



## A MESSAGE FROM ADVOCATES FOR PRESCRIPTION OPIOID DRUG REFORM

For more than a decade prescription opioids have been aggressively marketed to America's physicians for treatment of chronic, non-cancer pain of moderate severity. As a result, hydrocodone prescribing increased by 198%, fentanyl by 423%, oxycodone by 588%, and methadone by 933% during this period, and 80% of the world's prescription opioid supply is now consumed in the U.S. An unfortunate, but not surprising, parallel to this phenomenon has been a dramatic rise in the abuse of prescription opioids; these drugs are now second only to marijuana, and ahead of cocaine and heroin. Worse, recent data revealed that oxycodone was the most frequent cause of drug-related deaths reported to the FDA, that more than twice as many died from prescription opioids than from combat in Iraq in 2006, and that deaths from these drugs increased 160% from 1999-2004. Leading experts concur that a national epidemic of prescription opioid abuse and death exists, and that it is worsening.

The rationale for the explosion in prescription opioid use has been the allegation that chronic pain is substantially undertreated in this country. Its impetus has come from pain treatment medical professionals, pain advocacy groups, the pharmaceutical industry, and the media, reinforced by the perception that these are legitimate drugs with established efficacy, safety, and controls. These same entities have largely attributed the observed concomitant escalation in prescription opioid abuse and death to improper internet availability, illicit diversion, and the prevalence of drug addiction tendencies in our society. Very few of these premises can be supported by current statistics, scientific facts, and medical studies.

While it may be true that there has been historical undertreatment of chronic pain in the U.S., the degree of this has been overstated, and the issue has been distorted by failure to factor in types, causes, severity, and the expertise of prescribing physicians. Pain is a *symptom*, not a disease, and its proper management must involve accepted diagnostic determination of its nature and source. In contrast to chronic pain due to specific diseases such as cancer, nerve damage, or end-stage arthritis, central (brain) mediated pain, while just as real, has no demonstrable tissue pathology and has been proven to be affected by emotional and psychological factors. This is a critical distinction which mandates selectivity in pain treatment, especially since patients with central pain have been shown to receive less benefit from opioids and to have increased susceptibility to abuse, diversion, and addiction. Considering that they comprise the majority of chronic pain patients, that they are the largest segment taking prescription opioids, and that 90% of patients in pain management centers are on opioids, it is apparent that central pain patients are not being treated selectively. Also, based on data from the DEA and other studies, physicians not adequately trained in chronic pain management and/or unable to spend sufficient time with patients have been a sizeable contributing factor to the inappropriate, indiscriminate, and counterproductive overprescribing of opioid drugs.



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There are similar inaccuracies regarding the realities of prescription opioid pharmacology and control. Purdue Pharma (PP), the largest manufacturer of sustained-release opioids, failed to properly establish and correctly represent the effectiveness and addiction potential of its drug OxyContin, an omission whose effect was aggravated by unscrupulous and irresponsible marketing practices. Further, these deficiencies were not detected by the primary regulatory agency, the FDA, and were only addressed by the federal court system in the form of an indictment and sanctions in 2007. In truth, numerous independent studies have refuted the previously claimed low addiction potential and incidence of side effects of sustained-release opioid drugs, documented their actual high risk of tolerance, hyperalgesia and respiratory depression when combined with certain other medications and alcohol, and demonstrated lack of efficacy in the treatment of chronic non-cancer pain, especially that of central origin, for more than six months or in comparison to conventional opioid preparations.

The final mischaracterization of the existing prescription opioid drug problem surrounds the role of legitimate versus illicit use and causation. The position that this acknowledged epidemic is ascribable primarily to illicit sources, non-medical use, and poor judgment can no longer be supported. Not only is there reliable evidence that abuse, addiction, and death from prescription drugs--with opioids topping the list—now exceed that of non-prescription drugs, but also that it is legitimate, albeit excessive and improper, medical prescribing, not the internet or drug dealers, which leads to chemical dependence or diversion through family and friends. Further, a correct understanding of the mechanisms of addiction and the profound chemical effects of opioids on the brain precludes the assertion that most individuals freely “choose” this pathway/outcome.

When viewed in the light of objectivity, then, the origin and progression of what now constitutes one of the worst public health crises in U.S. history represents a chronology of abrogation of numerous medical, ethical, social, and governmental principles and priorities. These include purposeful misrepresentation of the chemical characteristics, safety, and clinical indications of sustained-release opioid drugs; egregiously self-serving and unconscionable marketing and financial agendas which unjustifiably elevated chronic pain to a disease entity and intentionally targeted physicians marginally trained in pain management ( both by PurduePharma--OxyContin); inadequate cognizance of and adherence to accepted criteria for medical diagnosis and treatment which generated hugely excessive quantities and availability of one of the intrinsically most high risk, dangerous classes of drugs (by complicit physicians); and despite inherent potential danger to the public welfare, insufficient monitoring and assessment of submitted data for new opioid drugs, and a lack of regulatory response to both legal sanctions and valid scientific recommendations for more restricted use of these medications (by the FDA).



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Although this is really a summary paper, it should make clear that the existing approach to the problem of chronic pain has not only been ineffective but has inflicted serious societal harm and personal suffering upon our nation, that ongoing attempts to redirect this effort have essentially been ignored or rebuffed by the FDA, and that SIGNIFICANT CHANGE is urgently needed. It is important to emphasize that we do not oppose use of prescription opioid drugs for patients truly in need of or likely to benefit from them; that is, *a program based on sound research and clinical data and outcomes, combined with other appropriate medical and non-medical treatment modalities, and administered selectively by properly trained and motivated medical professionals.*

For those interested, more detailed and specific discussion and references by those who have contributed to this document, as well as some recommendations for a new direction, are contained in the **Attachments**. As a group sharing the bond of the loss--to addiction or death from opioids--of a family member or loved one, it is our sincere hope that the Obama Administration, particularly those agencies most involved in drug and public health issues and safety, will respond to the challenge posed by the prescription opioid crisis, bringing to bear its already demonstrated passion, innovation, and competence.

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- Attachments:**
- 1) **Manchikanti, Laxmaiah, MD; Pain Physician 2008: 11:S63-S88**
  - 2) **Gelfand, S., MD ; “Perils of Pain Meds”; Rheumatologist: 2008 ; Commentary to the FDA; May, 2008**
  - 3) **Van Zee, Art, MD; “Roadmap to a Reduction in Opioid Abuse”**
  - 4) **“Why Are People Still Dying From OxyContin?”**
  - 5) **Jackson, Peter W.; Commentary to the FDA; May, 2008**
  - 6) **Hayes, Steve; Novus Detox Newsletter; 2008**
  - 7) **Van Rooyan, K/B; FDA Citizen Petition 2005 P-0076**

**“NEVER DOUBT THAT A SMALL GROUP OF THOUGHTFUL, COMMITTED CITIZENS CAN CHANGE THE WORLD; INDEED IT’S THE ONLY THING THAT EVER HAS” ..... Margaret Mead**



**Members of the Anesthetic and Life Support Drugs  
and the Drug Safety and Risk Management  
Committees**

**RE: May 5-6, 2008 FDA Meetings**

“The sad reality is that most medical professionals do not understand the difference between true physical pain and central or emotionally-generated pain [and other symptoms] derived through the mind-body connection; if they did we would not be in this mess. Emotionally-related pain derives from central or brain-related mechanisms which are often activated by a spectrum of environmental stresses including but not limited to human relationships [past or present, conscious or repressed] which amplify pain perception in the brain, a process called central pain sensitivity [which has been shown experimentally by functional MRI]. This type of pain comprises a large volume of the chronic noncancer pain population and is seen in patients with depression, anxiety disorders, nonstructural low back pain, tension headache, fibromyalgia syndrome, and others, with considerable overlap among them. These are the types of patients at high risk for opioid addiction, dependency, or death. There is no observable tissue pathology in these disorders, in contrast to chronic pain conditions caused by specific observable tissue lesions such as cancer, intractable nerve disease/damage, or end-stage [bone-on bone] arthritis. These latter types of conditions may respond to opioids under close supervision, although evidence for long-term benefit is scanty, and the danger of addiction is considerable in the presence of psychological co-morbidities or a history of prior substance abuse/misuse. Unfortunately, Purdue and the pain societies have forgotten about the first category of central, non-lesional types of chronic pain with no observable tissue pathology but with a high risk/benefit ratio to opiate therapy. “

The following is a partial list of important references in regard to central pain sensitivity [augmentation] states and the importance of multidisciplinary non-drug management that is well-known to the rheumatological community. Every member of the FDA Advisory Committee who will decide upon the NDA of a new formulation of OxyContin on May 5th should be aware of this data as well as the distinct probability that approval of this product and the distinct likelihood of deceptive marketing may give primary care providers a 'false sense of security' and unleash an additional wave of excessive prescribing which will add to the unacceptable volume of documented adverse and tragic outcomes. It has been well-documented that these chronic pain conditions affect huge numbers of individuals who comprise a large segment of the chronic noncancer pain population and in whom treatment with opioids is doomed to failure, unlike selected patients with acute pain, or those with chronic pain of cancer or other types of severe pain from documented intractable tissue pathology or damage. It is my sincere hope that the FDA will finally recognize the marked differences between these types of chronic pain and their very different approaches to management, including the limitations and consequences of long-term opioid therapy which has caused so much devastation to our nation.

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## Citizen Petition

The undersigned submits this petition under Section 505b of the Federal Food, Drug and Cosmetic Act to request the Commissioner of Food and Drugs to temporarily revoke and/or permanently amend the FDA actions identified below.

### **FDA Actions Taken:**

- 1) Title 21 CFR 314.105 Approval of (NDA) 020553 OxyContin  
12/12/95
- 2) Title 21 CFR 314.105 Approval of (NDA)021044 Palladone  
9/24/04
- 3) Title 21 CFR 314.70 Approval of Supplemental New Drug  
Applications providing for labeling changes of (NDA) 020553  
11-20-03 (1-15-02, 7-18-01, 7-25-97, 6-21-96)

### **Actions Requested by Petitioner:**

- 1) Temporary recall of approval of OxyContin (and generic equivalents)  
and removal from market until chemically reformulated by  
manufacturer(s) to drug of minimal abuse potential.
- 2) Temporary recall of approval of Palladone and removal from market  
until chemically reformulated by manufacturer to drug of minimal  
abuse potential.
- 3) Label changes limiting indications for OxyContin (and generic  
equivalents) to severe chronic pain from documented peripheral tissue  
disease processes.
- 4) Label changes limiting indications for Palladone to severe chronic  
pain from documented peripheral tissue disease processes.



## **I. Statement of Grounds – Overview**

Numerous reports from across the country of death and addiction caused by OxyContin clearly document a national problem of escalating opioid abuse, diversion, and inappropriate physician prescribing.

- A recent University of Michigan study conducted for the National Institute on Drug Abuse found that despite a 17% overall decrease in illicit drug use among teens over the past four years, there has been a 49% increase in OxyContin abuse. 1.9 million individuals have used OxyContin for non-medical purposes at least once in their lifetime [Ref. #2] and non-medical use by people 12 or older rose from 399,000 in the year 2000 to 2.8 million in the year 2003. Between 1997 and 2002, there was a 400% increase in the medical use of oxycodone. During that same period of time, there was a 300% increase in abuse of oxycodone as recorded by DAWN data [Ref. #3].
- In the year 2000, the OxyContin problem had been located primarily in Maine, Pennsylvania, Kentucky,, Virginia, West Virginia, and Alabama. By 2001, it was a major and emerging problem in South Carolina, Florida, Tennessee, Montana, Louisiana, Texas, and Washington State [Ref.#1]. By 2004, the OxyContin abuse problem had affected multiple other states. Parts of Canada now have severe OxyContin problems (Nova Scotia and Ontario).
- An April 2002 report from the DEA implicated OxyContin as the direct cause or main contributing factor in 146 deaths and a likely contributor in an additional 318 deaths. The DEA based its findings on a survey of state medical examiners using autopsy data. A total of 949 reports were received, half of which involved OxyContin. More current figures seem to be unavailable but the death rate since 2002 continues to escalate.
- Non-medical use of prescription painkillers now comprises 30% of emergency room visits. The Department of Justice reports 20,000 prescription painkiller emergency room visits in 2002 alone.
- OxyContin death and addiction is not limited to those taking it for non-medical uses. Since Purdue Pharma's 1997 launch of OxyContin



- into the moderate pain market and due to the company's aggressive and untruthful marketing campaign, increasing numbers of patients legally prescribed OxyContin have suffered tragic devastation of their lives and/or death (reports and stories of such patients can be found at [www.oxyconned.org](http://www.oxyconned.org) ).
- On October 25, 2004 John Walters, White House anti-drug czar, announced in Missouri that the National Synthetic Drugs Action Plan is in response to the increased abuse of methamphetamines, Ecstasy and OxyContin.
  - In an opinion issued on January 5, 2004 Judge Sidney Stein, federal judge in New York, ruled that the representations made by Purdue to the government concerning the effectiveness of OxyContin for chronic pain sufferers were fraudulent and misleading and that the patents issued to Purdue were therefore invalid. In particular, Judge Stein ruled that Purdue had misled the government by claiming that they had conducted clinical studies demonstrating OxyContin's unique pain-relieving qualities when **no such studies existed**.
  - In March, 2004 Lester Crawford, Acting Commissioner of the FDA, stated “ *As beneficiaries of the world's premiere health system, Americans should not have to endure preventable medical errors and adverse events related to medical products...Americans deserve better than settling for serious health consequences that can't be spotted until many years after a product has been on the market.*”

**It is near the one-year anniversary of the General Accounting Office report on OxyContin abuse and the Florida Hearings before the U.S. House of Representatives Subcommittee on Criminal Justice, Drug Policy and Human Resources, at the latter of which, Robert Meyer, M.D. outlined a number of laudable FDA actions to prevent prescription drug abuse. As documented above, however, these efforts have fallen short, as the incidence of addiction and death from OxyContin has continued to escalate. Clear evidence of the severity of these adverse events has been known for more than five years, and the time is thus overdue to implement the more stringent measures requested in this petition. If it is appropriate to reevaluate the Cox-2 inhibitor pain medications, there is certainly a need for the FDA to**



**reexamine regulation of the much more powerful and dangerous sustained-release opioids.**

## **II. STATEMENT OF GROUNDS – SPECIFICS FOR REQUESTS #1 and #2**

- In the current formulations of OxyContin and Palladone, full doses of oxycodone and hydromorphone can be easily converted from sustained to one-time immediate release. Ingestion of this immediate release form of the drug can be fatal or lead to opiate addiction. Large numbers of accidental overdoses of patients legally prescribed OxyContin have also been documented. ([www.oxyconned.org](http://www.oxyconned.org)).
- OxyContin (and soon Palladone) are easily available through Internet pharmacies. Legislation such as the Ryan Haight Act, co-sponsored by Senator Feinstein of California addresses this problem; however, the U.S. government is currently unable to regulate foreign online pharmacies. Unless OxyContin and Palladone are reformulated as abuse resistant, the current dangerously potent formulations will continue to be easily accessible.
- Randomized, double blind studies comparing OxyContin given every 12 hours with immediate-release oxycodone given four times daily demonstrated comparable efficacy and safety in chronic back pain [Ref. #4] and cancer pain [Ref. #5,6]. Compared with sustained release hydromorphone immediate release hydromorphone demonstrated **no difference** in efficacy and safety in cancer patients [Ref. #7,8]. Chou and colleagues in a recent review of the medical literature concluded that there is insufficient evidence to conclude that sustained release opioids have any better efficacy or safety than immediate release opioids [Ref.#9].
- Despite the wide publicity of the rapidly growing OxyContin problem since 2000, OxyContin sales have grown from about \$1.2 billion in 2000 to about \$1.9 billion in 2004 (IMS Health)----in spite of the lack of any scientific evidence that this is a better drug than what is available with other preparations.



- State Attorney General of Pennsylvania Jerry Pappert accurately stated that Purdue Pharma is not living up to its public commitment to reformulate OxyContin. He stated “We were told in April 2001 that they were aggressively researching adding anti-abuse ingredients to OxyContin, which would make the drug non-effective if a tablet was crushed and then snorted or taken intravenously by an abuser. The drug was expected to be ready in about three years. It is now (more than) three years later, and Purdue Pharma is currently stating in press reports that the drug development is 10 to 12 years away. They are working on a timetable that is financially best for them.” Pain Therapeutics Inc. (South San Francisco) has already received regulatory clearance to initiate clinical studies in the U.S. with Remoxy, a long-acting version of oral oxycodone that incorporates several abuse-deterrent properties. Additionally, a number of recent patent applications are pending, based on the strategy of combining an opioid with a chemical irritant that would be active when the drug is snorted, chewed or administered intravenously, but not when taken as prescribed, ie, swallowed whole [Attachment A]. Purdue Pharma’s claims that it will take 10-12 years to develop a less abuseable form of OxyContin are thus clearly inaccurate.
  
- By 2001, the increasingly widespread pain and suffering associated with the diversion of OxyContin abuse led some communities to formulate a national petition to recall Oxycontin [Attachment B] [www.recalloxycontinnow.org](http://www.recalloxycontinnow.org) . The underlying thesis of the petition was that the harm brought by the widespread availability of OxyContin on the market-place was simply greater than the benefits of the drug; that there were equally effective opioids available for treatment of severe pain, some of which posed less abuse potential; and that nothing short of a recall could begin to address the problem. The petition was introduced in California in late 2004. Currently over 8,000 individuals have signed the petition online or in person, further support for the position of this FDA Citizen Petition (signatures available upon request).

**At the February 2004 Florida hearing before the Subcommittee on Criminal Justice, Drug Policy and Human Resources, chairman Mark Souder emphasized the need for a regulatory plan that balances the**



**competing concerns of those suffering from chronic pain and those whose lives have been devastated by OxyContin. The above documentation establishes both the unacceptable (and unnecessary) danger inherent in the current chemical formulation of OxyContin and the equivalent effectiveness of other preparations. This petition's request for temporary recall of OxyContin (and generic equivalents) and Palladone until chemically reformulated by the manufacturer therefore would not compromise treatment of pain patients, would actually increase patient safety and is necessary if the single largest impetus for abuse of the drugs is to be eliminated.**

### **III. STATEMENT OF GROUNDS – SPECIFICS FOR REQUEST #3 and #4**

- Only two years after introducing OxyContin for the treatment of cancer-related and other severe pain, Purdue Pharma was allowed to extend its indications to moderate pain situations. At about the same time, the more potent 80 mg. And 160 mg. (1999) tablets were introduced. As a result of this expansion and Purdue Pharma's aggressive marketing, two-thirds of all OxyContin prescriptions are now for non-severe, non-cancer pain, and OxyContin is the most frequently prescribed narcotic type pain medication. That the opportunities for, and actual incidence of, OxyContin diversion and abuse have grown exponentially during this time period is not a coincidence.
- In spite of concerns expressed by DEA officials (Wall Street Journal, 9/27/04), the FDA recently approved similar indications for the use of Palladone, a drug acknowledged to be even more potent than OxyContin.
- The Risk Management Plan (RMP) for Palladone (notably omitted for OxyContin), which mandates Purdue Pharma's monitoring and reporting of adverse events related to the drug, really represents no improvement vis-à-vis a preventative effect on the OxyContin/Palladone problem. The RMP will only reinforce, in an after-the-fact manner, perspectives that are already well known, and depends for its impact on the fallacious premise that Palladone is appropriate for moderate pain. Having intervention strategies in place



“in case these things (abuse, addiction, death) occur” is analogous to closing the barn door after the horse is out.

- “Educational” OxyContin label changes have been made with FDA approval on five occasions, the 7/18/01 change notably acknowledging the issue of misuse and abuse of the drug. Although well intentioned, none of these changes has reduced the scope of the problem (as previously documented in this petition it has worsened significantly). This is because they do not address its root cause – failure to limit OxyContin use to severe, intractable pain from documented peripheral tissue disease processes.
- When Purdue Pharma was allowed to broaden the indications for OxyContin, the way was paved for the legitimate (prescribing) use of the drug in a large population of patients based on symptomatology only. Unlike severe, cancer-related pain, “moderate” pain can be treated as a “disease unto itself” without essential attention being paid to the underlying cause (diagnosis). This is akin to using narcotic type pain medications – known to be effective – to treat chronic cough without establishing the source of the cough (pneumonia, tuberculosis, lung cancer etc.) [Attachments C & D].
- It is well recognized that pain may be centrally (brain) mediated only and originate from a number of psychophysiologic entities not involving true tissue damage. Appropriate management of this no less real type of pain involves the use of many modalities other than narcotic drugs, which can actually have adverse effects on brain chemistry.

**Based on the above, there is no question that under current FDA prescribing regulations the harm produced by OxyContin considerably outweighs the benefits, and that continuing the current indication guidelines for OxyContin and Palladone will aggravate the societal devastation they have produced. These regulations also run contrary to both the stated mission of the FDA and several fundamental tenets of medical diagnosis and therapy. There is an urgent need for the FDA to rescind the current therapeutic parameters for OxyContin and Palladone, and to revert to “severe pain attributable to medically**



documented tissue disease processes” as the only indication for their use.

#### **IV. Concluding Statements**

**This petition has provided evidence that there is a national problem of crisis proportions involving inappropriate prescribing, diversion and abuse of the drug OxyContin, and that a similar situation will occur with Palladone in proportion to its prescribing and availability. It has established that the FDA allowing liberalization of the original indications for use of the drug(s) and the continued existence of a hazardous chemical formulation have enhanced both the availability and inherent dangers of OxyContin. The petition has demonstrated that there is insufficient scientific evidence that sustained release opioids offer the improved efficacy over immediate release forms to justify the increased risk. It has shown that previous/current efforts by the FDA to address the problem have been unsuccessful and that the situation is worsening. It has pointed out that allowing use of OxyContin and Palladone for “moderate” pain indications violates several basic and important principles of medical diagnosis and therapy, as well as the FDA’s responsibility to its citizens. Finally, the petition demonstrates that the more restrictive regulations requested, while perhaps logistically and politically challenging, are warranted both from an historical and scientific standpoint and it calls upon the FDA to exercise bold and responsible action that will prevent many future tragedies.**



## **Attachments**

- A. NATIONAL PETITION TO RECALL OXYCONTIN**  
Lee Coalition for Health
  
- B. COMMENTARY ON THE PITFALLS OF OPIOIDS FOR  
CHRONIC NON-MALIGNANT PAIN OF CENTRAL ORIGIN**  
Stephen G. Gelfand, M.D.
  
- C. OXYCONTIN RISKS AND THE FDA**  
Stephen G. Gelfand, M.D.



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**Certification Statement**

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

\_\_\_\_\_  
Signature 1/31/05  
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**ATTACHMENT A**

[www.recalloxycontinnow.org](http://www.recalloxycontinnow.org)



## RECALL OXYCONTIN NOW

The Lee Coalition for Health in Lee County, Virginia has initiated the **National Petition** to recall OxyContin. While this is a complicated issue with many factors to consider, we feel that the pain and suffering brought to countless families and communities by the abuse of the drug far surpasses the benefits. It is clear by now that the best interests of the public health are served by the recall of OxyContin.

### Why Recall OxyContin?

1. Fifteen months ago, we knew that some counties in Maine and our region in southwest Virginia were areas of heavy OxyContin abuse, dependence, and addiction. It's apparent over the last year that there has been extensive and rapid spread of this problem. There are major problems in Maine, Pennsylvania, New Jersey, Ohio, West Virginia, Maryland, Kentucky, Virginia, North Carolina, South Carolina, Florida, Louisiana, Mississippi, Wisconsin, Alaska, and Washington. It is being seen in a number of other areas. It is a national problem.
2. There are a number of important measures to take in trying to cope with this problem. Public education, prevention initiatives, more prudent physician prescribing, better tracking and detection systems for prescription fraud or diversion, more comprehensive law enforcement efforts, and greatly expanded treatment capacities -- are all critically important measures. However, all of these will move too slowly and will fall short in halting the rapid and devastating spread of the OxyContin abuse epidemic in the United States.
3. The pain and suffering brought to countless families and communities by the abuse of the drug greatly surpasses the benefits of the drug.
4. It is important to understand that there are very good alternatives to OxyContin for patients with severe pain. A recall of OxyContin would not mean that the medical community would be abandoning the treatment of severe pain. As physicians, this is one of our largest responsibilities -- the thoughtful and compassionate treatment of pain. There are several other good pain medications on the market that are as effective and as strong as OxyContin. These include transdermal fentanyl patches, sustained release morphine pills and methadone tablets. Patients with severe pain can be reassured that we do have equally effective medications and at least some of these have less abuse potential than OxyContin.
5. OxyContin can, should, and will be re-formulated to a preparation of much less abuse potential. It needs to be off the market until that is done.

Art Van Zee, MD and Vince Stravino, MD  
Lee Coalition for Health  
P.O. Box 578  
Pennington Gap, VA 24277

Prior to going online July 20, 2001 - Over 6.950 signatures received



[www.recalloxycontinnow.org](http://www.recalloxycontinnow.org)

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To: international

### National Petition to Recall OxyContin

Whereas, OxyContin abuse has reached epidemic proportions in many regions of the United States and has been destructive of countless futures, families, and communities; Whereas, public education; prevention initiatives; more prudent physician prescribing; improved treatment services; and more comprehensive law enforcement efforts---are all critically important, but much more is needed to halt the increasingly widespread abuse of Oxycontin; We, the undersigned, call upon the FDA and Purdue Pharma to recall OxyContin until it can be reformulated to a medication of minimal abuse potential.

Sincerely,

[The Undersigned](#)

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The [National Petition to Recall OxyContin](#) Petition to international was created by and written by [Art Van Zee, MD](#). This petition is hosted here at [www.PetitionOnline.com](http://www.PetitionOnline.com) as a public service. There is no express or implied endorsement of this petition by Artifice, Inc. or our sponsors. The petition scripts are created by Mike Wheeler at [Artifice, Inc.](#) For Technical Support please use

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## **Epidemic of OxyContin Abuse**

Dr. Art Van Zee

July 20, 2001

In my experience in primary care general internal medicine for the last 25 years in Lee County, there has always been a certain level of drug abuse -- both of illegal drugs and prescription drugs. However, there has never been anything like what we have witnessed in the last two years. There has been a virtual epidemic of Oxycontin abuse and subsequent opioid (narcotic) addiction. Oxycontin has been snorted or injected IV, males and females, from mid-teens to early forties. There have been numerous over-doses (some fatal), infections, increasing Hepatitis C, and occasional case of endocarditis related to this. Numerous young people have been losing their jobs, vehicles, houses, and children to this addiction. Many of these young people are very good kids, coming from good solid families, and who have had bright, promising futures until they did make the mistake of recreationally using and abusing prescription drugs. Oxycontin became rapidly addicting for them, and they have suffered severe consequences of their opioid addiction, devastating not only their own lives but the lives of their families and loved ones. There are very few families in our region who have not been directly or indirectly affected by this problem. The medical, personal, social, and societal toll has been, and continues to be, huge. The medical community has not had the capacity or resources to deal with the large scale opioid dependence that we have had. In-patient and out-patient facilities are limited. At our closest in-patient drug detoxification facility -- "The Laurels" in Lebanon, Virginia, the percent of patients using opioids has increased from 18% to 44% in the last 4 years. Our closest methadone maintenance clinic in Knoxville is a two and a half hour drive, and many parents leave at 4A.M. to drive their children down to the clinic. The DRD Knoxville Medical Clinic can document what a tremendous increase in opioid addiction there has been in the region in the last few years. The Life Center of Galax opened an out-patient methadone maintenance clinic in March, 2000 -- anticipating about 15 patients at the end of the first year, based on the known prevalence of heroin in the region. They had 30 admissions within the first two weeks of opening, and within 6 months had 254 patients, 95% of them entering the program with Oxycontin addiction. Law enforcement has been overwhelmed by the associated problems, as drug related crime has sky-rocketed. The county sheriffs in the region document that 70 - 80% of the major crime over the last two years has been drug related, and most of that Oxycontin.

The county Social Services Departments have likewise been over-whelmed. The number of children needing to be placed in foster care has tripled over the last 4 years in Lee County, primarily related to Oxycontin abuse.

In the spring of 2000, the Oxycontin abuse epidemic appeared from the media to be primarily located in southwest Virginia and Maine. Numerous other states now have major problems with this including Pennsylvania, Ohio, West Virginia, Kentucky, Maryland, North Carolina, South Carolina, Florida, Alabama, Mississippi, Louisiana, and Alaska. Other states including New Jersey, Arizona, Wisconsin, Michigan, and Kansas are beginning to record significant problems. Clearly, this is a growing national problem.

[www.recalloxycontinnow.org](http://www.recalloxycontinnow.org)



## Alternatives to OxyContin

There are several strong pain medications (opioids) which are just as effective as treating severe pain as in Oxycontin. There are no studies in the medical literature which demonstrate Oxycontin has clear cut superiority over immediate release oxycodone, controlled release morphine, transdermal fentanyl patches, or methadone when used in the treatment of severe pain. Some of these have less abuse potential, and some of these offer significant cost savings over Oxycontin. In reviewing oxycodone and Oxycontin in the September 17, 2001 issue, The Medical letter concluded:

"Oxycontin is a q12hour controlled-release formulation of oxycodone that can be used effectively in the treatment of pain due to cancer and, occasionally, other types of chronic pain. There is no evidence that oxycodone offers any advantage over appropriate doses of other opioids, and it appears to have the same potential for addiction as morphine."

Some of the studies are summarized briefly below--

### **Comparison: Immediate release oxycodone versus Oxycontin**

Hale ME, et al Efficacy and Safety of Controlled-Release Versus Immediate-Release Oxycodone: Randomized, Double-Blind Evaluation in Patients with Chronic Back pain Clin J Pain 1999 Sep;15(3): 179-83 \*\* Conclusions: 47 Patients randomized "controlled-release oxycodone given every 12 hours was comparable with immediate-release oxycodone given four times daily in efficacy and safety...."

Kaplan R, et al Comparison of Controlled-Release and Immediate-Release Oxycodone Tablets in Cancer Pain J Clin Oncol 1998 Oct;16(10):320-7 \*\* Conclusions: 160 patients, double blind study "CR and IR oxycodone were equally effective in the management of cancer-related pain" - - "...the adverse event profiles of CR and IR oxycodone were similar. Overall, however, significantly fewer adverse events were reported for CR oxycodone compared with IR oxycodone..." (somewhat less nausea and vomiting with CR oxycodone)

Stambaugh JE, et al Double-Blind, Randomized Comparison of the Analgesic and Pharmacokinetic Profiles of Controlled and Immediate-Release Oral Oxycodone in Cancer Pain Patients J Clin Pharmacol 2001 May;41(5):500-6 \*\* Conclusions: 32 Patients "CR provides equivalent analgesia as IR oxycodone with the same patient acceptance profile" "...similar incidences and numbers of reports of individual adverse events considered related to the IR and CR drug"

### **Comparison: Controlled-release morphine versus controlled-release oxycodone (Oxycontin)**

Heiskanen T and Kalso E. Controlled-release oxycodone and morphine in cancer related pain. Pain 1997 Oct;73(1):37-45 \*\* Conclusions: 45 Patients in a double-blind, randomized, cross-over "the two opioids provided comparable analgesia" "the total incidence of adverse experiences reported by the patients was similar, but significantly more vomiting occurred with morphine, whereas constipation was more common with oxycodone."



Mucci-LoRusso P, et al Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *European Journal of Pain* (1998) 2:239-249 \*\* Conclusions: 100 patients-- "controlled-release oxycodone was effective as controlled-release morphine in relieving chronic cancer-related pain.." "the side-effect profiles of CR oxycodone and CR morphine were similar overall in this trial."

Bruera E, et al Randomized, Double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *J. Clin Oncol* 1998 Oct;16(10):3222-9 \*\* Conclusions: 23 patients "There were no significant differences detected between the two treatments in ...adverse events, or clinical effectiveness..."

There are no studies that we are aware of comparing controlled-release oxycodone (Oxycontin) with transdermal fentanyl or oral methadone for treatment of severe chronic pain.

There are a few studies comparing transdermal fentanyl with oral morphine.

### **Transdermal fentanyl versus oral morphine**

Payne RJ Quality of life and cancer pain: satisfaction and side effects with transdermal fentanyl versus oral morphine. *Clin Oncol* 1998 April 16(4):1588-93 Conclusions: 504 patients "these data suggest that patients are more satisfied with transdermal fentanyl compared with sustained-release morphine"

Ahmedzai S.J. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. *J. Pain Symptom Management* 1997 May; 13(5):254-61 Conclusions: both were equally effective in terms of pain control: there was less constipation and sedation with fentanyl.

Art Van Zee, MD  
Lee Coalition for Health  
10/1/2001



[www.recalloxycontinnow.org](http://www.recalloxycontinnow.org)

## What is the Lee Coalition for Health?

Lee Coalition is a non profit- coalition of professionals and other concerned citizens founded 10 years ago to promote health and wellness issues in Lee County, Virginia. Some of the Coalition projects have included:

- An annual free cancer screening for Lee County residents for the last 10 years.
- Tobacco education in the middle schools.
- Smoking cessation classes.
- Fire prevention activities.
- Healthy heart cook- books.
- A community smoking cessation contest.
- After prom party.
- Asthma camp.
- Drug, alcohol, and tobacco prevention and treatment initiatives

### Attachment B



## COMMENTARY ON THE PITFALLS OF OPIOIDS FOR CHRONIC NON-MALIGNANT PAIN OF CENTRAL ORIGIN

Stephen G. Gelfand, M.D.

There is a serious medical and social problem today under intense media, law enforcement, and regulatory scrutiny concerning the misuse and abuse of OxyContin for chronic non-malignant pain. This situation has made the drug difficult to obtain for many patients with malignant and other types of intractable chronic pain, and has recently influenced the FDA to issue a black box warning in order to lessen the chance of inappropriate prescribing of this Schedule II narcotic. In addition to recent D.E.A. autopsy findings of nearly 300 OxyContin overdose deaths nationally since January 2000, there is a large volume of patients with chronic non-malignant pain who have become dependent or addicted as a result of legitimate prescriptions written for OxyContin [as well as other opioids]. In a recent case, the D.E.A. suspended physician narcotic licenses and closed a South Carolina pain clinic for the excessive prescribing of OxyContin, although the physicians involved believed they were following current established standards [New York Times, Dec. 10, 2001].

How did this situation occur? In the first place, on closer inspection, certain statements in the narcotic guidelines established by the Federation of State of Medical Boards [1] have received insufficient or cursory attention. These include the recommendations pertaining to the importance of psychological and substance abuse evaluations, the necessity for other treatments depending upon the etiology of the pain and extent of psychosocial impairment, and the requirement for consultation with or referral to an expert for comorbid psychiatric disorders. These are common omissions, particularly in rural environments, where the OxyContin problem first originated, and in which psychosocial factors receive less attention, resulting in fewer numbers of and referrals to mental health providers. Even before OxyContin, however, another opioid, hydrocodone, was one of the most widely abused drugs, particularly in rural areas of the South[2].

Clearly, the large volume of prescriptions and chronic use of OxyContin have increased the supply, availability, and opportunities for every type of abuse, while also filtering into our schools. Contributing to this situation has been an attempt to expand the indications for opioid therapy to the entire spectrum of chronic pain, regardless of cause. As a result of an organized educational and marketing campaign by the manufacturer of OxyContin and a number of pain societies, the message has spread that there is too much undertreatment of pain in general, and that opioids are safe in most instances and should be prescribed more often for chronic pain of all types [3,4]. There would be general agreement with this appeal if restricted to patients with cancer or other forms of intractable peripheral pathology, but it is also intended and has been used for many patients with non-malignant, non-structural chronic pain.

Since chronic widespread pain and psychological distress in the general population are closely associated [5], the indications for opioids have thus been expanded to this large population of patients with chronic pain of central affective origin, including those within the wide spectrum of fibromyalgia, one of the most common rheumatic disorders. Thus, the indications for opioid therapy has been extended to this large, heterogeneous group closely associated with a wide range of psychological distress, including the affective spectrum disorders [6]. It is these vulnerable patients who are at risk for the dangers of opioid therapy, especially in rural regions where insufficient attention is given to pain-generating and amplifying psychosocial factors, in lieu of a more patient-popular drug-oriented approach.

The current "pain revolution" has also widened the use of opioid drugs for chronic pain by focusing on quantitative criteria such as degrees of pain [a largely subjective parameter], rather



than on etiology. However, the degree of pain often correlates poorly with objective findings, and quantitative factors have different levels of significance for the types of chronic pain common to different specialties, i.e. oncology as opposed to rheumatology. This approach does not account for the essential distinctions in the biological and psychological origins of chronic pain subgroups, which are important to understand in making informed therapeutic decisions. Furthermore, the appeal to broaden the indications for opioids has also trivialized possible long-term adverse consequences, particularly of OxyContin [3,4]. Consequently, as cited above, a number of pain clinics have formed for the major reason of prescribing analgesics, especially opioids, while at the same time frequently downplaying or disregarding non-pharmacological approaches including psychological testing and management necessary for a large number of the chronic pain population. Thus, the combined effect of expanding the indications for opioid use, and insufficient attention to guideline recommendations, has facilitated the current environment of OxyContin abuse which has grown into a major medical, social, and law enforcement problem in many rural areas, as well as in an increasing number of metropolitan regions throughout the country. The extent of this situation, which often involves law-abiding citizens, was recently reported in special television broadcasts on both CBS News' 48 HOURS entitled "Addicted", anchored by Dan Rather, and MTV's: "True Life: I'm Hooked on OxyContin". Susan Zirinsky, executive producer of "Addicted" which aired on Dec. 12, 2001, states that "the growing addiction to prescription painkillers is a story that is touching every age group, and its effects are often devastating". In the last several years, OxyContin abuse and addiction have quickly spread and have reached epidemic proportions.

Pain is a complex sensation modulated by central brain pathways, including the nerve centers and networks responsible for emotions. The types of chronic pain for which opioids were originally intended are caused by pathological processes in tissues or organs from diseases such as cancer or intractable nerve or joint damage. In these conditions, the drugs combine with opioid receptors on nerve cell bodies in the brain and spinal cord which connect to and attenuate the electrical activity of these afferent nerve pathways stimulated by peripheral tissue lesions. However, in other common types of chronic pain, similar structural abnormalities in peripheral tissues are not present; instead pain is produced and intensified by central brain mechanisms, including emotions, which are stimulated by a spectrum of chronic psychological distress, and results in disordered central pain regulation and amplification [7]. This latter type of chronic pain includes the fibromyalgia syndrome, in which symptoms have neurophysiological correlates originating from persistent central nervous system activation from a large range and degree of stressful psychosocial life events [8]. The outcome is a persistent chronic stress response characterized by dysfunctional neuroendocrine reactivity to psychological, as well as to physical and physiological stressors [9,10,11]. Since opioids may have mood-elevating or altering effects, particularly in individuals with chronic pain and psychic distress [conscious or subconscious], these drugs may facilitate psychological dependence by their action on central affective nerve networks, as opposed to the peripheral afferent nerve pathways of tissue damage or destruction. In essence, it appears that opioids work on different nerve pathways in fibromyalgia than they do in cancer, intractable nerve damage, or end-stage arthritis. This central action may also occur in vulnerable patients with non-structural low back pain and tension headache.

The localization of opiates in the pleasure centers of the human brain and the recent demonstration of mu opioid receptors in the amygdala of nonhuman primates [12], a brain region essential for emotional content and behavior, is further evidence of the intimate relationship between emotional states and pain processing. In my view, the treatment of pain of central origin should focus on attenuating the causative and perpetuating psychobiological factors, rather than masking them with exogenous opioids. These drugs carry the risk of long-term dependency or



addiction by their direct effects on the emotional component of pain while depleting the brain's natural endogenous opioids.

Even in conditions of chronic pain associated with peripheral pathology such as the synovial inflammation or cartilage destruction of arthritis, central pain-modulating mechanisms may play an important role, a fact which has definite therapeutic implications. For instance, the recognition and management of underlying psychological disorders in patients with rheumatic diseases can significantly improve pain levels and function [13]. Self-management programs including education, exercise, and behavioral-cognitive therapies have likewise resulted in positive benefits beyond that of drug therapy alone [14,15]. Furthermore, dependence upon painkillers including opioids, may directly inhibit the learning of the construct of self-efficacy, which affirms the belief that people themselves, with their own resources, can significantly reduce pain and other symptoms [16]. Unfortunately for too many today, "taking a pill is easier than building the necessary will", a socio-cultural reality contributing to our national problem of prescription drug abuse, including that of OxyContin.

Self-efficacy and dependence upon drugs for pain are opposite therapeutic objectives. Although certain medications such as low dose tricyclic antidepressants for improved sleep, and SSRIs for depression and /or persistent pain are beneficial in selected patients, conventional drug management by itself has not been shown to improve outcomes in fibromyalgia [17,18]. The same conclusions also apply to chronic low back pain not caused by specific structural lesions. Both conditions frequently have multiple psychosocial and cognitive variables unique to each individual which need to be recognized and treated as part of a multidisciplinary treatment program including self-management techniques. Disregarding these factors, which are essential in the origin and amplification of symptoms, predisposes to polypharmacy, drug dependence, and a dysfunctional state in which each symptom is medicalized.

One of the most common reasons for patient visits today is the large range and severity spectrum of multiple unexplained symptoms, including pain, which are associated with stressful life events, psychological distress, depression, and anxiety disorders [19]. Fibromyalgia syndrome should be viewed and managed in this broader context, rather than as a discrete disease requiring medications [including opioids] as principle therapy. Recognition that a number of these patients would rather have a "physical disease" than confront the effects of stressful past or present life circumstances may be helpful in their overall evaluation process. Furthermore, this comprehensive approach considers the chronic muscle pain of fibromyalgia syndrome to be just one of many symptoms that can be generated by chronic tension and stress originating from biopsychosocial factors, rather than as a distinct disease in the traditional biomedical sense [8].

The lessons of OxyContin could serve to strengthen the importance of good clinical judgement and the need to evaluate each patient in context. This includes determining whether chronic pain originates from peripheral or central mechanisms, and adhering to the narcotic guideline recommendations for adequate psychosocial evaluations prior to prescribing opioids. Pain should not be treated in isolation without understanding its roots, just as fever mandates a search for causes. Undertreatment should refer not only to drug therapy, but also to the absence of important non-drug interventions. The appropriate management of chronic pain is multimodal including non-pharmacological therapies, especially for pain of central origin. Diagnosis and care should be individualized and involve other disciplines as indicated, including clinical psychology, psychiatry, stress management, health education, and physical and/or occupational therapy.

As a result of the OxyContin problem, certain pain societies are now calling for a more balanced approach to the diagnosis and management of chronic pain [20]. Hopefully, the aftermath of



OxyContin will show that a “one drug fits all” orientation to chronic pain is a risky practice with many pitfalls. In the public interest, more attention must be paid to proper patient selection rather than to marketing ploys intended to increase company drug sale figures.

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## **Attachment C**



## OXYCONTIN RISKS AND THE FDA

Drug safety is rapidly becoming a major public health issue as fueled by current events which reveal that the FDA has often failed to properly monitor the long-term risks of many pharmaceuticals that were often rapidly approved. The arthritis "painkillers" are now "under the gun", especially after the recent withdrawal of Vioxx by Merck & Co. because of an increased risk of cardiovascular events, even though the FDA had known about problems with this drug for years. Likewise, attention has now turned to Pfizer's blockbuster arthritis drug, Celebrex, because of a similar finding in just one study released by the drug company yesterday. Amazingly, the FDA has also been well aware of adverse events caused by the powerful time-released opioid, OxyContin during the last five years, especially after the indications for use were expanded from severe to MODERATE chronic pain. Yet they continue to exhibit inertia under the influence of the manufacturer, Purdue Pharma and other pain-related interests who have trivialized the potential adverse effects of this drug, while ignoring the continual pleas to remove moderate pain from indicated uses, despite mounting evidence of addiction, crime, overdose, and death. In addition to money and politics which have been well-documented, what are the actual medical reasons why the use of this very effective but potentially deadly pain reliever should be LIMITED only to patients with chronic pain caused by cancer, or other types of intractable tissue lesions which cause severe pain?

The important message of the pain movement, that pain is often under-treated, MUST also include the understanding that good medical management may require a whole range of options including pharmacological agents other than opioids as well as valuable non-drug therapies, the selection of which is based upon correctly diagnosing both the cause and type of chronic pain. There is no question that the case for opioids has been overstated, while at the same time other types of pain therapies have been understated, markedly increasing the volume of prescriptions for OxyContin sustained-release capsules which have then spilled into our streets and schools. In many instances, chronic pain and opioid therapy have become synonymous, as pain is superficially viewed as a "disease unto itself". In other words, symptoms have often been treated with opioids irrespective of cause. This is contrary to the principles of good medicine which teaches medical students to always search for the cause of symptoms, such as fever, cough, and pain. What if cough were treated in isolation without a complete evaluation for its potential underlying causes? Opioid drugs, which are also effective cough suppressants, would then be the main avenues of treatment, while the underlying causes of cough such as allergies, bronchitis, pneumonia, tuberculosis, or cancer may go undetected. Thus, unless pain is related to its cause, many untoward outcomes may ensue, particularly from the excessive, non-selective use of potent chemical compounds like OxyContin.

The brain plays a major role in the generation of the sensation and feeling of pain and in many instances may be the only source of pain [central pain], especially when pain does not originate from tissue destruction like cancer, but from a wide range of psychosocial stress [e.g. states of anxiety and/or depression which may be associated with muscle and joint pain as in fibromyalgia]. Broadening the indication for OxyContin to moderate pain opened up the use of this drug to a large population of patients with this type of central pain originating from biological brain mechanisms, but requiring therapies other than opioids which may have profound adverse effects on the brain. In this group of patients, opioids may not only be harmful but occasionally lethal. In addition, the



broadened indications for OxyContin have increased prescriptions to addicts and drug dealers which has fueled the explosion of addictive behavior, crime, and recreational drug use. The many tragic consequences from the wide availability of this powerful drug are vividly and well-documented on this excellent web site.

How can the FDA be holding an expert review in two months to re-evaluate all of the remaining Cox-2 inhibitor painkillers, while at the same time refuse to re-consider meeting to limit the indications for one of the most potent of all painkillers, OxyContin, especially in view of the numerous tragedies which have already occurred? Since higher doses over a prolonged time are major factors in the increased cardiovascular risks of the Cox-2 drugs, why are these issues not being addressed with OxyContin as well? Does anyone actually believe that chronic pain patients, with stress-related pain of central origin who are taking inappropriately high doses of OxyContin over time, have adequate mental and physical function, and are not at major risk for addiction, overdose, death, intentional suicide, and theft by others of their high-priced, time-released capsules so popular on the street? Unlike the situation with the Cox-2 agents, the dangers with OxyContin extend well beyond individual victims to widespread psychosocial effects upon families, friends, and society at large.

OxyContin is a valuable drug for severe chronic pain produced by documented tissue damage, but not for most of the large population of patients with non-tissue, central pain falling under the current troublesome "moderate" pain indication, which can usually be adequately treated with non-opioid interventions, as related to the correct diagnosis and derived from competent medical and psychosocial evaluations. The proper management of chronic non-malignant pain must be individualized and not oversimplified with a "trigger-happy" swift approach which promotes the economic interests of the drug companies at the expense of human lives. Is another disaster looming on the horizon with the approval of similar broad indications for the use of the new sustained-released opioid, Palladone? When will the FDA finally rise to the occasion and seriously monitor long-term drug safety issues while actively taking steps to limit the dangers of OxyContin and all other worrisome prescription drugs? Passive "intervention" influenced by the pharmaceutical industry will no longer suffice.

Perhaps the lessons of these recent events will engender more caution on the part of providers, drug companies, and healthcare regulatory agencies, and SOME DAY lead to a safer, less drug-oriented, more comprehensive approach to patient care.

Stephen G. Gelfand, MD, FACP, FACR- Rheumatologist

12/18/04



## Why Are People Still Dying From OxyContin?

(The Truth about Opioids)

September 20, 2006

Our federal government is turning its attention to the growing problem of prescription drug abuse in America, recognizing that the problem outweighs that of illicit drug use. Yet OxyContin has been in existence since 1995 and related deaths, addiction and adverse events recognized for close to a decade. So, why are people still dying from OxyContin (and other opioids)??

OxyContin came into existence in 1995, when Purdue Pharma managed to convince the FDA of its safety (not unlike the mistake made in 1898 when the FDA legalized heroin). Following FDA approval OxyContin sales literally skyrocketed, thanks largely to a well orchestrated but deceptive public relations campaign.

In 1995 and 1996 it was sold as a chronic pain medication for use with cancer patients. Then in 1997 Purdue Pharma began to push this drug into new markets such as back pain and injury. At the same time the company reached down into moderate pain treatment, adding a more potent dosage, beginning the manufacture of 80-milligram tablets to complement the smaller 10, 20 and 40-milligram pills already on the market. By 1998, fully two-thirds of all Oxy prescriptions issued were for non-cancer pain.

Cleverly, Purdue Pharma paid for hundreds of physicians to travel on junkets where they were educated about the benefits of OxyContin, a Schedule II drug without a “ceiling” on dosage. Those physicians were, in the manner of a pyramid building fashion, told they would be paid speakers’ fees for talking to other doctors about the benefits of OxyContin

By 1999, Purdue Pharma’s objectives included a reach toward one-half billion dollars in sales of their star drug, with their marketing efforts targeting more groups, including seniors with direct to consumer (DTC) advertising. Again, while the marketing effort sought to aggressively broaden market penetration, the manufacturing side of the company delivered an even more potent tablet, a 160-milligram pill.

By 2001, Purdue Pharma had comfortably rocketed past the one billion dollar mark in sales from this single drug, with the Company noting in passing that the challenges presented by mounting evidence of OxyContin abuse in Florida, Maine, Ohio and other states “...will continue to be a threat to the continued success of OxyContin tablets.”

In 2002, OxyContin sales hit the \$1.2 billion level, representing more than 80% of Purdue Pharma’s total revenue and the vast majority of its profitability, due in part to the advantage handed Purdue Pharma by the FDA. As Purdue Pharma’s marketing group noted in the face of mounting evidence that deaths in Florida and other states from Oxy exceeded deaths from heroin, “It is unlikely that an opioid approved by the FDA in the future will have as broad of an indication [or indicated usage] as OxyContin now enjoys.” Tragically, the FDA continued to be influenced, in a number of ways, by Purdue and once again, in 2004 approved an even stronger opioid, Palladone with broad indications. It is not coincidental that FDA personnel who were instrumental in OxyContin approval transitioned to consulting and employment positions with



Purdue.

For over ten years Purdue Pharma has spearheaded a well documented, concerted effort to aggressively market OxyContin to the GENERAL medical community for a wide variety of chronic non-cancer pain of moderate severity. And while the toll of deaths and addiction have continued to mount, the FDA, the Federal and State governments and the majority of the medical community have turned a blind eye, have bought the “party line” of the public health epidemic of under treated pain **without ever asking the right question**. The right question is NOT “ Is there under treated pain in America?” The right question is “HOW BEST do we treat pain in America?”

Purdue has led a large portion of the medical community (including dental surgeons, sport medicine specialists and countless general and family practitioners) to adopt OxyContin as the drug of choice, despite a mounting volume of adverse events, including opioid abuse, addiction, overdoses, deaths, diversion and crime. The growing volume of these adverse events is clearly seen in daily medical practice, and repeatedly reported both by the media and in a growing body of medical literature. The DEA’s analysis of physicians prescribing OxyContin found that the scope of medical specialties was wider for OxyContin than five other controlled-release, schedule II narcotic analgesics. The DEA expressed concern that this resulted in OxyContin’s promotion to physicians who were not adequately trained in pain management.

The fact is that although millions may have under treated chronic pain, the vast majority does NOT require opioids. Treatment of pain *must* include the understanding that good medical management may require a range of non-drug therapy options, as well as drugs other than opioids, based upon correct diagnosis of both the cause and type of chronic pain. The largest segment of the huge population of patients taking opioids and not coincidentally, the ones from whom Purdue has profited, is the segment with chronic non-cancer pain more related to psychological disorders, secondary gain motives and/or the mechanisms of tolerance and addiction than related to a tissue-derived source [1].

After the floodgates to the use of opioids were opened, large populations of patients were placed on these drugs indiscriminately, including those with a spectrum of psychiatric disorders, which predispose to addiction and diversion.

Over 90% of patients presenting to and in pain management centers are on opioids even though studies have shown that opioids generally provide approximately 35% relief in only 44% of the patients. In addition illicit drug use among patients in chronic pain receiving controlled substances has been shown to be 14% to 32% [2].

Those who promulgate that it is always a “choice” of OxyContin abusers to get high do not understand the mechanisms of addiction and the profound effects of this drug on the brain, particularly in those who never needed it in the first place. Many patients have been prescribed OxyContin by their providers for any kind of pain, most of who were misled to believe that it is safe.

Most unfortunately the indiscriminate prescribing of OxyContin by primary care physicians and others not trained in selective use of opioids and addiction for a wide spectrum of moderate and mild pain, has led these very physicians to adopt a defensive mode, protecting themselves against exposure and criticism. One mechanism for getting rid of the criticism has been a public relations campaign to convince the public about the importance of opioids to “relieve the suffering of



millions with undertreated pain”. This has worked *against* those who are truly good candidates for OxyContin, making it more difficult for them to obtain the benefits of OxyContin because the indiscriminate prescribing practices that have gone on for over a decade have resulted in addiction and abuse that is not *always* a result of an abuser seeking a high, but rather the result of a large population of prescription opioid-dependent patients. This public relations campaign was introduced, promoted and supported by the greed of Purdue Pharma. They, and other companies have intentionally equated opioid dependence and addiction with “legitimate” pain for their economic advantage and have therefore also relieved the many prescribing doctors of their complicity. Meanwhile, the toll of addiction, death, diversion and crime continues to mount.

The huge increase in the use of opioids for the management of chronic pain has been fueled by:

- Pharmaceutical companies false marketing and physician incentives
- Patient advocacy groups demanding opioids for benign pain
- Legitimacy provided by prescription drugs
- Misguided physicians denying/avoiding the truth concerning lack of confirmation of efficacy and safety of long term opioid therapy for chronic nonmalignant pain
- Lack of physician and patient education regarding effective non-opioid methods of pain management
- Media reports of under treated pain

To date, multiple randomized controlled trials regarding long term opioid therapy were for limited duration with most lasting less than eight months and fail to confirm the safety and efficacy of long term opioid therapy [3, 4, 5, 6, 7, 8, 9]. Considering this, the reports of a mounting toll of opioid abuse and addiction in the United States, and statistics documenting a high rate of premature deaths, overdoses, emergency room visits, diversion and crime over the last decade it is essential that the entire issue of opioid use for chronic noncancer pain be revisited. Opioid therapy for chronic, nonmalignant pain, if used *selectively* for intractable tissue-derived pain, especially in carefully screened and followed patients without significant psychiatric and/or addictive disorders can be beneficial. However, when over 90% of patients presenting to, and in pain management centers are on opioids and opioid abuse and addiction exceeds that of illicit drugs, it is time to fix a broken system.

In 2001 Connecticut State Attorney Richard Blumenthal sent a strong letter to Richard Sackler, president of Purdue Pharm stating the abuse, addiction, diversion and crime problems associated with OxyContin. He presented a course of responsible action for Purdue to follow that would have substantially curtailed the current situation.

In 2004 a father who lost his 22 year old son to OxyContin testified before the House Subcommittee on Criminal Justice, Drug Policy and Human Resources asking the legislators to take effective steps to monitor and curb the improper marketing and use of OxyContin At the Winter Park Florida subcommittee hearing Chairman Souder remarked that OxyContin was not good for moderate pain and that it had no place in that part of medical treatment.



In 2005 Citizen Petition 2005P-0076 was filed with the FDA requesting that OxyContin (and generics) and Palladone be temporarily removed from the market to be reformulated as abuse resistant AND that they be restricted for use with severe pain only.

Also in 2005 Congressman Lynch introduced H.R. 2195 calling for the removal of OxyContin from the market, stating that “there is compounding difficulty here in the fact that absent a significant number of drug-related deaths such as we have seen with Vioxx, Ephedra, and I’d argue OxyContin, once a drug receives FDA approval it is virtually impossible to require further research to improve its safety. That condition leaves legislators in a position where the only option we have is to recommend the banning of that pharmaceutical. Admittedly, that is not the ideal solution.” The truth about OxyContin, Purdue Pharma and governmental agency inaction was clearly stated at a U.S. House of Representatives Hearing before the Subcommittee on Regulatory Affairs of the Committee on Government Reform on September 13, 2005 **OxyContin and Beyond: Examining the Role of FDA and DEA in Regulating Prescription Painkillers.** Transcripts of the hearing should be mandatory reading for every member of Congress.

The warning signs have been there, the evidence of a broken system clearly visible, the requests and pleas to fix the faulty marketing and use of OxyContin and other opioids very clear.

Most recently, on July 26, 2006 a mother who lost her 24 yr. old son to OxyContin testified before the same House subcommittee that heard the testimony of the father of the 22 year old young man just two years prior. Will the voices of reason and rationality be ignored once again? Or will the deaths continue?

Without effective steps to monitor and curb the improper marketing and use of OxyContin and other opioids, as well as effective steps to bring proper balance to pain management treatment the answer is:

Yes, tragically, the deaths will continue.

***Electronically signed on September 20, 2006 by:***

**Stephen G. Gelfand, MD, FACP**

**Fred Pazur**

**Ed Bisch**

**Art Van Zee, MD**

**Barbara Van Rooyan**

**Betts Tully**



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## NOVUS MEDICAL DETOX CENTER OF PASCO COUNTY, LLC

### Do Opioids Actually Increase Pain?

By Steve Hayes, Director

As we discussed last week, Purdue Pharma is the maker and advocate of pushing OxyContin, legal heroin, in the name of profit. We are now a week closer to the FDA hearing where Purdue Pharma's application for their new "tamper proof" OxyContin will be reviewed. In last week's newsletter, we discussed some of the "dirty little secrets" about OxyContin that Purdue doesn't want anyone to know. We pointed out that Purdue certainly has no interest in people finding cures for their pain because then they purchase less of their product.

In this newsletter we will discuss the growing consensus among medical professionals that continued use of opioids like OxyContin actually increases pain—not alleviates it. During Larry G's Prescription Addiction Radio Show last Sunday night, Dr. Steve Gelfand discussed the growing number of properly done medical studies by respectable medical researchers that have reached this conclusion.

Before addressing Dr. Gelfand's comments and the results of other studies, it will be helpful to define a few terms. Generally, there are two types of pain that we experience. One is called neuropathic pain—which occurs when the nerves in the central or peripheral nervous system are not functioning properly. The other is the pain that we experience from injury or sometimes by chemicals in the body. These pain signals are sent by a sensory receptor cell called a nociceptor.

The studies often refer to hyperalgesia. Hyperalgesia simply means an increased sensitivity to pain which can be caused by damage caused to the nociceptors.

### **TOLERANCE OR OPIOID INDUCED PAIN**

It is widely known by medical practitioners that many people who are prescribed opioids like OxyContin for pain find that they have to continually increase the amount of opioids they take daily in order to get the same pain relief. In some cases, our patients were prescribed 20 milligrams of OxyContin per day and a year later were taking over 200 milligrams per day and were hopelessly dependent or addicted. Even on the higher dose, these patients said that the pain was actually worse.

For a long time, it was assumed that this increase in dosage was required because the opioid receptors became less sensitive to the opioids and larger doses were required to achieve the same stimulation of the receptors which would produce enough endorphins to control the pain. This is called opioid tolerance.

Now Dr. Gelfand and many other respected medical practitioners are challenging this tolerance theory. They agree that tolerance is real, but they also have concluded that a significant amount of the increased pain experienced by people taking opioids is actually caused by the opioids.



## DR. STEPHEN GELFAND

Dr. Gelfand is a board certified rheumatologist with more than 30 years of experience in the field. Rheumatologists treat arthritis, fibromyalgia, tendonitis and other soft tissue and joint disorders. Dr. Gelfand's patients are experiencing pain—often very severe and debilitating pain. He is the author of numerous articles on rheumatology and is considered an authority in his field.

Abraham Lincoln said, "Important principles may, and must, be inflexible." In a society where doctors like Dr. Stephen Gelfand can receive lucrative contracts from drug companies if they recommend the use of their products, Dr. Gelfand chooses to follow what should be a doctor's most important principle--the welfare of his patients has to come first. This principled stand has cost him money and sometimes subjected him to criticism from other doctors who have placed the value of the dollar over the welfare of the patient but Dr. Gelfand persists in his writing and on radio shows—like Larry G's Prescription Addiction show, to point out that the claims of the makers of the opioids are exaggerated and often just plain false.

Rather than just allowing his patients to become more and more dependent on opioids and seeing him—with a lucrative fee to him each time, Dr. Gelfand explains to his patients who have been taking higher and higher doses of opioids in an attempt to control their pain that they are on a path that will lead only to more pain and a deteriorating quality of life. He educates them on the medical literature that is concluding that the continued use of these opioids is actually making their pain worse. He explains that there are real alternatives and Dr. Gelfand's patients experience less pain and a much improved quality of life through the use of non-opioid treatments.

In his letter to the FDA's Dr. Throckmorton, Dr. Gelfand cited twenty-one articles/studies in the medical literature pointing out the dangers of opioid treatment for pain and the growing agreement that opioids actually increase pain.

## STUDIES SHOWING OPIOIDS INCREASE PAIN

In the November 13, 2003 *New England Journal of Medicine*, Dr. Ballantyne and Dr. Mao published *Opioid Therapy for Chronic Pain*. One of their conclusions was, "Long-term use of opioids may also be associated with the development of abnormal sensitivity to pain, and both preclinical and clinical studies suggest that opioid-induced abnormal pain sensitivity has much in common with the cellular mechanisms of neuropathic pain. Opioid-induced abnormal pain sensitivity has been observed in patients treated for both pain and addiction... Repeated administration of opioids not only results in the development of tolerance (a desensitization process) but also leads to a pro-nociceptive (sensitization) process... Thus, the need for dose escalation during opioid therapy — that is, the development of "apparent" opioid tolerance — may be the result of pharmacologic opioid tolerance, opioid-induced abnormal pain sensitivity, or disease progression."



In *Postoperative Hyperalgesia: Its Clinical Importance and Relevance*, published in *Anesthesiology*:Volume 104(3) March 2006, pp 601-607, Dr. Wilder-Smith and Dr. Arendt-Nielsen point out,

“We therefore have early evidence that opioids may cause hyperalgesia and that this can negatively impact early pain outcomes. However, further studies are clearly needed in this area, particularly with regard to chronic pain outcomes.”

In the *Pain Physician*, 2007 May;10:479-91, Dr. J. C. Ballantyne stated,

- Overall, the evidence supporting long-term analgesic efficacy is weak.
- The putative mechanisms for failed opioid analgesia (failed pain relief) may be related to (rampant) tolerance or opioid-induced hyperalgesia.
- The premise that tolerance can always be overcome by dose escalation is now questioned.
- Epidemiological (study of disease origin) studies are less positive, and report failure of opioids to improve QOL (quality of life) in chronic pain patients.

In the *Journal of Pain* 2006: 125: 172-179, Dr. Eriksen states, “...it is remarkable that opioid treatment of long term/chronic non-cancer pain does not seem to fulfill any of the key outcome opioid treatment goals: pain relief, improved quality of life and improved functional capacity.”

The February, 2008, issue of *PAIN*, the publication of the International Association For The Study of Pain, states, “Clinicians should consider the possibility of OIH (opioid induced hyperalgesia) when contemplating an adjustment of opioid dose when (1) previous opioid dose escalation has failed to provide the expected analgesic effect and (2) there is an inexplicable exacerbation of pain after an initial period of effective opioid analgesia. Increasing opioid dose may not always be the answer to ineffective opioid therapy, and under certain circumstances a smaller amount of opioid may lead to more effective pain reduction.

## WHAT DO WE KNOW?

It is not disputed that:

- OxyContin is causing thousands of deaths because it is being used as a replacement for heroin;
- OxyContin is causing deaths and addiction even though it was prescribed originally by a physician;
- Purdue’s attempt to get the FDA to allow them to promote a “tamper proof” version of OxyContin does nothing to address the devastation caused by the legal use of their drug;



- There are serious questions about the testing procedures and labs used by Purdue to “prove” that their new version of OxyContin is safer from being used like heroin;
- Neither Purdue nor the FDA is addressing the growing evidence that their drug may actually be creating pain and not relieving it.
- The FDA appears to be prepared to accept as true the statements a company that only a year ago pled guilty to lying about the addictive quality of OxyContin—something that raises serious doubts about the integrity of the FDA.

## CONCLUSION

Purdue Pharma is a corporation that employs thousands of people. Many of their employees have children. I would not want to be one of those parents who has to explain to their children why they continued to work for a company that admitted to lies that deliberately and directly, not indirectly or through some strange accident but deliberately, led to thousands of deaths, addiction and ruined lives all across America.

What do they say when their children ask about the classmate that died after taking the drug their parents helped make?

What do they say if their children ask why Purdue kept pushing more and more drugs in spite of the growing agreement that opioids actually increase pain?

What they say when they explain what type of work their parents do? Do they say, “My dad makes OxyContin—legal heroin.”

Unlike the Nazi guards at the concentration camps, these Purdue employees can’t say that they were only following orders--they were free to get other jobs.

I guess they can try to explain that they were making good money and this bought things. They certainly can’t say that they didn’t know that their employer’s products were destroying more and more lives every day.

At Novus Medical Detox Center, we daily work to help people regain their lives caused by prescription drugs like OxyContin. The FDA must take steps to control this dangerous drug—OxyContin—Legal Heroin.



## Roadmap to a Reduction in a National Crisis of Prescription Opiate Abuse

Controlled prescription drugs are now the fourth most abused substance in the U.S. behind only marijuana, alcohol, and tobacco. Prescription opioid abuse has been accelerating at an alarming rate as reflected in the DAWN data, admissions to drug treatment facilities, and rapidly rising opioid related over-dose deaths around the country. The OxyContin tragedy has been a major part of the story, but all prescription opioids are involved. Methadone has become the number one opioid involved in over-dose deaths in a number of states across the country. Responses to the problem from the pharmaceutical industry, the DEA, the FDA, and other parties involved have not significantly impacted the problem. The following proposed measures could very significantly reduce this growing national tragedy.

1. The FDA could set the standards that only opioid products that are abuse resistant could come to the market-place.
2. The FDA could change the indications for sustained-release opioids. Sustained release opioids would be available to all patients with cancer. For patients with severe chronic non-cancer pain sustained release opioids would be available on a “compassionate use” program (the prescribing physician having to document failure with non-opioids and immediate release opioid preparations).
3. The public health will best be served by a much empowered FDA with sufficient staffing to review and regulate marketing and promotion of controlled drugs. The unprecedented and aggressive marketing of OxyContin by Purdue Pharma played a major role in the OxyContin abuse problem. Public interest and the public health would be better served by a redefinition of acceptable and allowable marketing practices for opioids and other controlled drugs, and an empowered FDA to monitor and regulate such marketing.
4. The FDA could require, as a standard of marketing of controlled drugs, the use of a secure and tamper proof means of dispensing. Such devices are being developed that would be fixed or hand-held computerized devices that would minimize abuse and diversion. GW Pharmaceuticals is developing one such device. There may be others being developed as well.
5. The DEA could require 8-16 hours of CME on pain and addiction as a contingency for physicians prescribing of Schedule II and III drugs. Since methadone is a more complicated and particularly tricky drug to prescribe and monitor, it would be reasonable to require a dedicated four hour hours to obtain DEA certification to prescribe methadone for pain. While the DEA can not legally regulate the practice of medicine, there is precedence in buprenorphine---a



schedule III opioid—for the federally legislated requirement of special training and certification.

6. A national prescription drug monitoring program that was internet based and real time—in contrast to a multitude of state run programs that may not communicate well with each other—could well reduce some of the diversion nationally.
7. Long term studies through NIH or Institute of Medicine are needed to better define the questions and problems associated with the use of opioids for chronic non-cancer pain. The risks and benefits of long term opioid treatment, the risks of iatrogenic addiction, the functional out-comes, the comparison of high and low dose opioid regimens, and the comparison with other therapeutic options would greatly improve our knowledge and corresponding skills in prescribing opioids for chronic non-malignant pain.
8. Enhanced preventive measures to include the wide-spread use of proven effective curriculums in the school system would make a difference in the long run and be an important part of a long-term demand reduction strategy.
9. Much expanded treatment for prescription opioid abuse is a key element in the efforts to impact the problem and further demand reduction. Buprenorphine treatment is very effective and needs further promotion and utilization. Public policy changes in the past have created incentives/loan repayment for physicians to locate in medically under-served areas. Similar public policy changes could provide incentives and loan repayment options to encourage medical students and residents to enter the very under-served speciality of addiction medicine.

The prescription opioid abuse problem is a growing national tragedy that has been associated with much pain and suffering---for countless individuals who have become opioid addicted over their prescription drug use or abuse, and for the families of many who have lost a loved one to this problem. Current approaches have been ineffective in dealing with this escalating problem. Unless major and decisive steps are taken, this tragedy will continue.

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## SPEAK OUT RHEUMATOLOGY | GUEST COLUMNISTS ON WHAT MATTERS TO THEM

Picture of Dr. Gelfand?

# Perils of Pain Meds

## Opioid overuse is a dangerous path for patients and physicians >> By Stephen G. Gelfand, MD

I have read with interest the recent thoughtful editorials in *The Rheumatologist* about the future of rheumatology and our healthcare system in general. There is another problem affecting both the practice of rheumatology and primary care that is having a negative impact upon patient care, as well as on the careers of certain rheumatologists like myself. This problem concerns the overuse of prescription opioids for chronic non-cancer pain, including the rheumatic disorders—a practice which continues to grow with insufficient attention to the consequences. This has occurred irrespective of publications which confirm the importance of pain-relieving, non-drug therapies for most of the rheumatic disorders, as well as the pitfalls of opioid overuse for chronic non-cancer pain.<sup>1-4</sup> Some of these beneficial strategies include education, self-help courses, physical therapy and exercise programs, and psychological and behavioral approaches to pain management.

### Growth of Opioid Use

The main controversy involves the difference between selectivity in the use of opioids in chronic non-cancer pain for specific clinical indications versus non-selectivity for most types of chronic pain represented by the movement to expand the use of opioids beyond the pain of cancer. Selective instances in which opioids may be beneficial include intractable tissue-generated pain, such as that caused by nerve disease or damage or end-stage arthritis, especially in the absence of other options. However, the use of opioids in other types of chronic non-cancer pain, especially that of central origin, may increase risks while the benefits may be minimal. Examples include central pain sensitivity states such as fibromyalgia syndrome, especially if associated with co-morbid depression or anxiety states.

Over the last decade, an expansion in the use of opioids has been advocated by certain pain specialists as well as pharmaceutical companies. In my opinion, this has occurred in the absence of valid data that support the claims that opioids can effectively and safely be extended beyond cancer to most patients with chronic non-cancer pain with a low risk of addiction. Such claims have subsequently been found to be inaccurate, and the original statement about the low rate of addiction to a common oxycodone sustained-release formulation has been shown to be false (as recently admitted by pharmaceutical company executives as a result of a Federal indictment).

Recent reviews confirm the absence of reliable long-term randomized controlled trials that demonstrate the efficacy and safety of opioid therapy for chronic non-malignant pain for more than eight months.<sup>5-7</sup> Further, in addition to increasing the risk-benefit ratio, over-reliance on long-term opioid therapy in rheumatic disorders may impede the learning of important self-efficacy and self-management skills that enhance favorable therapeutic outcomes with less dependence upon pain-relieving drugs.

### Dangerous Drugs

Unfortunately, the non-selective and widespread use of prescription opioids, as well as illicit non-medical misuse, have contributed to a mounting toll of documented adverse events which were just starting to be

recognized six years ago. This includes the high incidence of abuse and diversion, the substantial risk of addiction, the growing problem of opioid-related crime, the increased availability and ease of access to opiate drugs by teenagers and young adults (who misperceive prescription drugs to be safe), and the soaring statistics of emergency department visits, overdose, and death.<sup>8</sup>

Recent data from the Centers for Disease Control and Prevention (CDC) on national total opioid-related poisoning deaths (without heroin or cocaine) showed that from 1999 to 2002 (the last CDC-calculated year) there was a 129% increase in mortality, from 1,942 deaths in 1999 to 4,451 in 2002.<sup>9</sup> Very likely, this figure has substantially increased in each subsequent year. A recent study in the *Archives of Internal Medicine* taken from drug mortality reports to the Food and Drug Administration (FDA), noted 5,548 oxycodone-related deaths from 1998 to 2005, making oxycodone the most common prescription drug of all drug mortality reports to the FDA.<sup>10</sup> The actual number of deaths is probably much higher since most opioid-related deaths are not reported to

the Medicaid population. Such patients may have had a better chance of responding to multidisciplinary management if timely specialty referrals were possible and were made at an earlier stage, prior to the start of opioid therapy, which often fosters passive treatment attitudes and “illness behaviors,” especially in the presence of poor coping skills and persistent psychosocial stress.

In view of the well-documented risks of opioids, careful patient selection and prudent use should be the standard. Pain should not be managed in isolation without an understanding of its roots, just as fever mandates a search for causes. Under-treatment should refer not only to drug therapy, but also to the absence of important non-drug interventions. Hopefully, this approach will reduce inappropriate opioid use as well as associated morbidity and mortality. *THE RHEUMATOLOGIST*

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There is a need to use opiate drugs selectively, prudently, cautiously, under close supervision, and for specific clinical indications.

the FDA. In Florida alone, as reported from the office of the Florida Medical Examiners in 2006, there were more than 4,300 total prescription opioid-related deaths with the three most common from methadone (974), oxycodone (923), and hydrocodone (731).<sup>11</sup> Lethal levels were found in 716 cases of methadone, 496 cases of oxycodone, and 236 cases of hydrocodone, although many opiate-related deaths occurred in the absence of lethal levels but in combination with other central nervous system-active agents.

### A Better Approach to Pain

In view of these statistics, there is a need to use opiate drugs selectively, prudently, cautiously, under close supervision, and for specific clinical indications. However, beneficial non-opioid self-management therapies are often neglected or underused, especially by primary care providers with not enough time to spend with their patients or because of a lack of or inadequate insurance coverage. This has led to a significant increase in the use of opioids (and other psychoactive agents) which has often resulted in polypharmacy and drug-dependent care becoming the rule for patients with every type of chronic non-cancer pain, particularly in rural areas.

I have observed many patients with intractable, non-inflammatory chronic pain, diffuse musculoskeletal tenderness, and severe underlying psychological distress (particularly depression) who have been inadequately diagnosed and managed solely with opioids and polypharmacy. Many of these patients are drug dependent (and often addicted), dysfunctional both mentally and physically, and frequently on or applying for disability, which is especially common in



## Therapeutic Opioids: A Ten-Year Perspective on the Complexities and Complications of the Escalating Use, Abuse, and Nonmedical Use of Opioids

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Therapeutic opioid use and abuse coupled with the nonmedical use of other psychotherapeutic drugs has shown an explosive growth in recent years and has been a topic of great concern and controversy. Americans, constituting only 4.6% of the world's population, have been consuming 80% of the global opioid supply, and 99% of the global hydrocodone supply, as well as two-thirds of the world's illegal drugs. With the increasing therapeutic use of opioids, the supply and retail sales of opioids are mirrored by increasing abuse in patients receiving opioids, nonmedical use of other psychotherapeutic drugs (in this article the category of psychotherapeutics includes pain relievers, tranquilizers, stimulants, and sedatives, but does not include over-the-counter drugs), emergency department visits for prescription controlled drugs, exploding costs, increasing incidence of side effects, and unintentional deaths.

However, all these ills of illicit drug use and opioid use, abuse, and non-medical use do not stop with adults. It has been shown that 80% of America's high school students, or 11 million teens, and 44% of middle school students, or 5 million teens, have personally witnessed, on the grounds of their schools, illegal drug use, illegal drug dealing, illegal drug possession, and other activities related to drug abuse.

The results of the 2006 National Survey on Drug Use and Health showed that 7.0 million or 2.8% of all persons aged 12 or older had used prescription type psychotherapeutic drugs nonmedically in the past month, 16.387 million, or 6.6% of the population, had used in the past year, and 20.3%, or almost 49.8 million, had used prescription psychotherapeutic drugs nonmedically during their lifetime. Sadly, the initiates of psychotherapeutic drugs used for nonmedical purposes were highest for opioids.

Therapeutic opioid use has increased substantially, specifically of Schedule II drugs. Apart from lack of effectiveness (except for short-term, acute pain) there are multiple adverse consequences including hormonal and immune system effects, abuse and addiction, tolerance, and hyperalgesia. Patients on long-term opioid use have been shown to increase the overall cost of healthcare, disability, rates of surgery, and late opioid use.

**Key words:** Controlled prescription drug abuse, opioid abuse, opioid misuse, nonmedical use of psychotherapeutic drugs, nonmedical use of opioids, National Survey on Drug Use and Health, National Center on Addiction and Substance Abuse at Columbia University

**Pain Physician 2008; Opioid Special Issue: 11:S63-S88**



**B**ased largely upon the 2006 National Survey on Drug Use and Health (1) and a review of the current literature, this article describes a 10-year perspective on the complex and complicated interrelationships between the therapeutic use of opioids and other psychotherapeutics and the consequences of escalating use, abuse, and non-medical use as it affects this nation's problems of substance abuse, mental health, disability, and our ailing healthcare system.

For the last several years in the United States, the treatment of chronic pain, therapeutic opioid use and abuse, and the nonmedical use of prescription drugs have been topics of intense focus and controversy (2-7). Due in some measure to the campaign of alleged undertreatment of pain, Americans, constituting only 4.6% of the world's population, have been consuming 80% of the global opioid supply, and 99% of the global hydrocodone supply, as well as two-thirds of the world's illegal drugs (2-5,8-10). Retail sales of opioid medications have increased from a total in 1997 of 50.7 million grams of commonly utilized opioids (including methadone, oxycodone, fentanyl base, hydro-morphone, hydrocodone, morphine, meperidine, and codeine) to 115.3 million grams in 2006, an overall increase of 127% with increases ranging from 196% for morphine, 244% for hydrocodone, 274% for hydro-morphone, 479% for fentanyl base, 732% for oxycodone, to 1177% for methadone (11). In 2005 and 2006, over 120 million prescriptions for hydrocodone were issued and hydrocodone continues to be the number one prescribed drug in the United States (3,4,9,11,12). Average sales of opioids per person have increased from 74 milligrams in 1997 to 329 milligrams in 2006, a 347% increase. It is no surprise then that surveys of nonprescription drug abuse (1,13-17), emergency department visits for prescription controlled drugs (18-22), unintentional deaths due to prescription controlled substances (23-31), therapeutic use of opioids, and opioid abuse (32-88) have been steadily rising.

The National Survey of American Attitudes on Substance Abuse XII: Teens and Parents (89) shows 80% of America's high school students, or 11 million teens, and 44% of America's middle school students, or 5 million teens, have personally witnessed, on the grounds of their schools, illegal drug use, illegal drug dealing, illegal drug possession, students drunk, and/or students high on drugs. It must be remembered that illegal is synonymous with illicit and includes

drugs such as marijuana/hashish, cocaine (including crack), heroin, hallucinogens, and inhalants as well as the nonmedical use of prescription drugs, which is also illicit and illegal.

This survey (89) also revealed that compared to teens at drug-free schools, teens at drug-infested schools are 16 times likelier to use an illegal drug other than marijuana or prescription drugs, 15 times likelier to abuse prescription drugs, 6 times likelier to get drunk at least once a month, and 5 times likelier to use marijuana. Sadly, since 2002 the proportion of students who attend schools where drugs are used, kept, or sold has jumped 39% for high school students and 63% for middle school students. What is also clear from this survey is that physicians' well intentioned, appropriate, and legitimate prescriptions are, at an alarmingly increasing rate, being tragically diverted for nonmedical use not only by adults, but also by high school and middle school students. We must now closely examine these unintended consequences.

### **NON-MEDICAL USE OF PSYCHOTHERAPEUTIC DRUGS**

Results of the 2006 National Survey on Drug Use and Health (NSDUH) (1), an annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), showed that an estimated 20.4 million, or 8.3% of Americans, aged 12 or older, were current (past month) illicit drug users. Illicit drugs include marijuana/hashish, cocaine, heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics (defined in this survey as prescription-type pain relievers, tranquilizers, stimulants, and sedatives) used nonmedically. Marijuana and Hashish were the most commonly used illicit drugs with 14.8 million current (past month) users, or 6% of the US population. Cocaine was used by 2.4 million, whereas hallucinogens were used in the past month by 1 million persons (Table 1 and Fig. 1). Next to marijuana, 7.0 million (2.8%) persons aged 12 or older had used prescription-type psychotherapeutic drugs nonmedically in the past month (current use). Of these, 5.2 million had used pain relievers, an increase from 4.7 million in 2005. The category of psychotherapeutics used in the tables and figures includes the nonmedical use of any prescription-type pain relievers, tranquilizers, stimulants, or sedatives. However, over-the-counter substances are not included in these studies. The categories of non-medical use of psychotherapeutics and pain relievers



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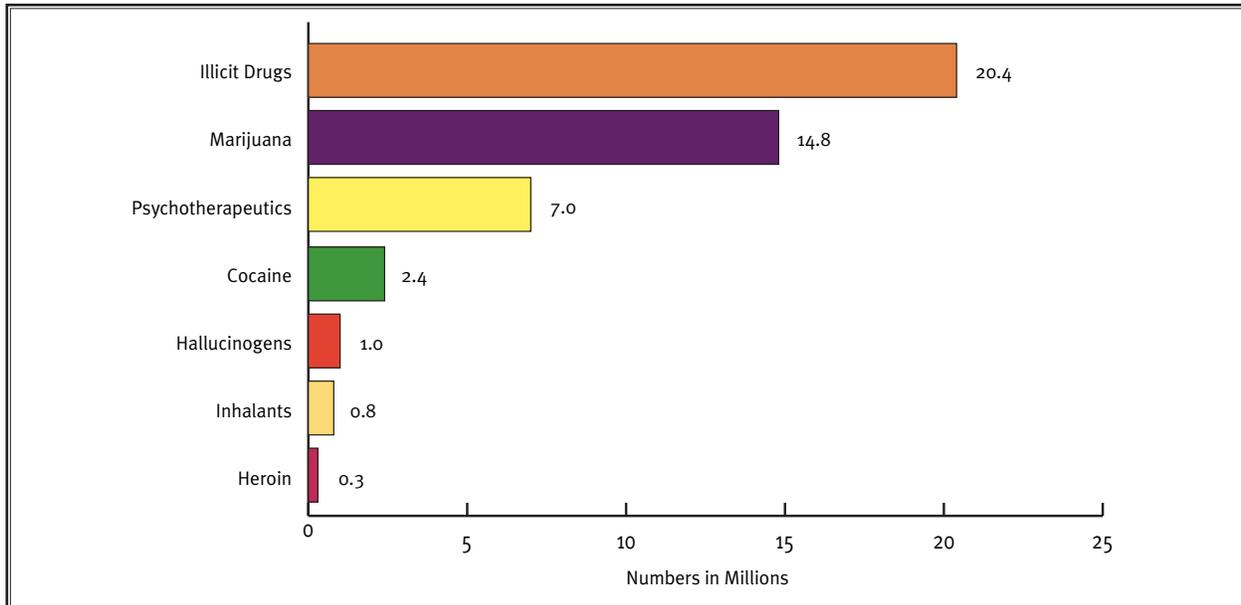


Fig. 1. Past month use of specific illicit drugs among persons aged 12 or older: 2006 (1).

Source: www.oas.samhsa.gov/nsduh/2k6nsduh/2k6results.pdf

Table 1. Types of illicit drug use in the past month among persons aged 12 or older: Numbers in thousands, from 1997 to 2006 (10 years).

Drugs	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	10-YEAR % change from 1997 to 2006
Nonmedical Use of Psychotherapeutics <sup>2</sup>	2,665 (1.2%)	2,477 (1.1%)	3,952 (1.8%)	3,849 (1.7%) <sup>a</sup>	4,811 <sup>c</sup> (2.1%)	6,210 <sup>a</sup> (2.6%)	6,336 (2.7%)	6,007 <sup>b</sup> (2.5%) <sup>b</sup>	6,405 (2.6%)	6,991 (2.8%)	162%
Pain Relievers	--	--	2,621 (1.2%)	2,782 (1.2%)	3,497 <sup>c</sup> (1.6%)	4,377 <sup>b</sup> (1.9%) <sup>a</sup>	4,693 (2.0%)	4,404 <sup>b</sup> (1.8%) <sup>a</sup>	4,658 <sup>a</sup> (1.9%)	5,220 (2.1%)	NA
OxyContin <sup>®</sup>	--	--	--	--	--	--	--	325 (0.1%)	334 (0.1%)	276 (0.1%)	NA
Tranquilizers	845 (0.4%)	655 (0.3%)	1,097 (0.5%)	1,000 (0.4%)	1,358 <sup>c</sup> (0.6%)	1,804 (0.8%)	1,830 (0.8%)	1,616 (0.7%)	1,817 (0.7%)	1,766 (0.7%)	109%
Stimulants	612 (0.3%)	633 (0.3%)	950 (0.4%)	788 (0.4%)	1,018 (0.5%)	1,218 (0.5%)	1,191 (0.5%)	1,189 (0.5%)	1,067 (0.4%)	1,191 (0.5%)	95%
Sedatives	187 (0.1%)	210 (0.1%)	229 (0.1%)	175 (0.1%)	306 (0.1%)	436 (0.2%)	294 (0.1%)	265 (0.1%)	272 (0.1%)	385 (0.2%)	106%
Marijuana and Hashish	11,109 (5.1%)	11,016 (5.0%)	10,458 (4.7%)	10,714 (4.8)	12,122 <sup>c</sup> (5.4%)	14,584 (6.2%)	14,638 (6.2%)	14,576 (6.1%)	14,626 (6.0%)	14,813 (6.0%)	33%
Cocaine	1,505 (0.7%)	1,750 (0.8%)	1,552 (0.7%)	1,213 (0.5%)	1,667 <sup>c</sup> (0.7%)	2,020 <sup>a</sup> (0.9%)	2,281 (1.0%)	2,021 <sup>a</sup> (0.8%)	2,397 (1.0%)	2,421 (1.0%)	61%
<b>TOTAL ILLICIT DRUGS<sup>1</sup></b>	<b>13,904 (6.4%)</b>	<b>13,615 (6.2%)</b>	<b>13,829 (6.3%)</b>	<b>14,027 (6.3%)</b>	<b>15,910<sup>c</sup> (7.1%)</b>	<b>19,522 (8.3%)</b>	<b>19,470 (8.2%)</b>	<b>19,071<sup>a</sup> (7.9%)</b>	<b>19,720 (8.1%)</b>	<b>20,357 (8.3%)</b>	<b>46%</b>

-- Not available.

a Difference between estimate and 2006 estimate is statistically significant at the 0.05 level.

b Difference between estimate and 2006 estimate is statistically significant at the 0.01 level.

c Difference between estimate and previous year estimate is statistically significant at the 0.01 level.

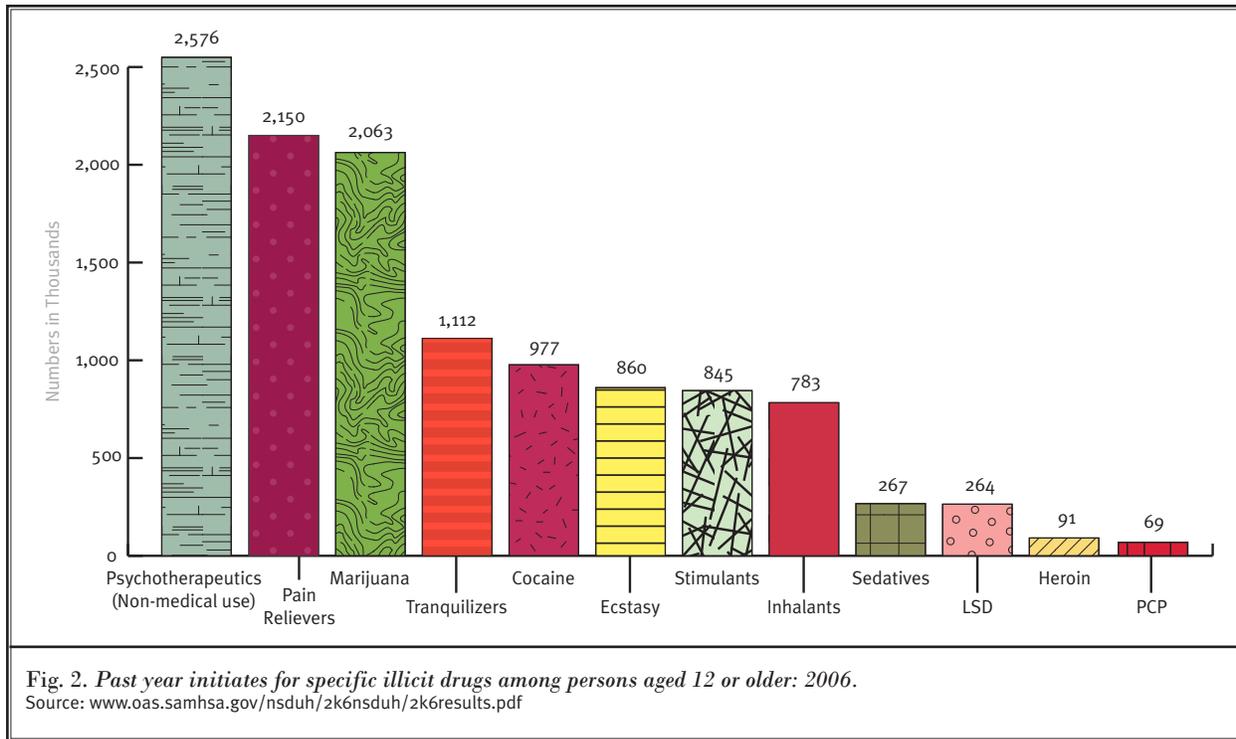
1 Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.

2 Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives, and does not include over-the-counter drugs.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1995 to 2006.



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were well ahead of the illicit use of cocaine, hallucinogens, inhalants, methamphetamine, heroin, and LSD.

The increases for current (past month) nonmedical use of psychotherapeutics over a period of the last 10 years (1997 to 2006) was 162% compared to 33% for marijuana and hashish and 61% for cocaine. In fact, psychotherapeutics were the only ones that showed significant increases from 2002 to 2006, whereas, marijuana and cocaine were similar over a period of 5 years. Statistics of new initiates continue to be grim.

In 2006, there were 2.6 million persons aged 12 or older who used psychotherapeutics nonmedically for the first time within the past year (Fig. 2). Numbers of new users for specific psychotherapeutics in 2006 were 2.2 million for pain relievers, 1.1 million for tranquilizers, 845,000 for stimulants, and 267,000 for sedatives (Table 2). The specific drug categories with the largest number of recent initiates among persons aged 12 or older were nonmedical use of pain relievers (2.2 million) and marijuana (2.1 million), followed by nonmedical use of tranquilizers (1.1 million), cocaine (1.0 million), ecstasy (0.9 million), stimulants (0.8 million), and inhalants (0.8 million) (Fig. 2). More strikingly, in

2006, the number of new nonmedical users of OxyContin aged 12 or older was 533,000 with an average age at first use of 22.6 years among those aged 12 to 49 (1,13-16).

Analysis of long-term statistics based on yearly use of illicit drugs are concerning. The past year use of illicit drugs in 2006 was 35.77 million, or 14.5% of the population (Table 3). Nonmedical use of psychotherapeutics for the past year in the 2006 survey was 16.287 million compared to 15.172 million in 2005 and 14.643 million in 2004, or 6.6% of the population aged 12 or older in 2006, 6.2% in 2005, and 6.1% in 2004, with significant increases. Of importance is the fact that nonmedical use of psychotherapeutics was just behind marijuana and hashish with 10.3% of the population aged 12 or older in 2006 which decreased from 10.6% in 2004 and 10.4% in 2005 (Fig. 3). However, nonmedical use of psychotherapeutics was higher than cocaine with 2.5% of the population in 2006, compared to 2.2% for heroin, and 1.6% for hallucinogens in 2006 overall, nonmedical use of psychotherapeutics increased 167% over a period of 10 years, compared to 31% for marijuana, 46% for cocaine, and an overall increase of illicit drug use of 48%.



## Therapeutic Opioid Use, Abuse, and Nonmedical Use

Table 2. Past year initiates for illicit drugs from 1997 to 2006 (numbers in thousands) for 10 years.

Drugs	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	10-YEAR % change from 1997 to 2006
Pain Relievers <sup>2</sup>	1,316	1,548	1,810	2,268	2,400	2,320	2,456 <sup>a</sup>	2,422 <sup>a</sup>	2,193	2,150	63%
Tranquilizers	668	860	916	1,298	1,212	1,184	1,071	1,180	1,286	1,112	66%
Stimulants	553	648	706	808	853	783	715	793	647 <sup>a</sup>	845	53%
Sedatives	120	147	164	191	225	209	194	240	247	267	123%
Marijuana	2,603	2,498	2,640	2,746	2,793	2,196	1,973	2,142	2,114	2,063	-21%
Cocaine	861	868	917	1,002	1,140	1,032	986	998	872	977	13%
Heroin	114	140	121	114	154	117	92	118	108	91	-20%

Note: 2002 to 2006 data is based on 2006 National Survey on Drug Use and Health Survey Report.

NOTE: Past year initiates are defined as persons who used the substance(s) for the first time in the 12 months prior to date of interview.

a Difference between estimate and 2006 estimate is statistically significant at the 0.05 level.

2 Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives, and does not include over-the-counter drugs.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1995 to 2006.

Table 3. Types of illicit drug use in the past year among persons aged 12 or older: numbers in thousands from 1997 to 2006 (10 years).

Drugs	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	10-YEAR % change from 1997 to 2006
Nonmedical Use of Psychotherapeutics <sup>2</sup>	6,111 (2.8%)	5,759 (2.6%)	9,220 (4.2%)	8,761 (3.9%)	11,102 <sup>c</sup> (4.9%)	14,680 <sup>b</sup> (6.2%)	14,986 <sup>b</sup> (6.3%)	14,643 <sup>b</sup> (6.1%)	15,172 <sup>a</sup> (6.2%)	16,287 (6.6%)	167%
Pain Relievers	--	--	6,582 (3.0%)	6,466 (2.9%)	8,353 <sup>c</sup> (3.7%)	10,992 <sup>b</sup> (4.7%)	11,671 <sup>a</sup> (4.9%)	11,256 <sup>b</sup> (4.7%)	11,815 <sup>a</sup> (4.9%)	12,649 (5.1%)	NA
OxyContin <sup>*</sup>	--	--	--	--	--	--	--	1,213 (0.5%)	1,226 (0.5%)	1,323 (0.5%)	NA
Tranquilizers	2,122 (1.0%)	1,940 (0.9%)	2,728 (1.2%)	2,731 (1.2%)	3,673 <sup>c</sup> (1.6%)	4,849 (2.1%)	5,051 (2.1%)	5,068 (2.1%)	5,249 (2.2%)	5,058 (2.1%)	138%
Stimulants	1,687 (0.8%)	1,489 (0.7%)	2,291 (1.0%)	2,112 (0.9%)	2,486 <sup>c</sup> (1.1%)	3,181 (1.4%)	2,751 <sup>b</sup> (1.2%)	2,918 <sup>a</sup> (1.2%)	2,771 <sup>b</sup> (1.1%)	3,394 (1.4%)	101%
Sedatives	638 (0.3%)	522 (0.2%)	631 (0.3%)	611 (0.3%)	806 (0.4%)	981 (0.4%)	831 (0.3%)	737 (0.3%)	750 (0.3%)	926 (0.4%)	45%
Marijuana and Hashish	19,446 (9.0%)	18,710 (8.6%)	19,102 (8.6%)	18,589 (8.3%)	21,086 <sup>c</sup> (9.3%)	25,755 (11.0%)	25,231 (10.6%)	25,451 (10.6%)	25,375 (10.4%)	25,378 (10.3%)	31%
Cocaine	4,169 (1.9%)	3,811 (1.7%)	3,742 (1.7%)	3,328 (1.5%)	4,186 <sup>c</sup> (1.9%)	5,902 (2.5%)	5,908 (2.5%)	5,658 (2.4%)	5,523 (2.3%)	6,069 (2.5%)	46%
<b>TOTAL ILLICIT DRUGS<sup>1</sup></b>	<b>24,189 (11.2%)</b>	<b>23,115 (10.6%)</b>	<b>25,402 (11.5%)</b>	<b>24,535 (11.0%)</b>	<b>28,409<sup>c</sup> (12.6%)</b>	<b>35,132 (14.9%)</b>	<b>34,993 (14.7%)</b>	<b>34,807 (14.5%)</b>	<b>35,041 (14.4%)</b>	<b>35,775 (14.5%)</b>	<b>48%</b>

Note: 2002 to 2006 data is based on 2006 National Survey on Drug Use and Health Survey Report.

Figures in ( ) indicate percentage.

-- Not available.

a Difference between estimate and 2006 estimate is statistically significant at the 0.05 level.

b Difference between estimate and 2006 estimate is statistically significant at the 0.01 level.

c Estimate is statistically different than previous year

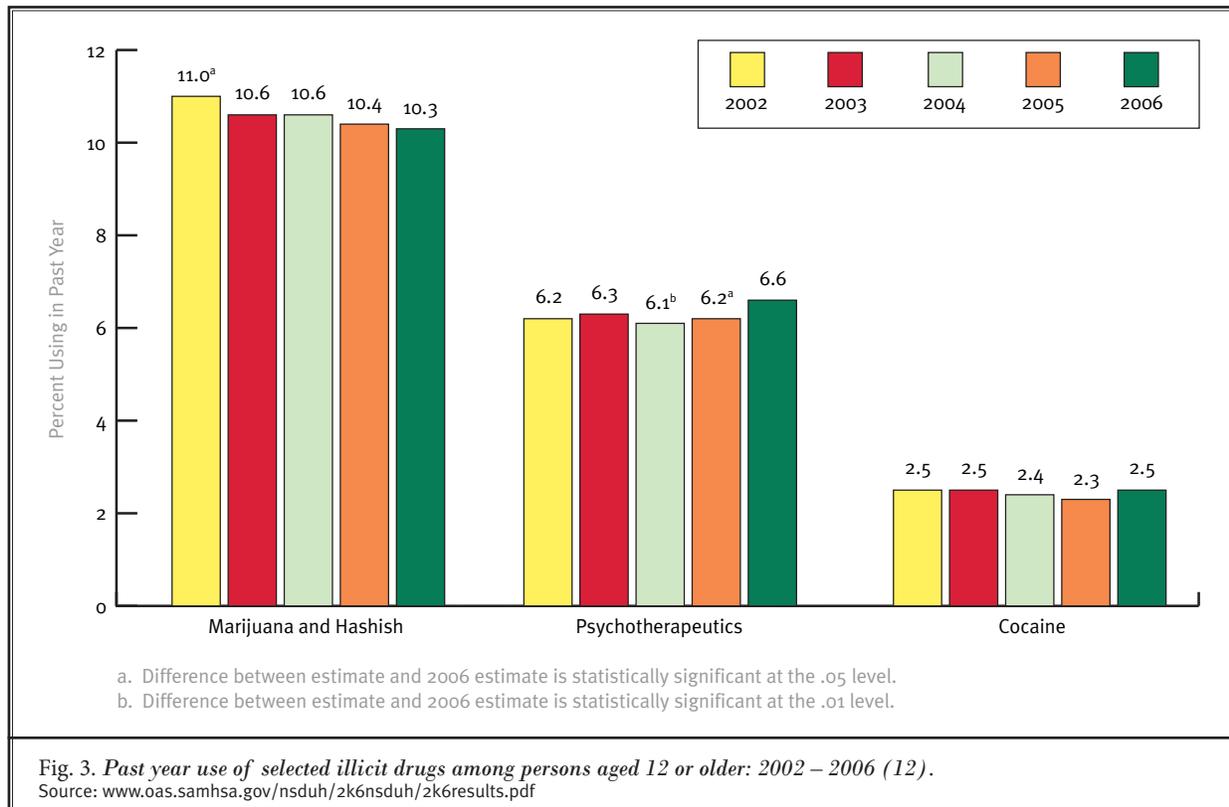
1 Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.

2 Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives, and does not include over-the-counter drugs.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1995 to 2006.



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Not surprisingly, lifetime use of illicit drugs (lifetime use indicates use of a specific drug at least once in the respondent's lifetime), including psychotherapeutics, among persons aged 12 or older has been increasing over the years (Table 4, Fig. 4). However, in 2006 the lifetime use of illicit drugs among persons aged 12 or older was slightly less than 2005 with 111,774 or 45.4% of the population, a decrease from 46.1% of the population in 2005. In contrast, nonmedical use of psychotherapeutics increased from 20% of the population in 2005 to 20.3% in 2006, or almost 50 million using prescription psychotherapeutic drugs for nonmedical purposes. Among the subgroups, only OxyContin increased significantly from 2004 to 2005 to 3,481, and to 4,098 in 2006, or 1.4% of the population in 2005 to 1.7% in 2006. Lifetime use of illicit drugs in persons aged 12 or older was topped by marijuana (39.8% of the population) followed by nonmedical use of psychotherapeutics (20.3% of the population). However, nonmedical use of psychotherapeutics was 153% higher than the lifetime use of cocaine (56%) or marijuana (38%), over a period of 10 years from 1997 to 2006.

### Abuse Based on Age

Rates of past month illicit drug use varied with age. Through the adolescent years from 12 to 17, the rates of current illicit drug use in 2006 increased from 3.9% at ages 12 or 13, to 9.1% at ages 14 or 15, to 16% at ages 16 or 17. However, the highest rate of 22.2% was noted among persons aged 18 to 20 (Fig. 5) (1). Even though the statistics show that adults aged 26 or older were less likely to be current drug users than their younger counterparts, overall there were more drug users aged 26 or older (11.4 million) than in the 12 to 17 year age group (2.5 million) and the 18 to 25 year age group (6.5 million) combined. In 2006, 9.8% of youths aged 12 to 17 were current illicit drug users: 6.7% used marijuana, 3.3% used prescription drugs nonmedically, 1.3% used inhalants, 0.7% used hallucinogens, and 0.4% used cocaine (1).

In 2006, young adults aged 18 to 25 demonstrated rates of current use of illicit drugs to be higher (19.8%) than for youths aged 12 to 17 and adults aged 26 or older, with 16.3% using marijuana, 6.4% using psychotherapeutics nonmedically, 2.2% using cocaine, and



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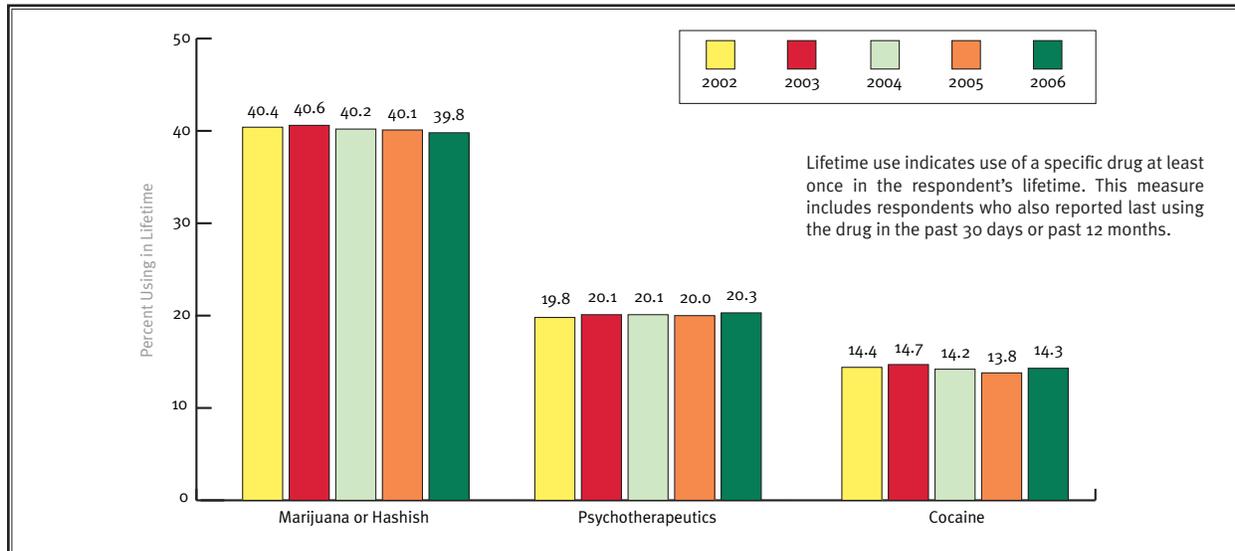


Fig. 4. Lifetime use of selected illicit drugs.

Source: www.oas.samhsa.gov/nsduh/2k6nsduh/2k6results.pdf

Table 4. Types of illicit drugs of lifetime use among persons aged 12 or older: numbers in thousands, 1997 – 2006.

Drug	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	% change from 1997 to 2006
Nonmedical Use of Psychotherapeutics <sup>2</sup>	19,671 (9.1%)	20,193 (9.2%)	34,076 (15.4%)	32,443 (14.5%) <sup>c</sup>	36,028 <sup>c</sup> (16.0%) <sup>c</sup>	46,558 <sup>b</sup> (19.8%)	47,882 <sup>a</sup> (20.1%)	48,013 (20.0%)	48,709 (20.0%)	49,842 (20.3%)	153%
Pain Relievers	--	--	19,888 (9.0%)	19,210 (8.6%)	22,133 <sup>c</sup> (9.8%) <sup>c</sup>	29,611 <sup>b</sup> (12.6%) <sup>b</sup>	31,207 <sup>b</sup> (13.1%)	31,768 <sup>a</sup> (13.2%)	32,692 (13.4%)	33,472 (13.6%)	NA
OxyContin <sup>®</sup>	--	--	--	--	--	1,924 <sup>b</sup> (0.8%) <sup>b</sup>	2,832 <sup>b</sup> (1.2%) <sup>b</sup>	3,072 <sup>b</sup> (1.3%) <sup>b</sup>	3,481 <sup>b</sup> (1.4%) <sup>b</sup>	4,098 (1.7%)	NA
Tranquilizers	6,931 (3.2%)	7,726 (3.5%)	13,860 (6.3%)	13,007 (5.8%)	13,945 (6.2%)	19,267 <sup>b</sup> (8.2%)	20,220 (8.5%)	19,852 <sup>a</sup> (8.3%)	21,041 (8.7%)	21,303 (8.7%)	207%
Stimulants	9,781 (4.5%)	9,614 (4.4%)	15,922 (7.2%)	14,661 <sup>c</sup> (6.6%) <sup>c</sup>	16,007 <sup>c</sup> (7.1%) <sup>c</sup>	21,072 (9.0%) <sup>b</sup>	20,798 (8.8%) <sup>a</sup>	19,982 (8.3%)	19,080 (7.8%)	20,118 (8.2%)	106%
Sedatives	4,080 (1.9%)	4,640 (2.1%)	7,747 (3.5%)	7,142 (3.2%)	7,477 (3.3%)	9,960 <sup>a</sup> (4.2%) <sup>b</sup>	9,510 (4.0%) <sup>a</sup>	9,891 <sup>a</sup> (4.1%) <sup>a</sup>	8,982 (3.7%)	8,822 (3.6%)	116%
Marijuana and Hashish	71,112 (32.9%)	72,070 (33.0%)	76,428 (34.6%)	76,321 (34.2%)	83,272 <sup>c</sup> (36.9%) <sup>c</sup>	94,946 <sup>a</sup> (40.4%)	96,611 (40.6%)	96,772 (40.2%)	97,545 (40.1%)	97,825 (39.8%)	38%
Cocaine	22,597 (10.5%)	23,089 (10.6%)	25,406 (11.5%)	24,896 (11.2%)	27,788 <sup>c</sup> (12.3%) <sup>c</sup>	33,910 (14.4%)	34,891 (14.7%)	34,153 (14.2%)	33,673 (13.8%)	35,298 (14.3%)	56%
<b>TOTAL ILLICIT DRUGS<sup>1</sup></b>	<b>76,960 (35.6%)</b>	<b>78,123 (35.8%)</b>	<b>87,734 (39.7%)</b>	<b>86,931 (38.9%)</b>	<b>94,140<sup>c</sup> (41.7%)<sup>c</sup></b>	<b>108,255<sup>b</sup> (46.0%)</b>	<b>110,205 (46.4%)</b>	<b>110,057 (45.8%)</b>	<b>112,085 (46.1%)</b>	<b>111,774 (45.4%)</b>	<b>45%</b>

-- Not available.

a Difference between estimate and 2006 estimate is statistically significant at the 0.05 level.

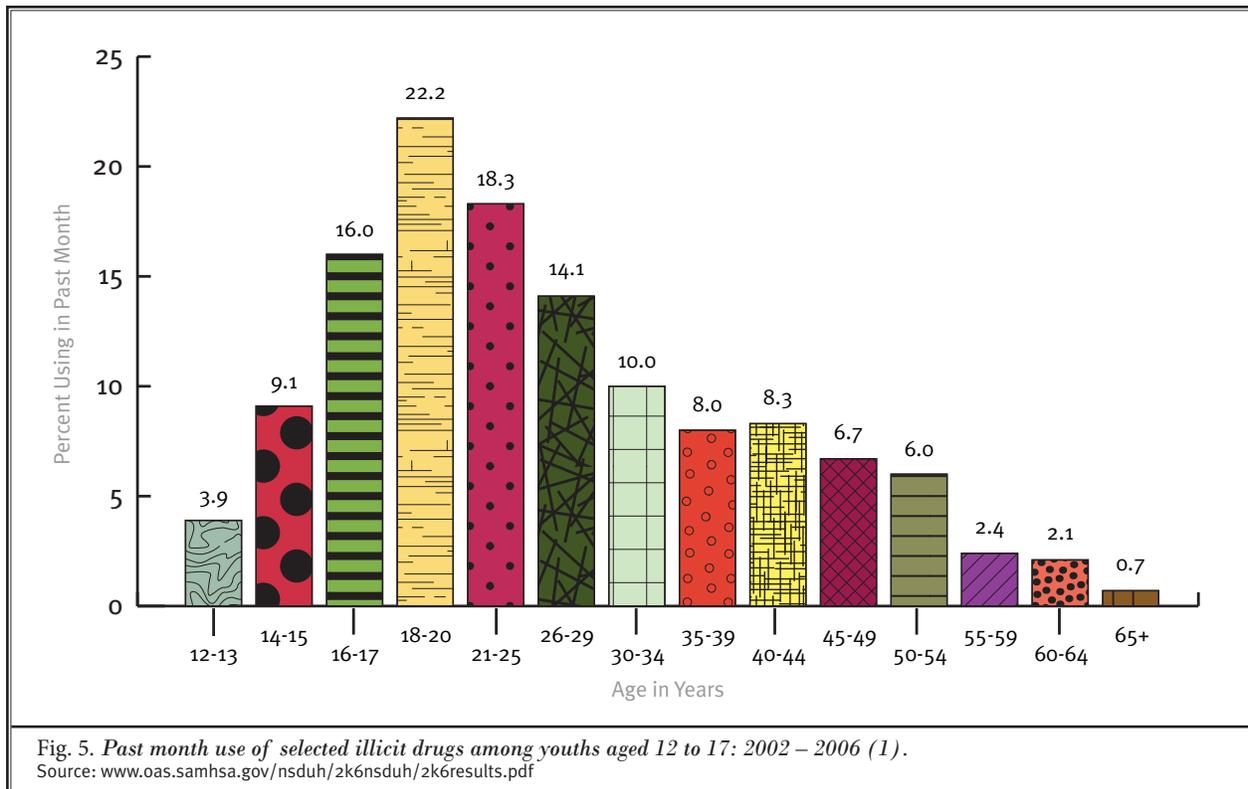
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<sup>1</sup> Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.<sup>2</sup> Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives, and does not include over-the-counter drugs.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1995 to 2006.

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1.7% using hallucinogens (Fig. 6). Past month non-medical use of prescription-type drugs among young adults increased from 5.4% in 2002 to 6.4% in 2006. This was primarily due to an increase in the rate of pain reliever use which was 4.1% in 2002 and 4.9% in 2006. Further, during the same period the nonmedical use of tranquilizers also increased from 1.6% to 2%.

Lifetime, past year, and current nonmedical use of psychotherapeutic drugs among young adults aged 18 to 25 also increased between 2002 and 2006, 27.7% vs. 30.3% for lifetime use, 14.2% vs. 15.5% for past year use, and 1.9% vs. 2.1% for current use, with increases in the rates of pain relievers and tranquilizer use (1).

### Gender

In 2006, the survey results were similar to prior years with males being more likely than females to be current illicit drug users (10.5% vs. 6.2%). However, the rate of past month marijuana use for males was about twice as high as the rate for females. The rate of past month nonmedical use of psychotherapeutic drugs increased from 2.8% to 3.2% among males, whereas there were no significant changes in the rate of past month drug use among females aged 12 or older (1).

### Pregnancy

Among pregnant woman aged 15 to 44 years, a significantly lower proportion of women used illicit drugs (4%) compared to their nonpregnant counterparts of 10% (1).

### Employment

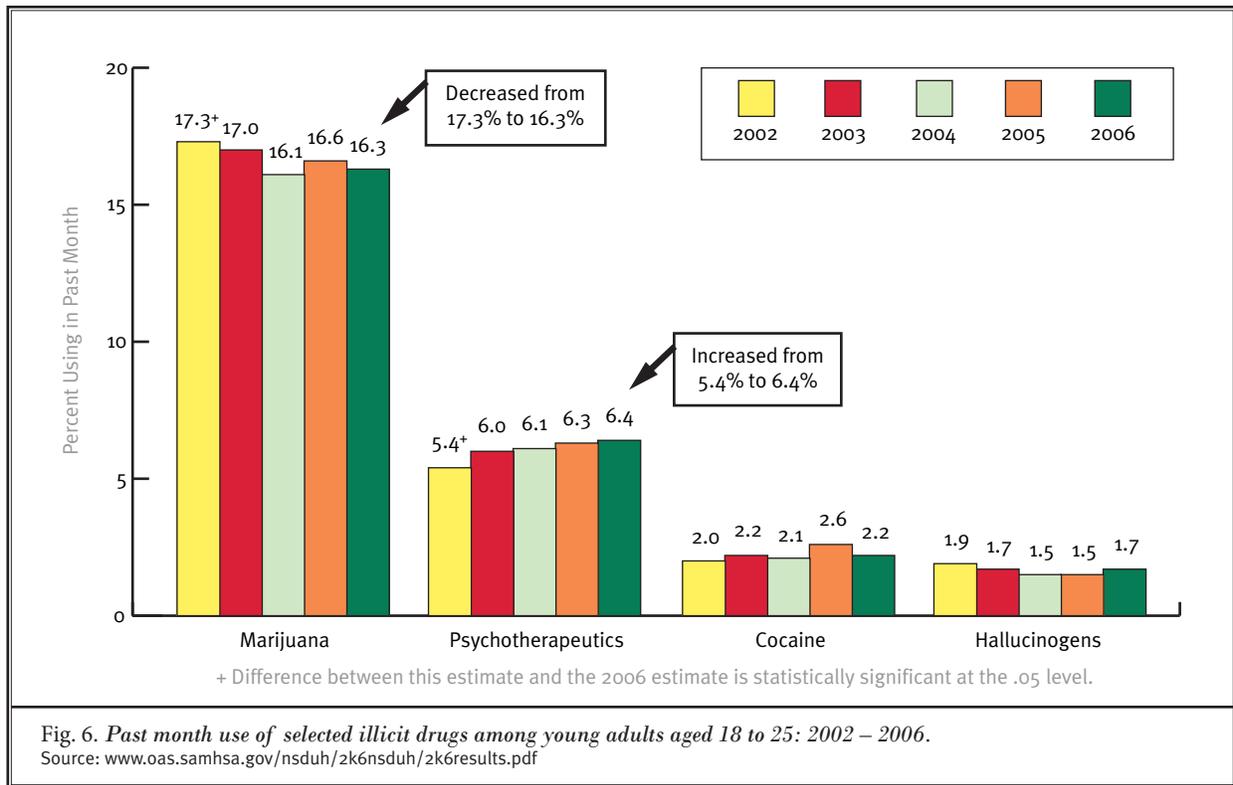
Employment also seems to have a significant influence. Among adults aged 18 or older, the current rate of illicit drug use was higher for unemployed persons (18.5%) than for those who were employed full-time (8.8%) or part-time (9.4%), the results being similar and comparable to 2005. Of approximately 18 million current illicit drug users aged 18 or older in 2006, nearly 75%, or over 13 million, were employed either full-or part-time (1).

### Region

There were also differences based on geographic area among persons aged 12 or older. The rate of current illicit drug use in 2006 was 9.5% in the West, 8.9% in the Northeast, 7.9% in the Midwest, and 7.4% in the South (12,88). Further, the rate of current illicit drug use in metropolitan areas was higher than the rate in



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nonmetropolitan areas with 8.7% in large metropolitan counties, 8.3% in small metropolitan counties, and 6.8% in nonmetropolitan counties as a group (1).

**Mental Health Problems**

The NSDUH survey of 2006 evaluated the prevalence and treatment of serious psychological distress (SPD) and major depressive episode (MDE) and the association of these problems with substance use and substance dependency or abuse. SPD is an overall indicator of the past year of psychological distress, whereas MDE is defined as a period of at least 2 weeks when a person experienced a depressed mood or loss of interest or pleasure in daily activities and had symptoms that met the criteria for a major depressive disorder (1).

**Adults Aged 18 or Older**

The prevalence of serious psychological distress in 2006 was shown in 24.9 million adults, representing 11.3% of all adults, with the highest rates being in adults aged 18 to 25 (17.7%) and lowest for adults aged 50 or older (6.9%) as shown in Fig. 7A (1). The prevalence of SPD among women aged 18 or older was higher (13.7%) than among men (8.7%) in that

age group (1).

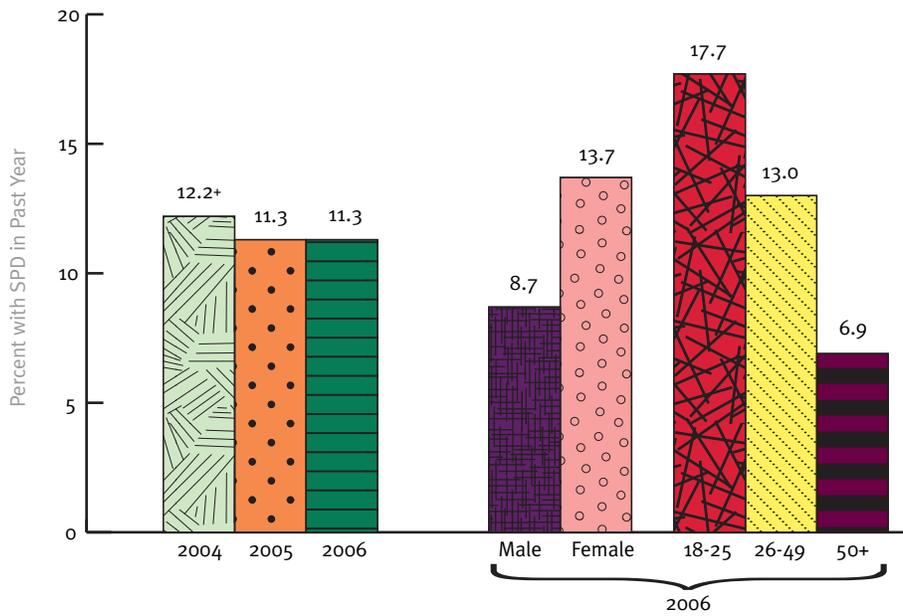
Past year illicit drug use was higher among adults aged 18 or older with SPD (27.2%) than among adults without SPD (12.3%). Overall there were 5.6 million adults (Fig. 7B) aged 18 or older with both SPD and substance dependence or abuse disorder in 2006, with only half (50.8%) receiving mental health treatment or substance abuse treatment at a specialty facility (1).

The prevalence of a major depressive episode in 2006 was 7.2% of persons aged 18 or older, or 15.8 million adults, with at least 1 major depressive episode in the past year. In 2006, an estimated 30.4 million persons aged 18 or older had had at least 1 MDE in their lifetime (13.9%) as illustrated in Fig. 8B (1). The rate was 15% among persons aged 18 to 25, 15.9% among persons aged 26 to 49, and 11.1% among persons aged 50 or older (1). In addition, the past year prevalence of MDE in 2006 was lowest for those aged 50 or older, whereas it was higher among adult females (Fig. 8B).

In 2006, an adult aged 18 or older with a combination of a major depressive episode and substance use and dependence or abuse in the past year was more likely than those with MDE to have used an illicit drug in the past year (27.7% vs 12.9%) (1). A similar pattern

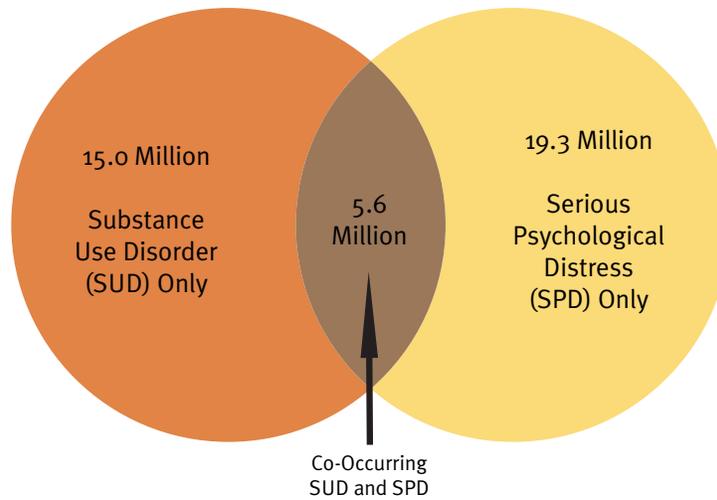


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+ Difference between this estimate and the 2006 estimate is statistically significant at the .05 level.

A. Serious psychological distress (SPD) in the past year among adults aged 18 or older, by year, gender, and age: 2004 – 2006 (1).

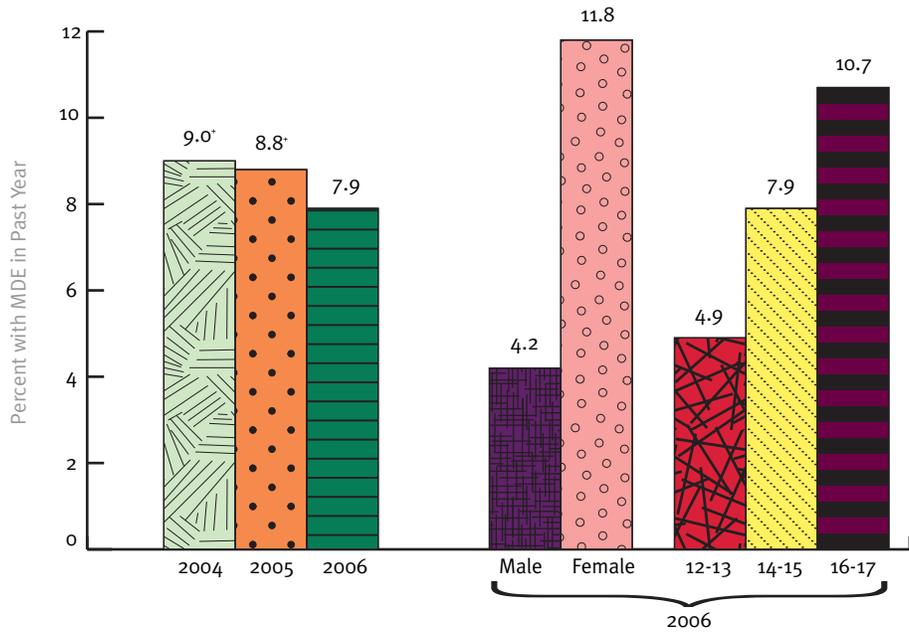


B. Co-occurrence of serious psychological distress and substance use disorder in the past year among adults aged 18 or older: 2006 (1).

Fig. 7. Serious psychological distress and substance abuse disorders. Source: www.oas.samhsa.gov/nsduh/2k6nsduh/2k6results.pdf

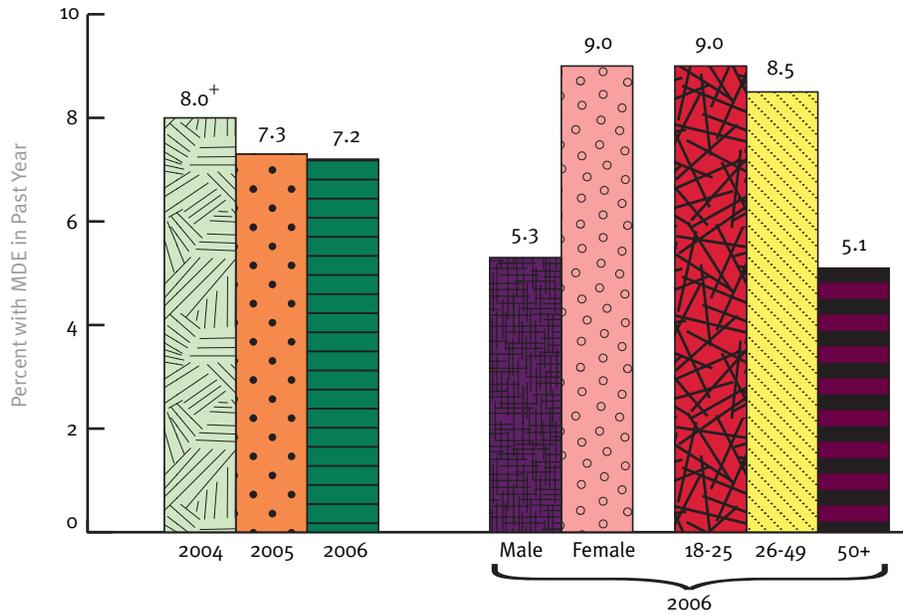


Therapeutic Opioid Use, Abuse, and Nonmedical Use



+ Difference between this estimate and the 2006 estimate is statistically significant at the .05 level.

A. Major depressive episode in the past year among youths aged 12 to 17, by year, gender, and age: 2004 – 2006.



+ Difference between this estimate and the 2006 estimate is statistically significant at the .05 level.

B. Major depressive episode in the past year among youths aged 18 or older, by year, gender, and age: 2004 – 2006.

Fig. 8. Prevalence of major depressive episode (MDE) (1).  
Source: www.oas.samhsa.gov/nsduh/2k6nsduh/2k6results.pdf



was observed for specific types of past year illicit drug use, such as marijuana and the nonmedical use of prescription-type psychotherapeutics. Thus, having MDE in the past year was associated with higher past year substance dependence or abuse among adults aged 18 or older, with approximately 24% being dependent on or having abused alcohol or illicit drugs, while among adults without MDE only 8.1% were dependent on or had abused alcohol or illicit drugs (1).

### Youths Aged 12 to 17

The prevalence of a major depressive episode in youths aged 12 to 17 in 2006 showed that 3.2 million (12.8%) reported at least 1 MDE in their lifetime and 2.0 million youths (7.9%) had an MDE during the past year. Among the youths aged 12 to 17, the past year prevalence of MDE ranged from 4% among 12 year olds to 11.1% among those aged 16 and 10.3% among those aged 17 (Fig. 8A) (1).

Among youths aged 12 to 17 with MDE, 34.6% had used illicit drugs during the same period. This was higher than the 18.2% of youths who did not have a past year MDE who had used illicit drugs during the past year. This pattern, however, was similar to specific types of illicit drug use including marijuana and the nonmedical use of prescription-type psychotherapeutics (1).

### Other Factors

Other factors described included criminal justice populations. In 2006, there were an estimated 1.6 million adults aged 18 or older on parole or other supervised release from prison during the past year, with 29.7% using illicit drugs, higher than the 7.9% of adults not on parole or supervised release. Further, the statistics are also grim in populations on probation with 31.9%, of 4.6 million adults, on probation at some time in the past year using illicit drugs, which is higher than the rate of 7.6% among adults not on probation in 2006 (1).

### Frequency of Abuse

Among past year marijuana users aged 12 or older in 2006, the following patterns were revealed (1):

- ◆ 12.3% used marijuana on 300 or more days within the past 12 months, translating to 3.1 million using marijuana on a daily or almost daily basis over a 12-month period. The results were similar to the estimate in 2005.
- ◆ 34.4%, or 5.1 million, used the drug on 20 or more days in the past month (current use).

### Driving

Driving under the influence of illicit drugs is criminal and dangerous to the public. In 2006, 10.2 million persons, or 4.2% of the population aged 12 or older, reported driving under the influence of illicit drugs during the past year. This rate was highest among young adults aged 18 to 25 with 13% (1).

### Source of Prescription Drugs

Of importance to the medical profession is the source of prescription-type pain relievers used non-medically. Among persons aged 12 or older who used pain relievers nonmedically in the past 12 months, 55.7% reported that the source of the drug was a friend or relative for free (1). An additional 19.1% reported that they got the drug from just 1 doctor. In contrast, only 3.9% got the pain relievers from a drug dealer or other stranger, and only 0.1% reported buying the drug on the internet (Fig. 9).

In 80.7% of the cases where nonmedical users of prescription pain relievers obtained their drugs from a friend or relative for free, the individuals indicated that their friend or relative had obtained the drugs from just 1 doctor (1). Only 1.6% reported that a friend or relative had bought the drug from a drug dealer or other stranger (Fig. 9). Even further striking is the fact that in 2006, over half (53.6%) of past year methamphetamine users reported that they obtained the methamphetamine they used most recently from a friend or relative for free, with an additional 21.4% buying it from a friend or relative. Only 1 in 5 users of methamphetamine (21.1%) bought it from a drug dealer or other stranger (1).

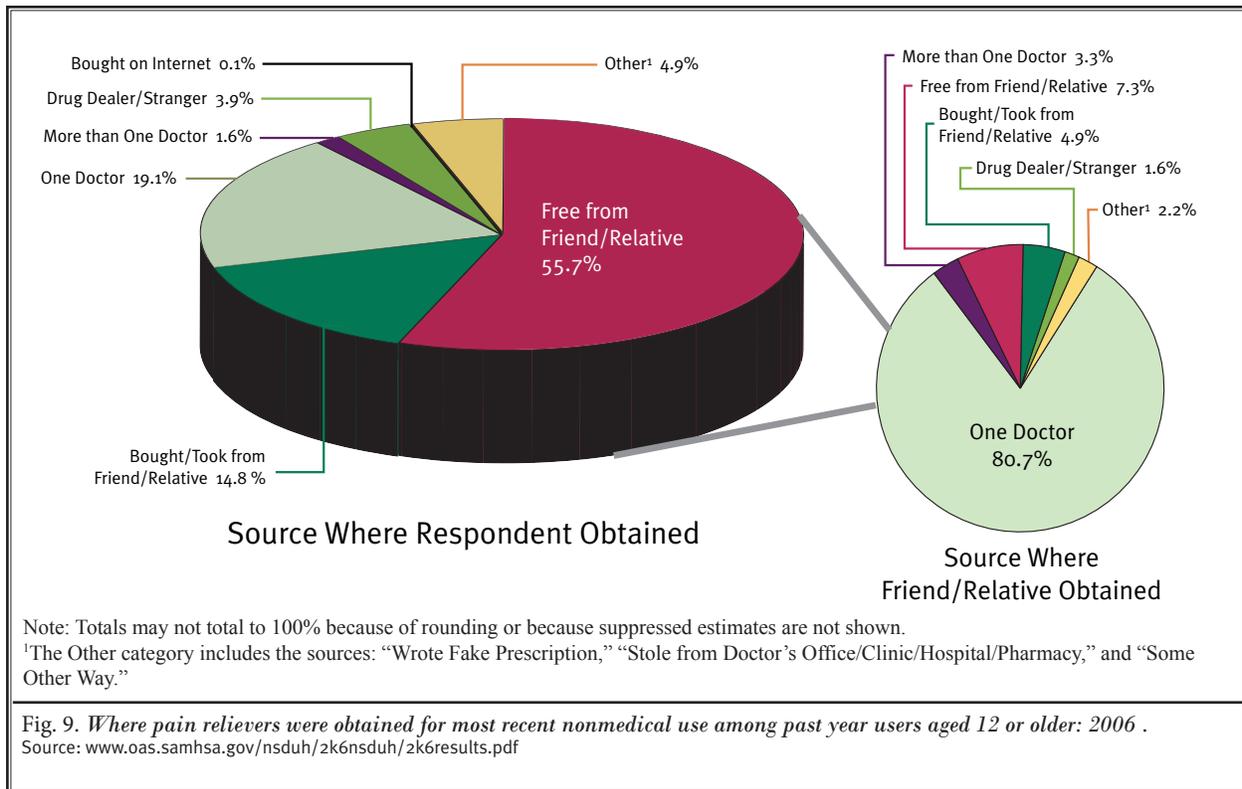
### ATTITUDES ON SUBSTANCE ABUSE

In a survey conducted by the National Center of Addiction and Substance Abuse at Columbia University (89), it was concluded that since 2002 the proportion of students who attend schools where drugs are used, kept, or sold has jumped 39% for high school students and 63% for middle school students. The CASA in-depth survey of drugs in schools shows that 8 out of 10 high school students (80%) and more than 4 out of 10 middle school students (44%) have personally witnessed:

- ◆ Illegal drugs used on the grounds of their schools.
- ◆ Illegal drugs sold on the grounds of their schools.
- ◆ Students keeping illegal drugs at school either on them or in their lockers.



### Therapeutic Opioid Use, Abuse, and Nonmedical Use



- ◆ Students high on drugs at school.
- ◆ Students drunk at school.

Essentially, this translates into startling facts that 16 million teens, which includes 11 million high schoolers and 5 million middle schoolers, are involved in drug use either with drug dealing and use, drug possession, or alcohol intoxication. The report shows that at least once a week, 22% of 12 to 17 year olds, or 5.7 million of the population, see drugs used or sold and students high or drunk on their school grounds.

It is no surprise that children who attend drug-infested schools are more likely to use drugs. Children at drug-infested schools are 16 times more likely to use illegal drugs other than marijuana or prescription drugs, 15 times more likely to use prescription drugs to get high, 6 times more likely to get drunk in a typical month, 5 times more likely to have used marijuana, and 4 times more likely to have smoked cigarettes.

Over the past 6 years, since 2002, the proportion of students attending middle schools where drugs are used, kept, or sold has increased by 63% and the proportion of students attending high schools where drugs are used, kept, or sold has increased by 39%. Since last

year, the proportion of teens attending schools where drugs are used, kept, or sold is on the rise for all types of schools with public high schools showing a 16% increase, private high schools showing a 38% increase, public middle school showing a 45% increase, and private middle schools showing a 50% increase (89).

While parents with their attitudes and expectations can significantly influence teen behavior and substance abuse risk in schools, unfortunately 59% believe the goal of making their child's school drug-free is unrealistic, while only 41% considered this a realistic goal. Another misunderstanding in the minds of parents is that the vast majority of parents (86%) associate college with drinking; even then, relatively few believe that their teen will drink a lot while in college (89).

#### Teen Risk Status

The National Survey of American Attitudes on Substance Abuse (89) showed 56% of American teenagers aged 12 to 17 are at a significant substance abuse risk with 15% at high risk, 41% at moderate risk, and only 44% in the low risk category.



### Exposure to Drugs

Thirty-one percent of high school students, or more than 4 million, and 9% of middle school students (more than 1 million) have experienced the use of illegal drugs, the sale of illegal drugs, students high on drugs, or students being drunk at least once a week on their school grounds (89). Table 5 illustrates the percentage of teens witnessing various activities at school.

Teens at drug-infested schools are more likely to use illegal drugs. Further, these teens are 15 times likelier to have used prescription drugs to get high and 5 times likelier to have used marijuana. In addition, it was also shown that teen risk scores are higher at drug-infested schools.

Availability fuels drug abuse, and, unfortunately, it is far too easy to obtain drugs in schools. As is evident by the statistics, 37% of these teens state that they can buy marijuana within a day, and 17% admit that they can buy marijuana within an hour.

Drug abuse has taken a sharp and dangerous turn at schools where students think that "cool" kids use drugs or alcohol. In fact, 20% of the teens surveyed say that the most popular kids at their school have a reputation for using illegal drugs, and 52% of kids believe that the use of alcohol or illegal drugs is cool. Further analysis shows at drug-infested schools, 46% believe in drinking a lot and 33% believe in using illegal drugs, whereas at drug-free schools the proportion is 15% and 6% respectively. The survey also shows that teens who say they are among the most popular kids at their school are likely to use illicit drugs (40% vs. 56%).

Table 5. *Percentage of teens, ages 12 to 17, who have witnessed the following at school\*.*

<b>Student Drug Possession</b>	<b>48%</b>
<b>Students High on Drugs</b>	<b>43%</b>
<b>Students Drunk</b>	<b>29%</b>
<b>Drug Use</b>	<b>22%</b>
<b>Drug Dealing</b>	<b>18%</b>

\* These add to more than 100% as teens could have responded yes to more than 1 occurrence.

Source: The National Center on Addiction and Substance Abuse. National survey of American attitudes on substance abuse XII: teens and parents. August 2007. [www.casacolumbia.org/absolutenm/articlefiles/380-2007%20Teen%20Survey%20XII.pdf](http://www.casacolumbia.org/absolutenm/articlefiles/380-2007%20Teen%20Survey%20XII.pdf) (89).

Startling statistics show that drugs and alcohol are abused irrespective of if students are in private or public schools and if they are in middle schools or high schools. Private schools are more likely to be drug-free than public schools, with 50% of the teens who attend public schools reporting that drugs are used, whereas only 32% of teens who attend private schools admit to it. In addition, smaller schools are more likely to be drug-free, with 38% of teens who attend schools with fewer than 1,000 students admitting to drug use in their school, whereas 60% of teens who attend schools with 1,000 or more students admitting to drug use in their school (89).

### Attitudes and Expectations of Parents

Unfortunately, over half of the parents whose children attend schools where drugs are used believe that the goal of making their child's school drug-free is unrealistic (89). Consequently, teens whose parents believe it is a very unrealistic goal to make their child's school drug-free have substance abuse risk scores that are more than 2 times greater than those of teens whose parents say the goal of making their teens school drug-free is realistic (1.58% vs. 0.59%).

Forty-one percent of parents believe it is not very likely that their teenager will use drugs and 17% believe that it will never happen. Only 39% say it is very or somewhat likely that their teenager will try an illegal drug in the future.

### Parent/Teen Disconnect

Parents and teens have a disconnect with different concerns and opinions regarding the problem of drugs. When parents are asked what they think their teenager would say is the most important problem he or she faces, 45% of parents cite social pressures. Only 11% cite drugs, including alcohol. In contrast, when asked to identify the most important problem kids their age face, 24% of teens cite drugs, including alcohol. Since 1995, more teens have cited drugs, alcohol, and tobacco as their top concerns than they have cited any other matter, and twice as many teens cite this as a concern as do their parents (89).



## Therapeutic Opioid Use, Abuse, and Nonmedical Use

**THERAPEUTIC USE OF OPIOIDS**

With the common occurrence of chronic pain in the United States, the ability of opioids to effectively and safely treat acute and cancer pain is one of several arguments that is used to support extending opioid treatment to patients with chronic pain, where there had previously been considerable caution based on fears of addiction (7). It is argued that physicians should be encouraged to prescribe opioids because they are indispensable for the treatment of pain and suffering, because uncontrolled pain may have deleterious physical effects, and because persistent pain destroys people's autonomy, dignity, and decision-making capacity (6,7,89). Thus, due to politics and emotional issues involved with efforts to improve awareness and treatment of chronic pain, the availability of opioids has increased dramatically in the past few decades. At the same time that multiple side effects, drug abuse, and addiction are recognized by these proponents, they continue to promote extensive opioid use under the umbrella of undertreatment of pain. Consequently, in spite of the considerable controversy over the use of opioids for the treatment of chronic pain of noncancer origin, opioid use has been exploding.

Caudill-Slosberg et al (74) evaluated the role of opioid prescriptions for musculoskeletal pain in the United States and compared the practices from 1980 to 2000. They analyzed the National Ambulatory Medical Care Survey — nationally representative survey of visits to office-based physicians — using data from 1980 – 1981 and 1999 – 2000, evaluating over 130,000 visits. Opioids doubled for chronic pain from 8% to 16% and for acute pain the increase was from 8% to 11%. In addition, they also showed that prescriptions of more potent opioids (hydrocodone, oxycodone, morphine) for chronic musculoskeletal pain increased from 2% to 9% in visits corresponding to 5.9 million visits in 2002 — an increase of 4.6 million visits from 1980. They concluded that while there was increased attention to pain treatment and opioid prescriptions sold, there was no increase in office visits for musculoskeletal pain complaints.

Vogt et al (75) evaluated analgesic usage for low back pain and its impact on healthcare costs and service use. In 2001, 55.5% of members with claims for low back services received analgesics costing a total of \$1.4 million, of which 68% were opioids. They also found that opioid use was associated with the high volume usage of low back pain services and correlated with the higher use of opioids in patients with psycho-

genic pain and low back pain related to orthopedic devices (fusion, etc.).

Luo et al (90) also evaluated patterns and trends in opioid use among individuals with back pain in the United States. They showed overall opioid use among 11.6% of individuals with back pain from a sample of 23.6 million in 1996 increasing to 12.6% in 1999 with a sample of 24.7 million individuals. The prescriptions showed an increase in oxycodone and hydrocodone with a decrease in propoxyphene.

A systematic review of opioid treatment for chronic back pain by Martell et al (32) showed variable prescribing patterns for opioids ranging from 3% to 66% for low back pain patients. They evaluated 11 studies describing the prevalence of opioid treatment for chronic back pain, most using a cross-sectional design. However, only 4 of the 11 studies, or approximately 36% of the studies, had reasonable quality rating scores of 12 or more out of a total of 27 (77-80). Prevalence estimates were highest in specialty treatment centers ranging from 11% to 66%, and lowest in primary care centers ranging from 3% to 31%.

In pain management settings, it has been reported that as many as 90% of the patients receive opioids for chronic pain management in spite of numerous issues involved (33-57). Further, it also has been shown that the majority of these patients were on opioids prior to presenting to an interventional pain management setting (33).

The therapeutic use of opioids has exploded in the United States, witnessed by increased sales of hydrocodone by 244% from 1997 to 2006, whereas methadone usage increased 1177% and oxycodone increased 732% (Table 6 and Fig. 10). Overall, opioids increased from 50.7 million grams of medication in 1997 to 115.3 million grams of medication in 2006, an increase of 127%. The estimated number of prescriptions filled for controlled substances increased from 222 million in 1994 to 354 million in 2003 (3,11,12).

The milligram per person use of therapeutic opioids in the US increased from 73.59 milligrams in 1997 to 329.23 milligrams per person in 2006, an increase of 347% (Table 7). During the same period the therapeutic use of methadone increased by 1129% mg/person, and oxycodone by 899% mg/person. This is also confirmed by the fact that between 1992 and 2002, the population of the United States increased by 13%, whereas, the number of prescriptions written for non-controlled drugs



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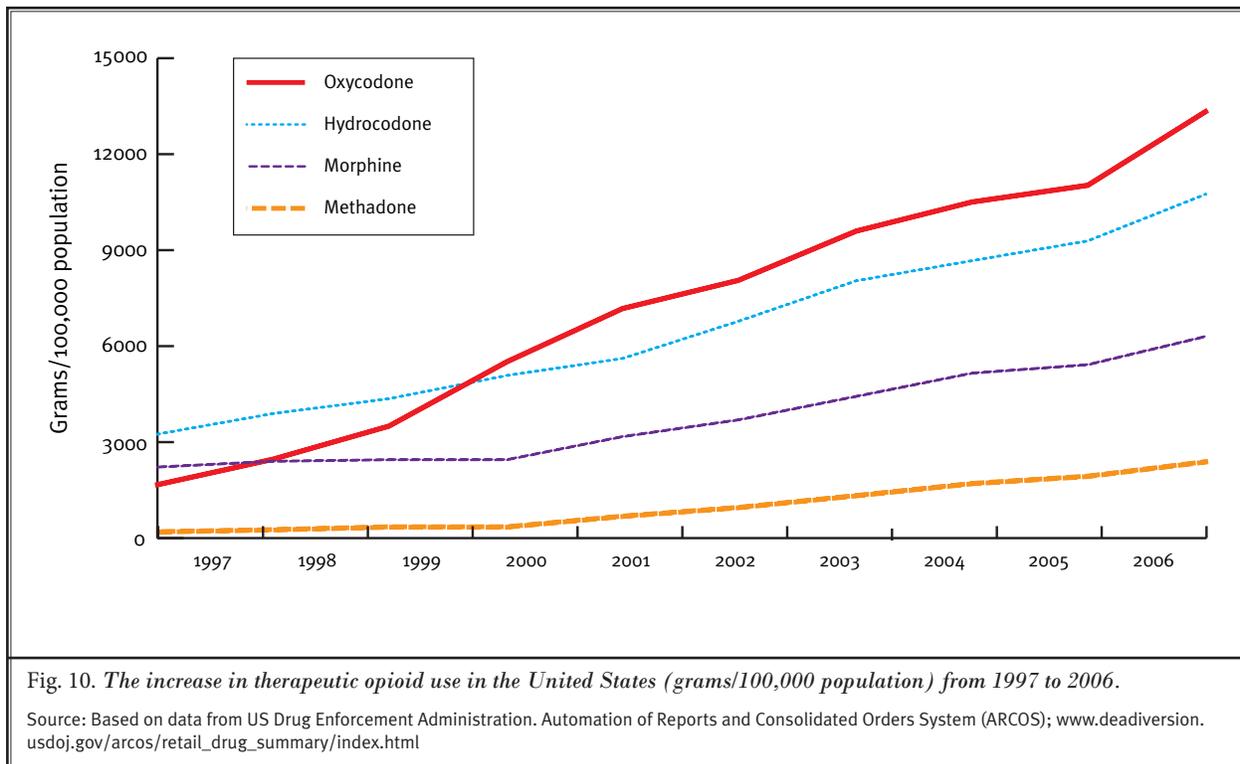
Table 6. Retail sales of opioid medications (grams of medication) from 1997 to 2006.

Drug	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	% of Change from 1997
Methadone	518,737	692,675 (34%)	964,982 (39%)	1,428,840* (48%)	1,892,691 (32%)	2,649,559 (40%)	3,683,881 (39%)	4,730,157 (28%)	5,362,815 (13%)	6,621,687 (23%)	1177%
Oxycodone	4,449,562	6,579,719 (48%)	9,717,600 (48%)	15,305,913 (58%)	19,927,286 (30%)	22,376,892 (12%)	26,655,152 (19%)	29,177,530 (9%)	30,628,973 (5%)	37,034,220 (21%)	732%
Fentanyl Base	74,086	90,618 (22%)	107,141 (18%)	146,612* (37%)	186,083 (27%)	242,027 (30%)	317,200 (31%)	370,739 (17%)	387,928 (5%)	428,668 (11%)	479%
Hydromorphone	241,078	260,009 (8%)	292,506 (12%)	346,574* (18%)	400,642 (16%)	473,362 (18%)	579,372 (22%)	655,395 (13%)	781,287 (19%)	901,663 (15%)	274%
Hydrocodone	8,669,311	10,389,503 (20%)	12,101,621 (16%)	14,118,637 (17%)	15,594,692 (10%)	18,822,619 (21%)	22,342,174 (19%)	24,081,900 (8%)	25,803,543 (7%)	29,856,368 (16%)	244%
Morphine	5,922,872	6,408,322 (8%)	6,804,935 (6%)	7,807,511 (15%)	8,810,700 (13%)	10,264,264 (16%)	12,303,956 (20%)	14,319,243 (16%)	15,054,846 (5%)	17,507,148 (16%)	196%
Codeine	25,071,410	26,018,054 (4%)	23,917,088 (-8%)	23,474,865* (-2%)	23,032,641 (-2%)	22,633,733 (-2%)	21,865,409 (-3%)	20,264,555 (-7%)	18,960,038 (-6%)	18,762,919 (-1%)	-25%
Meperidine (Pethidine)	5,765,954	5,834,294 (1%)	5,539,592 (-5%)	5,494,898* (-1%)	5,450,204 (-1%)	5,412,389 (-1%)	5,239,932 (-3%)	4,856,644 (-7%)	4,272,520 (-12%)	4,160,033 (-3%)	-28%
<b>Total</b>	<b>50,713,010</b>	<b>56,273,194 (11%)</b>	<b>59,445,465 (6%)</b>	<b>35,962,089.84 (15%)</b>	<b>75,294,939 (11%)</b>	<b>82,874,845 (10%)</b>	<b>92,987,076 (12%)</b>	<b>98,456,163 (6%)</b>	<b>101,251,950 (6%)</b>	<b>115,272,706 (14%)</b>	<b>127%</b>

Number in parenthesis is percentage of change from previous year.

\* For year 2000 data is not available, the average of 1999 and 2001 was taken.

Source: [http://www.deadiversion.usdoj.gov/arcos/retail\\_drug\\_summary/index.html](http://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.html) Access date: 3/13/08





## Therapeutic Opioid Use, Abuse, and Nonmedical Use

Table 7. The increase in therapeutic opioids use in the U.S. (mg/person) from 1997 to 2006.

Type	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	% of Change from 1997
Morphine	22.20	24.01	24.50	28.11	31.72	36.95	44.30	51.55	54.20	63.03	184%
Methadone	1.94	2.60	3.47	5.14*	6.81	9.54	13.26	17.03	19.31	23.84	1129%
Oxycodone	16.68	24.66	34.99	55.11	71.75	80.56	95.97	105.05	110.27	133.33	899%
Hydrocodone	32.49	38.93	43.57	50.83	56.15	67.77	80.44	86.70	92.90	107.49	231%
Fentanyl	0.28	0.34	0.39	0.53*	0.67	0.87	1.14	1.33	1.40	1.54	450%
<b>Total</b>	<b>73.59</b>	<b>90.54</b>	<b>106.92</b>	<b>139.72</b>	<b>167.1</b>	<b>195.69</b>	<b>235.11</b>	<b>261.66</b>	<b>278</b>	<b>329.23</b>	<b>347%</b>

\* For year 2000 data is not available, the average of 1999 and 2001 was taken.

Source: Data taken from U.S. Drug Enforcement Administration. Automation of Reports and Consolidated Orders System (ARCOS); www.deadiversion.usdoj.gov/arcos/retail\_drug\_summary/index.html. Access date: 3/13/08

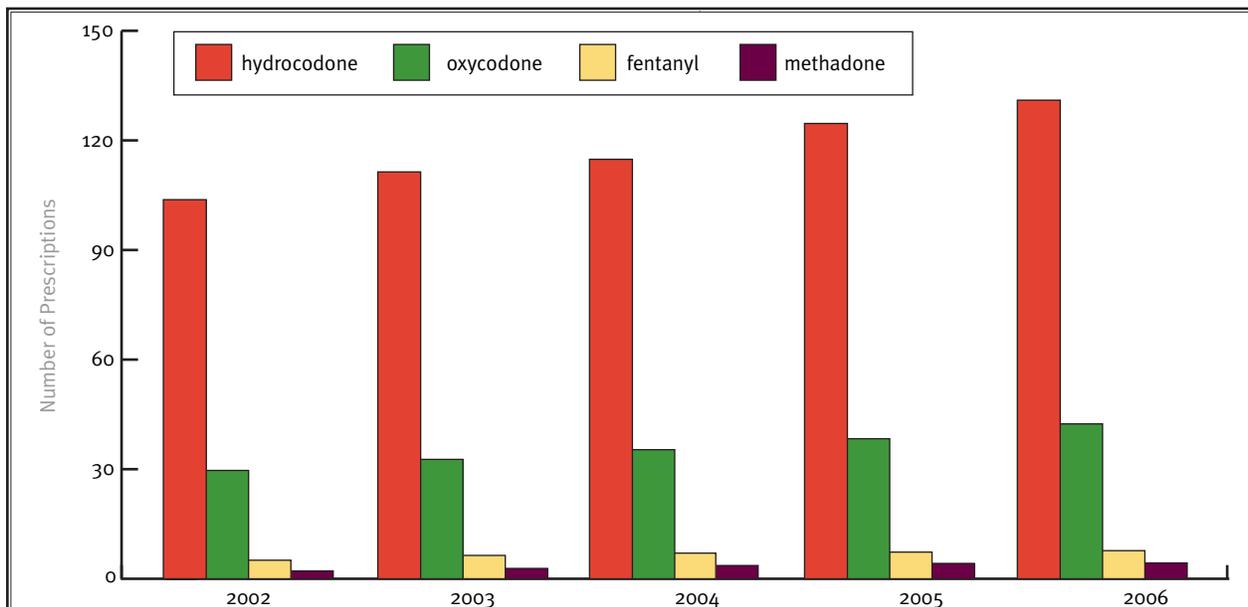


Fig. 11. Total prescriptions of selected narcotic analgesics (29).

Source: Methadone Morality Working Group Drug Enforcement Administration, Office of Diversion Control.

### Adverse Consequences

Opioids are associated with some well-known common side effects including nausea, sedation, euphoria, dysphoria, constipation, and itching. However, with chronic use, a different breed of side effects develop which includes hormonal and immune system effects, abuse and addiction, tolerance, and hyperalgesia. More importantly, opioid use has been associated with increased disability, medical costs, subsequent

surgery, and continued or late opioid use (72-76).

Vogt et al (75) reported an association between opioid prescribing and an increase in overall health-care costs for low back pain, implying higher levels of utilization. Similarly Mahmud et al (76) found an association between opioid use for more than a week for acute low back pain and disability duration in a worker's compensation cohort. Webster et al (72) showed



that patients receiving more than a 450 mg equivalent of morphine over a period of several months were, on average, disabled 69 days longer than those who received no early opioids, had 3 times increased risk for surgery, and had 6 times greater risk of receiving late opioids. Fillingim et al (79) indicated that opioid use was associated with greater self-reported disability and poorer function.

An epidemiological study from Denmark (66), where opioids are prescribed liberally for chronic pain, demonstrated worse pain, higher healthcare utilization, and lower activity levels in opioid treated patients compared to a matched cohort of chronic pain patients not using opioids, suggesting that when opioids are prescribed liberally, even if some patients benefit, the overall population does not.

### **Effectiveness of Opioid Treatment**

Multiple reviews have been published to evaluate the effectiveness of opioid therapy in chronic pain (6,7,32,62-65). Martell et al (32) in their systematic review failed to conclude that opioids provide efficacy for chronic pain. Ballantyne (7), after directly comparing the efficacy of different opioids, concluded that a nonsignificant reduction in pain was present from baseline. Chou et al (62) concluded that there was insufficient and poor evidence to prove the safety or effectiveness of any opioids. Kalso et al (63) concluded that the mean decrease in pain intensity in most studies was at least 30% and at least 44% of the patients continued treatment between 7 and 24 months. Furlan et al (65) concluded that strong opioids were more effective with pain relief and functional outcomes; however, drop-out rates averaged 33%.

Overall the evidence supporting the long-term analgesic efficacy is weak at best based on the present evidence. In addition, surprisingly, epidemiological studies are less positive with regards to function and quality of life and report the failure of opioids to improve quality of life in chronic pain patients (5-7,62-66).

### **PRESCRIPTION OPIOID ABUSE**

Prescription opioids are abused among the populations with or without pain, and in patients receiving or not receiving opioids. The abuse is associated with substantial risks to the patients and the nation as a whole with increasing emergency department visits, deaths, and federal drug spending.

### **Controlled Substances Abuse in Chronic Pain**

Opioids are by far the most abused drugs, especially in chronic pain settings. Other controlled substances including benzodiazepines, sedative-hypnotics, and central nervous system stimulants, though described as having less potential for abuse, are also of major concern. Numerous investigations (3,4,32-50,60,61,87) have illustrated drug abuse in 18% to 41% in patients receiving opioids for chronic pain.

Martell et al (32), in a systematic review of opioid treatment for chronic back pain, estimated the prevalence of lifetime substance use disorders to range from 36% to 56%, with an astounding estimate of 43% current substance use disorders. Sadly, aberrant medication-taking behaviors also ranged from 5% to 24%.

Chronic pain patients may not only abuse controlled substances by doctor shopping, etc., but they may also abuse or use illicit drugs in conjunction with controlled substances. Multiple investigators have studied the issue of illicit drug use in chronic pain patients receiving controlled substances (35-50). The results showed that illicit drug use in patients without controlled substance abuse was found in 14% to 16% of patients, and illicit drug use in patients with controlled substance abuse was present in 34% of the patients (35,37,38). In addition, illicit drug use was significant in chronic pain patients in general, and was also similar in patients using either long-acting or short-acting opioids (48). In other evaluations, it was shown that enhanced adherence monitoring will in fact decrease controlled substance abuse and illicit drug use (45,50).

Along with the increase of prescriptions for controlled drugs from 1992 to 2002 of 154% (67-69), there was also a 90% increase in the number of people who admitted abusing controlled prescription drugs. Mahowald et al (77) and White et al (91) evaluated opioid abuse in the insured population of the United States. Opioid abuse was determined to be present in 6.7 to 8 per 10,000 persons insured. However, opioid abusers also presented with multiple comorbidities and expenses 8 times higher than for nonabusers (\$15,884 vs. \$1,830).

The cost of opioid abuse is enormous. The White House Budget Office estimated drug abuse costs to the US Government to be approximately \$300 billion a year (3,4). The White House Office of National Drug Control Policy (ONDCP), a component of the Executive Office of the President, established by the Anti-Drug Abuse Act of 1998, has been spending \$12-13 billion each year.



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**Emergency Department Visits**

The Drug Abuse Warning Network (DAWN) publishes results of emergency department visits with drug misuse and abuse. In 2005, DAWN (18) published results with 816,696 emergency department visits involving an illicit drug. Of these, a majority, or 598,542 visits, were secondary to nonmedical use of prescription or over-the-counter pharmaceuticals or dietary supplements. Among these commonly reported substances, psychotherapeutic agents constituted 46% and central nervous system agents constituted 51% of the visits. Further, among the CNS agents the most frequent were opiates/opioid analgesics at 33% and methadone, oxycodone, and hydrocodone were the most frequent of these opioids:

- ◆ Hydrocodone/combinations in 51,225 ED visits (CI: 37,416-65,033),
  - ◆ Oxycodone/combinations in 42,810 ED visits (CI: 30,672-54,948), and
  - ◆ Methadone in 41,216 ED visits (CI: 29,249-53,184).
- Emergency department visits for narcotics were 160,363 in 2005 compared to 42,857 in 1995, a 274%

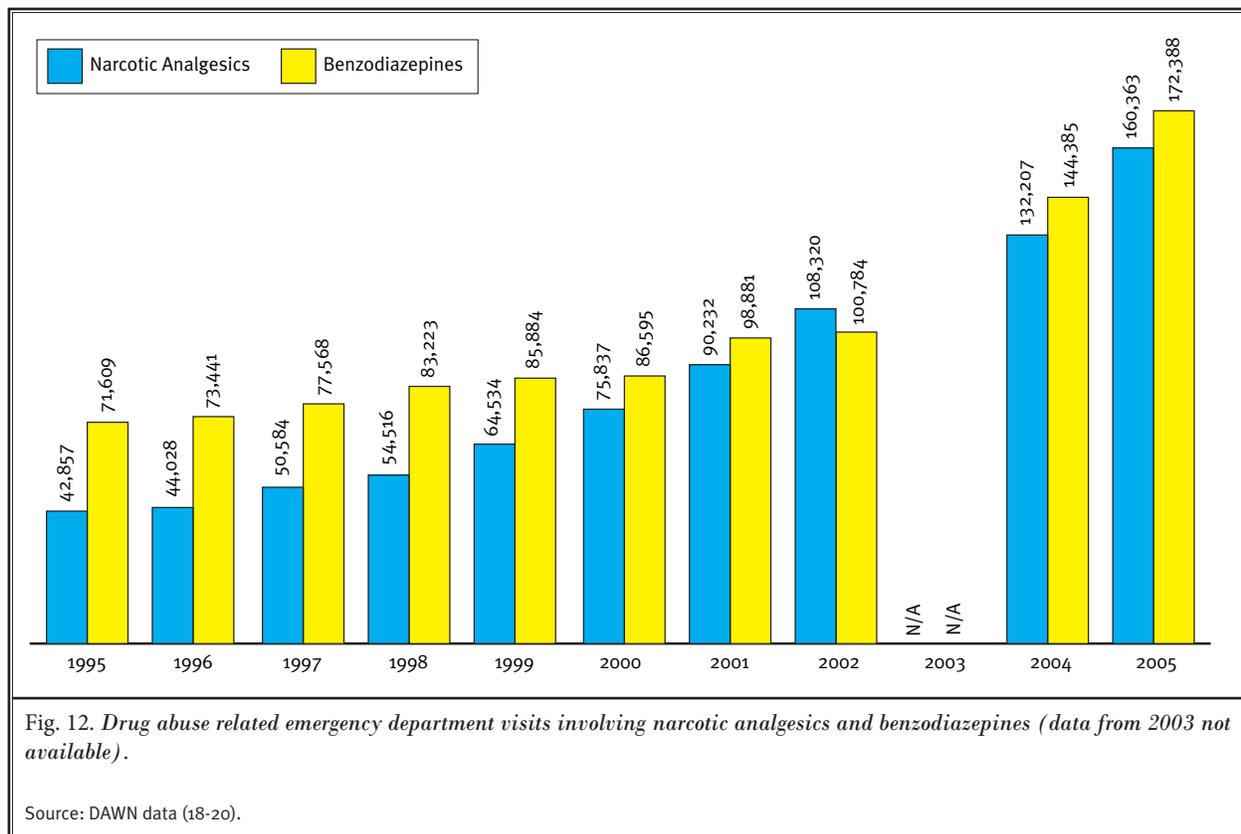
increase over a period of 11 years (Fig. 12). Among the psychotherapeutic agents, the anxiolytics (anti-anxiety agents, sedatives, and hypnotics) were the most frequent, occurring in 34% of the visits associated with nonmedical use of pharmaceuticals (4). DAWN estimated that 172,388 ED visits were associated with nonmedical use of pharmaceuticals involving benzodiazepines in 2005, compared to 71,609 in 1995, a 141% increase over a period of 11 years (18-20).

**Increasing Deaths**

Controlled substance abuse is not only associated with increasing costs, doctor shopping, theft, and emergency department visits, but also with deaths. Mortality data is obtained from DAWN Medical Examiner Reports (92), National Forensic Laboratory Information System (93), and National Center for Health Statistics (23,24,26,27).

**National Center for Health Statistics**

Reporting on unintentional drug poisoning mortality rates in the United States, Paulozzi et al (23) showed startling results with increasing deaths due





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to prescription opioids exceeding heroin and cocaine poisonings, with increased deaths matching the increased supply of opioids for each drug. Between 1999 and 2002 the number of opioid analgesic poisonings on death certificates increased 91.2% while heroin and cocaine poisoning increased 12.4% and 22.8%, with opioid analgesic poisonings listed in 5,528 deaths — more than either heroin or cocaine. In contrast, unintentional drug poisoning mortality rates increased on average 5.3% per year from 1979 to 1990, whereas the increase was 18.1% per year from 1990 to 2002.

In another report evaluating morbidity and mortality in February 2007, Paulozzi (24) revealed further startling facts and demonstrated that unintentional drug poisoning was second only to motor-vehicle crashes as the cause of death from unintentional injury in the United States. This updated study showed the number of unintentional poisoning deaths increased from 12,186 in 1999 to 20,950 in 2004, with an increase of age adjusted rate of 62.5% from 4.4 per 100,000 population in 1990 to 7.1 in 2004. The highest rate of deaths (59.6%) in 2004 were among persons aged 35 to 54 years. Among the opioids, methadone has been implicated in more unintentional poisoning deaths than any other opioid (25-27).

In an evaluation by the Office of Analysis and Epidemiology (24), methadone-related deaths from 1999 to 2004 increased 390%, whereas the number of all

poisoning deaths increased 54%. Further, poisoning deaths mentioning methadone increased from 4% of all poisoning deaths to 13% of all poisoning deaths. It was also shown that while all poisoning deaths increased 6% from 2002 to 2004, methadone deaths increased 29% (Table 8). The largest increases of deaths were noted in persons aged 15 to 24 years with a rate 11 times that of 1999 in 2004, even though most methadone deaths were in persons aged 35 to 44 and 45 to 54 years.

A reassessment of methadone mortality in 2007 (29,30) concluded that all available data indicated that methadone continues to be increasingly used, misused, diverted, and abused. Further, significant increases in methadone-related deaths are being reported which, in some areas, are outpacing other narcotics. On November 27, 2006, the Food and Drug Administration, in its public health advisory, warned that methadone use in pain control may result in death and life-threatening changes in breathing and heartbeat (94). Current methadone use continues to climb, and from 1998 through 2006, has increased by about 250%. Prescriptions for methadone have increased by nearly 700% from 1998 through 2006. Figure 13 illustrates the methadone distribution business activity comparison between narcotic treatment programs, pharmacies, hospitals, and practitioners.

Table 8. Number of poisoning deaths in which specific narcotic substances are mentioned, 1999 to 2004.

Substance	1999	2000	2001	2002	2003	2004	1999-2004	2003-2004
							Percent change	
Poisoning by all Narcotics and Psychodysleptics	9,995	10,173	11,480	14,247	15,731	16,735	68.1	6.4
Opium	4	2	5	3	4	1	-75.0	-75.0
Heroin	1,964	1,846	1,782	2,091	2,080	1,881	-4.2	-9.6
Other Opioids	2,757	2,932	3,484	4,431	4,877	5,242	90.1	7.5
Methadone	786	988	1,456	2,360	2,974	3,849	389.7	29.4
Other Synthetic Narcotics	732	784	962	1,301	1,406	1,668	127.9	18.6
Cocaine	3,832	3,565	3,840	4,612	5,212	5,461	42.5	4.8
Other Narcotics	2,902	2,880	2,881	3,143	3,117	2,761	-4.9	-11.4
Cannabis	37	41	37	50	61	99	167.6	62.3
LSD	3	3	2	0	1	1	-66.7	0.0
Other	9	8	7	5	6	5	-44.4	-16.7

Note: Substance-specific data are not additive because a death certificate could have multiple drugs listed.

Source: National Center for Health Statistics, National Vital Statistics System (26).



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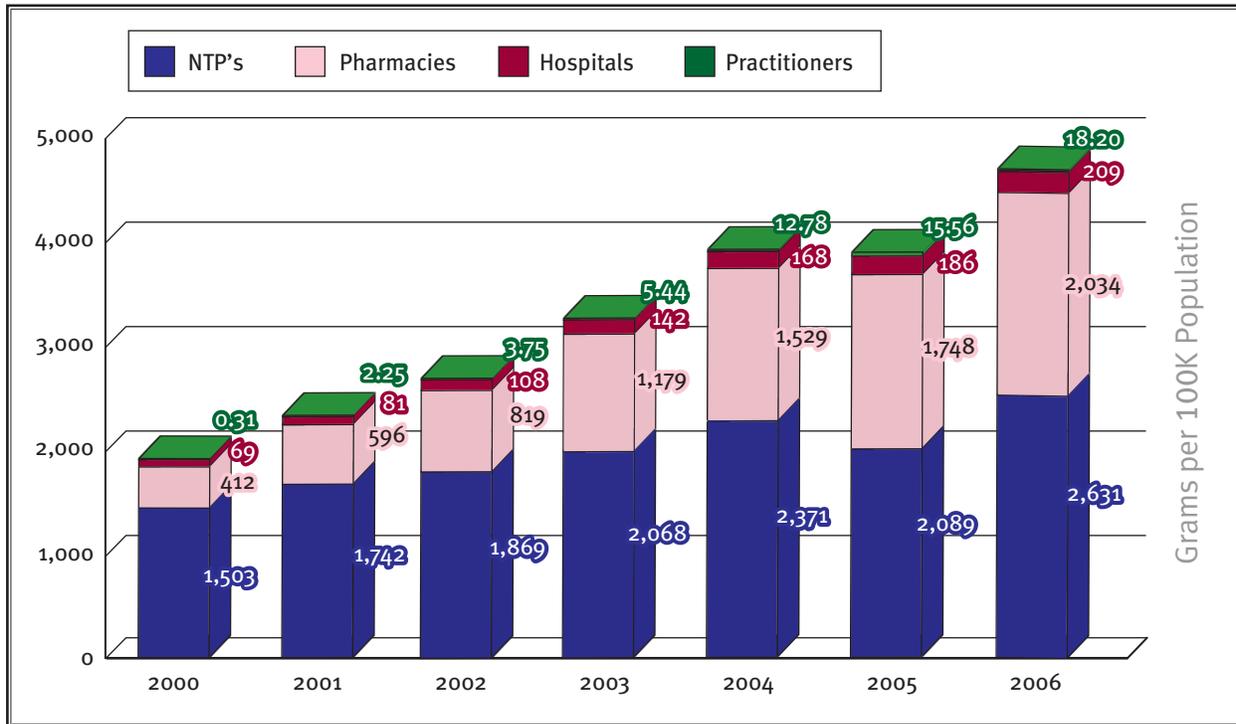


Fig. 13. 2000-2006 Methadone distribution business activity comparison.

Source: DEA ARCOS 04/2007.

National Forensic Laboratory Information System

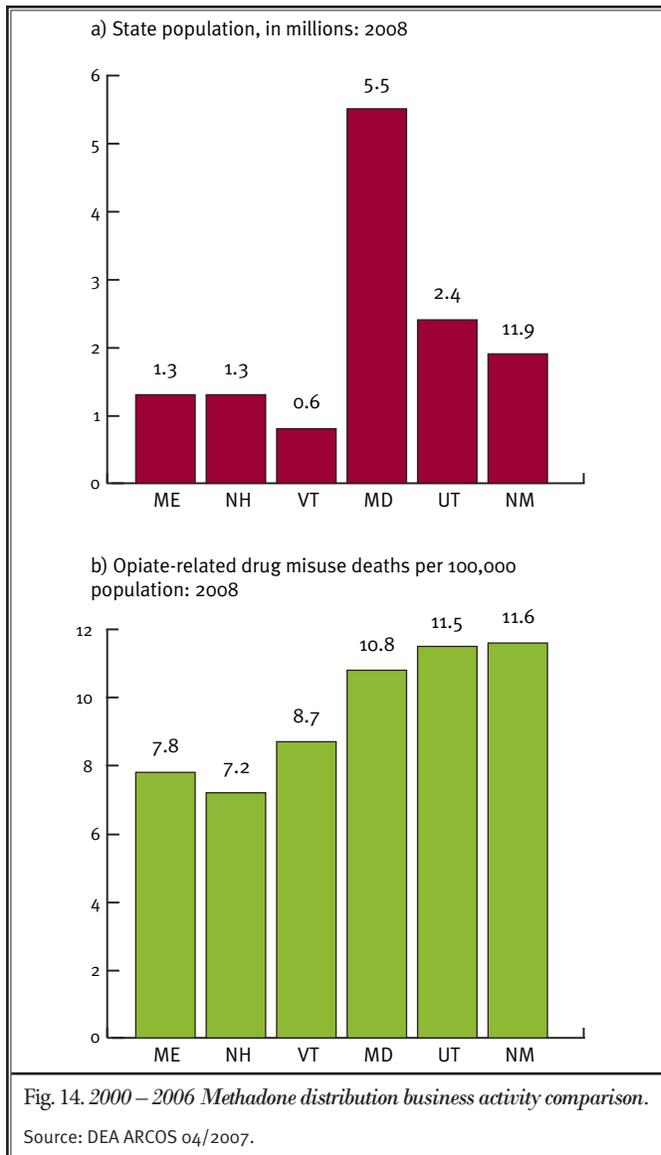
The National Forensic Laboratory Information System (NFLIS), sponsored by the Drug Enforcement Administration (DEA), is a program that systematically collects results from toxicological analysis conducted by state and local forensic laboratories on substances seized in law enforcement operations. Between 2001 and 2005, narcotic analgesics and benzodiazepines represented nearly 5% of all drugs analyzed (93). In comparison, in 2005, 33% of all exhibits were cannabis and 32% were cocaine. Alprazolam, hydrocodone, and oxycodone were the most commonly reported controlled prescription drugs, accounting for nearly 63% of all narcotic analgesics and benzodiazepines reported. From 2002 to 2006 methadone exhibits increased 170%. In addition, methadone was more likely to be involved in illicit activities, meaning diverted and abused, than either hydrocodone or oxycodone.

DAWN Medical Examiner Reports

The DAWN Medical Examiner Reports, also known as DAWN ME, include deaths directly caused by drug

use, misuse, or abuse, as well as deaths where the drug use, misuse, or abuse contributed to the death but did not cause it. The numbers are representative only of the locales for which they are reported and cannot be extrapolated nationwide (92). In the 6 states that participated in the mortality component of the Drug Abuse Warning Network, the rates of opiate related drug misuse deaths in 2003 ranged from 7.2 to 11.6 per 100,000 population. The 6 states participating in the mortality component of the DAWN were Maine, New Hampshire, Vermont, Maryland, Utah, and New Mexico. Death rates were lowest in New Hampshire and highest in New Mexico. Further, most opiate related drug misuse deaths involved multiple drugs in each of these 6 states. This evaluation also showed adults aged 35 to 54 had the highest rates of opioid misuse deaths in 5 of the 6 states except for Maine, where the highest rate was for adults aged 21 to 34. Figure 14 illustrates state population and opiate related drug misuse deaths. Table 9 illustrates involvement of oxycodone, hydrocodone, and methadone in opiate misuse deaths in 2003.

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### Deaths Due to Psychotherapeutic Drugs in Interventional Pain Management Practices

The literature on prevalence of deaths in pain management or specifically interventional pain management settings is not available.

### CONCLUSIONS

Based on the data provided in this review, it appears that there has been an escalation over the past 10 years not only of the therapeutic use of opioids and other psychotherapeutics, but of their abuse and non-medical use as well. Because hydrocodone has become the number one prescribed medication in America, it is not hard to see the huge impact that would have on the overall patterns of abuse and nonmedical use, especially since the illicit use of prescribed psychotherapeutics (including opioids, which are at the top of the list) now overshadows the use of nonprescription illicit drugs, and drug dealers are no longer the primary source of illicit drugs. Diversion through family and friends is now our greatest enemy and their source is more likely to be from 1 physician and not from doctor shopping.

And we cannot overlook the highly interactive pattern of effect and impact that is produced in the general areas of substance abuse, mental health, and overall healthcare. Because of the close interrelationship between mental disorders and substance abuse, “dual diagnosis” is becoming more prevalent. The question, of course, is the age-old chicken-or-the-egg question: which comes first? We will probably never know.

In the meantime, we are clearly challenged to be aware of the difficulties presented by the

Table 9. Involvement of oxycodone, hydrocodone, and methadone in opiate misuse deaths: 2003.

State	Oxycodone		Hydrocodone		Methadone		Total Opiate Misuse Deaths
	Deaths	Percent	Deaths	Percent	Deaths	Percent	
Maine	24	24%	7	7%	47	46%	102
New Hampshire	19	20%	7	8%	34	37%	93
Vermont	16	30%	8	15%	12	22%	54
Maryland	86	14%	15	3%	142	24%	595
Utah	72	27%	47	17%	93	34%	270
New Mexico	29	13%	22	10%	36	17%	218

Source: Substance Abuse and Mental Health Services Administration, Office of Applied Studies (2006). Opiate-related drug misuse deaths in 6 states: 2003. The New DAWN Report, issue 19.



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increased use of therapeutic opioids and to remember the physician's dictum: Do no harm. The alarming patterns described in this article require us as physicians to stop and ponder; to reflect upon our responsibilities; to ask ourselves what we can do to mitigate these problems; to investigate in more depth the real therapeutic advantages of opioid use, especially for chronic pain; to be more conservative in our therapeutic use of opioids; to invent newer strategies for the prevention of diversion; and most importantly, to be more proactive in educating our patients, their families, our congressional representatives and the public of the limitations of therapeutic use, and the dangers of abuse and non-medical use of opioids, and we must do so now.

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