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Clinical Review: The Treatment of Opioid Addiction with Buprenorphine

Learning Objectives:

- Review the induction, stabilization, and maintenance phases of the management of opioid addiction.
- Describe strategies for pharmacists and providers to promote successful opioid agonist treatment.
- Summarize best practices for responsible prescribing and dispensing of buprenorphine-containing products.

Key Points:

- Buprenorphine-containing products are an effective first-line treatment for opioid addiction.
- In recent years, policymakers at both the federal and state level are working to expand access to buprenorphine-containing products.
  - As of June 1, 2015, an approved *Treatment Authorization Request* (TAR) is no longer required by Medi-Cal for buprenorphine-containing products when prescribed by qualified physicians for the treatment of individuals with opioid addiction.
  - As of August 8, 2016, federal regulations now allow qualified providers to treat up to 275 patients with buprenorphine-containing products for opioid addiction.
- A review of claims data in the Medi-Cal fee-for-service population over a one-year time period (the year following the removal of the TAR restriction) showed 47% of beneficiaries are adherent to the buprenorphine treatment regimen and have extremely low concomitant use of any opioid during the same time period (3% concomitant use overall, and 2% use in the adherent group).
- In the Medi-Cal fee-for-service population, almost half (47%) of the paid claims for buprenorphine were for less than a 30 days supply, and for the group adherent to their buprenorphine treatment regimen, the average number of buprenorphine claims per beneficiary during the measurement year was 13.5 ± 6.5 (mean ± standard deviation) claims.
- Given the potentially high number of refill visits for patients who are adherent to their buprenorphine regimen, pharmacists should ensure their pharmacy is well-stocked with buprenorphine and the environment is safe and welcoming.

Background

Each day in the United States, 46 people die from an overdose of prescription opioid pain relievers.[1] In 2012, there were approximately 2.1 million people in the United States suffering from substance use disorders related to prescription opioid pain relievers and an estimated 467,000 addicted to heroin.[2]

The Drug Addiction Treatment Act of 2000 (DATA 2000) established a new paradigm for the medication-assisted treatment (MAT) of opioid addiction in the United States and enabled physicians to provide office-based treatment for opioid addiction.[3] This act allowed physicians to prescribe Schedule III, IV, or V medications that are approved by the United States Food and Drug Administration (FDA) for patients with opioid-use disorders. In October 2002, the FDA approved two Schedule III medications for the treatment of opioid addiction, the opioid partial

agonist medication buprenorphine and a combination of buprenorphine and naloxone (an opioid antagonist).[3,4]

Since that time, buprenorphine, both by itself and in combination with naloxone, has emerged as a first-line treatment for opioid addiction.[3-7] Buprenorphine has a reduced risk of overdose relative to full agonist therapies, and in combination with naloxone, has reduced abuse liability.[3-6] Buprenorphine is about 20 – 30 times more potent than morphine as an analgesic; however, high doses of buprenorphine have been shown to have a blunting effect on both physiological and psychological effects due to it being an opioid partial agonist.[8] By adding naloxone to buprenorphine, the potential euphoric high resulting from the injection of buprenorphine can be blocked.[8] Several reviews have concluded there is high-quality evidence to show that MAT with buprenorphine is effective in the maintenance treatment of opioid addiction and increases retention in treatment, especially when used in combination with psychosocial treatments (for example, contingency management, community reinforcement, psychotherapeutic counseling, and family therapy).[3,5,9]

Despite the success of MAT with buprenorphine-containing products, this treatment is highly underutilized and access is often restricted. In 2013, the Centers for Medicare & Medicaid Services (CMS) reported that prior authorization for buprenorphine use was required by 48 Medicaid programs and several states had lifetime limits on buprenorphine, even though evidence shows that opioid addiction is a chronic condition that may require ongoing treatment.[10] Recent efforts at the national level have been aimed at expanding access and removing restrictions to buprenorphine, including modification of legislative rules to increase the number of patients that providers are able to treat under the DATA 2000 waiver.[11] Currently, as of August 8, 2016, qualified providers may now treat up to 275 patients (up from 30 patients in 2000).[11] The stated intent of this increase was to allow greater access to buprenorphine-based MAT.[11]

Policy changes within the Medi-Cal program have also aimed to improve access to buprenorphine-containing products. Starting June 1, 2015, an approved TAR is no longer required for either buprenorphine or buprenorphine/naloxone when prescribed by qualified physicians for the treatment of individuals with opioid addiction. In addition, new formulations continue to be added as covered benefits for Medi-Cal beneficiaries, including the buccal film formulation of buprenorphine/naloxone, effective September 1, 2015 (see Table 1 for a complete list of available products).

Table 1. Available Dosage Forms and Strengths of Buprenorphine in the Medi-Cal Program

Drug	Formulation	Strength
Buprenorphine*	Sublingual tablets	2 mg and 8 mg
Buprenorphine/Naloxone*	Sublingual tablets	2 mg/0.5 mg and 8 mg/2 mg
		1.4 mg/0.36 mg and 5.7 mg/1.4 mg
	Sublingual film	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg
	Buccal film	2.1 mg/0.3 mg 4.2 mg/0.7 mg 6.3 mg/1.0 mg

* Limited to use for the treatment of opioid addiction by physicians with a DATA 2000 waiver. Restricted to 120 dosage units and a 30-day supply per dispensing. For current information, use the online Medi-Cal Formulary search tool available on the Formulary File Web page of the Department of Healthcare Services (DHCS) website.

The three phases of buprenorphine treatment for opioid addiction are induction, stabilization, and maintenance.[3,6,12] Each phase has different goals and a different suggested dosage of

buprenorphine-containing products. While each phase is summarized below in Table 2, comprehensive and detailed treatment guidelines are available within the Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction, available at the Substance Abuse and Mental Health Services Administration (SAMHSA) website.[3]

Table 2. Three Phases of Buprenorphine Treatment for Opioid Addiction[3,6,12]

	Induction – 1st Phase	Stabilization – 2nd Phase	Maintenance – 3rd Phase
Goals	• Begin transition from opioids of abuse to buprenorphine • Find minimum effective dosage of buprenorphine	• Elimination of objective evidence of opioid use • Reduce self-reported cravings	• Specific goals should be agreed upon by both the patient and the physician • Monitor cravings and prevent relapse
Duration	• Three to seven days	• Between one and two months	• Approximately nine weeks to >one year; begins when dosage is stable
Buprenorphine Regimen	• Begin with 4 – 8 mg and increase to 16 mg/day of buprenorphine on the second day, with further daily increases to a maximum of 32 mg/day	• Increase buprenorphine doses to as high as 32 mg/day, depending on cravings and side effects	• Maximum dosage of 32 mg/day, depending on cravings and side effects • Maintenance doses of at least 16 mg/day have been shown to be most effective
Treatment Guidelines	• Buprenorphine should be initiated 12 – 24 hours after short-acting opioid use and 24 – 48 hours after long-acting opioid use • Most patients should use buprenorphine/ naloxone tablets, although pregnant women should use the buprenorphine-only formulation	• Dosage adjustments may be necessary in the early stabilization phase • Daily dosing is recommended during induction and early stabilization	• Usual minimum length of treatment is one year and may be lifelong • Risks of relapse and overdose increase when maintenance therapy is discontinued • Buprenorphine tapers should be initiated only after careful consideration and under the close supervision of a physician

Buprenorphine Use in the Medi-Cal Fee-for-Service Population

A retrospective cohort study was conducted to assess the use of buprenorphine in the Medi-Cal fee-for-service population during the year following the policy change to not require an approved TAR. The initial study population included all continuously-eligible Medi-Cal fee-for-service beneficiaries with at least one paid claim for buprenorphine or buprenorphine/naloxone between June 1, 2015, and May 31, 2016. Demographic characteristics including gender, age, race/ethnicity, and geographic region of residence were reviewed for all beneficiaries in the study population.

Adherence to buprenorphine therapy was calculated for each beneficiary by determining the medication possession ratio (MPR), which calculates the sum of the days supply for all claims

during a defined period of time divided by the number of days elapsed during the period. For this analysis, the MPR was calculated beginning with the date of the first paid claim for buprenorphine during the measurement year, using the following equation:

$$\textbf{MPR} = \frac{\text{Total days supply for all buprenorphine paid claims for days between June 1, 2015, and May 31, 2016 (the measurement year)}}{\text{Total days between the first buprenorphine paid claim date during the measurement year and May 31, 2016 (the last day of the measurement year)}}$$

In order to account for beneficiaries with paid claims for days that extended beyond the measurement year, any medication possession days after May 31, 2016, were subtracted from the total days supply.

For example, during the measurement year, if a beneficiary had a total of twelve prescriptions of buprenorphine (each with a days supply of 28 days) and the first paid claim was on June 15, 2015, and the last paid claim was on May 15, 2016, the MPR for this beneficiary would be 92%, according to the following equation:

$$\textbf{MPR} = \frac{\text{[(12 paid claims x 28 days per claim) – 12 days outside of the measurement year)]}}{\text{(Total days between June 15, 2015, and May 31, 2016)}} = \frac{\text{324 days}}{\text{351 days}} = 92\%$$

Additional analyses were performed to evaluate the concomitant use of selected medications that may increase the risk of overdose and other adverse drug events among beneficiaries with paid claims for buprenorphine. All paid claims for drugs that may increase the risk of respiratory depression and/or overdose were reviewed for the study population during the measurement year, including other opioid medications (besides buprenorphine), benzodiazepines, barbiturates, and sleep aids. Concomitant use of these medications was also calculated for a subset of the study population with an MPR between 80% and 120% who appeared to be taking buprenorphine for opioid maintenance.

Results

A total of 5,657 continuously-eligible Medi-Cal fee-for-service beneficiaries had at least one paid claim for either buprenorphine or buprenorphine/naloxone between June 1, 2015, and May 31, 2016, with the majority of beneficiaries (n = 3,612; 64%) having 12 or fewer paid claims during the year. For this study population there were a total of 52,813 buprenorphine paid claims during the measurement year, with an average of 22.7 ± 9.7 (mean ± standard deviation) days supply per claim (range: 1 – 90 days). Almost half of buprenorphine paid claims (n = 24,491; 46%) were for a supply of less than 30 days. During the one-year measurement period, the average number of claims for buprenorphine-containing products per beneficiary was 9.3 ± 7.5 claims, with an average days supply during the year of 211.9 ± 136.5 days.

A review of demographic characteristics for the entire study population (Table 3) shows those beneficiaries with a paid claim for buprenorphine or buprenorphine/naloxone were predominantly 39 years of age and younger and white/Caucasian, non-Hispanic. The gender breakdown was almost equal, with 53% of the population male and 47% female. Finally, the distribution of beneficiaries by California region of residence shows the fewest beneficiaries in the study population reside in the Los Angeles and Central Valley regions, while the more rural North and Mountain region had the greatest number of beneficiaries in the study population. This variation in region of residence may be impacted by the migration of beneficiaries in specific counties into Medi-Cal managed care plans (MCPs).

Table 3. Demographic Characteristics of the Medi-Cal Fee-for-Service Study Population (n = 5,657)

Medi-Cal Fee-for-Service Population	
Gender	
• Male	**(n = 3,026), 53%**
• Female	**(n = 2,631), 47%**
Age*	
• 39 years of age and younger	**(n = 3,663), 65%**
• 40 years of age and older	**(n = 1,994), 35%**
Race/Ethnicity	
• White/Caucasian, non-Hispanic	**(n = 4,009), 71%**
• All other races/ethnicities	**(n = 1,648), 29%**
California Region of Residence (based on county)	
• Bay Area, including Alameda, Contra Costa, Marin, Napa, San Francisco, San Mateo, Santa Clara, Santa Cruz, Solano, and Sonoma Counties	**(n = 1,201), 21%**
• Southern California without Los Angeles, including Orange, Riverside, San Bernardino, San Diego, Santa Barbara, and Ventura Counties	**(n = 1,316), 23%**
• Los Angeles County	**(n = 581), 10%**
• Central/Southern Farm, including Fresno, Imperial, Kern, Kings, Madera, Merced, Monterey, San Benito, San Joaquin, San Luis Obispo, Stanislaus, and Tulare Counties	**(n = 651), 12%**
• North and Mountain, including Alpine, Amador, Butte, Calaveras, Del Norte, Glenn, Humboldt, Inyo, Lake, Lassen, Mariposa, Mendocino, Modoc, Mono, Nevada, Plumas, Shasta, Sierra, Siskiyou, Tehama, Trinity, and Tuolumne Counties	**(n = 1,331), 24%**
• Central Valley, including Colusa, El Dorado, Placer, Sacramento, Sutter, Yolo, and Yuba Counties	**(n = 577), 10%**

* There were less than 10 beneficiaries 17 years of age and younger in the study population and less than 10 beneficiaries 65 years of age and older in the study population.

As measured by the MPR, a total of 2,628 beneficiaries (47%) had a buprenorphine adherence rate between 80% and 120% during the measurement year. This means the amount of buprenorphine dispensed for these beneficiaries was for approximately the same number of days than had elapsed since the first paid claim for buprenorphine in the measurement year, within a reasonable error window on either side. Based on these data, these beneficiaries were included in the opioid maintenance population. Only a small portion (n = 130; 2%) of the study population had an MPR greater than 120%, which meant the amount of buprenorphine dispensed was for a greater number of days than had elapsed. The remaining 2,899 beneficiaries (51%) had an MPR less than 80%. Among the 2,628 beneficiaries classified as the opioid maintenance subgroup, the average number of claims for buprenorphine-containing products per beneficiary increased to 13.5 ± 6.5 claims, with an average days supply during the year of 321.5 ± 67.7 days.

As shown in Table 4, there were very few beneficiaries in the study population with paid claims for selected drugs that may increase the risk of overdose and other adverse drug events when taken with buprenorphine-containing products, and even less use of these drugs among those in the opioid maintenance group. Among those 157 beneficiaries with at least one paid claim for any other opioid medication, more than half had only one paid claim (n = 90; 57%). When these opioid claims were reviewed for temporal proximity, the vast majority of these beneficiaries were tapering to opioids with a lower morphine equivalency before initiating buprenorphine therapy or the claims were prior to a paid claim for a buprenorphine-containing product. Among those in the opioid maintenance group, almost all beneficiaries (n = 34; 83%) had a total days supply of other opioid medications of 30 days or less.

Table 4. Use of Selected High-Risk Medications Among Medi-Cal Fee-for-Service Beneficiaries with at Least One Paid Claim for Buprenorphine-Containing Products Between June 1, 2015, and May 31, 2016

	Entire Study Population (n = 5,657)	Opioid Maintenance Group (n = 2,628)
Concomitant use of:		
• Any other opioid medication	**(n = 157), 3%**	**(n = 41), 2%**
• Any benzodiazepine	**(n = 101), 2%**	**(n = 35), 1%**
• Any prescription sleep aid	**(n = 30), <1%**	**(n < 10), <1%**
• Any barbiturate	**(n < 10), <1%**	**(n < 10), <1%**

Finally, a review of the 656 beneficiaries with only one paid claim for buprenorphine indicated a slightly higher rate of paid claims for other opioids during this one-year period (n = 36; 5%), more than double the rate of the opioid maintenance group.

Conclusion/Discussion

Medication-assisted treatment of opioid addiction with buprenorphine is effective, yet underutilized. The Medi-Cal fee-for-service data show almost half of patients who initiate treatment with buprenorphine continue to be adherent to their buprenorphine regimen. Physicians can help combat opioid addiction by becoming buprenorphine-certified and maximizing the number of patients they treat, while pharmacists can bridge communication with patients receiving buprenorphine treatment and providers to help mitigate side effects and improve adherence to treatment regimens.

Clinical Recommendations

- General Recommendations:
  - Buprenorphine can, and should, be used to effectively manage opioid addiction.
  - Buprenorphine information for providers and patients can be found online, including at BupPractice, which was developed by Clinical Tools, Inc. (CTI) with funding from the National Institute on Drug Abuse and at the Substance Abuse and Mental Health Services Administration website.
  - Educate patients regarding the risks of using benzodiazepines and other central nervous system depressants (including alcohol) while taking any buprenorphine-containing product.
  - Instruct patients to keep buprenorphine-containing products in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death.
  - Let patients know it is against the law to sell or give away buprenorphine-containing products to anyone else, even if they have similar signs and symptoms.
  - Advise patients seeking to discontinue buprenorphine-containing products to work closely with their provider in order to develop a tapering schedule.
  - Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events.
- Recommendations for Providers:
  - There are not enough qualified providers to treat all the patients with opioid addiction in California. Providers are encouraged to complete the eight hours of required buprenorphine training and apply for a waiver to prescribe buprenorphine. The *Waiver Notification Form SMA-167* is available at the Buprenorphine Waiver Notification Web page of the SAMHSA website.

- For providers with a current waiver to treat patients with buprenorphine who are not currently treating their allowed maximum number of patients, continue to offer medication-assisted treatment for opioid addiction with buprenorphine to qualified patients.
- Before writing the first prescription for a buprenorphine-containing product for opioid addiction:
  - ❖ Assess the patient to verify they meet the diagnostic criteria for opioid addiction.
  - ❖ Counsel the patient on the risks and safe storage of buprenorphine products.
  - ❖ Complete the Appropriate Use Checklist, which is available as part of the buprenorphine Risk Evaluation and Mitigation Strategy on the FDA website (or use another method specific to the provider's office practice).
  - ❖ Prescribe a limited amount of medication at the first visit.
  - ❖ Anticipate and define a plan for relapse.
- While the patient is being treated with buprenorphine:
  - ❖ At intervals commensurate with patient stability, schedule a return visit. Weekly or more frequent visits are recommended during the first month.
  - ❖ At the return visit, assess the patient's compliance with the medication, appropriateness of dosage prescribed, receipt of necessary psychosocial support, and adequate progress towards treatment goals.
  - ❖ Continue to monitor patients for illicit drug use, cravings, and triggers to relapse.

- Recommendations for Pharmacists:
  - Ensure that buprenorphine is in stock and available to meet demand for frequent refills.
  - Create a safe and welcoming environment for those patients filling prescriptions for buprenorphine. Be friendly, compassionate, and understanding, particularly in the earlier stages of treatment when patients may be quite uncomfortable.
  - Reach out to patients who do not pick up their refills. Pharmacists know when patients do not show up for refills and can play a vital and active role in encouraging adherence to buprenorphine therapy.
  - Verify prescriptions for buprenorphine-containing products come from providers in compliance with the provisions of DATA 2000. Pharmacists can verify the validity of a provider's DATA 2000 waiver by calling 1-866-BUP-CSAT (1-866-287-2728), or emailing info@buprenorphine.samhsa.gov.
  - Enroll in and access California's updated prescription drug monitoring program, available on the Controlled Substance Utilization Review and Evaluation System (CURES 2.0) Web page of the Office of the Attorney General website.
  - Provide the Medication Guide to patients each and every time the medicine is dispensed and discuss the risks and side effects associated with buprenorphine products, including what to do if patients experience side effects.

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