

Perspective Review

Therapeutic Use, Abuse, and Nonmedical Use of Opioids: A Ten-Year Perspective

Laxmaiah Manchikanti, MD¹, Bert Fellows, MA¹, Hary Ailinani, MD² and Vidyasagar Pampati, MSc¹

From: ¹Pain Management Center of Paducah, Paducah, KY; and ²Shore-Long Island Jewish Health System, Bayside, NY

Dr. Manchikanti is Medical Director of the Pain Management Center of Paducah, Paducah, KY, and Associate Clinical Professor of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY. Bert Fellows is Director Emeritus of Psychological Services at the Pain Management Center of Paducah, Paducah, KY. Dr. Ailinani is Resident of Physical Medicine and Rehabilitation, PGY-4, North Shore-Long Island Jewish Health System, Bayside, NY. Mr. Pampati is a Statistician at the Pain Management Center of Paducah, Paducah, KY.

Address correspondence: Laxmaiah Manchikanti, M.D. 2831 Lone Oak Road Paducah, Kentucky 42003 E-mail: drlm@thepainmd.com

Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: None.

Manuscript received: 08/23/2010
Accepted for publication: 09/03/2010

Free full manuscript: www.painphysicianjournal.com

The treatment of chronic pain, therapeutic opioid use and abuse, and the nonmedical use of prescription drugs have been topics of intense focus and debate. After the liberalization of laws governing opioid prescribing for the treatment of chronic non-cancer pain by state medical boards in the late 1990s, and with the introduction of new pain management standards implemented by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in 2000, opioids, in general, and the most potent forms of opioids including Schedule II drugs, in particular, have dramatically increased.

Despite the escalating use and abuse of therapeutic opioids, nearly 15 to 20 years later the scientific evidence for the effectiveness of opioids for chronic non-cancer pain remains unclear. Concerns continue regarding efficacy; problematic physiologic effects such as hyperalgesia, hypogonadism and sexual dysfunction; and adverse side effects – especially the potential for misuse and abuse – and the increase in opioid-related deaths.

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. Retail sales of commonly used opioid medications (including methadone, oxycodone, fentanyl base, hydromorphone, hydrocodone, morphine, meperidine, and codeine) have increased from a total of 50.7 million grams in 1997 to 126.5 million grams in 2007. This is an overall increase of 149% with increases ranging from 222% for morphine, 280% for hydrocodone, 319% for hydromorphone, 525% for fentanyl base, 866% for oxycodone, to 1,293% for methadone. Average sales of opioids per person have increased from 74 milligrams in 1997 to 369 milligrams in 2007, a 402% increase.

Surveys of nonprescription drug abuse, emergency department visits for prescription controlled drugs, unintentional deaths due to prescription controlled substances, therapeutic use of opioids, and opioid abuse have been steadily rising.

This manuscript provides an updated 10-year perspective on therapeutic use, abuse, and non-medical use of opioids and their consequences.

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 2010; 13:401-435

After the liberalization of laws governing opioid prescribing for the treatment of chronic non-cancer pain by state medical boards in the late 1990s (1), and with the introduction of new pain management standards for inpatient and outpatient medical care implemented by the

Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in 2000 (2), many physicians and organizations began advocating for increased usage of opioids in the treatment of chronic pain (3-14). Opioids, in general, and the most potent forms of opioids including Schedule II drugs, in particular, have

dramatically increased (15-17). This dramatic increase has been due to a shift in the regulations largely driven by published, albeit weak, evidence suggesting that opioids could be used safely in selected persons with chronic non-cancer pain (18,19), by the advocacy of physicians and others who felt constrained by the near absolute prohibition of such before that time (6) and by consensus of professional societies of pain specialists who believe that chronic pain had been previously undertreated (13). Despite the escalating use and abuse of therapeutic opioids (4), nearly 15 to 20 years later the scientific evidence for the effectiveness of opioids for chronic non-cancer pain remains unclear. Concerns continue regarding efficacy (3-5,19,20); problematic physiologic effects such as hyperalgesia (21), hypogonadism and sexual dysfunction (22); and adverse side effects – especially the potential for misuse and abuse (23,24) – and the increase in opioid-related deaths (25-40). Meanwhile, numerous efforts by organizations for appropriate use and exercise of constraints have been misrepresented, with these opinions used to a minimum extent (3,4,10,41-47).

The treatment of chronic pain, therapeutic opioid use and abuse, and the nonmedical use of prescription drugs have been topics of intense focus and debate (3-5,47-99). Due in some measure to the campaign of alleged undertreatment of pain (100-122), 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 (4,10-12,122,123). Retail sales of commonly used opioid medications (including methadone, oxycodone, fentanyl base, hydromorphone, hydrocodone, morphine, meperidine, and codeine) have increased from a total of 50.7 million grams in 1997 to 126.5 million grams in 2007. This is an overall increase of 149% with increases ranging from 222% for morphine, 280% for hydrocodone, 319% for hydromorphone, 525% for fentanyl base, 866% for oxycodone, to 1293% for methadone (14). 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 (10,14,123-125). Average sales of opioids per person have increased from 74 milligrams in 1997 to 369 milligrams in 2007, a 402% increase. It is no surprise then that surveys of nonprescription drug abuse (4,126-131), emergency department visits for prescription controlled drugs (132-138), unintentional deaths due to prescription controlled substances (28-40,139-145), therapeutic

use of opioids, and opioid abuse (15-17,48-103,140,146-174) have been steadily rising.

Chronic pain has been defined by the American Society of Interventional Pain Physicians (ASIPP) (175,176) as, "pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal, that is associated with chronic pathologic processes that cause continuous or intermittent pain for months or years that may continue in the presence or absence of demonstrable pathology; may not be amenable to routine pain control methods; and healing may never occur."

Chronic persistent pain can cause significant impairment of physical and psychological health, and performance of social responsibilities, including work and family life (175-182). While modern medicine has shown significant improvements in the understanding of pain (including diagnosis and treatment) (175,176,183-227), chronic pain continues to be an epidemic resulting in vocational, social and family discord, which may make the difference between life and death, and is accompanied by claims of inadequate treatment (100-121,175,176,228-231).

Prevalence and associated disability continue to increase. Harkness et al (179), in a 2000 publication, showed that there was a large difference in the prevalence of musculoskeletal pain over a 40-year period of investigation. The results showed that overall, the prevalence of low back pain increased from 8.1 to 17.8% in males, and it increased from 9.1 to 18.2% in females. Similarly, Freburger et al (180) reported the rising prevalence of chronic low back pain following an evaluation of North Carolina (USA) households conducted in 1992 and repeated in 2006. The results showed an increasing prevalence of chronic impairing low back pain over the 14-year interval from 3.9% in 1992 to 10.2% in 2006, with an overall increase of 162% in low back pain and an annual increase of 11.6% associated with care-seeking and disability.

1.0 NONMEDICAL USE OF PSYCHOTHERAPEUTIC DRUGS

Results of the 2008 National Survey on Drug Use and Health (NSDUH) (126), an annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), showed that an estimated 20.1 million, or 8.0% of Americans, aged 12 or older, were current (past month) illicit drug users. Illicit drugs include marijuana, cocaine, heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics (defined

in this survey as prescription-type pain relievers, tranquilizers, stimulants, and sedatives) used nonmedically. Marijuana was the most commonly used illicit drugs with 15.2 million current (past month) users, or 6.1% of the US population. Cocaine was used by 1.9 million, whereas hallucinogens were used in the past month by 1.1 million persons (Fig. 1 and Table 1). Next to marijuana, 6.2 million (2.5%) persons aged 12 or older had used prescription-type psychotherapeutic drugs non-medically in the past month (current use). Of these, 4.7 million had used pain relievers. 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 nonmedical use of psychotherapeutics and pain relievers were well ahead of the illicit use of cocaine, hallucinogens, inhalants, methamphetamine, heroin, and LSD.

1.1 Current Nonmedical Use

The increases for current (past month) nonmedical use of psychotherapeutics from 1998 to 2008 was 151% compared to 33% for marijuana and hashish and 61%

for cocaine as shown in Table 1 (4,126). In fact, psychotherapeutics were the only ones that showed significant increases from 2002 to 2008, whereas, marijuana and cocaine were similar over a period of 5 years. Table 1 also illustrates a 10-year increase of 175% in the non-medical use of tranquilizers in contrast to 109% from 1997 to 2006 with increases of stimulants and sedatives of 43% and 11%.

Overall, there has been some decrease in the current use of all illicit drugs from 2002 to 2008, as shown in Fig. 2.

1.2 Past Year Initiates

In 2008, there were 2.5 million persons aged 12 or older who used psychotherapeutics nonmedically for the first time within the past year. Numbers of new users for specific psychotherapeutics in 2008 were 2.2 million for pain relievers, 1.1 million for tranquilizers, 599,000 for stimulants, and 181,000 for sedatives (Table 2 and Fig. 3). The specific drug categories with the largest number of recent initiatives among persons aged 12 or older were nonmedical use of pain relievers (2.176 million) and marijuana (2.208 million), followed by nonmedical use of tranquilizers (1.127 million), cocaine

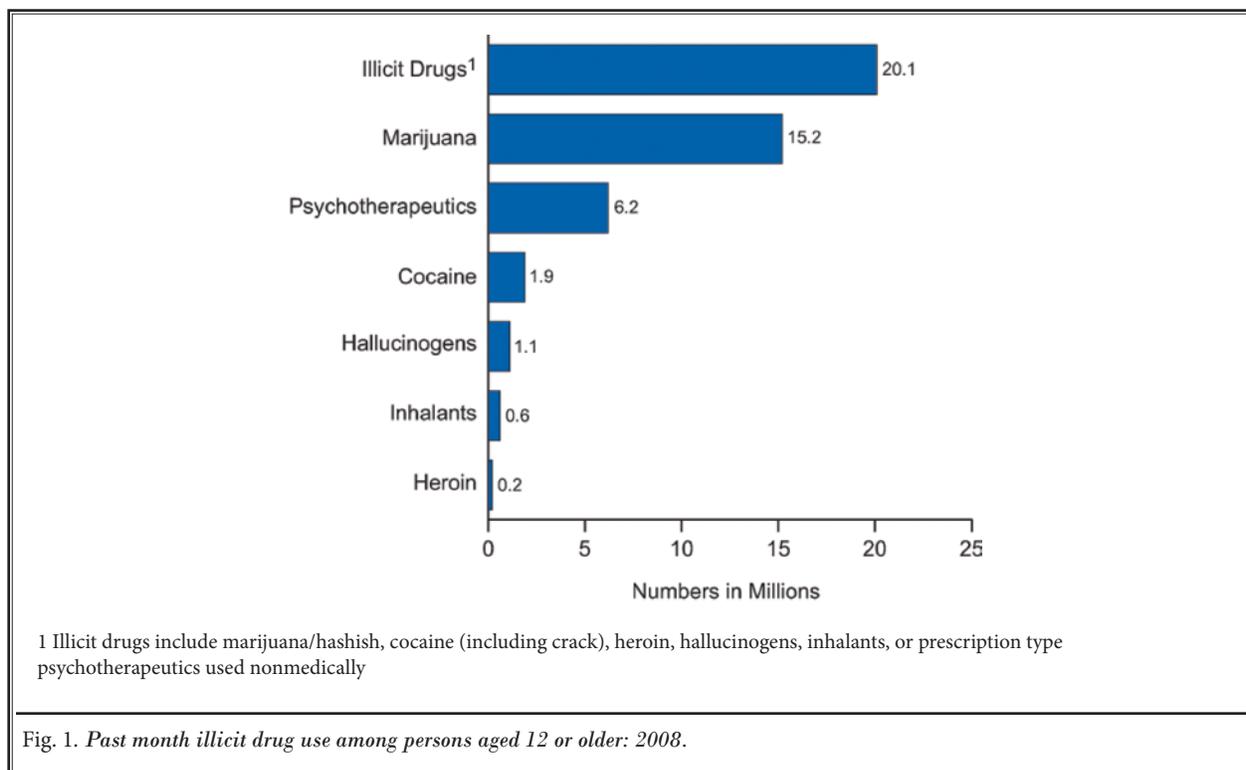


Table 1. Types of illicit drug use in the past month among persons aged 12 or older: Numbers in thousands, from 1998 to 2008.

Drugs	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	10-YEAR % change from 1998 to 2008
Nonmedical Use of Psychotherapeutics ^{2,3}	2,477 (1.1%)	3,952 (1.8%)	3,849 (1.7%)	4,811 (2.1%)	6,287 (2.7%)	6,451 (2.7%)	6,110 (2.5%)	6,491 (2.7%)	7,095 ^b (2.9%)	6,895 ^a (2.8%)	6,224 (2.5%)	151%
Pain Relievers	--	2,621 (1.2%)	2,782 (1.2%)	3,497 (1.6%)	4,377 (1.9%)	4,693 (2.0%)	4,404 (1.8%)	4,658 (1.9%)	5,220 (2.1%)	5,174 (2.1%)	4,747 (1.9%)	NA
OxyContin [®]	--	--	--	--	--	--	325 (0.1%)	334 (0.1%)	276 (0.1%)	369 (0.1%)	435 (0.2%)	NA
Tranquilizers	655 (0.3%)	1,097 (0.5%)	1,000 (0.4%)	1,358 (0.6%)	1,804 (0.8%)	1,830 (0.8%)	1,616 (0.7%)	1,817 (0.7%)	1,766 (0.7%)	1,835 (0.7%)	1,800 (0.7%)	175%
Stimulants	633 (0.3%)	950 (0.4%)	788 (0.4%)	1,018 (0.5%)	1,303 ^b (0.6%)	1,310 ^b (0.6%)	1,312 ^b (0.5%)	1,188 ^b (0.5%)	1,385 ^b (0.6%)	1,053 (0.4%)	904 (0.4%)	43%
Sedatives ³	210 (0.1%)	229 (0.1%)	175 (0.1%)	306 (0.1%)	436 ^b (0.2%)	294 (0.1%)	265 (0.1%)	272 (0.1%)	385 (0.2%)	346 (0.1%)	234 (0.1%)	11%
Marijuana and Hashish	11,016 (5.0%)	10,458 (4.7%)	10,714 (4.8%)	12,122 (5.4%)	14,584 (6.2%)	14,638 (6.2%)	14,576 (6.1%)	14,626 (6.0%)	14,813 (6.0%)	14,448 (5.8%)	15,203 (6.1%)	38%
Cocaine	1,750 (0.8%)	1,552 (0.7%)	1,213 (0.5%)	1,667 (0.7%)	2,020 (0.9%)	2,281 (1.0%)	2,021 (0.8%)	2,397 (1.0%)	2,421 (1.0%)	2,075 (0.8%)	1,855 (0.7%)	6%
TOTAL ILLICIT DRUGS ¹	13,615 (6.2%)	13,829 (6.3%)	14,027 (6.3%)	15,910 (7.1%)	19,522 (8.3%)	19,470 (8.2%)	19,071 (7.9%)	19,720 (8.1%)	20,357 (8.3%)	19,857 (8.0%)	20,077 (8.0%)	47%

-- Not available. Note: 2002 to 2008 data is based on 2008 National Survey on Drug Use and Health Survey Report.

a Difference between estimate and 2008 estimate is statistically significant at the 0.05 level. b Difference between estimate and 2008 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. Illicit drugs other than marijuana include cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. The estimates for nonmedical use of psychotherapeutics, stimulants, and methamphetamine incorporated in these summary estimates do not include data from the methamphetamine items added in 2005 and 2006. 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. 3 Estimates of nonmedical use of psychotherapeutics, stimulants, and methamphetamine in the designated rows include data from methamphetamine items added in 2005 and 2006 and are not comparable with estimates presented in NSDUH reports prior to the 2007 National Findings report. For the 2002 through 2005 survey years, a Bernoulli stochastic imputation procedure was used to generate adjusted estimates comparable with estimates for survey years 2006 and later.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1998 - 2008.

Source: <http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.pdf> (126) Access date 3/16/2010

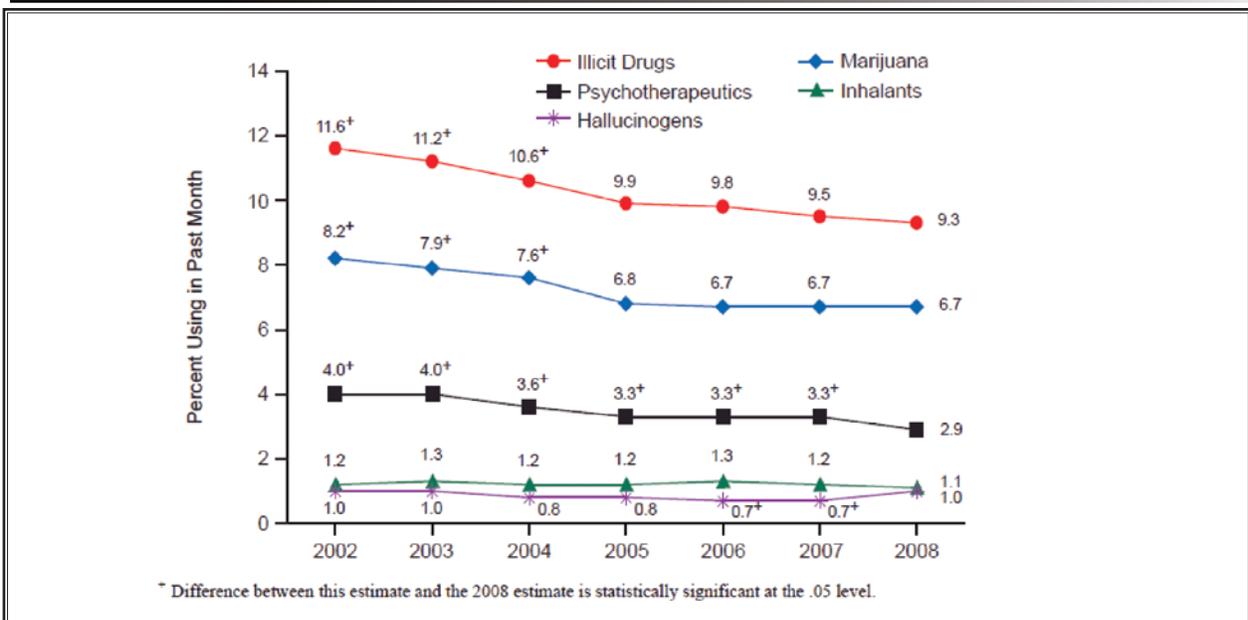


Fig. 2. Past month illicit drug use among persons aged 12 or older, by age: 2008.

Source: <http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.pdf> Access date 3/16/2010

(0.722 million), ecstasy (0.9 million), stimulants (0.599 million), and inhalants (0.729 million) (Fig. 3). More strikingly, in 2008, the number of new nonmedical users of OxyContin (oxycodone) aged 12 or older was 478,000 with an average age at first use of 22.6 years among those aged 12 to 49 (126).

1.3 Past Year Use

Analysis of long-term statistics based on yearly use of illicit drugs are concerning, despite some decreases. The past year use of illicit drugs in 2008 was 35.525 million, or 14.2% of the population (Table 3). Nonmedical use of psychotherapeutics for the past year in the 2008

Table 2. Past year initiates for illicit drugs from 1998 to 2008 (numbers in thousands) for 10 years.

Drugs	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	10-YEAR% change from 1998 to 2008
Pain Relievers ²	1,548	1,810	2,268	2,400	2,320	2,456	2,422	2,193	2,150	2,147	2,176	41%
Tranquilizers	860	916	1,298	1,212	1,184	1,071	1,180	1,286	1,112	1,232	1,127	31%
Stimulants ²	648	706	808	853	783	715	793 ^a	647	845 ^b	642	599	-8%
Sedatives	147	164	191	225	209	194	240	247	267	198	181	23%
Marijuana	2,498	2,640	2,746	2,793	2,196	1,973	2,142	2,114	2,063	2,090	2,208	-12%
Cocaine	868	917	1,002	1,140	1,032 ^b	986 ^b	998 ^b	872 ^a	977 ^b	906 ^b	722	-17%
Heroin	140	121	114	154	117	92	118	108	91	106	114	-19%

-- Not available. Note: 2002 to 2008 data is based on 2008 National Survey on Drug Use and Health Survey Report.
 a Difference between estimate and 2008 estimate is statistically significant at the 0.05 level. b Difference between estimate and 2008 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. Illicit drugs other than marijuana include cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. The estimates for nonmedical use of psychotherapeutics, stimulants, and methamphetamine incorporated in these summary estimates do not include data from the methamphetamine items added in 2005 and 2006.
 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. 3 Estimates of nonmedical use of psychotherapeutics, stimulants, and methamphetamine in the designated rows include data from methamphetamine items added in 2005 and 2006 and are not comparable with estimates added in NSDUH reports prior to the 2007 National Findings report. For the 2002 through 2005 survey years, a Bernoulli stochastic imputation procedure was used to generate adjusted estimates comparable with estimates for survey years 2006 and later.
 Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1998 - 2008.
 Source: <http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.pdf> (126) Access date 3/16/2010

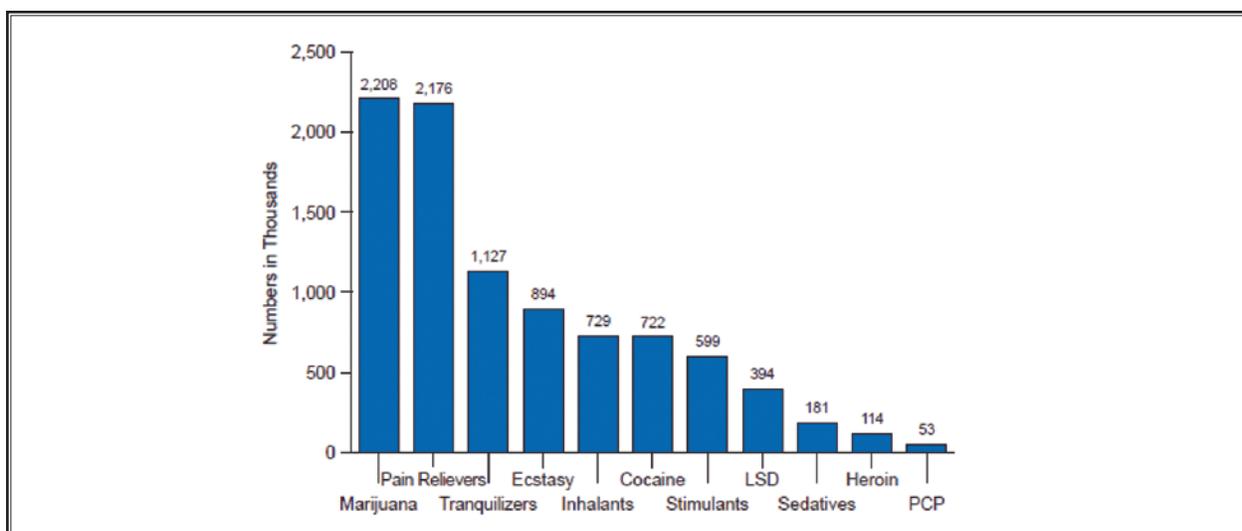


Fig. 3. Past year initiates for specific illicit drugs among persons aged 12 or older: 2008.

Source: <http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.pdf> (126) Access date 3/16/2010

Table 3. Types of illicit drug use in the past year among persons aged 12 or older: numbers in thousands from 1998 to 2008 (10 years).

Drugs	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	10-year % change from 1998 to 2008
Nonmedical Use of Psychotherapeutics ^{2,3}	5,759 (2.6%)	9,220 (4.2%)	8,761 (3.9%)	11,102 (4.9%)	14,795 (6.3%)	15,163 (6.4%)	14,849 (6.2%)	15,346 (6.3%)	16,482 ^b (6.7% ^b)	16,280 ^a (6.6% ^a)	15,166 (6.1%)	163%
Pain Relievers	--	6,582 (3.0%)	6,466 (2.9%)	8,353 (3.7%)	10,992 ^a (4.7%)	11,671 (4.9%)	11,256 (4.7%)	11,815 (4.9%)	12,649 (5.1% ^a)	12,466 (5.0%)	11,885 (4.8%)	NA
OxyContin [®]	--	--	--	--	--	--	1,213 ^a (0.5%)	1,226 (0.5%)	1,323 (0.5%)	1,422 (0.6%)	1,459 (0.6%)	NA
Tranquilizers	1,940 (0.9%)	2,728 (1.2%)	2,731 (1.2%)	3,673 (1.6%)	4,849 (2.1%)	5,051 (2.1%)	5,068 (2.1%)	5,249 (2.2%)	5,058 (2.1%)	5,282 (2.1%)	5,103 (2.0%)	163%
Stimulants ³	1,489 (0.7%)	2,291 (1.0%)	2,112 (0.9%)	2,486 (1.1%)	3,380 ^b (1.4% ^b)	3,031 ^a (1.3% ^b)	3,254 ^b (1.4% ^b)	3,088 ^a (1.3% ^b)	3,791 ^b (1.5% ^b)	2,998 (1.2%)	2,639 (1.1%)	77%
Sedatives	522 (0.2%)	631 (0.3%)	611 (0.3%)	806 (0.4%)	981 ^b (0.4% ^b)	831 ^a (0.3% ^a)	737 (0.3%)	750 (0.3%)	926 ^b (0.4% ^b)	864 ^a (0.3% ^a)	621 (0.2%)	19%
Marijuana and Hashish	18,710 (8.6%)	19,102 (8.6%)	18,589 (8.3%)	21,086 (9.3% ^c)	25,755 (11.0% ^a)	25,231 (10.6%)	25,451 (10.6%)	25,375 (10.4%)	25,378 (10.3%)	25,085 (10.1%)	25,768 (10.3%)	38%
Cocaine	3,811 (1.7%)	3,742 (1.7%)	3,328 (1.5%)	4,186 (1.9% ^c)	5,902 ^a (2.5% ^b)	5,908 ^a (2.5% ^b)	5,658 (2.4% ^a)	5,523 (2.3%)	6,069 ^b (2.5% ^b)	5,738 (2.3%)	5,255 (2.1%)	38%
TOTAL ILLICIT DRUGS ¹	23,115 (10.6%)	25,402 (11.5%)	24,535 (11.0%)	28,409 (12.6% ^c)	35,132 (14.9% ^a)	34,993 (14.7%)	34,807 (14.5%)	35,041 (14.4%)	35,775 (14.5%)	35,692 (14.4%)	35,525 (14.2%)	54%

-- Not available.

Note: 2002 to 2008 data is based on 2008 National Survey on Drug Use and Health Survey Report. a Difference between estimate and 2008 estimate is statistically significant at the 0.05 level. b Difference between estimate and 2008 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. Illicit drugs other than marijuana include cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. The estimates for nonmedical use of psychotherapeutics, stimulants, and methamphetamine incorporated in these summary estimates do not include data from the methamphetamine items added in 2005 and 2006.

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.

3 Estimates of nonmedical use of psychotherapeutics, stimulants, and methamphetamine in the designated rows include data from methamphetamine items added in 2005 and 2006 and are not comparable with estimates presented in NSDUH reports prior to the 2007 National Findings report. For the 2002 through 2005 survey years, a Bernoulli stochastic imputation procedure was used to generate adjusted estimates comparable with estimates for survey years 2006 and later.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1998 - 2008.

Source: <http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.pdf> (126) Access date 3/16/2010

survey was 15.166 million or 6.1% population aged 12 or older, compared to 16.280 million or 6.6% in 2007 and 16.482 million in 2006, or 6.7% of the population. 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 2008 which increased from 10.1% in 2007. Overall, nonmedical use of psychotherapeutics increased 163% from 1998 to 2008 in contrast to 167% from 1997 to 2006, compared to marijuana 31% versus 38%, 46% in cocaine to 38%, and overall illicit drug use of 48% versus 54% during the past year.

1.4 Lifetime Use

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). In 2008, the lifetime use of illicit drugs among persons aged 12 or older was slightly more than 2007 with 117,325 or 47% of the population, an increase from 46.1% of the population in 2007. In contrast, nonmedical use of psychotherapeutics increased to 20.8% in 2008, or almost 52 million using prescription psychotherapeutic drugs for nonmedical purposes. Among the

Therapeutic Use, Abuse, and Nonmedical Use of Opioids: A Ten-Year Perspective

Table 4. Types of illicit drugs of lifetime use among persons aged 12 or older: numbers in thousands, 1998 – 2008.

Drug	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	% change from 1998 to 2008
Nonmedical Use of Psychotherapeutics ²	20,193 (9.2%)	34,076 (15.4%)	32,443 (14.5%)	36,028 (16.0%)	47,958 ^b (20.4%)	49,001 ^b (20.6%)	49,157 (20.4%)	49,571 ^a (20.4%)	50,965 (20.7%)	50,415 (20.3%)	51,970 (20.8%)	157%
Pain Relievers	--	19,888 (9.0%)	19,210 (8.6%)	22,133 (9.8%)	29,611 ^b (12.6% ^b)	31,207 ^b (13.1% ^a)	31,768 ^b (13.2% ^a)	32,692 ^b (13.4%)	33,472 (13.6%)	33,060 ^a (13.3%)	34,861 (14.0%)	NA
OxyContin [®]	--	--	--	--	1,924 ^b (0.8% ^b)	2,832 ^b (1.2% ^b)	3,072 ^b (1.3% ^b)	3,481 ^b (1.4% ^b)	4,098 ^b (1.7% ^b)	4,354 (1.8%)	4,842 (1.9%)	NA
Tranquilizers	7,726 (3.5%)	13,860 (6.3%)	13,007 (5.8%)	13,945 (6.2%)	19,267 ^b (8.2%)	20,220 (8.5%)	19,852 ^a (8.3%)	21,041 (8.7%)	21,303 (8.7%)	20,208 (8.2%)	21,476 (8.6%)	178%
Stimulants	9,614 (4.4%)	15,922 (7.2%)	14,661 (6.6%)	16,007 (7.1%)	23,496 ^b (10.0% ^b)	23,004 ^a (9.7% ^b)	22,297 (9.3% ^b)	20,983 (8.6%)	22,468 (9.1% ^a)	21,654 (8.7%)	21,206 (8.5%)	121%
Sedatives	4,640 (2.1%)	7,747 (3.5%)	7,142 (3.2%)	7,477 (3.3%)	9,960 ^a (4.2% ^b)	9,510 (4.0% ^a)	9,891 (4.1% ^a)	8,982 (3.7%)	8,822 (3.6%)	8,396 (3.4%)	8,882 (3.6%)	91%
Marijuana and Hashish	72,070 (33.0%)	76,428 (34.6%)	76,321 (34.2%)	83,272 (36.9% ^c)	94,946 ^b (40.4%)	96,611 ^b (40.6%)	96,772 ^b (40.2%)	97,545 ^b (40.1%)	97,825 ^b (39.8% ^a)	100,518 (40.6%)	102,404 (41.0%)	42%
Cocaine	23,089 (10.6%)	25,406 (11.5%)	24,896 (11.2%)	27,788 (12.3%)	33,910 ^b (14.4%)	34,891 ^a (14.7%)	34,153 ^b (14.2%)	33,673 ^b (13.8%)	35,298 (14.3%)	35,882 (14.5%)	36,773 (14.7%)	59%
TOTAL ILLICIT DRUGS ¹	78,123 (35.8%)	87,734 (39.7%)	86,931 (38.9%)	94,140 (41.7% ^c)	108,255 ^b (46.0%)	110,205 ^b (46.4%)	110,057 ^b (45.8% ^a)	112,085 ^b (46.1%)	111,774 ^b (45.4% ^b)	114,275 ^a (46.1%)	117,325 (47.0%)	50%

-- Not available.

Note: 2002 to 2008 data is based on 2008 National Survey on Drug Use and Health Survey Report.

a Difference between estimate and 2008 estimate is statistically significant at the 0.05 level.

b Difference between estimate and 2008 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. Illicit drugs other than marijuana include cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. The estimates for nonmedical use of psychotherapeutics, stimulants, and methamphetamine incorporated in these summary estimates do not include data from the methamphetamine items added in 2005 and 2006.

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.

3 Estimates of nonmedical use of psychotherapeutics, stimulants, and methamphetamine in the designated rows include data from methamphetamine items added in 2005 and 2006 and are not comparable with estimates presented in NSDUH reports prior to the 2007 National Findings report. For the 2002 through 2005 survey years, a Bernoulli stochastic imputation procedure was used to generate adjusted estimates comparable with estimates for survey years 2006 and later.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1998 - 2008.

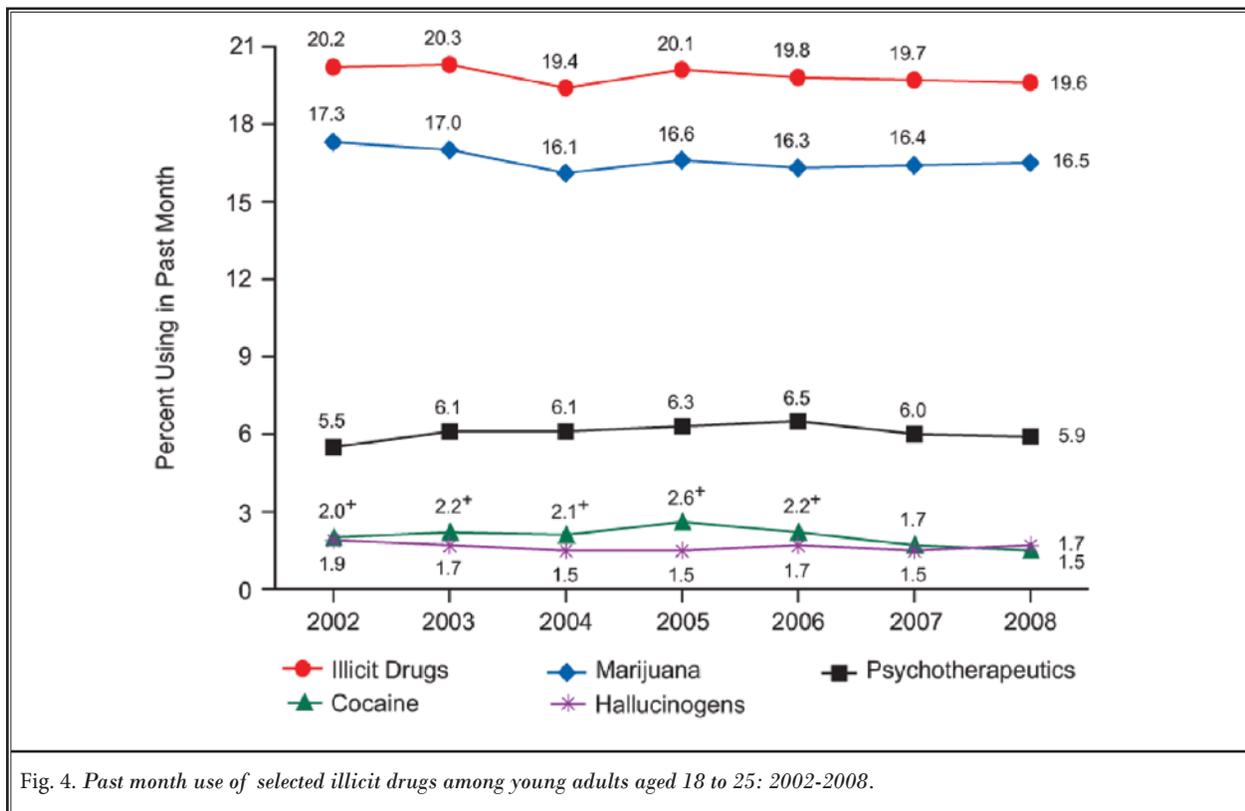
Source: <http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.pdf> (126) Access date 3/16/2010

subgroups, only OxyContin increased significantly from 3,481 in 2005 to 4,842 in 2008, or 1.4% of the population in 2005 to 1.9% in 2008. Lifetime use of illicit drugs in persons aged 12 or older was topped by marijuana (41.0% of the population) followed by nonmedical use of psychotherapeutics (20.8% of the population). Further, nonmedical use of psychotherapeutics was 157% higher than the lifetime use of cocaine (59%) or marijuana (42%), from 1998 to 2008.

1.5 Abuse Based on Age

In 2008, young adults aged 18 to 25 demonstrated

rates of current use of illicit drugs to be higher (19.6%) than for youths aged 12 to 17 (9.3%) and adults aged 26 or older (5.9%), with 16.5% using marijuana, 5.9% using psychotherapeutics nonmedically, 1.5% using cocaine, and 1.7% using hallucinogens (Fig. 4). Past month nonmedical use of prescription-type drugs among young adults increased from 5.5% in 2002 to 5.9% in 2008. 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 of time, the non-medical 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 (126).

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 2008 increased from 3.3% at ages 12 or 13, to 8.6% at ages 14 or 15, to 15.2% at ages 16 or 17. The highest rate of 21.5% was noted among persons aged 18 to 20 (Fig. 5) (126). In 2008, adults aged 26 or older were less likely to be current drug users than youths aged 12 to 17 or young adults aged 18 to 25 (5.9 vs. 9.3 and 19.6 percent, respectively). However, there were more drug users aged 26 or older (11.3 million) than users in the 12-to-17-year age group (2.3 million) and 18-to-25-year age group (6.5 million) combined.

1.6 Abuse Based on Gender

In 2008, the survey results were similar to prior years with males being more likely than females to be current illicit drug users (9.9% vs. 6.3%). Males were more likely than females to be past month users of marijuana (7.9% vs. 4.4%). However, males and females

had similar rates of past month nonmedical use of psychotherapeutic drugs (2.6% and 2.4%, respectively), pain relievers (2.0% and 1.8%), tranquilizers (0.7% and 0.8%), stimulants (0.4% for both), and sedatives (0.1% for both) (126).

1.7 Abuse During Pregnancy

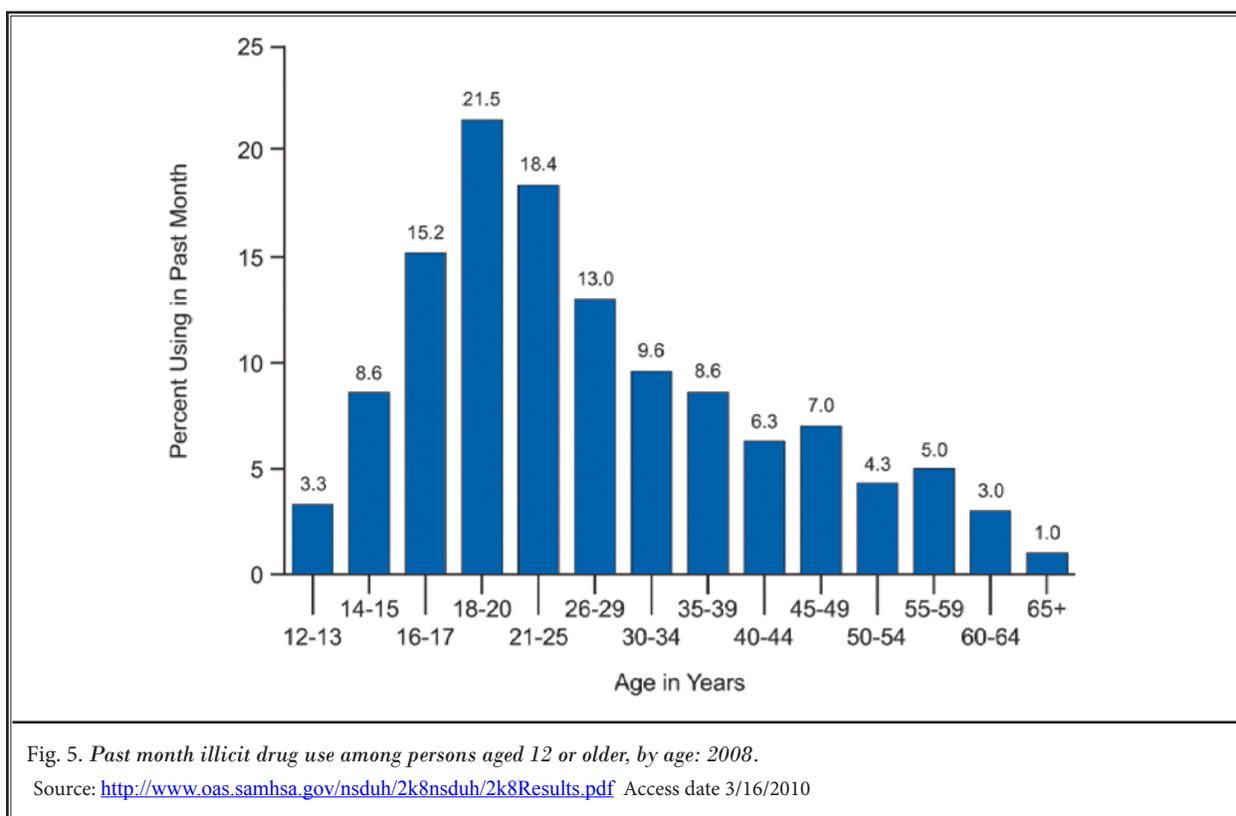
Among pregnant women aged 15 to 44 years, a significantly lower proportion of women used illicit drugs (5.1%) compared to their nonpregnant counterparts of 9.8% in the past month based on data averaged for 2007 and 2008 (126).

1.8 Abuse Based on Employment

Employment also seems to have a significant influence in 2008. Among adults aged 18 or older, the rate of illicit drug use was higher for unemployed persons (19.6%) than for those who were employed full time (8%) or part time (10.2%) (126).

1.9 Regional Variations

There were also differences based on geographic area among persons aged 12 or older in 2008. The rate of current illicit drug use in 2008 was 9.8% in the West,



8.2% in the Northeast, 7.6% in the Midwest, and 7.1% in the South (126). Further, the rate of current illicit drug use in metropolitan areas was higher than the rate in non-metropolitan areas with 8.5% in large metropolitan counties, 8.1% in small metropolitan counties, and 6.3% in non-metropolitan counties as a group (126).

1.10 Drug Abuse Among Criminals

In 2008, adults aged 18 or older who were on parole or a supervised release from jail during the past year had higher rates of dependence on or abuse of a substance (27.8%) than their counterparts who were not on parole or supervised release during the past year (8%). In 2008, probation status was associated with substance dependence or abuse. The rate of substance dependence or abuse was 34% among adults who were on probation during the past year, which was significantly higher than the rate among adults who were not on probation during the past year was 8.4% (126).

1.11 Driving Under the Influence

Driving under the influence of illicit drugs is criminal and dangerous to the public. In 2008, 10 million

persons, or 4.0% 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 12.3% (126).

1.12 Frequency of Abuse

Among past year marijuana users aged 12 or older in 2008, the following patterns were revealed (126):

- ◆ 15.0% used marijuana on 300 or more days within the past 12 months, translating to 3.9 million using marijuana on a daily or almost daily basis over a 12-month period.
- ◆ 35.7%, or 5.4 million, used the drug on 20 or more days in the past month (current use).

2.0 MENTAL HEALTH PROBLEMS AND NONMEDICAL USE OF DRUGS

The NSDUH survey of 2008 evaluated the prevalence and treatment of serious mental illness (SMI), 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 30 days

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 (126). Further, SPD indicates a respondent recently experienced heightened distress symptomatology that may be affecting health and behavior during the past 30 days. However, this distress may be part of a chronic psychological disturbance (even SMI) or may represent a temporary disturbance that could subside after a brief period of adjustment.

2.1 Serious Medical Illness and Drug Abuse

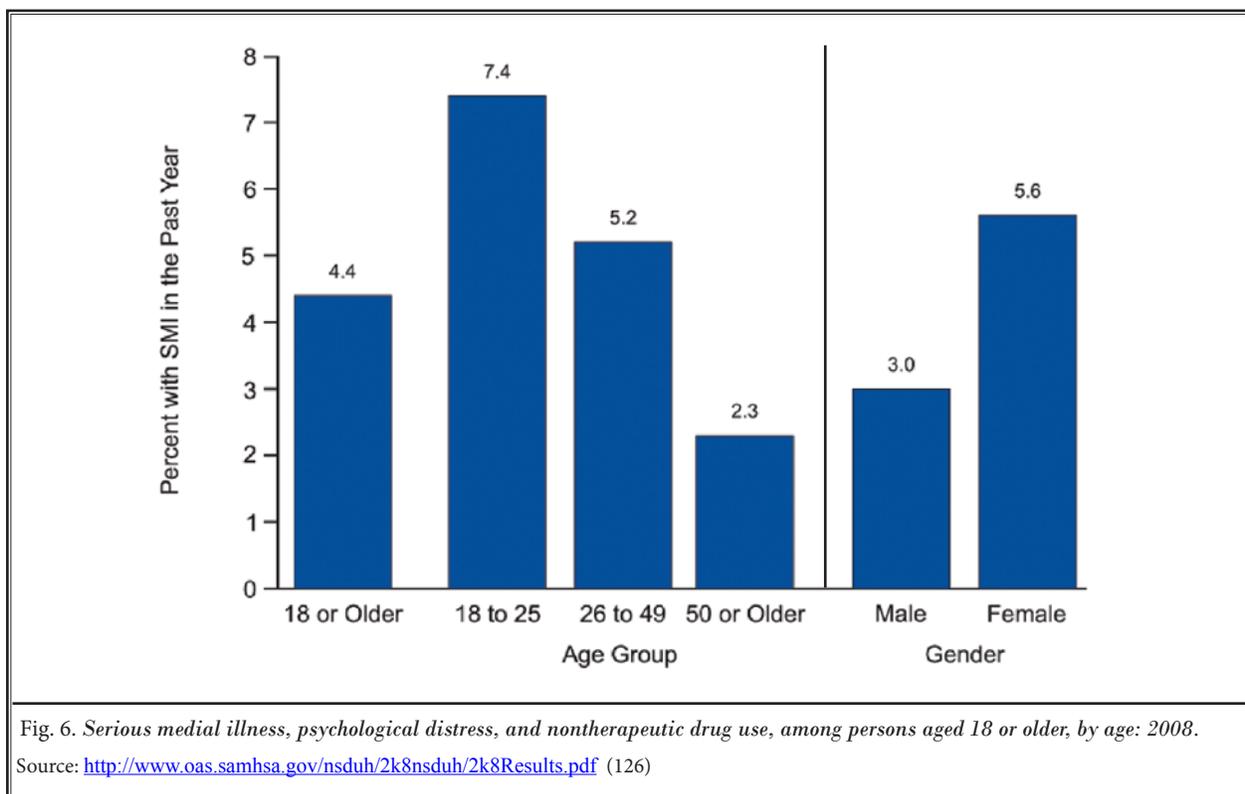
The prevalence of SMI in 2008 was shown in 9.8 million adults, representing 4.4% of all adults, with the highest rates being in adults aged 18 to 25 (7.4%) and lowest for adults aged 50 or older (2.3%) as shown in Fig. 6 (126). The prevalence of SPD among women aged 18 or older was higher (5.6%) than among men (3.0%) in that age group (126).

Past year illicit drug use was higher among adults aged 18 or older with past year SMI (30.3%) than among adults without SMI (12.9%). SMI in the past year was associated with past year substance dependence of abuse

in 2008 in 25.2% or 2.5 million dependent on or abusing illicit drugs or alcohol, compared to adults without SMI, this population was 8.3% or 17.9 million.

2.2 Major Depressive Episodes and Drug Abuse

The prevalence of a MDE in 2008 was 6.4% of persons aged 18 or older, or 14.3 million adults, with at least one MDE in the past year. Over one in 25 adults or 4.2% (9.5 million) people had past year MDE with severe impairment. Even then, the past year prevalence of MDE in 2008 was lower for those aged 50 or older (4.5%) compared with rates among persons aged 18 to 25 (8.7%) and those aged 26 to 49 (7.4%). However, the past year prevalence of MDE was higher among adult females than among adult males, 8.1% versus 4.6%. In addition, among women, past year MDE rates were higher with 12.1% for 18 to 25 year olds, 8.8% for 26 to 49 year olds compared with those of 50 or older with only 6%. Further, the prevalence of MDE also varied by race and ethnicity with highest rate among persons reporting 2 or more races (12.7%), while rates for single race groups were 7% among whites, 5.2% among Hispanics, 4.9% among American Indians or Alaska Natives, 4.9% among blacks, and 3.6% among Asians.



In addition, in 2008 the past prevalence of MDE with severe impairment for adults aged 18 or older was higher among unemployed persons (6.6%) than among persons employed full time (3.2%).

In 2008, an adult aged 18 or older with a combination of a MDE 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 (27.2% vs 13.0%) (126). A similar pattern 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 20.3% being dependent on or having abused alcohol or illicit drugs, while among adults without MDE only 7.8% were dependent on or had abused alcohol or illicit drugs (126). These numbers have slightly decreased from 2006. Figure 7 illustrates substance abuse in adults by MDE.

The prevalence of a MDE in youths aged 12 to 17 in 2008 showed that 2.0 million (8.3%) reported at least one MDE during the past year. Among youths aged 12 to 17, the past year prevalence of MDE ranged from 3.9% among 12-year-olds to 11.6%

among those aged 16, and 10.6% among those aged 17 (126).

Among youths with MDE aged 12 to 17, 37.4% had used illicit drugs in 2008, in contrast to 34.6% in 2006. This was higher than the 17.2% of youths in the past year that did not have a MDE but had used illicit drugs. This pattern, however, was similar to specific types of illicit drug use including marijuana and the nonmedical use of prescription-type psychotherapeutics (126).

2.3 Serious Psychological Distress and Drug Abuse

In 2008, the prevalence of past 30-day SPD among adults aged 18 or older was an estimated 10.2 million representing 4.5% of all US adults. The rates of SPD were highest for adults aged 18 to 25 and lowest for adults aged 50 or older (7.5% versus 2.9%). In addition, the rates were higher among unemployed adults than among adults employed full-time (10.2% versus 3.3%), part-time (4.4%), or other persons not in the labor force (6.1%).

Illicit drug use was higher among patients with SPD than adults without SPD (19.6% versus 7.3%). In 2008, past 30-day use of illicit drugs other than marijuana was higher among adults with SPD than among adults without SPD (12.3% versus 2.9%).

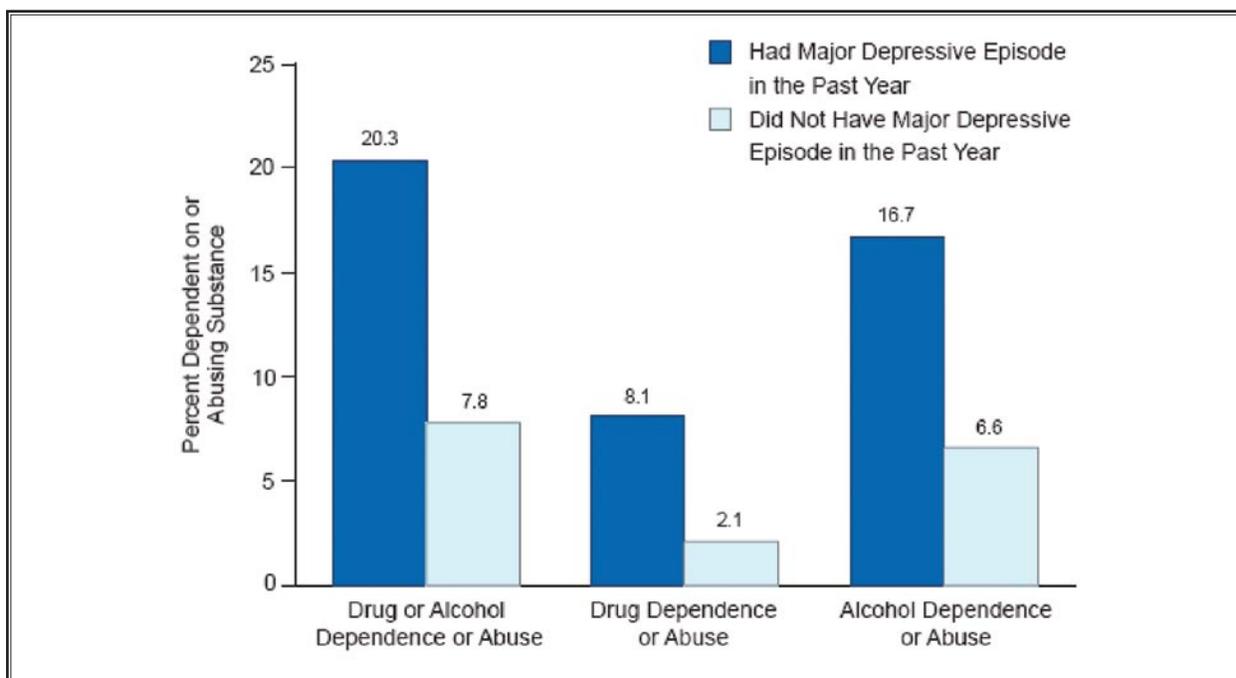


Fig. 7. Substance dependence or abuse among adults age 18 or older, by major depressive episode in the past year: 2008. Source: <http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.pdf> (126)

2.4 Mental Health Services

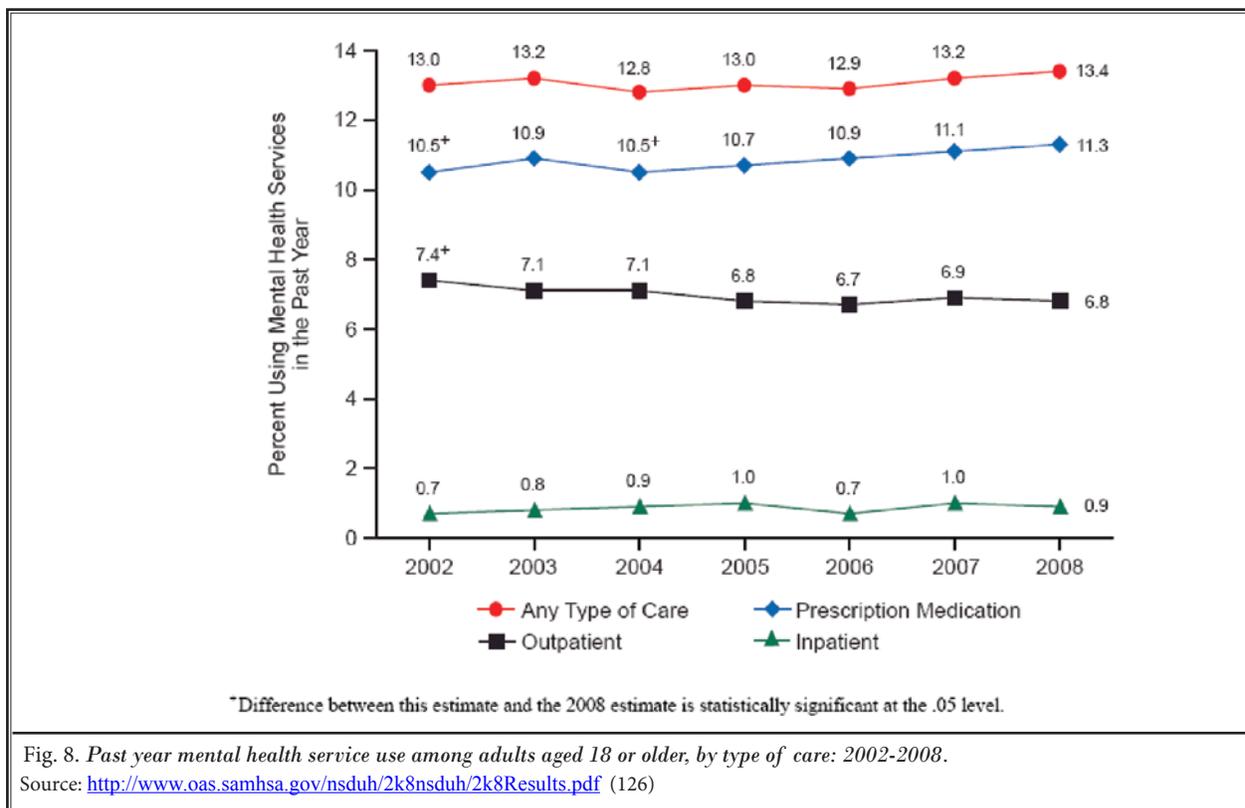
The 2008 survey showed that 30 million adults received mental health services during the past 12 months which was similar to 2007 (13.4% versus 13.2%) (Fig. 8).

In 2008, the type of mental health services most often received by adults aged 18 or older was prescription medication (11.3%), followed by outpatient services (6.8%). Even though the rates of these services were similar to those in 2007, the percentage of adults between 2002 and 2008, who received outpatient services declined from 7.4% to 6.8%, while the percentage increased from 10.5% to 11.3% in those receiving prescription medication. In contrast, approximately 2 million adults or 0.9% of the population aged 18 years or older received inpatient care for mental health problems during the past year, which was similar findings in 2007.

Age, gender, and ethnicity variables affected the rate of mental health services received. The 2008 report showed that adults aged 18 to 25 had a lower rate of mental health service use (10.8%) than adults aged 26 to 49 (14%) and aged 50 or older (13.6%). Further, men were less likely than women to receive both outpatient

mental health services (5% versus 8.5%) and prescription medication (7.5% versus 14.8%) for mental health problems in the past year. Regarding race, the rates of mental health service use for adults reporting 2 or more races was 18.8%, 16% for whites, 13.2% for American Indians or Alaska Natives, 8.7% for blacks (up from 6.8% in 2007), 6.8% for Hispanics, and 4.5% for Asians.

Despite widespread use of mental health services in 2008, there were 10.6 million adults (4.7%) who reported an unmet need for mental health care in the past year, including 5.1 million adults who did not receive any type of mental health service in the past year and 17.9% or 5.4 million reporting an unmet need for mental health care. The barriers to mental health care included the inability to afford care (42.7%), the belief at the time that the problem could be handled without care (28.5%), not knowing where to go for care 19.8%, and not having the time to go for care (13.9%). As shown in Fig. 9, 8.5% of the patients were concerned with confidentiality. Health insurance either did not cover care or did not cover care appropriately in 15.2% of patients, and 7.2% believed that the treatment would not help.



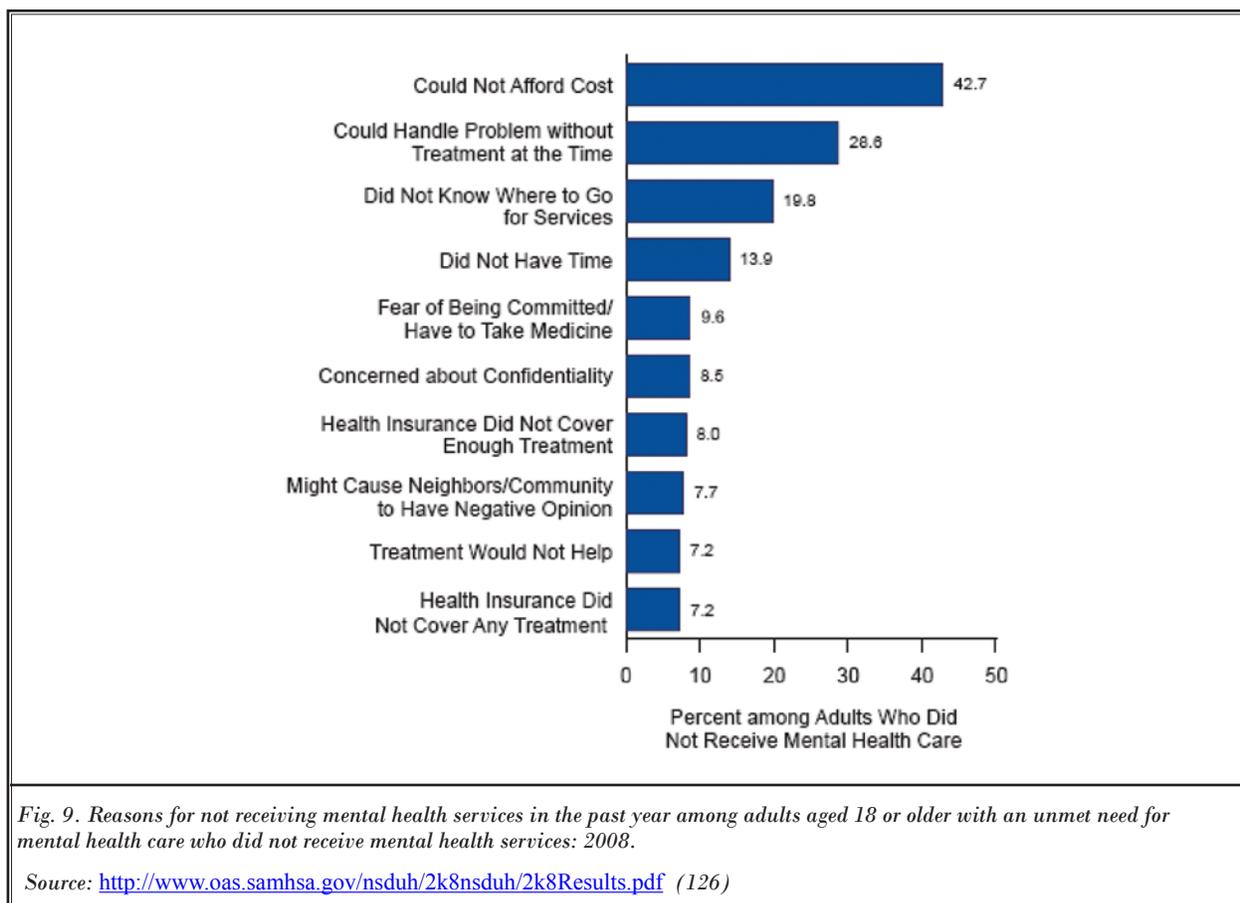
Among youths aged 12 to 17, 3.1 million or 12.7% received treatment or counseling, either inpatient or outpatient, for problems with behavior or emotions in a speciality mental health setting. In addition, 11.8% of youths received services in an educational setting, and 2.9% received mental health services in a general medical setting in the past 12 months. However, female youths were more likely than male youths to report using outpatient specialty mental health services (13.6% versus 9.3%), educational services (13% versus 10.5%), or general medical-based services (3.2% versus 2.6%), even though there was no significant gender difference in the use of inpatient specialty mental health services.

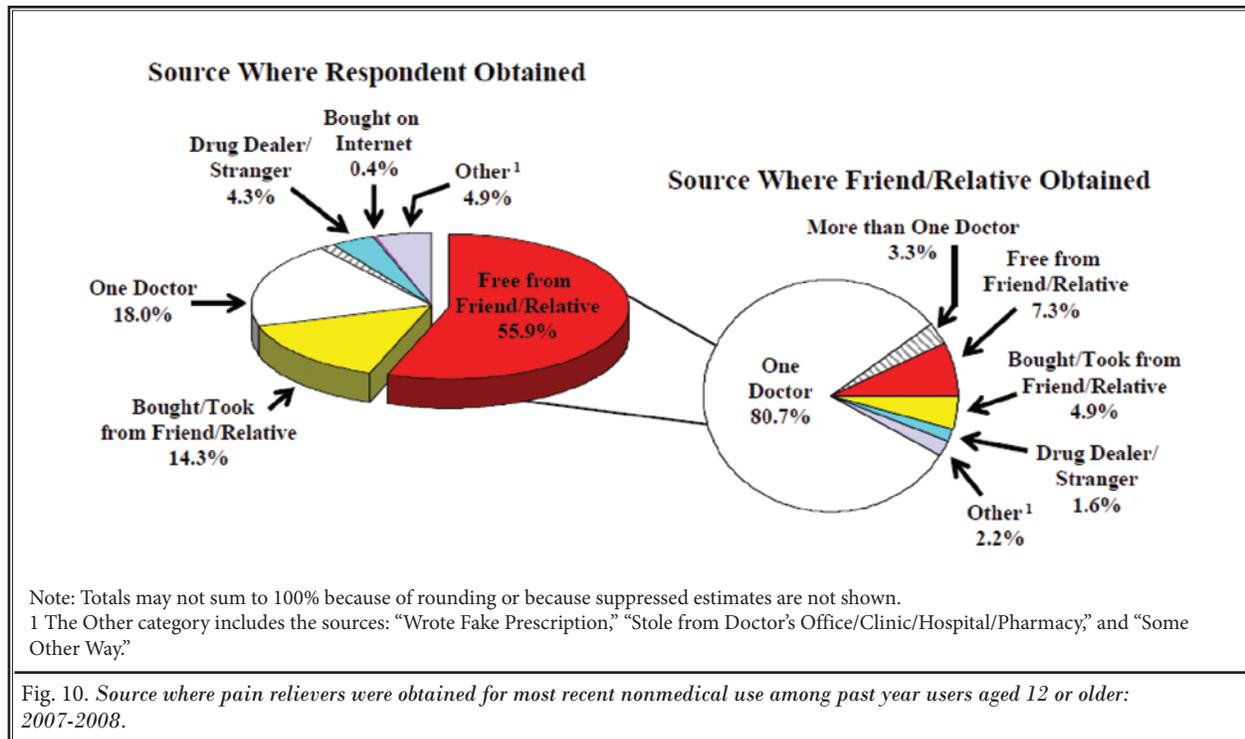
3.0 SOURCE OF PRESCRIPTION DRUGS

Of importance to the medical profession is the source of prescription-type pain relievers used nonmedically. Among persons aged 12 or older who used pain relievers nonmedically in the past 12 months, 55.9% reported that they received the drug for free from a

friend or relative (126). Another 8.9% bought the drug from a friend or relative, and 5.4% took them from a friend or relative without asking. An additional 18% reported that they got the drug from just one doctor. In contrast, only 4.3% got the pain relievers from a drug dealer or other stranger, and only 0.4% reported buying the drug on the internet (Fig. 10).

In 81.7% of the cases where nonmedical users of prescription pain relievers obtained their drugs for free from a friend or relative, the individuals indicated that their friend or relative had obtained the drugs from just one doctor (126). Only 1.6% reported that a friend or relative had bought the drug from a drug dealer or other stranger. Even more striking is the fact that in 2007-2008, 42.8% of past year methamphetamine users reported that they obtained the methamphetamine they used most recently for free from a friend or relative, with an additional 30.1% buying it from a friend or relative. Only one in 5 users of methamphetamine (21.17%) bought it from a drug dealer or other stranger (126).





4.0 THERAPEUTIC OPIOIDS

Opioids have been used for thousands of years to treat pain and continue to be one of the most commonly prescribed medications for pain (3,19,46,140). Opioids are a class of drugs that relieve pain by binding to and blocking certain receptors located in the brain and spinal cord. However, while opioid use for acute pain, post surgical pain, and palliative care is accepted in the United States, and many other countries, there is debate about whether opioids are appropriate for the treatment of chronic non-cancer pain (3,5,19,46,140,232-243). In fact, the United States, which differs from other western countries, made it illegal for physicians to prescribe opioids for addiction. Consequently, physicians in the United States could face loss of license, loss of practice, and possible imprisonment, and in fact still do (19). The efficacy of opioids for chronic non-cancer pain has been demonstrated in only short-term trials, which includes opioids for neuropathic pain, but, evidence on the efficacy and effectiveness of these agents for a long duration of treatment which is typical for chronic non-cancer pain is limited (3,5,19,46,140,232,233). In addition, numerous concerns have been raised about adverse effects including the development of psychologic addiction or abuse, or both, that may arise with long-

term use (232). Even then, it has been stated that the chilling effect United States regulations had on opioid treatment of pain have been countered by pain (opioid) advocacy, which successfully restored opioid treatment of acute and cancer pain. Further, based on the ability of opioids to effectively and safely treat acute and cancer pain, several arguments have been made to support extending opioid treatment to patients with chronic pain, attempting to remove the previously exercised caution based on fears of addiction. It is argued that physicians should be encouraged to prescribe opioids because they are indispensable for the treatment of pain and suffering (19,236), because uncontrolled pain may have deleterious physical effects (19,237-239), and because persistent pain destroys people's autonomy, dignity, and decision-making capacity (19). Thus, with advocacy groups and physician advocating unlimited opioids, mainly due to politics and emotional issues involved with efforts to improve awareness and treatment of chronic pain, the availability and utilization of opioids has increased dramatically in the past few decades (4).

The frequent and escalating use of opioids in managing chronic non-cancer pain has become a major health care issue in the United States placing a

significant strain on the economy with the majority of patients receiving opioids for chronic pain. This necessitates an increased production of opioids, leading to escalating cost of opioid use, even with normal intake (3-5,19,46,140,232-235). Above all, the additional costs of misuse, abuse, and addiction are incalculable (3,5,14,47-99,126-174,240-247). Finally, comorbidities including psychological and physical conditions and numerous other risk factors are common in chronic pain and add significant complexities to the physician managing these patients (175,176,248-260).

Several published guidelines and consensus statements recommend the judicious use of opioids in appropriately selected patients with chronic non-cancer pain who have not responded to other treatments and analgesic medications (3,5,13,19,46,140,232-235,260-262). However, serious issues remain along with uncertainty about the optimal use of opioids for chronic non-cancer pain. The adverse effects, lack of functional status improvement, excessive use, abuse, and diversion are common issues with opioid administration (3,5,19,46,140,232-235).

4.1 Escalating Therapeutic Opioid Use

In a large US survey, the proportion of office visits for chronic musculoskeletal pain in which opioids were prescribed doubled from 8% in 1980 to 16% in 2000 (15). Over the same 2 decades, the proportion of office visits in which prescriptions for potent opioids were given increased from 2% to 9% with usage of more potent opioids such as morphine, hydromorphone, oxycodone, and fentanyl increasing. In a study of commercial and medicaid insurance plans from 2000 to 2005, Sullivan et al (17) evaluated trends in opioid therapy for chronic non-cancer pain into different types of populations – national and commercially insured population, and state-based and publicly-insured (Arkansas Medicaid) population — over a 6-year period. The results showed that the proportion of the enrollees receiving the diagnosis of chronic non-cancer pain increased 33% in the health care population and 9% in the medicaid population, along with a proportion of enrollees with chronic pain who received opioids in 58% of HealthCore and 29% of medicaid. Cumulative yearly opioid dose (in mg morphine equivalents) received by chronic pain patients treated with opioids increased 38% in HealthCore and 37% in medicaid due to increase in number of days supplied rather than dose/day supplied. Use of short-acting Schedule II opioid increased most rapidly, in both

groups 54% versus 38% and in cumulative over year dosage of 95% in HealthCore and 191% in medicaid. However, these trends have occurred without any significant change in the underlying population prevalence of chronic pain or new evidence of the efficacy of long-term opioid therapy. Consequently, the authors concluded that this phenomenon likely represents a broad-based shift in opioid treatment philosophy. In another study, Boudreau et al (16) evaluated trends in long-term opioid therapy for chronic non-cancer pain in adult enrollees for 2 health plans serving over 1% of the US population from 1997 to 2005. Over the study period, incident long-term use increased from 8.5 to 12.1 per 100,000 in group health (6%) percent change in rates annualized (PCA), and 6.3 to 8.6 per 100,000 at Kaiser Permanente of Northern California (5.5% PCA). Prevalent long-term use doubled from 23.9 to 46.5 per 1,000 at group health (8.5% PCA), and 21.5 to 39.2 per 1,000 at Kaiser Permanente (8.1% PCA). Non-Schedule II opioids were the most commonly used opioid among patients engaged in long-term opioid therapy, particularly at Kaiser Permanente. Long-term use of Schedule II opioids also increased substantially at both health plans. They also showed that among prevalent long-term users in 2005, 28.6% at group health and 30.2% at Kaiser Permanente were also regular users of sedative hypnotics. They concluded that long-term opioid therapy for non-cancer pain is increasingly prevalent, but the benefits and risks associated with such therapy are inadequately understood. Further, concurrent use of opioids and sedative-hypnotics was unexpectedly common and concerning.

Vogt et al (156) evaluated analgesic usage for low back pain and its impact on health care 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 psychogenic pain and low back pain related to orthopedic devices (fusion, etc.).

Luo et al (98) 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.

Dhalla et al (39) showed opioid analgesic prescriptions in Ontario increasing from January 1991 to May 2007 by 29%, from 458 to 591 prescriptions per 1,000 individuals annually. However, the number of oxycodone prescriptions rose more than 850% during the same period, from 23 per 1,000 individuals in 1991 to 197 per 1,000 in 2007. In addition, the prescribing of hydromorphone, fentanyl, and morphine also increased considerably over the same period — even though the total number of prescriptions for these drugs was far lower than that for oxycodone-containing products. By 2006, oxycodone accounted for 32% of the almost 7.2 million prescriptions for opioids dispensed that year. Of the 2.3 million oxycodone prescriptions dispensed in 2006, 28% were for long-acting formulation. In addition, from 2001 to 2007, the average amount of long-acting oxycodone dispensed per prescription increased by 24%, from 1,830 mg to 2,280 mg. Similarly, opioid-related deaths doubled from 13.7 per million in 1991 to 27.2 per million in 2004. The addition of long-acting oxycodone to the drug formulary was associated with a 5-fold increase in oxycodone-related mortality and a 41% increase in overall opioid-related mortality. Further, use of health care services in the month before death was common with 66.4 of them visiting a physician in the month before death and 56.1% had filled a prescription for an opioid in the month before death. The authors (40) suggested that a significant portion of the increase was associated with the addition of long-acting oxycodone to the provincial drug formulary.

4.2 Evidence Synthesis

Multiple systematic reviews have been conducted evaluating the efficacy, effectiveness, side effects, abuse and diversions of opioids (5,18,48,166,170,171,232-235,263-279). However, concrete evidence of the effectiveness and safety of opioids in chronic pain has not been demonstrated. The foundation of the argument for use of opioids is the unique analgesic efficacy of opioids, and based on surveys, case series, occasional open-label follow-up studies, as well as some randomized controlled trials and epidemiological studies, opioid use has escalated in the United States. It is also argued, based on the clinical experience of opioid maintenance treatment for addicts that patients on stable regimens can be fully functional in society, and in the workplace despite their choice use of substances known to effect cognitive function. Nevertheless, the argument to apply the same knowledge and experience to chronic pain patients seems to be reasonable (271-274). In addition,

the early experience with tolerance to the analgesic effects of opioids was treated by dose escalations as a therapeutic maneuver, while the ongoing experience suggests a less rosy state of affairs (19). Recent systematic reviews by Chou et al (5,233-235) and Noble et al (232) yielded useful guidance. Noble et al (232) concluded that many patients discontinue long-term opioid therapy due to adverse events or insufficient pain relief; however, weak evidence suggests that patients were able to continue opioids long-term and experience clinically significant pain relief. The findings with regards to quality life or functional improvement were inconclusive. They also reported many minor adverse events like nausea and headache, but serious adverse events including iatrogenic opioid addiction were rare. In plain language summary, they concluded that proper management of a type of strong pain killer (opioids) in well-selected patients with no history of substance, addiction, or abuse, can lead to long-term pain relief for some patients with a very small risk of developing addiction, abuse, or other serious effects. They however cautioned that the evidence supporting these conclusions is weak, and longer-term studies are needed to identify the patients who are more likely to benefit from treatment. Chou et al (5,233-235), concluded that chronic opioid therapy can be an effective therapy for carefully selected and monitored patients with chronic non-cancer pain. They also reported that opioids are also associated with potentially serious harms, including opioid-related adverse effects and outcomes related to the abuse potential of opioids. Thus, both guidelines or manuscripts recommended opioids in the face of weak evidence and escalating use, abuse, and serious adverse effects, though in a small proportion of patients (4,48-56,61-66).

4.3 Escalating Quantity of Opioids

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 the numerous issues involved (49-70,146,147). Further, it also has been shown that the majority of these patients were on opioids prior to presenting to an interventional pain management setting (49).

The therapeutic use of opioids has exploded in the United States, witnessed by increased sales of hydrocodone by 280% from 1997 to 2007, whereas methadone usage increased 1,293% and oxycodone increased 866% (Table 5). Overall, opioids increased from 50.7 million grams of medication in 1997 to 126.5 million

Therapeutic Use, Abuse, and Nonmedical Use of Opioids: A Ten-Year Perspective

grams of medication in 2007, an increase of 149%. The estimated number of prescriptions filled for controlled substances increased from 222 million in 1994 to 354 million in 2003 (123-125).

The milligram per person use of therapeutic opioids in the US increased from 73.59 milligrams in 1997 to 369.19 milligrams per person in 2007, an increase of 402% (Table 6 and Fig. 11). During the same period the therapeutic use of methadone increased by 1,124%

mg/person, and oxycodone by 899% mg/person. This is also confirmed by the fact that between 1992 and 2003, the population of the United States increased by 13%, whereas, the number of prescriptions written for non-controlled drugs increased by 154%.

4.4 Adverse Consequences

Opioids are associated with some well-known common side effects including nausea, sedation, euphoria,

Table 5. Retail sales of opioid medications (grams of medication) from 1997 to 2007.

Drug	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	% 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%)	7,228,219 (9%)	1293%
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%)	42,977,043 (16%)	866%
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%)	463,340 (8%)	525%
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%)	1,011,028 (12%)	319%
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%)	32,969,527 (10%)	280%
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%)	19,051,426 (9%)	222%
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%)	18,840,329 (0.4%)	-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%)	3,936,179 (-5%)	-32%
Total	50,713,010	56,273,194 (11%)	59,445,465 (6%)	35,962,089.84 (15%)	75,294,939 (11%)	82,874,845 (10%)	92,987,076 (12%)	98,456,163 (6%)	101,251,950 (6%)	115,272,706 (14%)	126,477,091 (10%)	149%

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 Access date: 8/25/2010

Source for 2007 data - <http://www.justice.gov/ndic/pubs33/33775/dlinks.htm>

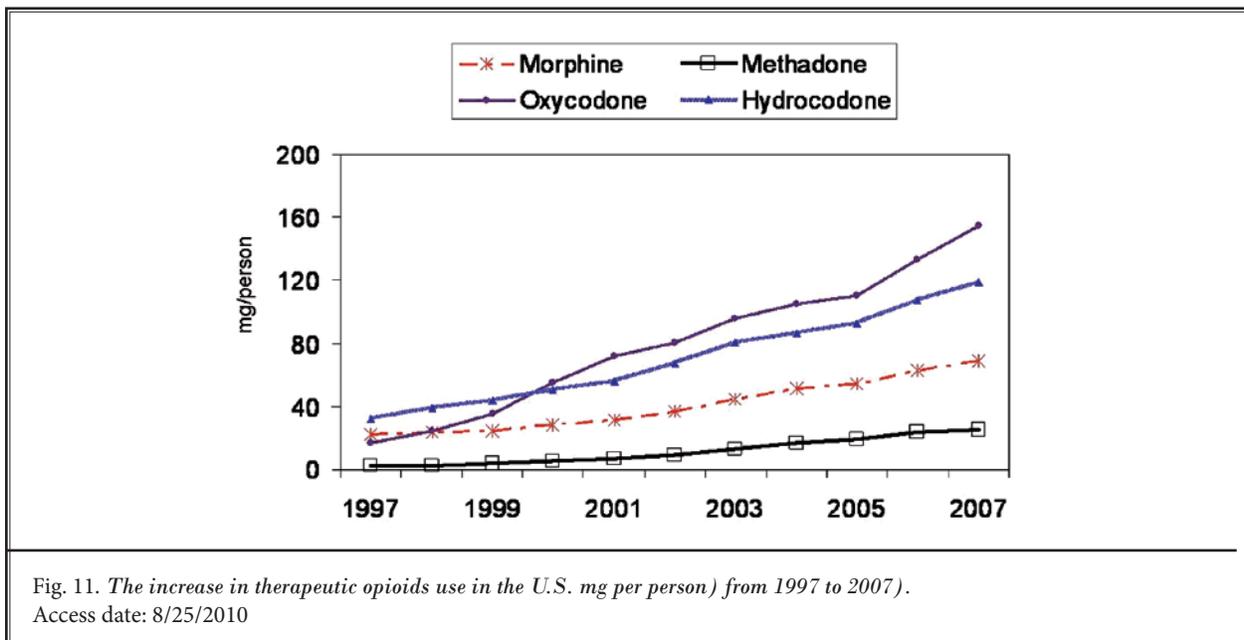
Table 6. The increase in therapeutic opioids use in the U.S. (mg/person) from 1997 to 2007.

Type	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	% of Change from 1997
Methadone	1.94	2.60	3.47	5.14*	6.81	9.54	13.26	17.03	19.31	23.84	25.50	1214%
Oxycodone	16.68	24.66	34.99	55.11	71.75	80.56	95.97	105.05	110.27	133.33	154.73	899%
Fentanyl	0.28	0.34	0.39	0.53*	0.67	0.87	1.14	1.33	1.40	1.54	1.67	496%
Hydrocodone	32.49	38.93	43.57	50.83	56.15	67.77	80.44	86.70	92.90	107.49	118.70	265%
Morphine	22.20	24.01	24.50	28.11	31.72	36.95	44.30	51.55	54.20	63.03	68.59	209%
Total	73.59	90.54	106.92	139.72	167.1	195.69	235.11	261.66	278	329.23	369.19	402%

* 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: 8/25/2010

Source for 2007 data - <http://www.justice.gov/ndic/pubs33/33775/dlinks.htm>



dysphoria, constipation, and itching. However, with chronic use, a different breed of side effects develops, 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 (15,154-157).

Vogt et al (156) 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 (157) 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 (154) 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 (153) indicated that opioid use was associated with greater self-reported disability and poorer function.

Franklin et al (275) studied early opioid prescription and subsequent disability among 18,443 workers with lost work time work-claims with nearly 14% of the sample were receiving work disability compensation at one-year, more than one-third of the worker's received an opioid prescription within 6 weeks, and 50.7% of these received at the first medical visit. Rhee

et al (276) showed in a sample of 13,760 patient with low back pain due to mechanical causes, 45% of the patients used narcotic drugs. Narcotic-use in patients with low back pain had significantly higher rates of comorbid conditions than patients with low back pain not using narcotic drugs including hypertension, arthritis, depression, anxiety, and cancer. Emergency room visits were also higher for patients with narcotics along with health care costs which were approximately 3 times per patients using narcotic drugs compared to those not using them.

An epidemiological study from Denmark (174), where opioids are prescribed liberally for chronic pain, demonstrated worse pain, higher health care 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.

Overall, it appears that epidemiological studies are less positive with regard to function and QOL and report the failure of opioids to improve QOL in chronic pain patients (277). By contrast, Eriksen et al (167) demonstrated worse pain, higher healthcare utilization, and lower activity levels in opioid-treated patients compared with a matched cohort of chronic pain patients not using opioids. Other studies have also shown that instead of improving functional status, opioid use has been associated with increased disability, medical costs,

subsequent surgery, and continued or late opioid use (15,154-157).

Apart from pain relief, functional status improvement and healthcare utilization, another important function when patients are on chronic opioid therapy is driving capability (278,279). Fishbain et al (279) in a structured, evidence-based review of impairment in driving-related skills in opioid-dependent or opioid-tolerant patients, concluded that the majority of the reviewed studies appeared to indicate that opioids do not impair driving-related skills in opioid-dependent or tolerant patients. However, the research was inconclusive in one of the 5 areas relating to the potential impairment in cognitive function of opioid-maintained patients. The research was conclusive that there was no impairment of psychomotor abilities of opioid-maintained patients; no impairment of psychomotor abilities immediately after being given doses of opioids; no greater incidence in motor vehicle violations or motor vehicle accidents versus comparable controls of opioid-maintained patients; and no impairment as measured in driving simulators and on-road driving by opioid-maintained patients. These opinions did not correlate with a narrative review by Strassels (278), indicating that cognitive function can be influenced by the use of opioid analgesics, although the effects vary among drugs.

4.4.1 Complications

Complications due to opioid administration concern all medical practitioners (12,25,27,36,37,42,144,214,280-283). Commonly known side effects of opioids include constipation, pruritus, respiratory depression, nausea, vomiting, delayed gastric emptying, sexual dysfunction (42), muscle rigidity and myoclonus (284,285), sleep disturbance (286), pyrexia, diminished psychomotor performance (278,279), cognitive impairment (287), hyperalgesia (19,42,46,288), dizziness and sedation, all reflecting the effects of opioids on multiple organ systems (44).

Adverse events, in general, appear to fall into 2 broad categories: non-life-threatening and life-threatening. Hydrocodone may cause sensorineural hearing loss due to possible genetic polymorphisms (289). More serious adverse events, such as respiratory depression and death, have been seen with the use of fentanyl buccal tablets for breakthrough pain. Drug deaths from opioids are a serious and increasing issue (25,36,37,144,280,282,283).

Opioids have also been described to have multiple drug interactions. A drug interaction occurs when the

amount or the action of a drug is altered by the administration of another drug or multiple drugs. Multiple hepatic drug interactions may influence opioid drug levels (42,44).

5.0 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.

Along with the increase of prescriptions for controlled drugs from 1992 to 2003 of 154% (151), there was also a 90% increase in the number of people who admitted abusing controlled prescription drugs. Mahowald et al (158) and White et al (290) 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 (10,123). 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.

5.1 Opioid Abuse in Chronic Pain

The central question when prescribing opioids for chronic noncancer pain is how best to balance the risk of opioid abuse with the pain relief provided by these medications (4,10,19,25,36,37,45,46,49,51-55,60,61,63-66,144,164,234,235,280,282,283,291-295). While proponents claim extremely low levels of opioid abuse (296), opioids are by far the most abused drugs, especially in chronic pain management settings (4,12,19,25,36,37,46,144,234,235,280). Numerous investigations have illustrated drug abuse in 18-41% of patients receiving opioids for chronic pain (10,48,49,51-55,60,61,63-66,294,295,297).

Martell et al (48), 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 a 43% current substance use disorder rate. Furthermore, aberrant medication-taking behaviors ranged from 5 to 24%.

Multiple investigators have also studied the issue of illicit drug use in chronic pain patients receiving controlled substances (51,61,63-66,294,295). The results showed that illicit drug use in patients without controlled substance abuse was found in 14–16% of patients and illicit drug use in patients with controlled substance abuse was present in 34% of the patients (51,53,54). Illicit drug use was significant in chronic pain patients in general, but illicit drug use was similar in patients using either long-acting or short-acting opioids (64). In a study on effective monitoring of opiates in chronic pain patients evaluating 111,872 specimens collected over a 1-year time period from pain treatment facilities throughout the USA (294), and in another study evaluating 938,586 specimens, a significant proportion were shown to have abnormal drug testing with nonprescribed medications, illicit drugs and inappropriate intake of drugs (295). In other evaluations, it was shown that adherence monitoring will in fact decrease controlled substance abuse and illicit drug use (61,66).

Along with an increase of prescriptions for controlled drugs from 1992 to 2002 of 154%, there was also a 90% increase in the number of people who admitted abusing controlled prescription drugs. Studies also evaluated opioid abuse in the insured population of the USA (290). Opioid abuse was determined to be present in 6.7–8 per 10,000 persons insured; however, opioid abusers presented with multiple comorbidities and expenses 8-times higher than for nonabusers (US \$15,884 vs. \$1830).

5.2 Drug Diversion

Prescription drug ‘diversion,’ defined as the unlawful channeling of regulated pharmaceuticals from legal sources to the illicit market place, has been a topic of widespread commentary, and is of interest to regulators and providers (298). The abuse of many different prescription drugs has been escalating since the early to mid-1990s (298,299). Diversion can occur in many ways, including the illegal sale of prescriptions by physicians, patients and pharmacists, doctor shopping, forgery, robbery and theft. However, it has been shown that the majority of the drugs come from a single physician’s prescription and that family members share it (4). Inciardi et al (298) described diversion as a disorganized for-profit industry. They described it as ‘disorganized’ because there are so many different players involved in the phenomenon, including physicians, pharmacists and other healthcare

professionals; drug abusers, patients, students, street dealers and white collar criminals; tourists, saloon keepers and all types of service personnel, to name but a few. Federal agencies maintain that the diverted drugs enter the illegal market primarily through ‘doctor shoppers,’ inappropriate prescribing practices by physicians and improper dispensing by pharmacists (298). Inciardi et al (298) in a study of the mechanisms of prescription drug diversion among drug-involved club- and street-based populations, concluded that while doctor shoppers and the internet receive much of the attention regarding diversion, the data showed there are numerous active street markets involving patients, Medicaid recipients and pharmacists as well. They also suggested that the contributions of residential burglaries, pharmacy robberies and thefts and ‘sneak thefts’ to the diversion problem may have been understated.

In an updated manuscript, Inciardi et al (299) described the results of an ultra-rapid assessment of prescription opioid abuse and diversion in an urban community. They reported that the primary sources of prescription drugs on the street were the elderly, patients with pain and doctor shoppers, as well as pill brokers and dealers who work with all of the former. They also described that the popularity of prescription drugs in the street market was rooted in the abusers’ perceptions of these drugs as less stigmatizing, less dangerous and less subject to legal consequences than illicit drugs. Furthermore, they showed that the abuse of prescription opioids also appears to serve as a gateway to heroin use.

6.0 DRUG POISONING AND DEATHS

Unintentional drug poisonings in the United States are common. Unintentional, or accidental, with no harm intended, includes drug overdoses resulting from drug misuse, drug abuse, and taking too much of a drug for medical reasons (300).

6.1 Emergency Department Visits

The Drug Abuse Warning Network (DAWN) publishes results of emergency department visits with drug misuse and abuse. In 2008, DAWN (132) published results with over one million emergency department visits involving an illicit drug.

- ◆ Hydrocodone/combinations in 89,047 emergency department visits,
- ◆ Oxycodone/combinations in 105,208 emergency department visits, and;

- ◆ Methadone in 63,629 emergency department visits.

Emergency department visits for narcotics were 305,885 in 2008 compared to 42,857 in 1995, a 614% increase over a period of 13 years (Fig. 12). Among the psychotherapeutic agents, the anxiolytics (anti-anxiety agents, sedatives, and hypnotics) were the most frequent, occurring in 30% of the visits associated with nonmedical use of pharmaceuticals (132). DAWN estimated that 271,700 emergency department visits were associated with nonmedical use of pharmaceuticals involving benzodiazepines in 2008, compared to 71,609 in 1995, a 279% increase over a period of 13 years (71,132-134).

In 2008, DAWN estimates show that prescription or over-the-counter drugs used nonmedically were involved in 1.0 million emergency department visits, and illicit drugs were involved in 1.0 millions visits (Fig. 13).

6.2 Deaths Due to Opioids

Drug overdose death rates have risen steadily in the United States since 1970 as illustrated in Fig 14. In 2007, 27,658 unintentional drug overdose deaths occurred in the United States. Drug overdose deaths

were second only to motor vehicle crash deaths among leading causes of unintentional injury death in 2007 in the United States. Consequently, rates have increased roughly 5-fold since 1990. Age-adjusted rates of drug overdose deaths for whites have exceeded those among African-Americans since 2003. It has been stated that increasing drug overdose death rates is largely because of prescription opioid painkillers. In 2007, the number of deaths involving opioid analgesics was 9.3 times the number involving cocaine and 5.38 times the number involving heroin. Figure 15 illustrates unintentional drug overdose deaths by major type of drug in the United States from 1999 to 2007. It has been reported that these deaths are secondary to an unusual increase of prescription opioids during the last 20 years which has been over 10-fold because of a movement toward more aggressive management of pain.

Significant regional variations also have been reported in relations to overall drug overdose death rates. It has been shown that states in the Appalachian region and the Southwest have the highest death rates (Fig. 16). The highest drug overdose death rates was found in West Virginia, which was nearly 7 times that of state with the lowest drug overdose death rate, South Dakota. In 2007,

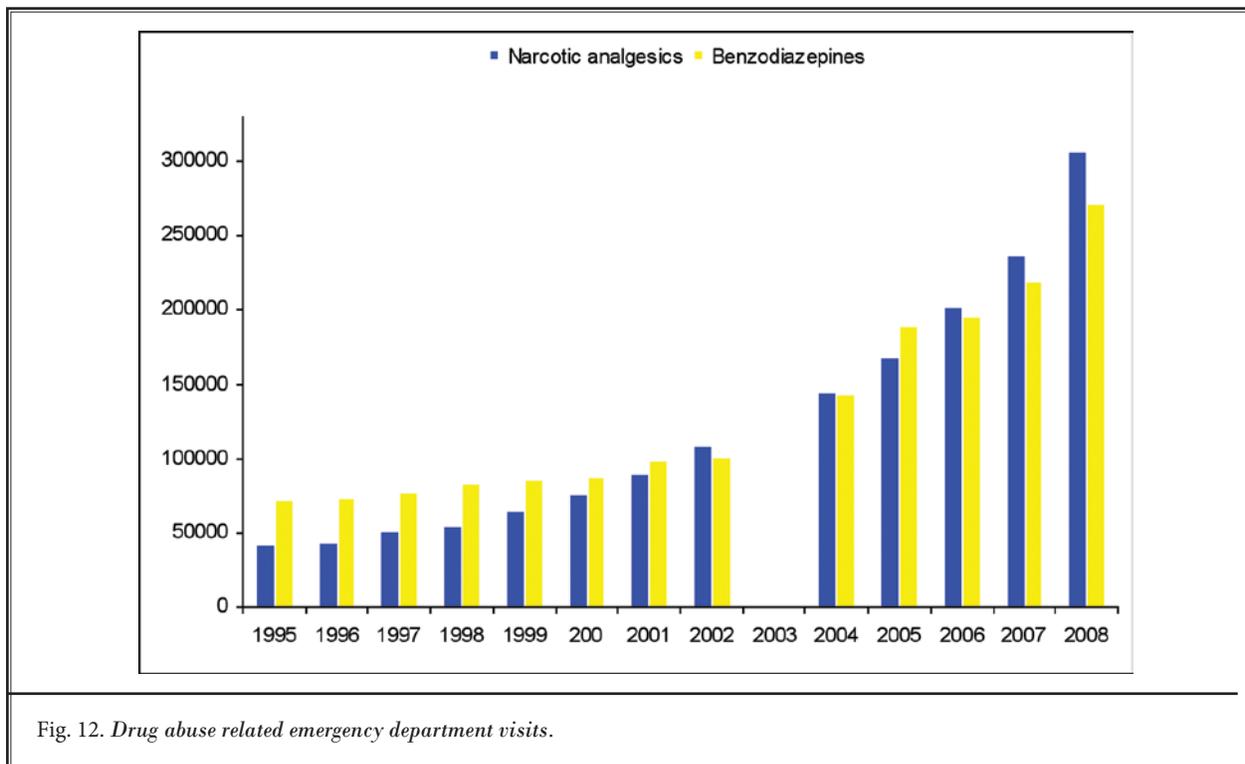


Fig. 12. Drug abuse related emergency department visits.

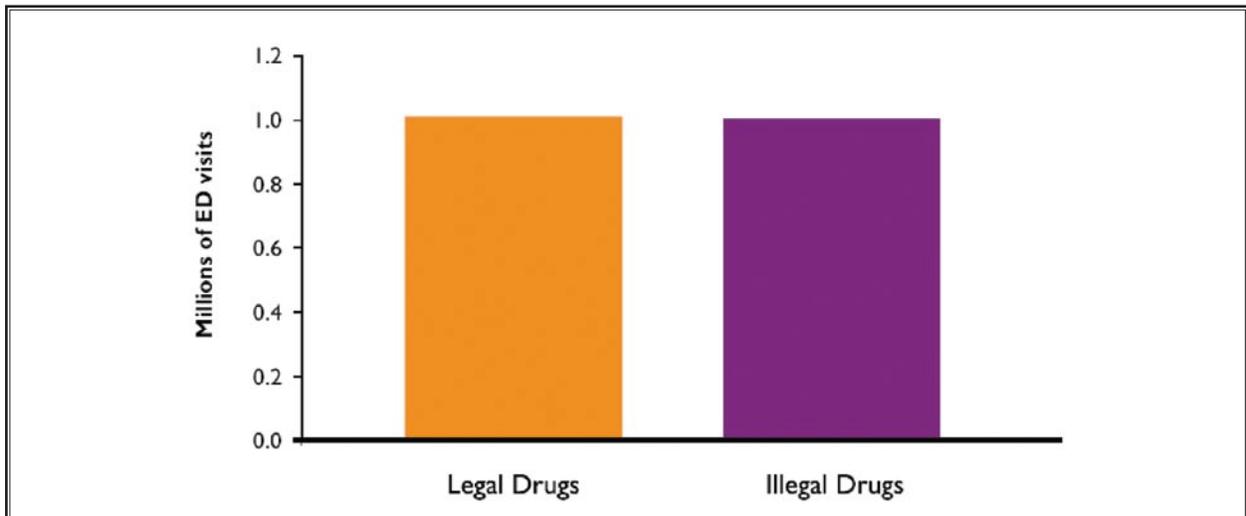


Fig. 13. *Estimated numbers of emergency department visits involving legal drugs used nonmedically and illegal drugs, United States, 2008.*
 Source: Drug Abuse Warning Network.

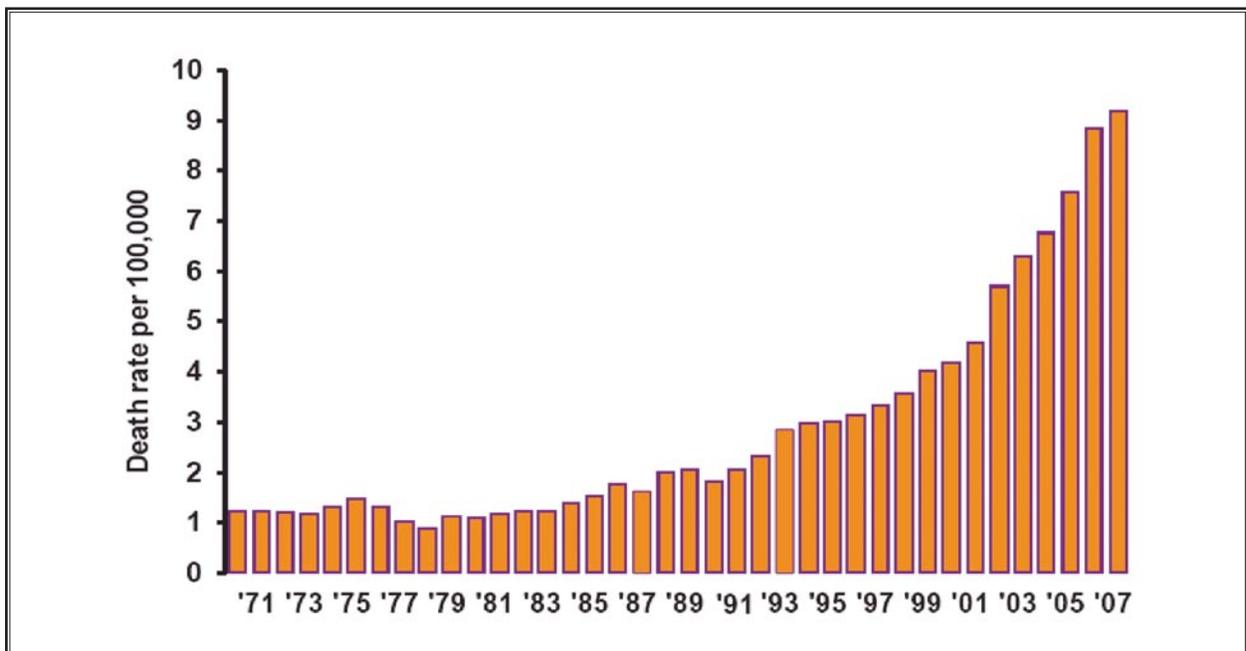
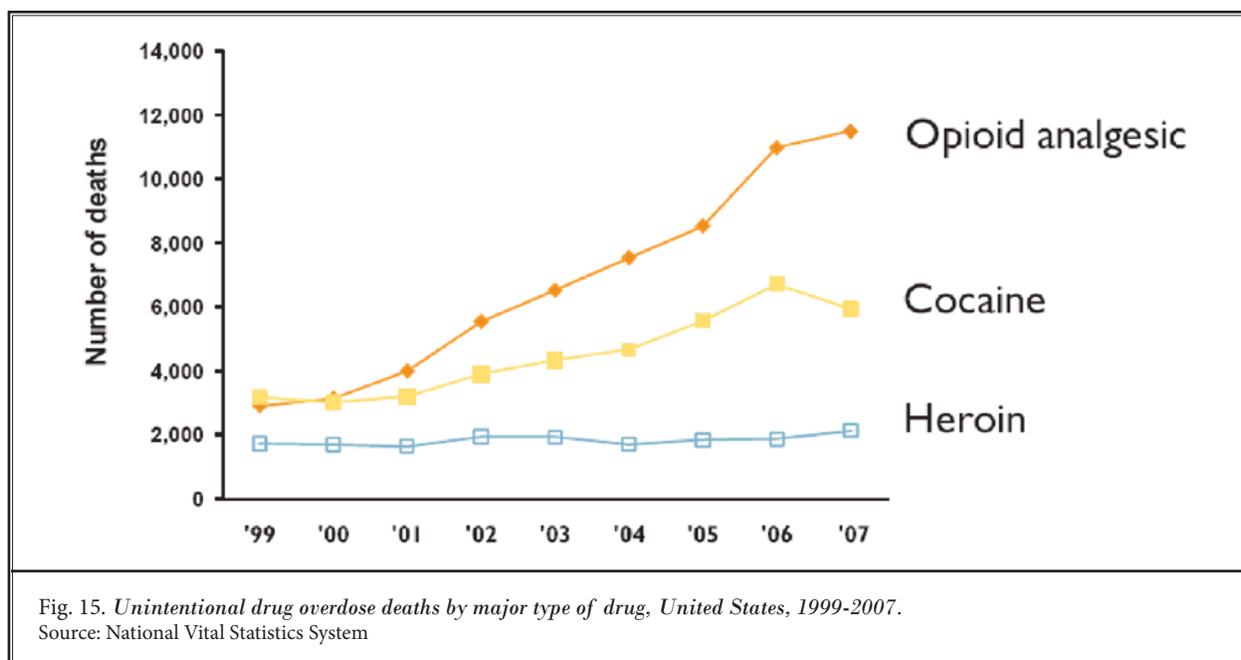


Fig. 14. *Rate of unintentional drug overdose deaths in the United States, 1970-2007.*
 Source: National Vital Statistics System

states such as California and New York had some of the lowest overall death rates among all states because of low opioid overdose rates. In contrast, in the early 1990's these states had some of the highest overall rates, largely because of high heroin and cocaine overdose rates.

It also has been demonstrated that men and middle aged people are more likely to die from drug overdosage. In 2007, 18,029 drug overdose deaths occurred among males and 9,626 among females (Fig. 17). Essentially, male rates have doubled and female rates



have tripled since 1999. In general, it has been stated that men have historically had higher rates of substance abuse than women.

Further, for both sexes, the highest rates were in the 45 to 54 years old age group with rates declining dramatically after the age of 54. Finally, after age 64, the male and female rates become comparable, probably as a result of the reduction of the rates of substance abuse with age.

6.3 Methadone Deaths

As previously indicated, the 2007 DAWN results (132) found methadone to be the number 3 opioid related to emergency room visits, causing 63,629 visits. Of greater concern is the shocking increase in methadone-related deaths.

Until the late 1990s, methadone was predominantly used for the management of heroin addiction. In 2006, with 4 million methadone prescriptions written for pain relief, and steady increases since then, it has become one of the most widely prescribed opioid painkillers (301). Table 7 illustrates this fact by comparing the alarmingly steady increase in methadone distribution activity (33). This table shows that the 2002-2007 distribution of methadone by business categories associated with pain management such as pharmacies, hospitals and practitioners, almost tripled, rising from about 2.3 million grams to about 6.5 million grams (33).

In November 2008, the Methadone Mortality Work Group of the Office of Diversion Control, Drug Enforcement Administration showed that from 2000 to 2005 methadone ranked at the top in percent of increase in the cause of poisoning deaths in the United States and has shown a dramatic percentage of increase over all other causes of poisoning deaths over this time period. This coincides with the Centers for Disease Control (CDC) report of the number of poisoning deaths involving methadone increasing from 790 in 1999 to 5,420 in 2006.

According to Nicholas Reuter, a public health analyst (301), the increasing use of methadone also coincides with concern over the abuse potential of OxyContin and the search for a relatively inexpensive long-acting opioid pain-killer alternative. Reuter's data indicates that only one-third of all methadone prescriptions in 2008 were for treatment of drug addiction. There is a danger in this differential usage of methadone as it is able to suppress withdrawal symptoms for 24 hours, but is only effective as a painkiller for 4-8 hours. It can stay in the system for as long as 59 hours and pain patients may inadvertently overdose by taking the methadone too often or at excessive dosages allowing for the build-up of toxic levels and possible life-threatening changes in respiratory and cardiac function (301).

Another complicating issue is that methadone has unique pharmacological properties that many physician and consumers are unaware of especially as it enters

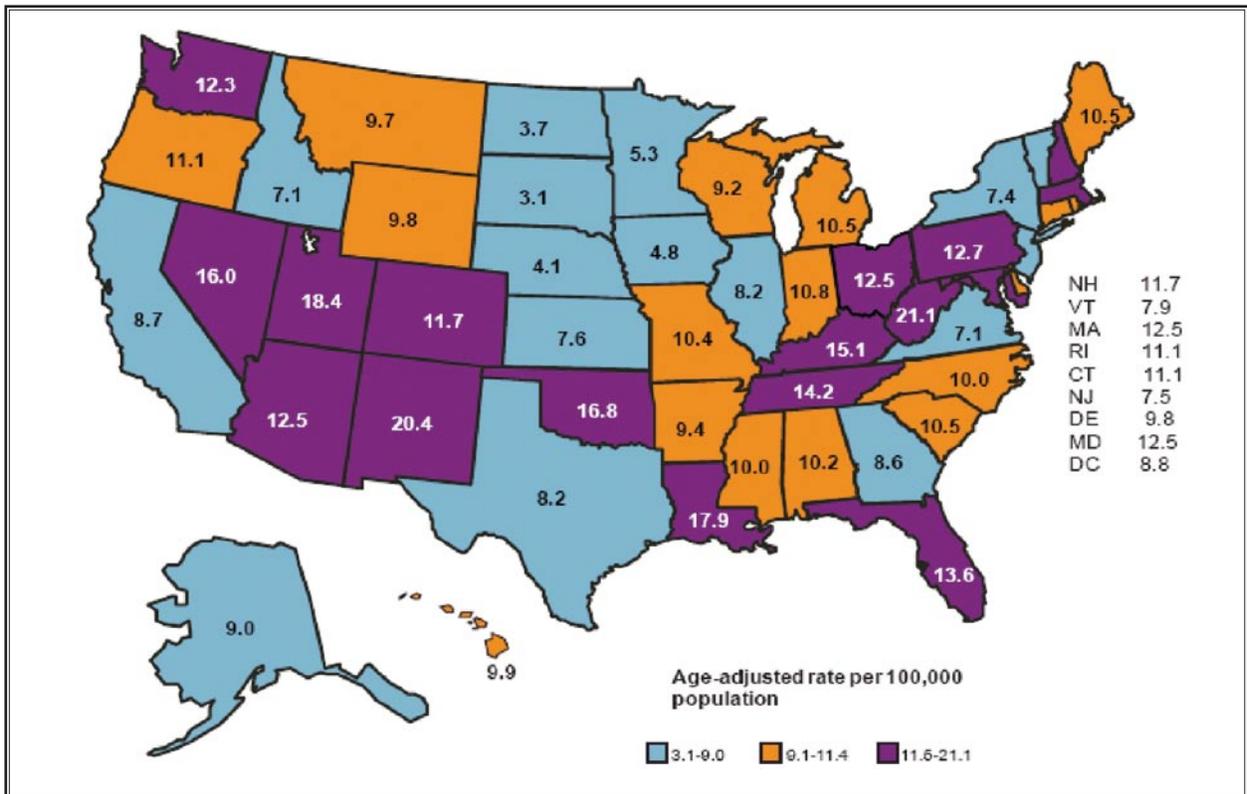


Fig. 16. Drug overdose death rates by states, 2007.
Source: National Vital Statistics System

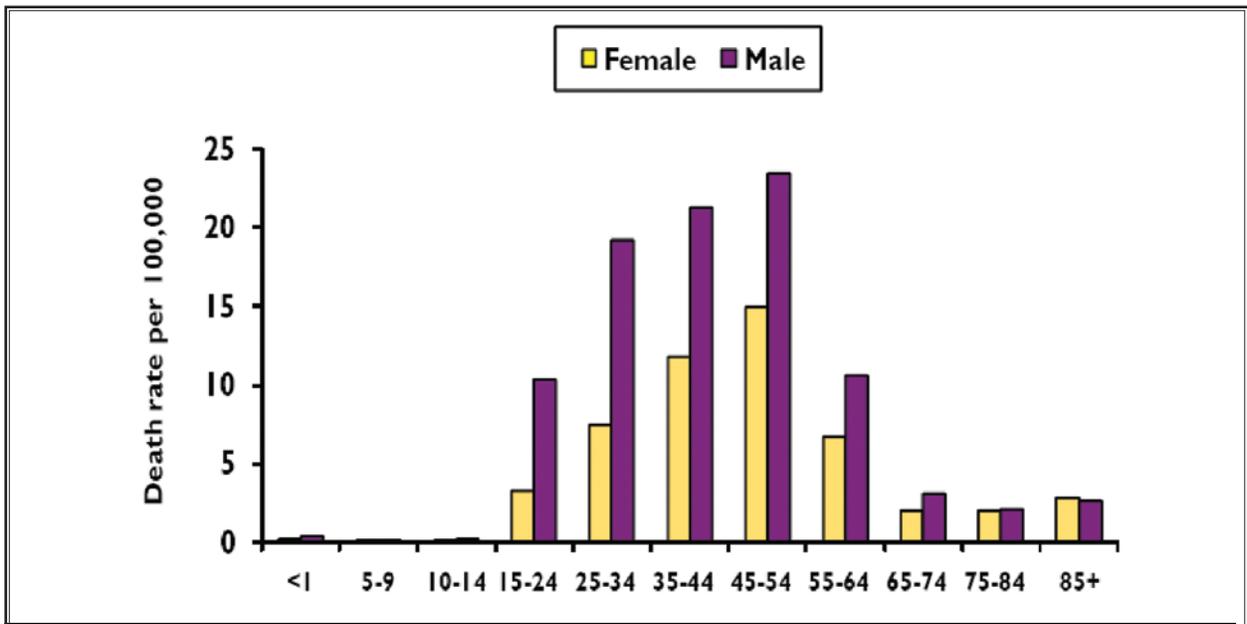


Fig. 17. Unintentional drug overdose death rates by sex and age group, United States, 2007.
Source: National Vital Statistics System

Table 7. Methadone Distribution by Type of Business, 2002 to 2007

	2002	2003	2004	2005	2006	2007
OTPS	5,262,052	5,743,272	6,584,721	6,892,025	7,345,623	6,451,288
Hospitals ^a	309,315	393,685	466,352	521,216	584,144	590,649
Pharmacies	2,329,083	3,274,331	4,246,007	4,863,736	5,986,488	6,442,516
Other practitioners ^b	10,381	15,113	35,492	43,260	51,046	49,503

Source: GAO analysis of DEA methadone distribution data. GA-09-341

Notes: Methadone distribution numbers are in grams. Prior to 2002 DEA's methadone distribution data did not track sales to OTPs, therefore, data prior to 2002 is not included.

^aDEA reports that in hospitals methadone may be dispensed or administered for pain management. Hospitals may also dispense or administer methadone for addiction treatment when patients are admitted to the hospital for another condition but require treatment for opiate addiction during their stay.

^bIn addition to issuing prescriptions for controlled substances that patients can have filled in retail pharmacies, appropriately licensed practitioners may also dispense controlled substances directly to patients. DEA officials said that while practitioners may dispense methadone directly in their offices for pain management purposes, it is not a common practice. Officials did not have information on the specific types of practitioners who are dispensing methadone directly.

into the world of street abuse (301). Both professional continuing education and public service announcements are focused on this in order to ameliorate this problem, which also includes ignorance about the lethal potential of mixing methadone with benzodiazepines. At least one-half of all reported opioid-related deaths involved other drugs such as heroin or cocaine in 15% of cases and benzodiazepines such as Xanax or Valium in 17% of cases (301). CDC's National Center for Health Statistics reports mortality rates, but they are derived from death certificates and there are no current estimates of whether these deaths were the result of legally prescribed drugs or not (301). We can be certain, however, that based on all of the other evidence and indicators that a significant proportion of these deaths were due to illicit drug use, abuse, misuse, or illegal diversion.

The picture that emerges from the available data clearly indicates that methadone is not simply a benign management tool for the treatment of drug addiction nor is it any less benign in its role as a painkiller. The current age demographics show an increasing danger for younger age groups with an 11-fold increase in the 15-24 year age group (301), especially when used in conjunction with benzodiazepines and/or alcohol. Its potential for diversion is, to some degree, compromised by the huge utilization in narcotic treatment programs, a group already prone to habits of diversion, abuse, and experimentation. What is also clear is that 73-79% of the deaths are unintentional (301) and with increased professional education, public education and pro-active programs such as the National All Schedules Prescription Electronic Reporting (NASPER) legislation are to some extent preventable.

6.4 Deaths in Interventional Pain Management Practices

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

From March 2003 to February 2007, Manchikanti et al (27) evaluated 2,179 patients were receiving opioids in 2003, 2,445 in 2004, 2,804 in 2005, and 2,965 in 2006.

There were a total of 91 deaths, of which 60 were categorized as natural deaths, 25 were characterized as accidental deaths, and 6 were characterized as suicidal. Of the 18 drug poisoning deaths, 5 deaths were positively related to prescription drugs, 7 deaths were probably related to prescription drugs, and 6 deaths had no relation to the prescription drugs provided.

They concluded that, in an interventional pain management practice (a tertiary referral center), the total prevalence of opioid related deaths varied from 0.46 to 1.78 per 1,000 from 2003 to 2006 with a total of 12 deaths over a period of 4 years. The deaths definitely related to opioid prescriptions were 5 with a rate of 0 to 1.43 per 1,000 over a period of 4 years.

CONCLUSIONS

What emerges from the available data utilized in this review is the conclusion that over the past 10 years there has been an escalation of the therapeutic use of opioids and other psychotherapeutics and of their abuse and nonmedical use as well. As a consequence of the fact that hydrocodone has become the number one prescribed medication in America, it is not difficult to see the significant impact that this has had on the overall patterns of abuse and nonmedical use, particularly since

the illicit use of prescribed psychotherapeutics (including opioids, which are currently at the top of that list) now overshadows the use of nonprescription illicit drugs. Drug dealers are no longer the primary source of illicit drugs. Our greatest enemy now is diversion through family and friends and their source is more likely to be from 1 physician and not from doctor shopping.

We must also consider the highly interactive pattern of effect and impact that exists in the general areas of substance abuse, mental health, and overall healthcare. Due to the close interrelationship between mental disorders and substance abuse, "dual diagnosis" is becoming more prevalent. This begs the age-old question of which comes first, the chicken-or-the-egg? We will probably never know.

We are clearly left with the challenge to be aware of the difficulties presented by our increased reliance on the use of therapeutic opioids to treat chronic and acute pain and to remember the physician's dictum: Do no harm. Because of the alarming patterns described in this article we are required as physicians to become more diligent in our efforts to ensure proper prescrip-

tion and utilization of therapeutic opioids and to investigate in more depth the real therapeutic advantages of opioid use, especially for chronic pain. We need to be sensitive to our responsibilities in mitigating these problems and to ask ourselves whether we need to be more conservative in our therapeutic use of opioids. We are challenged to invent newer strategies for the prevention of diversion among which perhaps the greatest would be the proactive education of our patients, their families, our congressional representatives and the general public of the limitations of therapeutic use, and the dangers of abuse and nonmedical use of opioids. There is an urgency created by this alarming trend that requires our immediate attention and it behooves us to take action now.

ACKNOWLEDGEMENTS

The authors wish to thank Sekar Edem for assistance in the search of the literature, Tom Prigge for manuscript review, and Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript.

REFERENCES

1. Federation of State Medical Boards of the US. Model guidelines for the use of controlled substances for the treatment of pain: A policy document of the Federation of State Medical Boards of the United States, Inc., Dallas, TX 1998.
2. Phillips DM. JCAHO pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations. *JAMA* 2000; 284:428-429.
3. Trescot AM, Helm S, Hansen H, Benjamin R, Glaser SE, Adlaka R, Patel S, Manchikanti L. Opioids in the management of chronic non-cancer pain: An update of American Society of the Interventional Pain Physicians' (ASIPP) guidelines. *Pain Physician* 2008; 11:S5-S62.
4. Manchikanti L, Singh A. Therapeutic opioids: A ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 2008; 11: S63-S88.
5. Chou R, Huffman L. *Use of Chronic Opioid Therapy in Chronic Non-cancer Pain: Evidence Review*. American Pain Society; Glenview, IL: 2009.
6. Hill CS. Government regulatory influences on opioid prescribing and their impact on the treatment of pain of non-malignant origin. *J Pain Symptom Manage* 1996; 11:287-298.
7. Lamberg L. New guidelines on managing chronic pain in older persons. *JAMA* 1998; 280:311.
8. Melzack R. The tragedy of needless pain. *Sci Am* 1990; 262:27-33.
9. Franklin GM, Rahman EA, Turner JA, Danielle WE, Fulton-Kehoe D. Opioid use for chronic low back pain. A prospective, population-based study among injured workers in Washington state, 2002-2005. *Clin J Pain* 2009; 25:743-751.
10. Manchikanti L. National drug control policy and prescription drug abuse: Facts and fallacies. *Pain Physician* 2007; 10:399-424.
11. Califano JA. *High Society: How Substance Abuse Ravages America and What to Do About It*. Perseus Publishing, New York, 2007.
12. Kuehn BM. Opioid prescriptions soar: http://www.ampainsoc.org/pub/pdf/Opioid_Final_Evidence_Report.pdf
13. increase in legitimate use as well as abuse. *JAMA* 2007; 297:249-251.
14. The American Academy of Pain Medicine, the American Pain Society. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain* 1997; 13:6-8.
15. United Nations Office on Drugs and Crime. 2007 World Drug Report.
16. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 versus 2000. *Pain* 2004; 109:514-519.
17. Boudreau D, Von Korff M, Rutter CM, Saunders K, Ray GT, Sullivan MD, Campbell CI, Merrill JO, Silverberg MJ, Banta-Green C, Weisner C. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiol Drug Saf* 2009; 18:1166-1175.
18. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000-2005 in commercial and Medicaid insurance plans: The

- TROUP study. *Pain* 2008; 138:440-449.
18. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: Report of 38 cases. *Pain* 1986; 25:171-186.
 19. Ballantyne JC. Opioid analgesia: Perspectives on right use and utility. *Pain Physician* 2007; 10:479-491.
 20. Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: A systematic review and literature synthesis. *Clin J Pain* 2008; 24:497-508.
 21. Angst MS, Clark JD. Opioid-induced hyperalgesia: A qualitative systematic review. *Anesthesiology* 2006; 104:570-587.
 22. Abs R, Verhelst J, Maeyaert J, Van Buyten JP, Opsomer F, Adriaensen H, Verlooy J, Van Havenbergh T, Smet M, Van Acker K. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab* 2000; 85:2215-2222.
 23. Bernstein D, Stowell AW, Haggard R, Worzer W, Polatin PB, Gatchel RJ. Complex interplay of participants in opioid therapy. *Pract Pain Manage* 2007; 7:10-36.
 24. Robinson RC, Gatchel RJ, Polatin P, Deschner M, Noe C, Gajraj N. Screening for problematic prescription opioid use. *Clin J Pain* 2001; 17:220-228.
 25. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, Crosby AE, Paulozzi LJ. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA* 2008; 300:2613-2620.
 26. Paulozzi LJ, Ryan GW. Opioid analgesics and rates of fatal drug poisoning in the United States. *Am J Prev Med* 2006; 31:506-511.
 27. Manchikanti KN, Manchikanti L, Damron KS, Pampati V, Fellows B. Increasing deaths from opioid analgesics in the United States: An evaluation in an interventional pain management practice. *J Opioid Manage* 2008; 4:271-283.
 28. Paulozzi L. Unintentional poisoning deaths — United States, 1999 – 2004. Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep* 2007; 56:93-96. www.cdc.gov/mmwr/preview/mmwrhtml/mm5605a1.htm
 29. U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment, Division of Pharmacologic Therapies. Methadone-Associated Mortality: Report of a National Assessment. dpt.samhsa.gov/reports/index.htm
 30. Fingerhut LA. Increases in methadone related deaths: 1999 – 2004. Health EStats. Hyattsville, MD: National Center for Health Statistics; 2006. www.cdc.gov/nchs/products/pubs/pubd/hestats/methadone1999-04/methadone1999-04.htm
 31. Centers for Disease Control and Prevention (CDC). Unintentional and undetermined poisoning deaths — 11 states, 1990 – 2001. *MMWR Morb Mortal Wkly Rep* 2004; 53:233-238.
 32. Hughes AA, Bogdan GM, Dart RC. Active surveillance of abused and misused prescription opioids using poison center data: A pilot study and descriptive comparison. *Clin Toxicol (Phila)* 2007; 45:144-151.
 33. Methadone Mortality Working Group Drug Enforcement Administration, Office of Diversion Control, April 2007. www.deadiversion.usdoj.gov/drugs_concern/methadone/methadone_presentation0407_revised.pdf
 34. US Department of Health and Human Services. Substance Abuse and Mental Health Services Administration (SAMHSA). Background Information for Methadone Mortality — A Reassessment. Sponsored by the Center for Substance Abuse Treatment, Substance Abuse, and Mental Health Services Administration. Washington, DC. July 20, 2007.
 35. GAO Report. United States General Accounting Office. *Prescription Drugs. OxyContin Abuse and Diversion and Efforts to Address the Problem*. GAO Publication No. GAO-4-110, December 2003.
 36. Warner M, Chen LJ, Makuc DM. Increase in fatal poisonings involving opioid analgesics in the United States, 1999--2006. NCHS data brief, no 22. Hyattsville, MD: National Center for Health Statistics; 2009.
 37. Centers for Disease Control and Prevention (CDC). Overdose deaths involving prescription opioids among Medicaid enrollees - Washington, 2004-2007. *MMWR Morb Mortal Wkly Rep* 2009; 58:1171-1175.
 38. Paulozzi LJ, Logan JE, Hall AJ, McKinstry E, Kaplan JA, Crosby AE. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. *Addiction* 2009; 104:1541-1548.
 39. Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ* 2009; 181:891-896.
 40. Toblin RL, Paulozzi LJ, Logan JE, Hall AJ, Kaplan JA. Mental illness and psychotropic drug use among prescription drug overdose deaths: A medical examiner chart review. *J Clin Psychiatry* 2010; 71(4):491-496.
 41. Smith HS, Deer TR, Staats PS, Singh V, Sehgal N, Cordner H. Intrathecal drug delivery. *Pain Physician* 2008; 11:S89-S104.
 42. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R. Opioid complications and side effects. *Pain Physician* 2008; 11:S105-S120.
 43. Smith H. Peripherally-acting opioids. *Pain Physician* 2008; 11:S121-S132.
 44. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain Physician* 2008; 11:S133-S154.
 45. Manchikanti L, Atluri S, Trescot AM, Giordano J. Monitoring opioid adherence in chronic pain patients: Tools, techniques and utility. *Pain Physician* 2008; 11:S155-S180.
 46. Trescot AM, Datta S, Glaser S, Sehgal N, Hansen H, Benyamin R, Patel S. Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician* 2008; 11:S181-S200.
 47. Smith HS. Opioid-related issues “popping” up again. *Pain Physician* 2008; 11:S1-S4.
 48. Martell BA, O'Connor PG, Kerns RD, Beck WC, Morales KH, Kosten TR, Fjell DA. Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. *Ann Intern Med* 2007; 146:116-127.
 49. Manchikanti L, Damron KS, McManus CD, Barnhill RC. Patterns of illicit drug use and opioid abuse in patients with chronic pain at initial evaluation: A prospective, observational study. *Pain Physician* 2004; 7:431-437.
 50. Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain* 1992; 8:77-85.
 51. Manchikanti L, Pampati V, Damron KS,

- Beyer CD, Barnhill RC, Fellows B. Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. *J KY Med Assoc* 2003; 101:511-517.
52. Manchikanti L, Damron KS, Pampati V, McManus CD. Prevalence of illicit drug use among individuals with chronic pain in the Commonwealth of Kentucky: An evaluation of patterns and trends. *J Ky Med Assoc* 2005; 103:55-62.
 53. Manchikanti L, Damron KS, Beyer CD, Pampati V. A comparative evaluation of illicit drug use in patients with or without controlled substance abuse in interventional pain management. *Pain Physician* 2003; 6:281-285.
 54. Manchikanti L, Pampati V, Damron KS, Beyer CD, Barnhill RC. Prevalence of illicit drug use in patients without controlled substance abuse in interventional pain management. *Pain Physician* 2003; 6:173-178.
 55. Manchikanti L, Manchukonda R, Pampati V, Damron KS, Brandon DE, Cash KA, McManus CD. Does random urine drug testing reduce illicit drug use in chronic pain patients receiving opioids? *Pain Physician* 2006; 9:123-129.
 56. Vaglianti RM, Huber SJ, Noel KR, Johnstone RE. Misuse of prescribed controlled substances defined by urinalysis. *WV Med J* 2003; 99:67-70.
 57. Katz NP, Sherburne S, Beach M, Rose RJ, Vielguth J, Bradley J, Fanciullo GJ. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. *Anesth Analg* 2003; 97:1097-1102.
 58. Passik SD, Kirsh KL, McDonald MV, Ahn S, Russak SM, Martin L, Rosenfeld B, Breitbart WS, Portenoy RK. A pilot survey of aberrant drug-taking attitudes and behaviors in samples of cancer and AIDS patients. *J Pain Symptom Manage* 2000; 19:274-286.
 59. Michna E, Jamison RN, Pham LD, Ross EL, Nedeljkovic SS, Narang S, Palombi D, Wasan AD. Urine toxicology screening among chronic pain patients on opioid therapy: Frequency and predictability of abnormal findings. *Clin J Pain* 2007; 23:173-179.
 60. Manchikanti L, Damron KS, Pampati V, McManus CD, Weaver SE. Prospective evaluation of patients with increasing opiate needs: Prescription opiate abuse and illicit drug use. *Pain Physician* 2004; 7:339-344.
 61. Manchikanti L, Cash KA, Damron KS, Manchukonda R, Pampati V, McManus CD. Controlled substance abuse and illicit drug use in chronic pain patients: An evaluation of multiple variables. *Pain Physician* 2006; 9:215-226.
 62. Manchikanti L, Giordano J, Fellows B, Manchukonda R, Pampati V. Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients. *J Opioid Manage* 2007; 3:89-100.
 63. Ives TJ, Chelminski PR, Hammett-Stabler CA, Malone RM, Perhac JS, Potisek NM, Shilliday BB, DeWalt DA, Pignone MP. Predictors of opioid misuse in patients with chronic pain: A prospective cohort study. *BMC Health Serv Res* 2006; 6:46.
 64. Manchikanti L, Manchukonda R, Pampati V, Damron KS. Evaluation of abuse of prescription and illicit drugs in chronic pain patients receiving short-acting (hydrocodone) or long-acting (methadone) opioids. *Pain Physician* 2005; 8:257-261.
 65. Manchikanti L, Pampati V, Damron KS, McManus CD. Evaluation of variables in illicit drug use: Does a controlled substance abuse screening tool identify illicit drug use? *Pain Physician* 2004; 7:71-75.
 66. Manchikanti L, Manchukonda R, Damron KS, Brandon D, McManus CD, Cash KA. Does adherence monitoring reduce controlled substance abuse in chronic pain patients? *Pain Physician* 2006; 9:57-60.
 67. Substance Abuse and Mental Health Services Administration, Office of Applied Studies (April 6, 2007). The NS-DUH Report: Patterns and Trends in Nonmedical Prescription Pain Reliever Use: 2002 to 2005. Rockville, MD. <http://oas.samhsa.gov/2k7/pain/pain.htm>
 68. Office of National Drug Control Policy Executive Office of the President. Teens and prescription drugs. An analysis of recent trends on the emerging drug threat. February 2007. www.theantidrug.com/pdfs/TEENS_AND_PRESCRIPTION_DRUGS.pdf
 69. Monitoring the Future (MTF), National Institute on Drug Abuse (NIDA). 2006. www.monitoringthefuture.org/pubs/monographs/overview2006.pdf
 70. Partnership for a Drug-Free America, The Partnership Attitude Tracking Study (PATS): Teens in grades 7 through 12, 2005. May 16, 2006. www.drugfree.org/Files/Full_Teen_Report
 71. Centers for Disease Control and Prevention (CDC). Emergency department visits involving nonmedical use of selected prescription drugs - United States, 2004-2008. *MMWR Morb Mortal Wkly Rep* 2010; 59:705-709.
 72. Pauly V, Frauger E, Pradel V, Rouby F, Berbis J, Natali F, Reggio P, Coudert H, Micallef J, Thirion X. Which indicators can public health authorities use to monitor prescription drug abuse and evaluate the impact of regulatory measures? Controlling high dosage buprenorphine abuse. *Drug Alcohol Depend* 2010; Aug 7. [Epub ahead of print].
 73. Hernandez SH, Nelson LS. Prescription drug abuse: Insight into the epidemic. *Clin Pharmacol Ther* 2010; 88:307-317..
 74. Rigg KK, Ibañez GE. Motivations for non-medical prescription drug use: A mixed methods analysis. *J Subst Abuse Treat* 2010; Jul 27. [Epub ahead of print]
 75. DuPont RL. Prescription drug abuse: An epidemic dilemma. *J Psychoactive Drugs* 2010; 42:127-132.
 76. Skurtveit S, Furu K, Bramness J, Selmer R, Tverdal A. Benzodiazepines predict use of opioids--a follow-up study of 17,074 men and women. *Pain Med* 2010; 11:805-814.
 77. Back SE, Payne RL, Simpson AN, Brady KT. Gender and prescription opioids: Findings from the National Survey on Drug Use and Health. *Addict Behav* 2010; 35:1001-1007.
 78. Fenton MC, Keyes KM, Martins SS, Hasin DS. The Role of a Prescription in Anxiety Medication Use, Abuse, and Dependence. *Am J Psychiatry* 2010; Aug 4. [Epub ahead of print].
 79. Wu LT, Woody GE, Yang C, Blazer DG. Subtypes of nonmedical opioid users: Results from the national epidemiologic survey on alcohol and related conditions. *Drug Alcohol Depend* 2010; Jun 24. [Epub ahead of print].
 80. Hall MT, Howard MO, McCabe SE. Subtypes of adolescent sedative/anticholinergic misusers: A latent profile analysis. *Addict Behav*. 2010; 35:882-889.
 81. Bray RM, Pemberton MR, Lane ME, Hourani LL, Mattiko MJ, Babeu LA. Substance use and mental health trends among U.S. military active duty personnel: key findings from the 2008

- DoD Health Behavior Survey. *Mil Med* 2010; 175:390-399.
82. Pradel V, Delga C, Rouby F, Micallef J, Lapeyre-Mestre M. Assessment of abuse potential of benzodiazepines from a prescription database using 'doctor shopping' as an indicator. *CNS Drugs* 2010; 24:611-620.
 83. Heit HA, Gourlay DL. Tackling the difficult problem of prescription opioid misuse. *Ann Intern Med* 2010; 152:747-748.
 84. Starr TD, Rogak LJ, Passik SD. Substance abuse in cancer pain. *Curr Pain Headache Rep* 2010; 14:268-275.
 85. Kornør H, Pedersen W, von Soest T, Rossow I, Bramness JG. Use of benzodiazepines and cannabis in young adults. *Tidsskr Nor Laegeforen* 2010; 130:928-931.
 86. Peralta RL, Steele JL. Nonmedical prescription drug use among US college students at a Midwest university: A partial test of social learning theory. *Subst Use Misuse* 2010; 45:865-887.
 87. Spiller H, Bailey JE, Dart RC, Spiller SS. Investigation of temporal changes of abuse and misuse of prescription opioids. *J Addict Dis* 2010; 29:78-83.
 88. Simmons S. Teens and prescription drugs: A potentially dangerous combination. *Nursing* 2010; 40:42-46.
 89. Carson HJ, Knight LD, Dudley MH, Garg U. A fatality involving an unusual route of fentanyl delivery: Chewing and aspirating the transdermal patch. *Leg Med (Tokyo)* 2010; 12:157-159.
 90. Crofford LJ. Adverse effects of chronic opioid therapy for chronic musculoskeletal pain. *Nat Rev Rheumatol* 2010; 6:191-197.
 91. Palmiere C, Staub C, La Harpe R, Mangin P. Parental substance abuse and accidental death in children. *J Forensic Sci* 2010; 55:819-821.
 92. Hanson K. A pill problem: prescription drug abuse is the fastest growing form of substance abuse. *State Legis* 2010; 36:22-25.
 93. Inciardi JA, Surratt HL, Cicero TJ, Rosenblum A, Ahwah C, Bailey JE, Dart RC, Burke JJ. Prescription drugs purchased through the internet: Who are the end users? *Drug Alcohol Depend* 2010; 110:21-29.
 94. Boyd CJ, Teter CJ, West BT, Morales M, McCabe SE. Non-medical use of prescription analgesics: A three-year national longitudinal study. *J Addict Dis* 2009; 28:232-242.
 95. Monte AA, Mandell T, Wilford BB, Tenynson J, Boyer EW. Diversion of buprenorphine/naloxone coformulated tablets in a region with high prescribing prevalence. *J Addict Dis* 2009; 28:226-231.
 96. Comer SD, Sullivan MA, Vosburg SK, Kowalczyk WJ, Houser J. Abuse liability of oxycodone as a function of pain and drug use history. *Drug Alcohol Depend* 2010; 109:130-138.
 97. Franklin GM, Mai J, Wickizer T, Turner JA, Fulton-Kehoe D, Grant L. Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002. *Am J Ind Med* 2005; 48:91-99.
 98. Luo X, Pietrobon R, Hey L. Patterns and trends in opioid use among individuals with back pain in the United States. *Spine (Phila Pa 1976)* 2004; 29:884-891.
 99. Pletcher MJ, Kertesz SG, Kohn MA, Gonzales R. Trends in opioid prescribing by race/ethnicity for patients seeking care in US emergency departments. *JAMA* 2008; 299:70-78.
 100. Brennan MJ, Stanos S. Strategies to optimize pain management with opioids while minimizing risk of abuse. *PM R* 2010; 2:544-558.
 101. Rodriguez KL, Hanlon JT, Perera S, Jaffe EJ, Sevick MA. A cross-sectional analysis of the prevalence of undertreatment of nonpain symptoms and factors associated with undertreatment in older nursing home hospice/palliative care patients. *Am J Geriatr Pharmacother* 2010; 8:225-232.
 102. Candiotti KA, Gitlin MC. Review of the effect of opioid-related side effects on the undertreatment of moderate to severe chronic non-cancer pain: tapentadol, a step toward a solution? *Curr Med Res Opin* 2010; 26:1677-1684.
 103. Fairchild A. Under-treatment of cancer pain. *Curr Opin Support Palliat Care* 2010; 4:11-15.
 104. Claxton RN, Blackhall L, Weisbord SD, Holley JL. Undertreatment of symptoms in patients on maintenance hemodialysis. *J Pain Symptom Manage* 2010; 39:211-218.
 105. Edrington J, Sun A, Wong C, Dodd M, Padilla G, Paul S, Miaskowski C. Barriers to pain management in a community sample of Chinese American patients with cancer. *J Pain Symptom Manage* 2009; 37:665-765.
 106. Deandrea S, Montanari M, Moja L, Apollone G. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol* 2008; 19:1985-1991.
 107. Popenhagen MP. Collaborative practice. Undertreatment of pain and fears of addiction in pediatric chronic pain patients: How do we stop the problem? *J Spec Pediatr Nurs* 2006; 11:61-67.
 108. O'Malley P. The undertreatment of pain: ethical and legal implications for the clinical nurse specialist. *Clin Nurse Spec* 2005; 19:236-237.
 109. Stalnikowicz R, Mahamid R, Kaspi S, Brezis M. Undertreatment of acute pain in the emergency department: A challenge. *Int J Qual Health Care* 2005; 17:173-176.
 110. Primm BJ, Perez L, Dennis GC, Benjamin L, Clark W, Keough K, Leak WD, Payne R, Smith D, Sullivan LW; National Medical Association. Managing pain: The challenge in underserved populations: Appropriate use versus abuse and diversion. *J Natl Med Assoc* 2004; 96:1152-1161.
 111. [No authors listed]. Undertreatment of pain litigation. *J Pain Palliat Care Pharmacother* 2003; 17:274-275.
 112. Dahl JL, Bennett ME, Bromley MD, Joranson DE. Success of the state pain initiatives: Moving pain management forward. *Cancer Pract* 2002; 10:S9-S13.
 113. Frank-Stromborg M, Christensen A. A serious look at the undertreatment of pain: Part I. *Clin J Oncol Nurs* 2001; 5:235-236.
 114. Frank-Stromborg M, Christensen A. A serious look at the undertreatment of pain: Part II. *Clin J Oncol Nurs* 2001; 5:276-278.
 115. Cleeland CS. Undertreatment of cancer pain in elderly patients. *JAMA* 1998; 279:1914-1915.
 116. Resnik DB, Rehm M, Minard RB. The undertreatment of pain: Scientific, clinical, cultural, and philosophical factors. *Med Health Care Philos* 2001; 4:277-288.
 117. Sutters KA, Miaskowski C. Inadequate pain management and associated morbidity in children at home after tonsillectomy. *J Pediatr Nurs* 1997; 12:178-185.
 118. Breitbart W, Rosenfeld BD, Passik SD, McDonald MV, Thaler H, Portenoy RK. The undertreatment of pain in ambulatory AIDS patients. *Pain* 1996; 65:243-249.

119. Passik SD, Squire P. Current risk assessment and management paradigms: Snapshots in the life of the pain specialist. *Pain Medicine* 2009; 10: S101-S114.
120. Tsao JC, Stein JA, Dobalian A. Sex differences in pain and misuse of prescription analgesics among persons with HIV. *Pain Medicine* 2010; 11:815-824.
121. Hadjistavropoulos T, Marchildon GP, Fine PG, Herr K, Palley HA, Kaasalainen S, Béland F. Transforming long-term care pain management in North America: The policy-clinical interface. *Pain Medicine* 2009; 10:506-520.
122. Manchikanti L, Whitfield E, Pallone F. Evolution of the National All Schedules Prescription Electronic Reporting Act (NASPER): A public law for balancing treatment of pain and drug abuse and diversion. *Pain Physician* 2005; 8:335-347.
123. Manchikanti L. Prescription drug abuse: What is being done to address this new drug epidemic? Testimony before the Subcommittee on Criminal Justice, Drug Policy, and Human Resources. *Pain Physician* 2006; 9:287-321.
124. www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.htm
125. Testimony of Nora D. Volkow, M.D., Director, National Institute on Drug Abuse, National Institutes of Health, U.S. Department of Health and Human Services, before the Subcommittee on Criminal Justice, Drug Policy, and Human Resources Committee, July 26, 2006.
126. Substance Abuse and Mental Health Services Administration. (2009). *Results from the 2008 National Survey on Drug Use and Health: National Findings* (Office of Applied Studies, NSDUH Series H-36, DHHS Publication No. SMA 09-4434). Rockville, MD. <http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.pdf>
127. Substance Abuse and Mental Health Services Administration (2006). Results from the 2005 National Survey on Drug Use and Health: National Findings. (Office of Applied Studies, NSDUH Series H-30, DHHS Publication No. SMA 06-4194). Rockville, MD. www.oas.samhsa.gov/nsduh/2k5nsduh/2k5Results.pdf
128. Substance Abuse and Mental Health Services Administration (2005). Overview of Findings from the 2004 National Survey on Drug Use and Health. (Office of Applied Studies, NSDUH Series H-27, DHHS Publication No. SMA 05-4061). Rockville, MD. www.oas.samhsa.gov/nsduh/2k4nsduh/2k4Overview.pdf
129. Substance Abuse and Mental Health Services Administration (2004). Overview of Findings from the 2003 National Survey on Drug Use and Health. (Office of Applied Studies, NSDUH Series H-24, DHHS Publication No. SMA 04-3963). Rockville, MD. www.oas.samhsa.gov/NHSDA/2k3NSDUH/2k3OverviewW.pdf
130. Substance Abuse and Mental Health Services Administration (2003). Overview of Findings from the 2002 National Survey on Drug Use and Health. (Office of Applied Studies, NSDUH Series H-21, DHHS Publication No. SMA 03-3774). Rockville, MD. www.oas.samhsa.gov/NHSDA/2k2NSDUH/2k2SoFOverviewW.pdf
131. Substance Abuse and Mental Health Services Administration (2002). Results from the 2001 National Household Survey on Drug Abuse: Volume I. Summary of National Findings. (Office of Applied Studies, NHSDA Series H-17, DHHS Publication No. SMA 02-3758). Rockville, MD. www.oas.samhsa.gov/nhsda/2k1nhsda/PDF/cover.pdf
132. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. (June 18, 2010) The DAWN Report: Trends in Emergency Department Visits Involving Nonmedical Use of Narcotic Pain Relievers. Rockville, MD, 2010. www.oas.samhsa.gov/2k10/DAWN016/OpioidED.htm
133. Drug Abuse Warning Network, 2004: National Estimates of Drug-Related Emergency Department Visits DAWN Series D-28, DHHS Publication No. (SMA) 06-4143, Rockville, MD, April 2006. www.dawninfo.samhsa.gov/pubs/edpubs/default.asp
134. Drug Abuse Warning Network, 2003: Interim National Estimates of Drug-related Emergency Department Visits DAWN Series D-26, DHHS Publication No. (SMA) 04-3972, Rockville, MD, December 2004. www.dawninfo.samhsa.gov/pubs/edpubs/default.asp
135. US Department of Health and Human Services. Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA). Drug Abuse Warning Network. The DAWN Report. Narcotic analgesics, 2002 update. September 2004.
136. US Department of Health and Human Services. Office of Applied Studies, Substance Abuse, and Mental Health Services Administration (SAMHSA). Drug Abuse Warning Network. The DAWN Report. Benzodiazepines in drug abuse-related emergency department visits, 1995-2002. April 2004.
137. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *Drug Abuse Warning Network, 2006: National Estimates of Drug-Related Emergency Department Visits*. DAWN Series D-30, DHHS Publication No. (SMA) 08-4339, Rockville, MD, 2008.
138. Substance Abuse and Mental Health Services Administration. Drug Abuse Warning Network, 2007: Area profiles of drug-related mortality. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2009. HHS publication no. SMA 09-4407. <http://dawninfo.samhsa.gov/pubs/mepubs/>
139. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiol Drug Saf* 2006; 15:618-627.
140. Manchikanti L, Benyamin R, Datta S, Vallejo R, Smith HS. Opioids in chronic non-cancer pain. *Expert Rev Neurother* 2010; 10:775-789
141. Fingerhut LA. Increases in poisoning and methadone-related deaths: United States, 1999-2005. Health E-Stats. National Center for Health Statistics; February 2008. <http://www.cdc.gov/nchs/data/hestat/poisoning/poisoning.pdf>
142. Centers for Disease Control and Prevention (CDC). Prescription drug overdose: State health agencies response (2008). http://www.cdc.gov/HomeandRecreationalSafety/pubs/RXReport_web-a.pdf
143. Centers for Disease Control and Prevention (CDC). Unintentional drug poisoning in the United States. July 2010. <http://www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf>
144. Wunsch MJ, Nakamoto K, Behonick G, Massello W. Opioid deaths in rural Virginia: A description of the high prevalence of accidental fatalities involving prescribed medications. *Am J Addict* 2009; 18:5-14.
145. Centers for Disease Control and Prevention (CDC). Nonpharmaceutical fentanyl-related deaths--multiple states, April 2005-March 2007. *MMWR Morb Mortal Wkly Rep* 2008; 57:793-796.

146. Boyd CJ, McCabe SE, Cranford JA, Young A. Adolescents' motivations to abuse prescription medications. *Pediatrics* 2006; 118:2472-2480.
147. Friedman RA. The changing face of teenage drug abuse — the trend toward prescription drugs. *N Engl J Med* 2006; 354:1448-1450.
148. Bennett DS, Simon S, Brennan M, Shoemaker SA. Prevalence and characteristics of breakthrough pain in patients receiving opioids for chronic back pain in pain specialty clinics. *J Opioid Manage* 2007; 3:101-106.
149. Davstad I, Stenbacka M, Leifman A, Beck O, Korkmaz S, Romelsjo A. Patterns of illicit drug use and retention in a methadone program: A longitudinal study. *J Opioid Manag* 2007; 3:27-34.
150. Havens JR, Oser CB, Leukefeld CG. Increasing prevalence of prescription opiate misuse over time among rural probationers. *J Opioid Manage* 2007; 3:107-112.
151. Kelly A. Accidental overdoses from legal drugs. The Council of State Governments. *State News*, February 2009.
- <http://www.healthstates.csg.org/NR/rdonlyres/3F157E26-8562-4F09-BD45-DFC39D17A918/0/AccidentalOverdoseSNFEB092.pdf>
152. Kell M. Monitoring compliance with OxyContin prescriptions in 14,712 patients treated in 127 outpatient pain centers. *Pain Med* 2005; 6:186-187.
153. Fillingim RB, Doleys DM, Edwards RR, Lowery D. Clinical characteristics of chronic back pain as a function of gender and oral opioid use. *Spine (Phila Pa 1976)* 2003; 28:143-150.
154. Webster BS, Verma SK, Gatchel RJ. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery, and late opioid use. *Spine (Phila Pa 1976)* 2007; 32:2127-2132.
155. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on Problems of Drug Dependence task force on prescription opioid non-medical use and abuse (position statement). *Drug Alcohol Depend* 2003; 69:215-232.
156. Vogt MT, Kwok CK, Cope DK, Osial TA, Culyba M, Starz TW. Analgesic usage for low back pain: Impact on health care costs and service use. *Spine (Phila Pa 1976)* 2005; 30:1075-1081.
157. Mahmud MA, Webster BS, Courtney TK, Matz S, Tacci JA, Christiani DC. Clinical management and the duration of disability for work-related low back pain. *J Occup Environ Med* 2000; 42:1178-1187.
158. Mahowald ML, Singh JA, Majeski P. Opioid use by patients in an orthopedics spine clinic. *Arthritis Rheum* 2005; 52:312-321.
159. Fanciullo GJ, Ball PA, Girault G, Rose RJ, Hanscom B, Weinstein JN. An observational study on the prevalence and pattern of opioid use in 25,479 patients with spine and radicular pain. *Spine (Phila Pa 1976)* 2002; 27:201-205.
160. Polatin PB, Kinney RK, Gatchel RJ, Lillo E, Mayer TG. Psychiatric illness and chronic low-back pain. The mind and the spine—which goes first? *Spine (Phila Pa 1976)* 1993; 18:66-71.
161. Bramley-Moore SR, Wodak AD, Day RO, Lauchlan RL. Patterns of analgesic prescribing for patients with chronic non-malignant pain in NSW. *Aust J Hosp Pharm* 1998; 28:83-88.
162. Ready LB, Sarkis E, Turner JA. Self-reported vs. actual use of medications in chronic pain patients. *Pain* 1982; 12:285-294.
163. Maxwell JC. *Trends in the Abuse of Prescription Drugs*. Gulf Coast ATTC, Austin Treatment, 2006.
164. Wiedemer NL, Harden PS, Arndt IO, Gallagher RM. The opioid renewal clinic: A primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. *Pain Med* 2007; 8:573-584.
165. Bloodworth D. Issues in opioid management. *Am J Phys Med Rehabil* 2005; 84:S42-S55.
166. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic non-cancer pain: A meta-analysis of effectiveness and side effects. *Can Med Assoc J* 2006; 174:1589-1594.
167. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain. An epidemiological study. *Pain* 2006; 125:172-179.
168. Office of Applied Studies (2007). Changes in Prevalence Rates of Drug Use between 2002-2003 and 2004-2005 among states. Rockville, MD: Substance Abuse and Mental Health Administration. www.oas.samhsa.gov/StateChanges/3trends.doc
169. Trescot AM, Boswell MV, Atluri SL, Hansen HC, Deer TR, Abdi S, Jasper JF, Singh V, Jordan AE, Johnson BW, Cicala RS, Dunbar EE, Helm II S, Varley KG, Suchdev PK, Swicegood JR, Calodney AK, Ogoke BA, Minore WS, Manchikanti L. Opioid guidelines in the management of chronic non-cancer pain. *Pain Physician* 2006; 9:1-40.
170. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: A systematic review. *J Pain Symptom Manage* 2003; 26:1026-1048.
171. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain* 2004; 112:372-380.
172. Tripp DA, VanDenKerkhof EG, McAlister M. Prevalence and determinants of pain and pain-related disability in urban and rural settings in southeastern Ontario. *Pain Res Manag* 2006; 11:225-233.
173. Blyth FM. Chronic pain — is it a public health problem? *Pain* 2008; 137:465-466.
174. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *Eur J Pain* 2006; 10:287-333.
175. Manchikanti L, Boswell MV, Singh V, Benyamin RM, Fellows B, Abdi S, Buenaventura RM, Conn A, Datta S, Derby R, Falco FJE, Erhart S, Diwan S, Hayek SM, Helm S, Parr AT, Schultz DM, Smith HS, Wolfer LR, Hirsch JA. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. *Pain Physician* 2009; 12:699-802.
176. Manchikanti L, Singh V, Datta S, Cohen SP, Hirsch JA. Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain Physician* 2009; 12:E35-E70.
177. Eriksen J, Ekholm O, Sjogren P, Rasmussen NK. Development of and recovery from long-term pain. A 6-year follow-up study of a cross-section of the adult Danish population. *Pain* 2004; 108:154-162.
178. Pleis JR, Lethbridge-Çejku M. Summary health statistics for U.S. adults: National Health Interview Survey, 2006. National Center for Health Statistics. *Vital Health Stat* 2007; 10:1-153.
179. Harkness EF, Macfarlane GJ, Silman AJ, McBeth J. Is musculoskeletal pain more common now than 40 years ago?: two population-based cross-sectional studies. *Rheumatology (Oxford)* 2005;

- 44:890-895.
180. Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, Castel LD, Kalsbeek WD, Carey TS. The rising prevalence of chronic low back pain. *Arch Intern Med* 2009; 169:251-258.
 181. Martin BI, Turner JA, Mirza SK, Lee MJ, Comstock BA, Deyo RA. Trends in health care expenditures, utilization, and health status among US adults with spine problems, 1997-2006. *Spine (Phila Pa 1976)* 2009; 34:2077-2084.
 182. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet* 1999; 354:1248-1252.
 183. Atluri S, Datta S, Falco FJE, Lee M. Systematic review of diagnostic utility and therapeutic effectiveness of thoracic facet joint interventions. *Pain Physician* 2008; 11:611-629.
 184. Falco FJE, Erhart S, Wargo BW, Bryce DA, Atluri S, Datta S, Hayek SM. Systematic review of diagnostic utility and therapeutic effectiveness of cervical facet joint interventions. *Pain Physician* 2009; 12:323-344.
 185. Datta S, Lee M, Falco FJE, Bryce DA, Hayek SM. Systematic assessment of diagnostic accuracy and therapeutic utility of lumbar facet joint interventions. *Pain Physician* 2009; 12:437-460.
 186. Conn A, Buenaventura R, Datta S, Abdi S, Diwan S. Systematic review of caudal epidural injections in the management of chronic low back pain. *Pain Physician* 2009; 12:109-135.
 187. Parr AT, Diwan S, Abdi S. Lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain: A systematic review. *Pain Physician* 2009; 12:163-188.
 188. Benyamin RM, Singh V, Parr AT, Conn A, Diwan S, Abdi S. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. *Pain Physician* 2009; 12:137-157.
 189. Buenaventura RM, Datta S, Abdi S, Smith HS. Systematic review of therapeutic lumbar transforaminal epidural steroid injections. *Pain Physician* 2009; 12:233-251.
 190. Epter RS, Helm S, Hayek SM, Benyamin RM, Smith HS, Abdi S. Systematic review of percutaneous adhesiolysis and management of chronic low back pain in post lumbar surgery syndrome. *Pain Physician* 2009; 12:361-378.
 191. Manchikanti L, Glaser S, Wolfer L, Derby R, Cohen SP. Systematic review of lumbar discography as a diagnostic test for chronic low back pain. *Pain Physician* 2009; 12:541-559.
 192. Manchikanti L, Dunbar EE, Wargo BW, Shah RV, Derby R, Cohen SP. Systematic review of cervical discography as a diagnostic test for chronic spinal pain. *Pain Physician* 2009; 12:305-321.
 193. Singh V, Manchikanti L, Shah RV, Dunbar EE, Glaser SE. Systematic review of thoracic discography as a diagnostic test for chronic spinal pain. *Pain Physician* 2008; 11:631-642.
 194. Wolfer L, Derby R, Lee JE, Lee SH. Systematic review of lumbar provocation discography in asymptomatic subjects with a meta-analysis of false-positive rates. *Pain Physician* 2008; 11:513-538.
 195. Hayek SM, Helm S, Benyamin RM, Singh V, Bryce DA, Smith HS. Effectiveness of spinal endoscopic adhesiolysis in post lumbar surgery syndrome: A systematic review. *Pain Physician* 2009; 12:419-435.
 196. Hirsch JA, Singh V, Falco FJE, Benyamin RM, Manchikanti L. Automated percutaneous lumbar discectomy for the contained herniated lumbar disc: A systematic assessment of evidence. *Pain Physician* 2009; 12:601-620.
 197. Singh V, Manchikanti L, Benyamin RM, Helm S, Hirsch JA. Percutaneous lumbar laser disc decompression: A systematic review of current evidence. *Pain Physician* 2009; 12:573-588.
 198. Singh V, Benyamin RM, Datta S, Falco FJE, Helm S, Manchikanti L. Systematic review of percutaneous lumbar mechanical disc decompression utilizing Dekompressor. *Pain Physician* 2009; 12:589-599.
 199. Manchikanti L, Derby R, Benyamin RM, Helm S, Hirsch JA. A systematic review of mechanical lumbar disc decompression with nucleoplasty. *Pain Physician* 2009; 12:561-572.
 200. Helm S, Hayek S, Benyamin RM, Manchikanti L. Systematic review of the effectiveness of thermal annular procedures in treating discogenic low back pain. *Pain Physician* 2009; 12:207-232.
 201. Manchikanti L, Singh V, Helm S, Schultz DM, Datta S, Hirsch J. An introduction to an evidence-based approach to interventional techniques in the management of chronic spinal pain. *Pain Physician* 2009; 12:E1-E33.
 202. Manchikanti L, Boswell MV, Singh V, Derby R, Fellows B, Falco FJE, Datta S, Smith HS, Hirsch JA. Comprehensive review of neurophysiologic basis and diagnostic interventions in managing chronic spinal pain. *Pain Physician* 2009; 12:E71-E120.
 203. Manchikanti L, Boswell MV, Datta S, Fellows B, Abdi S, Singh V, Benyamin RM, Falco FJE, Helm S, Hayek S, Smith HS. Comprehensive review of therapeutic interventions in managing chronic spinal pain. *Pain Physician* 2009; 12:E123-E198.
 204. Manchikanti L, Singh V, Pampati V, Boswell MV, Benyamin RM, Hirsch JA. Description of documentation in the management of chronic spinal pain. *Pain Physician* 2009; 12:E199-E224.
 205. Manchikanti L, Helm S, Singh V, Benyamin RM, Datta S, Hayek S, Fellows B, Boswell MV. An algorithmic approach for clinical management of chronic spinal pain. *Pain Physician* 2009; 12:E225-E264.
 206. Staal JB, de Bie RA, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low back pain: An updated Cochrane review. *Spine (Phila Pa 1976)* 2009; 34:49-59.
 207. Chou R, Huffman L. *Evaluation and Management of Low Back Pain: Evidence Review*. American Pain Society; Glenview, IL: 2009. <http://www.ampainsoc.org/pub/pdf/LBPEvidRev.pdf>
 208. Chou R, Baisden J, Carragee EJ, Resnick DK, Shaffer WO, Loeser JD. Surgery for low back pain: A review of the evidence for an American Pain Society Clinical Practice Guideline. *Spine (Phila Pa 1976)* 2009; 34:1094-1109.
 209. Chou R, Loeser JD, Owens DK, Rosenquist RW, Atlas SJ, Baisden J, Carragee EJ, Grabojs M, Murphy DR, Resnick DK, Stanos SP, Shaffer WO, Wall EM; American Pain Society Low Back Pain Guideline Panel. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: An evidence-based clinical practice guideline from the American Pain Society. *Spine (Phila Pa 1976)* 2009; 34:1066-1077.
 210. Manchikanti L, Cash KA, McManus CD, Pampati V, Singh V, Benyamin RM. The preliminary results of a comparative effectiveness evaluation of adhesiolysis and caudal epidural injections in managing chronic low back pain secondary to spinal stenosis: A randomized,

- equivalence controlled trial. *Pain Physician* 2009; 12:E341-E354.
211. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. A comparative effectiveness evaluation of percutaneous adhesiolysis and epidural steroid injections in managing lumbar post surgery syndrome: A randomized, equivalence controlled trial. *Pain Physician* 2009; 12:E355-E368.
 212. Manchikanti L, Cash KA, McManus CD, Pampati V, Smith HS. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 1. Discogenic pain without disc herniation or radiculitis. *Pain Physician* 2008; 11:785-800.
 213. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 2. Disc herniation and radiculitis. *Pain Physician* 2008; 11:801-815.
 214. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 3. Post surgery syndrome. *Pain Physician* 2008; 11:817-831.
 215. Manchikanti L, Cash KA, McManus CD, Pampati V, Abdi S. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 4. Spinal stenosis. *Pain Physician* 2008; 11:833-848.
 216. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. Cervical epidural injections in chronic discogenic neck pain without disc herniation or radiculitis: Preliminary results of a randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:E265-E278.
 217. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. The effectiveness of fluoroscopic cervical interlaminar epidural injections in managing chronic cervical disc herniation and radiculitis: Preliminary results of a randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:223-236.
 218. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of the effectiveness of lumbar interlaminar epidural injections in managing chronic pain of lumbar disc herniation or radiculitis: A randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:343-355.
 219. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin R. Preliminary results of a randomized, double-blind, controlled trial of fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar discogenic pain without disc herniation or radiculitis. *Pain Physician* 2010; 13:E279-E292.
 220. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Effectiveness of thoracic medial branch blocks in managing chronic pain: A preliminary report of a randomized, double-blind controlled trial; Clinical trial NCT00355706. *Pain Physician* 2008; 11:491-504.
 221. Manchikanti L, Singh V, Falco FJ, Cash KA, Fellows B. Cervical medial branch blocks for chronic cervical facet joint pain: A randomized double-blind, controlled trial with one-year follow-up. *Spine (Phila Pa 1976)* 2008; 33:1813-1820.
 222. Manchikanti L, Singh V, Falco FJ, Cash KA, Pampati V. Lumbar facet joint nerve blocks in managing chronic facet joint pain: One-year follow-up of a randomized, double-blind controlled trial: Clinical Trial NCT00355914. *Pain Physician* 2008; 11:121-132.
 223. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of lumbar facet joint nerve blocks in managing chronic low back pain: A randomized, double-blind, controlled trial with a 2-year follow-up. *Int J Med Sci* 2010; 7:124-135.
 224. Manchikanti L, Singh V, Falco FJE, Cash KA, Fellows B. Comparative outcomes of a 2-year follow-up of cervical medial branch blocks in management of chronic neck pain: A randomized, double-blind controlled trial. 2010; 13:437-450.
 225. Deyo RA, Mirza SK, Turner JA, Martin BI. Overtreating chronic back pain: Time to back off? *J Am Board Fam Med* 2009; 22:62-68.
 226. Carragee EJ, Deyo RA, Kovacs FM, Peul WC, Lurie JD, Urrútia G, Corbin TP, Schoene ML. Clinical research: Is the spine field a mine field? *Spine (Phila Pa 1976)* 2009; 34:423-430.
 227. Manchikanti L, Singh V, Pampati V, Smith HS, Hirsch JA. Analysis of growth of interventional techniques in managing chronic pain in Medicare population: A 10-year evaluation from 1997 to 2006. *Pain Physician* 2009; 12:9-34.
 228. Yeung SS, Genaidy A, Deddens J, Alhemo A, Leung PC. Prevalence of musculoskeletal symptoms in single and multiple body regions and effects of perceived risk of injury among manual handling workers. *Spine (Phila Pa 1976)* 2002; 27:2166-2172.
 229. Moulin DE, Clark AJ, Speechley M, Morley-Forster PK. Chronic pain in Canada – prevalence, treatment, impact and the role of opioid analgesia. *Pain Res Manage* 2002; 7:179-184.
 230. Mailis-Gagnon A, Nicholson K, Yegneswaran B, Zurowski M. Pain characteristics of adults 65 years of age and older referred to a tertiary care pain clinic. *Pain Res Manage* 2008; 13:389-394.
 231. MacFarlane GJ, McBeth J, Garrow A, Silman AJ. Life is as much a pain as it ever was. *Br Med J* 2000; 321:897.
 232. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, Schoelles KM. Long-term opioid management for chronic non-cancer pain. *Cochrane Database Syst Rev* 2010; 1:CD006605.
 233. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain. *J Pain* 2009; 10:113-130.
 234. Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miaskowski C. Research gaps on use of opioids for chronic non-cancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain* 2009; 10:147-159.
 235. Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic non-cancer pain: Prediction and identification of aberrant drug-related behaviors: A review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain* 2009; 10:131-146.
 236. AAPM Council on Ethics. American Academy of Pain Medicine. Ethics Charter www.painmed.org/productpub/pdfs/EthicsCharter.pdf. 2005
 237. Carr DB, Goudas LC. Acute pain. *Lancet*

- 1999; 353:2051-2058.
238. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; 362:1921-1928.
 239. Brennan TJ, Kehlet H. Preventive analgesia to reduce wound hyperalgesia and persistent postsurgical pain. Not an easy path. *Anesthesiol* 2005; 103:681-683.
 240. Leigh JP, Sheetz RM. Prevalence of back pain among full-time United States workers. *Br J Med* 1989; 4:651-657.
 241. Manchikanti L, Hirsch JA. Obama health care for all Americans: Practical implications. *Pain Physician* 2009; 12:289-304.
 242. Asche CV, Kirkness CS, McAdam-Marx C, Fritz JM. The societal costs of low back pain: Data published between 2001 and 2007. *J Pain Palliat Care Pharmacother* 2007; 21:25-33.
 243. Saastamoinen P, Leino-Arjas P, Laaksonen M, Lahelma E. Socio-economic differences in the prevalence of acute, chronic and disabling chronic pain among ageing employees. *Pain* 2005; 114:364-371.
 244. Hartvigsen J, Frederiksen H, Christensen K. Physical and mental function and incident low back pain in seniors: A population-based two-year prospective study of 1,387 Danish twins aged 70 to 100 years. *Spine (Phila Pa 1976)* 2006; 31:1628-1632.
 245. Hestbaek L, Leboeuf-Yde C, Kyvik KO. Is comorbidity in adolescence a predictor for adult low back pain? A prospective study of a young population. *BMC Musculoskelet Disord* 2006; 7:29.
 246. Ritzwoller DP, Crouse L, Shetterly S, Rublee D. The association of comorbidities, utilization and costs for patients identified with low back pain. *BMC Musculoskelet Disord* 2006; 7:72.
 247. Centers for Disease Control and Prevention. Prevalence of disabilities and associated health conditions among adults: United States, 1999. *MMWR Morb Mortal Wkly Rep* 2001; 50:120-125.
 248. Leijon O, Wahlström J, Mulder M. Prevalence of self-reported neck-shoulder-arm pain and concurrent low back pain or psychological distress: Time-trends in a general population, 1990-2006. *Spine (Phila Pa 1976)* 2009; 34:1863-1868.
 249. Brage S, Sandanger I, Nygård JF. Emotional distress as a predictor for low back disability: A prospective 12-year population-based study. *Spine* 2007; 32:269-274.
 250. Dersh J, Gatchel RJ, Mayer T, Polatin P, Temple OR. Prevalence of psychiatric disorders in patients with chronic disabling occupational spinal disorders. *Spine* 2006; 31:1156-1162.
 251. Gureje O, von Korff M, Kola L, Demttenaere K, He Y, Posada-Villa J, Lepine JP, Angermeyer MC, Levinson D, de Girolamo G, Iwata N, Karam A, Guimaraes Borges GL, de Graaf R, Browne MO, Stein DJ, Haro JM, Bromet EJ, Kessler RC, Alonso J. The relation between multiple pains and mental disorders: Results from the World Mental Health Surveys. *Pain* 2008; 135:82-91.
 252. Manchikanti L, Pampati V, Fellows B, Rivera JJ, Damron KS, Beyer CD, Cash KA. Influence of psychological factors on the ability to diagnose chronic low back pain of facet joint origin. *Pain Physician* 2001; 4:349-357.
 253. Manchikanti L, Cash KA, Pampati V, Fellows B. Influence of psychological variables on the diagnosis of facet joint involvement in chronic spinal pain. *Pain Physician* 2008; 11:145-160.
 254. Manchikanti L, Manchikanti K, Cash KA, Singh V, Giordano J. Age-related prevalence of facet joint involvement in chronic neck and low back pain. *Pain Physician* 2008; 11:67-75.
 255. Pampati S, Cash KA, Manchikanti L. Accuracy of diagnostic lumbar facet joint nerve blocks: A 2-year follow-up of 152 patients diagnosed with controlled diagnostic blocks. *Pain Physician* 2009; 12:855-866.
 256. Manchikanti L, Pampati S, Cash KA. Making sense of accuracy of diagnostic lumbar facet joint nerve blocks: An assessment of implications of 50% relief, 80% relief, single block or controlled diagnostic blocks. *Pain Physician* 2010; 13:133-143.
 257. Rivera JJ. Reliability of psychological evaluation in chronic pain in an interventional pain management setting. *Pain Physician* 2005; 8:375-383.
 258. Manchikanti L, Pampati V, Damron KS, Beyer CD, Barnhill RC. Evaluation of psychological status in chronic low back pain: Comparison with general population. *Pain Physician* 2002; 5:149-155.
 259. Manchikanti L, Fellows B, Singh V. Understanding psychological aspects of chronic pain in interventional pain management. *Pain Physician* 2002; 5:57-82.
 260. British Pain Society. Recommendations for the appropriate use of opioids for persistent non-cancer pain. A consensus statement prepared on behalf of the Pain Society, the Royal College of Anaesthetists, the Royal College of General Practitioners and the Royal College of Psychiatrists. London, UK: *The British Pain Society*; 2004.
 261. Graziotti P, Goucke R, for the Directors of the Australian Pain Society. The use of oral opioids in patients with chronic nonmalignant pain: Management strategies. Perth, Australia: *Australian Pain Society*; 2002.
 262. Jovey RD, Ennis J, Gardner-Nix J, Goldman B, Hays H, Lynch M, Moulin D, Canadian Pain Society. Use of opioid analgesics for the treatment of chronic non-cancer pain--a consensus statement and guidelines from the Canadian Pain Society, 2002. *Pain Res Manage* 2003; 8:3A-28A.
 263. Eisenberg E, McNicol E, Carr DB. Opioids for neuropathic pain (review). *Cochrane Database Syst Rev* 2006; 3:CD006146.
 264. Deshpande A, Furlan A, Mailis-Gagnon A, Atlas S, Turk D. Opioids for chronic low back pain (review). *Cochrane Database Syst Rev* 2007; 3:CD004959.
 265. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis: A systematic review and metaanalysis. *J Rheumatol* 2007; 34:543-555.
 266. Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic non-cancer pain: A systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage* 2008; 35:214-228.
 267. Clark AJ, Ahmedzai SH, Allan LG, Camacho F, Horbay GL, Richarz U, Simpson K. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. *Curr Med Res Opin* 2004; 20:1419-1428.
 268. Devulder J, Richarz U, Nataraja SH. Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. *Curr Med Res Opin* 2005; 21:1555-1568.
 269. Hollingshead J, Duhmke R, Cornblath D. Tramadol for neuropathic pain. *Cochrane Database Syst* 2006; 3:CD003726.
 270. Moore RA, McQuay H. Prevalence of opioid adverse events in chronic non-

- malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther* 2005; 7:R1046-R1051.
271. Dole V. What we have learned from three decades of methadone maintenance treatment. *Drug & Alcohol Review* 1994; 13:3-4.
 272. Brecher E, Editors of *Consumer Reports Magazine*. Chapter 15. How well does methadone maintenance work? In: *The Consumers Union Report on Licit and Illicit Drugs*. Schaffer Library of Drug Policy, 1972. <http://www.druglibrary.org/schaffer/library/studies/cu/CU15.html>
 273. Tennant FS J, Uelman GF. Narcotic maintenance for chronic pain: Medical and legal guidelines. *Postgrad Med* 1983; 73:81-94.
 274. Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treatment with long-term analgesics. *Ann Clin Psychiatry* 1992; 4:185-192.
 275. Franklin GM, Stover BD, Turner JA, Fulton-Kehoe D, Wickizer TM; Disability Risk Identification Study Cohort. Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *Spine (Phila Pa 1976)* 2008; 33:199-204.
 276. Rhee Y, Taitel MS, Walker DR, Lau DT. Narcotic drug use among patients with lower back pain in employer health plans: A retrospective analysis of risk factors and health care services. *Clin Ther* 2007; 29:2603-2612.
 277. Becker N, Sjogren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain centre compared to general practice: A randomised controlled trial. *Pain* 2000; 84:203-211.
 278. Strassels SA. Cognitive effects of opioids. *Curr Pain Headache Rep* 2008; 12:32-36.
 279. Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS. Are opioid-dependent/tolerant patients impaired in driving-related skills? A structured evidence-based review. *J Pain Symptom Manage* 2003; 25:559-577.
 280. Woodcock J. A difficult balance – pain management, drug safety, and the FDA. *N Engl J Med* 2009; 361:2105-2107.
 281. Manchikanti L, Manchikanti KN, Pampati V, Cash KA. Prevalence of side effects of prolonged low or moderate dose opioid therapy with concomitant benzodiazepine and/or antidepressant therapy in chronic non-cancer pain. *Pain Physician* 2009; 12:259-267.
 282. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: A literature review. *Eur J Pain* 2007; 11:490-518.
 283. Ruan X. Drug-related side effects of long-term intrathecal morphine therapy. *Pain Physician* 2007; 10:357-366.
 284. Mercadante S. Pathophysiology and treatment of opioid-related myoclonus in cancer patients. *Pain* 1998; 74:5-9.
 285. Han PK, Arnold R, Bond G, Janson D, Abu-Elmagd K. Myoclonus secondary to withdrawal from transdermal fentanyl: Case report and literature review. *J Pain Symptom Manage* 2002; 23:66-72.
 286. Moore P, Dimsdale JE. Opioids, sleep, and cancer-related fatigue. *Med Hypotheses* 2002; 58:77-82.
 287. Ersek M, Cherrier MM, Overman SS, Irving GA. The cognitive effects of opioids. *Pain Manag Nurs* 2004; 5:75-93.
 288. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain. *Clin J Pain* 2008; 24:469-478.
 289. Ho T, Vrabec JT, Burton AW. Hydrocodone use and sensorineural hearing loss. *Pain Physician* 2007; 10:467-472.
 290. White AG, Birnbaum HG, Mareva MN, Daher M, Vallow S, Schein J, Katz N. Direct costs of opioid abuse in an insured population in the United States. *J Manag Care Pharm* 2005; 11:469-479.
 291. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain* 2007; 129:355-362.
 292. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy R. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *JAMA* 2003; 289:2370-2378.
 293. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain* 2007; 8:573-582.
 294. Evans M, Kriger S, Gunn J, Schwilke G. Effective monitoring of opiates in chronic pain patients. *Pract Pain Manag* 2009; 9:32-33.
 295. Couto JE, Romney MC, Leider HL, Sharma S, Goldfarb NI. High rates of inappropriate drug use in the chronic pain population. *Popul Health Manage* 2009; 12:185-190.
 296. Adams EH, Breiner S, Cicero TJ, Geller A, Inciardi JA, Schnoll SH, Senay EC, Woody GE. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. *J Pain Symptom Manage* 2006; 31:465-476.
 297. Petraglia F, Porro C, Facchinetti F, Cicoli C, Bertellini E, Volpe A, Barbieri GC, Genazzani AR. Opioid control of LH secretion in humans: menstrual cycle, menopause and aging reduce effect of naloxone but not of morphine. *Life Sci* 1986; 38:2103-2110.
 298. Inciardi JA, Surratt HL, Kurtz SP, Cicero TJ. Mechanisms of prescription drug diversion among drug-involved club- and street-based populations. *Pain Med* 2007; 8:171-183.
 299. Inciardi JA, Surratt HL, Cicero TJ, Beard RA. Prescription opioid abuse and diversion in an urban community: the results of an ultrarapid assessment. *Pain Med* 2009; 10:537-548.
 300. Unintentional Drug Poisoning in the United States. Centers for Disease Control and Prevention. July 2010. <http://www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf>
 301. Boyles S. CDC: Alarming increase in methadone deaths. Deaths from opioid painkillers have tripled since 1999. WebMD Health News. September 30, 2009.

