Provider Education
& Communication

Narcotic Safety Initiative

Pain & Opioid Tapering Management Webinar Series

When to Begin Patients on Buprenorphine and Why the Pharmacology Matters

(November 1, 2017)

Learning objectives

At the completion of this webinar, the learner will be able to:

- Explain the pharmacology of buprenorphine
- Describe **when** to use buprenorphine for pain management and/or for treatment of opioid dependency
- Describe **how** to use buprenorphine for pain management and/or for treatment of opioid dependency
- List characteristics of patients and/or situations where buprenorphine is a recommended treatment for pain management or opioid dependency

Blue Shield's Narcotic Safety Initiative (NSI)

To reduce opioid use by 50 percent among Blue Shield members with non-cancer pain by the end of 2018

- Reduce number of members on chronic high doses
- Prevent progression from acute to chronic use
- Reduce number of prescriptions and refills for those newly starting opioids

Through evidence-based interventions

When to Begin Patients on Buprenorphine and Why the Pharmacology Matters

R. Corey Waller M.D., M.S., DFASAM
Sr. Medical Director, Education and Policy
The National Center for Complex Health and Social Needs

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Demographics and cultural disparity

- CDC study on prescription opioid overdose trends (1999-2014)
  - Men > women (but mortality gap between ♀ and ♂ is closing)
  - Ages 25 to 54
  - Non-Hispanic whites + American Indian/Alaskan Natives > blacks and Hispanics
  - Access issue? Non-Hispanic white patients are more likely to receive an opioid than other racial/ethnic groups in the ER (Pletcher MJ)

Topics we will cover today…

Section	Title
1	Regulatory requirements
2	Workflow and documentation
3	Pharmacology of buprenorphine and naloxone
4	Patient characteristics
5	Inducting
*	Your questions

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*Regulatory requirements

DATA 2000 = Drug Addiction Treatment Act
An amendment to the Controlled Substances Act signed into law in 2000. DATA makes it possible for qualified physicians to prescribe buprenorphine for opioid detoxification and maintenance therapy.

- Physicians must take and pass an eight hour course and meet other qualifications. Nurse practitioners and physician assistants must take a 24-hour course.
  - Once approved, can apply for a special waiver which allows them to treat addiction with buprenorphine/naloxone medications
- DATA 2000 caps the number of addicted patients a physician can treat at any one time to 30 through the first year following certification.
  - Expandable to 100 patients … and possibly up to 275

* See the appendix for FAQs about buprenorphine regulation

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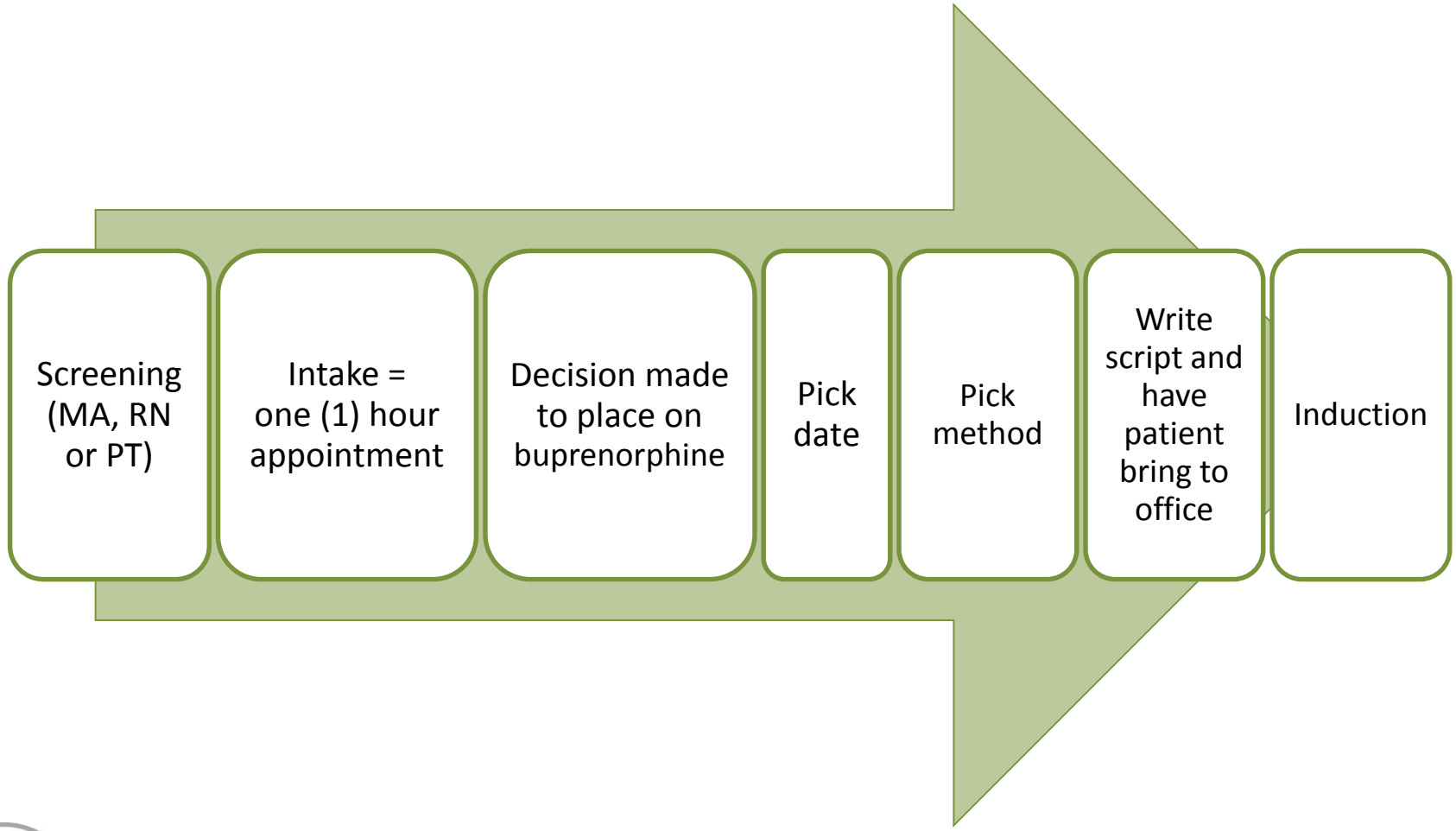
Opioid use disorder (OUD) work flow in primary care



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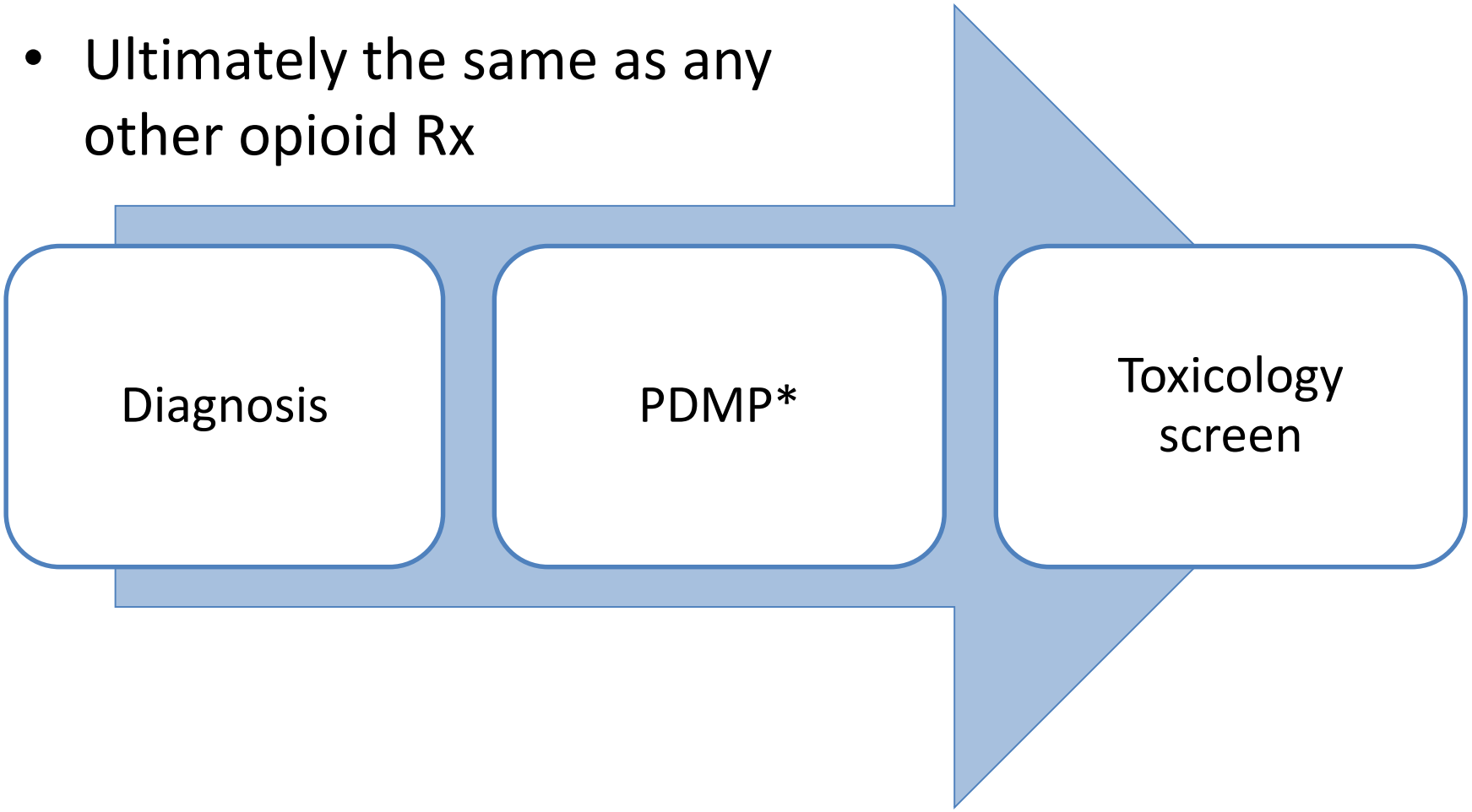
Pain management workflow in primary care

- Ultimately the same as any other opioid Rx



* PDMP = Prescription Drug Monitoring Program

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Patient documentation

- History of present illness (HPI)
  - DSM 5 criteria or DAST criteria met
  - Drug use from age of 12 to current
  - Co-occurring evaluation
  - Physical exam
    - Focused on mental status
    - Sequela of drug abuse (e.g., injection marks, superficial skin infections, murmurs)

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Patient documentation *continued*

- **Labs**
  - Hep C, HIV, STDs, CMP, CBC, UDS
- **Diagnosis**
  - Use DSM 5 designation
- **Plan**
  - Include medication dose and frequency
  - Include behavioral health referral and basic plan (e.g., CBT, DBT, 12-Step, contingency management)
  - Other drug use and plan of action (e.g., Benzo, MJ)

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Office-based documentation

- Keep an active list of current patients (seen within the last 30 days)
- Keep a list of past patients and note reason they are no longer being treated by you
- Call your regional DEA agent and ask for a preemptive visit and evaluation

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Buprenorphine pharmacology

- Semisynthetic, highly lipophilic thebaine derivative
- 25 to 50 times more potent than morphine
- Tolerable dose range (4 to 32 mg SL daily to every third day) for addiction pharmacotherapy
- Partial agonist
  - Respiratory ceiling effects, so safer in overdose
  - Less/absent effects in μ-dependent addicts

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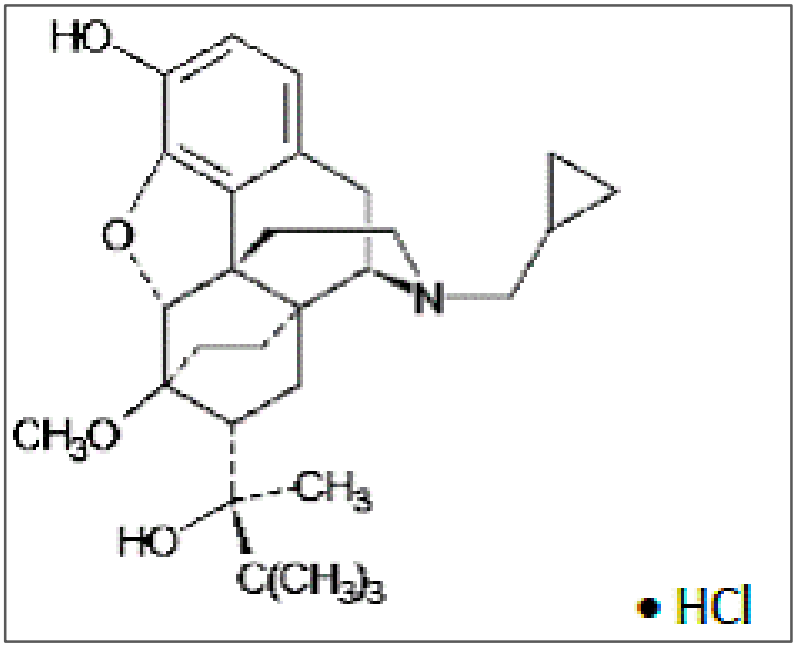
Buprenorphine structure and where it works



- Partial Mu (μ) agonist
- Kappa antagonist
  - Less euphoria

Intrinsic activity

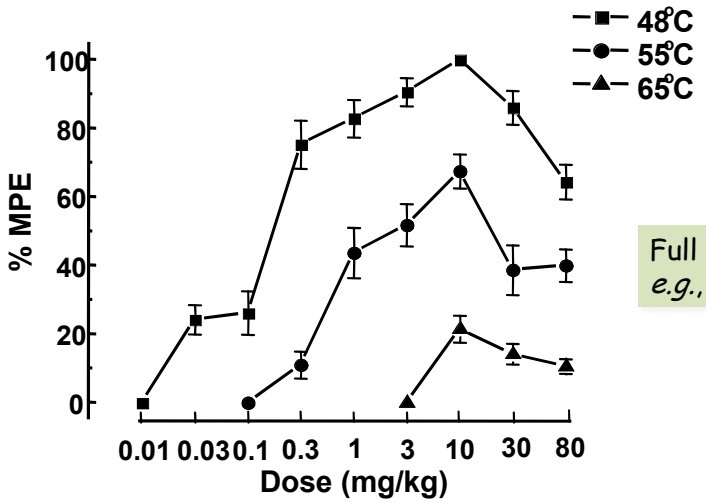
Receptor	Affinity (K_i, nM)	Intrinsic activity (% Effect)
m	0.08	38
d	0.42	0
k	0.11	10
ORL-1	285	60

Huang *et al*. (2001) JPET 297:688–695

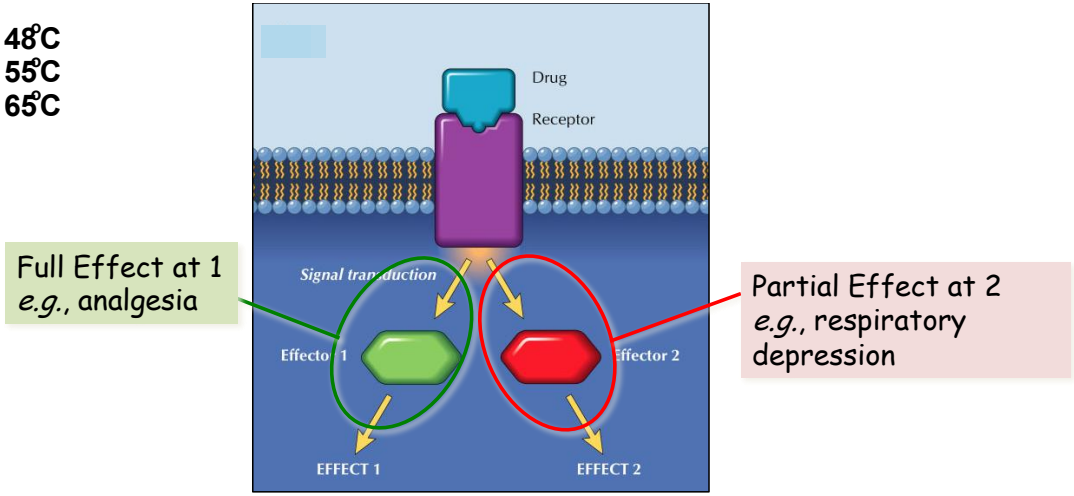
Is buprenorphine "really" a partial agonist?

Efficacy is *situation-dependent*

Antinociception: (MoTF-W x°C)



Raffa & Ding (2007) Acute Pain 9:145–152



Raffa & Pergolizzi (2013) Pain Practice 13:33–39

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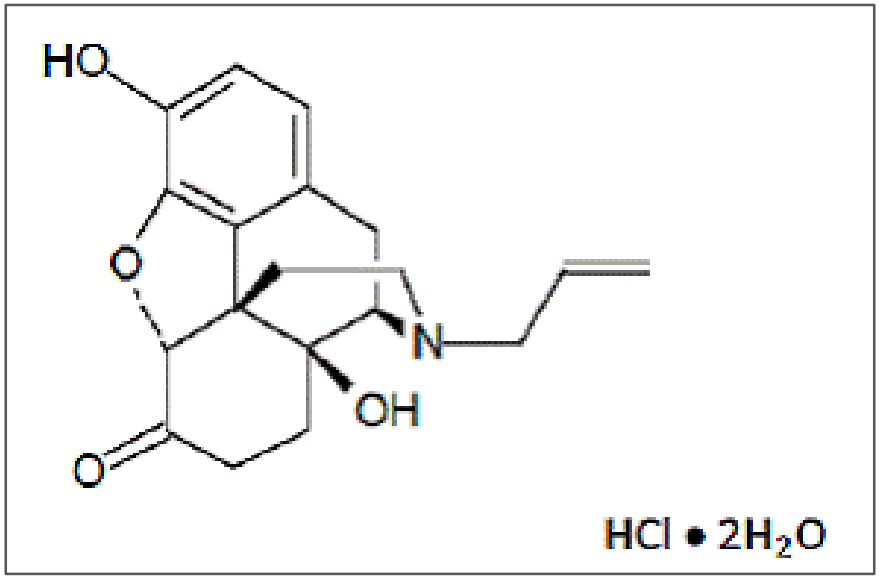
Absorption and distribution of buprenorphine

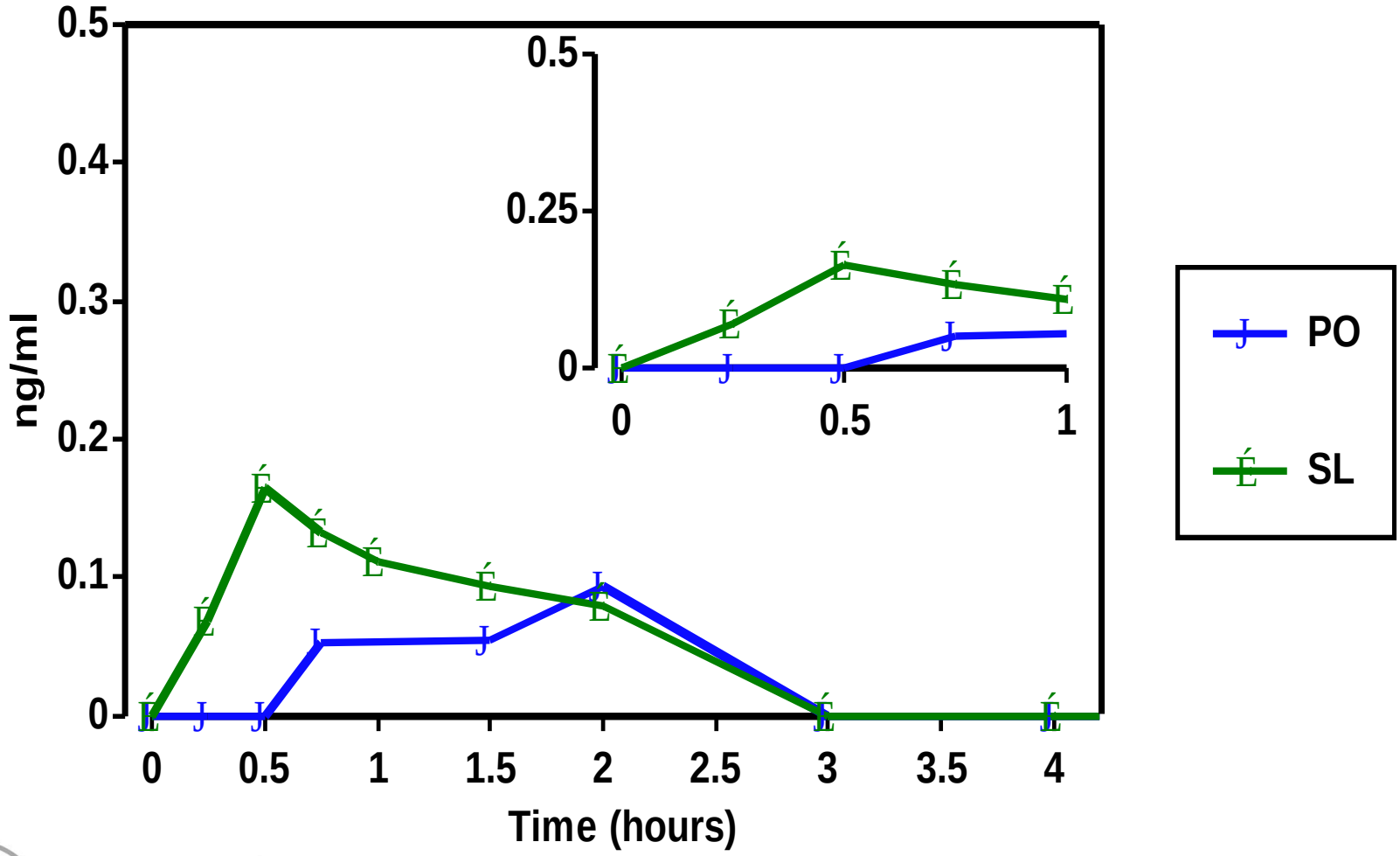
- Sublingual bioavailability of 30 to 50 percent (liquid) to 15 to 25 percent (tablets)
- Poor oral bioavailability
  - In one study, oral bioavailability of an analgesic dose of 0.4 mg was 16 percent
  - Little data on larger buprenorphine doses

Naloxone

- Mu opioid receptor antagonist
- Poorly absorbed SL
- Full bioavailability when given parenterally

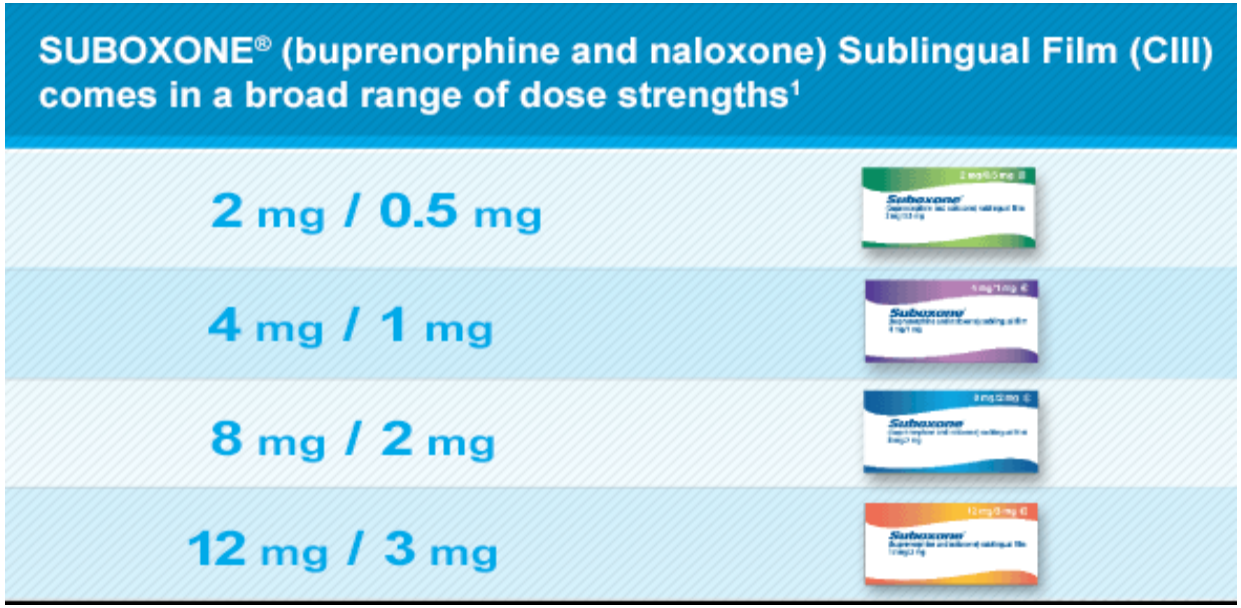


Plasma naloxone levels



Suboxone®

- Available in both tablets and film
  - First generation tablets can require up to 10 minutes to dissolve
  - Film dissolves in 3 to 5 minutes



Zubsolv®

- New oral tablets dissolve in 2 to 3 minutes, are white in appearance, and menthol-flavored

Dosage	Shape
1.4 mg / 0.36 mg	Triangular
5.7 mg / 1.4 mg	Round
8.6 mg / 2.1 mg	Diamond
11.4 mg / 2.9 mg	Capsule

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Bunavail®

- Buccal mucosal film strip intended for application to the buccal mucosa

Dosage	Type
2.1 / 0.3 mg	Bup/naloxone (2.2 cm^2 film)
4.3 / 0.7 mg	Bup/naloxone(4.4 cm^2 film)
6.3 / 1 mg	Bup/naloxone (6.5 cm^2 film)

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Dose equivalents: Buprenorphine/naloxone

Suboxone (SL-film)	Zubsolv (ODT)	Bunavail (B-film)
2 mg / 0.5 mg	1.4 mg / 0.36 mg	---
4 mg / 1 mg	2.9 mg / 0.71 mg	2.1 mg / 0.3 mg
8 mg / 2 mg	5.7 mg / 1.4 mg	4.2 mg / 0.7 mg
12 mg / 3 mg	8.6 mg / 2.1 mg	6.3 mg / 1 mg
----	11.4 mg / 2.9 mg	----

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How buprenorphine is eliminated

- Buprenorphine is metabolized by the liver, via **CYP3A4** (also **CYP2C8** seems to be involved) into norbuprenorphine
- The **glucuronidation** of buprenorphine is primarily carried out by **UGT1A1 and UGT2B7**, and that of norbuprenorphine by **UGT1A1 and UGT1A3**
- These glucuronides are eliminated mainly through excretion into the bile
- The elimination half-life of buprenorphine is 20 to 73 hours (mean 37)
- Due to the mainly hepatic elimination, there is no risk of accumulation in people with renal impairment

Buprenorphine is appropriate for a patient in these situations…

OUD

- Positive DSM 5 with a score of 2 or greater
- Positive DAST with a score of 6 or greater for opioids
- Per the SAMHSA guidelines, a patient should have a one (1) year history of OUD prior to use of methadone– however, many caveats
- No guidance on buprenorphine

Pain management

- CDC and VADoD guidelines
  - Fail all non-pharmacological methodologies
  - Fail non-opioid medications
- Risky behaviors
- Apnea risk
- Good first-line choice

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Therapy considerations

- Choosing the right patient
- What is the long-term goal?

Before the first dose…

- Obtain informed consent
- Conduct a physical exam
- Run a toxicological evaluation
- Check PDMP

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First dose when flipping from full agonist opioids

- Patient should be completely negative for opioids in the urine, or in mild-to-moderate withdrawal based on COWS*
- Patients who are negative for opioids can be given up to 8 mg
- Patients who are positive for opioids but in moderate withdrawal, can receive 2 to 4 mg
  - If the withdrawal worsens, can give up to 24 mg to abate symptoms

* COWS = Clinical Opioid Withdrawal Scale

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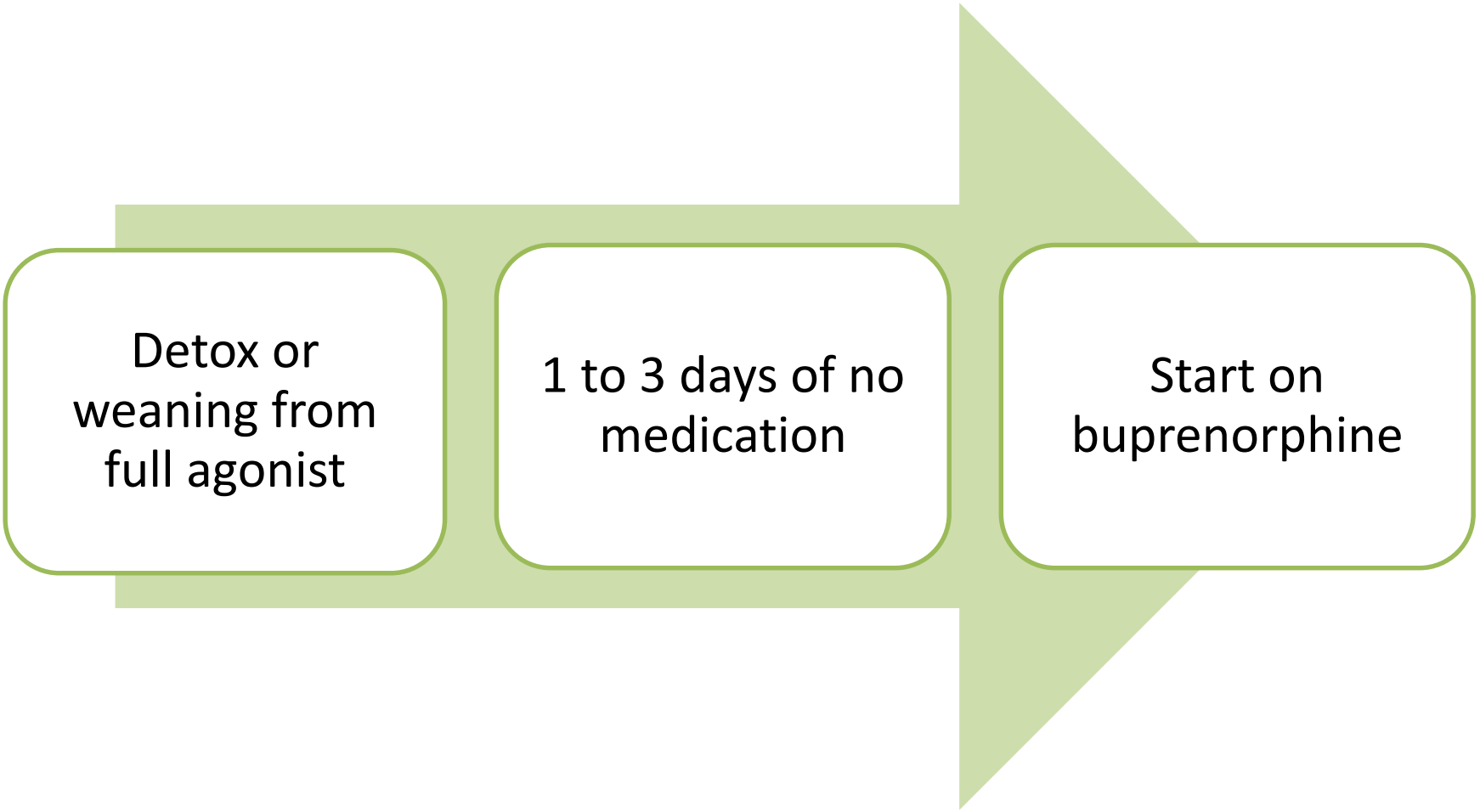
Typical opioid “flip”



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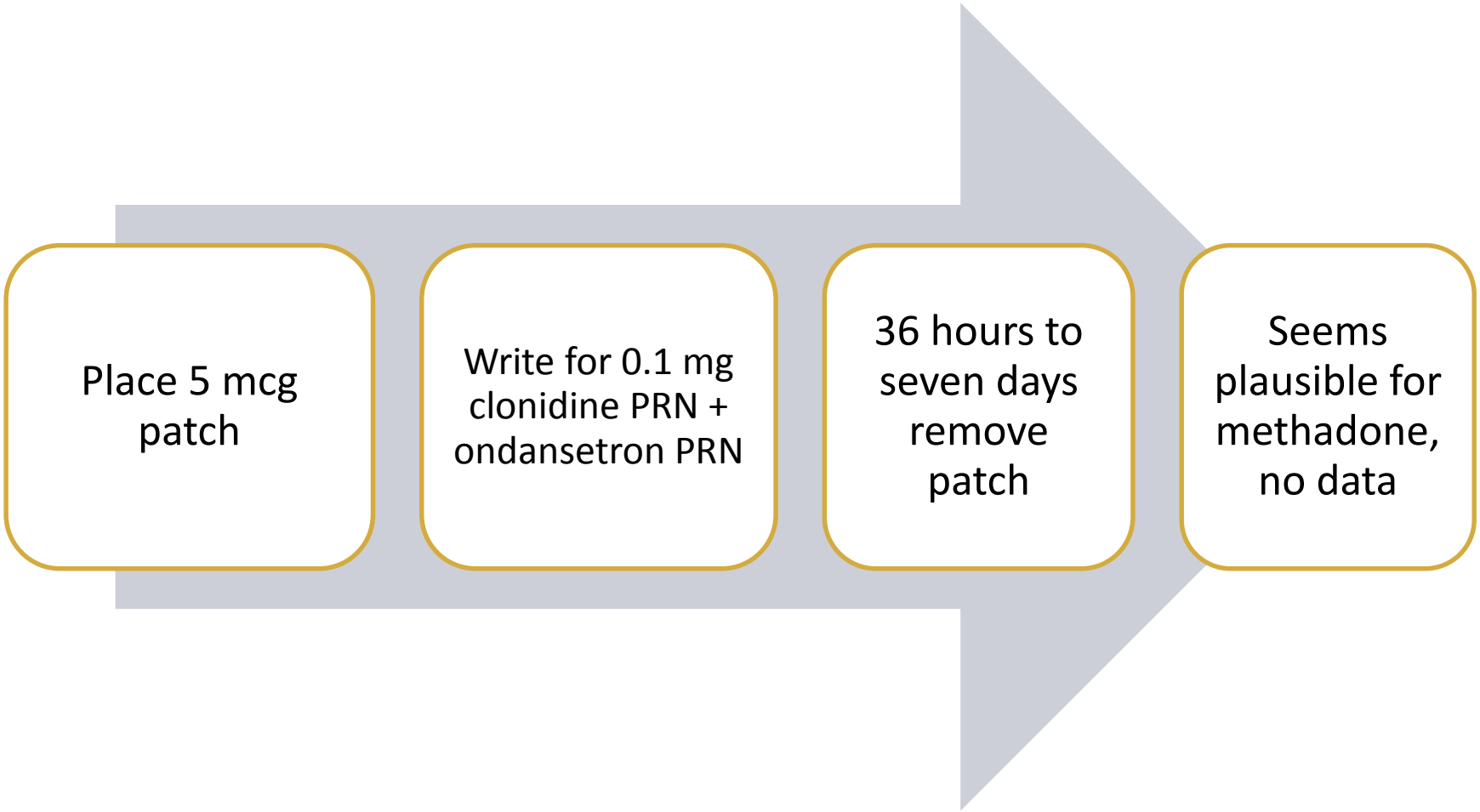
Other types of induction – Butrans®

- Place transdermal buprenorphine patch on the skin
- It takes 36 hours to peak
- After 36 to 48 hours, remove the patch and give first SL buprenorphine dose of 4 to 8 mg

Butrans® bridge



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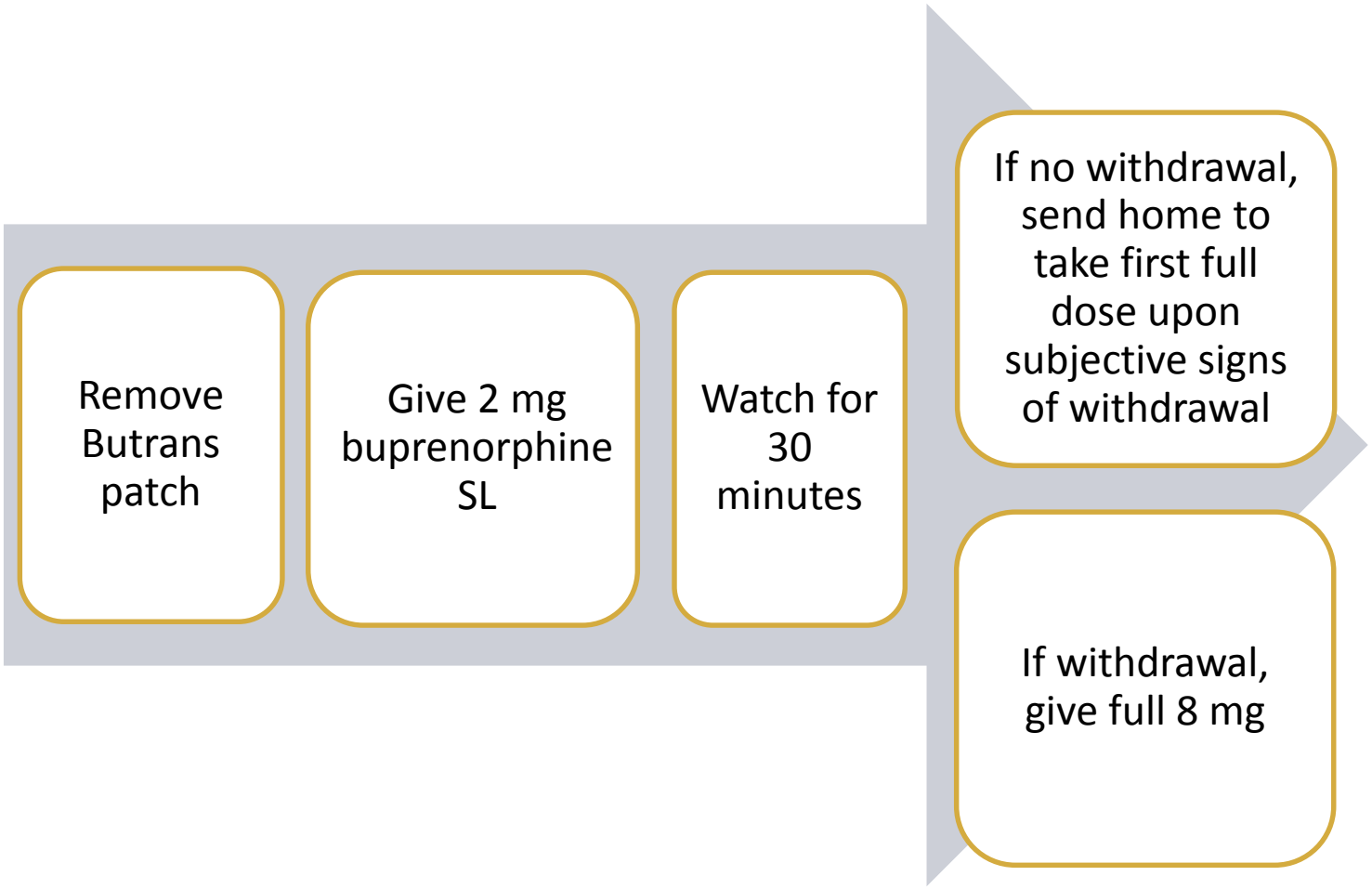
Butrans® bridge *(continued)*



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Conclusions

- Workflow is similar to other chronic disease management
- The pharmacology matters and is unique
- Finding the right patient at the right time is important
- Follow the induction path and it is really anticlimactic

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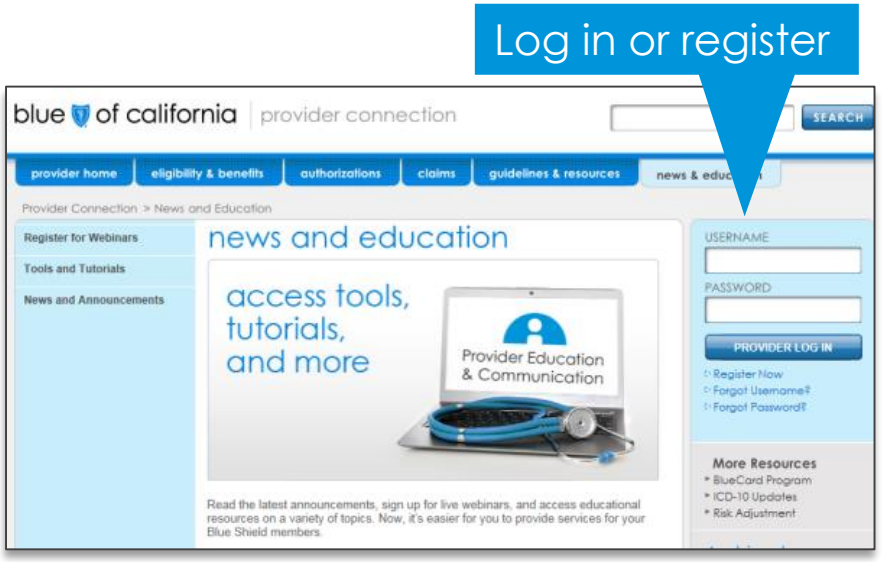

Visit Blue Shield's News & Education page to sign up for webinars as well as access tools and resources to help you serve Blue Shield members.

We're planning the 2018 series!

Share your suggestions via the evaluation for this webinar, and look for email announcements in 2018.

Narcotic Safety Initiative

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Appendix

- FAQs: Buprenorphine regulation (slides 36-40)
- Presentation references (slide 41)

FAQ: Buprenorphine regulations

With a DATA 2000 waiver, can I prescribe approved buprenorphine products for opioid addiction in more than one practice location? Can I dispense approved buprenorphine products from more than one location?

- Physicians with DATA 2000 waivers may prescribe approved buprenorphine products for opioid addiction in any appropriate practice setting in which they are otherwise credentialed to practice (e.g., office, hospital).

- However, they may store and dispense approved buprenorphine products (or any other controlled substances) only at the practice address(es) that they have registered with the DEA.

- Only one DATA-waiver unique identification number will be issued for each DATA-waived physician, no matter how many practice locations or DEA registrations a physician may have.

FAQ: Buprenorphine regulations

I've heard this new model for the treatment of opioid addiction referred to as "office-based opioid therapy." Does that mean that physicians with DATA 2000 waivers can use approved buprenorphine products to treat opioid addiction only in the office-based setting?

- No. Treatment of opioid addiction under the authority of a DATA 2000 waiver is not confined to the office-based setting.

- Physicians with DATA 2000 waivers may treat opioid addiction with approved buprenorphine products in any practice settings in which they are otherwise credentialed to practice and in which such treatment would be medically appropriate (e.g., office, community hospital, health department).

FAQ: Buprenorphine regulations

Can physicians and other authorized hospital staff administer buprenorphine to a patient who is addicted to opioids but who is admitted to a hospital for a condition other than opioid addiction?

- Neither the Controlled Substances Act (as amended by the Drug Addiction Treatment Act of 2000) nor DEA implementing regulations (21 CFR 1306.07(c)) impose any limitations on a physician or other authorized hospital staff to maintain or detoxify a person with an opioid treatment drug like buprenorphine as an incidental adjunct to medical or surgical conditions other than opioid addiction.

- Thus, a patient with opioid addiction who is admitted to a hospital for a primary medical problem other than opioid addiction (e.g., myocardial infarction) may be administered opioid agonist medications (e.g., methadone, buprenorphine) to prevent opioid withdrawal that would complicate the primary medical problem.

- A DATA 2000 waiver is not required for practitioners in order to administer or dispense buprenorphine (or methadone) in this circumstance. It is good practice for the admitting physician to consult with the patient's addiction treatment provider, when possible, to obtain treatment history.

FAQ: Buprenorphine regulations

May physicians in residency training programs obtain DATA waivers?

- The DATA legislation does not specify that a physician in a residency training program who otherwise meets the qualifications for a DATA waiver is ineligible to apply for and obtain a waiver.

- Therefore, SAMHSA has granted DATA waivers to physicians in residency training who have unrestricted licenses and the appropriate DEA registration.

- Individual states may have laws with more restrictive rules regarding who may prescribe or dispense Schedule III narcotic drugs for detoxification or maintenance treatment.

FAQ: Buprenorphine regulations

Are there specific Federal record keeping requirements for office-based opioid therapy?

- DEA record keeping requirements for office-based opioid therapy go beyond the Schedule III record keeping requirements.
- According to DEA: Practitioners must keep records (including an inventory that accounts for amounts received and amounts dispensed) for all controlled substances dispensed, including approved buprenorphine products (21 PART 1304.03[b]).
- In some cases, patients return to the prescribing physician with their filled approved buprenorphine products prescriptions so that the practitioner can monitor the induction process.
- While it is acceptable for the patient to return to the practitioner with their filled prescription supplies, practitioners shall not store and dispense controlled substances that are the result of filled patient prescriptions.

Presentation references

- Kranzler, Ciraulo and Zindel, Clinical Manual of Addiction Psychopharmacology (2nd addition) American Psychiatric Publishing. 2014
- The ASAM National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use. 2015
- The State of Michigan MAT Treatment Guidelines For Opioid Use Disorder, R. Corey Waller. 2014
- Anna Ferrari∗, Ciro Pio Rosario Coccia, Alfio Bertolini, Emilio Sternieri. Methadone—metabolism, pharmacokinetics and interactions,*Section of Toxicology and Clinical Pharmacology, University of Modena and Reggio Emilia, Policlinico, Largo del Pozzo, 71-41100 Modena, Italy.* Accepted 4 May 2004
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