipolar disorder) [30,31]. One study reported that drug abuse was significantly higher in patients with depression (12%) than in nondepressed patients (5%) [31]. Social factors associated with an increased risk for opioid abuse include a history of legal problems or motor vehicle accidents [30].

The development of true addiction to prescription opioids is rare in people without a history of substance abuse. A recent evidence-based, structured meta-analytic review demonstrated that consistent exposure to opioid therapy in chronic

pain patients would only lead to addiction in a small percentage of patients (3.27%) [32]. The study demonstrated that the rate of abuse/addiction was even lower if patients were preselected for the absence of a current or past history of alcohol/illicit drug use or abuse/addiction. The rate of abuse/addiction due to prescription opioids in patients with no previous or current history of abuse/addiction was calculated at 0.59% [32]. Evidence indicates that while up to 20% of pain patients may use opioids for nonmedical purposes and 40% exhibit aberrant drug-related behaviors, true addiction occurs in only 2–5% of the overall population of patients with pain [29]. A recent evaluation of opioid-specific abuse and dependence disorders in a sample of patients (N = 801) being treated with prescription opioid therapy in a primary care setting demonstrated an incidence rate of 3.8% for opioid use disorders as defined by the DSM-IV criterion [33]. The authors interpreted this rate as insufficient to justify sacrificing appropriate and effective treatment for individuals with severe chronic pain, especially given the lack of useful therapeutic alternatives for those patients. The results do, however, emphasize the need to monitor patients for aberrant medication behaviors and for prompt attention to these behaviors by the clinician.

There exist distinct classes of individuals who misuse or abuse prescription opioids with different motives, frequency of use, and methods of use. Inexperienced recreational users most often administer prescription opioids via the oral route, although they may occasionally also crush extended-release products to cause the product to "dose-dump" (rapid drug release in a short period of time of the entire amount or a significant fraction of the drug) for the nonmedical goal of altering one's state of consciousness (i.e., getting "high"). This category of users often takes more than the prescribed dose of the drug to facilitate euphoria and comprises high school or college students with little drug tolerance who are at increased risk for adverse consequences relative to more experienced users who have developed tolerance [13,34]. Experienced prescription opioid abusers usually prefer intranasal or intravenous routes of administration and frequently attempt to compromise the controlled-release features of opioid medications to facilitate more rapid bioavailability and euphoria associated with administration via these routes [13,34].

As mentioned previously, patients with a history of substance abuse have the highest risk for abusing prescription opioids. A small prospective study of 20 patients with a history of substance abuse treated with opioid therapy found 9 patients (45%) who were suspected of having prescription opioid abuse problems [35]. In this study, patients who developed abusive prescription drug-taking behavior were typically opioid or polysubstance abusers, were not engaged in recovery programs, and had poor family support [35]. Another study looked at the incidence and antecedents of nonmedical prescription opioid use in 28- to 40-year-olds (N = 3,163) with no prior history of nonmedical opioid use. New nonmedical use was reported by 23 participants, all of whom had a history of marijuana and/or amphetamine use [36].

Pharmacoeconomic Context of Nonmedical Prescription Opioid Use

Illicit prescription opioid use is costly to individuals, insurance companies, and society as a whole. In 2001, a cost-of-illness assessment of health care treatment, criminal justice, and workplace expenses due to nonmedical prescription opioid use estimated costs to be $2.6 billion, $1.4 billion, and $4.6 billion, respectively [3], which has contributed to rising health care costs. A retrospective study of insured patients with claims associated with ICD, 9th revision, Clinical Modification (ICD-9-CM) codes for opioid abuse found that mean annual direct health care costs were more than eight times higher for abusers than for nonabusers ($15,884 vs $1,830, respectively, in 2003 dollars), and drug costs were more than five times higher for abusers than for nonabusers ($2,034 vs $386, respectively) [37]. The study found that these costs are due primarily to the higher prevalence rates of a number of specific comorbidities, including non-opioid poisoning (78 times higher), hepatitis (A, B, or C; 36 times higher), pancreatitis (21 times higher), and psychiatric illness (9 times higher), in the opioid-abusing group than in the group of nonabusers [37].

The cost of substance abuse treatment also contributes to the increasing health care costs associated with the illicit use of prescription opioids. The number of admissions to treatment centers for prescription opioid abuse rose from 15,611 in 1994 to 63,243 in 2004, a more than fourfold increase [38]. Comparatively, admissions for all types of substance abuse rose only by 12.21% in that time frame [38]. Different groups have used pharmacoeconomic analyses to determine the cost efficiency of treatments for prescription opioid abuse. One cost–benefit analysis used information

from the California Treatment Outcome Project, which collected 2000–2001 data from 43 different substance abuse treatment providers in 13 counties in California [39]. The report found that, on average, substance abuse treatment costs $1,583 and is associated with a monetary benefit to society of $11,487, representing a greater than 1:7 ratio of cost to benefit; this large cost-efficiency ratio is due primarily to reductions in criminal activity and increased earnings from employment. Other studies have examined the cost-effectiveness of specific substance abuse treatment options, such as methadone maintenance. One study took into account the lifetime impact of criminal activity, arrests, and potential incarceration, unemployment, and health care utilization, as well as the possible need for multiple treatment episodes, and calculated that for every $1 spent on methadone maintenance, there is an economic benefit equaling about $76 [40].

The terminology used to describe drug abuse continues to evolve and is not always consistent with the ICD-9 definition of drug abuse, which serves to compound the difficulty of assessing the overall pharmacoeconomic burden of prescription opioid abuse. Therefore, it is difficult to make specific claims regarding pharmacoeconomic analyses of prescription opioid abuse or the options for treating these drug abusers. Having a clearer understanding of cost-effective treatment options, however, will certainly translate into funding for programs that display the greatest effectiveness in terms of treatment for prescription opioid abuse.

Reducing the Burden of Nonmedical Prescription Opioid Use

Treatment and Rehabilitation of Nonmedical Prescription Opioid Use

The treatment and rehabilitation of prescription opioid abusers is a medical and societal imperative if the burden associated with prescription opioid abuse is to be mitigated. Psychosocial strategies are an important nonpharmacologic approach to treating patients who are abusing prescription opioids [41]. These strategies usually entail addressing motivation, being involved in 12-step recovery programs, undergoing cognitive–behavioral therapy, teaching coping skills, providing positive or negative reinforcement, helping patients deal with painful emotions, improving interpersonal functioning, and, when appropriate, fostering compliance with pharmacotherapy [41]. Used in combination with pharmacologic therapy, psychosocial interventions are likely to be effective [42–44].

A common pharmacologic approach to treatment is drug replacement therapy, which involves using a controlled drug as a substitute for the illicit use of a different drug [45]. For opioid addiction, replacement therapy has long involved the dispensing of methadone, an approach most often used for treatment of addiction to heroin and less often for prescription opioid addiction [45–47]. Buprenorphine is increasingly used in opioid replacement therapy [48]. In 2002, the Food and Drug Administration approved the use of the partial μ-opioid receptor agonist buprenorphine for the treatment of opioid addiction [48]. Buprenorphine is often combined with an opioid antagonist such as naloxone for the treatment of opioid addiction [43,44,49]. Buprenorphine has pharmacologic characteristics that make it an attractive alternative to methadone [50], the specifics of which are beyond the scope of this article. Compliance when using drug replacement therapies can be difficult, because these medications provide little, if any, reinforcement or euphoria when taken, decreasing the incentive to continue taking the medication [50]. Clearly, pharmacologic therapies must be combined with behavioral strategies in order for long-term abstinence to be achieved.

In addition to the availability of pharmacologic treatment options, there are now novel scientific initiatives intended to produce prescription opioid medications that reduce the risk of nonmedical use. There is ongoing development of new opioid formulations that have been designed to resist or deter physical manipulations and chemical extractions commonly performed by individuals in pursuit of a "high" [51]. These efforts are described in detail in a subsequent chapter of this supplement, "Update on Abuse-Resistant and Abuse-Deterrent Approaches to Opioid Formulations." Efforts to reduce illicit opioid use are not limited to pharmacologic formulations, however, and also can encompass statewide drug control programs created through legislation.

Prescription Monitoring Programs

Prescription monitoring programs (PMPs), purportedly useful for identifying, reducing, and possibly eliminating routes of diversion, are often one of the state's principal diversion control instruments [52]. Historically, these have been "multiple

copy prescription programs" (MCPPs), a type requiring physicians to use government-issued serialized prescription forms (e.g., duplicate or triplicate forms). For example, with a triplicate form, the issuing physician and dispensing pharmacist will each retain a copy, with the third copy being sent to the relevant government agency. The serialized prescription forms were applied solely to schedule II medications, the only medications indicated for severe pain, and the programs were administered by state law enforcement agencies [52]. These serialized prescription forms were periodically reviewed to provide law enforcement, prescribers, and dispensers with information on patients who might be "doctor shopping" or physicians who might be issuing prescriptions for nonmedical purposes. However, the overall usefulness of MCPPs was diminished because there often was a considerable lag between the time prescription information was submitted and when it was eventually compiled for analysis, if it ever was compiled; these programs, therefore, could not actively monitor diversion or abuse in a timely manner [53].

The unique characteristics of MCPPs and their exclusive use for schedule II medications led to evidence suggesting that these programs inadvertently stigmatize the medications as well as the practitioners who prescribe them [54]. This stigmatization, stemming from practitioners' concerns about government scrutiny of their prescribing practices, frequently led physicians to prescribe schedule III and IV medications to avoid surveillance [55–57], which has been referred to as the "substitution effect" [57]. As a result, practitioners who prescribed schedule III and IV medications likely were not able to manage severe pain adequately because these medications are not indicated for such treatment. Also, decreased prescribing of schedule II medications in states with PMPs was not clearly indicative of reduced diversion [58].

Electronic data transfer (EDT) programs, which have generally replaced MCPPs, frequently collect prescription information for more than just schedule II substances (usually schedules II, III, and IV) [59,60]. Because practitioners' potential therapeutic armamentarium would be severely limited by avoiding all EDT-monitored medications, these programs seem to negate the substitution effect. Unlike MCPPs, EDT programs tend to be administered by state health agencies. Although these programs collect prescription information in a more timely fashion, most still cannot be considered truly "real-time." Importantly, the laws that establish EDTs often explicitly state that the program has the dual objective of reducing abuse and diversion while not interfering with medication availability and effective patient care. As with MCPPs, the effectiveness of these programs in reducing incidents of medication abuse or diversion is not well studied [60–63].

Of the 38 states that now have legislation that creates EDT programs for multiple medication schedules, more than half have established these programs within the past 3 years. Eleven other states are in the process of considering such programs. The recent proliferation of EDT systems seems to be a direct result of the National All Schedules Prescription Electronic Reporting Act of 2005 (NASPER), which offers grants to states to develop a PMP only if it is an EDT program encompassing medications from at least schedules II–IV [63]. Under this federal law, the secretary of Health and Human Services is required to evaluate whether the programs established through NASPER avoid interfering with legitimate prescribing to patients for valid medical purposes (e.g., pain relief) and effectively identify or prevent genuine episodes of abuse and diversion [53]. Given the above EDT characteristics, it is likely that these PMPs have a better chance than MCPPs for improving patient care. However, there are no available data providing evidence about whether these NASPER-inspired programs negatively affect patient care or achieve their primary goal of protecting public safety by preventing the illicit use and distribution of controlled substances. Overall, EDT programs, while not a panacea for reducing all problems of nonmedical prescription opioid use or for medication diversion occurring outside the physician–patient context, have the potential to be valuable drug control tools if constructed and implemented properly [64].

Conclusion

For decades, national surveys have been instituted to estimate the prevalence of the nonmedical use of drugs but their data collection methodologies have differed, including the operationalization of nonmedical use. Nevertheless, taken together, these various measures unambiguously demonstrate increasing nonmedical use of prescription opioids, whether it be self-reported use or ED visits due to adverse events resulting from opioid use. Such nonmedical use is associated with a considerable cost to society such as increased health care expenditures, including substance

abuse treatment, economic productivity loss, and criminal activity and incarceration. Perhaps the greatest cost of illicit prescription opioid use has been its stifling effect on the prescribing habits of practitioners and its contribution to the undertreatment of pain, perpetuated often by health care professionals' erroneous beliefs about the factors that constitute a diagnosis of addiction or knowledge of how to validly identify and attribute aberrant drug-related behaviors. Many states have implemented a PMP designed specifically to identify the diversion of prescription medication, which also could be used as a mechanism for entry into treatment for individuals the system detects. All of these approaches are employed to minimize the substantial health care cost and societal impact of illicit medication use. An accurate understanding of the prevalence, current conceptualization, and clinical and pharmacoeconomic contexts of nonmedical prescription opioid use is essential for effectively reducing this public health problem.

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