



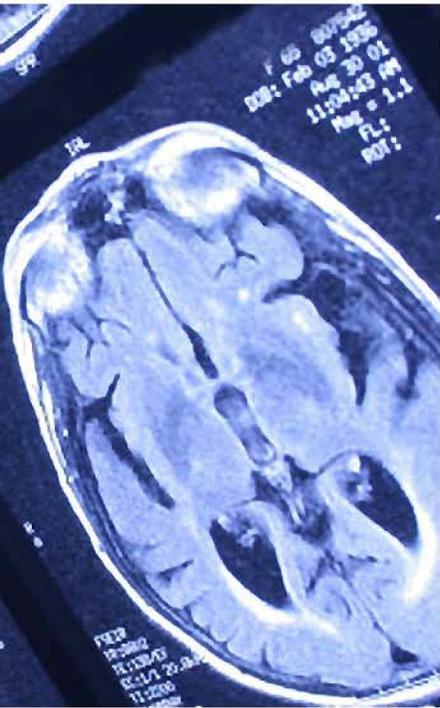
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A confluence of current research reveals varied findings which impact our understanding of who is at risk for drug abuse. Patterns of prescription opioid abuse and comorbidity, the unique characteristics of adolescent brain function that lead to risky behavior, the vulnerability of some medical specialties to substance abuse and the potential of case management for reducing relapse inform our awareness of the particular risks for abuse within certain population groups.

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Edited by Eric A. Voth, MD, FACP and David A. Gross, MD, DFAPA, our intended readership includes clinicians, clinical researchers, policymakers, prevention specialists and the interested public.



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COMMENTARY

Understanding the “Compassion” Issues

Patterns and Characteristics of Prescription Opioid Abuse in the United States

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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 ($p<0.01$) 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 studies^{73,74}: 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

Theodore J. Cicero

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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 as Vice 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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Neurobiology of Addiction and the Adolescent Brain

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Abstract

Examining the neurobiology of addiction, the roles that comorbidity, stressors and genes play in brain reward circuitry and the changes in the adolescent brain enable us to understand why adolescence is a time of increased risk taking and, subsequently, increased risk of substance abuse. Untreated comorbid disorders, genetic predisposition, environmental stressors, personality and age of onset of use are factors which may add to both risk and a more chronic and severe form of addiction.

Introduction

Addiction can be broadly described as a large range of recurring compulsive behaviors in a specific activity in which an individual continues to engage despite harmful consequences to the individual's social, biological and psychological health. Although the term is often associated with drug addictions, this definition can include such behaviors as compulsive gambling and overeating. Although drug dependence, as defined by [Diagnostic and Statistical Manual of Mental Disorders](#) (DSM-IV TR), is considered a disease state, the term addiction is not yet considered to be synonymous with this terminology. Also, drug dependence that involves drug withdrawal is distinct from addiction which involves compulsive use despite adverse consequences. Addiction for the purposes of this chapter will consider the DSM-IV-R definition of drug dependence.

Addiction to drugs and alcohol can occur anytime throughout the life of an individual. However, the age of onset is crucial to long, chronic and relapsing effects of substance abuse. Age is a risk factor likely to influence the onset of substance use during childhood and adolescence. Youngsters who begin drinking early, 11-12 years of age, had a higher percentage probability of meeting the DSM III-R criteria for substance abuse (13.5%) and substance dependence (15.9%), compared to those who began drinking at age 13 or 14 (13.7% and 9.0%, respectively). Those who initiated drinking at age 19 or 20 had rates of 2% and 1%. Schukit (1) has noted that the age when a substance abuser was most likely to have started drinking was 13, when first drunk was age 15, had their first problem associated with drinking at age 18, and first dependence was age 25-40. Death was most likely to occur at age 60. Importantly, rapid progression of alcohol and drug disorders occurred often with earlier age of onset and frequency, not duration of use (2; 3). Those individuals with earlier onset had a shorter time span from first exposure to dependence than did adult onset groups (4). Age of onset of heavy drinking also predicted alcohol-related problems (5). Early age of onset also influenced higher risks for the use of other substances, as noted in this case scenario. Adolescent onset adults had higher lifetime rates of cannabis and hallucinogen use disorders, shorter times between the development of their first and second dependence diagnosis and higher rates of disruptive behaviors and major depression (4).

Although early use may help to predict the risk of developing a substance abuse disorder (SUD), many teens who abuse substances will not develop an addiction following the maturation of the prefrontal cortex (PFC) in the early twenties (6). It is important to know the neurobiology of addiction, if and when it does occur, in order to understand the roles that comorbidity, stressors and genes play in these pathways which make the development of addiction more likely. It is also important to understand the changes that the adolescent brain undergoes in order to understand why this is a time of increased risk taking. Certain comorbid conditions may affect the brain reward circuitry leading to self medication of these conditions. However, if these comorbid conditions are detected early and treated, like Attention Deficit Hyperactivity Disorder/Attention Deficit Disorder (ADHD/ADD), the risk of developing a substance abuse disorder may be reduced. Stress or genes may be inherited that may increase the sensitivity to the reinforcing effects of the drugs on the brain reward circuitry. The goal of this article is to first discuss the neurobiology of addiction then to cite specific examples of how stressors, genes and comorbid conditions can influence the brain reward circuitry to increase the risk for substance abuse. Finally, the development of the adolescent brain will be discussed in order to understand why this stage of development is associated with the increased risk taking that can lead to substance abuse.

Changes in the Brain Reward Circuitry That Lead to Addiction

First, one must understand how one learns that a stimulus is salient so that the individual will learn to seek out the salient stimuli. When an individual uses cocaine, there is a rapid increase in dopamine in the shell of the nucleus accumbens (NAc). Since the cocaine is taken intravenously in this example, dopamine levels increase more rapidly and at higher levels, and therefore, greater magnitude is given to the pleasurable high. Now dopamine will be given off even only when one is anticipating using the drug (7). The evolution of this process will be discussed below. First, the shell of the NAc and dopamine are

involved in acute drug reinforcement but the core of the NAc; the basolateral amygdala and the OFC are involved in the chronic drug use that leads to addiction. The latter does not involve dopamine but rather the recruitment of glutamatergic efferents from the OFC to the core of the NAc (7; 8).

What causes the PFC (anterior cingulate and the orbital frontal cortex) to no longer recognize previously salient reinforcers and to recognize only drugs with chronic substance use? Chronic drug use causes changes in the intracellular level that cause changes in circuitry that lead to dysregulation of the reward circuitry involving the PFC, basolateral amygdala and the core of the NAc.

Changes in the intracellular level have been described as three stages (7): the acute stage, the transition stage and the end (addiction) stage.

Stage 1 - Acute Drug Effects

A review has shown that following the acute administration of cocaine, dopamine levels of the NAc are elevated with little effect on glutamatergic tone, to increase locomotor activity, and stimulate rewarding processes (9;10;11). However, the D1 dopamine receptor is stimulated, and the D1 dopamine receptor stimulation causes:

1. Activation of cAMP dependent protein kinase (PKA)
2. PKA induced phosphorylation of transcriptional regulator cAMP response element binding protein CREB
3. Induction of early gene products like cFOS.

cFOS causes neuroplastic changes that are short lived since the molecule cFOS is very unstable. This transcription factor activates genes that produce dynorphin, which causes dysphoria during early drug withdrawal, and genes that inhibit dopamine and locus ceruleus (lc) opioid receptors which, in turn, decrease drug reward. The transcription factor cFOS is so unstable that it dissipates in 4 to 12 hours. Therefore, limited exposure to drugs will enable the system to return to normal.

Stage 2 - Transition to Addiction

Chronic repeated administration of the drug causes stimulation of the D1 receptor to produce proteins with long half lives, such as delta FosB. Delta FosB modulates the transcription of the synthesis of certain AMPA glutamate receptor subunits and cell signaling enzymes. A GluR1 glutamate receptor in the ventral tegmental area (VTA) forms after discontinuation of substances like cocaine. Also, animals with activated Delta FosB have exaggerated sensitivity to the rewarding effects of drugs (9). In addition, Delta FosB also increases Cdk5, which, in turn, blocks the stimulating effects of cocaine or blocks the anxiolytic effect of alcohol so that, in both instances, more cocaine or alcohol is needed to get the same effect (12). Cdk5 may be one of the reasons tolerance occurs in substance abusers. Hence, if the above is true, Delta FosB may increase the rewarding effects of drugs, causing an individual to seek out these rewarding effects more often, and when the individual does, more of the drug must be used to give the same rewarding effect.

Other changes in circuitry during transition stage:

PFC to the NAc

During chronic drug use and withdrawal periods, there is an increase of G protein binding AGS3. Increased AGS3 levels inhibit D2 receptor signaling and correspondingly increase D1 receptor signaling which cause increased activity of projections from the PFC (in this case the anterior cingulate and the OFC) to the core of the nucleus accumbens which mediates behavior. What do these changes mean? The PFC determines what stimuli should be sorted out. However, these changes reduce the salience of non-drug motivational stimuli so that normal stimuli like food are no longer salient. The PFC becomes hypoactive to previously salient stimuli. However, when drug associated stimuli are available, there is a profound activation of the PFC and glutamatergic drive to the core of the NAc, and drug craving occurs. The changes in determining what is now salient (drugs) and the activation of the PFC to the core of the NAc to produce craving move the brain from a transitional stage to the end stage of addiction. As previously mentioned, glutamate plays a more important role in drug seeking after chronic drug use as dopamine (which is involved in acute reinforcement of drugs). The NAc core increases release of glutamate in response to stimuli that induce drug seeking and intake. Such stimuli may be a cue previously associated with drug use or a mild stressor.

Stage 3 - End Stage Addiction

Changes in protein expression that mediate the transition to addiction may induce changes in protein expression that move from temporary and reversible to permanent.

What effect does glutamate produced by the NAc have on permanent adaptations that lead to continued drug use? Two things occur. First, when presynaptic glutamate is released, the GluR2/3 inhibitory autoreceptor becomes less effective. Less glutamate is released in the NAc after cocaine withdrawal; therefore, presynaptic inhibitory GluR2/3 tone is decreased, and more glutamate is released in the core of the NAc when a mild stressor or a cue associated with drug use occurs. Increase in glutamate postsynaptically causes an increase in proteins that cause rigid dendritic morphology and signaling.

The role of the amygdala is to recognize the cue-associations with drug use. In this scenario, the basolateral amygdala would recognize cue-associations with drug use (motivationally relevant events) and trigger the PFC to exert (salience) its effect on the nucleus accumbens (to mediate behavior). Thus, the PFC would not be able to restrict the compulsion to seek out stimuli which have cue-associations with drug use (7; 8). Hence, this process may correlate to addiction or the loss of control, when the addict continues to use even though there is no longer pleasure in using the drug. The changes that occur after chronic drug use are more permanent than changes that occur during acute drug use and may be the reason why relapse occurs in addicts. Since adolescents may not be able to differentiate between motivationally relevant events (see developmental effects below) when addiction occurs, the PFC may increase the seeking out of risky behaviors whether they are relevant or not, or addiction may tune the otherwise more sensitive amygdala found during adolescence into a more sensitive drug state amygdala which now seeks out only drug associated relevant events once drug use begins.

To reiterate, addiction is caused by the development of a negative emotional state involving the hypothalamic pituitary axis (HPA) that occurs when not using. The neurobiological basis of the negative emotional states, the continued use of substances to ward off these negative affective states and the increased motivation to seek out substances of abuse come from two sources which include decreased reward circuitry and increased anti-reward circuitry. As noted below in Figure 1, cues would affect the drive to seek out drugs in the VTA and the basolateral amygdala that affect changes in drug circuitry, but changes in the anti-reward system (that would affect seeking out drugs to relieve stress) would occur in the extended amygdala (7;13).

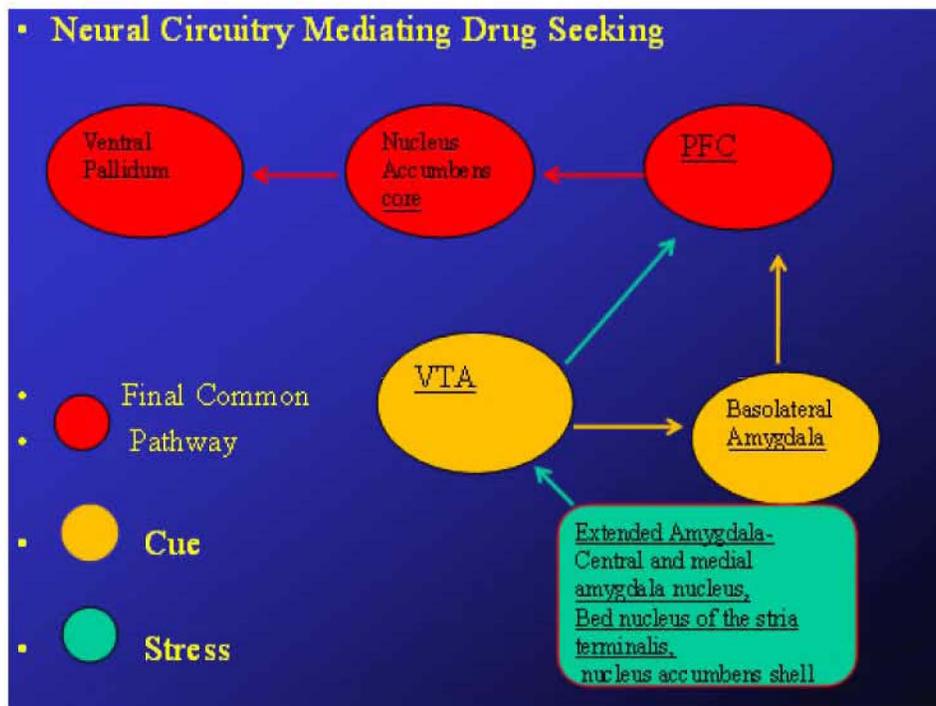


Figure 1
 Role of the reward circuitry and anti-reward circuitry from a developmental perspective.
 Adapted from Koob, G & LeMoal M, *Addiction and the anti-reward system Annual Rev Psychol.* 2008 59:29-53.

Stressors

Any compromise that would cause fetal distress or hypoxia increases the risk for the development of ADHD or learning disorders that could lead to an increased risk for substance abuse later in life. However, factors such as trauma, prenatal and postnatal stress and early life rearing experiences may alter addiction pathology later in life through changes in gene expression through chromatin remodeling without changes in DNA sequences (13; 14; 15). The interplay between stressors in the environment and genes (epigenetics) is crucial to explore when considering processes that may increase the risk for developing substance abuse. Prenatal, postnatal and abusive events that occur in childhood may cause an alteration on the expression of genes that may dysregulate the HPA which would increase the sensitivity to stress and the risk for using substances to relieve this stress. The use of substances to relieve the stress also dysregulates the HPA axis, leading to a vicious cycle of worsening sensitivity to stress each time substances are used to relieve the stress. Adolescence increases the risk of experimenting during this period. Adolescence also seems to be a time where there is increased sensitivity to stress. Therefore, there is an increased vulnerability during adolescence to abuse substances which would dysregulate the HPA and increase the likelihood of developing a substance abuse problem. However, the road to addiction that involves the interchange between stress, the environment and developmental factors during

adolescence may only occur in individuals who inherit genes that make one more susceptible to becoming addicted under these circumstances. In the latter case, certain environmental effects can cause permanent changes in circuitry that could cause an increase in substance abuse and increase the risk for moving from substance abuse to addiction. These factors, coupled with a family history of substance abuse, may be the reason some adolescents move rapidly from one substance of abuse to another. Thus, the story of addiction and how it occurs is extremely complex. Therefore, individual pieces of the puzzle must be explored based on present knowledge. Such entities as the specific role of stress on the HPA, genes, personality, drug history, comorbidity, developmental issues and changes in the reward circuitry should be explored. First, the role of stress on the HPA will be discussed.

Effect of Stress and Substances of Abuse on the HPA-Koob's (13) Model Anti-reward System

The anti-reward system involves the hypothalamic pituitary axis (HPA) and norepinephrine (NE) in the brain stress/emotional system and neuropeptide Y (NPY) in the antistress system.

Role of the Reward Circuitry System and the Anti-reward System

First, all drugs have positive reinforcing effects. During acute drug use, all drugs increase dopamine in the shell of the NAc and activate the HPA. Both of these processes increase drug reward (8; 16). The role of the prefrontal cortex (PFC) on the NAc and directing the salience given to the reward will be discussed later. However, the system can still revert to normal or homeostasis if chronic drug use does not occur.

However, if chronic drug use occurs, a process known as the opponent-process theory (17) can occur that leads to motivation to use drugs. Here an affective or hedonic habituation occurs (tolerance) and a negative affective or hedonic withdrawal (abstinence) process occurs. This would increase the motivation to use drugs to ward off the negative effects of withdrawal and tolerance which would promote the substance abuser to use more drugs to get the same effect. However, all drugs have common effects during withdrawal, including a decrease in D2 receptors (see "changes in brain reward circuitry"), hypofunctioning of the orbital frontal cortex (OFC) and increases in adrenocorticotrophic hormone (ACTH), corticosterone and corticotrophin releasing factor (CRF) by overactivating the HPA axis. Continued use leads to increased CRF and increasing anxiety each time the individual is abstinent.

Furthermore, overactivation of the HPA axis during chronic drug use also increases Norepinephrine (NE) (in the bed nucleus of the stria terminalis of the extended amygdala) which increases sensitivity to stress. Increases in ACTH, corticosterone, CRF and NE are part of the recruitment of brain stress/emotion systems. In addition, during chronic drug use, a decrease in neuropeptide Y (NPY) in the central and medial nucleus of the extended amygdala occurs. The change in NPY is referred to as a dysregulation of the brain antistress system. All these changes in CRF, NE and NPY are referred to as the anti-reward system.

The continued dysregulation of the reward circuitry system associated with tolerance causes the further recruitment of the anti-reward. As this occurs, the individual becomes more sensitive to stress each time drugs are used; therefore, the individual is more likely to seek out drugs to relieve the stress. Each time drugs are used, the continued decrease in reward function in the brain reward system and the increased recruitment of the brain anti-reward system moves the brain from a reversible state where homeostasis could have been reinstated to a more dysregulated state. This dysregulation occurs through a process known as allostasis. Allostasis is the attempt of the brain to achieve stability through change. Instead of the allostatic state reaching stability, it instead causes chronic pathological states and damage. A change in baseline occurs such that environmental events that would normally elicit drug seeking behavior have more impact - hence the brain is more sensitive to stress (16) induced drug seeking and involves input into the extended amygdala (8;13). Of course, as noted above, if a person has had chronic stressful experiences such as sexual abuse in her childhood, this may cause an alteration of the expression of genes that may dysregulate the HPA axis. These alterations would increase the sensitivity to stress and increase the risk for using substances to relieve this stress. Therefore, chronic stressors that occur before drug use occurs may set the stage so that the HPA system is less likely to return to normal once drug use and experimentation begins.

Role of Genes Molecular genetics

As noted above, stressors can turn on genes that can lead to the dysregulation of the HPA axis. In fact, high alcohol preferring rats that have increased anxiety-like responses have been shown to have lower NPY activity, which is involved in the anti-reward system. However, they also have decreased dopaminergic activity. The number of dopamine receptors genetically inherited may play another role in genetic vulnerability. However, an increase in dopamine can decrease the number of postsynaptic receptors, which causes the PFC to no longer recognize normal reinforcers as salient. The role of D2 receptors may also influence compulsion, according to Volkow. When D2 receptors are decreased in the nucleus accumbens, there is a corresponding decrease in metabolism in the orbital frontal gyrus and the cingulate gyrus. The cingulate gyrus initiates the ability to restrain control, and the orbital frontal gyrus shifts attention to what is salient. If the orbital frontal gyrus is destroyed, Volkow believes the drug abuser will continue to use drugs, even if using them is no longer pleasurable. Therefore, if decreased D2 receptors decrease the metabolism in the cingulate gyrus (so it can no longer inhibit the drive to use drugs) and the orbital frontal gyrus (so that it continues to compulsively use what it sees as salient, drugs, even though it is no longer pleasurable to do so), a person who has inherited decreased D2 receptors would be at more risk for developing substance abuse (18). In fact, Volkow (19, 20) has shown on PET scans that non-alcoholic family members in alcoholic families had higher than normal D2 receptor levels in

the caudate and ventral striatum and metabolism in the anterior cingulate (Brodman area 24/25) orbitofrontal (Brodman area 11) and the prefrontal cortex (Brodman area 9/10). These individuals also had personality scores of positive emotionality on the MMPI. This suggests that higher D2 receptor levels could protect against alcoholism by regulating circuits involved in inhibiting behavioral responses and in controlling emotions. To further illustrate this, when Thanos, et al (21; 22) increased D2 receptors in mice (by using an adenovirus), alcohol consumption by the mice decreased by 70 percent. Therefore, people born with an increase in D2 receptors may be at less risk to develop substance abuse, and those who inherit a decrease in D2 receptors may be more vulnerable.

Couple the decreased D2 receptors with the changes that occur in the motivational circuitry during adolescence (see developmental vulnerability below), and it becomes clear why exposure to substances of abuse during adolescence may increase the risk for developing substance abuse.

Studies of Inheritability

Adoption studies have shown increased risk for alcoholism of adopted away children of alcoholics (23) and increased risk for substance abuse other than alcohol (24). However, alcohol use by adoptive parents did not increase risk for alcohol abuse in adoptive children (25).

Adoptive studies have shown that genetic susceptibility seemed to be a stronger predictor of risk for substance abuse than exposure to adoptive parents using substances. However, both genetic and environmental influences may be correlated to substance initiation, whereas progression to substance abuse and dependence may be more related to genetic factors alone. In adoption studies conducted by Kenneth Kendler (26), 485 monozygotic and 335 dizygotic twins demonstrated that cannabis use was influenced by genetic and familial environmental factors, whereas cannabis abuse and dependence were solely related to genetic factors. This was also true for cocaine use versus abuse and dependence (27). Marc Schukit (28) has shown greater tolerance in children of alcoholics. In his study, children of alcoholics had to use greater proportions of alcohol before the reflex response to a stimulus was delayed to the same degree found in responses of children of non-alcoholics. In children of non-alcoholics, reflex response to a stimulus was delayed to the same degree on lower proportions of alcohol. This diminished response to alcohol was also measured by subjective feelings, levels of body sway, electrophysiological functioning and change in three hormones.

Personality, Drug History and Comorbidity

Although Koob and LeMoal (13) state that personality, drug history and comorbidity are more likely to influence drug use later, they all have some root in early childhood and adolescent behavior. Seldom does any substance abuser develop substance dependence without some significant precursors in their developmental history. Certainly, comorbid conditions can get worse under the influence of drugs and alcohol, but few individuals develop new comorbid conditions without some relevant family history. Therefore, one could argue that personality, drug history and comorbidity which originates in childhood and adolescence may together increase the likelihood of moving from substance abuse to a more severe form of dependence or addiction as the individual moves into and through adulthood. ADHD/ADD will be used as an example to illustrate how early detection and treatment can decrease the risk of substance use.

ADHD

It is well recognized that ADHD with conduct disorder has a much greater risk for developing substance abuse than ADHD alone. In fact, in a twin study done by Elizabeth Disney (13) of 626 pairs of 17-year-old twins, ADHD did not increase the risk for substance abuse unless it was associated with a co-occurring conduct disorder. Biederman, et al (86) have shown that untreated ADHD has more risk for future substance abuse than ADHD that is treated. If an adolescent has ADHD and is not treated, the risk of developing substance use disorder is two times higher than those who have ADHD and were treated with stimulants. The role of stimulants in the treatment of ADHD and possible explanations for the decreased risk for substance abuse will be discussed below. However, untreated ADHD seems to involve an underactive anterior cingulate and PFC (31;32). The role of the anterior cingulate and PFC in inhibiting impulsivity found with ADHD patients could increase the risk of using substances of abuse and lead to substance abuse and addiction.

Exposure to stimulants for treatment of ADHD/ADD

Since there is so much controversy over the use of stimulants in the treatment of attention deficit hyperactivity disorder/attention deficit disorder (ADHD/ADD), a common pediatric disease, some point of clarification between the uses of stimulants for medicinal versus recreational purposes should be noted.

First and foremost, one must consider the speed with which substances of abuse move through the blood brain barrier. Swanson and Volkow (33) have pointed out that the liability of a drug to cause reinforcing acute euphoric feelings is associated with the instant high achieved by using drugs of abuse either by smoking, snorting or using intravenously. There is a rapid dopamine blockade of dopamine transporters in the ventral striatum (containing the shell of the nucleus accumbens), causing a euphoric high. However, methylphenidate taken orally does not produce this rapid high because it enters the brain barrier more slowly and is less associated with a high that causes a reinforcing effect of the drug. In fact, oral methylphenidate may not induce craving even if it is taken by a cocaine addict. Volkow, et al (34) have shown that 20 mg of oral methylphenidate will not elicit drug craving unless it is associated with a cocaine

cue. Therefore, adolescent substance abusers who have used cocaine or other substances linked to abuse should not use stimulants as first line treatment for ADHD since it is difficult to prevent the drug craving associated with the cues of cocaine use. If the ADHD is severe and no other medication has been helpful in treating the substance abusing ADHD adolescent, one must be cautious in using stimulants without rigorous relapse prevention, if at all. Care must be used in adolescents using cigarettes who are also ADHD. Upadhyaya, in unpublished research, has shown that nicotine in ADHD patients can reinforce the effects of stimulants, whereas the effects of stimulants are not reinforcing in ADHD patients who did not smoke cigarettes.

Although early use and abuse of alcohol increased the risk of later substance abuse, new studies on the use of stimulants for the treatment of ADHD/ADD may actually decrease the risk of developing substance abuse. Reasons for this may be explained by research done by Castellanos (35). Castellanos reviewed total cerebral volume of treated and untreated adolescents with ADHD. Total white matter in the unmedicated ADHD adolescents was lower than medicated and normals. It is hypothesized that perhaps the trophic effect on myelination, dendritic branching and length of spines in the treated ADHD youth was somehow protective. How might this occur? Luna (36) has shown that a normal process that occurs during adolescence is an increase in myelination. The effect is an increase in processing speed. Therefore, the lack of myelination may decrease processing speed, and these effects may increase the risk for substance abuse related to poor academic success.

Research by Thanos et al (37) may give further explanation for the role between early use of stimulants for medicinal reasons and decreased risk for development of substance abuse. As noted before, overexpression of D2 receptors reduces alcohol and cocaine self administration in mice (20;21; 38), decreases drug liking and may be protective against substance abuse in humans (19;22). Thanos found significantly reduced rates of cocaine self stimulation during adulthood in periadolescent rats treated with 2mg/kg oral methylphenidate for eight months as compared to periadolescent rats treated with 1mg/kg or rats receiving water. The availability of D2 receptors was significantly lower after two months of treatment in rats given 1 or 2 mg/kg of methylphenidate compared with control rats, but after 8 months of treatment it was significantly higher. The rats given 2mg/kg of methylphenidate at eight months had greater D2 receptor binding availability than rats given 1mg/kg. Therefore, consistent methylphenidate treatment (started in adolescence) attenuated cocaine self-administration during adulthood.

Therefore, if patients with ADHD are treated as children, this treatment may reduce the risk for the development of substance abuse disorder.

Personality

Temperament may explain why some adults continue to demonstrate characteristics of dependence. Both Robert Cloninger (25) and Thomas Babor (39) identified personality traits consistent with those who have poorer prognoses. Cloninger's type 2 and Babor's type B alcoholics share common characteristics: early onset of spontaneous alcohol-seeking behavior; diagnosis during adolescence; rapid course of onset; genetic precursors that put them at risk to develop substance abuse; severe symptoms of deviant behavior, including fighting and arrests when drinking; and greater psychological vulnerability. Cloninger's type 2 and Babor's type B alcoholics may be related to youth who are thought to have conduct disorder. The conduct disorder is thought to be related to genetic vulnerability, negative environmental factors (poverty, parental neglect, marital discord, parental illness and/or parental alcoholism) and are thought to have an impairment in frontal lobe activity which affects their ability to plan, to avoid harm and to learn from negative consequences - traits often found in the type 2 or type B alcoholics. The same type of personality characteristics were found in kindergartners who had an increased risk for development of SUD in adolescence (40).

More recent research has tried to describe the relationship between personality and risk taking behaviors in six areas including smoking, drinking, drugs, sex, driving and gambling (41). Risk taking across all six areas was related to impulsivity, sensation seeking, aggression and sociability but not to neuroticism-anxiety and activity.

Development of the Adolescent Brain

Obviously, if psychiatric disorders and learning disorders are detected early and treated, there is less risk for developing substance abuse. However, adolescence is a time of experimentation. Why do adolescents experiment with risky behaviors? Much of this may be due to the dramatic changes that occur during adolescence. The following is an explanation of these changes.

The literature suggests that adolescent cognitive development is progressively increasing during adolescence and that this cognitive control capacity is positively associated with maturation or increased activity within the prefrontal cortex (41;42;43). Therefore, one would assume that there would be a linear increase in changes in behavior with better control during adolescence as compared to childhood. However, adolescence has shown to be a developmental stage associated with suboptimal choices or a nonlinear change in behavior from childhood to adulthood. If cognitive control and an immature PFC were the basis for suboptimal choice behavior, then children should behave remarkably similar or even worse than adolescents, given their less developed prefrontal cortex and cognitive abilities. Thus, immature prefrontal function alone cannot account for adolescent behavior.

It has been suggested that perhaps researchers should consider adolescence as a period where two separate entities are independently working, lack of cognitive control (immature prefrontal cortex) and risk taking (due to earlier maturation of the nucleus accumbens (44; 45; 46, 47, 48,49)). According to this model, the individual is biased more by functionally mature limbic regions during adolescence (i.e., imbalance of limbic relative to prefrontal control) compared to children for whom these systems (i.e., limbic and prefrontal) are both still developing and to adults for whom these systems are fully mature. Further, the model reconciles the contradiction of health statistics of risky behavior during adolescence with the astute observation by Reyna & Farley (50) that adolescents are able to reason and understand risks of behaviors in which they engage. However, during emotionally salient situations, the limbic system will win over control systems, given its maturity relative to the prefrontal control system.

Casey and colleagues' (unpublished) neurobiological model proposes that the combination of heightened responsiveness to rewards and immaturity in behavioral control areas may bias adolescents to seek immediate rather than long-term gains, perhaps explaining their increase in risky decision-making and impulsive behaviors. They hypothesized that relative to children and adults, adolescents would show exaggerated activation of the accumbens in concert with less mature recruitment of top down prefrontal control regions. Recent work showing delayed functional connectivity between these prefrontal and limbic subcortical regions in adolescence relative to adults provides a mechanism for the lack of top down control of these regions (Hare et al, in press Bio Psychiatry).

Development of Goal-Directed Behavior

Specifically, a review of the literature suggests that impulsivity diminishes with age across childhood and adolescence (46; 47; 48) and is associated with protracted development of the prefrontal cortex (49).

In contrast to impulse/cognitive control, risk taking appears to increase during adolescence relative to childhood and adulthood and is associated with subcortical systems known to be involved in evaluation of rewards. Human imaging studies that will be reviewed suggest an increase in subcortical activation (e.g., accumbens) when making risky choices (51;52;53) that is exaggerated in adolescents, relative to children and adults (44; 45). These findings suggest different trajectories for reward- or incentive-based behavior, with earlier development of these systems relative to control systems that show a protracted and linear developmental course in terms of overriding inappropriate choices and actions in favor of goal-directed ones.

Evidence from Neuroimaging Studies of Human Development

Studies have begun to focus primarily on the region of the accumbens, a portion of the basal ganglia involved in predicting reward, rather than characterization of the development of this region in conjunction with top down control regions (PFC). A recent report of less ventral prefrontal activity in adolescents relative to adults during a monetary decision-making task on risk-taking behavior has been shown, however (54).

Given evidence of prefrontal regions in guiding appropriate actions in different contexts (55), immature prefrontal activity might hinder appropriate estimation of future outcomes and appraisal of risky choices and might thus be less influential on reward valuation than the accumbens. During adolescence, relative to childhood or adulthood, the immature ventral prefrontal cortex may not provide sufficient top down control of robustly activated reward processing regions (e.g., accumbens), resulting in less influence of prefrontal systems (orbitofrontal cortex) relative to the accumbens in reward valuation.

Why Would the Brain Be Programmed To Develop This Way?

Evolutionarily speaking, adolescence is the period in which independence skills are acquired to increase success upon separation from the protection of the family. Seeking out same-age peers and fighting with parents, which all help get the adolescent away from the home territory for mating, are seen in other species including rodents, nonhuman primates and some birds (56). Humans had to engage in high-risk behavior to leave their family and village to find a mate at the same time when hormones drive adolescents to seek out sexual partners. In fact, Luna, et al (26) have suggested that these risk taking behaviors may be necessary to sculpt the brain in order to reach the adult pattern necessary for efficient processing. Hence, adolescence is a crucial period of plasticity when brain circuitry and behavior are beginning to be established. Risk taking and novelty seeking may provide a mechanism for increasing exposure to the environment necessary for successful sculpting of the brain. However, in today's society when adolescence may extend indefinitely, with children living with parents and having financial dependence and choosing mates later in life, this evolution may be deemed inappropriate. Secondary to extended adolescence, many high risk behaviors may be engaged in that could increase chances for harmful circumstances (e.g., injury, depression, anxiety, drug use and addiction (57)).

Biological Predispositions, Development and Risk

Impulsivity plays a major role in risk for developing an SUD. Mischel showed that children typically behave in one of two ways: 1) either they ring the bell almost immediately in order to have the cookie, which means they only get one; or 2) they wait and optimize their gains, and receive both cookies. This observation suggests that some individuals are better than others in their ability to control impulses in the face of highly salient incentives, and this bias can be detected in early childhood (58) and remain throughout adolescence and young adulthood (59). Some theorists have postulated that dopaminergic mesolimbic circuitry, implicated in reward processing, underlies risky behavior (60). Individual differences

in this circuitry, such as allelic variants in dopamine-related genes resulting in too little or too much dopamine in subcortical regions, might relate to the propensity to engage in risky behavior (61). The NAc has been shown to increase in activity immediately prior to making risky choices on monetary-risk paradigms (51;52;53), and as described previously, adolescents show exaggerated accumbens activity to anticipated or rewarding outcomes relative to children or adults (44;45). However, some adolescents may be more prone than others to engage in risky behaviors. Therefore, it is important to consider individual variability when examining complex brain-behavior relationships related to risk taking and reward processing in developmental populations.

To explore individual differences in risk taking behavior, Galvan and colleagues (46) recently examined the association between activity in reward-related neural circuitry in anticipation of a large monetary reward with personality trait measures of risk taking and impulsivity in adolescence. Functional magnetic resonance imaging and anonymous self-report rating scales of risky behavior, risk perception and impulsivity were acquired in individuals between the ages of 7 and 29 years. There was a positive association between accumbens activity and the likelihood of engaging in risky behavior across development. This activity varied as a function of individuals' ratings of anticipated positive or negative consequences of such behavior. Those individuals who perceived risky behaviors as leading to dire consequences activated the accumbens less to reward. This association was driven largely by the children, with the adults rating the consequences of such behavior as possible. These findings suggest that during adolescence, some individuals may be more prone to engage in risky behaviors due to developmental changes in concert with variability in a given individual's predisposition to engage in risky behavior (46). Cloninger's Type 2 personality may be one explanation for this variability since negative consequences do not have much bearing on choices made by these individuals.

The question as to whether changes in impulsivity could also be a variability was also studied by Galvan (46). Impulsivity is associated with immature ventral prefrontal development and gradually diminishes from childhood to adulthood (49). The negative correlation between impulsivity ratings and age in the study by Galvan and colleagues (46) further supports this notion. In contrast, risk taking is associated with an increase in accumbens activity (51;52;53) that is exaggerated in adolescents, relative to children and adults (44; 45). Thus, adolescent choices and behavior cannot be explained by impulsivity or protracted development of the prefrontal cortex alone, as children would then be predicted to be greater risk takers. The findings not only provide a neural basis for why some adolescents are at greater risk than others, but also a basis for how adolescent behavior is different from children and adults in risk taking.

Collectively, these data suggest that although adolescents as a group are considered risk-takers (62), some adolescents will be more prone than others to engage in risky behaviors, putting them at potentially greater risk for negative outcomes. Further, these individual and developmental differences may help explain vulnerability in some individuals to risk-taking associated with substance use and, ultimately, addiction.

In conclusion, human imaging studies show structural and functional changes in frontostriatal regions (49; 63; 64; 65; 66) that seem to parallel increases in cognitive control and self-regulation (42; 68; 69; 70). These changes appear to show a shift in activation of prefrontal regions from diffuse to more focal recruitment over time (68; 70;71;72;73) and elevated recruitment of subcortical regions during adolescence (47;68;73). Although neuroimaging studies cannot definitively characterize the mechanism of such developmental changes, these changes in volume and structure may reflect development within, and refinement of, projections to and from these brain regions during maturation suggestive of a fine-tuning of the system with development.

Taken together, the findings synthesized here indicate that increased risk taking behavior in adolescence is associated with different developmental trajectories of subcortical pleasure and cortical control regions. These developmental changes can be exacerbated by individual differences in activity of reward systems. Although adolescence has been distinguished as a period characterized by reward seeking and risk taking behaviors (56; 62), individual differences in neural responses to reward predispose some adolescents to take more risks than others, putting them at greater risk for negative outcomes. These results provide crucial groundwork by synthesizing the various findings related to risk taking behavior in adolescence and in understanding individual differences and developmental markers for propensities to engage in negative behavior.

Role of Family and Peers During Key Developmental Stages

Modeling the use of alcohol or drugs by parents when children are young increases the notion that drugs and alcohol are not harmful substances, and this risk factor increases the risk for using as a teen (75). Peers have a stronger influence on adolescents than their parents and not only influence initiation of use but relapse (76;77). Neurobiological reasons for this can be found in a study by Steinberg, et al (78). Examination of fMRI data indicated that the presence of peers activated certain regions that were not activated when peers were not present during a risky driving game. These regions included increased activity in the medial frontal cortex, left ventral striatum (primarily the accumbens), left superior temporal sulcus and the left medial temporal structures. This increased activity in the presence of peers was associated with a significant increase in oxytocin which heightened adolescents' attentiveness to memory for social information. Therefore, after puberty adolescents are more likely to seek out risky behaviors, especially in the presence of their peers. This oxytocin may also explain the role of sex hormones during puberty and the increase in risk taking behavior. Although sex hormones may not influence the amygdala and the accumbens directly, the influence of sex hormones on oxytocin and the corresponding effect of

oxytocin in regulating social bonding and recognition and memory of social stimuli in combination with the reasons for increased risk taking behavior may more correctly explain the increase in risk taking, especially in the presence of peers.

Conclusion

As noted by Iacono, et al (79) at the neurobiologic level, behavioral disinhibition can occur via bottom up mechanisms whereby stimuli acquire excessive salience or motivational drive is high or via failure of top down control mechanisms. During adolescence, the bottom up mechanisms become more important and may explain why adolescents experiment more with risky behaviors during this developmental stage. Special care should be given to the access to substances of abuse during adolescence. For instance, unused medications for pain in the home should be properly monitored so as to avoid the use of these substances by adolescents. Underage drinking is still an important factor, and adolescents should be monitored by parents during this risky period. Obviously, if an adolescent is using or experimenting with substances of abuse and the patient is being treated with a stimulant for ADHD/ADD, careful monitoring should be used by the physician involved. If a patient is abusing substances, it is critical to determine whether a stimulant is appropriate to use under these circumstances in order to ensure that the stimulant will also not be abused, diverted or contribute to a worsening of the substance abuse. During these situations, other medications like atomoxetine should be considered for the treatment of ADHD/ADD. However, one cannot discuss onset of substance abuse without addressing risk factors which may lead to abuse. No one risk factor leads to substance abuse. In fact, the more risk factors an individual has, the greater the risk of developing the disorder. Untreated comorbid disorders, genetic predisposition, environmental stressors, personality and age of onset of use are factors which may add to the increased risk for using substances of abuse during adolescence and may contribute to a more chronic and severe form of addiction. Therefore, one must understand risk factors and never underestimate the importance of early intervention. No one can understand addiction without understanding when, where and why risk factors began from a developmental perspective. For these reasons, addiction may be thought of as having pediatric origins. Early intervention can obviously decrease the risk of developing substance abuse. However, missed opportunities to intervene may increase the probability of using during adolescence.

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Physicians Impaired by Substance Abuse Disorders

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Abstract

Physicians are at risk for substance abuse disorders at rates comparable to non-physicians. While overall substance abuse is no more common in physicians than in age-matched controls, abuse of prescription drugs and opiates is more common in physicians. Also, certain specialties, such as anesthesiology, are overrepresented among substance abusers. Detection of a physician impaired by substance abuse is a challenge, since a physician's practice is often the last segment of life to be impacted. While colleagues are ethically obligated to report an impaired physician, they are less likely to do so if the physician's career and reputation will be immediately destroyed. Physician Health Programs (PHPs) in each state have guidelines for treatment and monitoring, and the prognosis for the physician addict is excellent.

Keywords: Impaired Physician, Physician's health, Prescription drug abuse

Definition

Physician Impairment, according to the American Medical Association (AMA), is any physical, mental or behavioral disorder that interferes with the physician's ability to engage safely in professional activities (1). Although the impairment of physicians can also be due to mental illness, neurological problems, and infectious diseases such as HIV or Hepatitis C, we will review specifically the impairment of physicians as a result of substance use, abuse or dependency. This is particularly relevant, since overall, physicians may have more narcotic and other prescription misuse than any other profession or group, and the disease of addiction impairs more physicians than any other disorder or disease (2). Some experts consider the term *impaired physician* to be archaic, demeaning, and inaccurate given that many physicians with these problems are able to continue working if they are treated and monitored.

Policy and Physician Health Programs

While physicians have long been susceptible to substance abuse disorders (SUDs), national attention was not received until the AMA Council on Mental Health's 1972 paper promoting state programs for the impaired physician. Still today, though, an AMA consensus statement acknowledges that not enough has been done to address mental health issues among physicians (3).

The public has no tolerance for impaired physicians, with most patients accepting only abstinence for any practicing physician (4). However, physicians are not commonly tested for substance use. Drug testing is performed for other professions where public safety is involved, such as transportation, yet drug testing is rarely a condition for employment for physicians.

While the public advocates for punishment of impaired physicians as the single best method for protecting patients from physician addicts, we argue that punishing physicians for substance abuse is not the best approach. Patient safety is most compromised while the impaired physician is in practice. Thus, encouraging the identification and treatment of impaired physicians is paramount for improving physicians' and patients' health. Survey data suggests that colleagues are less likely to report a doctor with an SUD if this doctor will face immediate and severe consequences for his actions. While many states have confidential treatment programs, with an estimated 8,000 practicing doctors enrolled nationwide, some states do not maintain an impaired physician's anonymity and immediately suspend an impaired physician's medical license. Exempting impaired physicians from punitive action also encourages them to proactively seek treatment and increases the likelihood that they will receive the comprehensive treatment they require.

Nearly all states have legal requirements that physicians report impaired colleagues to the Board of Medicine or PHP (5). Colleagues must play a role in the identification of impaired physicians. Many states allow for this to be done anonymously. The AMA Code of Medical Ethics informs physicians that they have an ethical obligation to report impaired, incompetent, and unethical colleagues. A 2002 Ethics Survey found that 65% of physicians would report an impaired colleague to the state medical board or chief of staff. However, many experts believe that this number simply reflects physicians' understanding of what they should do if they encountered an impaired physician, rather than what they actually would do in this situation. Experts argue that many physicians would prefer to speak to their colleagues about their problems rather than turn them in. In reality, most impaired physicians are referred for treatment by their family members or law enforcement (after a DUI, domestic violence report, or buying illegal drugs).

Physicians are particularly astute in their substance use and are overwhelmingly in denial. Most areas of the physician's personal life are affected prior to an apparent impact on clinical performance. In fact, clinical performance is often the last facet of a physician's life to be impacted by substance abuse. The fact that physicians' work is impacted very late in the course of substance-induced impairment actually contributes to the overwhelming denial we see from physicians with SUDs. Thus, by the time work-related impairment is apparent, the illness is severe and warrants prompt action. While it could take as long as fifteen years before an alcohol dependent physician might be impaired to the point that the user or colleagues recognize the need for treatment, the IV fentanyl user may require intervention within months. Indeed, one study found the mean duration of physicians' substance-related problems before treatment was 6-7 years (6).

Epidemiology

The number of physicians diagnosed and treated for a substance abuse disorder has increased significantly over the past decade (7). Medical students are also increasingly recognized as having substance misuse, abuse, or dependence. This is likely due to increased awareness and detection.

The leading cause of physician impairment is chemical dependency. Estimates suggest that approximately 15% of physicians will be impaired at some point in their careers. While this rate is no different from the rates in the general public, we would expect the rate of substance abuse to be lower than in the public, since all-cause mortality is lower among physicians than the general public, and because physicians smoke less and exercise more than age-matched non-physicians. Also, among professionals, physicians are over-represented in treatment for substance abuse disorders. Further examination of this overall rate reveals a number of troubling patterns. Furthermore, it is unclear how many physicians initiate and/or maintain an SUD through self-prescription, misuse of prescriptions, or use of illegal drugs.

Prescription misuse, opiate abuse and dependence, and suicide appear to be more common among physicians than their matched controls. is this the same reference as 8? In not, it requires a reference.. Although alcohol abuse and dependence are no more common among physicians than similarly matched controls, alcohol is the most commonly abused substance among physicians (8). Physicians have higher rates of abuse of prescription drugs; most notably, rates of physician misuse of benzodiazepines and opioids are up to five times higher than in an age matched population (9). Abuse of these drugs can be considered prescription misuse and are often self-prescribed, perhaps for self-medication. These patterns are particularly troubling because physicians have easy access to these prescriptions and are assumed to be educating their own patients about the appropriate use of medications (i.e. only take medications prescribed for them and only take medication according to the dose and directions prescribed). One possible implication of physicians' misuse of prescription medications is that physicians' familiarity with prescription drugs can lead to overconfidence about drug use and a false belief that substance use can be controlled without resulting in dependence or abuse.

2007 data from 109 physicians receiving treatment at a PHP showed a distribution of abused drugs as below (10).

Drug of Abuse	Percent
Alcohol	39.5
Opioids	33.9
Cocaine	11.9
Sedatives	3.7
Marijuana	2.8
Inhalants	1.8
Amphetamines	1.8
Other	4.6

Drug use often began before medical school and residency (11-13). Although some data suggests drug use increases in medical school, evidence for this conclusion is limited and varied. Surveys of medical students cannot be readily published for fear that the student drug users will be identified or the school will be branded as a drug-using institution. Strikingly, in one study of substance use among medical students, 17% of survey respondents used cocaine in medical school (14). It is imperative to learn more about substance use by medical students because use patterns appear different from the past, with more drug use and less alcohol use. Additionally, medical students may unfortunately choose professional specialties where their drug use as students and experimentation could rapidly lead to addiction and death.

Highest Risk Careers

Several theories exist to explain the prevalence of addiction among physicians, including stress, chronic fatigue, and access. Additionally, the same factors that contribute to non-physicians becoming substance

abusers could be at play. These factors include a genetic predisposition, particular personality characteristics, and youth experimentation. In support of this, studies have found that three-fourths of physicians with substance use disorders have a family history of addiction (15-16).

In data from PHP programs, impaired physicians are often family practitioners, emergency medicine physicians, and anesthesiologists (17-18). Additional studies found an overrepresentation of anesthesiologists, emergency medicine doctors, and surgeons among opiate abusers (19). Among all surgeons captured in a survey study from 1978-2002, 7% reported alcohol dependence (20). Data suggests that female surgeons have the highest incidence of alcohol abuse of all female physicians (21).

Anesthesiologists have a higher rate of substance abuse than any other specialty. For example, in 2003, while anesthesiologists represented only 5.6 % of Florida's physicians, they accounted for 25% of Florida's impaired physicians referred for an SUD (10). Anesthesiologists have the highest rate of narcotics and IV drug use of any medical specialty (22). Fentanyl is the controlled substance most often abused by anesthesiologists (23).

Table 2: PHP program participants by medical specialty, Florida 2007 (10).

Specialty	Percent
Anesthesiology	21
ER	18
Surgery	6
Family Medicine	6
OB/GYN	6
Radiology	6
Pathology	6
Orthopedics	3
Neurology	3
Psychiatry	3

Much research has also been done to understand why physicians in a particular specialty are more prone to SUDs. The apparent increased vulnerability of anesthesiologists has been attributed to everything from boredom, stress, and access, to a theory that certain specialties may preferentially attract physicians who are interested in using mind-altering drugs, to a theory that predilection for developing an SUD is related to work-related exposure to drugs with abuse potential (i.e. anesthesiologists have higher rates of SUDs because they, while in the operating room are continuously being exposed to drugs with abuse potential/reference ?)). Physicians do have much greater access to drugs than does the general population (24). While access can generally explain some of the trends in narcotic usage among physicians, access alone cannot account for some obvious discrepancies in data on substance abuse by physicians. For example, oncologists have access to many pain medications but very uncommonly become addicts. Alternatively, the field might be particularly attractive to those interested in mind-altering medications. Perhaps the same medical students who use drugs might be interested in anesthesia. Additionally, a recent hypothesis explores the operating room as a hazardous work environment that can sensitize the brain to drugs via secondhand exposure. The occupational hazard hypothesis, which found fentanyl and propofol in its bioactive form in the OR, suggests that these exposures can lead to neuronal sensitization and increased risk for developing addiction (25-26). Today, there is a heightened awareness in anesthesia programs, which might be contributing to the high reporting rates of substance abuse disorders in anesthesiology (22). However, despite this awareness in anesthesiology, the use of controlled substances has not significantly declined (23).

Other Impairment and Comorbidities

While we focus on impairment from substance abuse, it is important to recall that impairment can occur from other physical or mental limitations. Additionally, substance abuse disorders often occur concurrently with other mental illness. For example, the two most common comorbid diagnoses for the physician opiate addict are depression and cigarette smoking.

Physician substance abuse is associated with increased risk of suicide (27-29). Suicide rates are 40% higher in male physicians than age-matched peers and 130% higher in female physicians than age-matched peers. Among physicians, anesthesiologists have higher rates of suicide (30-32). This data can be skewed since physicians are more likely to succeed at suicide than are non-physicians. However, suicides by physicians may be underreported or erroneously reported as accidents by the pathologist or medical examiner.

Mental health problems frequently begin before medical school and may worsen during training. A review of 40 studies of medical students found that medical students are more likely to have higher levels of depression and suicide than age-matched cohorts (33-34).

Assessment and Treatment Outcomes

When receiving appropriate assessment and treatment, the prognosis for a physician with chemical dependence is excellent. Evidence suggests they can return to both professional and personal productivity. PHPs report high rates of professionals returning to work; a pooled sample of over 900 physician participants in 16 state PHP programs found an overall return to work rate of 72%. Additionally, for the 50% of physicians who completed the program, the rate of return to work was 91.4% (35). This is commonly attributed not only to the highly structured programs, which we will discuss below, but also the high cost of failure, which includes loss of medical license, income, reputation, and the significant reward of being able to return to practice if sobriety is maintained.

Abstinence is the goal for physicians impaired by substance abuse disorders. Opioid addict physicians, unlike their nonphysician counterparts, are consistently referred to detox and long-term treatment rather than Methadone Maintenance Treatment (MMT). In a 5-year study of 26 physicians in Florida's Professional Recovery Network for opioid abuse/dependence, no opioid addict physicians were referred or treated with MMT, and all were referred for detoxification and long-term treatment (36).

Physician addicts can have greater than 80% successful 5-year outcomes compared to most addiction treatment outcome studies, which report 6-month success rates ranging from 30-60%. Factors associated with physicians' high recovery rates include last-onset addiction (MDs using drugs in their 30s or 40s, not in their teens), long-term treatment with inpatient and 5-year outpatient components, having their career in jeopardy, random urine testing, and 12-step recovery groups. Additionally, treatment at a facility that has expertise in treating impaired physicians may result in a more favorable outcome.

Positive prognoses were associated with affiliation with Alcoholics Anonymous/Narcotics Anonymous, acceptance of addiction as a disease, honesty, and acceptance of spiritual principles (37). While AA and other 12-step programs are recommended and proven, this should be in addition to intensive treatment modalities (38) such as therapy for the individual, appropriate pharmacologic treatment of any comorbid psychiatric conditions, and family therapy.

In one study from the Washington Physicians Health Program (39), relapse was associated with past potent opioid use, coexisting psychiatric disorders, and a family history of addiction. Multi-substance abuse was also associated with failed treatment (40). Physicians who did not return to work were more likely to be using opioids or IV drugs (41). Thus, anesthesiologists have the greatest battle, with high risk for both relapse and accidental overdose. Relapse rates in anesthesia approach 20% (42). In one survey of 159 anesthesiology training programs, 34% of opioid users and 70% of non opioid abusers were able to return to anesthesia (43). This survey found 14 cases of suicide or lethal overdose among those returning to anesthesia, and in 16 percent of these 14 cases, death was the initial indicator or relapse. In another survey, 19% of anesthesiology training programs had at least one fatality (44). With the knowledge that fentanyl and propofol are in the air in the OR, perhaps additional counseling of the impaired anesthesiologist is necessary before a return to the field and toxic OR.

Although there is lore of a "needle barrier," which implies that IV addicts have the worst outcomes, recent trials and reports suggest otherwise. Data from a 5-year study in the state of Florida's impaired physician program found that outcomes were independent of type of drug used or route of administration. More than 88% of physicians who used crack, injected drugs, or both, had negative drug tests and positive physician assessment for 5-years and returned to work (45). Additionally, evidence from Florida also suggests that there is not significant outcome disparity between those who turned themselves in for treatment voluntarily and those who entered treatment by coercion.

Following successful completion of treatment, physicians enter into a multiple year contract with the PHP outlining conditions for return to practice. The contract includes:

- ▶ Avoidance of all mood altering drugs,
- ▶ Randomized drug testing (in urine, and in some states, testing of hair),
- ▶ Participation in weekly monitored group sessions with other physicians under contract,
- ▶ Attendance in weekly groups such as Caduceus or International Doctors in Alcoholics Anonymous, as well as AA or NA,
- ▶ Professional follow-up with an addiction specialist,
- ▶ Precise outline of consequences should the physician violate the contract.

This contract between the impaired physician and the PHP seems quite powerful and effective. In a study of 233 physicians under contract with North Carolina Physicians Health Program for the period 1995-2000, 91% had a good outcome (46).

Despite these encouraging statistics, physician impairment remains a serious issue in public health and patient safety. In order to achieve the best outcome for the physician and public, we must get better both at recognizing substance abuse disorders in our colleagues and in referring them early for treatment.

Biography

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Kimberly Gold is a fourth year medical student at the Yale University School of Medicine. She received her Bachelor of Arts from Columbia University. She is applying for residency in Internal Medicine and is interested in medical errors, patient safety, and the health of physicians.

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Scott Teitelbaum, M.D., F.A.A.P., A.S.A.M. received his undergraduate degree in Psychology at Lehigh University. He attended medical school at Rochester University. Completing his residency in Pediatrics at University of Connecticut, Dr. Teitelbaum served in private practice for ten years at Teitelbaum & Katz Pediatrics in Middletown, Connecticut after which he completed his Postdoctoral Fellowship in Addiction Medicine under the mentorship of Dr. Mark Gold and Dr. Kenneth Thompson at the University of Florida. Additionally, Dr. Teitelbaum completed a fellowship in Child Psychiatry at the University of Florida. Joining the Faculty in 2002, Dr. Teitelbaum serves as the Medical Director for the Florida Recovery Center, Director of Adolescent Recovery Services and Clinical Associate Professor for the Department of Psychiatry as well as the Department of Pediatrics. Additionally, he currently serves as the Clinical Chief of the Addiction Medicine Division within the Department of Psychiatry. His expertise in Addiction Medicine goes beyond chemical dependence and includes an intensive, in depth knowledge of compulsive gambling. He has been involved in the treatment and evaluation of compulsive gamblers on a statewide level. Dr. Teitelbaum currently serves as an Expert Panelist and Speaker for The National Youth Anti-Drug Media Campaign which is sponsored by The White House, Office of National Drug Control Policy. In addition to being board certified as a Pediatrician, Dr. Teitelbaum is certified by the American Society of Addiction Medicine and is a certified medical review officer.

Conflict of Interest Statement:

I declare that I have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled Physicians Impaired by Substance Abuse.

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The Use of Intervention and Case Management Models in Maximizing Recovery and Reducing Relapse Risks for Substance Abusers

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Abstract

This paper will explore the use of intervention and case management models in working with individuals who have been diagnosed with substance use disorders. Substance use disorders, or addictions, are defined as a disease; a concept supported by the medical and psychiatric communities. As such, it is considered chronic and progressive, and without a cure. Individuals diagnosed with substance use disorders are especially prone to relapse. High incidences of relapse will be discussed and relapse prevention measures as used during the course of treatment will be reviewed.

Substance abuse disorders tend to be difficult to treat, which has impelled treating professions to investigate alternate avenues of treatment delivery, such as intervention and case management. The utilization of both methods will be reviewed in depth. The rationale for the use of these models will be explored throughout. The continuum of substance abuse treatment will be identified as paramount in effectively decreasing the risk of relapse. Deficits in continuing care planning during the course of residential treatment and subsequent transition to an outpatient level of care will be reviewed. For reasons outlined within this paper, acceptance of both intervention and case management models can be challenging.

Keywords: Case management, relapse prevention, intervention, continuum of care, substance abuse.

Substance use disorders affect millions of individuals nationwide. The problems associated with these disorders are pervasive and destructive. Today, in the United States there are an abundance of treatment programs available to treat substance use disorders and the number of individuals actively seeking treatment and recovery has increased. A review of relapse statistics, however, yields disappointing results. It has been estimated that approximately 40% of all patients admitted for chemical dependency treatment in the United States are relapsers who have been previously treated for chemical dependency (1). Additionally, 47% of patients treated in private treatment programs will return to chemical use within the first year following treatment. (1) Most relapses occur within the first 18 months of recovery, and most of these occur within just the first six months of recovery (2).

Heightened relapse rates persist in frustrating professionals committed to treating the chemically dependent person and have prompted the need to explore and utilize additional methods and models of treatment intervention in an attempt to decrease the likelihood of relapse once treatment is initiated.

The substance abusing population tends to present with complicated clinical pictures. They may have deeply ingrained defense mechanisms that hinder their motivation for treatment or recovery and make treating these disorders more difficult. Chemically dependent individuals frequently experience co-existent issues secondary to their addiction such as comorbid psychiatric disorders, complicated medical issues, and legal problems. Substance abusers are defined as having complex needs and require continual rather than episodic drug abuse treatment (3).

The terms 'substance abuse,' 'chemical dependency,' and 'addiction' will be used interchangeably throughout this paper. The terms 'slip' and 'relapse' will also be used on a regular basis. The term 'slip' is defined as a brief or one time use of a substance following a period of abstinence whereas the term 'relapse' will refer to a full return of active substance use following a period of abstinence. As noted, high relapse rates have prompted treatment professionals to identify alternate models of treatment to assist their client in maintaining longer periods of abstinence and recovery. Intervention and case management models are two such alternate approaches that will be explored in detail throughout the course of this document.

Both models, and especially the case management model, incorporate the tenets of relapse prevention programming. From a public health perspective, relapse prevention can be considered a form of tertiary prevention, the goal to prevent relapse (and promote progress) in individuals who have already developed an addiction problem and have made a commitment to abstinence (4).

Addiction is widely accepted as a chronic and progressive disease that is said to be incurable, only managed. The disease concept of addiction is such that it suggests that once an individual has been

diagnosed with an addiction, the only real effective management of the addiction, or disease, is abstinence. An individual can have the disease of addiction, but can be in recovery. As such, the intervention and case management models are palliative in nature and aim to effectively manage the disease while promoting ongoing recovery. As with other chronic disorders, the only realistic expectation for the treatment of addiction is patient improvement rather than a cure.(5)

Intervention and Case Management: Approaches and Similarities

Intervention can be viewed as both a method for initiating treatment and recovery as well as a tool for promoting stabilization during crisis events. Case management is described as a model of service delivery that seeks to ensure and maintain continuity of care. The roles of the intervention specialist and case manager are similar in terms of their primary functions. Both the intervention specialist and case manager assumes the responsibility of engaging an individual in the treatment and recovery process, overseeing the coordination of care, serving as advocates for the client, providing education and continual support, and attempting to either initiate or re-initiate treatment.

The principal difference between the two specialists is best identified and tied to the level of care their client is currently receiving. Though intervention specialists perform the same key functions as case managers, their role is central to initiating treatment with clients whom have yet to commit to receiving professional care. The case manager, conversely, actively works with the client along the continuum of care including the residential (secondary) and the outpatient (tertiary) level of care.

Intervention

The use of professional intervention in initiating treatment and engaging a chemically dependent individual into treatment has been gaining popularity. Agencies offering intervention services are now more widely available.

It is not unusual for substance abusers active in their addictions to have difficulty appreciating the extent of their substance abuse or their need for treatment. He or she may be fundamentally unwilling to take the steps necessary to initiate the process of abstinence and recovery despite the negative consequences that may result from continued usage. Deeply ingrained defense mechanisms such as denial, minimization, and rationalization can hinder the substance abusing individual's personal ability to view the destructive path that results from ongoing substance abuse.

Intervention is a technique used to interrupt patterns of ongoing substance abuse. Its focus is on persuading treatment resistant and active substance abusers to make use of available professional help.

The process of intervention begins when family members or other concerned persons engage the services of an intervention specialist. It is likely that these support systems have previously made personal pleas to their loved one to receive professional help, often to no avail.

Until fairly recently, the benefits of utilizing intervention techniques had been questioned. Substance abuse professionals employed within the fields of addiction and mental health, as well as advocates of 12-step programs, expressed concern around the dynamics of the use of this motivational technique. Apprehension had been voiced by others "forcing" the addict/alcoholic into recovery, as opposed to allowing them to "hit bottom." Advocates for the use of formalized intervention techniques countered that intervention is a realistic, established, and effective means of helping substance abusers initiate recovery and that further risks associated with ongoing substance abuse such as death, could and should be avoided. Once the individual is a client within the treatment environment, the opportunity for insight usually develops. This fosters active motivation towards ongoing abstinence.

Interventionists are typically trained professionals who have varied responsibilities in addition to the actual facilitation of the intervention meeting. They provide education and support to both the substance abuser and their families, identify barriers to initiating and completing treatment, perform detailed needs assessments, attempt to ascertain appropriate levels of care, and identify suitable treatment options for clients. Additional core functions of intervention specialists relate to the coordination of treatment efforts, the facilitation of referrals to programs, and arranging for admission into a chosen treatment program. Intervention specialists serve as the primary point of contact for families, clients, and colleagues during this initial phase of treatment. The role of the intervention specialist in planning and facilitating an intervention is particularly analogous to that of a case manager as had been noted earlier.

Trained intervention specialists are experienced in identifying which program would be most suitable for their client's individual needs. This is achieved via the consideration of several factors including the client's gender, age, financial means for treatment, clinical needs, and any secondary diagnoses that may exist. Appropriate treatment matching can increase the probability of treatment retention and completion. An additional benefit of treatment matching is the likelihood of the client having a positive treatment experience.

The role of the intervention specialist does not normally conclude at the time of the client's admission into a treatment program. He or she may be responsible for ensuring that his or her client's needs are being met during the course of treatment. When possible, intervention specialists work in partnership with the residential treatment team in developing a comprehensive and individualized continuing care plan that will be utilized upon discharge.

Thus, the role of intervention specialist is varied and can be viewed to be critical in engaging resistant substance abusers to pursue recovery as well as by playing a key role in managing the initial part of the continuum of care.

Case Management Model

Case management is an approach to service delivery that works to ensure that clients with complex, multiple problems, and disabilities receive all the services they need in a timely, effective, and appropriate fashion (6).

This service delivery model can trace its roots to the discipline of social work. However, no formal or universal definition is assigned to describe the term 'case management.' Case management models, like the definitions of case management, vary with the context (7).

The term 'case management' has appeared in social services literature more than 600 times in the past 30 years (7). Case management service is not in and of itself a new or innovative service approach. Despite its historical prevalence and popularity, it remains an underutilized adjunct to treating substance abusers.

The case management model of treatment has been historically linked with the delivery of services within a hospital-based setting and most commonly within the professional disciplines of psychiatry and medicine. Case management is generally best associated with past legislation relating to psychiatric deinstitutionalization which, decades ago, escalated its overall popularity. The case management model had rarely been applied to the treatment of substance using clients. Substance abusers historically were never institutionalized as often as were persons with chronic mental illness and so were not directly impacted by legislation. Substance abusers were not generally targeted for the development of categorical systems of service delivery and were not generally recipients of case management services. (7)

Similar to deinstitutionalization efforts of the past, many modern chemically dependent individuals find themselves having to rely more and more on programs outside of residential settings. Private treatment programs can be significantly pricey, community-based programs may have long waiting lists, and insurance coverage for substance use disorders can be dismal, all of which prompt the need to explore alternate options for care. Alternate options for care, however, may be insufficient.

Intervention and Case Management in the Residential Setting

Upon admission into a treatment program, it is customary for the client to be assigned to one principal staff member who assumes the task of treatment planning and coordination of care. This staff member may be referred to as the client's primary therapist. Additional responsibilities of this staff member may include the referral of the client to in-house specialists such as spiritual counselors, nutritionists, psychiatrists, and others for consultation and treatment. Additionally, the primary therapist may also be charged with the development and construction of the client's continuing care or discharge plan. In many respects, this staff member serves as the client's case manager.

Clients who are the recipients of care on a residential basis can benefit from this level of care for several reasons. This setting provides clients with the ability to focus on their substance abuse issues within an environment where drugs and/or alcohol are inaccessible. Treatment schedules are typically very structured and promote consistency and regularity. Clients have the advantage of receiving ongoing clinical services provided by multi-disciplinary professionals. Additionally, the client housed within this clinical setting is afforded a temporary reprieve from having to deal with the day to day stressors of everyday life. The client is usually provided with the opportunity to participate in various treatment approaches such as individual psychotherapy sessions, therapeutic process groups, family therapy sessions, and educational didactic groups.

Many residential programs have adopted formal relapse prevention programming elements into their treatment regimen as a means of educating clients about the very real possibility of relapse post treatment. Clients are encouraged to identify their personal relapse triggers, to develop action plans designed to avoid these triggers, and to develop coping plans to effectively deal with these triggers if encountered post treatment that would otherwise jeopardize their recovery.

Relapse prevention planning generally focuses on the more obvious or overt triggers, such as people (drug dealers, using friends/family), places (bars), events (celebrations), and mood events (positive or negative). Less obvious triggers such as the very real pressures and concerns of day to day life may be disregarded as non-essential. Many individuals in early recovery are ill prepared to deal with the stressors that may simply not be avoidable, and many identify "stress" as a primary trigger without clearly identifying the specific sources of stress.

Although high risk situations can be conceptualized as the immediate determinants of relapse episodes, a number of less obvious factors also influence the relapse process. These covert antecedents include lifestyle factors such as overall stress level (8).

A continuing care or discharge plan generally includes relapse prevention measures previously identified by the client. It rests upon the optimistic assumption that the client intends to continue treatment in some form on an outpatient basis and is committed to ongoing recovery. However, many continuing care plans tend to be overly simplistic in design. A typical discharge plan generally provides a written set of guidelines for the newly recovering person to follow such as 12-step meeting attendance, obtaining a

sponsor, and selecting a home group. More sophisticated plans may include the name and contact information for a recommended clinician or outpatient program for continued care. More often than not, the actual plan does not resemble or attempt to replicate the services offered at the residential level such as the varied treatment modalities (individual, group, family therapy, nutrition, etc). Additionally, most plans provide directives on "what to do" and fail to inform the client on "how to do it."

For example, a client may have a discharge plan that suggests continued adherence to their prescribed medication regimen. However, it may not identify a practitioner to prescribe these medications or consider the possibility that the client may not be able to financially afford the medications on an ongoing basis.

Furthermore, continuing care plans may lack directions for dealing with typically non-clinical issues such as how to seek employment or construct a resume, manage time efficiently, or locate a treatment provider for ongoing care. The very real pressures of finances, employment, housing, and perhaps reunifying with and caring for children can be very stressful to the newly recovering and usually vulnerable individual (7).

Real life issues or stressors may include the need to handle financial responsibilities appropriately, obtain employment, make childcare arrangements, have means of transportation, and maintain household responsibilities. The authentic challenge of meshing recovery needs with the demands of daily life can contribute to amplified stress levels and situations that could result in slips or relapses. The case management model assumes that the client has very specific recovery and mental health needs as well as non clinical needs (financial, employment, life skills, etc) that need to be addressed as part of the overall continuing care plan (7). Because addiction affects so many facets of the addicted person's life, a comprehensive continuum of services promotes recovery and enables the substance abuse client to fully integrate into society a healthy, substance free individual (7).

Case Management and Intervention in the Outpatient Setting

Making the transition from inpatient/residential to the outpatient setting can be extremely challenging for a newly recovering individual. The utilization of case management services can be significantly advantageous to the client. Without a case manager to guide the client through the continuum of care, the newly discharged client assumes the responsibility of following a continuing care plan without the benefit of a treatment coordinator.

In general, outpatient programs and outpatient service providers (therapists, psychiatrists, and internists) practice within the scope of their profession and typically do not assume the role of "point of contact person." As such, they may be required to rely solely on the independent reporting of their client. Such information may be misleading or inaccurate. Case management is needed because in most jurisdictions, services are fragmented and inadequate to meet the needs of the substance abusing population (7).

Because a variety of professionals with specialized skills are involved in a treatment program, it is helpful to have one person aware of all the forces acting on the person (9). Thus, the use of a primary case manager to assume this role can be extremely helpful in bridging communication gaps among providers, providing timely updates, and ensuring that all providers are privy to critical information about the progress of their patient or client.

During this phase of treatment, the case manager continually assesses for plan compliance and progress and makes revisions as needed. The case manager is aware that in addition to the client's immediate recovery and mental health needs, the need to refer to ancillary services such as vocational counseling, social service agencies, and financial counseling is equally important to the overall functioning of the client. Therefore, a key function of case management at this level is to perform in depth needs assessment and to facilitate referrals. Case managers advocate for their clients, assist their clients in applying for ancillary services, and negotiate fees on behalf of the client. Whether through simple referral, advocacy, or skills training, it can be argued that by helping clients obtain resources they will be less likely to relapse (10).

Another critical, yet less utilized function of case management is the use of life skills training. Life skills training assists clients in developing or maintaining the skills necessary to support their recovery process and to reduce their overall stress level.

Improvement of basic life skills may be needed with issues relevant to time management, home organization, budget/money management, appointment coordination, transportation, and overall lifestyle balance. Inadequate coping or life skills issues can increase the risk of relapse. There is a higher likelihood of a relapse immediately following treatment, but incremental changes in coping skills lead to a decreased probability of relapse over time (11).

The objective of the case manager in working with clients to develop and maintain mastery of basic life skills is to decrease their stress level when the existing skills set is inadequate, to promote self sufficiency, and to encourage clients to act as proactive agents in their own lives. Educating clients on how to establish goals and providing them with skills training to successfully meet these goals empowers clients and can positively reinforce continued behavior.

As identified, the period of initial abstinence and recovery, particularly in the outpatient treatment setting, can be a very trying time for the client and thus may increase the potential for relapse. Because the disease of addiction is chronic in nature, it is also exceptionally prone to lapses and relapses. Clients that

slip or relapse during this phase of treatment will require immediate, rapid, and efficient intervention in order to successfully minimize the negative effects associated with ongoing or sustained use. The case manager is frequently the first professional to be aware of a slip or relapse and quickly notifies all pertinent supports. Immediate and competent intervention can reduce the length of time between periods of lapse or relapse and can reduce the likelihood of the client needing to be re-admitted into a hospital or residential treatment program.

Who Benefits the Most from the Case Management Model

It can be argued that most chemically dependent individuals would benefit from case management services. However, specific sub-populations such as young adults, chronic relapsers, those diagnosed with multiple disorders in addition to substance abuse, and older adults may benefit the most.

Young adults, due to their chronological age and limited life experience, may require additional assistance in the area of life skills development. They also tend to benefit from the additional supervision a case manager can provide. Similarly, individuals with longstanding histories of treatment and recovery attempts will also profit from the supplemental assistance of a case manager. Many such clients, as a result of repeated treatment attempts, may present as "institutionalized" and are only able to function well within the confines of a residential setting. They may have particular difficulty meshing their recovery needs and non-clinical needs on an outpatient basis.

Clients who have been diagnosed with co-occurring diagnoses which is common with substance abusers (depression, anxiety, bipolar disorder, eating disorders, ADD/ADHD, etc.) have multiple areas which need ongoing consideration and management. Several chemically dependent individuals experience medical and legal difficulties associated with their previous abuse of substances which may also need specialized attention. These clients will likely need additional support in problem solving these areas.

Older adults benefit from having a case manager to effectively coordinate their overall medical and psychological care. The need for a primary point of contact when working with older adults is critical as many providers may be part of the treatment team and ongoing communication among them is necessary.

Criticism of the Case Management Model/Identified Problems with Its Use

Despite the numerous ways that the intervention and case management models can aid in facilitating the process of ongoing recovery with chemically dependent individuals, these approaches remain largely underutilized.

Many professionals who treat substance use disorders, particularly on an outpatient basis, may not be aware of the advantage of referring their clients or patients to a case manager. The variability in social services configurations has led to many different implementations of case management, resulting in conceptual disagreements about case management and difficulty in assessing its value (7).

Inpatient or residential staff members may be unacquainted with firms that provide case management services to their client, or they may minimize the added value that this type of service can provide. As noted earlier, despite the fact that residential programs typically offer an array of services to their clients, continuing care plans frequently do not bear a resemblance to the outlined discharge plan.

Critics of the case management model have suggested that they view case management services as enabling. It has been opined that the client ought to be able to achieve recovery-related tasks without the guidance of a secondary person. Case managers do not enable their clients but teach and empower their clients to assume reasonable responsibilities and assist them in areas where they display limitations or encounter difficulty. It can be argued that withholding support in areas where clients possess limited skills may serve to handicap the client and may hinder his or her ability to successfully navigate through critical issues.

Additionally, some case managers have experienced conflict with their colleagues or other agencies serving the addicted population. They may demonstrate resistance to receiving clinical input from non-physicians or credentialed mental health providers. Service agencies often do not recognize the authority of a case manager (3).

Resistance to case management services has also been noted by staunch proponents of the 12-step program. Generally, their maintained stance is that in order to effectively engage in the process of recovery, the client needs to practice the philosophy of "keeping it simple." While in theory this line of thinking can be viewed as reasonable, it is argued that very little about addiction or recovery is, in fact, simple. Promoting this message without supporting the client by providing them with the tools or services to assist them in maintaining this philosophy can be detrimental to the process and/or success of ongoing abstinence.

The recent emergence of professionals and agencies which offer services called "sober coaching or recovery coaching" may be confused for case management services. Simply defined, sober or recovery coaches tend to be individuals who themselves are recovering addicts or alcoholics. They aim to assist their clients in understanding the principles of the 12-step program; attend 12-step meetings with them, and help them identify potential sponsors. As illustrated throughout this paper, case managers provide more in-depth services and are not aligned with any one treatment philosophy.

Another problem inherent in the use and implementation of the case management model is that firms providing case management services may be scarce and widely unavailable. Community agencies may offer case management services though they may have long waiting lists or strict eligibility requirements.

It has become popular for some transitional living or halfway house programs to include in-house case management services within their existing programs. They may offer a resident the opportunity to work with a case manager who is also a staff member of their program.

Initially, it might appear that though the inclusion of this service type within a halfway house program could be useful, yet problems can be identified with this combination of service programming. These types of programs (also called sober residences and three quarter-way houses) may offer limited services such as transportation to appointments and referrals to outside agencies under the guise of providing case management. As previously described, actual clinical case management services are much broader in scope and do not limit resources for one or two needs. Additionally, the potential for unhealthy and unethical dual relationships may exist. Most reputable halfway houses or transitional living programs maintain strict rules on the use of substances during a client's residence. If the client's landlord or halfway house staff member dually serves as the case manager, disclosure of a slip or relapse may jeopardize the client's ability to maintain their residence.

In addition, the client may at some point have issues with roommates or resident managers and may want to seek alternate housing options. Dual relationships have the potential to hinder the client's ability to be truthful with their case manager and could serve to prevent the case manager from truly meeting their client's needs.

Along these lines, case managers should always avoid real or perceived alliances with any one program, agency, or professional. If the intervention specialist or the case manager is to serve as an advocate for their clients, follow them through the continuum of care, and maintain neutrality at all times, it is essential that allegiances and dual relationships are regularly avoided.

Summary:

The use of intervention and case management models can make significant contributions to the addictions and mental health fields by providing non-traditional services to a population which can be extremely challenging to work with. The roles and responsibilities of both the intervention specialist and case manager are very similar as identified throughout this paper. The utilization of both these models enables one professional or agency to follow the client through primary, secondary, and tertiary care.

Moreover, both case management and intervention models can be considered cost effective treatment options as they emphasize relapse prevention programming. Case managers actively seek to provide their clients with quality services that are also affordable. They assist their clients in applying for available benefits such as medication patient assistance benefits, public health services, and charitable services.

In summary, the case management model is tremendously similar to a model termed The Care Management of Chronic Addictions Model. This model is defined as, "(a) model that accepts chronicity, recognizes limits of treatment methods, is palliative (non curative) in nature, stresses long term management and treats addiction like other chronic diseases such as bipolar disorder or diabetes." (12)

Biography

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Kate Caravella is the founder of ICM Associates, Inc. - a Florida based firm specializing in family interventions and intensive case management. Kate is a Certified Addictions Counselor in the State of Florida, a level one Board Registered Intervention Specialist, and has the designation of level one National Certified Addictions Counselor. Kate has worked in the fields of substance abuse and mental health for 16 years.

Conflict of Interest Statement:

I declare that I have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled: The Use of Intervention and Case Management Models In Maximizing Recovery and Reducing Relapse Risks For Substance Abusers, except for the following:

President/CEO of ICM Associates, Inc.

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COMMENTARY

Eric A. Voth, MD, FACP

To the frustration and concern of many internationally recognized experts in drug policy, the American College of Physicians has advanced a position paper boldly supporting the use of marijuana for medicinal purposes. The footprints of the Marijuana Policy Project (MPP) are all over this position paper which was supposed to have been a neutral and objective look at the status of marijuana and cannabinoids. The MPP has subsequently used the ACP position as a centerpiece as they sponsor a similar position in the AMA house of delegates.

My specific concerns about the position paper are as follows:

There exists a selective element to the paper that excludes the opposition viewpoint. Positions 1-3 are generally reasonable. However, the conclusions 4 and 5 are not consistent with the literature and essentially allowing marijuana to be prescribed. This is contrary to the formal FDA position. The FDA position opposing medical excuse marijuana was excluded from the discussion as were other works which oppose medical excuse marijuana.

Furthermore, the paper blurs the distinction between research into the use of cannabinoids and the use or alleged benefits of marijuana.

The Institute of Medicine evaluation is heavily quoted. However, as a consultant and contributor to the IOM study, I am concerned that the most restrictive conclusions of the IOM study were conspicuously excluded such as the following:

*Recommendation 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve **only short-term marijuana use (less than six months); be conducted in patients with conditions for which there is reasonable expectation of efficacy; be approved by institutional review boards; and collect data about efficacy.***

The section immediately following was excluded:

***If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids, and their synthetic derivatives.** Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but such trials could be a first step towards the development of rapid-onset, non-smoked cannabinoid delivery systems.*

Also excluded:

*Recommendation 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) **must meet the following conditions:***

- ▶ *failure of all approved medications to provide relief has been documented;*
- ▶ *the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs;*
- ▶ *such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness;*
- ▶ *and involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.*

The problems involving state ballot initiatives and legislative initiatives were not explored at all. Also conspicuously absent were papers or references that oppose marijuana as medicine.

The ACP should oppose efforts to bypass the FDA and create medicine by popular vote, particularly in an effort to support consumer protection, and needs to either revise or abandon its current flawed position on marijuana. If the ACP refuses to revise its policy statement, then it needs to, at minimum, allow the development of a separate position paper called, "**Opposing** Research Into the Therapeutic Role of Marijuana."

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Chairman, the Institute on Global Drug Policy

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Table 1.

Understanding the "Compassion" Issues

Eric A. Voth, M.D., FACP

Chairman, The Institute on Global Drug Policy

We must differentiate between **cannabis (i.e. marijuana) and cannabinoids**. Just because a cannabinoid may have benefits does not mean that marijuana would.

It is not compassionate to settle for smoking pot in seriously ill or dying patients. This means that we would be settling for impure, non-standardized, smoked plant products rather than demanding reliable, effective, quality medications for debilitated or dying patients.

Below are some of the disorders that marijuana advocates contend that marijuana will help relieve:

- ▶ Nausea from cancer chemotherapy - Neither marijuana nor cannabinoids have been evaluated against the newer effective anti-nausea medicines such as Zofran or Kytril. Marijuana and pure THC are only approximately as effective as the ancient medication compazine. The newer medicines have far fewer side effects than cannabinoids.
- ▶ Glaucoma – There is no evidence that cannabinoids slow the progression of optic nerve deterioration, blindness, or any element of the disease. Marijuana would need to be used several times daily and has far more toxicity than available prescribed medications.
- ▶ Appetite in AIDS wasting or cancer - While cannabinoids and cannabis increase appetite, it appears that only body fat is increased. Healthy nutrition would need to increase lean body mass in order for the weight gain to be beneficial to the subject.
- ▶ Pain: While cannabinoids may have some benefit in modulating pain, they are no more effective than currently available medicines called neuroleptics or opiate-based pain medications. They also have a very small therapeutic window, so higher doses can actually increase pain.
- ▶ Spasticity in Multiple Sclerosis – While cannabinoids can reduce some muscle spasticity, they impair stable gait (ability to walk). They are generally more toxic than available MS medicines.
- ▶ Depression and anxiety – There is no compelling evidence that marijuana helps these disorders. In fact, marijuana is a cause of psychosis, enhances anxiety in some people, and higher doses actually cause depression. It also causes dependence.
- ▶ Headaches and menstrual cramps – Marijuana is dangerous in women of child-bearing age because of toxic effects on the fetus. There is also no clear evidence that marijuana actually benefits these disorders any more than sedatives, and perhaps only from the intoxicating properties.

Table 2.

FDA Statement Position on marijuana for medicinal applications

FOR IMMEDIATE RELEASE Statement April 20, 2006 Media Inquiries: FDA Press Office, 301-827-6242 Consumer Inquiries: 888-INFO-FDA

Inter-Agency Advisory Regarding Claims That Smoked Marijuana Is a Medicine

Claims have been advanced asserting smoked marijuana has a value in treating various medical conditions. Some have argued that herbal marijuana is a safe and effective medication and that it should

be made available to people who suffer from a number of ailments upon a doctor's recommendation, even though it is not an approved drug.

Marijuana is listed in schedule I of the Controlled Substances Act (CSA), the most restrictive schedule. The Drug Enforcement Administration (DEA), which administers the CSA, continues to support that placement and FDA concurred because marijuana met the three criteria for placement in Schedule I under 21 U.S.C. 812(b)(1) (e.g., marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision). Furthermore, there is currently sound evidence that smoked marijuana is harmful. A past evaluation by several Department of Health and Human Services (HHS) agencies, including the Food and Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA) and National Institute for Drug Abuse (NIDA), concluded that no sound scientific studies supported medical use of marijuana for treatment in the United States, and no animal or human data supported the safety or efficacy of marijuana for general medical use. There are alternative FDA-approved medications in existence for treatment of many of the proposed uses of smoked marijuana.

FDA is the sole Federal agency that approves drug products as safe and effective for intended indications. The Federal Food, Drug, and Cosmetic (FD&C) Act requires that new drugs be shown to be safe and effective for their intended use before being marketed in this country. FDA's drug approval process requires well-controlled clinical trials that provide the necessary scientific data upon which FDA makes its approval and labeling decisions. If a drug product is to be marketed, disciplined, systematic, scientifically conducted trials are the best means to obtain data to ensure that drug is safe and effective when used as indicated. Efforts that seek to bypass the FDA drug approval process would not serve the interests of public health because they might expose patients to unsafe and ineffective drug products. FDA has not approved smoked marijuana for any condition or disease indication.

A growing number of states have passed voter referenda (or legislative actions) making smoked marijuana available for a variety of medical conditions upon a doctor's recommendation. These measures are inconsistent with efforts to ensure that medications undergo the rigorous scientific scrutiny of the FDA approval process and are proven safe and effective under the standards of the FD&C Act. Accordingly, FDA, as the federal agency responsible for reviewing the safety and efficacy of drugs, DEA as the federal agency charged with enforcing the CSA, and the Office of National Drug Control Policy, as the federal coordinator of drug control policy, do not support the use of smoked marijuana for medical purposes.

<http://www.fda.gov/bbs/topics/news/2006/new01362.html>