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Current State of Opioid Therapy and Abuse

Laxmaiah Manchikanti^{1,2} · Adam M. Kaye³ · Alan D. Kaye⁴

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Abstract Currently, there is growing tension between the twin challenges of opioid therapy for chronic pain and adverse consequences of abuse, leading to multiple complications including respiratory failure and death. The recent data from Centers for Disease Control and Prevention (CDC) have shown continued escalation of prescription opioid use with opioid overdose deaths topping all previous estimations. Numerous policy initiatives, advisories, and guidelines have been advanced through the years to control the opioid epidemic. The strategies to prevent opioid abuse and to maintain opioid therapy when medically necessary fall into primary and secondary prevention categories. The primary prevention category is extremely crucial, since it involves education of primary care providers and patients at the starting point of

opioid therapy. The education of surgeons and other prescribers is as crucial as the education of primary care physicians.

Keywords Chronic opioid therapy · Opioid abuse · Opioid adverse consequences · Opioid deaths · Opioid overdoses · Prescription drug monitoring programs (PDMPs) · Abuse resistance opioids

Introduction

The current state of opioid therapy and abuse continues to increase the tension between the twin challenges of opioid therapy for chronic pain and its abuse leading to dependency, addiction, hyperalgesia, and death among various other complications [1•, 2•, 3•, 4, 5•]. Chronic pain, which affects a large proportion of the population, not only in the USA, but across the globe, is associated with functional loss and disability, reduced quality of life, increasing health care costs, and premature death, which continue to escalate [6–10]. Similarly, the prescription of opioids associated with complications of abuse also continues to escalate across the globe [1•, 2•, 3•, 4, 5•, 11–17, 18•, 19, 20•, 21, 22•, 23, 24•, 25–29, 30•, 31–36]. Drug abuse, while most prevalent in the USA, is also a problem in other places around the globe including Canada, Australia, Europe, the UK, and other countries. Policy makers have responded with efforts to curb the growing epidemic of misuse, and a global alarm has been sounded among countries wishing to avoid this epidemic [16]. The USA has been the foremost country in the global consumption of opioids, with Canada, Denmark, Germany, Australia, the UK, and other countries following it. In fact, during 2010, Canada topped the USA with over 750 morphine equivalents per capita followed by 690 morphine equivalents in the USA [4].

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However, the prevalence of chronic pain and associated disability has been increasing in the general population and specifically in the elderly across the globe [2•, 4, 26, 30•].

Current State of Opioid Therapy

Opioid prescribing, along with opioid sales, and associated complications have increased worldwide. Atluri et al. [3•], in an assessment of the trends and medical use and misuse of opioid analgesics from 2004 to 2011, showed an increase in the medical use of all opioids ranging from 37 % for methadone to 2318 % for buprenorphine with a 20 % decrease for codeine. In addition, they also showed an overall increase of opioid usage of 690 % from 1996 to 2004, with misuse increasing by 4680 % from 1996 to 2011. Prescriptions for opioid analgesics in the USA increased substantially from 2002 to 2010 but then decreased slightly from 2011 to 2013 with 76 million prescriptions in 1991 and 2007 million in 2013 [2•, 36]. A parallel relationship between the availability of prescription opioid analgesics through legitimate pharmacy channels and the diversion and abuse of these drugs associated with adverse outcomes was demonstrated [1•, 2•, 3•].

Opioid prescriptions for chronic non-cancer pain skyrocketed in the late 1990s. Reports showed that from 1990 to 1996, the trend of increasing medical use of opioid analgesics to treat pain did not appear to contribute to an increase in health due to the consequence of opioid analgesic abuse [37]. In addition, the second publication with data from 1997 to 2002, also added to the fuel with a conclusion that an increase in the medical use of opioids was the general indicator of progress in providing pain relief with the caveat that increases in abuse of opioids was a growing public health problem and should be addressed by identifying the causes of sources of diversion, without interfering with legitimate medical practice and patient care [38]. However, assessment of the data from 2000 to 2013 [2•, 3•] has shown that the policies of the first two studies have lead to increasing opioid prescriptions strongly correlated with prescription opioid fatalities. Opioid prescriptions and rates of opioid diversion and abuse increased from 1990 to 2010 but have been flat or decreased from 2011 to 2013 [2•]. The rate of opioid-related deaths rose and fell in a similar pattern, rising again in 2014 [1•, 2•]. Multiple policies contributed to rising opioid prescriptions and deaths, including lifting of the restrictions on opioid prescribing by state medical boards, which was considered as the primary driver [39], standards for both inpatient and outpatient pain management implemented in 2000 by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) which considered pain the fifth vital sign [40•], and, finally, the concept of a patient's right to pain relief resulting in validation of a physician's need to increase their opioid prescribing. During the same period, many like-minded physicians and a number of organizations also called

for increasing opioid treatment for patients with chronic non-cancer pain [30•, 40•]. At the same time, the pharmaceutical industry took advantage of these trends and unleashed their marketing machine, promoting all types of opioids for all types of pain, ignoring the lack of evidence, safety, and inappropriate use and adverse consequences. Thus, even as of today, with the explosion of literature and continued approval of multiple new strong opioids, there is a lack of evidence for long-term opioid therapy [33, 34, 41–44].

Between 2009 and 2013, there was a 9.2 % decline in the prevalence of people filling prescriptions for opioids, yet both the number of prescriptions filled for patients and the number of days of medication per prescription increased by approximately 8.4 % [36]. It has been estimated that more than 9.4 million insured Americans were longer-term users of opioids, based on 2013 US census data [45]. Further, this data also shows that almost half (46.9 %) of new opioid users who take these medications for more than 30 days in the first year continue using them for 3 years or longer [36]. This data is echoed by multiple publications [46, 47•, 48–51]. Thielke et al. [46] in a study of chronic opioid therapy in two large health plans showed that over 80 % of participants continued higher-dose opioid use at 1 year, regardless of reported problems, concerns, side effects, pain reduction, or perceived helplessness. In a prospective evaluation of psychotherapeutic and illicit drug use in patients presenting with chronic pain at the time of initial evaluation [47•], 94 % of patients were on long-term opioids, 35 % were also on benzodiazepines in combination with opioids, and nearly half of the patients were receiving more than 40-mg equivalence of morphine on a long-term basis, initiated and maintained by primary care physicians. Thus, opioid overuse pain syndrome has been described [20•]. Further, the majority of the prescriptions are provided by primary care physicians in the USA [22•, 24•, 48].

It further has been shown that the prevalence of longer-term opioid use increases with age and is highest among those aged 65 and older, with 8.9 % of that population taking opioid pain medications in 2013 [52]. In fact, older Americans were taking opioids only for pain treatment with increasing frequency, up 4.5 % from 2009 to 2013, whereas the number of seniors using only non-steroidal anti-inflammatory drugs (NSAIDs) declined at the same time by 5.1 %. Further declines in NSAIDs may be seen with recent Food and Drug Administration (FDA) warnings about NSAID use [53]. The surveys also showed that among patients using opioids on a longer-term basis, almost 30 % had concurrent prescriptions for benzodiazepines, 28 % had prescriptions for muscle relaxants, and 8 % of patients were taking all three types of medications during the same time period. Thus, it has been determined that nearly 60 % of opioid medication users were taking a risky combination of prescription drugs.

Problems similar to those in the USA have been described in other countries. Weisberg et al. [16] shared concerns about

an opioid consumption epidemic lurking at a similar level in the UK. They showed that per capita consumption of opioids in the UK in 2010 was comparable to that of the USA in 1999, which was the beginning of a steep increase in opioid prescribing, arguably a “tipping point” in opioid misuse in the USA. In fact, a survey of attitudes toward, and practice of, opioid prescription analgesics for chronic non-malignant pain in general practice in the UK [52] showed almost three quarters of general practitioners sometimes or frequently prescribed strong opioids for chronic non-cancer pain.

Canada also has been facing similar issues as the USA with increasing opioid prescriptions and related adverse consequences. Fisher et al. [18•] described that consumption of prescription opioids in Canada has steeply risen through the years 2000 to 2010 to population levels which are second only to the USA in global comparison with common key indicators of morbidity and mortality also increasing sharply [17, 18•].

Australia has faced significant increases in opioid prescription issues, along with their adverse consequences [19]. There is ample evidence that a positive correlation exists between the magnitude of prescription opioid analgesic utilization and harms arising from both their dependence and fatal overdoses.

Germany also faces similar problems, however, with less intensity. In an evaluation of opioid therapy in the treatment of chronic pain conditions in Germany, Werber et al. [15] showed that the number of opioid prescriptions increased linearly from 2006 to 2010. They showed that in 2006, 5.7 % of the population obtained at least one prescription for an opioid medication, which increased to 5.9 % in 2009.

Current State of Opioid Abuse and Adverse Consequences

The Centers for Disease Control and Prevention (CDC) added the unprecedented increase in opioid pain reliever consumption leading to the worst drug overdose epidemic in the US history and opioid overdose prevention to the list of the top five public health challenges [54]. In addition to the CDC's activities educating about the adverse consequences of opioids including deaths and other harms, they also have undertaken the development of opioid guidelines for primary care physicians [55].

A recent CDC report from the USA has shown that since 2000, the rate of deaths from opioid overdoses increased significantly from 7.9 per 100,000 in 2013 to 9.0 per 100,000 in 2014, a 14 % increase [1•]. This report also showed that in 2014, opioids were involved in 28,647 deaths, or 61 % of all drug overdose deaths, tripling since 2000 (Fig. 1). In addition, the report also showed that in the USA, a 15-year increase in overdose deaths involving prescription opioid pain relievers and a recent search in illicit opioid overdose deaths, driven largely by heroin, shows two distinct but interrelated trends. However, the origin of prescriptions, which has been

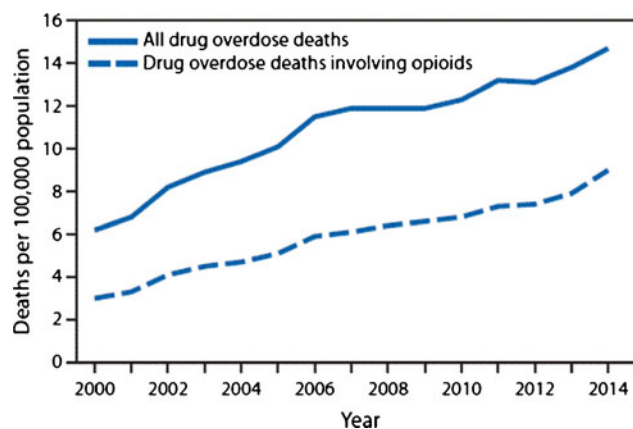


Fig. 1 Age-adjusted rate* of drug overdose deaths† and drug overdose deaths involving opioids§,¶—United States, 2000–2014 from Rudd et al. [1•]

inaccurately ascribed to pain physicians [22•, 24•, 48], has been shown to be related to mostly primary care and surgical specialties. All pain management specialties were lower than primary care in number of opioid prescriptions provided.

Even more disturbing is the fact that more than 90 % of patients who survive a prescription opioid overdose continue to be prescribed opioids after the event, usually by the same prescriber, but at a lesser dose [56]. This report also showed that at 2 years, the cumulative incidence of repeat overdose was 17 % for patients receiving high dosages (≥ 100 mg of morphine equivalent dosage per day) of opioids after the index overdose, 15 % for those receiving moderate dosage (50 to <99 mg of morphine equivalent dosage per day), 9 % for those receiving low dosage (<50 mg of morphine equivalent dosage per day), and 8 % for those receiving no opioids. This practice continues to be prevalent despite multiple guidelines advising otherwise.

Opioid abuse has become a significant public health problem globally, specifically in the USA [1•, 2•, 3•, 4, 5•, 6–17, 18•, 19, 20•, 21, 22•, 23, 24•, 25–29, 30•, 31–36]. The economic burden of prescription opioid use, misuse, abuse, and adverse consequences is enormous across the globe [57, 58]. The non-medical use of opioid costs has been estimated as \$53.4 billion yearly, including \$42 billion in lost productivity [59]. Opioid abusers have been shown to have health care costs that are nearly nine times higher than non-abusers [60]. Further, prescription opioids also have been shown to be a gateway drug for heroin, with a study showing that as many as 80 % of heroin users first took prescription opioids [11, 61]. As early as 2001, Strassels [57] estimated that the total cost of prescription opioid abuse was \$86 billion, including workplace, health care, and criminal justice expenditures. A study of commercially insured beneficiaries in the USA found that mean per capita annual direct health care costs from 1998 to 2000 for abusers of prescribed and non-prescribed opioids

were \$16,000 compared to non-users with approximately \$1,800 who had at least one prescription insurance claim [61]. Further, inpatient expenditures accounted for 46 % of the total cost for abusers, whereas it was 17 % for non-abusers, with abusers being likely to visit the emergency department four times more frequently.

The Office of National Drug Control Policy (ONDCP) reports that the cost of drug abuse in the USA continues to escalate with costs of \$193 billion in 2007 [62]. Chou et al. [44], in a systematic review, concluded that while there is insufficient evidence to determine the effectiveness of long-term opioid therapy for improving chronic pain and function, the evidence supported a dose-dependent risk for serious harms.

Addiction, a common adverse consequence of opioid misuse, is defined as continued use of a drug despite negative consequences [63]. Consequently, opioids are described as highly addictive because they induce euphoria or positive reinforcement, and cessation of chronic use produces dysphoria with negative reinforcement. The literature shows structural and functional changes in regions of the brain that mediate effect, impulse, reward, and motivation with chronic exposure to opioids [64, 65]. According to the federal government's National Survey on Drug Use and Health (NSDUH), four out of five current heroin users report that their opioid use began with opioid pain relievers, indicating an important connection between the opioid addiction epidemic and the heroin addiction epidemic. Opioid use and simultaneous addiction escalated based on a 1986 observational study of 38 chronic patients by Portenoy and Folley [66], concluding that opioids could be prescribed safely on a long-term basis. Despite an extremely low level of evidence, this paper was widely cited to support the expanded use of opioids for chronic non-cancer pain.

Accidental overdose is a common cause of death in individuals suffering from opioid addiction [67]. These deaths are most common in individuals suffering from opioid addiction or in long-term opioid users, specifically those taking high doses with or without a history of substance use disorder.

Apart from addiction, a property of opioid drugs is their tendency for tolerance. Tolerance occurs when the person no longer responds to the same dosage, necessitating a higher dose to achieve the same results. Tolerance hinges on the ability of abused opioids to desensitize the brain's own natural opioid system, making it less responsive over time [68]. This tolerance also contributes to the high risk of overdose.

There is growing evidence suggesting that abusers of prescription opioids are shifting to heroin as prescription drugs become less available or harder to abuse [11, 35]. Of particular concern has been the rise in new populations, particularly young people. The exclusive use of heroin more than doubled

from 2008 to 2014 from 4.3 to 9 % [11, 35]. However, those using prescription opioids and heroin increased more dramatically than heroin alone [11, 35]. Further, the number of past year heroin users in the USA nearly doubled in 2012, from 380,000 in 1999 to 670,000 in 2012 [35]. The data from the CDC showed that heroin overdose death rates increased by 26 % from 2013 to 2014 and have more than tripled since 2010, from 1 per 100,000 in 2010 to 3.4 per 100,000 in 2014 [1••]. In addition, heroin is of higher risk than opioid poisoning because of its purity and injection capabilities along with possible contamination and concomitant use with potent prescription opioids, linking to transmission of human immunodeficiency virus (HIV), hepatitis (especially hepatitis C), sexually transmitted infections, and other diseases.

Cardiovascular side effects are occasionally observed with chronic opioid therapy, specifically with methadone [69–71]. Consequently, the safety of methadone has been called into question by data indicating a large increase in the number of methadone-associated overdose deaths. Methadone deaths in the USA increase steadily from about 800 in 1999 to a high of about 5500 in 2007 with a decrease to about 4900 in 2008 [69]. However, the recent data [1••] shows that between 2013 and 2014, the age-adjusted rate of death involving methadone remained unchanged. Even then, about one of every three opioid-related deaths is associated with methadone ingestion, a substantially higher proportion than any other prescription opioid, with methadone prescriptions constituting only one tenth of overall opioid prescriptions. As a result, multiple guidelines have been developed [69, 71] and the FDA has issued a limit of 30 mg per day of methadone for chronic non-cancer pain.

Multiple endocrine disturbances have been reported with chronic opioid therapy. However, this evaluation showed limited assessment with only erectile dysfunction [24•, 44].

Balancing Opioid Therapy and Abuse

Numerous policy initiatives, advisories, guidelines, and prescription drug monitoring programs (PDMPs) have been advanced through the years to curb opioid use and abuse with marginal effect except at some state levels [5••, 17, 18•, 19, 20••, 29, 30•, 31–33, 43, 46, 54, 55, 63, 72–96]. The Washington State Agency Medical Directors Group, a collaboration of Washington State Agencies with inclusion of clinical and academic experts, developed the Washington State Interagency Guideline on Opioid Dosing for Chronic Non-Cancer Pain [79]. These guidelines provided specific dosing guidance including the recommendation that providers seek pain management consultation, guidance on best practices, and web-based continuing medical education. Since the guideline was released, they have observed decreases in opioid doses, a decrease in the percentage of patients going on to chronic opioid use, a leveling in opioid poisonings, and a

decrease in opioid fatalities within the Washington State Worker's Compensation system [79]. However, their study also showed that methadone poisonings occurred at 10 times the rate of other prescription opioid poisonings and increased between 2006 and 2010. Nuckols et al. [41] have reviewed opioid-prescribing guidelines of chronic pain with a systematic review and critical appraisal. They showed that 13 guidelines met selection criteria. Most guidelines recommended that clinicians avoid doses greater than 90 to 200 mg of morphine equivalence per day, have additional knowledge to prescribe methadone, recognize the risk of fentanyl patches, titrate cautiously, and reduce doses by at least 25 to 50 % when switching opioids. These guidelines also agreed that opioid risk assessment tools, written treatment agreements, and urine drug testing can mitigate risks [30, 83, 88, 92, 97]. The guidelines developed by the CDC for primary care settings with dose limitations, limitations on number of days in acute pain, and utilization of various other modalities of treatments may be the first step to curb opioid use.

In response to prescription opioid abuse, misuse, and overdose, some concerned physicians and researchers formed a group to identify practical approaches to more cautious opioid prescribing in community practice. This group, known as Physicians for Responsible Opioid Prescribing (PROP), a non-profit organization with no pharmaceutical industry funding or ties and advised by experts from general medicine, pain medicine, and addiction medicine on long-term opioid therapy, has developed educational materials for clinicians [98]. However, similar to many other groups, even though they may not have any direct conflicts, they do have indirect conflicts along with confluence of interest [99, 100].

In support of opioid therapy, even though there is no significant evidence on a long-term basis for chronic non-cancer pain, it is generally accepted that some patients do improve and many of them function well at low doses [101]. Consequently, it is essential to keep access to these medications; at the same time, a prudent approach must be taken about preventive strategies. These strategies fall into two groups, the primary prevention and secondary prevention.

Primary Prevention

The interventions in primary prevention include prescriber and patient education, avoidance, and careful initiation of opioid therapy in acute pain with limited duration therapy.

Education is the foremost strategy. Education must be with support from pharmaceutical agencies. Even though multiple organizations including the American Medical Association (AMA) and National Institute of Health (NIH) boast establishment of Centers of Excellence in Pain Education (CoEPE) for Physician Training with online courses, clinical guidelines, and standards, these have been very ineffective. Education should start in medical school

and continue through the life of the practice. Lack of education has been the primary focus of many of the surveys.

Secondary Prevention

Authorities have inappropriately focused on pain physicians, even though the majority of the prescriptions are provided by primary care physicians. Further, emphasis of short-term treatment as 120 days and with application of laws after 120 days of treatment is ludicrous. As shown in multiple evaluations, patients are dependent after 30 days; thus, the issue becomes one of maintenance of dependence.

Apart from prescriber education, patient education is crucial, not only when they present for care in pain clinics but at the first treatment level by primary care physicians. In fact, education must be started in school and community settings to prevent initiation of prescription opioid misuse. There are multiple programs available to provide such education; however, it appears that these have been extremely ineffective thus far.

In contrast, secondary prevention strategies include appropriate initiation and maintenance of chronic opioid therapy, PDMPs, opioid overdose prevention strategies, and expansion of access to medications for addiction treatment and use of abuse-deterrent technology.

Finally, law enforcement initiatives would serve as primary and secondary preventive strategies.

Adherence Monitoring Strategies

Clinical and behavioral assessment of patients is crucial. This is supplemented by modalities such as PDMPs and urine drug testing. PDMPs are statewide databases that monitor information about prescribing controlled substances. The American Society of Interventional Pain Physicians (ASIPP) sponsored the National All Schedules Prescription Electronic Reporting Act (NASPER); however, due to politics and the influence of multiple organizations, which have since then changed their minds, a national program was not established [72]. Instead, a compromise was reached and state programs have been established with funding from the Hal Rogers PDMP. Now, all states except Missouri operate PDMPs. Current efforts continue to focus on standardization, intraoperability, and promoting consistent use as initiated in the NASPER program. All programs have been proactive in reporting prescribing patterns to physicians, licensing boards, and law enforcement, requiring registration of all physicians. There has been a significant increase in use of PDMPs with multiple initiatives by the states. Multiple advantages and disadvantages of prescription monitoring programs have been discussed [80–82].

Adherence monitoring also includes treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain [83–97]. In a systematic review, published in

2010 with available evidence until June 2009, Starrels et al. [83] found relatively weak evidence supporting the effectiveness of opioid treatment agreements and urine drug testing in reducing opioid misuse by patients with chronic pain. However, there has been significant evidence since 2009.

Abuse-Deterrent Technology

Proponents of abuse-deterrent technology have described the advantages and the efficacy that they will reduce opioid abuse. Supporters claim [84, 85, 91] that abuse-deterrent technology will address opioid abuse along with cost savings; however, others [86] are skeptical of the role of abuse-deterrent extended release formulations to reduce the misuse and abuse.

Routes of abuse in which abuse-deterrent technology is designed to prevent include inhalation, oral, intravenous, intramuscular, subcutaneous, or smoking. Manipulative methods in which abuse-deterrent technology is designed to prevent include crushing, grinding, dissolving with chemicals such as alcohol, or extraction with heat or cold.

There are three types of drug formulations currently developed with abuse-deterrent technology. Physical barriers, such as polyethylene oxide, prevent accidental crushing or chewing, providing a benefit to patients who may do this without intent of tampering. Physical barriers to chewing or crushing do not add to risk of adverse events for abusers or non-abusers. Opioids with mechanisms of action based on precipitating adverse events as a means of deterring inappropriate use have risks, regardless of the patient's level of compliance. Sequestered aversive agents, such as niacin, will cause adverse events in patients who chew or crush tablets accidentally without intent of abuse, and even intact tablets with sequestered aversive agents may produce adverse events from aversive component in some fully compliant patients.

The extent of deterrence with these agents is unclear because individuals who intentionally abuse opioids may be willing to endure the discomfort of the aversive agent's adverse events. Although sequestered opioid antagonists, such as naloxone, may represent a more effective approach to pharmacologically deterring abuse by rendering the opioid ineffective, there is evidence of sudden opioid withdrawal in patients who chewed their tablet, even accidentally. Finally, abuse-deterrent technology constitutes only a small proportion of prescriptions of long-acting opioids, which in themselves are a small percentage of overall prescriptions [84, 85, 91].

Opioid Overdose Prevention Programs

Opioid overdose prevention programs include the naloxone distribution program, as well as referrals to methadone buprenorphine clinics or rehabilitation programs. Expansion of access to medications for addiction treatment with methadone, buprenorphine, and naltrexone has been advocated.

While there are mixed feelings about the efficacy of these treatments, which in themselves create addiction, the effectiveness continues to be debated. A systematic review, assessing community opioid overdose prevention and naloxone distribution programs, suggests that opioid users can and will use naloxone to reverse opioid overdoses when properly trained, and this training can be provided successfully through community-based opioid overdose prevention programs [87, 88].

Conclusion

The current state of opioid therapy and abuse continues to evolve with changing roles and opinions. Thus far, guidelines developed by interested parties and adapted by medical licensure boards have failed to curb opioid abuse. Opioid abuse is at epidemic levels, and trends do not indicate any immediate solutions overnight. Appropriately developed guidance, focusing on education at the primary care level, may allow physicians to continue to provide opioid therapy to those who are in need of it and avoid abuses.

Compliance with Ethical Standards

Conflict of Interest Laxmaiah Manchikanti has provided limited consulting services to Semnur Pharmaceuticals, Incorporated, which is developing non-particulate steroids.

Adam M. Kaye declares no conflict of interest.

Alan D. Kaye is a speaker for Depomed, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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