Health Policy

Opioid Epidemic in the United States

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Over the past two decades, as the prevalence of chronic pain and health care costs have exploded, an opioid epidemic with adverse consequences has escalated. Efforts to increase opioid use and a campaign touting the alleged undertreatment of pain continue to be significant factors in the escalation. Many arguments in favor of opioids are based solely on traditions, expert opinion, practical experience and uncontrolled anecdotal observations. Over the past 20 years, the liberalization of laws governing the prescribing of opioids for the treatment of chronic non-cancer pain by the state medical boards has led to dramatic increases in opioid use. This has evolved into the present stage, with the introduction of new pain management standards by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) in 2000, an increased awareness of the right to pain relief, the support of various organizations supporting the use of opioids in large doses, and finally, aggressive marketing by the pharmaceutical industry. These positions are based on unsound science and blatant misinformation, and accompanied by the dangerous assumptions that opioids are highly effective and safe, and devoid of adverse events when prescribed by physicians.

Results of the 2010 National Survey on Drug Use and Health (NSDUH) showed that an estimated 22.6 million, or 8.9% of Americans, aged 12 or older, were current or past month illicit drug users, The survey showed that just behind the 7 million people who had used marijuana, 5.1 million had used pain relievers. It has also been shown that only one in 6 or 17.3% of users of non-therapeutic opioids indicated that they received the drugs through a prescription from one doctor.

The escalating use of therapeutic opioids shows hydrocodone topping all prescriptions with 136.7 million prescriptions in 2011, with all narcotic analgesics exceeding 238 million prescriptions. It has also been illustrated that opioid analgesics are now responsible for more deaths than the number of deaths from both suicide and motor vehicle crashes, or deaths from cocaine and heroin combined. A significant relationship exists between sales of opioid pain relievers and deaths. The majority of deaths (60%) occur in patients when they are given prescriptions based on prescribing guidelines by medical boards, with 20% of deaths in low dose opioid therapy of 100 mg of morphine equivalent dose or less per day and 40% in those receiving morphine of over 100 mg per day. In comparison, 40% of deaths occur in individuals abusing the drugs obtained through multiple prescriptions, doctor shopping, and drug diversion.

The purpose of this comprehensive review is to describe various aspects of crisis of opioid use in the United States. The obstacles that must be surmounted are primarily inappropriate prescribing patterns, which are largely based on a lack of knowledge, perceived safety, and inaccurate belief of undertreatment of pain.

Key words: Opioid abuse, opioid misuse, nonmedical use of psychotherapeutic drugs, nonmedical use of opioids, National Survey on Drug Use and Health, opioid guidelines.

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The Institute of Medicine (IOM) recently published a report on relieving pain in America (1,2). The report identified multiple facts, including that there are more than 116 million Americans with pain persisting from weeks to years, with financial costs ranging from $560 billion to $635 billion per year. The report alluded to the serious problem of the diversion and abuse of opioid drugs, questioning their long-term usefulness. The IOM committee reported that when opioids are used as prescribed; they can be safe and effective for acute postoperative pain, procedural pain, and patients nearing the end of life who desire more pain relief. While the IOM committee does promote pain treatment, including opioids, they do acknowledge a serious crisis in the diversion and abuse of opioids and a lack of evidence for the long-term usefulness of opioids in treating chronic pain. Along with increases in the prevalence of chronic pain, health care costs, and adverse consequences due to opioid use, the opioid crisis is escalating (1-49). Despite mounting evidence, efforts to increase opioid use based on the alleged undertreatment of pain continue (50-63). In fact, Stein (64) summarized the evidence succinctly, noting that "many arguments in favor of opioids are solely based on traditions, expert opinion, practical experience, and uncontrolled anecdotal observations."

Starting in the late 1990's, state medical boards curtailed restrictions on laws governing the prescribing of opioids for the treatment of chronic non-cancer pain, resulting in a dramatic increase in the number of prescriptions (65). This development gathered momentum with the introduction of new pain management standards for in-patient and out-patient medical care implemented by the Joint Commission on the Accreditation of Health Care Organizations (JCAHO) in 2000 (66) and an increased awareness of the right to pain relief, both of which provided justification for physicians. (67-70). Other factors fueling an increase in prescriptions included aggressive marketing by the pharmaceutical industry, the promotion of opioids by numerous physicians and a call for for the increased use of opioids in the treatment of chronic non-cancer pain by myriad organizations. These positions, alongside continued assertions that pain is undertreated, were largely based on untenable science and misinformation, and contended that opioids are highly effective and safe without adverse effects when prescribed by physicians (31,60,66,71-90). Moreover, a recent examination of model guidelines for curtailing controlled substance abuse revealed that the guidelines appeared instead to condone an increase in prescribing (50,91-93). This is illustrated by the language in the model guidelines, which state (65), "no disciplinary action will be taken against a practitioner based solely on the quantity and/or frequency of opioids prescribed." Thus, the use of opioids in general, including long-acting and potent forms of opioids, have dramatically increased due to a shift in regulations largely driven by published, albeit extremely weak, evidence suggesting that opioids are not only highly effective, but also safe in selected persons with chronic non-cancer pain, even though this selection criteria are extremely weak and these guidelines have only facilitated overuse of opioids (31,71,94-98). Nearly 2 decades later, the scientific evidence for the effectiveness of opioids for chronic non-cancer pain remains unclear (35,71,96,99-119). In addition to ongoing concerns with regard to the lack of effectiveness of opioids in chronic non-cancer pain (31-38,96,99-119), there is growing evidence of multiple physiologic and non-physiologic adverse effects, such as opioid hyperalgesia (32,95,96,107,112-124), misuse and abuse (31-39,71,95,96,102,103,110-115,125-140), the inability of providers to identify and monitor misuse and overuse (31,32,36,95,96,126,127,130,138-151), and a steady increase in opioid-related fatalities (32,34,37,129,130,152-163). In fact, in 2008 drug poisoning in the United States has been reported to contribute to one death every 15 minutes (160). Furthermore, opioids have been shown to contribute to one death every 36 minutes in the United States in 2008. Correlating with these fatalities, sales and substance abuse treatment admissions have increased substantially (125-127,159,160,164-168).

With the above background highlighting a steady increase in fatalities with opioid use and very little evidence of effectiveness, it remains to be seen who will ultimately bear the responsibility for the premature adoption of opioids as a treatment standard (116). It has been speculated that in the coming years, there will likely be an extensive "postmortem" on the massive opioid treatment movement and the escalating social crisis that has accompanied it (116). It is universally accepted that this massive treatment movement has led to huge collateral damage in terms of diversion, misuse, and abuse of opioids. The widespread use of opioids for chronic non-cancer pain is in direct violation of the established cardinal principles of medical intervention – that there be compelling evidence of the benefit of a therapy prior to its large-scale use (116).

A cautious approach has been advocated in recent years by many (17,33,35,49,110-115,117-119,169). This

manuscript is undertaken to evaluate the escalating opioid crisis which although heavily regulated, continues to be uncontrolled.

1.0 Non-Medical Use of Psychotherapeutic Drugs

1.1 Current Non-Medical Use

Results of the 2010 National Survey on Drug Use and Health (NSDUH) (170), an annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), showed that an estimated 22.6 million, or 8.9% of Americans, age 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 non-medically. Marijuana was the most commonly used illicit drug with 17.4 million current (past month) users, or 6.9% of the US population. Cocaine was used by 1.5 million, whereas hallucinogens were used in the past month by 1.2 million persons (Fig. 1 and Table 1). Next to marijuana, 7.0 million (27%) persons age 12 or older had used prescription-type psychotherapeutic drugs non-medically in the past month (current use). Of these, 5.1 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 lysergic acid diethylamide (LSD).

Overall, there has been an increase in the current use of all illicit drugs and marijuana, without any change for psychotherapeutics and hallucinogens and a decrease for cocaine from 2002 to 2010, as shown in Fig. 2.

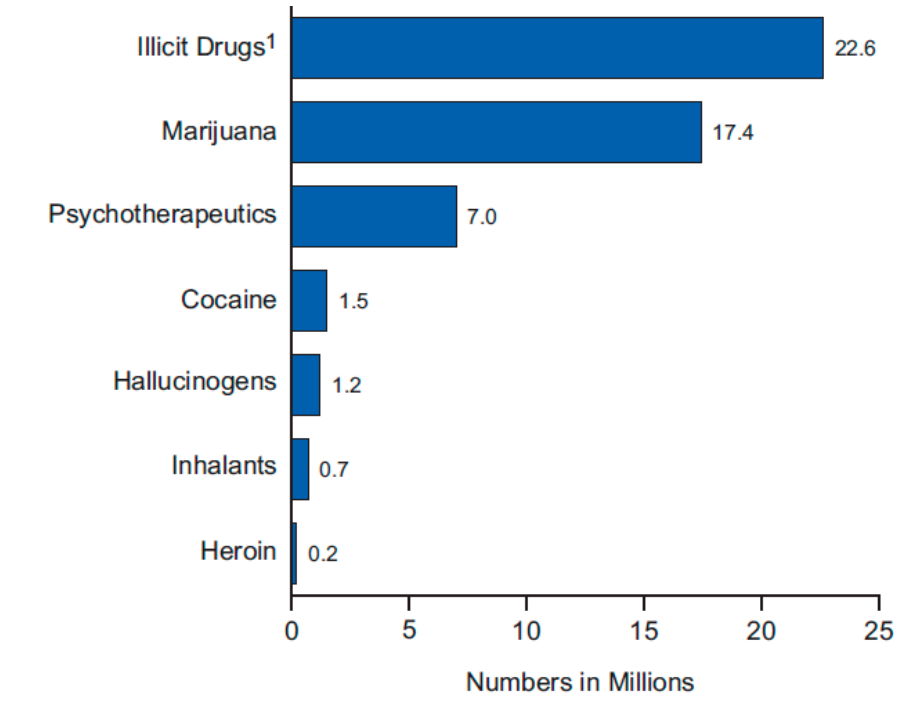


Fig. 1. *Past month illicit drug use among persons aged 12 or older: 2010.*

Source: Substance Abuse and Mental Health Services Administration. *Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings*. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012.

Table 1. *Types of illicit drug use in the past month among persons aged 12 or older: Numbers in thousands, from 1998 to 2010.*

Drugs	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	12-Year % change from 1998 to 2010
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%[b])	6,895[a] (2.8%[a])	6,224 (2.5%)	6,953 (2.8%)	6,967 (2.7%)	181%
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%)	5,257 (2.1%)	5,100 (2.0%)	NA
OxyContin®	--	--	--	--	--	--	325 (0.1%)	334 (0.1%)	276 (0.1%[a])	369 (0.1%)	435 (0.2%)	510 (0.2%)	564 (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%)	2,010 (0.8%)	2,160 (0.9%)	230%
Stimulants	633 (0.3%)	950 (0.4%)	788 (0.4%)	1,018 (0.5%)	1,303[b] (0.6%[b])	1,310[b] (0.6%[b])	1,312[b] (0.5%[b])	1,188[b] (0.5%[b])	1,385[b] (0.6%[b])	1,053 (0.4%)	904 (0.4%)	1,290 (0.5%)	1,077 (0.4%)	70%
Sedatives[3]	210 (0.1%)	229 (0.1%)	175 (0.1%)	306 (0.1%)	436[b] (0.2%[b])	294 (0.1%)	265 (0.1%)	272 (0.1%)	385 (0.2%[a])	346 (0.1%)	234 (0.1%)	370 (0.1%)	374 (0.1%)	78%
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%)	16,718 (6.6%)	17,373 (6.9%)	58%
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	1,855	1,637 (0.7%)	1,466 (0.6%)	-16%
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%)	21,813 (8.7%)	22,622 (8.9%)	66%

-- 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 - 2010.

www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

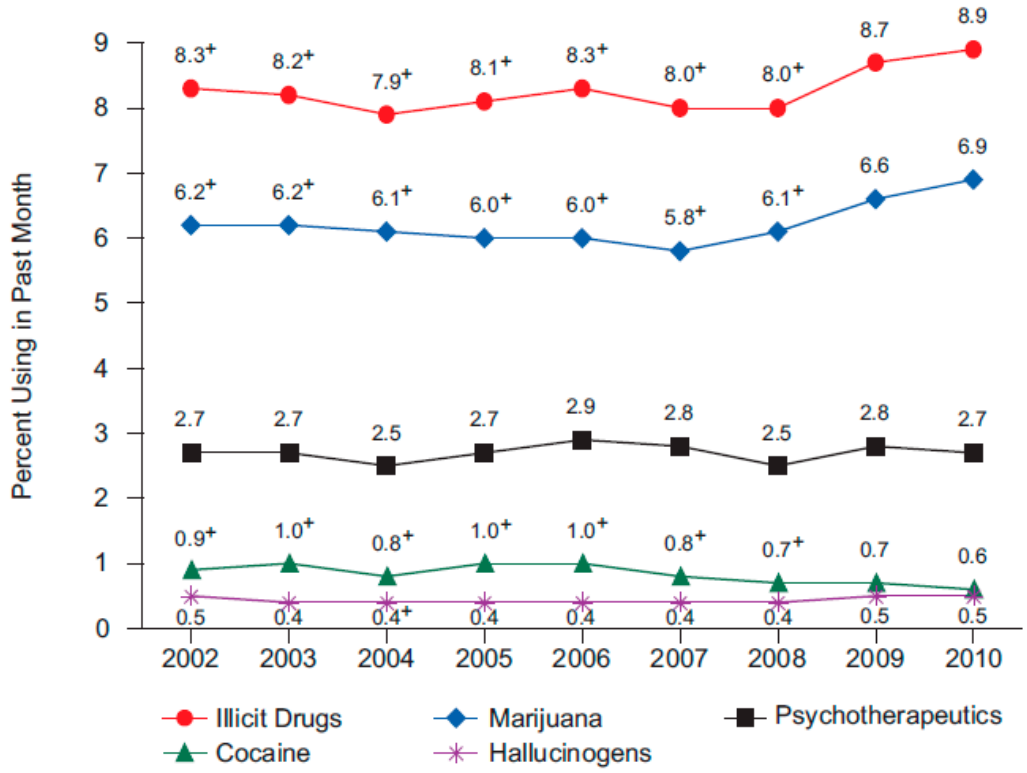


Fig. 2. *Past month use of selected illicit drugs among persons aged 12 or older: 2002-2010.*
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

1.2 Past Year Initiates

In 2010, there were 2.4 million persons age 12 or older who used psychotherapeutics non-medically for the first time within the past year. Numbers of new users for specific psychotherapeutics in 2010 were 2.0 million for pain relievers, 1.2 million for tranquilizers, 624,000 for stimulants, and 252,000 for sedatives (Table 2 and Fig. 3). The specific drug categories with the largest number of recent initiatives among persons age 12 or older were nonmedical use of pain relievers (2,004 million) and marijuana (2,426 million), followed by nonmedical use of tranquilizers (1,238 million), ecstasy (0.937 million), inhalants (0.793 million), cocaine (0.637 million), and stimulants (0.624 million) (Fig. 3). More strikingly, in 2010, the number of new nonmedical users of OxyContin (oxycodone) age 12 or older was 598,000 with an average age at first use of 22.8 years among those age 12 to 49 (170).

1.3 Past Year Use

The analysis of long-term statistics based on yearly use of illicit drugs is disturbing. The past year use of illicit drugs in 2010 was 38.806 million, or 15.3% of the population (Table 3). Nonmedical use of psychotherapeutics for the past year in the 2010 survey was 16.031 million or 6.3% population age 12 or older, compared to 2.6% of the population in 1998. Of importance is the fact that nonmedical use of psychotherapeutics was just behind marijuana and hashish with use by 11.5% of the population age 12 or older in 2010, increased from 8.6% in 1998. Overall, nonmedical use of psychotherapeutics increased 178% from 1998 to 2010, compared to marijuana 56% and cocaine at 17%.

1.4 Lifetime Use

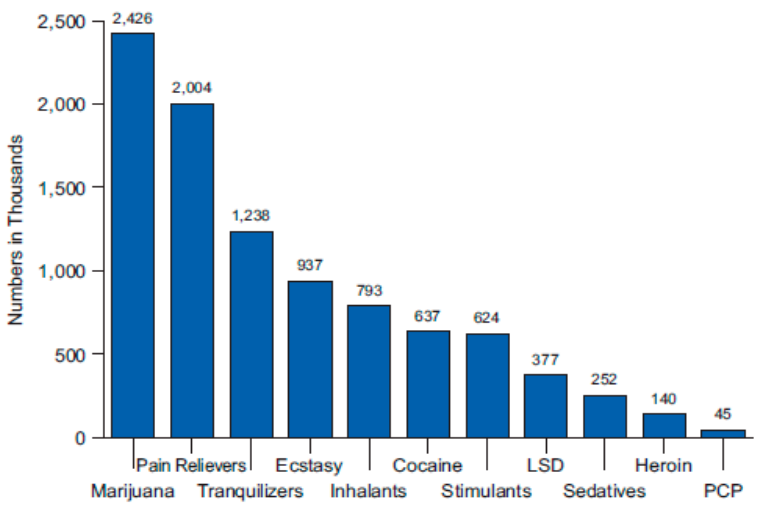
Lifetime use of illicit drugs (lifetime use indicates use of a specific drug at least once in the respondent's

Table 2. *Past year initiates for illicit drugs from 1998 to 2010 (numbers in thousands) for 12 years.*

Drugs	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	12-Year % change from 1998 to 2010
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	2,179	2,004	29%
Tranquilizers	860	916	1,298	1,212	1,184	1,071	1,180	1,286	1,112	1,232	1,127	1,226	1,238	44%
Stimulants[2]	648	706	808	853	783	715	793[a]	647	845[b]	642	599	702	624	-4%
Sedatives	147	164	191	225	209	194	240	247	267	198	181	186	252	71%
Marijuana	2,498	2,640	2,746	2,793	2,196	1,973	2,142	2,114	2,063	2,090	2,208	2,361	2,426	-3%
Cocaine	868	917	1,002	1,140	1,032[b]	986[b]	998[b]	872[a]	977[b]	906[b]	722	617	637	-27%
Heroin	140	121	114	154	117	92	118	108	91	106	114	180	140	0%

Note: 2002 to 2008 data is based on 2008 National Survey on Drug Use and Health Survey Report.
-- Not available.
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. See Section B.4.8 in Appendix B of the Results from the 2008 National Survey on Drug Use and Health: National Findings.
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: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

lifetime), including psychotherapeutics, among persons age 12 or older has been increasing over the years (Table 4). In 2010, the lifetime use of illicit drugs among persons age 12 or older was slightly more than 2009 with 119,508 or 47.1% of the population. Similarly, nonmedical use of psychotherapeutics remained the same from 2009 with 20.4% in 2010, or almost 51.6 million using prescription psychotherapeutic drugs for nonmedical purposes. Among the subgroups, only OxyContin increased significantly from 1.9 million in 2005 to 6.1 million in 2010, or 0.8% of the population in 2005 to 2.4% in 2010 (171). Lifetime use of illicit drugs in per-



Note: The specific drug refers to the one that was used for the first time, regardless of whether it was the first drug used or not.

Fig. 3. *Past year initiates for specific illicit drugs among persons aged 12 or older: 2010*.
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

sons age 12 or older was topped by marijuana (41.9% of the population) followed by nonmedical use of psychotherapeutics (20.4% of the population).

1.5 Abuse Based on Age

In 2010, young adults age 18 to 25 demonstrated rates of current use of illicit drugs to be higher (21.5%) than for youths age 12 to 17 (10.1%) and adults age 26 or older (6.6%), with 6.9% using marijuana, 2.7% using psychotherapeutics non-medically, 0.6% using cocaine, and 0.5% using hallucinogens among young adults 18-25 (Fig. 4). Past month nonmedical use of prescription-type drugs among young adults increased from 20.2% in 2002 to 21.5% in 2010. 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 (170). As illustrated in Figure 5, overall illicit drug use increased from 8.3% to 8.9% in 2010 in the age group from 18 to 25.

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 2010 increased from 4.0% at ages 12 or 13, to 9.3% at ages 14 or 15, to 16.6% at ages 16 or 17 (170). The highest rate of 23.1% was noted among persons age 18 to 20, with the next highest rate among 21 to 25 year olds 20.5% (Fig. 6) (144). In 2010, adults age 26 or older were less likely to be current drug users than youths age 12 to 17 or young adults age 18 to 25 (6.6 versus 10.1 and 21.5%, respectively). However, there were more drug users age 26 or older (12.8 million) than users in the 12-to-17-year age group (2.5 million) and 18-to-25-year age group (7.3 million) combined.

1.6 Abuse Based on Gender

In 2010, the survey results were similar to prior years with males being more likely than females to be current illicit drug users (11.2% versus 6.8%). Males were more likely than females to be past month users of marijuana (9.1% versus 4.7%). Rates of past month nonmedical use of psychotherapeutic drugs among males and females was 3% and 2.5%, pain relievers was 2.3% and 1.7%, cocaine was 0.8% and 0.4% and hallucinogens was 0.6% and 0.3% (170).

1.7 Abuse During Pregnancy

Among pregnant woman age 15 to 44 years, a significantly lower proportion of women used illicit drugs in the past month (4.4%) compared to 10.9% of their

Table 3. *Types of illicit drug use in the past year among persons aged 12 or older: numbers in thousands from 1998 to 2010 (12 years).*

Drugs	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	12-year % change from 1998 to 2010
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%)	16,006 (6.4%)	16,031 (6.3%)	178%
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%)	12,405 (4.9%)	12,213 (4.8%)	85% From 1999
OxyContin®	--	--	--	--	--	--	1,213[a] (0.5%)	1,226 (0.5%)	1,323 (0.5%)	1,422 (0.6%)	1,459 (0.6%)	1,677 (0.7%)	1,869 (0.7%)	54% From 2004
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%)	5,460 (2.2%)	5,581 (2.2%)	188%
Stimulants3	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%)	3,060 (1.2%)	2,887 (1.1%)	94%
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%)	811 (0.3%)	907 (0.4%)	56%
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%)	28,521 (11.3%)	29,206 (11.5%)	56%
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%)	4,797 (1.9%)	4,449 (1.8%)	17%
TOTAL ILLICIT DRUGS1	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%)	37,957 (15.1%)	38,806 (15.3%)	68%

-- Not available.

Note: 2002 to 2010 data is based on 2010 National Survey on Drug Use and Health Survey Report. a Difference between estimate and 2010 estimate is statistically significant at the 0.05 level. b Difference between estimate and 2010 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 non-medically. 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: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170). Access date 2/22/2012

Table 4. *Types of illicit drugs of lifetime use among persons aged 12 or older: numbers in thousands, 1998 – 2010.*

Drug	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	12-Year % change from 1998 to 2010
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%)	51,771 (20.6%)	51,641 (20.4%)	156%
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%)	35,046 (13.9%)	34,776 (13.7%)	75% From 1999
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%)	5,829 (2.3%)	6,121 (2.4%)	218% From 2002
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%)	21,755 8.6%)	22,103 (8.7%)	186%
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%)	21,930 (8.7%)	21,660 (8.5%)	125%
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%)	8,605 (3.4%a)	7,631 (3.2%)	64%
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%)	104,446 (41.5%)	106,232 (41.9%)	47%
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%)	36,599 (14.5%)	37,210 (14.7%)	61%
TOTAL ILLICIT DRUGS1	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%)	118,705 (47.1%)	119,508 (47.1%)	53%

-- Not available.

Note: 2002 to 2010 data is based on 2010 National Survey on Drug Use and Health Survey Report.

a Difference between estimate and 2010 estimate is statistically significant at the 0.05 level.

b Difference between estimate and 2010 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 non-medically. Illicit drugs other than marijuana include cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used non-medically. 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: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

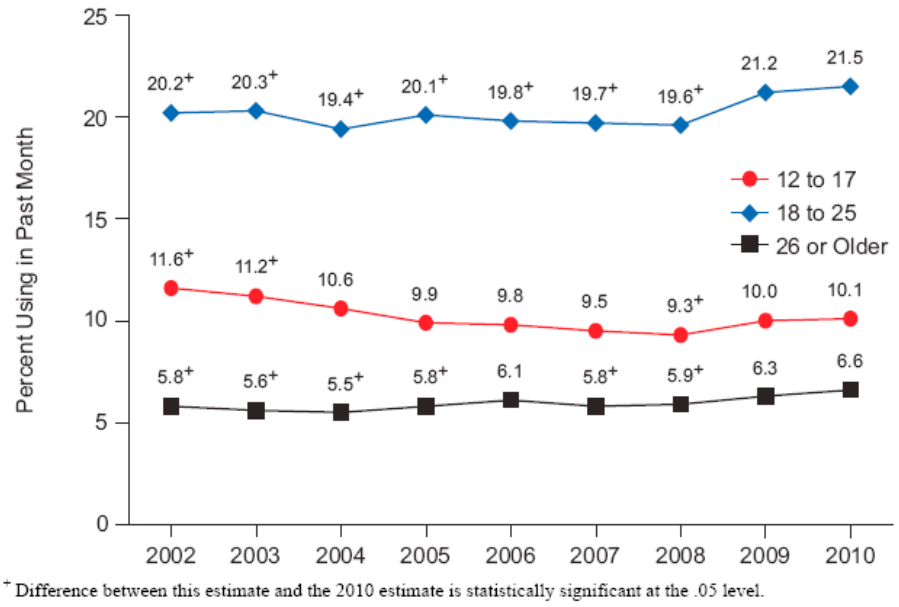


Fig. 4. *Comparative analysis of past month use of illicit drugs among various age groups.*
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

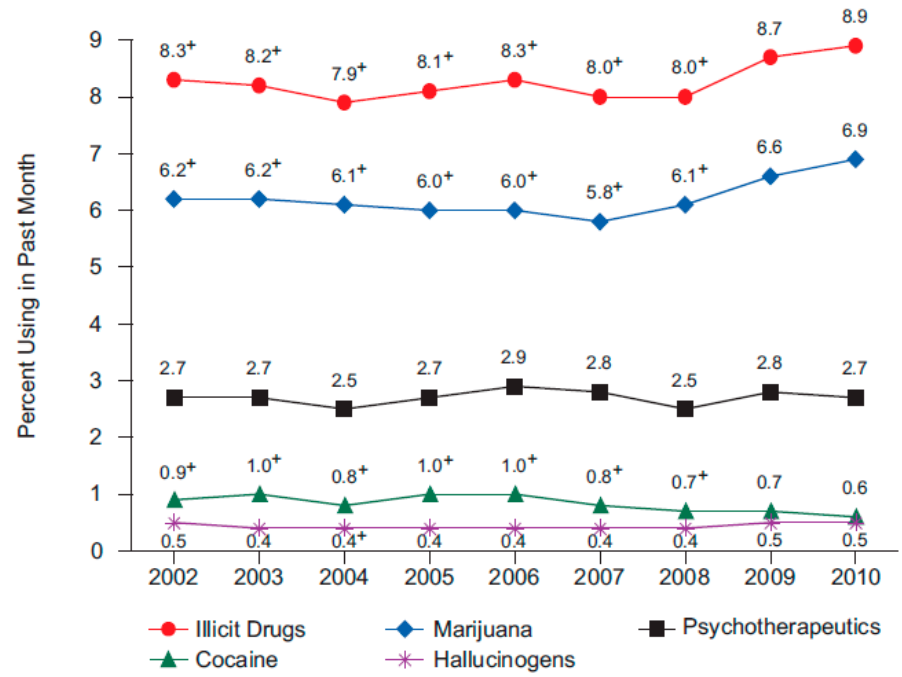


Fig. 5. *Past month use of selected illicit drugs among young adults aged 18 to 25: 2002-2010.*
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

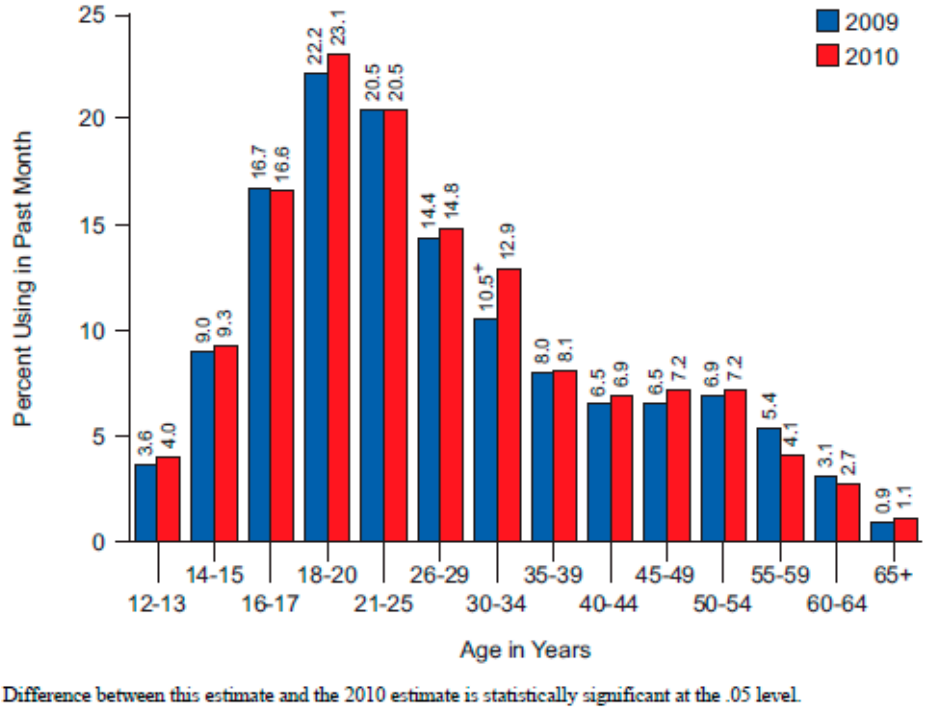


Fig. 6. *Past month illicit drug use among persons aged 12 or older, by age: 2009 and 2010.*
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

nonpregnant counterparts. These figures are based on data averaged for 2009 and 2010 (170).

1.8 Abuse Based on Employment

Employment also seemed to have a significant influence in 2010. Among adults age 18 or older, the rate of illicit drug use was higher for unemployed persons (17.5%) than for those who were employed full time (8.4%) or part time (11.2%) (170).

1.9 Regional Variations

There were also differences based on geographic area among persons age 12 or older in 2010. The rate of current illicit drug use in 2010 was 11.0% in the West, 9.4% in the Northeast, 8.2% in the Midwest, and 7.8% in the South (170). Further, the rate of current illicit drug use in metropolitan areas was higher than the rate in non-metropolitan areas with 9.4% in large metropolitan counties, 8.8% in small metropolitan counties, and 7.5% in non-metropolitan counties as a group (170).

1.10 Drug Abuse Among Criminals

In 2010, an estimated 1.5 million adults age 18 or older who were on parole or supervised release from jail during the past year had higher rates of dependence on or abuse of a substance (27%) than their counterparts who were not on parole or supervised release during the past year (8.7%). In 2010, probation status was associated with substance dependence or abuse. The rate of substance dependence or abuse was 29.9% 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 8.3% (170).

1.11 Driving Under the Influence

Driving under the influence of illicit drugs is a criminal act and dangerous to the public. In 2010, 10.6 million persons, or 4.2% of the population age 12 or older, reported driving under the influence of illicit drugs during the past year. This rate was highest among young adults age 18 to 25 with 12.7% (170).

1.12 Frequency of Abuse

Among past year marijuana users age 12 or older in 2010, the following patterns were revealed (170):

- 15.7% used marijuana on 300 or more days within the past 12 months, translating to 4.6 million using marijuana on a daily or almost daily basis over a 12-month period.
- 39.9%, or 6.9 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 2010 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 (171). 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 2010 was shown in 11.4 million adults, representing 5.0% of all adults, with the highest rates being in adults age 18 to 25 (7.7%) and lowest for adults age 50 or older (3.2%) as shown in Figure 7 (171). The prevalence of SPD among women age 18 or older was higher (6.5%) than among men (3.4%) in that age group (171).

2.2 Major Depressive Episodes and Drug Abuse

The prevalence of a MDE in 2010 was 6.8% of persons age 18 or older, or 15.5 million adults, with at least one MDE in the past year. The number of adults who had past year MDE was 6.8%. Even then, the past year

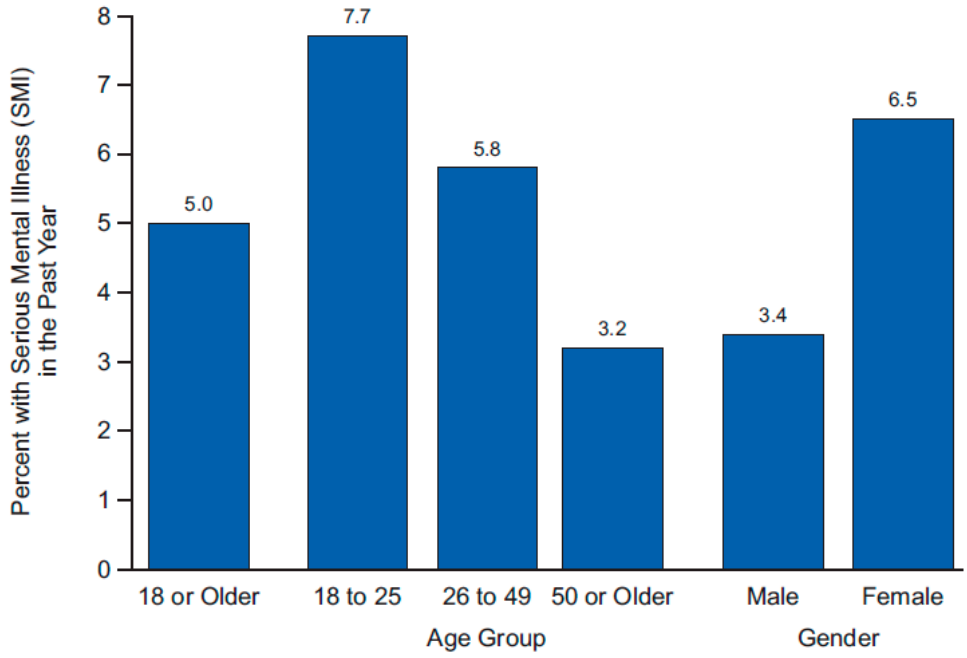


Fig. 7. *Serious mental illness, psychological distress, and nontherapeutic drug use, among persons age 18 and older, by age, 2010.* Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Mental Health Findings. www.samhsa.gov/data/NSDUH/2k10MH_Findings/2k10MHResults.pdf (171) Access date 2/23/2012

prevalence of MDE in 2010 was lower for those age 50 or older (5.6%) compared with rates among persons age 18 to 25 (8.2%) and those age 26 to 49 (7.5%). However, the past year prevalence of MDE was higher among adult females than among adult males, 8.4% versus 5.1%. In addition, among women, past year MDE rates were higher with 11.3% for 18 to 25 year olds, 9.2 for 26 to 49 year olds compared with those of 50 or older with only 6.7%. Further, the prevalence of MDE also varied by race and ethnicity with the highest rate among persons reporting 2 or more races (10.8%), while rates for single race groups were 7.3% among whites, 5.6% among Hispanics, 7.7% among American Indians or Alaska Natives, 5.8% among blacks, and 3.8% among Asians.

In addition, in 2010 the past prevalence of MDE with severe impairment for adults age 18 or older was higher among unemployed persons (9.3%) than among persons employed full time (5.4%).

In 2010, an adult age 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 (22.0% versus 7.9%) (171). 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. Figure 8 illustrates substance abuse in adults by MDE.

The prevalence of a MDE in youths age 12 to 17 in 2010 showed that 1.9 million (8.9%) reported at least one MDE during the past year. Among youths age 12 to 17, the past year prevalence of MDE ranged from 3.3% among 12-year-olds to 10.9% among those age 16, and 10.3% among those age 17 (171).

Among youths with MDE age 12 to 17, 37.2% had used illicit drugs in 2010, in contrast to 37.4% in 2008. This was higher than the 17.8% 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 (171).

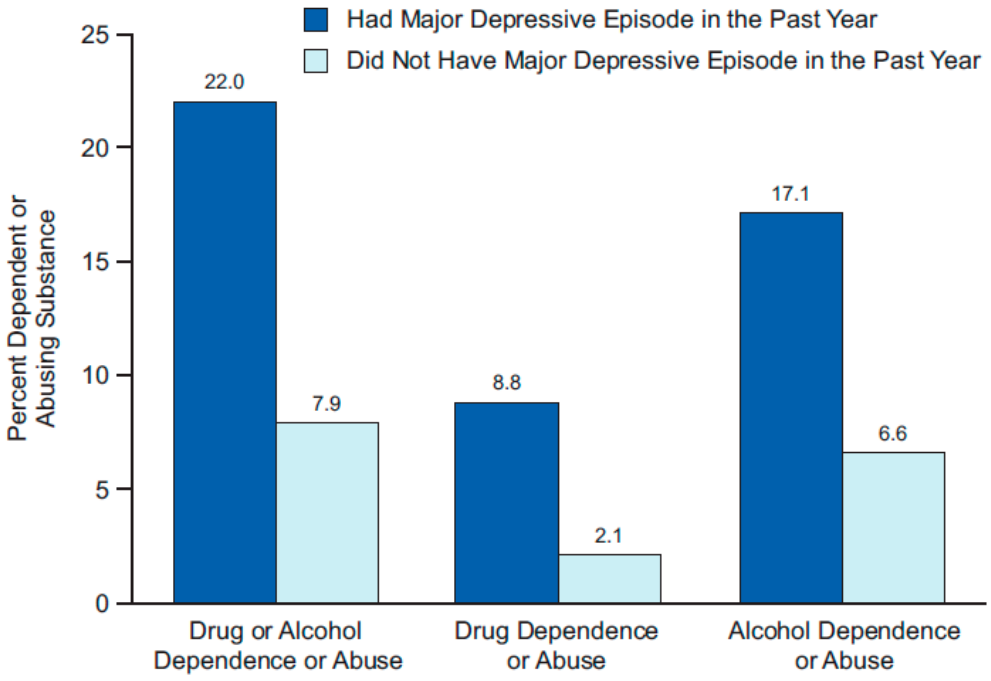


Fig. 8. *Substance dependence or abuse among adults age 18 or older, by major depressive episode in the past years, 2010.*
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Mental Health Findings. www.samhsa.gov/data/NSDUH/2k10MH_Findings/2k10MHResults.pdf (171) Access date 2/23/2012

3.0 Where Do Non-Therapeutic Drugs Come From?

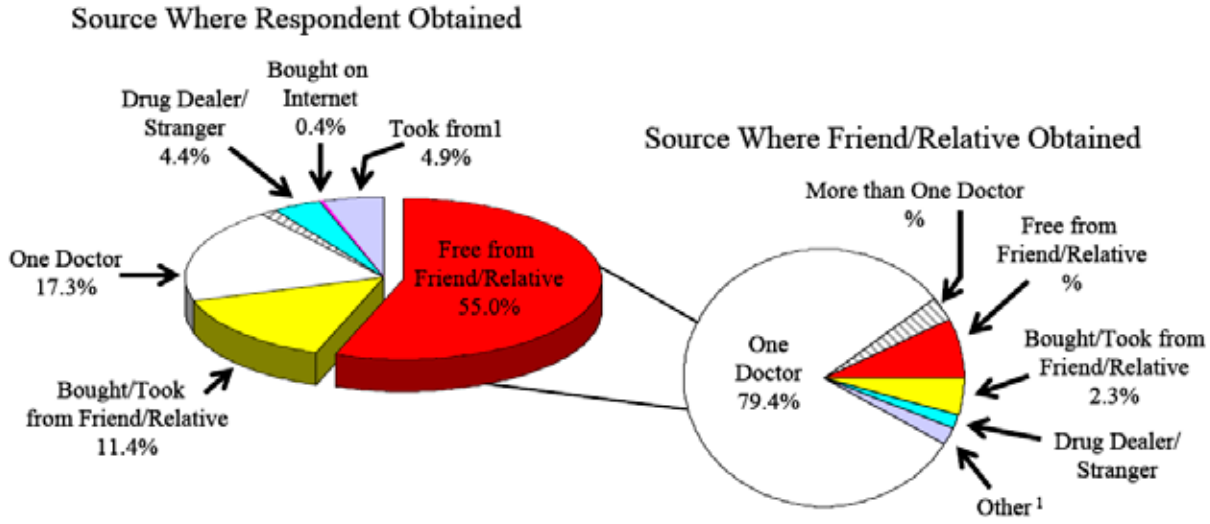
Among persons aged 12 or older in 2009-2010 who used pain relievers nonmedically in the past 12 months, 55% obtained pain relievers from a friend or relative for free (170). Among the remaining 45%, 11.4% bought them from a friend or relative (which was significantly higher than the 8.9% from 2007-2008), and 4.8% essentially stole them from a friend or relative (Fig. 9). However, only one in 6 or 17.3% indicated that they received the drugs through a prescription from one doctor, while only 4.4% received pain relievers from a drug dealer or other stranger, and 0.4% bought them on the Internet, with no significant changes from 2007 to 2008.

Even more striking is the fact that in 2009-2010, 41.5% 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 30.7% buying it from a friend or relative (170).

4.0 Escalating Use Of Therapeutic Opioids

The escalating use of therapeutic opioids, specifically in high doses over long periods of time or even lifetime use of long-acting drugs, and the combination of long and short-acting drugs continue to have serious consequences for costs of health care and economic stability.

The data overwhelmingly suggest that the increased supply of opioids, high medical users, doctor shoppers, and patients with multiple comorbid factors contribute to the majority of fatalities. The quadrupled sales of opioid analgesics between 1999 and 2010 are a perfect example of the therapeutic opioid explosion. The data on sales and distribution of opioids show an increase from 96 mg morphine equivalents per person in the United States in 1997 to 710 mg per person in 2010 (34,153). This has been estimated to be the equivalent of 7.1 kg of opioid medication per 10,000 persons or enough to supply every adult American with 5 mg of hydrocodone every 6 hours for 45 days. Sales of hy-



Note: Totals may not sum to 100% because of rounding or because suppressed estimates are not shown.

One took them from a friend or relative without asking

Fig. 9. *Source where pain relievers were obtained for most recent nonmedical use among past year users age 12 or older: 2009-2010.* Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Mental Health Findings. www.samhsa.gov/data/NSDUH/2k10MH_Findings/2k10MHResults.pdf (171) Access date 2/23/2012

drocodone have increased by 280% from 1997 to 2007, whereas methadone usage has increased 1,293% and oxycodone usage by 866%, as illustrated in Table 5 (32). The estimated number of prescriptions filled for opioids exceeded 256 million in the United States in 2009, with 234 million prescriptions for immediate-release (IR) opioids and 22.9 million for extended-release (ER) opioids with significant increases from 21.3 million for

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: www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.html Access date: 8/25/2010
Source for 2007 data - www.justice.gov/ndic/pubs33/33775/dlinks.htm
Adapted from: Manchikanti L, et al. Therapeutic use, abuse, and nonmedical use of opioids: A ten-year perspective. Pain Physician 2010; 13:401-435 (32).

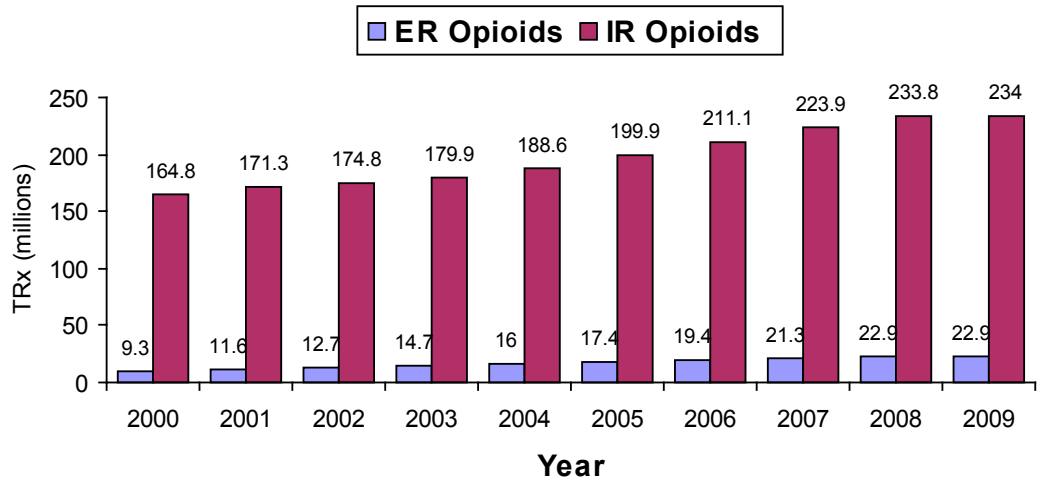


Fig. 10. *Total number of prescriptions dispensed for ER/LA and IR opioids from U. S. outpatient retail pharmacies, year 2000 – 2009 (173).*
Source: SDI, Vector One ®: National (174).

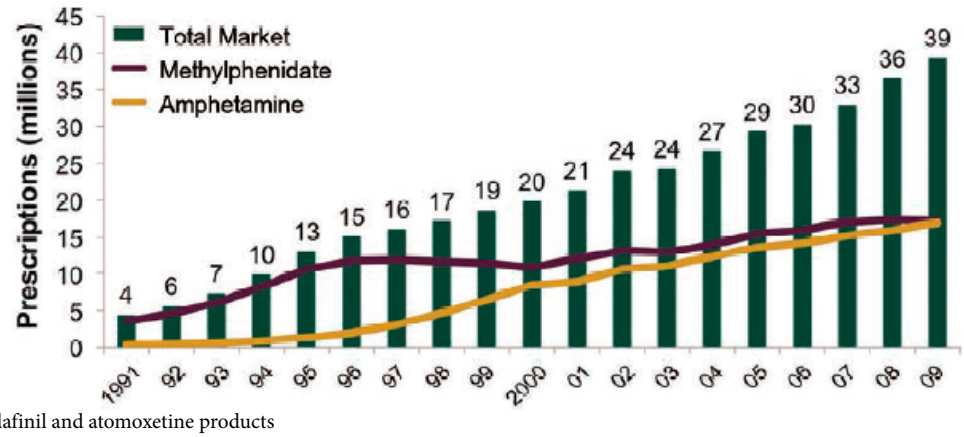
ER opioids and from 223.9 million for IR opioids from 2007 as illustrated in Figure 10 (172-174). The data are even more compelling when compared from 2002 to 2009 with an increase from 9.3 million for ER opioids to 22.9 million, a 146% increase, and from 164.8 million to 234 million for IR opioids, a 42% increase with an annual increase of 21% for ER opioids and 6% for IR opioids. Most prescriptions were for hydrocodone and oxycodone-containing products (84.9%) and issued for short treatment courses, 19.1% for less than 2 weeks, 65.4% for 2-3 weeks. Of these, however, approximately 12% of the prescriptions were issued to those aged 10 to 29 years. This may signal a potential problem for this population, as this is also the population most likely to abuse drugs and develop addictions (172). In addition, the data also illustrates an 8-fold increase in stimulant prescriptions from 1991 to 2009 as illustrated in Fig. 11.

Table 6 illustrates hydrocodone with acetaminophen being the number one prescription from 2006 through 2011 (175). However, narcotic analgesics constitute number 4 in the proportion of patients treated in selected therapies with hypertension, topping at 42.4 million and narcotic analgesics at 15.6 million, constituting number 10 in spending in leading therapy areas with oncologicals constituting 23.2 billion and narcotic analgesics constituting 8.3 billion in 2011 as illustrated in Tables 7 and 8 and Fig. 12 (175).

The United Nations Office on Drugs and Crime, in an evaluation of the world supply of opioid, shows 90% of the global consumption of morphine, fentanyl, and oxycodone registered in 2009 occurring in Australia, Canada, New Zealand, the United States and several European countries (60,85).

Another World Health Organization (WHO) report (87) showed that based on the statistics from the International Narcotics Control Board (INCB) in 2003, 6 developed countries accounted for 79% of global morphine consumption, whereas developing countries which represent 80% of the world population accounted for only about 6% of global morphine consumption. In addition, the most recent data showed that in 2007, 6 developed countries reported the highest level of morphine consumption and 132 of the 160 signatory countries that require reporting of consumption were below the global mean as illustrated in Fig. 13. This simply illustrates that millions of patients with moderate to severe pain caused by different diseases and conditions may not be getting treatment to alleviate their suffering in some countries, while more of them are receiving it in other countries such as the United States, which uses 99% of the world's supply of hydrocodone and 83% of the world's oxycodone (176-178).

Gram for gram, people in the United States consume more narcotic medication than any other nation worldwide. The International Narcotic Control Board, a division of the United States, estimates global pharmaceutical companies produce more than 75 tons a year of oxycodone, compared with 11.5 tons in 1999,



*excludes modafinil and atomoxetine products

Fig. 11. Projected number of prescriptions for stimulants dispensed by U.S. retail pharmacies, 1991-2009.*
Source: SDI, Vector One ®: National (174).

Table 6. *Top medicines by prescriptions*.

DISPENSED PRESCRIPTIONS MN		2007	2008	2009	2010	2011
Total US Market		3,825	3,866	3,949	3,993	4,024
1	Hydrocodone/acetaminophen	120.9	125.5	129.4	132.1	136.7
2	Levothyroxine sodium	97.4	98.9	100.2	103.2	104.7
3	Simvastatin	49.0	68.0	84.1	94.4	96.8
4	Lisinopril	71.5	77.2	83.0	87.6	88.8
5	Amlodipine besylate	40.8	46.0	52.1	57.8	62.5
6	Omeprazole (RX)	27.7	35.8	45.6	53.5	59.4
7	Metformin HCL	49.2	51.6	53.8	57.0	59.1
8	Azithromycin	47.1	51.9	54.7	53.6	56.2
9	Amoxicillin	54.0	51.3	52.9	52.4	53.8
10	Alprazolam	41.4	43.3	45.3	47.7	49.1
11	Hydrochlorothiazide	48.5	48.5	47.9	47.8	48.1
12	Zolpidem tartrate	34.5	39.1	42.7	43.7	44.6
13	Atorvastatin	65.8	58.5	51.7	45.3	43.3
14	Furosemide	44.7	44.4	43.8	43.6	42.3
15	Oxycodone/acetaminophen	31.3	33.6	36.7	37.9	38.8
16	Fluticasone	23.9	26.2	30.1	34.8	38.4
17	Citalopram HBR	18.1	22.6	27.3	32.2	37.8
18	Metoprolol tartrate	43.5	38.4	41.1	38.9	37.8
19	Sertraline HCL	33.4	33.7	34.8	36.2	37.6
20	Metoprolol succinate	33.0	41.5	26.9	33.0	34.5
21	Warfarin sodium	34.4	34.9	35.7	35.6	33.9
22	Tramadol HCL	20.6	23.3	25.5	28.0	33.9
23	Potassium	36.7	35.8	35.2	34.7	33.7
24	Prednisone	25.9	27.1	27.8	28.7	33.7
25	Atenolol	45.0	42.0	39.5	36.4	33.4

Source: IMS Health, National Prescription Audit, Dec. 2011 (175).
Notes: Report reflects prescription-bound products including insulins and excluding other products such as OTC. Table shows leading active-ingredients or ingredient fixed-combinations, and includes those produced by both branded and generic manufacturers. Includes all prescriptions dispensed through retail pharmacies - including independent and chain drug stores, food store pharmacies and mail order as well as long-term care facilities. Prescription counts are not adjusted for length of therapy. 90-day and 30-day prescriptions are both counted as one prescription.

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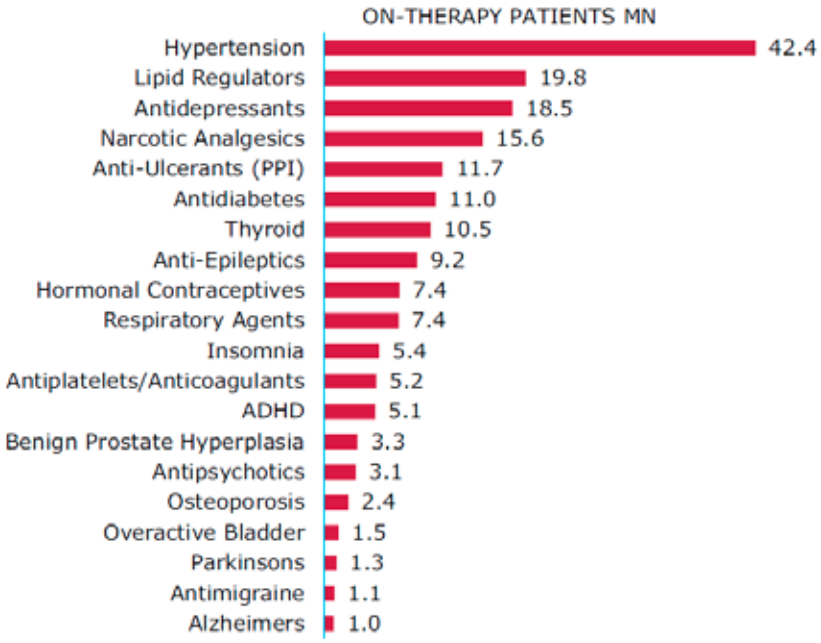
of which more than 80% of is consumed in the United States. The International Narcotics Board also reports that U.S. demand for hydrocodone, the most commonly prescribed opioid, is about 27.4 million grams annually compared to 3,237 grams for Britain, France, Germany, and Italy combined (61,177,178).

Caudill-Slosberg et al (165) in one of the earliest evaluations demonstrated that opioid use doubled from 8% in 1980 to 16% in 2000. The data also illustrates that from 1999 to 2002, 4.2% of U.S. adults reported the use of opioid analgesics for pain within the past month (179). In a report of opioid use in one of the states in the United States (Utah) (180), the data showed that 20.8% of adults had been prescribed an opioid in the last year and that 29.1% of these prescriptions were for long-term pain. Sullivan et al (181) also showed over a 6 year period that the proportion of enrollees receiving opioids with a diagnosis of chronic



Source: IMS Health, LifeLink, Dec 2011

Fig. 12. *Treated patients in selected therapy.*

Table 7. *Spending based on the therapeutic class.*

SPENDING $BN		2007	2008	2009	2010	2011
Total US Market		280.5	285.7	300.7	308.6	319.9
1	Oncologics	18.1	19.7	21.5	22.3	23.2
2	Respiratory Agents	15.1	16.0	18.1	19.3	21.0
3	Lipid Regulators	19.4	18.1	18.6	18.8	20.1
4	Antidiabetics	12.2	13.6	15.8	17.7	19.6
5	Antipsychotics	12.8	14.3	14.7	16.2	18.2
6	Autoimmune Diseases	7.6	8.6	9.7	10.6	12.0
7	Antidepressant	11.7	11.7	11.5	11.6	11.0
8	HIV Antivirals	6.2	7.1	8.2	9.3	10.3
9	Anti-Ulcerants	14.6	14.2	14.1	11.9	10.1
10	Narcotic Analgesics	6.7	7.3	8.0	8.4	8.3
11	ADHD	4.0	4.7	5.8	6.7	7.9

SPENDING $BN		2007	2008	2009	2010	2011
12	Platelet Aggregation Inhibitors	5.0	5.7	6.5	7.1	7.8
13	Angiotensin II Inhibitors	6.5	7.6	8.6	8.7	7.6
14	Multiple Sclerosis	3.4	4.1	5.0	5.8	7.1
15	Vaccines (Pure, Comb, Other)	5.9	5.0	4.7	5.7	6.3
16	Anti-Epileptics	10.0	11.1	6.9	5.6	5.9
17	Erythropoietins	4.1	4.5	4.7	4.8	5.2
18	Immunostimulating Agents	8.4	6.9	6.3	6.1	5.1
19	Hormonal Contraceptives	4.1	4.1	4.1	4.2	4.5
20	Antivirals, excl. Anti-HIV	3.6	3.9	4.8	3.2	3.7

Source: IMS Health, National Prescription Audit, Dec. 2011 (175).

Notes:
Therapy areas are based on proprietary IMS Health definitions. Report reflects prescription-bound products including insulins and excluding other products such as OTC. Includes all prescriptions dispensed through retail pharmacies - including independent and chain drug stores, food store pharmacies and mail order as well as long-term care facilities. Prescription counts are not adjusted for length of therapy. 90-day and 30-day prescriptions are both counted as one prescription.

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Table 8. *Top therapeutic classes by prescriptions.*

DISPENSED PRESCRIPTIONS MN		2007	2008	2009	2010	2011
Total US Market		3,825	3,866	3,949	3,993	4,024
1	Antidepressants	237	241	247	254	264
2	Lipid Regulators	233	242	254	260	260
3	Narcotic Analgesics	231	239	241	244	238
4	Antidiabetics	165	166	169	172	173
5	Ace Inhibitors (Plain & Combo)	159	163	166	168	164
6	Beta Blockers (Plain & Combo)	162	164	163	162	161
7	Respiratory Agents	147	147	152	153	153
8	Anti-Ulcerants	134	139	146	147	150
9	Diuretics	137	135	132	131	128
10	Anti-Epileptics	102	110	116	122	128
11	Tranquillizers	98	101	104	108	111
12	Thyroid Preparations	103	104	105	107	110
13	Calcium Antagonists (Plain & Combo)	87	90	93	96	98
14	Antirheumatic Non-Steroid	90	91	92	93	97
15	Hormonal Contraceptives	94	94	93	91	90
16	Angiotensin II Inhibitors	83	86	85	84	86
17	Broad Spectrum Penicillins	77	74	77	76	77
18	Macrolides & Similar Type Antibiotics	63	66	69	67	69
19	Hypnotics & Sedatives	58	60	63	63	63
20	Vitamins & Minerals	60	59	58	58	60

Source: IMS Health, National Prescription Audit, Dec. 2011 (175).
Appendix notes:
Therapy areas are based on proprietary IMS Health definitions. Report reflects prescription-bound products including insulins and excluding other products such as OTC. Includes all prescriptions dispensed through retail pharmacies - including independent and chain drug stores, food store pharmacies and mail order as well as long-term care facilities. Prescription counts are not adjusted for length of therapy. 90-day and 30-day prescriptions are both counted as one prescription.

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non-cancer pain and opioid prescriptions increase. Opioids are also used commonly in combination with sedative hypnotics. Vogt et al (182) in an evaluation of analgesic usage for low back pain and its impact on health care costs and service use showed that in 2001, a total of $1.4 million was spent on opioids, which constituted 68% of prescriptions for analgesics.

The data from reports and pain management settings is disconcerting. Over 90% of patients received opioids for chronic pain management (32,169,172,183-188). Even more alarming, however, is the fact that the majority of the prescriptions are from outside pain management settings. Volkow et al (172) showed that only a small proportion of prescriptions were from pain clinics or specialists from anesthesiology in 2009. Moreover, Deyo et al (31) illustrated that approximately 20% of patients in primary care settings were long-time opioid users with 61% receiving a course of opioids. In young veterans, Wu et al (189) showed that prevalence of chronic opioid use increased from 3% in 2003 to 4.5% in 2007. Patients on average were exposed to 2 different opioids and had 3 different opioid prescribers. Not surprisingly, 80% of the opioid prescriptions during the study were prescribed by pri-

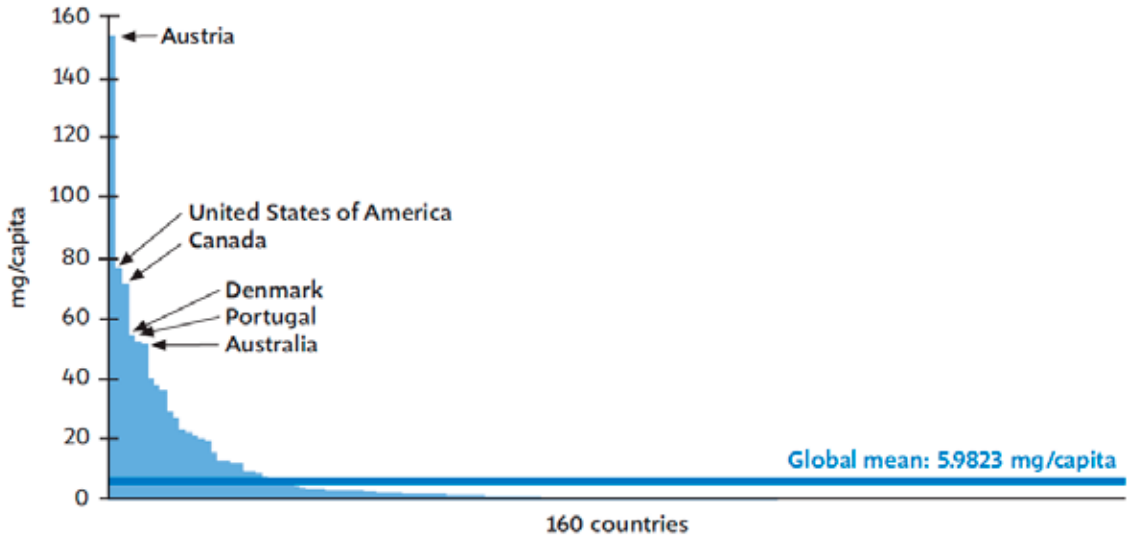


Fig. 13. *Global morphine consumption in 2007 (mg/capita).*
Source: International Narcotics Control Board, United Nations data. Graphic created by the Pain and Policy Study Group, University of Wisconsin/WHO Collaborating Center, 2009.

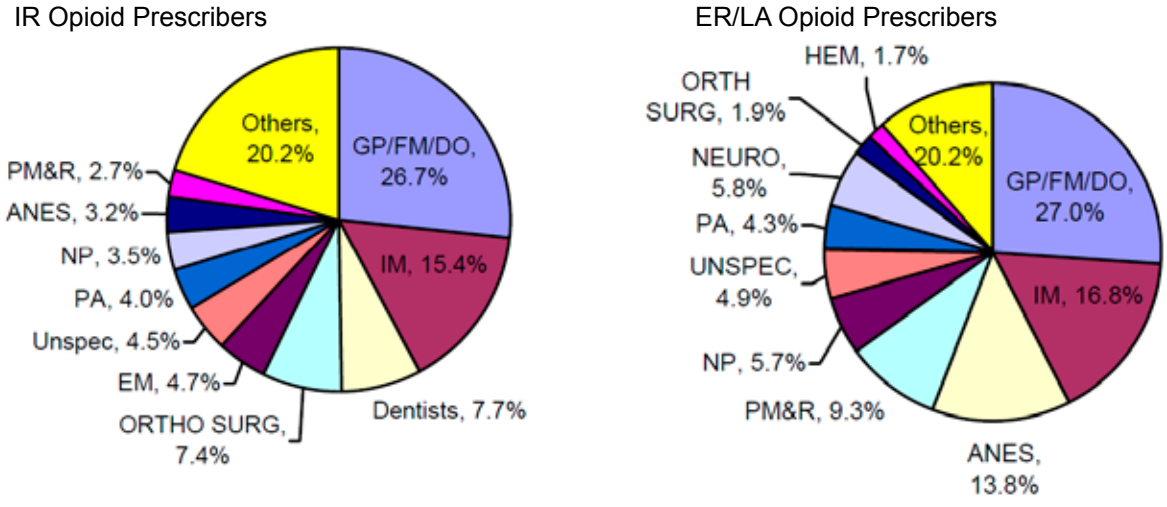


Fig. 14. *Total number of prescriptions dispensed in the U.S. by top 10 prescribing specialties for IR and ER/ LA opioids, year 2009 (173).* Source: SDI, Vector One ®: National (174).

mary care providers, and less than 1% was from pain specialists.

In fact, the data illustrates that in 2009 (Fig. 14). among the top 10 specialties of those prescribing immediate release opioids were general practitioners/family medicine 26.7%, internal medicine 15.4%, anesthesiologists constituting 3.2%, and physical medicine and rehabilitation specialists constituting 2.7% (173,174). In contrast, for ER or long-acting opioids in 2009, anesthesiologists constituted 13.8% and physical medicine and rehabilitation constituted 9.3%, with general practitioners, family medical doctors, osteopaths, and internal medicine specialists still dominating the field with 27% and 16.8%, in essence exceeding their prescriptions of immediate release opioids (173,174).

5.0 Relationship of Escalating Opioid Use and Adverse Consequences

While numerous adverse effects have been reported, ever increasing opioid related fatalities, including drug poisoning deaths, are crucial. In the United States, in 2008, one or more prescription drugs were involved in 20,044 of the 27,153 deaths with a specified drug. Opioid pain relievers were involved in 14,800 drug overdose deaths, compared to 11,500 of 27,500 fatal unintended drug overdose deaths in 2007 – an increase of 3,300 in just one year (160). Alarmingly, in 2007 there were more opioid analgesic overdose deaths than overdoses involving heroin and cocaine combined (Fig. 15). In addition, during the same time frame, drug-related suicides also increased, with opioid analgesics being involved in roughly 3,000 of the 8,400 overdose deaths in the United States in 2007 that were suicide or of undetermined intent (190). Complicating these grave statistics, for every unintentional overdose death related to an opioid analgesic, 9 are admitted for substance abuse treatment, 35 visit emergency departments, 161 report drug abuse or dependence, and 461 report non-medical uses of opioid analgesics (34). Not surprisingly, in 2007, non-suicidal drug poisoning deaths exceeded both motor vehicle traffic and suicide deaths in 20 states, with data from Ohio illustrating that the number of deaths from unintentional drug poisoning surpassed the numbers of deaths from both suicide and motor vehicle crashes combined (190-192). Thus, it has been concluded that opioid analgesics contributed to fatalities based on opioid abuse and increasing doses, doctor shopping, and other aspects of drug abuse as illustrated in Fig. 16 (160). The data from emergency department visits sadly illustrate that opioids, sedatives, and non-prescription sleep aides are often taken more than prescribed or solely for the feeling they cause, and that this trend is steadily increasing (170).

The Centers for Disease Control and Prevention (CDC) (34) also reported the percentage of prescription drug overdoses by risk group in the United States. This report showed that approximately 80% of prescribed low-doses (less than 100 mg of morphine equivalent dose per day – considered as high dose by many) were by a single practitioner, accounting for an estimated 20% of all prescription overdoses (Fig. 17). In contrast, among the remaining 20% of patients, 10% of prescribed high doses (greater than 100 mg morphine equivalent dose per day) (193-195) per day of opioids by single prescribers account for an estimated 40% of the prescription opioid overdoses (131,195). The remaining 10% of patients seeing multiple doctors and typically involved in drug diversion contribute to 40% of overdoses (152). Furthermore, among persons who died of opioid overdoses, a significant proportion did not have a prescription in their records for the opioid that killed them; in West Virginia, Utah, and Ohio, 25% to 66% of those who died of pharmaceutical overdose used opioids originally prescribed to someone

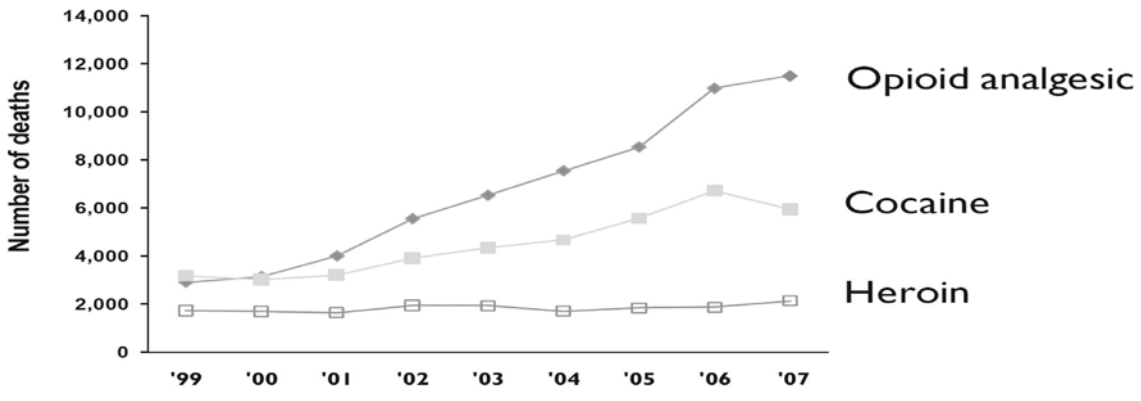
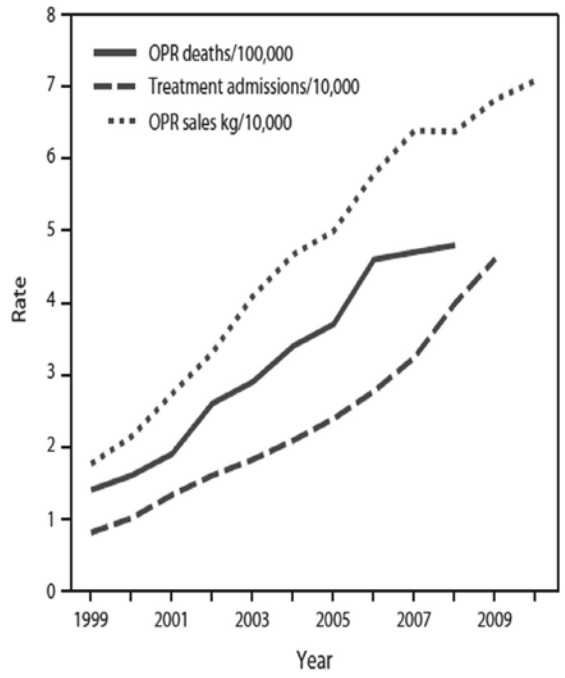


Fig. 15. *Deaths from unintentional drug overdoses in the United States according to major type of drug, 1999-2007.*
Source: Centers for Disease Control and Prevention. Unintentional Drug Poisoning in the United States. July 2010. http://www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf (190).



* Age-adjusted rates per 100,000 population for OPR deaths, crude rates per 10,000 population for OPR abuse treatment admissions, and crude rates per 10,000 population for kilograms of OPR sold.

Fig. 16. *Rates of opioid pain reliever overdose death, opioid pain relief treatment admissions, and kilograms of opioid pain relievers sold – United States, 1999-2010.*
Source: Centers for Disease Control and Prevention. Vital signs: Overdoses of prescription opioid pain relievers – United States, 1999-2008. MMWR. Morb. Mortal Wkly. Rep. 60, 1487-1492 (2011) (160).

else (152,192,196).

The responsible opioid prescription community considers that the adverse consequences of appropriately prescribed and used opioids are least considered, as the blame is placed predominantly on abuses and overuses (49,71,116-119). Consequently, it is coupled with a lack of evidence regarding long-term benefits and ample evidence that the increased prescription of opioids is fueling an epidemic of addiction and overdose deaths. This crisis is rooted in a lack of education and misinformation, leading to overprescribing and a tendency to focus on ineffective strategies (49,71,197-199). In fact, the majority of cases involving injury and death occur in people using opioids exactly as prescribed, not just those misusing or abusing them (71). Even more importantly, most studies indicate that patients on long-term opioid therapy are unlikely to stop even if analgesia and function are poor and safety issues arise. Frequently, despite good relief and improvement in function with modalities other than opioids including interventional techniques and surgery, patients continue on opioids (200-215).

Even though there is no evidence to support the previous teaching that long-acting opioids can provide better analgesia, and less risk for abuse than immediate release products (32,71,96,100,103,107,116-119,216), the use of higher doses, with a combination of short-acting and long-acting opioids, continues to escalate. Thus, it is believed that commencing long-acting opioid therapy is often the starting point for high dose opi-

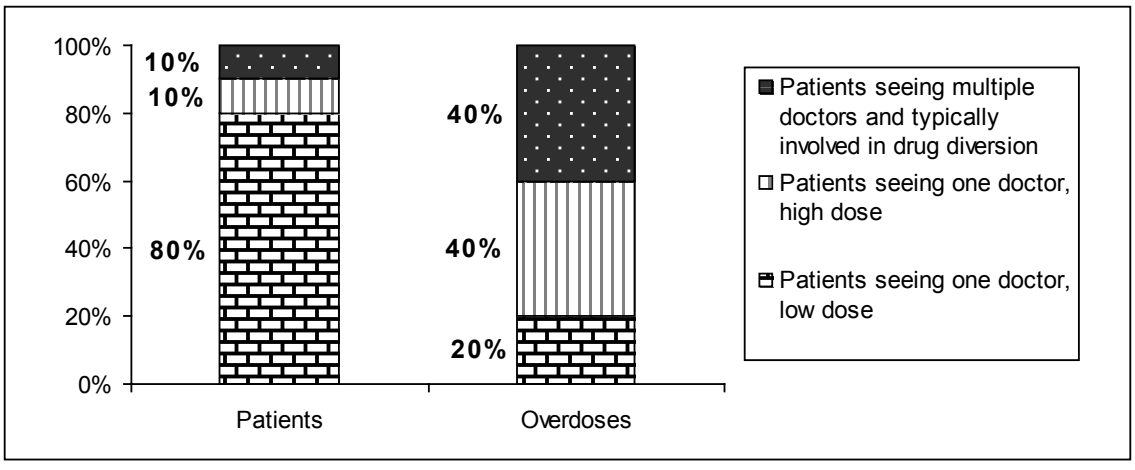


Fig. 17. *Percentage of patients and prescription drug overdoses, by risk group – United States.*
Source: Centers for Disease Control and Prevention. CDC grand rounds: Prescription drug overdoses – a U.S. epidemic. MMWR. Morb. Mortal Wkly. Rep. 61, 10-13 (2012) (34).

oid therapy, a practice that growing evidence suggests is harmful to patients and increases the black market availability of opioids through diversion (71,217-222).

Multiple studies in the literature (23,32,37,46-49,223-236) have reported an association between opioid prescribing and overall health status, with increased disability, medical costs, subsequent surgery, and continued or late opioid use. Overall, the epidemiologic studies are less positive with regards to improvement in function and quality of life with opioids in chronic pain patients (110,116-119,170,232,237). In fact, in an epidemiologic study from Denmark (23) where opioids are prescribed liberally for chronic pain, it was demonstrated that in patients receiving opioids, pain was worse, health care utilization was higher, and activity levels were lower compared to a matched cohort of chronic pain patients not using opioids. This study suggested that when opioids are prescribed liberally, even if some patients benefit, the overall population does not. Another study (33) also reported worse pain, higher health care utilization, and lower activity levels in opioid-treated patients compared to matched cohort of chronic pain patients not using opioids. Sjøgren et al (49) in a population-based cohort study on chronic pain and the role of opioids, showed that the odds of recovery from chronic pain were almost 4 times higher among individuals not using opioids compared with individuals using opioids. In addition, they also showed that use of strong opioids was associated with poor health-related quality of life, and higher risk of death. In addition, opioid abuse in chronic pain has been highly prevalent, along with illicit drug usage in addition to misuse or abuse of therapeutic opioids (32,143-152,183-188).

Conclusion

What emerges from the available data utilized in this review is the conclusion that over the past 20 years there has been an escalation of the therapeutic use of opioids and other psychotherapeutics as well as their abuse and nonmedical use. 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 is now inappropriate prescribing patterns, based on a lack of knowledge, perceived safety, and undertreatment of pain.

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