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PROCEEDINGS

Chronic Pain, Chronic Opioid Addiction: a Complex Nexus

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Abstract Over the past two decades, there has been a significant increase in the prescribing of opioids, with associated increases in opioid addiction and overdose deaths. This article reviews the evidence for the effectiveness and risk of developing an opioid use disorder (OUD) in those patients treated with chronic opioid therapy (COT) for chronic non-cancer pain (CNCP). Rates of development of OUD range from 0–50 %, and aberrant drug related behaviors (ADRBs) are reported to be 20 %. Health care providers must properly assess, screen, and carefully monitor patients on COT utilizing evidence-based tools.

Keywords Chronic pain · Addiction · Toxicology · Alcohol dependence · Drug dependence

Introduction

Over the last 20 years, there has been a significant increase in the prescribing of opioids for chronic non-cancer pain. There has been a concomitant increase in prescription opioid-associated overdose deaths, emergency department visits related to prescription opioids, and admissions to drug treatment facilities secondary to prescription opioids. The latest data from the CDC report approximately 16,000 overdose deaths related to prescription opioids annually, and total poisoning deaths now outnumber motor vehicle accident deaths. Therefore, proper evaluation and monitoring are essential when a patient is being evaluated for chronic opioid therapy for chronic non-cancer pain.

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Chronic Pain and Opioid Therapy

Opioid therapy is regarded as necessary in the treatment of acute pain, such as post-operative pain. Chronic opioid therapy (COT) is often utilized in palliative care and cancer pain paradigms. However, COT remains controversial for the treatment of chronic non-cancer pain (CNCP), which often leads to physical dependence and may resemble an addictive disorder. Identifying addiction in the complex interaction between chronic opioids and CNCP presents a clinical challenge. Many patients presenting with CNCP, who are treated with chronic opioids, overlap with people who develop opioid use disorder and require methadone or buprenorphine maintenance. Often, these are the "same people" with different clinical presentations.

Pain is referred to as the "fifth vital sign" and has been broadly defined as "whatever the experiencing person says it is, existing whenever he says it does", implying that it may involve more than a physical sensation [1]. More recently, pain has also been defined as a "biopsychosocial phenomenon that includes sensory, emotional, cognitive, developmental, behavioral, spiritual, and cultural components" [2]. The link between pain and addiction can be seen in the overlap of the terminology used in the definition of addiction as "a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations."

The challenge with both chronic pain and addiction is that there are no physical instruments to measure intensity. Pain is

as reported by the patient, and addiction severity can be similarly ambiguous. There are emerging imaging studies, which may provide objective criteria. For example, brain imaging studies may make it possible to determine if acute back pain will develop chronicity by measuring circuits forming between pain and reward areas of the brain.

Physical dependence is the physical adaptation in the brain to taking an opioid regularly, defined by the development of withdrawal symptoms when the opioid is withdrawn, the dose is reduced, or an opioid antagonist is administered. Similar adaptations occur with regular use of alcohol or benzodiazepines. Physical dependence occurs within a few days of dosing with opioids, although it varies among patients, and is a normal and expected response to continuous opioid therapy. Physical dependence does not necessarily mean addiction. If a patient on COT has only physical dependence and tolerance, with no adverse behavioral problems, they will not meet criteria for an opioid use disorder with the Diagnostic and Statistical Manual of Mental Disorders (DSM) V criteria.

Mu-opioid receptors are located widely in the brain, but in addiction medicine, the limbic system is primarily involved in the euphorigenic or rewarding properties of opioids. The pain center is the periaqueductal gray area sub-serving analgesia, and the locus coeruleus is the main noradrenergic area of the brain responsible for the autonomic withdrawal signs and symptoms. Animals, including humans, will avidly self-administer a certain number of drugs into their reward system to increase dopamine levels; however, they will not self-administer opioids into the periaqueductal gray area, because there is apparently no reward/dopamine increase for doing so. But when an opioid is administered systemically, the opioid attaches to mu receptors in all areas of the brain.

People who eventually become addicted to opioids may have started out taking opioids in response to acute pain, such as post-operatively, and report that the first time they took the opioid, they felt not only relief from their acute pain but also felt relief from anxiety, depression, felt relaxed, or less shy. The issue is the opioids are affecting all areas of the brain, rather than being isolated to the pain center. Opioid receptors are located all over the body and serve different functions in different anatomical locations. There are receptors for pleasure and analgesia, but there are also receptors in the gut that cause constipation, which is an unwanted side effect of opioid therapy. Endogenous opioids, or endorphins, are produced by the central nervous system and pituitary glands, are involved in the pleasure/reward system, and provide analgesia and mood regulation, among many other functions.

Shared comorbidities of CNCP and addiction such as anxiety and depression, human suffering, financial problems, functional disability, cognitive disturbances, sleep disturbances, family and social problems, and secondary physical problems are common in both conditions. A meta-analysis of 56 articles linking pain and depression found that 65 % of those with depression have significant pain and 50 % of those in pain clinic have depression. Pain negatively affects depression outcomes and vice versa. Pain and depression are often linked, which is the reason SNRIs (e.g., duloxetine) were developed, to treat both simultaneously. In patients with addictive disorders, 60.31 % have comorbid mood disorders and 42.63 % have anxiety disorders [3]. A community study found that patients with depression, anxiety, dysthymia, and PTSD were significantly more likely to be prescribed prescription opioids [4]. Taken together, these studies demonstrate the overlay between CNCP, addiction, and the likelihood of being prescribed COT.

In a recent publication, Sullivan et al summarized many of the challenges and dilemmas in the prescribing of COT for CNCP [4]. They point out that most studies are 12 weeks in duration, that pain is only reduced 30 % compared to placebo, and that there is an inverse correlation between being prescribed COT and return to work. They have coined the term, "adverse selection," to indicate that those patients most vulnerable to develop an opioid use disorder are the patients most often selected for COT.

Iatrogenic addiction occurs when a patient, with a negative personal or family history for alcohol or drug addiction, is appropriately prescribed a controlled substance and subsequently in the therapeutic course meets the diagnostic criteria for addiction to that substance. This is a diagnostic dilemma, because the patient is able to legally fill a prescription, instead of having to use illegal channels. De novo iatrogenic addiction is found to occur in 0–50 % of COT patients, while aberrant/problematic behaviors are common at ~20 %, which is more likely the figure for substance use disorder [5]. Rates are always higher for patients with a past history of addiction. Aberrant or problematic behavior does not necessarily mean there is addiction—it must be considered in context.

A systematic review of 17 studies on the development of addiction following treatment with opioids for pain found very low rates for incidence and prevalence, concluding that COT for CNCP is not associated with a major risk for developing an opioid use disorder (OUD). The authors state "the most impressive finding of the present review is the deficiency of good-quality studies on this matter" [6]. A critique of this review "concurs with the authors who have concluded that existing research is inadequate for estimating the rate of iatrogenic addiction in patients treated with COT for CNCP." "Systematic reviews of many irrelevant, inadequate, and incomparable studies cannot substitute for properly designed studies," the author concludes [7].

Another meta-analysis conducted to determine the percentage of CNCP patients exposed to COT develop addiction and/or aberrant drug-related behaviors concluded that "the results of this evidence-based structured review indicate that COT exposure will lead to abuse/addiction in a very small percentage of patients. This percentage can be dramatically decreased by preselecting CNCP patients, who have no previous/current history of drug/alcohol abuse/addiction" [8]. Aberrant drug-

related behavior (ADRB) rates in the range of 15 % seem more realistic than addiction rates. A systematic review on opioid treatment for back pain found that aberrant medication-taking behaviors occur in up to 24 % of patients while the current literature suggests approximately 30 % of people put on chronic opioid therapy for chronic non-cancer pain will develop a problem [9], but it is hard to determine whether it qualifies as a substance use disorder using DSM V criteria. Most patients put on opioids stop on their own due to adverse side effects. There is a dearth of data on the effectiveness of COT for CNCP beyond 16 weeks.

Another area of uncertainty is the validity of monitoring tools, such as patient provider agreements and urine drug testing. There is limited evidence that screening for opioid abuse using an instrument reduces abuse, although it is recommended. There is good evidence that urine drug screening reduces abuse of prescription opioids. There is good to fair evidence that prescription-monitoring programs reduce drug abuse and doctor shopping. Only fair evidence indicates that prescription-monitoring programs reduce ED visits, overdoses, or deaths.

"Universal precautions" means that all patients receiving controlled medications have a random periodic urine drug test, receive a patient-provider agreement, and are checked on the PDMP. Just because a patient is elderly, it does not mean they are exempt, as the elderly are a common source of diverted medication for their children and grandchildren. Screening tests such as the Opioid Risk Tool (ORT), SOAPP, and others are used to monitor those patients with higher risk (for example, history of drug abuse, sexual abuse, etc.). Such a patient may require closer monitoring. Sometimes family members, spouses, or other significant others can be enlisted to help monitor and dispense medication.

Untreated pain is a trigger for relapse. Many studies show opioid addicted pain patients, unable to receive a prescription medication, use heroin to treat their pain. Alternatively, the opioids themselves can trigger a relapse, so extra precautions must be taken. A multidisciplinary pain treatment team may be effective in such circumstances, but insurance issues, access to such programs, etc. make this multidisciplinary approach uncommon at this time. With accumulating evidence of effectiveness, more such programs will hopefully become available in the future.

Opioid metabolism can make interpretation of drug testing in these patients quite difficult. Some opioids are directly metabolized to other opioids that themselves are used therapeutically. Oxycodone, for example, is metabolized to oxymorphone and morphine can be metabolized to hydromorphone. When appropriate, selecting an opioid that does not have confusing metabolites may simplify drug screen interpretation. For example, there are no pharmacologic agents similar to methadone metabolites. When monitored during opioid therapy, patients should avoid eating poppy seeds, which can make a UDS positive for opiates, depending where the threshold for opioid screening is set [10].

Methadone is FDA approved for treatment of both pain and addiction, but the regulations differ. For use in addiction, it must be administered from federally licensed clinics (MMTP/OTP), which are not authorized to dispense methadone for the treatment of pain. Methadone doses should be divided and given three or four times daily for pain treatment, because the analgesic effect only lasts 6–8 h, shorter than its anti-craving and anti-withdrawal effect. Addiction dosing is q 24 h, while analgesic dosing is q 6–8 h, and MMTPs can only administer treatment once a day. A health care provider cannot prescribe methadone or any other opioid besides buprenorphine for the treatment of opioid addiction for either withdrawal or maintenance. A recent study found that sublingual use of buprenorphine could treat both pain and opioid use disorder, which may be the medication to consider when treating chronic pain in a patient with current OUD [11].

Conclusion

When prescribing COT for CNCP became more common, the assumption was that a person with no risk factors for addiction could use opioids long-term, could easily taper off, and discontinue use without much of a problem. This turned out not to be the case clinically. Many patients continue to find tapering off long-term COT to be very challenging.

Physical dependence and/or aberrant or problematic behavior do not necessarily equal addiction, in the case of chronic opioid use for chronic non-cancer pain. Patients with current/past history of addiction/sexual abuse or any psychological problems are highest risk and require a multidisciplinary team. Not every person with chronic pain experiences emotional suffering, but a suffering person may be more susceptible to developing a substance use disorder when treated with opioids, as opioids have the nearly unique effect of relieving suffering. It is important to monitor patients using universal precautions and follow all state and federal guidelines.

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Compliance with Ethical Standards

Conflicts of Interest None

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