



Chronic Pain Management Using Buprenorphine: Questions and Considerations

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More than fifty million Americans currently are living with chronic pain unrelated to cancer. The costs associated with chronic pain are approximately ninety billion dollars annually. During the last two decades of the twentieth century, there has been increased interest in support of fundamentally changing how physicians treat chronic pain conditions (1, 2, 3). Pressure from national agencies and worldwide organizations has led to increased attention to untreated and undertreated pain symptoms (4). At the same time, pharmaceutical companies were marketing new products that were anticipated to be safer and to have lower dependence potential (5). In response, many physicians were enticed to prescribe opioids for chronic noncancer pain. By 2002, prescriptions for OxyContin alone had reached 6.2 million per year (6).

Today, opioid analgesics are the most prescribed medication in the United States, (7) and a clear reliance on prescribing these medications rather than getting to the underlying causes is now part of the standard for "pain management" medical practices (4). Not surprisingly, as rates of prescription opioids increase, so have the negative effects including addiction and unintentional drug poisoning deaths (8). There is a close correlation between death and the amount of opioid medication sold.

A recent study of the Treatment Episode Data Set (TEDS) revealed that admissions to substance abuse treatment programs for abuse of prescription pain relievers increased over 400 percent (9). Prescription opioid abuse in the US has overtaken illicit opioid (heroin) abuse and has grown to epidemic proportions. In spite of rising rates of nonmedical use of opioids (rates of nonmedical use of prescription pain relievers involve 5.2 million Americans), the medical field maintains that the potential for addiction is not sufficient to prohibit the use of narcotic medications (10).

In February 2008, the American Pain Society and the American Academy of Pain Medicine published "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain" (11). The guidelines offer clinical suggestions for appropriately managing pain while accounting for the risk of potential dependence (12). In addition to current prevention and awareness initiatives, national agencies such as the US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) have also started to investigate the effectiveness of previous measures to curb misuse and abuse of opioid medication (12). Despite these efforts, rates of nonmedical use of prescription pain relievers involve more than 5.2 million Americans (13).

Behavioral abuse and dependence patterns often develop during the course of prescribed treatment. Currently, many rehabilitation centers offer variable durations for detoxification, individual and group therapy, and recommendations for continuing care through such programs as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) (14). However, with relapse rates so high, many clients have turned to medication-assisted treatment (formerly called maintenance) programs that provide long-lasting opioids such as methadone (Dolophine) or buprenorphine (Suboxone and Subutex). Today, there are currently over 1,000 clinics authorized to dispense methadone (15) and over 1,500 treatment centers authorized to dispense buprenorphine in the US (16). This review will focus on the clinical uses, potential problems, and implications for treatment using buprenorphine.

Science and Pharmacology of Buprenorphine

The US Food and Drug Administration approved buprenorphine in 2002 for the treatment of opioid dependence (17). Under the Drug Addiction Treatment Act of 2000, buprenorphine is available for use through physicians registered with the Substance Abuse and Mental Health Administration (18). There are currently more than 12,000 physicians waived by the FDA to prescribe buprenorphine in a clinical office setting (19). Buprenorphine's unique pharmacology causes less of the same negative side effects commonly seen with morphine and methadone (e.g., respiratory depression, cognitive impairment, and euphoria more likely to be associated with craving and abuse) and has opened the way for treatment of opioid dependence in new settings. This allows treatment options to reach those who may not have previously had access or don't feel comfortable with other treatment settings such as a methadone clinic (18).

Classified as a Schedule III narcotic, buprenorphine is a semi-synthetic opioid that is an antagonist at kappa opioid receptor sites (19) and a partial agonist of mu-opioid receptors (20). Activation of mu-receptors produces some of the most common effects associated with opioids, i.e., pleasure and pain relief (20). By not fully stimulating mu-receptors, the cognitive and euphorigenic effects of buprenorphine are consequently not as intense as full agonist opioids such as morphine or oxycodone. Buprenorphine does not provide the same levels of pleasure and positive mood elevation, nor does it cause cravings as strong as commonly abused opioids such as heroin, oxycodone, hydrocodone, morphine, and others. Due

to its high affinity for mu-receptors, buprenorphine is not easily displaced and prevents the intense effects of other subsequently used opioids (19). It will also dislodge a previously or presently used opioid from receptor sites (20).

Buprenorphine also has high affinity with kappa receptors as an antagonist (21). Kappa receptors have been shown to play a role in opposing the rewarding effects of drugs of abuse (22). By preventing the dysphoric effects of kappa-receptor stimulation, buprenorphine is able to elevate mood (23) and show anxiolytic properties (24). Blocking kappa receptors may also contribute to buprenorphine's analgesic properties (21).

Buprenorphine has been touted as a safe, low risk option for treatment of opioid dependence (25) because of its mild effects and a ceiling effect at high doses (25). Yet, despite the apparent advantages of buprenorphine over other opioid maintenance medications, an abuse potential remains. Use of buprenorphine for diversion has been reported internationally (26). Also, using buprenorphine illicitly to avoid withdrawal symptoms (called "bridging") until further use of other illicit substances can resume is an alarming trend (27). Furthermore, when combined with benzodiazepines, there is an increased incidence of adverse effects including overdose and death (28). One new and dangerous trend is the rise of "user - how to" websites touting the effects of "bup" combined with promethazine, temgesic, hydroxyzine, and benzodiazepines as the "new heroin substitute."

Early development of buprenorphine has transferred from liquid injections (because of abuse potential) to sublingual solutions (because of practical limitations and limited oral bioavailability) and is now available in two forms of sublingual tablets (26, 29). Tablets that contain only buprenorphine are marketed as Subutex. The risk potential for diversion remains with Subutex because tablets can easily be broken down, dissolved, and the solution injected. The second tablet form, Suboxone, was developed to incorporate naloxone (Narcan), a mu-opioid receptor competitive antagonist. Naloxone has low bioavailability when taken sublingually; however, when injected it produces a precipitated opioid withdrawal syndrome. The negative effects of the withdrawal syndrome are meant to deter intravenous abuse and have shown to be effective when compared to Subutex (26).

Clinical Efficacy Studies

Medication-assisted treatment programs that use methadone have been shown to reduce the spread of HIV, decreasing use of illicit opioids, criminal activity, and prolonging average time until next relapse (29). One of the most cited outcomes of buprenorphine maintenance is rates of treatment retention (30). Among combination treatment options, detoxification using buprenorphine and psychosocial treatments is more effective than use of pharmacological treatments alone (31) and reflects established research indicating that the use or abuse of a substance implicates changes to more than just physiological processes.

Does Buprenorphine Cause Hyperalgesia?

Drug use has been positively correlated with pain tolerance and has been shown to vary depending on the type of drug used (32). Pain intolerance due to substance use may even appear to cause hyperalgesia in certain patients (33, 34). Recovering drug addicts have shown higher levels of pain tolerance than their currently using peers, demonstrating that the hyperalgesic effects of opioids are drug and dose specific (32). In other words, opioids may cause more pain. Once the hyperalgesic effects begin to offset the analgesic properties of the prescribed opioid, pain treatment becomes more difficult (34). This inadvertent increase in pain tolerance hinders adequate pain management in patients with comorbid chronic pain conditions. This effect may not be as pronounced with patients receiving buprenorphine maintenance treatment versus treatment with full opioid agonists (35).

Acute pain treatment can be hindered by the use of buprenorphine as well. Due to its pharmacological properties, emergency care centers will find it difficult to control acute pain by administering full agonist opioids because their effects will be blunted by the adherent buprenorphine molecule (36). Opioid tolerance also contributes to diminished pain relief as a result of the chronic use of a long lasting opioid. Special consideration needs to be given to potential circumstances that buprenorphine maintenance treatment patients may encounter during the course of their treatment.

Where does that leave the addiction professional with respect to clients on buprenorphine in your practice setting? Here are several key questions which will challenge each of us as we attempt to assess and treat opioid-dependent clients.

1. Is the brain of the opioid addict more normal with buprenorphine than without, as many medication assistance proponents assert? At least with methadone dependent addicts, it has been shown that the brain dopamine transport system is impaired compared to abstinent opioid addicts (37).
2. Is there a reasonable hope of achieving a buprenorphine-free state once it has been started? If so, when is the logical time to attempt withdrawal? After six weeks, six months, two years? If withdrawal fails, is that because of dependence on buprenorphine, which is extremely difficult to discontinue, or is relapse inevitable in the absence of some opioids? We all know that discontinuing maintenance doses of opioids is extremely difficult, but is that because of withdrawal (protected with buprenorphine), or is it because the brain requires a medication like buprenorphine to function and feel normal?
3. There are clinics that have sprung up in some cities that include buprenorphine treatment among a vast "service line" menu including Botox, Restalyne, liposuction, and teeth whitening. Do we truly expect an addict to find recovery in such a setting?

4. How are you to manage these clients as an addiction professional? It is your task to help clients find quality in their lives. Can you steer them to buprenorphine-friendly meetings? Should the maintained addict go to mainstream meetings and hide the fact that they are on buprenorphine? It is not uncommon for addicts who disclose their status to be ostracized or encouraged to discontinue medications by nonprofessional peers. Can you help clients navigate these difficult waters and develop a supportive community to help them as they live life on life's terms?
5. Some feel that opioid-free is simply not an achievable state; the data appear to suggest low percentages of successful abstinence. Where are all the addicts who are successful? There are thousands of opioid addicts in recovery who have abstained through the help of the twelve step fellowships for decades. We know it can be done, but how can we tell who is likely to be successful?
6. Do we commit everyone to maintenance for life? Is this "harm reduction," or are we actually doing harm by using medications for all without attempting to help clients achieve a drug-free state? Do we try abstinence a time or two or ten? Do we eventually accept buprenorphine maintained recovery as a reasonable alternative? Do we try again for abstinence after a time? If so, when?

These and other questions need to be studied in order for us to develop a national policy for buprenorphine in opioid dependence and provide the best care for all.

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