Buprenorphine and CBD Products in Pain Management

VISN7 Academic Detailing Service

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VISN7 Academic Detailing Team

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Objectives

1. Identify patients with chronic pain and opioid use disorder (OUD) who may benefit from buprenorphine.
2. Evaluate different buprenorphine formulations' place in therapy and create a risk mitigation plan for the treatment of chronic pain with or without OUD.
3. Discuss available literature on indications that may benefit from CBD treatment.
4. Review VHA directives and regulatory issues surrounding cannabinoids.
5. Describe currently available cannabinoid products on the market, their indications for use, and concerns with product reliability.
6. Discuss the process to order and interpret urine drug tests for buprenorphine and cannabinoids.

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Opioid Use Disorder (OUD)

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OUD

- **Lifetime prevalence for OUD among patients receiving long-term opioid therapy is estimated to be approximately 41%.**

28% for mild symptoms

10% for moderate symptoms

3.5% for severe symptoms

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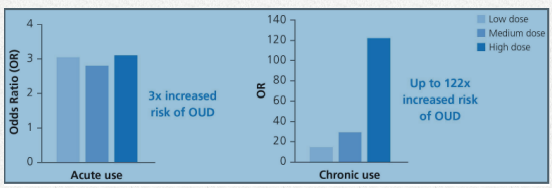
Both **dose** and **duration** of opioid therapy have been shown to be important determinants of OUD risk



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Identifying Veterans with OUD

- Drug craving or inability to control use may go unrecognized if patients continue to receive opioids
- Aberrant behaviors may become more apparent and reveal an OUD when opioids are tapered or discontinued or as tolerance begins to develop
- When performing a physical examination in a Veteran with suspected OUD or on an opioid:

✓ Look for signs and symptoms of opioid intoxication and/or withdrawal

✓ Look for indications of IV drug use

✓ Order a random UDS to check for unexpected findings

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	DSM-5 Criteria	Example Behaviors
1.	Craving or strong desire or urge to use opioids	Describes constantly thinking about/needing the opioid
2.	Recurrent use in situations that are physically hazardous	Repeatedly driving under the influence
X	Tolerance	Needing to take more and more to achieve the same effect (asking for increased dose without worsened pain)**
X	Withdrawal (or opioids are taken to relieve or avoid withdrawal)	Feeling sick if opioid is not taken on time or exhibiting withdrawal effects**
5.	Using larger amounts of opioids or over a longer period than initially intended	Taking more than prescribed (e.g. repeated requests for early refills)
6.	Persisting desire or unable to cut down on or control opioid use	Has tried to reduce dose or quit opioid because of family's concerns about use but has been unable to
7.	Spending a lot of time to obtain, use, or recover from opioids	Driving to different doctor's offices every month to get renewals for various opioid prescriptions
8.	Continued opioid use despite persistent or recurrent social or interpersonal problems related to opioids	Spouse or family member worried or critical about patient's opioid use; spouse divorcing Veteran because of use
9.	Continued use despite physical or psychological problems related to opioids	Unwilling to discontinue or reduce opioid use despite non-fatal accidental overdose
10.	Failure to fulfill obligations at work, school, or home due to use	Not finishing tasks at work due to taking frequent breaks to take opioid; getting fired from jobs
11.	Activities are given up or reduced because of use	No longer participating in weekly softball league despite no additional injury or reason for additional pain

OUD= meets 3 or more criteria
*(*excluding tolerance and withdrawal)*

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Determining Severity of OUD

Mild	Presence of 2-3 symptoms	*Patient may be managed with close monitoring and comprehensive approach such as a Pain PACT or Primary Care based buprenorphine/naloxone clinic*
Moderate	Presence of 4-5 symptoms	*MAT recommended*
Severe	Presence of 6 or more symptoms	

MAT = Medication assisted treatment

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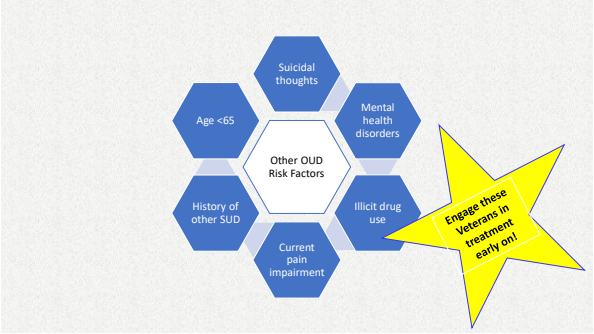

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Goals of Pain Treatment in Patients with OUD

Improve pain and maximize functionality

Prevent relapse and/or exacerbation of OUD

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Buprenorphine in Chronic Pain

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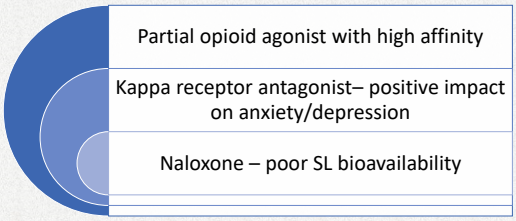
Buprenorphine/Suboxone Pharmacokinetics



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Literature for Use of Buprenorphine for Pain

CA pain

- 11 studies compared BUP to another pain medication
- 5 found superiority to the comparator, 3 found no differences to the comparator, 3 found inferiority to the comparator in terms of side effects or patient preference
- All studies reported that SL BUP showed some effectiveness for chronic pain

SL BP chronic pain

- 10 studies identified including 1190 patients with various pain conditions including general chronic pain, sickle-cell, cancer pain, osteoarthritis, and nociceptive pain
- All studies reported that SL BUP showed some effectiveness for chronic pain

Conversion from full dose opioid to buprenorphine

- Overall, patients reported a 51% decrease in pain scores before and after conversion to SL BUP (7.2 points -> 3.5 points; $P < 0.001$)
- 34 of 35 patients reported a decrease in pain

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Advantages of Buprenorphine

- ceiling effect on respiratory depression
- less euphoria
- reduced tolerance
- easier withdrawal
- less impairment of cognitive function and psychomotor activity
- lower incidence of constipation
- reduced endocrine and hyperalgesic effects

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Oral Buprenorphine Products			
Generic Name	Buprenorphine (transdermal patch)	Buprenorphine (buccal films)	Buprenorphine/naloxone; Buprenorphine (SL tablet)
Brand Name	Butrans®	Belbuca®	Suboxone®, Subutex®
Formulary Preference	Formulary PADR Required	Formulary PADR Required	Must be X-waivered to prescribe
Dosing Frequency	Weekly	BID	BID or TID (pain dosing)
Inclusion Criteria	Moderate to severe chronic pain requiring continuous, around-the-clock opioid analgesic for an extended period of time and deemed high risk for traditional opioid therapy		
Exclusion Criteria	Significant respiratory depression, conditions predisposing to significant respiratory depression including acute or severe bronchial asthma, known/suspected paralytic ileus, long QT syndrome, or taking a Class IA or III antiarrhythmic		
Recommended Conditions for Use	Failed attempts to taper off opioids due to physiologic opioid dependence		
	Long term opioid therapy of ≤ 80 MEDD	Long term opioid therapy of ≤ 160 MEDD	Suspected OUD + chronic pain —OR— Failed or have a contraindication/intolerance to other buprenorphine formulations (i.e >160 MEDD)

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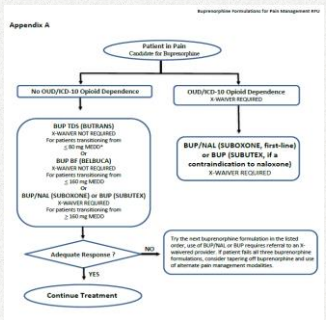
VA RFU for Buprenorphine Products

- How do you choose?
- Gray areas with Butrans and Belbuca
- Should everyone get x-waivered?



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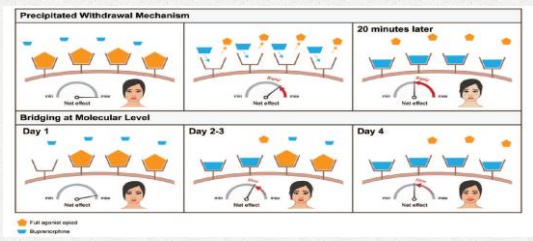
Buprenorphine Precipitated Withdrawal



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Dosing Approaches for SL Formulations

Option 1: Traditional Approach

- Taper down to 60-80 MEDD
- Hold full mu agonist (see chart below)
- Transition based on pre-taper MEDD

Medication/Formulation	Amount of Time to Hold
IR Formulation	8 hours
SA Formulation	12 hours
Fentanyl	3 days
Methadone	3-5 days

*Typically transition to 2mg BID or TID (or lower if patient is on very low MEDD) and titrate as needed

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Dosing Approaches for SL Formulations

Option 2: Overlapping Approach

- Start with very low dose of SL buprenorphine or buprenorphine/naloxone
- Increase dose over 4-5 days (target dose based on pre-taper MEDD; see chart below)
- Once at therapeutic dose, stop full mu agonist

Target Dose Based on Pre-Taper MEDD
<100 MEDD = 2mg BID or TID
100-150 MEDD = 2mg TID
> 150 MEDD = 4mg TID

Day	BUP/NAL (Only BUP dose listed)	Oxycodone SA
1	0.5mg BID	80mg TID
2	1mg BID	80mg TID
3	1mg TID	80mg TID
4	2mg TID	80mg TID
5	4mg TID	Discontinue
≥6	Adjust dose to symptoms	None

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Risk Mitigation

- **Shared Decision**
  - **SOAPP-R**
  - **COMM**
- **PDMP**
- **Naloxone**
- **Urine Drug Test**

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Buprenorphine Drug Screening

- Which test do you order to monitor buprenorphine?
  - Drug Test General (a.k.a. Gen Tox) or standard UDS if available locally

```
Specimen: URINE (T-7X100);    Accession: SEND 20 25845;
Report Released Date/Time: Aug 11, 2020@14:23
Comment:

   The following compounds were detected:
       Cotinine (Nicotine Metabolite)
       Caffeine
       Norbuprenorphine (Buprenorphine Metabolite)
       Buprenorphine
       Hydroxyzine
```

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Suboxone Success Story

- 35-year-old male with chronic knee pain for >15 years on chronic opioids, and provoked DVT (immobility) presented as a walk-in to the pain pharmacy clinic. In the month before this appt, he had been seen on 4 occasions for uncontrolled pain and had run out of his opiates early multiple times.
  - Previous opiate regimen: oxycodone/APAP 10mg/325mg q6h prn + oxycodone/APAP 5/325mg prn (up to three doses a week)
  - Buprenorphine/naloxone education completed, and patient agreed to transition
  - Buprenorphine/naloxone 2/0.5mg QID started
    - Pt already in withdrawal at time of initiation due to running out early

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Suboxone Success Story

- 1 week after initiation: States his pain is much improved, and that he "wishes he had listened months ago"
- Maintained on buprenorphine/naloxone 2/0.5mg QID + an extra dose every few days prn
- No walk-ins, no early refill requests, pain improved (last pain score in March 2020: 5, down from 10 in Jan 2020)

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CPRS Coding for Pain vs OUD: *What code do I Use?*

Bup for OUD
- **F11.2x** –Opioid dependence

Bup for Pain
- **Z79.891**-Therapeutic Long-term (current) Use of Opioid Analgesics

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INTERESTED IN GETTING YOUR X-WAIVER?

- Still required if using Suboxone for pain management
- Recent VA memo stating that Suboxone treatment should have no local barriers or restrictions

UPCOMING HALF & HALF
MEDICATION FOR OPIOID USE DISORDER
WAIVER TRAINING

DEC 11, 2020 2PM TO 6:30PM EST

8 8-HOUR REMOTE TRAINING FOR MEDICAL PROVIDERS TO BEGIN QUALIFYING FOR A MOUD WAIVER TO PRESCRIBE AND DISPENSE BUPRENORPHINE. PARTICIPANTS WILL BE EMAILED THE LINK TO COMPLETE THE OTHER 8 HOURS ONLINE. NPI AND DEA MUST COMPLETE AN ADDITIONAL 16 HOUR COURSE WHICH CAN BE FOUND HERE.

"A Camera and Registration are required to attend this free training"

For registration details email matthew.dungon1@va.gov

Future Half & Half Waiver Trainings:
- 1/19/2021
- 3/1/2021
- 7/22/2021
- *Email now to reserve your spot!

FREE self-paced online training also available at:
https://pcssnow.org/medications-for-addiction-treatment/

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CANNABINOIDS

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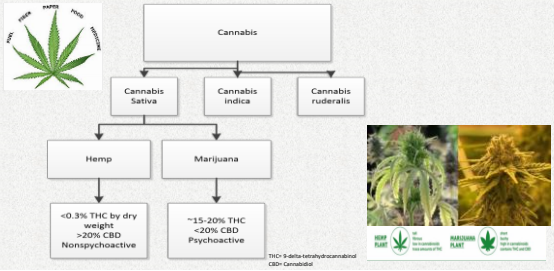
Cannabis Confusion: Hemp vs. Marijuana



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PHYTOCANNABINOIDS

THC

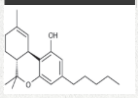
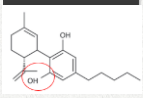


Table 1. Effects of THC and CBD

Effects	Tetrahydrocannabinol	Cannabidiol
Analgesic	+	++
Anticonvulsant	+	++
Antiemetic	+	+
Anti-inflammatory	–	++
Antioxidant	+	++
Anxiolytic/ antipsychotic	±	++
Euphoria	++	–
Muscle relaxation	++	+
Sedation	+	+
Tachycardia/ hypertension	+	–

"+" = evidence of causing the effect; "-" = no evidence of causing the effect; "±" = mixed evidence on causing the effect.
Information from: Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 2003;42:327-60.

CBD



Graphic taken from ACSAP 2020

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CBD Drug Interactions

3A4	2C19	2C9	2D6/1A2?
• Ketoconazole • Verapamil/Diltiazem • Macrolides • Rifampin • **Tacrolimus**	• Cimetidine • PPIs • **Clopidogrel** • Primidone • Benzos?	• **Warfarin** • Phenytoin	• TCAs • SSRIs • **Antipsychotics**

*Many CBD products also contain variable amounts of THC which = more potential for drug interactions!

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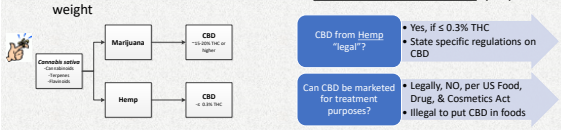
Farm Bill of 2018

- Removed hemp from the definition of marijuana in the Controlled Substances Act (CSA)
- How is hemp now defined?
  - Cannabis, and derivatives of cannabis, with **no more than 0.3% of THC** by dry weight



https://crsreports.congress.gov/product/pdf/R/R45525

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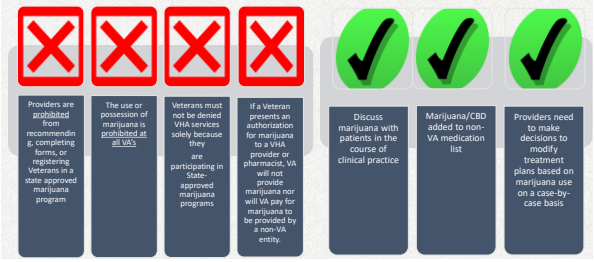
Prescribing Implications: VHA Directive 1315

- **Federally, Marijuana is Schedule 1**: High potential for abuse with no accepted medical indication



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Approved Cannabinoid Based Medications

Drug	Product Origin	Schedule	Indications
Marinol, Syndros (Dronabinol) Oral capsule, oral solution Approved 1985	Synthetic THC	Schedule III (Marinol)/Schedule II (Syndros)	Chemotherapy induced nausea/vomiting and AIDS-related loss of appetite
Cesamet (Nabilone) Oral capsule Approve 1985	Synthetic analog of THC	Schedule II	Chemotherapy induced nausea and vomiting
Sativex (Nabiximols) Oral spray Not approved in US	1:1 CBD to THC	Not available in US, used in 27 other countries	Multiple sclerosis-related spasticity and adjunctive analgesic in cancer patients
Epidiolex (Cannabidiol) Oral solution Approved 2018	Purified plant derived CBD	Initially Schedule V, descheduled April 2020	Lennox-Gastaut Syndrome and Dravet Syndrome

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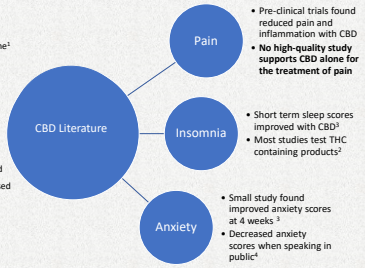
CBD Literature

- Epilepsy is only recognized indication for CBD alone[1]
- CBD/THC combination approved for multiple sclerosis and cancer pain outside US

General Literature Limitations

- Most studies include CBD combined with other cannabinoids
- Low quality of evidence based on study design
- Insufficient information on the CBD products used
- Dose, route, efficacy, and adverse effects vary based on products used



- Pre-clinical trials found reduced pain and inflammation with CBD
- **No high-quality study supports CBD alone for the treatment of pain**

- Short term sleep scores improved with CBD[3]
- Most studies test THC containing products[2]

- Small study found improved anxiety scores at 4 weeks [3]
- Decreased anxiety scores when speaking in public[4]

1. National Academies of Sciences, Engineering, and Medicine. 2017
2. JAMA. 2015;313(24):2456-2473
3. Perm J 2019;23:18-41
4. Neuropsychopharmacology. 2011 May;36(6):1219-26.

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CBD Products

- 14% of Americans report using CBD products
- Most common reasons were pain, anxiety, and insomnia
- Many formulations
  - Vaping
    - EVALI a major concern in unregulated vaping products
  - Oral tablets
  - Foods
  - Sublingual sprays
  - Oils
  - Tinctures
  - Topical formulations

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Product Reliability - CBD

- CBD products are largely unregulated and testing isn't required
  - Product reliability, dose accuracy, contamination concerns

- **JAMA 2017:** CBD products tested in lab for cannabinoid content
  - 84 products analyzed
- **Results:**
  - 26% contained **less** CBD than labeled
  - 43% contained **more** CBD than labeled
  - 31% were accurately labeled
  - 21% had detectable levels of THC

JAMA. 2017 Nov 7;318(17):1708-1709

https://apnews.com/article/7b452f4af90b4620ab0ff0eb2cca62cc

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CANNABINOID UDS/UDT FAQS

- **Which urine drug test should I order?**
  - UDS (in-house, immunoassay): 50 ng/mL
  - UDT (send-out, GC-MS @ Quest): 100 ng/mL
- **Patient states they are only using CBD oil. Will drug screen be negative?**
  - It depends
    - On the product→
      - "Pure CBD oil" is rarely pure
      - Trace THC below legal limit of 0.3% may still test positive
    - On the test →
      - UDS may cross-react with other cannabinoids besides THC
      - UDT will only test positive for THC

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CANNABINOID UDS/UDT FAQS

- **How long after last use of THC will test still be positive?**
  - Single use: 2-8 days
  - Chronic use: 20-30 days
- **Aren't there a lot of things that cause false positives for marijuana?**
  - Yes:
    - Dronabinol
  - Maybe:
    - Efavirenz
    - Proton pump inhibitors (PPIs)
    - Hemp products
  - *Not anymore:*
    - NSAIDs

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UDS/ UDT Results

Test	Result / Status
OPIATES*	NEG
AMPHETAMINE/METHAMPHETAMINE SCREEN*	NEG
BUPRENORPHINE*	NEG
OXYCODONE (URINE)*	NEG
METHADONE SCREEN*	NEG
CREATININE (URINE)*	142.1
COCAINE*	NEG
CANNABINOIDS*	POS
BENZODIAZEPINES*	NEG

Specimen: URINE; Accession: SEND 20 18143; Provider: [redacted]
Report Released Date/Time: Sep 09, 2020@15:21
Comment:
DRUG TEST, GENERAL TOX -
DRUG TEST, GENERAL TOX - The following compounds were detected:
DRUG TEST, GENERAL TOX - Hydroxybupropion (Bupropion Metabolite)
DRUG TEST, GENERAL TOX - Tramadol
DRUG TEST, GENERAL TOX - Quetiapine
DRUG TEST, GENERAL TOX - THC-COOH
DRUG TEST, GENERAL TOX - For a list of compounds and limits of
DRUG TEST, GENERAL TOX - detection go to:
DRUG TEST, GENERAL TOX - http://education.questdiagnostics.com/faq/FAQ101
DRUG TEST, GENERAL TOX -

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KEY TAKEAWAYS:

- Buprenorphine can used for the treatment of pain, especially in patients with a history of long-term opiate use requiring around the clock pain treatment
- Marijuana remains schedule 1 on a federal level, and VHA practitioners are prohibited from recommending/prescribing
- CBD
  - Lack of consistency/reliability in commercially available products
  - Has not demonstrated efficacy treating the most common indications for which patients take it

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Thank you for participating today!

- Claiming your CME credit:
  - Must have pre-registered in TMS for attending today's session.
  - Complete program evaluation within 30 days.
  - Pharmacists: must have you NABP number added to TMS profile.

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VISN7 ACADEMIC DETAILING TEAM

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Buprenorphine and CBD Products in Pain Management

Questions/Discussion

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