Current Pain and Headache Reports (2018) 22:25
https://doi.org/10.1007/s11916-018-0679-3

OTHER PAIN (A KAYE AND N VADIVELU, SECTION EDITORS)

Recommendations for Substance Abuse and Pain Control in Patients with Chronic Pain

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Abstract

Purpose of Review In the present investigation, current literature on the relationship between substance abuse and pain is evaluated in order to improve clinical management and its implications on the increasingly challenging chronic pain and substance abuse epidemic. The relationship between substance abuse and chronic pain are evaluated, and this review provides recommendations on the management of this special patient population.

Recent Findings Currently, there are limited guidelines for prescribing opioids and other analgesics in the chronic pain population. As this field of practice continues to evolve, it is essential for clinicians to serve as the gatekeepers to monitor for misuse and safety. Multiple studies have indicated that illicit drug use and opioid abuse affect over 9% of patients. Although there are numerous reasons for seeking illicit drugs and abusing them, it is essential that clinicians identify factors which place certain patients at high risk and accordingly, to screen these patients in order to optimize their management.

Summary The high prevalence of patients with chronic pain who also screen positive for drug use emphasizes the importance and increasingly pressing need to evaluate and to manage chronic pain in this population.

Keywords Substance abuse · Pain control · Chronic pain · Opioid · Addiction · Prescription

Introduction

In the USA alone, approximately 100 million people are affected by chronic pain, and it is one of the leading causes for seeking medical care [1]. Up to 90% of patients affected by chronic pain have been found to be on opioid therapy in pain management settings [2]. Patients suffering from chronic pain commonly suffer from concomitant drug use disorders. Cross-sectional surveys [3–5] in patients given medication-assisted treatment, including buprenorphine or methadone, report a prevalence of chronic pain that ranges from 36 to 61%. Another survey which was conducted among opioid-dependent veterans who were treatment-seeking found that 52% reported also suffering from moderate to severe chronic pain [6]. The exact extent of severity and prevalence of pain-related dysfunction and chronic pain in patients with prescription misuse or illicit drug use is unknown. However, studies by different groups of investigators have estimated that over 9% of patients with chronic pain receiving opioids had a prevalence of drug abuse [7–9]. It is proposed that patients seek alcohol and numerous illicit drugs including marijuana and heroin for their analgesic properties in order to self-medicate

This article is part of the Topical Collection on *Other Pain*

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Published online: 19 March 2018

their pain, which explains the association between substance abuse and pain [10]. It has been proposed that another explanation for substance abuse is that patients seek psychoactive substances in order to self-medicate distressing symptoms such as posttraumatic stress [11, 12].

There is undoubtedly a complex relationship between substance abuse and pain, although the optimal management of this challenging clinical picture has yet to be established. The purpose of this investigation is to review the current literature on the relationship between substance abuse and pain in order to improve clinical management and its implications on the increasingly pressing chronic pain and substance abuse epidemic.

Terminology

Terms that are frequently used in association with substance abuse are often confusing and ambiguous. In order to clarify the definitions for these terms, numerous associated terms are defined.

Substance Abuse

Substance abuse can be defined as the aberrant utilization of drugs without monitoring by a physician or other qualified professional, in terms of method used, quantity taken, or both. Countless features, including economic, psychological, physical, and legal harm, make up abuse. Abusive behaviors include seeking drugs from different clinicians to obtain a bigger supply of drugs, crushing tablets to destroy controlled-release mechanisms for a greater euphoric experience.

Substance Misuse

Substance misuse is the incorrect use of prescription medication or use for reasons for which it was not prescribed, whether this is unintentional or intentional. As an example, a patient forming the habit of ingesting an opioid as a sleep aid demonstrates substance misuse. Similarly, another patient taking a controlled-release opioid that was intended to be taken on a regularly timed regimen instead on a need-dependent basis also unintentionally demonstrates substance misuse.

Drug Addiction

Addiction is a physiological process in which a patient finds the effects of a substance so rewarding that he or she finds it difficult to manage the appropriate usage of the drug. It is defined by the loss of control of the management of the drug, craving and impulse for the drug, and for continued use of the drug despite being aware of its adverse consequences [13].

Pseudoaddiction

Pseudoaddiction is the phenomenon that manifests when a patient displays drug-seeking behavior resembling that of true addicts when their pain is inadequately managed. Its distinction from addiction is that this drug-seeking behavior resolves once the dosages of pain medication is appropriately increased in order to sufficiently manage their pain [14]. Even if this is not a common cause of opioid negligence, making the distinction between addiction and pseudoaddiction is essential in preventing cases of inadequate pain management.

Common Drugs of Abuse

Marijuana

The most widely used illicit drug is marijuana [15], which is obtained from the extract of the dried leaves of the plant *Cannabis sativa* [16]. Delta-9-tetrahydrocannabinol (THC) is the active ingredient in marijuana with a biphasic effect on the autonomic nervous system [17]. At higher concentrations, the parasympathetic system is activated, and activity of the sympathetic system is decreased, resulting in hypotension and bradycardia. On the other hand, at lower doses, the sympathetic system is activated and parasympathetic activity is decreased, causing increased heart rate and mild increases in blood pressure. Acute intoxication presents with euphoria, paranoia, anxiety, and depression in cognitive and psychomotor abilities. Management of acute intoxication from marijuana is largely supportive. Dowling et al. [18] demonstrated that marijuana use increases the risk of prescription drug abuse.

Hallucinogens

Hallucinogens that are most commonly abused are phencyclidine (PCP) and lysergic acid diethylamide (LSD). PCP causes a dissociative state associated with agitation, hallucinations, and delirium. Adverse effects of the drug include severe sympathetic activation, respiratory depression, and delirium. LSD is a semi-synthetic found in ergot and morning glory seeds. Adverse effects of drug include hyperthermia, nausea, perspiration, tachycardia, hypertension, hyperglycemia, and dry mouth. These effects and flashbacks can be exacerbated by serotonin reuptake inhibitors and marijuana [16].

Other drugs that are commonly abused include alprazolam and methoxetamine, which are both structurally similar to phencyclidine (PCP). Methoxetamine is a ketamine analog that is also informally referred to as "special K." Methoxetamine is popular in the UK, and it can be injected intravenously and has the potential for more widespread use through purchase on the Internet. Little else is known about its patterns of abuse or its users [19].

Alcohol

Alcohol intoxication presents with signs of depression of the central nervous system, including slurred speech, bradycardia, respiratory depression, hypotension, and coma. Alcohol abuse is most commonly found in young adults and in late adolescence [20]. Intoxication is managed with intravenous hydration and repletion of electrolytes [21]. Alcohol abuse is managed in the acute setting with observation, supportive treatment, and close monitoring of the patient's ability to maintain a patent airway.

Cocaine

From 2010 through 2014, the age-adjusted rate of drug overdose deaths for cocaine increased from 1.4 per 100,000 population to 1.8 per 100,000 population [22]. Cocaine significantly affects both the central nervous system and the renal system. It functions by inhibiting the dopamine transporter, which effectively decreases dopamine uptake at the synaptic cleft, thereby increasing dopamine concentration in the synapse and resulting in the feeling of euphoria. It also blocks sympathomimetic neurotransmitters such as serotonin, norepinephrine, and dopamine [23]. Increased sympathomimetic tone is mediated by inhibited reuptake of dopamine and norepinephrine [24], resulting in a buildup of catecholamines and increase in heart rate and blood pressure [25]. The adverse complications of acute intoxication include seizures, coronary vasospasm, myocardial ischemia, and stroke [26]. Patients may present with palpitations or dyspnea. Acute intoxication is treated with benzodiazepines.

Heroin

Related to its low cost and easy accessibility, there has been a significant increase in the use of heroin in the USA [27•]. Heroin has a very short half-life, and withdrawal occurs within several hours, making it especially addictive following experimentation. Its effects include miosis, hypothermia, bradycardia, and respiratory depression [16]. Complications of respiratory depression secondary to acute intoxication may necessitate endotracheal intubation or mechanical ventilation, and the administration of naloxone.

Prescription Drug Abuse

The Centers for Disease Control and Prevention (CDC) has reported the abuse of prescription drugs an epidemic in the USA [19]. The National Institutes of Health (NIH) estimates that about 20% of Americans have participated in the nonmedical use of prescription drugs, which makes prescription drugs the second most commonly used illicit drug behind marijuana. Due to the rapidly growing national epidemic, it has attracted the attention of various government organizations, including the US Department of Justice and the Whitehouse's Office of National Drug Control Policy (ONDCP) [28]. These organizations have conducted surveys and continuously incorporate strategies in attempts to reduce the risk for prescription drug misuse [19]. It should be noted that primary care physicians are by far the greatest prescribers of opioid medications nationwide.

Prescription drugs that are most often abused fall under three categories: stimulants, pain relievers, and sedatives. Studies approximate that these substances are utilized outside their recommended guidelines in 7.2, 13.5, and 2.9% of the population, respectively [19]. Opioids are both the most frequently abused of the prescription drugs and the drugs with the most adverse complications. The pain relievers that are most commonly abused include morphine, hydromorphone, methadone, hydrocodone, oxycodone, pentazocine, codeine, propoxyphene, and fentanyl. Other prescription drugs that are commonly abused include alprazolam and methoxetamine [19].

Patients with history of drug addiction or drug abuse can be classified within three main categories: patients currently using drugs, patients with history of drug use in the past, and patients undergoing buprenorphine or methadone maintenance programs. It is important to conduct a comprehensive history of this patient population, including clarification of which substances have been used and for how long; any previous treatment for their substance abuse; motivation to participate in a treatment program; how long the duration of sobriety is in patients undergoing recovery; and how their sobriety is maintained. Inquiring about the patient's psychiatric history is also helpful in order to conduct an optimal evaluation [19].

Management of Prescription Drug Abuse

Methadone

Methadone is the primary therapy in prescription drug abuse. Methadone is a synthetic μ-opioid receptor agonist that can cause severe respiratory depression when given in doses that exceed the patient's tolerance level, similar to other opiate agonists. Studies have shown that patients suffering from opioid addiction do not seek the usual doses of IV morphine, do not report euphoria, and report relief from withdrawal symptoms [29]. The recent rise in methadone-related deaths is largely attributed to the negligence of its regulation as a treatment for pain [30], likely due to increasing doses too rapidly, and its adverse respiratory depressive effects [31]. It is well tolerated with a high oral bioavailability, allowing for

outpatient management, but a very wide half-life requiring an individualized management plans.

Buprenorphine

Buprenorphine is a semi-synthetic μ-opioid partial agonist with weak partial activity as an agonist at delta and kappa opioid receptors. Since the approval by the FDA and DEA for the office-based use of buprenorphine as a treatment for patients addicted to opioids, its use as a therapy for choice in prescription medication abuse has grown [19]. It is commonly prescribed in patients with history of addiction. Due to its high affinity for the μ receptor coupled with its slow dissociation [32], buprenorphine has a long duration of action and a potency that is up to 25–40-fold greater than that of morphine. Predictors of buprenorphine therapy outcomes include income, current cocaine and opiate use, and depression [33]. Of note, despite findings that buprenorphine therapy reduces illicit opiate use during maintenance treatment, more than 90% of patients relapse into illicit use of opiates once the drug is tapered [34].

Oxymorphone

Oxymorphone is a semi-synthetic opioid that may be a novel treatment option in patients with history of substance abuse. It is more potent than morphine by up to 6–8-fold. It can be administered in patients with addictive disorder to manage moderate to severe pain, and can also be given preoperatively in order to decrease anxiety and maintain anesthesia [19].

Urine Drug Testing

Qualitative and quantitative urine drug tests are important tools for determining opioid risk management, which are utilized in clinical practice and routinely used in patients with non-cancer pain on chronic opioid therapy. In general, patients being prescribed opioids should be divided into low, moderate, and high risk for potential abuse with a written policy that correlates with frequency of drug testing and have each patient sign an opioid agreement which describes in detail expectations for the patient receiving opioid medications. For example, state laws, which may vary slightly, in general, would require patients who additionally take illicit drugs or alcohol be identified as violated their opioid agreement and no longer receive opioid medications. Thus, urine drug testing is critical in the oversight and overall compliance of patients who are receiving these agents. There are two main forms of urine drug tests: screening tests, e.g., qualitative testing, which are given in the clinician's office or sent to a lab and are associated with potential false positive and false negatives, and confirmatory or quantitative tests, which are lab-based and measure actual drug levels [35, 36••]. In this regard, for example, fentanyl and many other substances are not measured through qualitative testing, and therefore, quantitative testing is required for precise clarification and understanding of patient compliance or potential abuse.

Utility in Cancer Pain

Although nationwide guidelines have been developed for the assessment of opioid abuse risk in patients with non-cancer pain via urine drug tests and screening questionnaires, there are little to no guidelines in screening patients with cancer pain on chronic opioid therapy. Despite increasing concerns for increased risk of opioid abuse in cancer patients, there are few studies investigating the utility of urine drug screens [37, 38]. Rauenzahn et al. [39] recently conducted a retrospective chart review of supportive clinic patients in order to characterize the population of cancer patients in the ambulatory setting with abnormal urine drug screenings and to ascertain the value of the role urine drug tests in improving therapeutic evaluations. They found that a significant portion of the ambulatory patients who participated in the study had abnormal urine drug tests. In fact, almost 50% of the patients tested positive for illicit drugs including cocaine and heroin or for non-prescribed opioids. Additionally, 39% of patients had unexpectedly negative urine drug tests, which raised concerns for opioid hoarding and diversion [39]. The findings of this study raise the question of whether there is utility in conducting urine drug tests in chronic opioid cancer patients in order to improve pain management and risk stratification in this patient population.

A study by Arthur et al. [40] investigated whether there were any determining characteristics associated with clinicians who ordered urine drug tests for patients receiving chronic opioid therapy. It demonstrated that urine drug tests are not routinely used in the outpatient care setting in patients with advanced cancer on chronic opioid therapy. Out of the 61 patients (of a total of 1058) who underwent urine drug tests in this study, 33 patients (or 54%) were found to have abnormal results. Hydrocodone was the most recurrently unexpectedly present or absent opioid reported in the tests. Arthur et al. therefore advise routine monitoring, discerning use of urine drug tests, and universal screening in the outpatient setting for patients receiving chronic opioid therapy for cancer pain.

Chronic Pain

An essential constituent of patient management is pain control, which encompasses a physical, emotional, psychological, and economical burden on patients and their caretakers. Pain management continues to be a source of significant economic burden as a disability, in increasing healthcare costs, and in

decreasing productivity [41]. Optimal pain management is vital in both the inpatient and outpatient surgery setting. In fact, up to 70% of patients report postoperative moderate-to-severe pain [42, 43].

Chronic pain is one of the leading causes for patients seeking medical care. Non-cancer chronic pain, defined as lasting more than 6 months, is most commonly due to centralized pain such as headaches or fibromyalgia (26%), back pain (20%), and arthritis (13%) [44]. Up to a third of adults in the USA report pain, and among them approximately 10% report suffering from chronic pain [45•]. Patients suffering from chronic pain are often managed with physical therapy, psychological therapy, cognitive behavioral therapy, and biofeedback in conjunction with medications [46, 47]. As a consequence, many of these patients seek out physicians and are prescribed drugs that may potentially lead to abuse or dependency. Some patients are required to be subjected to drug testing or be treated by a single provider in order to minimize the risk of medication misuse [2]. Despite these preventative measures, prescription abuse continues to remain an immensely problematic health concern.

Opioid overdoses now surpass motor vehicle accidents as cause of deaths [48••], and in 2013, up to two million people age 12 and up were either dependent on or abused opioid analgesics [49]. And though sales of prescription opioids within the USA have increased drastically by 300% since 1999, self-reported pain has remained largely unchanged [50].

In a cross-sectional analysis of patients participating in the Assessing Screening Plus Brief Intervention's Resulting Efficacy to Stop Drug Use (ASPIRE) study, a randomized trial evaluating the efficacy of intervention for patients who screened positively for misuse of prescription drug or illicit drug use over 3 months, Alford et al. (10) demonstrated that pain-related dysfunction and pain should be attended to in patients with history of substance abuse. Eighty-seven percent of the participants reported chronic pain (13% mild, 24% moderate, 36% severe). A significant portion of participants with history of illicit drug use (i.e., cocaine, marijuana, heroin) reported seeking the drug(s) to self-treat their pain. Of the participants with history of prescription drug misuse, 81% reported the pain to be the motivation for these behaviors. Alcohol abuse was also found to be a substance of abuse for self-medicating pain (79% of high-risk alcohol users reported doing so in order to self-medicate their pain).

The association between chronic pain and substance use is one that warrants important clinical application to management of patients that fall under this category. If patients are seeking illicit drugs in order to self-medicate their pain, they may be hesitant to reduce their intake or adhere to advice for abstinence if their pain symptoms are not sufficiently managed. Furthermore, literature has shown that chronic pain is independently associated with substance use relapse following detoxification [51, 52]. Addressing symptoms of pain is therefore critical in the management of patients with history or increased risk of substance abuse [53••, 54••].

Risk Factors for Pain

Features that have been associated with higher risk for severe pain include unemployment, lower level of education, increased age, and visitations to non-primary care-based facilities including hospitalizations and visits to emergency departments and to urgent care centers. Other characteristics associated with greater pain include low overall health status, anxiety, depression, and Hispanic ethnicity [10]. In fact, the association between chronic pain and anxiety and depression [55], increased age [56], and greater utilization of healthcare [57] have been well studied. Although the associations between lower level of education, race, unemployment, and pain remain unclear, these qualities are associated with lower socioeconomic status, which has been correlated with a greater severity and prevalence of chronic pain [58].

Opioid Use Disorders and Pain

Despite efforts to prevent opioid abuse, there has been an upward trend in the prevalence of opioid use disorders alongside the increase in opioid analgesic prescriptions [59]. There has also been a parallel nationwide increase in the use of heroin [60]. Studies have demonstrated that patients with history of mental health diagnoses, chronic pain, and history of substance abuse are at an increased risk for mismanaged opioid use [61–63]. Furthermore, once an opioid use disorder has been diagnosed and the patient has received treatment for it, studies have shown that patients with prescription opioid use disorders often have better outcomes relative to patients with heroin and prescription opioid issues or heroin-only issues. The improved outcomes in these studies were defined as fewer reported opioid-positive urine tests and completion of treatment [64, 65]. Investigation of the pathway to developing an opioid use disorder has been scarce, despite the increasingly pressing need for investigations of this issue, given the rise in both the use and prevalence of opioid use disorders.

Stumbo et al. [66] sought to further investigate this pathway to developing opioid use disorders in a qualitative analysis study by documenting subjects' explanatory models for how they developed an opioid use disorder (including prescription opioids and/or heroin). A prior study with the same study aim reported that the fear of undertreated pain and chronic pain was a pathway to opioid use disorder [67]. Moreover, this also produced obstacles to treatment [68]. Based on the findings suggestive of inadequate pain management as a key driver in the misuse

of opioid, Stumbo et al. [66] emphasize the importance in raising awareness in clinicians to setting appropriate pain management goals and expectations, promoting effective communication and feedback from patients on the effective relief of the treatment. The study also found that in some patients, even brief exposures to opioids for a surgical or dental procedure, acute injury, or short-term episode of brief pain could expose a pathway to a dependence on opioids. Prior substance abuse among patients seeking treatment of pain was another factor that increased the risk of opioid use disorder.

Another recent study by Weiss et al. [67] sought to characterize the reasons for prescription opioid use in prescription opioid-dependent patients seeking treatment, and to investigate whether chronic pain changes the reasons. The report demonstrated that the most common reason for starting to use opioids in patients with and without chronic pain was pain relief. Of the subjects without chronic pain, 49% reported pain relief as their primary reason for starting opioid use. Of the subjects with chronic pain, over 80% reported pain relief as their primary reason. Another reason for initiating opioid usage was in order to get high—other reasons, including for anxiety or sleep improvement, were uncommon in both study arms. Of note, avoiding withdrawal was reported as the most significant reason for current use of prescription opioids, regardless of history of chronic pain.

Pain-Related Medical Cannabis Use and Substance Use Disorder

Surveys regarding the medical use of cannabis have revealed that up to 45–80% of users solicit cannabis for pain-related reasons [69–71]. Notwithstanding the significant number of patients who take cannabis for pain-related reasons, there is a lack of studies examining characteristics of this subset of patients. What little research has been conducted has demonstrated that lifelong and recent substance use is more commonly found in patients seeking cannabis for any reason. For instance, one study [70] found that of the subjects in the study looking for medical cannabis licensure, 68% reported non-prescription opioid use within the last 30 days. Furthermore, studies have approximated that the rates of patients reporting pain within the past year in the setting of substance use disorder ranges from 17 to 34% [6, 72, 73]. This association between reported pain and substance use disorder is worrisome considering findings that have reported a direct association between poorer treatment outcomes and pain [72, 74].

Ashrafioun et al. [75] conducted a study at a large residential abstinence-based substance use disorder treatment center to further investigate the association between pain, substance abuse, and pain-related medical cannabis use. The study found that participants taking medical cannabis for pain reported a more severe history of substance abuse, such as taking prescription analgesics without prescription, even when compared to other participants receiving substance use disorder treatments. These findings were consistent with prior studies that reported more severe substance use in patients who report having pain [6, 72, 74]. Ashrafioun et al. [75] propose that this relationship may be because patients suffering from more severe substance abuse are more likely to seek different kinds of substances, including medical cannabis, or alternatively that patients seeking medical cannabis suffer from greater levels of pain. These findings have an important implication in incorporating an assessment of pain in the treatment of substance abuse.

Future Perspective

Several studies have found a clinical relationship between substance abuse and a greater history of substance abuse in patients who report having pain, especially chronic pain [6, 72, 74–76]. It has been shown that following detoxification, chronic pain is independently associated with substance use relapse [51, 52]. Drug abuse of prescription pain medications is an increasingly complex and growing national problem in the USA. Common medications abused include pain medications such as opioids, and other drugs such as stimulants, and sedatives. Prescription drug abuse can lead to falls, infections, overdose, and death, and efforts to curb it are vital [77]. The curbing of prescription drug abuse would require the involvement of prescribers, pharmacies, and health insurance companies. The SAMHSA (Substance Abuse and Mental Health Services Administration) has adopted a Public Health Approach with early intervention, prevention, treatment, and recovery using available support services.

Conclusion

Pain control is truly a challenge in patients with chronic pain with a concomitant history of substance abuse. As guidelines for prescribing opioids and other analgesics continues to evolve, it is essential for clinicians to serve as the gatekeepers to monitor for misuse and safety. The high prevalence of patients with chronic pain who also screen positive for drug use emphasizes the importance of evaluating and managing chronic pain in this population. Written policies are highly beneficial when patients attempt to violate opioid agreements by taking illicit substances or manipulate clinicians to receive medications earlier. Multiple studies have indicated that illicit drug use and opioid abuse affect over 9% of patients [7].

Although there are numerous reasons for seeking illicit drugs and abusing them, it is essential that clinicians identify factors that place certain patients at high risk and accordingly screen these patients in order to optimize their management.

Compliance with Ethical Standards

Conflict of Interest Nalini Vadivelu, Alice M. Kai, Gopal Kodumudi, Dan Haddad, Vijay Kodumudi, Niketh Kuruvilla, Alan David Kaye, and Richard D. Urman declare no conflict of interest.

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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