What Every Dentist Should Know for Patients Taking Suboxone (Buprenorphine/Naloxone)

ROBERT E. JOHNSON, III ▲ MORTON B. ROSENBERG, DMD

Mr. Johnson is a third-year predoctoral student at the Tufts University School of Dental Medicine. Dr. Rosenberg is professor emeritus of oral and maxillofacial surgery at the Tufts University School of Dental Medicine and professor of anesthesiology at the Tufts University School of Medicine.

INTRODUCTION

Suboxone® (buprenorphine/naloxone) is approved by the U.S. Food and Drug Administration (FDA) for opioid maintenance therapy.[1,2] The purpose of this article is to provide dentists with an understanding of the patient taking Suboxone and its clinical considerations. In order to do so, it is necessary to first describe the nature of the drug, the scope of the opioid epidemic and dentistry's role, the effects of chronic opioid use, and the use of Suboxone in the treatment of opioid addiction.

OPIOID EPIDEMIC AND DENTISTRY

Mortality from the abuse of prescription opioids is greater than that of heroin and cocaine combined.[3] The increase in nonmedical opioid use is the result of a greater number of prescriptions in the treatment of legitimate pain by health care professionals. In 2010, there were 15.5 million opioid-dependent people in the world, with the highest prevalence in males, those 25–29 years of age, and in Australasia, Western Europe, and North America.[4] In the United States, 4.5 million people over the age of 12 have reported nonmedical use of opioids in one month.[5] Due to the prevalence of this problem, it is necessary for dentists to be prepared to identify and treat patients misusing opioids.

The role of dentists in this epidemic has been examined and reported. A 2008 study in Utah found that 72% of dental patients indicated having leftover opioids after treatment, and 71% reported keeping them.[6] This data suggests that more than half of all opioids prescribed in dentistry in 2008 in Utah went unused and were not disposed of, making these drugs available for abuse. Another study examining opioid abuse found that 37.5% of dental patients prescribed an opioid for dental pain repurposed their prescription for nonmedical use.[7] The most commonly abused opioids are immediate release (IR), and dentists are the second-leading prescribers of IR opioids relative to all medical specialties, representing 12% of such prescriptions.[5,6] Not only must dentists be prepared to treat this patient population, but also they must be educated in preventing opioid abuse.

This crisis has been addressed in the medical and dental literature, and in more stringent rules and regulations regarding opioid prescribing at the national and local levels. Massachusetts has been remarkably proactive in working toward reducing excessive opioid prescriptions. In February 2016, a collaborative effort by the Massachusetts Department of Public Health, the Massachusetts Dental Society, the Boston University Henry M. Goldman School of Dental Medicine, the Harvard School of Dental Medicine, and the Tufts University School of Dental Medicine resulted in "Dental Education Core Competencies for the Prevention and Management of Prescription Drug Misuse." This initiative is intended to enhance dental education to "provide dental students with a strong foundation in prevention, identifying substance use disorders, managing the complex patient requiring effective pain management, and referring patients for appropriate treatment."[8]

OPIOID PHYSICAL DEPENDENCE AND ADDICTION

Opioid agonist therapy is well established in the treatment of both opioid addiction and physical dependence.[1] Although both conditions are treated similarly, it is important to differentiate the two and to understand their underlying mechanisms.

In one study, Kosten and George explain the progression of opioid physical dependence and addiction.[9] Physical dependence occurs when an individual becomes more susceptible to withdrawal symptoms due to an increase in tolerance. Tolerance occurs when exceedingly larger doses of a drug are required in order to achieve

a similar effect. Physical dependence is a normal process that is easily managed with medication and eventual tapering of dosing.

Opioid addiction entails uncontrollable cravings, and uncontrollable and compulsive use of opioids despite causing harm to self or others. Addiction is a disease comprised of somatic, psychological, and behavioral symptoms, and as such, treatment is less predictable than that of physical dependence.[9]

Addiction and physical dependence do not necessarily occur together, but are both commonly seen in chronic use of opioids. The μ opioid receptors of the central nervous system stimulate reward centers, similar to sex and eating. The sensation of pleasure that is experienced is largely due to both dopamine release from the ventral tegmental area and the mesolimbic reward system, and is the driving force for opioid abuse. The compulsive use that is seen in those who become addicted is due to their associating environmental conditions of drug intake with feelings of pleasure.[9] Those environmental conditions become triggers for future drug seeking.

In addition to increasing feelings of pleasure, opioids decrease norepinephrine release from the locus ceruleus (LC) of the brain. Norepinephrine normally increases wakefulness, breathing, and blood pressure. With continued opioid use, the LC increases production to overcome expected opioid suppression; thus, tolerance occurs. When opioids are no longer introduced, withdrawal symptoms—jitters, anxiety, muscle cramps, and diarrhea—occur due to the excessive production of norepinephrine.[9]

BUP/NAL OPIOID MAINTENANCE THERAPY

Suboxone is a mixed opioid agonist-antagonist containing the active ingredients buprenorphine and naloxone (BUP/NAL) that was approved in 2002 by the FDA as a Schedule III drug for office-based opioid addiction treatment.[3] It is delivered once daily in a 4:1 ratio as a sublingual film with available dosages of 2.0:0.5mg, 4.0:1.0mg, 8.0:2.0mg, and 12.0:3.0mg.[2]

Buprenorphine (BUP) was originally synthesized in 1966 and became available as an opioid analgesic in the United States in 1985.[10] The unique pharmacologic profile of BUP has led to its popularization in opioid maintenance therapy. As a partial μ opioid receptor agonist with high-receptor affinity, BUP effectively outcompetes other opioids to stimulate the μ receptor to a lesser degree.[3] Not only does BUP initially outcompete other opioids, but also it has a slow rate of dissociation from the μ receptor and a long half-life of 24–42 hours, thereby outlasting other opioids, as well.[11] In addition, BUP is a full kappa opioid receptor antagonist. The antagonistic property of BUP is favorable, as the kappa receptor is responsible for the dysphoria and psychosis caused by opioid use.[12]

Naloxone (NAL) is most commonly used as an opioid reversal agent, as it is a broad opioid receptor antagonist with high receptor affinity.[13,14] It was added to BUP in opioid maintenance therapy to decrease intravenous abuse potential.[13] At low doses, it inhibits undesirable side effects of opioids, such as drowsiness, respiratory depression, and decreased blood pressure without reversing desired analgesia. However, at high doses, NAL outcompetes opioids to antagonize the receptors, causing withdrawal symptoms, and therefore deters abuse.[3] NAL effectively inhibits the expected suppressive action of opioids and precipitates a situation similar to the individual abruptly being deprived of opioids altogether.

The difference in bioavailability and duration of action between BUP and NAL when administered sublingually allows for an effective combination.[13] BUP has greater bioavailability (40% versus 10%) and a longer duration of action (966 minutes versus 105 minutes) than NAL and therefore exerts the greater effect.[3] These differences are compounded when delivered in a 4:1 ratio. Although NAL is delivered at a desirable low dose sublingually, its bioavailability increases to produce undesirable withdrawal symptoms when administered intravenously.[15]

COMPARING BUP/NAL WITH METHADONE

Since 1949, methadone has been a first-line treatment for opioid addiction and dependence, and is still effectively used in opioid maintenance therapy.[16] However, BUP/NAL offers several pharmacologic and practical advantages.

The side effects of BUP are within the expected opioid spectrum but are diminished due to its ceiling dose effect at the opioid receptor, leading to an improved safety profile. Specifically, after 12 mg is exceeded, there is no further analgesic effect.[2,17] The result is less respiratory depression and sedation than with methadone. BUP offers additional advantages to the cardiac patient, as it has not been found to prolong the QT interval and thus does not increase risk of torsade des pointes, as has been found with methadone.[18,19] Treatment efficacy between methadone and BUP/NAL in opioid maintenance therapy has generally been found to be comparable for those retained in treatment, although several studies report a higher retention rate in methadone therapy.[11] The comparable effectiveness of methadone to BUP/NAL is inconclusive and further studies are required to determine which therapy is most appropriate per individual.

BUP/NAL does, however, have the distinct advantage of accessibility. Due to the FDA's approval of office-based treatment of opioid addiction, specially trained primary care physicians can prescribe BUP/NAL, whereas methadone is only available in specialty methadone clinics.[16]

TREATING PAIN IN THE BUP/NAL PATIENT

The role of the dentist in addressing dental pain in a patient taking BUP/NAL centers on managing the patient's pain without compromising opioid maintenance therapy. Due to the stress and anxiety that accompanies pain, poor pain management can put recovering patients at risk for relapse.[6] It is imperative that in addition to pharmacological pain management, the dentist communicate concerns and expectations with the patient, the patient's prescribing physician or addiction clinic, and the patient's family or support network. Proper authorization must be obtained from the patient in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and state privacy laws.

Opioid analgesics are not recommended as first-line pain management in this patient population. Not only do opioids increase the risk for relapse, but opioid analgesics are much less effective in the BUP/NAL patient due to the high affinity of BUP for the μ opioid receptor as a partial agonist.[6,11] Although, to a lesser degree, BUP does provide some analgesia, and effective pain management can usually be accomplished through adjunct treatment with NSAIDs, acetaminophen, and/or Advil.[3]

Pain management recommendations for the BUP/NAL patient include only employing opioids when necessary. The use of multimodal pain management strategies, such as "preemptive NSAIDs to limit pain severity, long-acting local anesthetics to delay pain onset, and corticosteroids to limit postoperative inflammation and swelling to diminish or eliminate the need for opioid analgesics,"[20] has been proven to provide better pain management than single-entity opioids and to have comparable outcomes to peripheral and opioid combination drugs.[6,20,21] Patients under active opioid management therapy are often cooperative and even enthusiastic about alternatives to opioids, as they are aware of the risk opioids pose to recovery.

In the event that adequate pain management is not achieved, further consultation with the BUP/NAL prescribing physician may be required. Although further investigation is necessary to determine optimal peri- and post-operative analgesia strategies in the BUP/NAL patient, several options exist. Increasing the frequency of BUP/NAL dosing may elicit a greater analgesic effect, short-acting opioids may be administered in addition to BUP/NAL, or BUP/NAL treatment may be discontinued 3–7 days prior to treatment and replaced with traditional opioid analgesics temporarily.[22,23] The aforementioned treatment options should only be employed with close collaboration with the patient's physician. It is also advisable to procure all necessary consents, including the risk for patient relapse.

OTHER CONSIDERATIONS

Pain management is the most complex issue in treating BUP/NAL patients, but there are other clinical considerations. BUP is metabolized by hepatic cytochrome P450 (CYP) enzymes; CYP3A4 dealkylates BUP to norbuprenorphine, with limited involvement by CYP2C8.[24] Due to their theoretical ability to increase/decrease plasma concentrations of BUP, CYP3A4 inhibitors/inducers should be avoided or closely monitored.[2] Notable examples include benzodiazepines (diazepam and flunitrazepam), fluconazole, clarithromycin, rifampin, and antidepressants, such as fluoxetine.[3]

In general, central nervous system depressants, such as benzodiazepines, sedatives, tranquilizers, antidepressants, and alcohol should be avoided. Alcohol and benzodiazepines have been established as risk factors for both relapse and—in exceedingly rare cases—death. Diazepam has notably been reported to affect respiratory function.[3]

Following hepatic metabolism, norbuprenorphine undergoes glucuronidation via UDP-glucuronosyl transferases (UGT) and conjugation, and is then excreted by the biliary system and excreted in the feces with minimal renal involvement. NAL is also metabolized via the liver but is excreted in the urine.[24] Hepatorenal functions should be monitored.

The sublingual delivery of BUP/NAL may cause swollen and/or painful tongue, general redness and/or numbness within the oral cavity, and vomiting.[2] Special care should be taken to identify any of these manifestations during intraoral exams. Reported xerostomia or observed hyposalivation should also be addressed, as a moist mouth is required for optimal film absorption.[3] As is necessary before prescribing any drug, a thorough review of patient health history must be conducted.

CONCLUSION

Dentists must be prepared to treat opioid patients at all stages of use, recovery, and abstinence. This article is intended to prepare dental providers for patients presenting in their chair who are on Suboxone opioid maintenance therapy. A thorough health history should not only inquire about current Suboxone use, but also previous use. This can help to indicate what stage of recovery the patient is in and to start a dialogue. Dentists should also be prepared to identify opioid abuse in those patients not receiving active therapy. Due to required special training, not all physicians prescribe Suboxone.[3] It is advised that all dentists are equipped to refer to a local Suboxone-prescribing physician if opioid abuse is suspected.

Opioid addiction is underreported in clinical practice.[6] As a general dentist with the benefit of regular patient contact, it is important to communicate history of abuse when referring to specialists. The average age individuals first use opioids nonmedically is 20, which is also the average age for third-molar extractions by oral and maxillofacial surgeons, the majority of which are accompanied with an opioid prescription.[6,25] In conclusion, due to the scale of the opioid epidemic and effectiveness of Suboxone opioid management therapy, dentists must be prepared to treat these patients effectively and safely. **JMDS**

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