Long-Acting Injectable Buprenorphine

Update and Best Practices

PRESENTED BY:
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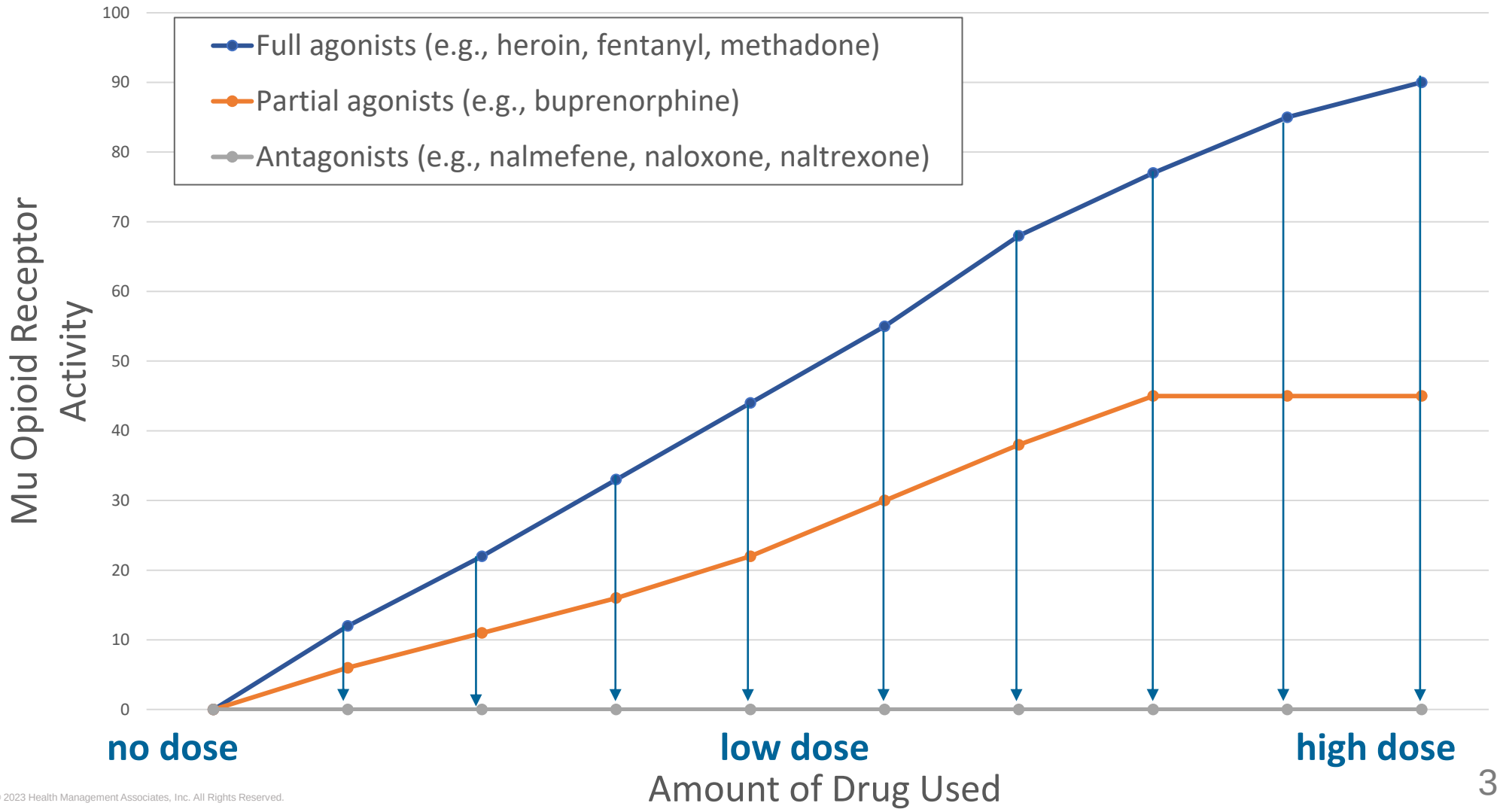
LEARNING OBJECTIVES

At the end of this presentation, participants will be able to discuss:

1. Pros and cons of different long-acting buprenorphine formulations
2. Initiating long-acting formulations of buprenorphine
3. Monitoring someone on long-acting formulations of buprenorphine
4. Discontinuing long-acting formulations of buprenorphine

FULL, PARTIAL, OR NO EFFECT

Buprenorphine, nalmefene, naloxone, and naltrexone can all cause precipitated withdrawal.



BUPRENORPHINE OVERVIEW

Partial mu opioid agonist with ceiling effect

- Does not result in "getting high" for some with physiologic dependence on opioids
- Higher doses do not produce more respiratory depression; ceiling effect to respiratory depression
  - Therefore, buprenorphine less likely to cause overdose on methadone

May result in sedation or opioid intoxication in "opioid naïve" people but still has less respiratory depression than methadone

Starting buprenorphine when opioid receptors are saturated causes precipitated withdrawal

Start buprenorphine when patient is in moderate withdrawal, then buprenorphine binds receptors & relieves withdrawal

HMA DHCS

BUPRENORPHINE PROPERTIES

- Typical dose 16-32 mg/ day
- Dosing <16 mg/day is NOT evidence based & rarely effective
  - Does not provide sufficient relief from cravings
- Ceiling effect
  - Doses above 32 mg are no more effective for treatment of OUD
  - Doses above ~32 mg do not cause more euphoria
- Binds strongly & can't be "kicked off" by opioids until it naturally dissociates from receptor; nalmefene or naloxone can displace buprenorphine
  - Other opioids are not as effective when buprenorphine is present
    - Therefore, buprenorphine is a deterrent to other opioid use
    - Methadone still allows other opioids to bind the receptors

HMA DHCS

CASE STUDY

- Male with a history of myasthenia gravis and blood clot in his leg with opioid use disorder.
- Started on extended-release injectable buprenorphine 8 months ago while incarcerated.
- Returns to jail.
- Seen by RN in booking and note says,
  - “I DON’T USE HEROIN ANYMORE. I’M TAKING ALL OF MY MEDICATIONS.”

WHY USE EXTENDED-RELEASE (ER) BUPRENORPHINE?

PROS AND CONS OF EXTENDED-RELEASE BUPRENORPHINE

PROS

- Decreased staff time for administration monthly instead of daily
- No risk of diversion/theft/loss/"forgetting"
- No "horrible taste"
- Stable blood levels – no "ups and downs"
- Present for many months post injection; gradual withdrawal if discontinued

CONS

- Present for many months post injection; might present difficulties if pain management is needed
- Painful injection
- Fear of needles/injection
- Up front costs higher than sublingual
- Must obtain from a special pharmacy, due to risk evaluation and mitigation strategy (REMS) requirements

HMA DHCS

WHY USE EXTENDED-RELEASE BUPRENORPHINE?

Patient has witnessed diversion

- Reasons for diversion
  - Patient threatened by others for buprenorphine
  - Patient giving medication to someone in need
  - Patient saving medication for later

Toxicology is inconsistent with expectations

- No norbuprenorphine detected?
- No buprenorphine detected?
- Ongoing opioid use?
  - Is dose of medication adequate?
  - Are there drug interactions? Or untreated co-occurring disorders?

Cost effective or other nonpatient specific reason(s)

HMA DHCS

BUPRENORPHINE FORMULATIONS: EFFECTIVENESS AND COSTS

Effectiveness

- Some data to support increased efficacy of injection over sublingual formulations

Cost effectiveness in community

- Costs of drug, newly acquired Hepatitis C Virus, emergency department visits, hospital admissions, days in crisis stabilization, detoxification or rehabilitation, criminality, and lost wages

Cost effectiveness in carceral settings

- Upfront cost of injection must be balanced with lower healthcare costs, less staff time to administer, etc.
- In a jail, the lower healthcare costs may not occur during a short sentence

COMPARISON BETWEEN AGENTS

- Formulations
- Similarities
- Differences
- Initiation
- Outcomes
- Adverse outcomes

ER BUPRENORPHINE SIMILARITIES

- Pharmacy needs certification to order & dispense (see links below)
- Medication is not dispensed to patient; must go to the location of the healthcare provider and provider must have DEA at this address
- Medication must be given subcutaneous (SC) injection, because
- Intravenous (IV) administration can be fatal
- There is insufficient data for use in pregnancy

Finding REMS certified pharmacies:
https://www.sublocaderems.com/Content/pdf/certified-pharmacies.pdf
https://brixadirems.com/

ER BUPRENORPHINE DIFFERENCES

	Brixadi®		Sublocade®
Dosing options	Weekly: 8 mg, 16 mg, 24 mg, 32 mg	Monthly: 64 mg, 96 mg, 128 mg	300mg for 2 months, then 100mg after or 300mg monthly
Delivery mechanism	Fluid crystal (liquid crystalline gel)		Atrigel
Lump present/ removable	No lump present/not removable		Lump present/removable up to 14 days
Storage	No refrigeration required		Refrigeration required; requires 15 min to reach room temperature; can be left out for up to 7 days
Injection	90 degrees, doesn't depend on amount of tissue because needle is smaller		Angle depends on the amount of subcutaneous tissue, 45 degrees
Injection site(s)	Buttock, thigh, abdomen, or *upper arm after 4th injection only *10% lower plasma levels for arm		Abdomen only, don't rub it

Source:
https://www.sublocade.com/?utm_campaign=BR%20%7C%20PAT%20%7C%20Sublocade&utm_source=google&utm_medium=cpc&utm_term=sublocade%20package%20insert&gclid=Cj0KCQiAraSPBhDuARIsAM3Js4oP0ALIv7cFyvUlLQqFeiyHTuSmgGFwFZrNgasBNLv3kLEYU08FpQQaAoScEALw_wcB&gclsrc=aw.ds
https://www.brixadi.com/pdfs/brixadi-prescribing-information.pdf

BUPRENORPHINE EXTENDED-RELEASE (ER) FORMULATIONS DIFFERENCES

Brixadi®

- Weekly
  - 8mg in 0.16ml
  - 16mg in 0.32ml
  - 24mg in 0.48ml
  - 32mg in 0.64ml
- Monthly
  - 64mg in 0.18ml
  - 96mg in 0.27ml
  - 128mg in 0.36ml

Sublocade®

- Weekly - not available
- Monthly
  - 100mg in 0.5ml
  - 300mg in 1.5ml

EXTENDED-RELEASE BUPRENORPHINE: INITIATION

Sublocade®

- Indication opioid use disorder
- If patient is not currently on buprenorphine and is having objective evidence of opioid withdrawal, then
  - Give 2-8mg of SL buprenorphine
  - If tolerated, give additional SL buprenorphine
  - Stabilize dose & treat for 7 days
  - Then 300 mg for 2 months, followed by 100mg thereafter

Brixadi®

- Indication: opioid use disorder
- If the patient is not currently on buprenorphine and has objective evidence of opioid withdrawal
  - Give 4mg sublingual dose
  - If tolerated, then administer 16mg Brixadi®
  - Administer 8mg Brixadi® within 3 days
  - Can administer an additional 8mg in first week
  - Give total of 4 weekly injections, then monthly, injection
- If on buprenorphine (±naloxone) use schedule below

Daily dose of sublingual buprenorphine	BRIXADI (weekly)	BRIXADI (monthly)
≤ 6 mg	8 mg	--
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

Note: One SUBOXONE® (buprenorphine and naloxone) 8 mg/2 mg sublingual tablet provides equivalent buprenorphine exposure to one SUBUTEX® (buprenorphine HCl) 8 mg sublingual tablet or one Zubsolv® (buprenorphine and naloxone) 5.7 mg/1.4 mg sublingual tablet.

HMA DHCS

ER BUPRENORPHINE OUTCOMES

Brixadi® outcomes

- Injectable out-performed sublingual for opioid negative urine samples

Sublocade® outcomes

- Injectable out-performed placebo for abstinence from opioids

Source:
https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/210136Orig1s000TALtr.pdf
Haight BR Lancet 2019
Lowfall MR JAMA Intern Med 2018

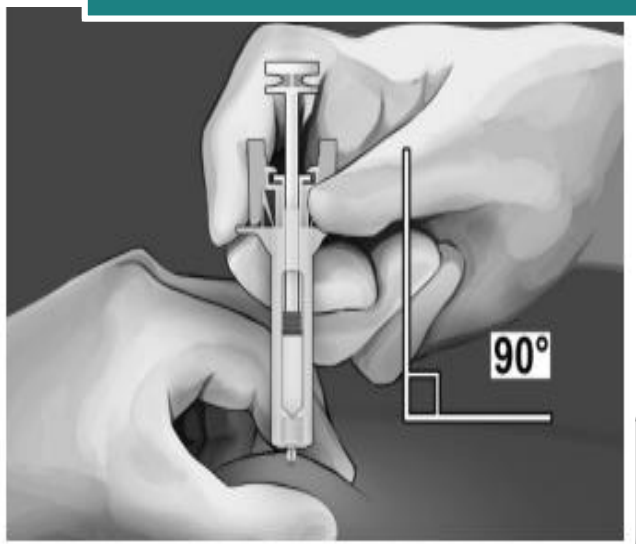
ER BUPRENORPHINE ADVERSE REACTIONS

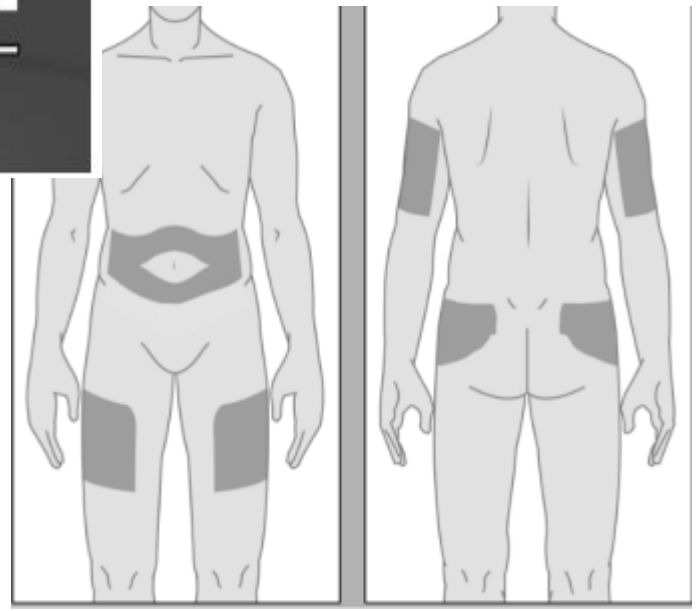
Adverse reactions in > 5% of subjects:		
	Brixadi®	Sublocade®
Headache	X	X
Constipation	X	X
Nausea	X	X
Vomiting		X
Fatigue		X
Insomnia	X	
Urinary tract infection	X	
Increased liver enzymes		X
Injection site redness	X	
Injection site itching	X	X
Injection site pain		X

Source: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/210136Orig1s000TALtr.pdf
Haight BR Lancet 2019
Lowfall MR JAMA Intern Med 2018

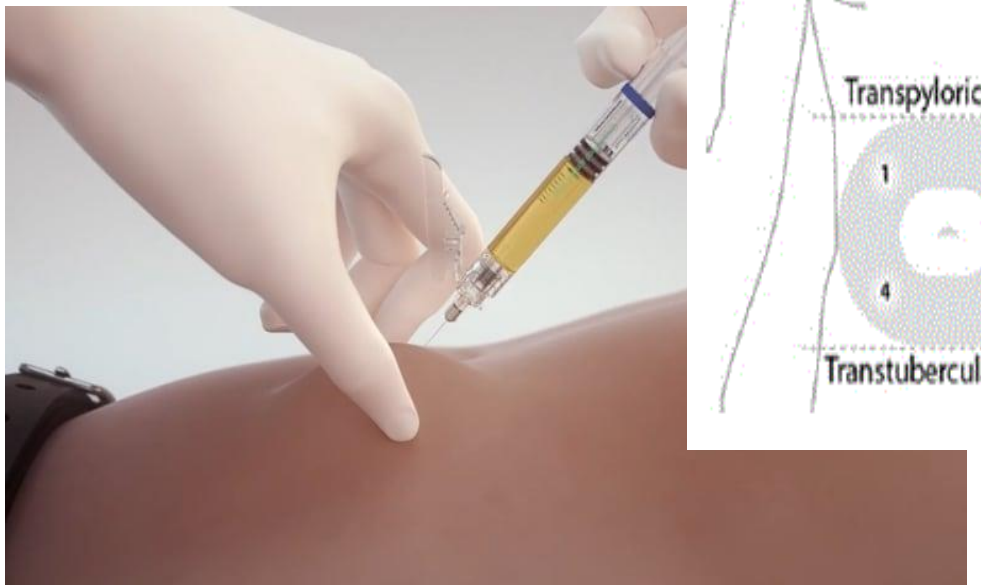
GIVING THE INJECTIONS

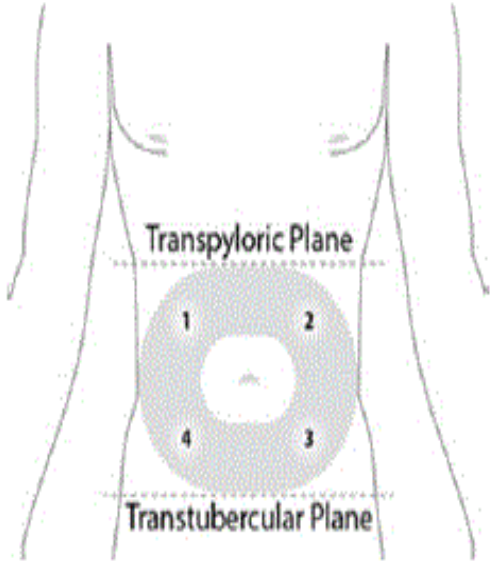
Brixadi®





Sublocade®





Grayken Center for Addiction Training and Technical Assistance, Boston Medical Center, Office Based Addiction Treatment Extended-Release Buprenorphine: An Instructional Guide
https://www.youtube.com/watch?v=y9UP6C5Gsf8

ER BUPRENORPHINE MONITORING

Monitor for:

- Effectiveness via self report, visible symptoms, and behavior
- Toxicology testing
  - Low levels of norbuprenorphine with SC or IV injections or intranasal compared to sublingual
- Liver function tests (blood) – pretreatment for baseline
  - Brixadi® – periodic monitoring
  - Sublocade® – monthly during treatment, especially on 300mg

ER BUPRENORPHINE: DISCONTINUATION

- Generally, no withdrawal symptoms
- Transmucosal buprenorphine could be given if withdrawal symptoms occurred
- Brixadi® after reaching steady state*
  - Detectable plasma levels for 1 month for weekly injections
  - Detectable plasma levels for 4 months for monthly injections
- Sublocade®**
  - Detectable plasma levels for 12 months

*Brixadi steady state=(4 weeks for weekly & 4 months for monthly)
**Sublocade steady state at 4-6months

REENTRY AND EXTENDED-RELEASE INJECTIONS

- Release from incarceration has always been unpredictable
- Reentry planning should begin upon admission
- If the person is on MOUD at the time of entry to jail
  - Obtain consent to communicate with prescriber
  - Communicate release to the provider as quickly as possible

- If the person is initiated (or continued) on MOUD while incarcerated
  - First dose: provide documentation to the patient, along with how/ where to obtain post release care
  - Not all providers have staff to administer ER buprenorphine
  - Not all pharmacies are allowed to carry ER buprenorphine
  - Provide additional documentation to the patient with all dose changes and each injection
- DC paperwork
  - To patient
  - To receiving provider

USE WITHIN CRIMINAL JUSTICE

Preference for monthly injections in jail

- Reduced risk of opioid use, withdrawal, and overdose
- Reduced risk of engaging in criminal activities
- Less perceived stigma
- Positively affected interactions with peers and CJ staff
- Perceived efficacy
- Improved likelihood of employment

"I don't have to worry about if I lose my medicine, if I go on vacation"
"functionally I can work, I don't wake up sick everyday"

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8800291/

COMPARISON OF AGENTS FOR OUD

- Community buprenorphine treatment retention in those released from jail was
  - 69% for those randomized to Injectable Buprenorphine
  - 35% for those randomized to Sublingual Buprenorphine

Lee, JD, et. al. Comparisons of Treatment Retention of Adults with Opioid Addiction Managed with Extended-Release Buprenorphine vs Daily Sublingual Buprenorphine-Naloxone at Time of Release from Jail. JAMA Open Network 4 (9). 2021

NEW SOUTH WALES CORRECTIONAL CENTERS

- Open label, non-randomized study of MOUD program
  - 78% reported having heard threats, coercion, or intimidation related to opioid agonist diversion at baseline
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9291502/

- ER buprenorphine cheaper compared to methadone and sublingual buprenorphine in Australia
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9644557/

SUMMARY

- 2 options for extended-release buprenorphine
  - Have not been compared head-to-head
  - Trials were conducted with different comparators & different end points
- Advantages of Brixadi®
  - Can start with only 1 sublingual dose
    - Compared to 7 days for Sublocade®
  - More dosing options with Brixadi®
  - More dosing locations with Brixadi®
  - No refrigeration required for Brixadi®
  - No lump present for Brixadi®, i.e., probably less likely to be diverted

POLL QUESTION

Can your patient pick up their extended-release buprenorphine prescription from any of the following?

Walgreens
Rite Aid
Target
CVS
Walmart
None of the above

Photo Microsoft online photos

BRIXADI® RESOURCES

- Brixadi Rems Home. Brixadi REMS. (2023, July 7). https://brixadirems.com/
- D'Onofrio G, Hawk KF, Herring AA, Perrone J, Cowan E, McCormack RP, Dziura J, Taylor RA, Coupet E, Edelman EJ, Pantalon MV, Owens PH, Martel SH, O'Connor PG, Van Veldhuisen P, DeVogel N, Huntley K, Murphy SM, Lofwall MR, Walsh SL, Fiellin DA. The design and conduct of a randomized clinical trial comparing emergency department initiation of sublingual versus a 7-day extended-release injection formulation of buprenorphine for opioid use disorder: Project ED Innovation. Contemp Clin Trials. 2021 May;104:106359. doi: 10.1016/j.cct.2021.106359. Epub 2021 Mar 16. PMID: 33737199; PMCID: PMC9153252. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9153252/
- Frost M, et al. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder. Addiction. 2019 Aug;114(8):1416-1426. doi: 10.1111/add.14636. Epub 2019 Jun 3. PMID: 31013390; PMCID: PMC6771955. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6771955/
- Lofwall MR, et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. JAMA Intern Med. 2018 Jun 1;178(6):764-773. doi: 10.1001/jamainternmed.2018.1052. PMID: 29799968; PMCID: PMC6145749. https://pubmed.ncbi.nlm.nih.gov/29799968/
- Parsons G, Ragbir C, D'Agnone O, Gibbs A, Littlewood R, Hard B. Patient-Reported Outcomes, Experiences and Satisfaction with Weekly and Monthly Injectable Prolonged-Release Buprenorphine. Subst Abuse Rehabil. 2020 Nov 2;11:41-47. doi: 10.2147/SAR.S266838. PMID: 33173372; PMCID: PMC7648142. https://pubmed.ncbi.nlm.nih.gov/33173372/
- Walsh SL, et al. Effect of Buprenorphine Weekly Depot (CAM2038) and Hydromorphone Blockade in Individuals With Opioid Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2017 Sep 1;74(9):894-902. doi: 10.1001/jamapsychiatry.2017.1874. PMID: 28655025; PMCID: PMC5710238.NCT02357901

SUBLOCADE® RESOURCES

- Certified pharmacies - sublocade rems. (n.d.). https://www.sublocaderems.com/Content/pdf/certified-pharmacies.pdf
- Grayken Center for Addiction Training and Technical Assistance (2023), Office Based Addiction Treatment (OBAT) Clinical Guidelines. Boston Medical Center, https://www.addictiontraining.org/documents/resources/22_2021_Clinical_Guidelines_1.12.2022_fp_th%2528003%2529.29.pdf
- Grayken Center for Addiction (2023) Extended-Release Buprenorphine: An instructional Guide https://www.youtube.com/watch?v=y9UP6C5Gsf8
- Haight BR, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019 Feb 23;393(10173):778-790. doi: 10.1016/S0140-6736(18)32259-1. Epub 2019 Feb 18. PMID: 30792007.NCT02044094-
- Ling W, Nadipelli VR, Solem CT, Ronquest NA, Yeh YC, Learned SM, Mehra V, Heidbreder C. Effects of monthly buprenorphine extended-release injections on patient-centered outcomes: A long-term study. J Subst Abuse Treat. 2020 Mar;110:1-8. doi: 10.1016/j.jsat.2019.11.004. Epub 2019 Nov 15. PMID: 31952623. https://pubmed.ncbi.nlm.nih.gov/31952623/
- Nasser AF, et al. Sustained-Release Buprenorphine (RBP-6000) Blocks the Effects of Opioid Challenge With Hydromorphone in Subjects With Opioid Use Disorder. J Clin Psychopharmacol. 2016 Feb;36(1):18-26. doi: 10.1097/JCP.0000000000000434. PMID: 26650971; PMCID: PMC5549150.

EXTENDED-RELEASE BUPRENORPHINE: THE DEVIL IS IN THE DETAILS

PATIENT SPECIFIC EXTENDED RELEASE INJECTABLES

- Prescriber writes Rx specifically for patient
- Medication is delivered from pharmacy with REMS certification; facility does not have to be REMS certified
- Prescriber must have DEA registered to jail location
- Minimal storage required
- Must coordinate delivery timing with dosage timing
- Patient might leave jail before dose is administered
- Outpatient clinics may have to work with several specialty pharmacies based on patient's insurance
- Prior Authorization is NOT required in CA for Sublocade®
- Manufacturer of Brixadi®, is addressing formulary issues with CA

NON-PATIENT SPECIFIC (STOCK) EXTENDED RELEASE INJECTABLES

- Facility
  - gets REMS certified
  - obtains meds from distributor
  - "stocks" ER- buprenorphine at facility
- REMS certification at facility level requires facility to
  - designate Authorized Representative
  - train staff
  - establish P&Ps
  - notify the healthcare provider not to dispense directly to patients
  - maintain records
  - undergo audit if selected
- More flexible dosing because medication is on premises in multiple doses
- Requires more storage and controlled substance storage management
- Outpatient facilities bill insurance directly

JAIL-BASED EXPERIENCE WITH EXTENDED-RELEASE BUPRENORPHINE

SOLANO EXPERIENCE – RENEE SMITH

Ordering Sublocade® in bulk (non-patient specific)

- Facility becomes REMS certified (through Indivior)
- County is a member of MMCAP. This is a buying group (find out if your county is a member).
- Develop pricing agreement with Indivior (allows for 18-19% discount)
- Choose from 3 certified Sublocade® distributors. Solano chose Henry Schein as they were already a vendor with the county.
- MMCAP Membership allows for easy purchase through distributor.
- Develop MOU with distributor which solidifies Sublocade® pricing inclusive of Indivior discount. Order Sublocade® in bulk (non-patient specific).

SOLANO EXPERIENCE – RENEE SMITH

- Provider and patient engage in shared decision making regarding who will get extended-release buprenorphine
  - Some patients prefer this
  - Continuity from outpatient prescriber
  - Will be used for those who divert sublingual buprenorphine in-custody.
  - Will be used for re-entry due to limited capacity for immediate appointments in community post release.
- Challenges with extended-release (not with patient specific medication)
  - Not all outpatient providers are providing access to extended-release buprenorphine
  - Perceived need for supplemental sublingual buprenorphine until steady state is reached

CONTACT US

FOR ANY QUESTIONS OR COMMENTS

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POLLING QUESTIONS

1. Overall, today's webinar was:
   A. Very useful
   B. Somewhat useful
   C. Not very useful
   D. Not useful at all

2. The material presented today was:
   A. At the right level
   B. Too basic
   C. Too detailed

REFERENCES/ RESOURCES

- Zubieta et al. (2000). Buprenorphine-Induced Changes in Mu-Opioid Receptor Availability in Male Heroin-Dependent Volunteers: A Preliminary Study. Neuropsychopharmacology 23:326–334.
- https://www.sublocade.com/Content/pdf/prescribing-information.pdf: Sublocade package insert
- https://www.sublocaderems.com/Content/pdf/certified-pharmacies.pdf: Finding REMS certified pharmacies for Sublocade.
- Haight, B R, et al. (2019) Efficacy and Safety of a Monthly Buprenorphine Depot Injection for Opioid Use Disorder: A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Lancet 393 (10173), 778-790.
- Lofwall MR et al. (2018) Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. JAMA Intern Med. 1;178(6):764-773.
- Shulman, M. et al. (2019) Buprenorphine Treatment for Opioid Use Disorder: An Overview. CNS Drugs Actions, 33 (6), 567-580.
- Jackson H, Mandell K, Johnson K, Chatterjee D, Vanness DJ. Cost-Effectiveness of Injectable Extended-Release Naltrexone Compared With Methadone Maintenance and Buprenorphine Maintenance Treatment for Opioid Dependence. Subst Abus. 2015;36(2):226-231. doi:10.1080/08897077.2015.1010031
- Marchand, DK, Young, C, and Loshak, H. (2019) Buprenorphine for Opioid Use Disorder: A Review of Comparative Clinical Effectiveness, Safety, Cost-Effectiveness, and Guidelines. Ottawa (ON). Canadian Agency for Drugs and Technology in Health.
- https://www.brixadi.com/?utm_source=google&utm_medium=cpc&utm_campaign=23_Brixadi_HCP_Branded_Brand&utm_content=Branded_Cost_Phrase&utm_term=brixadi&gclid=Cj0KCQjw5f2lBhCkARIsAHeTvlg1G-DcX0QrmFqteRrbPlZZDpP8bsYRQ0un8ww0elLRek0pWeWRaZ4aApfkEALw_wcB&gclsrc=aw.ds
- https://brixadirems.com/
- https://www.brixadi.com/pdfs/brixadi-prescribing-information.pdf
- Frost M, Bailey GL, Lintzeris N, Strang J, Dunlop A, Nunes EV, Jansen JB, Frey LC, Weber B, Haber P, Oosman S, Kim S, Tiberg F. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder. Addiction. 2019 Aug;114(8):1416-1426. doi: 10.1111/add.14636. Epub 2019 Jun 3. PMID: 31013390; PMCID: PMC6771955.
- Walsh SL, Comer SD, Lofwall MR, Vince B, Levy-Cooperman N, Kelsh D, Coe MA, Jones JD, Nuzzo PA, Tiberg F, Sheldon B, Kim S. Effect of Buprenorphine Weekly Depot (CAM2038) and Hydromorphone Blockade in Individuals With Opioid Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2017 Sep 1;74(9):894-902. doi: 10.1001/jamapsychiatry.2017.1874. PMID: 28655025; PMCID: PMC5710238.
- Nasser AF, Greenwald MK, Vince B, Fudala PJ, Twumasi-Ankrah P, Liu Y, Jones JP 3rd, Heidbreder C. Sustained-Release Buprenorphine (RBP-6000) Blocks the Effects of Opioid Challenge With Hydromorphone in Subjects With Opioid Use Disorder. J Clin Psychopharmacol. 2016 Feb;36(1):18-26. doi: 10.1097/JCP.0000000000000434. PMID: 26650971; PMCID: PMC5549150.
- Cheng A, Badolato R, Segoshi A, McDonald R, Malone M, Vasudevan K, Badiei B, Sugarman A, Macdonald R, Mangat J, Giftos J, Lee JD, Tofighi B. Perceptions and experiences toward extended-release buprenorphine among persons leaving jail with opioid use disorders before and during COVID-19: an in-depth qualitative study. Addict Sci Clin Pract. 2022 Jan 29;17(1):4. doi: 10.1186/s13722-022-00288-4. PMID: 35093164; PMCID: PMC8800291.