THE JOURNAL OF
GLOBAL DRUG POLICY AND PRACTICE

Patterns and Characteristics of Prescription Opioid Abuse in the United States

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Acknowledgements: The research was supported by grants DA020791and DA021330.

Abstract

Initially, this paper will discuss the basis for scheduling drugs under the Controlled Substances Act and the impact of scheduling on the therapeutic use of opioid analgesics. Second, we will discuss the highly favorable risk-benefit ratio for opioid analgesics and the inappropriate use of abuse as an adverse event in the risk-benefit analysis: abuse is rarely an adverse event of the therapeutic use of opioids, but rather occurs in the individuals who have diverted the drug for off-label, inappropriate use. Third, and perhaps most important, we have reviewed the relationship between therapeutic exposure to opioid analgesics and abuse of those drugs. In so doing, it is possible to define "outliers" in which abuse is disproportionately high relative to exposure. Using the latter method, geographic areas can be found where focused efforts should be made to understand the nature of disproportionate abuse. Finally, we will review the characteristics of those at risk for abuse to help physicians treating pain to recognize those vulnerable individuals who may be at risk for abuse and, therefore, should be monitored closely.

1. Prescription Opioids and the Controlled Substances Act

Prescription opioid analgesic abuse has been a persistent national problem for decades, particularly in certain areas, most notably the Appalachian region of the United States.(1-4) Against the backdrop of a relatively low, but sustained, level of prescription opioid abuse nationwide for the past 40 years, there was a sharp increase in prescription drug abuse beginning in late 1995 and extending to the present time.(5-10)

While the reasons for this steady growth in prescription opioid analgesic abuse are largely unknown, prior research examining trends in the abuse of tramadol and other more potent opioids 5,7 indicates that reasons most often given by recreational and addicted prescription opioid users include:

1. Prescription drugs are relatively easily obtained as opposed to the great difficulty and perceived danger in obtaining heroin and other illicit drugs.

2. The purchase of illicit drugs on the street, such as heroin, was closely monitored by law enforcement officials and arrests were, therefore, far more likely for heroin than for legal drugs, such as opioid analgesics.

3. The use/abuse of prescription drugs is more socially acceptable among peers compared with heroin or cocaine.

4. The purity and the dosage of prescription medications are highly predictable, and consequently, they are much safer to use than illicit drugs.

5. When heroin is unavailable, these drugs serve as acceptable, although not preferred, substitutes.

6. These drugs can be useful as self-medications to relieve symptoms of heroin withdrawal or in an effort to detoxify.

As controlled substances, this increase in abuse has quite naturally evoked worries by regulatory authorities – the Food and Drug Administration (FDA) and, particularly, the Drug Enforcement Administration (DEA) – that this epidemic of abuse may, if real, mandate further controls. For example, serious concerns have been voiced and a case made that hydrocodone preparations, with acetaminophen or ibuprofen, be moved from Schedule III to II. In this context, the Controlled Substances Act (CSA) requires an 8 factor analysis, shown in Table 1, which examines the potential abuse of new or old drugs by collecting data on their biochemical and pharmacological similarity to opioids that have already been

controlled. It should be obvious that some of these 8 factors are vague and somewhat ambiguous (e.g. "What, if any, risk there is to the public's health") and, given that the law implementing the CSA is now nearly 40 years old, it employs antiquated definitions that have little scientific relevance in the modern scientific literature, such as "psychic" or "physiological" dependence liability. Several examples will illustrate this point.

The CSA was intended to deal with the public health consequences of abuse as defined in the appropriate medically relevant terms: compulsive use of drugs for non-therapeutic purposes (i.e. mood altering effects) which is destructive and does great harm to the individual and/or society (e.g. theft, trading sex for drugs, and so forth). Unfortunately, regulatory agencies often regard the incidence of suicide or other adverse events as a threat to the public health. Clearly, suicide is most unfortunate and is certainly a matter of deep public health concern, but suicide is the end result of an individual with serious psychiatric disturbances who believes that his/her life is not worth living or that others (e.g. friends, society) would be better off without the individual. Thus, suicide may be a public health crisis if rates grew at some unanticipated rate which cannot be explained, but clearly, suicide is the focus and it makes no difference what weapon, drug, chemical, or other poison was used to accomplish the goal. Thus, to claim the CSA covers suicide because an overdose of a drug of abuse was used as the means to end – suicide – is illogical and clearly was not the purpose of factor 6 in the CSA. It could be argued that accidental overdose, because of a poor therapeutic index, is a legitimate public health concern, and we agree with this assertion. However, it seems clear that there are other ways in which the FDA can handle this rather than invoking factor 6 of the CSA.

In addition, and perhaps most importantly, the terms psychic or physiological dependence, while they may have had relevance in the 1960s, have none today. Physical dependence does indeed develop with opioids as it does with most drugs used chronically. Dependence is a broad label for a series of neurobiological adaptations which occur during chronic exposure to any one of a number of drugs – such as anti-depressants, high blood pressure medications, and opioids. When the drug is abruptly removed, the neuroadaptations which have occurred during chronic opioid administration are now inappropriate, which results in a series of signs and symptoms, collectively referred to as the withdrawal syndrome. However, unless the withdrawal syndrome leads to drug seeking behavior, the terms withdrawal or physical dependence have little relevance to abuse liability.

Nonetheless, the 8 factor analysis, though scientifically outdated, is still carried out, and, as a consequence, a drug is placed in one of 5 schedules as shown in Table 2. Schedule 1 is reserved for drugs with extremely high abuse potential but no known medical efficacy (e.g. heroin, crack, methamphetamines). Schedule 2 drugs may have the same level abuse potential as those in schedule 1, but in this case the drugs are extremely efficacious ones, which need to be used carefully with abuse monitored closely. Drugs in all of the remaining schedules have medical efficacy with decreasing levels of abuse potential (i.e. III>IV>V).

The intent of the CSA was three-fold: First, to warn physicians about the potential for abuse of new and old medications; second, to provide control by the DEA of importation quotas for the raw materials for opioid drugs; and, third, oversight of physicians by licensing them, providing guidelines for use of drugs, and investigating what they – the DEA – might consider an inappropriate use of scheduled drugs. The latter role of the DEA – as a police force – produces a very chilling effect on the willingness of physicians to prescribe controlled substances for two reasons: First, because scheduling indicates high abuse, there is a largely unwarranted fear by physicians of opioid dependence/abuse in patients in which the drug is used therapeutically, often referred to as "iatrogenic abuse"; and, second, the oversight by the DEA, the regulatory requirements imposed by the DEA, and fear of unscheduled audits greatly dampen the enthusiasm to prescribe these drugs. In fact, many doctors will now refer patients with chronic pain requiring opioid treatment to pain clinics and other physicians willing to employ high-dose opioids regimens to control pain.

The FDA and DEA clearly and properly indicate that the CSA does not inhibit the practice of medicine, and, thus, they argue that simply because a drug is scheduled, it should not influence a medically appropriate decision to use it. While certainly technically correct, the reality is that physicians' prescribing practices are definitely influenced by the scheduling statutes, which makes them more inclined not to use opioid analgesics. This in turn, has, at least to a significant extent, led to the substantial under-treatment of chronic pain in this country.

2. Risk-Benefit Ratios of Opioid Analgesics

All drugs have adverse events associated with their therapeutic use. The dilemma for physicians and federal agencies is to decide how much risk is acceptable to offset the benefits of using a particular drug. In this discussion it is clear that it is important to stress that the ***rate*** at which an adverse event occurs as a function of legitimate therapeutic use of the drug is the most appropriate measure of a risk-benefit assessment, rather than the number of adverse events alone. This point is illustrated most clearly with non-steroidal anti-inflammatory drugs (NSAIDS). In terms of number of adverse events alone, tens of thousands of people experience gastrointestinal bleeds attributable to NSAIDS, some of which are fatal (perhaps 15,000 deaths/year) or require hospitalization.(11, 12) However, given the fact that these drugs are highly efficacious, they have a favorable risk-benefit ratio and are still widely used in clinical practice. Thus, if drug control policy is based on simply the number of adverse events and ignores the risk-benefit ratio, this seems contrary to protecting the public health.

In addition, it is important to emphasize that even with a low incidence rate, the raw number of adverse events rises as the number of persons exposed expands. For example, if only 0.01% of all individuals who are prescribed a drug develop an adverse reaction, the number of cases would be 100 if 1 million patients are prescribed the drug or 1,000 if 10 million people are exposed. Thus, the sheer number of cases could distort a very low incidence rate which might otherwise be indicative of a very favorable risk–benefit ratio. Clearly, the only valid index of a drug's risk–benefit ratio is the rate of an adverse event, which takes into account the total number of persons who are prescribed the drug.

The rate of an adverse event has traditionally been expressed as the number of adverse events divided by the number of people benefitting from the therapeutic use of the drug. Thus, if one reads the Physician Desk Reference,(13) rates of occurrence of adverse events are listed as the percentage of people who experience an adverse event while using the drugs therapeutically at the doses recommended.

The problem with abuse as an adverse event, and hence, the calculation of a risk-benefit ratio, is that abuse is not generally associated with therapeutic use of opioid analgesics. Rather, diversion to an unintended population (e.g. recreational or street drug abusers) is the most frequent pattern of abuse. Thus, we believe that it is wrong to treat abuse as an adverse event which systematically develops as the opioids are used therapeutically. There is very little data to suggest that abuse is a natural by-product of therapeutic use. Regrettably, regulatory agencies have frequently overlooked this point and have consistently used abuse as the major risk of using these drugs therapeutically. We need to change this emphasis on abuse for two reasons: First, such analyses place drugs with substance abuse potential in an entirely different category than any other medically used class of drugs which seems difficult to justify on any level; and, second, given the dampening effects of a decision to schedule drugs under the Controlled Substances Act (CSA) on physicians' prescribing practices, very efficacious and valuable medications are used much less frequently than they should be. With all this stated, we believe there is a more favorable risk-benefit ratio for opioids than there is for any other class of drugs. The enormous benefits of treating pain, which affects 47 million people, greatly outweigh the "risk" of abuse by non-patients.

3. The History of Prescription Drug Abuse

The non-medical use of pharmaceutical opioids has been a longstanding problem in the United States. There has been some speculation that the trend began early in the eighteenth century with Thomas Dover, a student of British physician Thomas Sydenham.14 Known as the "English Hippocrates" and the father of clinical medicine, Sydenham had been a strong advocate of the use of opium for the treatment of disease. Following the path of his mentor, Dover developed a form of medicinal opium known as *Dover's Powder*, which contained one ounce each of opium, ipecac, and licorice, combined with saltpeter, tartar, and wine.(15) It was introduced in England in 1709, but quickly made its way to the American colonies and remained one of the most widely used opium preparations for almost two centuries. The attraction of Dover's Powder was in the euphoric and anesthetic properties of opium, and its introduction apparently started a trend. By the latter part of the eighteenth century, patent medicines containing opium were readily available throughout urban and rural America, and by the closing years of the nineteenth century the abuse of these drugs had become widespread.(14,16-18) The abuse of opioids continued throughout the twentieth century. The first general population survey of drug abuse undertaken in the U.S., conducted in New York State in 1970,(19) found the abuse of prescription opioids to be common. Subsequent surveys as well as focused research studies documented the continuing abuse of prescription opioids.(20-24) Moreover, from the 1970s through the 1990s, several prescription opioids cycled in and out of the American drug scene – pentazocine (T's & blues) and propoxyphene (Darvon) in particular – while others, such as hydromorphone (Dilaudid) and hydrocodone (Vicodin), maintained a steady presence.(23,25-28) By the close of the 1990s, it had become clear from data gathered through the Drug Abuse Warning Network (DAWN), NIDA's Community Epidemiology Work Group (CEWG), the Monitoring the Future (MTF) surveys, and the NHSDA (now referred to as the National Survey on Drug Use and Health, or NSDUH) that prescription opioid abuse was on the upswing.(29)

4. The Epidemiology of Prescription Drug Abuse

The National Survey of Drug Use and Health found that the numbers of new, non-medical users of prescription opioids (primarily products containing codeine, hydrocodone, and oxycodone) increased from 600,000 in 1990 to over 2.4 million in 2004, marking it as the drug category with the largest number of new users in 2004.(30) In addition, reports from the Drug Abuse Warning Network indicate that abuse-related emergency department (ED) visits involving narcotic analgesics increased by 153% from 1995 through 2002,(31) and during the same period, abuse-related ED visits involving benzodiazepines increased by 41%.(32) Similar increases are reflected in drug abuse treatment admissions data.(29) As with illicit drugs, the precise number of prescription drug abusers would be difficult to estimate, given the limitations of general population surveys. Nevertheless, some good indicators are available. The 2004 NSDUH, for example, found significant increases in the non-medical lifetime use of prescription opioids among persons ages 12 and older between 2002 and 2004, from an estimated 29.6 million to 31.8 million users. Significant increases have been observed among 18-25 year olds in particular. In addition, data from the NSDUH indicate a continuing upward trend in past month use of opioids. Among those ages 18-25, past month non-medical use of pain relievers rose from 4.1% in 2002 to 4.7% in 2004.30 The latest NSDUH also captures the increased popularity of particular types of prescription drugs. Specifically, between 2003 and 2004, statistically significant increases occurred in the use of Vicodin, Lortab or Lorcet; Percodan, Percocet, or Tylox; hydrocodone products; OxyContin and oxycodone products.(30)

In addition, data from DAWN indicate that ED visits involving prescription drugs have been on the rise. Specifically, in 2002, opioid pain relievers accounted for 10% of all drug mentions in ED visits, with hydrocodone and oxycodone accounting for the majority of cases. Between 1994 and 2002, mentions of oxycodone increased 450%, while mentions of hydrocodone increased 170%. The majority of the ED visits involved multiple drugs for both oxycodone (71%) and hydrocodone (78%). The most frequently cited substances found in combination with these drugs were alcohol, benzodiazepines, other opioids, and cocaine. Drug abuse treatment admission data also indicate that prescription drug abusers represent a growing proportion of treatment enrollees. Between 1993 and 2003, the admission rates for opioids other than heroin increased by 223%(.33) In 2003, there were 50,946 treatment admissions of primary non-heroin opioid abusers. Among these, almost 60% were poly-drug users with alcohol, marijuana, and tranquilizers among the most commonly reported secondary substances of abuse.33 Moreover, data from 2003 indicate that over 4% of the nearly 1.9 million documented treatment admissions mentioned a prescription drug as the *primary* complaint, with non-heroin opiates accounting for 2.8% of all admissions. Importantly, as illustrated in Figure 1, treatment admission rates involving prescription opioids increased more in non-metropolitan and rural areas than in large urban areas.

5. The Diversion of Prescription Opioids

Prescription drug diversion involves the unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace,(34) and the phenomenon has been a topic of widespread commentary since the latter part of the 1990s.(29,35-39) The Drug Enforcement Administration (DEA) has estimated that prescription drug diversion is a $25 billion-a-year industry(40) and that diversion can occur along all points in the drug delivery process, from the original manufacturing site to the wholesale distributor, the physician's office, the retail pharmacy, or the patient.(41) It is generally believed that the major mechanisms of diversion include: the illegal sale and recycling of prescriptions by physicians and pharmacists; "doctor shopping" by individuals who visit numerous physicians to obtain multiple prescriptions; theft, forgery, or alteration of prescriptions by patients; robberies and thefts from manufacturers, distributors, and pharmacies; and thefts of institutional drug supplies. Furthermore, there is growing evidence that diversion of significant amounts of prescription opioids occurs through residential burglaries(42-45) as well as cross-border smuggling at both retail and wholesale levels.(46) In addition, recent research by the investigators and others in the prescription drug abuse field has documented diversion through such other channels as: "shorting" (undercounting) and pilferage by pharmacists and pharmacy employees; medicine cabinet thefts by cleaning and repair personnel in residential settings; theft of guests' medication by hotel housekeeping staff; and Medicare and Medicaid fraud by patients, pharmacies, and street dealers.(34,46-48) Moreover, it would appear that pill abusing middle and high school students are obtaining their drugs through medicine cabinet thefts and medication trading. Finally, a number of observers consider the Internet to be a significant source for illegal purchases of prescription drugs.49,50 And there are likely numerous other sources. Although national surveys and monitoring systems are documenting widespread abuse of prescription opioids, and numerous scientific papers over the years have discussed the problems associated with diversion,(29,34,51-57) empirical data on the scope, magnitude, and epidemiology of diversion are largely unavailable and remain absent from the literature. In fact, at a recent meeting sponsored by the College on Problems of Drug Dependence focusing on the "Impact of Drug Formulation on Abuse Liability, Safety, and Regulatory Decisions," representatives from government regulatory agencies, the pharmaceutical industry, and the research community agreed that: a) there are no data on the magnitude of particular types of diversion; b) there are no systematic data on how the massive quantities of abused prescription drugs are reaching the streets; and c) there are no empirical data that might be used for making regulatory decisions and for developing prescription drug prevention and risk management plans.(47,48,50,58-62) In addition, although a number of studies have addressed the patterns of prescription drug abuse and diversion among health care professionals,(34,63-66) little is known about the magnitude and mechanisms of diversion among current and former pain patients who abuse prescription opioids.

6. Determinants of Prescription Opioid Abuse and Comorbidity

Recent epidemiological evidence clearly demonstrates elevated rates of a spectrum of psychiatric disorders in individuals reporting lifetime use of or abuse/dependence on prescription opioid medications. Specifically, Huang et al(67) analyzed data from 42,300 individuals from the U.S. household population interviewed as part of the National Epidemiologic Survey of Alcohol and Related Conditions.(68,69) Their analyses, summarized in Table 3, indicated dramatically elevated odds of other drug use disorders, antisocial personality disorder, and mood and anxiety disorders. While information from large scale samples of individuals seeking treatment for prescription opioid abuse/dependence, treatment referral biases,(70,71) and other factors suggest that, if anything, rates of these disorders may be further elevated in those seeking treatment.

In several thousand persons admitted to drug treatment clinics in recent studies, we have confirmed these findings and extended them by looking at the possibility of gender differences.(72) As shown in Figure 2, physical and mental health (SF36v2) were very poor in both male and female prescription opioid abusers, but females were more ill and dysfunctional than males in all physical and particularly emotional domains.

6.1 Co-Morbidity with Alcohol Abuse, Nicotine Dependence and Other Substances of Abuse

Table 4 shows that over 40% of both males and females satisfied DSM IV criteria for alcohol abuse. Nearly 70% of the sample of prescription opioid users smoked regularly, and most of these met criteria for nicotine dependence - 66% of all male and 74% of female prescription opioid abusers. As shown in Table 4, the age of first use of nicotine, alcohol, marijuana, licit (e.g. Adderall and Ritalin) and illicit (e.g.

cocaine/crack) drugs occurred at a very early age (13-19), well before the initial use of prescription opioids (22 years of age). It also appears that prescription opioid abuse led to the initial use of heroin: Over 90% of the total population of prescription opioid misusers indicated that their use of prescription opioids to get high led them to use heroin. Conversely only 8-9% of all subjects indicated that heroin was the first opioid they used to get high.

6.2 Source of Drugs

As shown in Table 4, friends/relatives, dealers, and doctor's prescriptions, respectively, were the most common source of drugs, with well over 60% of the population endorsing one or more of these sources. However, there were substantial gender and age-related differences in the use of dealers and doctor's prescriptions. As shown in Figure 3, although dealers were used by nearly 90% of males and females under age 20, there was a significant drop to less than 50% of those in the oldest age group. Overall, males were more likely (OR=1.64, reference group = female, dealer yes =1, dealer no =0, $p<0.01$) as females to use a dealer to obtain prescription opioids. Doctor's prescriptions, as a source of drugs, displayed the opposite effect (Figure 3). Females were more likely than males (OR=1.71, reference group = male, doctor Rx yes =1, doctor Rx no =0, $p<0.01$) to use doctor's prescriptions to obtain opioids across all age groups: Over 40% of females under the age of 20 got a prescription for an opioid analgesic compared to only 21% of the males. The use of doctor's prescriptions increased with age such that it was a major source of drugs in both sexes over 40. Forged (10%) or stolen prescriptions (<25%) were used relatively infrequently as a source of drugs and the Internet rarely (<8%).

6.3 Mental and Physical Health Status

As shown in Figure 3, male and female prescription opioid abusers had significantly poorer physical and mental health than their respective national norms on the SF36v2. While this was true for both sexes, as shown in Figure 3 and Table 5, for all 8 SF-36 domains, females were more ill and dysfunctional than males.

6.4 Pain and First Use of Opioids

As shown above and in Table 6, chronic bodily pain was a significant co-morbid factor in both males and females. Moreover, 79% of males and 85% of females indicated that their first exposure to an opioid was a legitimately prescribed opioid analgesic for pain. The average age was 21.5 (± 0.72) for males and 22.3 (± 0.68) for females. Over 62% of all males and 70% of females indicated that their first use of opioids for pain led them to use the drugs to get high even when their pain subsided.

6.5 Co-morbid Psychopathology

While the SF36v2 health survey suggested poor general physical health in prescription opioid abusers, as shown in Figure 3 and Tables 5 & 6, the most striking difference was the extremely poor mental health scores in all prescription opioid users compared to national norms ($p<0.001$). However, females clearly had significantly ($p<.01$) more psychopathology than males. As shown in Table 6, 66% of females and 54% of the males self-reported that they had been treated for a psychiatric disorder in the past 12 months. Depression was the most frequent diagnosis followed by anxiety disorders, bipolar disorder, and attention deficit disorders; females had much higher rates of anxiety disorders than males (OR=1.74, reference group = male, anxiety yes =1, anxiety no =0, $p<0.05$), while males had more attention deficit disorders than females (OR=1.49, reference group = female, ADD yes =1, ADD no =0, $p=0.27$).
Our results and those reviewed above suggest that a small number of "at risk" opioid naive pain patients, who might abuse their therapeutically appropriate opioid analgesics, can be identified by assessing pre- and co-morbid substance abuse and significant psychopathology. Furthermore, gender must also be considered as a part of any comprehensive pain treatment program.

7. Relationship Between Abuse and Therapeutic Exposure

As mentioned above, there has been a surge in abuse of prescription opioid analgesics over the past decade.(73-78) In the present studies we sought to address a fundamentally important assumption made implicitly by federal regulatory agencies and in the drug abuse literature(79) that to our knowledge has never been addressed with any scientific data: that the abuse of opioid analgesics in a specific community is directly proportional to the therapeutic use of that drug.80 The methods for our study have been described elsewhere,(80) but, briefly, we plotted the number of abuse cases obtained from a national sample of drug abuse treatment centers against the number of patients prescribed up to 8 different opioids (dubbed URDDs for unique recipients of dispensed drugs).

Figure 4 shows the relationship between the number of abuse cases and URDDs for all of the drugs we studied. The data are the total events—URDDs and abuse cases—for the last four calendar quarters we studied. Two things are obvious from this figure: first, no abuse (0 cases) of opioid analgesics was one of the most prominent responses for at least one quarter of the study for each drug; and, second, high levels of abuse occurred, for the most part, in ZIP codes in which the use was correspondingly high. Table 7 shows the odds ratios of cases being above 5 for a 10-fold increase in the URDDs for each of the eight drugs of interest from the period from the 2nd quarter of 2005 to the 1st quarter of 2006. All of the eight odds ratios were significantly greater than 1; they ranged from 2.3 for hydromorphone to 44.3 for fentanyl. From the data shown in Figure 4, we calculated the rate of abuse which corresponds to the 95th percentile— 1.62 cases/1000 URDDs (1.62%)—such that rates to the left of the line are indices of disproportionately high abuse and were designated as 'signals' of abnormally high abuse relative to exposure.

7.1 Location of signals of disproportionately high abuse

Figure 5 shows the number of ZIP codes for each drug which were greater than the 95th percentile for the first Quarter of 2006, and, thus, constitute a signal of disproportionately high abuse. The strongest signals by far occurred for ER oxycodone > buprenorphine ≈ methadone > hydromorphone, indicating that the abuse of these drugs relative to therapeutic exposure was disproportionately high in more ZIP codes than the other drug classes. On the other hand, very few signals were found for other drugs, notably the two most commonly used opioid analgesics - IR oxycodone and hydrocodone - indicating their abuse was not disproportionately high relative to exposure. Figure 6 shows a graphical depiction of regions of the country with signals of abuse for one to four of the eight drugs we monitored; Table 8 shows the actual signal sites with the rates of abuse specified. It is apparent that signals of abuse occurred most commonly in small urban and suburban/rural areas, particularly suburban areas of the country's largest cities in the Northeast corridor and the small urban/rural areas of Montana. Relevant to the last point, Table 9 demonstrates that despite a broad representation of treatment centers in all areas of the country, the distribution of the signals of abuse was heavily skewed in the direction of suburban and rural areas.

7.2 Discussion

Our data indicate that there is a statistically significant correlation between legitimate, therapeutic exposure to opioid analgesics and the magnitude of abuse. While this seems logical and intuitive, the relationship has only been inferred previously.81 What this means, of course, is that in areas in which a drug is used widely for therapeutic purposes there is, unfortunately, a coincident increase in availability to those who use drugs non-therapeutically. It seems reasonable to assume that a small percentage of every opioid drug prescribed is diverted and used non-therapeutically (e.g., to get high). Thus, when a great deal of drug is prescribed, the actual numbers of cases of abuse will rise accordingly. This postulate assumes that the value of a drug for non-therapeutic purposes determines the level of diversion, and, as a result, the relative rates of abuse for specific opioid analgesics reflect their abuse liability. It is further assumed that the rate of abuse will remain constant across the country (i.e., abuse rates closely track exposure). If this is true, then if a specific area of the country has disproportionately high levels of abuse, this would suggest that some regionally specific factors make this area unique. The fact that there are, as we have found, signals of high abuse in very discrete loci is not new, since it has been shown for decades that prescription drug abuse (opioids, sedatives, and stimulants) is indigenous to certain areas,82-85 including the Northeast, and that 'epidemics' of abuse often appear suddenly in as few as three to five cities and then quickly dissipate. It is noteworthy that the 'signals' of abuse we found in our studies, while present to some extent in larger cities, are for the most part, concentrated in small- to medium-sized urban, suburban, and rural areas. The reasons for this are unclear, but several prominent possibilities exist, as suggested in earlier studies73,74: First, very cheap heroin is often not readily available in non-urban areas; second, prescription drug abuse has been indigenous for decades in some rural areas82-85; third, prescription drugs are often viewed as 'legal', more socially acceptable, and can be obtained relatively easily in much safer locations than heroin; and finally, the cost of prescription drugs at $1–$2/mg may be less of an obstacle to their use in suburban, small urban, and rural areas than it is in the inner cities where financial resources are more limited.

Our observation that therapeutic exposure to a drug leads to corresponding increases in abuse has far-reaching implications vis-à-vis the use of analgesic drugs and the public health. What seems clear is that the public health would not be well served by the simplest conclusion - reducing the therapeutic use of drugs will also reduce abuse. Rather, a risk-benefit ratio needs to be determined for each drug which takes into account the degree of exposure. Most importantly, we believe that this ratio needs to be held constant regardless of exposure. That is, as with all drugs used in medical practice, if a rate of any adverse event of 1 case/1000 URDDs (i.e., 0.1%) is judged to be an acceptable risk-benefit ratio, then this should be true if one thousand or one million patients are legitimately prescribed the drug. Thus, if drug control policy is based on simply the number of abuse cases and ignores the risk-benefit ratio, this is not only contrary to protecting the public health, but more importantly, places drugs with substance abuse potential in an entirely different category than any other medically used class of drugs.

In conclusion, our results demonstrate that there is an excellent correlation between therapeutic exposure to opioid analgesics and their abuse. This is certainly not a unique property of opioid analgesics since all drugs have adverse events which increase in number as more patients are prescribed the medication. Thus, proper medical practice dictates that before a drug is used a risk-benefit ratio should be constructed which balances the efficacy of the drug against its adverse events. The most meaningful index of the safety of the drug and the tolerability of adverse events is: number of adverse events/1000 people using the drug therapeutically. Obviously, the lower the rate the safer the drug, but, most importantly, this ratio places the incidence of adverse events in perspective by correcting for exposure. We argue that the same risk-benefit analysis should be applied to opioid analgesics; unfortunately, all too often regulatory agencies, such as the FDA and DEA, focus solely on the numbers of cases of abuse, non-corrected for exposure, in the control of these medications. This treats opioid analgesics differently than all other drugs and seems not only scientifically and clinically indefensible, but contributes to the under treatment of pain in this country by overstating the incidence of abuse which, in turn, nurtures 'opioid phobia' among physicians. We believe the rate of abuse described in this paper—cases of abuse per thousand patients using the drug—best describes the risk-benefit ratio of this vitally important class of drugs and should be used as the basis for evidence-based medical use of these drugs.

8. Conclusion

Although there has been an upsurge in the abuse of prescribed opioid analgesics over the past decade,

we believe much of this increase is due to an equally prominent upsurge in the therapeutic use of these drugs. That is, if a small percentage of opioids used therapeutically are diverted for non-therapeutic purposes, and if this is held constant, then naturally the incidence of abuse will increase as therapeutic availability increases. Nonetheless, it is apparent that the rate of abuse of prescription opioids has increased slightly more rapidly than can be predicted solely on the basis of the considerations outlined above. It appears that those most prone to abuse have an extensive degree of physical disease, particularly psychopathology. Given the characterization of those at risk for abuse, physicians should be able to recognize these individuals and use opioids carefully in this group. Moreover, given the intrinsic co -morbidity in chronic pain patients, it seems clear, as stressed previously,86,87 that any comprehensive pain management program should treat not only pain and the underlying physical disease state causing the pain, but other co-morbid physical and psychiatric conditions as well. Moreover, given the pharmacological complexity of managing pain with opioids, including breakthrough pain, the involvement of pain management specialists in the treatment plan for most of those in chronic pain seems appropriate to provide optimal treatment.

Biography

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Theodore J. Cicero serves as a Professor of Neuropharmacology and Neurobiology, and also as Vice Chairman for Research, in the Department of Psychiatry at Washington University School of Medicine. He served asVice Chancellor for Research at Washington University from 1996 –2006. Dr. Cicero received his Ph.D. in Neuropharmacology from Purdue University in 1969. He has been at Washington University since that time, becoming a tenured professor of Psychiatry and Neurobiology in 1978. In addition to his university positions, Dr. Cicero serves on the Editorial Board of many journals and is an expert advisor to the World Health Organization Substance Abuse Advisory Group. He is also past chairperson of the Food and Drug Administration Drug Abuse Advisory panel (1985 – 1993). Dr. Cicero is a life fellow of the American College of Neuropharmacology and past president (then Chairman) of the College on Problems of Drug Dependence (1984-1985). He has remained active in CPDD for well over 35 years. Dr. Cicero has over 180 publications related to the neurobiological substrates of substance abuse and prescription opioid abuse and has active grants from the National Institute of Drug Abuse.

Conflict of Interest Statement:

Supported in part by NIH grant (DA020791). Although Drs. Cicero, Inciardi and Surratt serve as consultants to a number of pharmaceutical firms that market opioid analgesics, there is no overlap at all in terms of areas of consultation and this research, nor was any funding provided by a pharmaceutical firm. Theodore J. Cicero had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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