Extended-Release Buprenorphine: Sharing Clinical Pearls, Protocols and Possibilities from 3000 Injections

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#ASAMAnnual2022

Our Background

- Tower Health Addiction Medicine (Reading, PA)
  - Outpatient practice
  - Hospital inpatient consults
  - Detox/rehab center (previously)
- More than 300 patients on/previously on monthly extended-release buprenorphine
- Experience with > 3000 injections

Learning Objectives

- By the end of the presentation, attendees will be able to:
  - List the unique pharmacologic properties of extended-release buprenorphine
  - Manage common patient concerns such as getting “too much” or “too little” medication, and injection site complications
  - Apply “tricks of the trade”, including utilizing blood levels, appropriate limited sublingual buprenorphine supplementation, and novel dosing protocols
  - Address common social/logistical challenges that arise with using extended-release buprenorphine

Disclosure Information

- Sahithi Gosala, MD, FASAM
  - No Disclosures
- Lee Radosh, MD, FAAFP, FASAM
  - No Disclosures
- William Santoro, MD, DABAM, FASAM
  - No Disclosures

- Currently there is only one available monthly injectable buprenorphine
  - Some information presented is from that product's information
  - Thus, we sometimes use trade name (Sublocade)
- All pictures are de-identified and/or have permission of the patient

Agenda

- Phenomenal pharmacology (Dr. Santoro)
- Clinical conundrums (Dr. Radosh)
- Alternative applications (Dr. Gosala)

Why This Is Important

Phenomenal Pharmacology

Image courtesy of https://pixabay.com/vectors/injection-syringe-vaccine-medical-5842438/

Brief Review: Opioid Receptors and Pharmacology

Agonists

- Bind to the receptor
- Fully activates receptor
- Highly reinforcing
- Most likely to develop tolerance

Antagonists

- Bind to the receptor
- No biological response
- Blocks opiates
- Least likely to develop tolerance

Partial Agonists

- Bind to the receptor
- Activates at a lower level
- Less reinforcing
- Less likely to develop tolerance

Package Insert Instructions[1]

- Concentrations
  - 300 mg/1.5 mL
  - 100 mg/0.5 mL
- Prefilled syringe with a 19 Gauge 5/8-inch needle
- “The recommended dose of SUBLOCADE is two monthly initial doses of 300 mg followed by 100 mg monthly maintenance doses”
- “Increasing the maintenance dose to 300 mg monthly may be considered for patients in which the benefits outweigh the risks”

1. Indivior, Sublocade Prescribing Information

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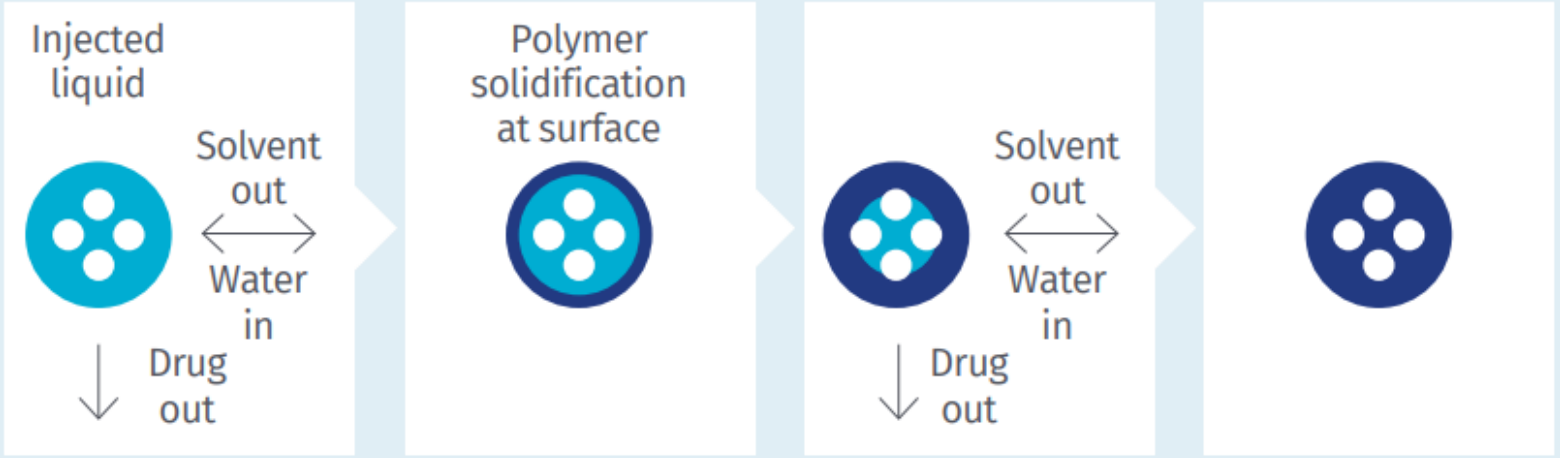
How It Works[1]

ATRIGEL Delivery System



SUBLOCADE™ sustained-release formulation of buprenorphine. SUBLOCADE™ uses the ATRIGEL delivery system, a solution consisting of a biodegradable poly-(DL-lactide-co-glycolide) co-polymer dissolved in N-methyl pyrrolidone (NMP), a water-miscible biocompatible solvent. After subcutaneous injection, NMP interacts with body fluids that replace the NMP in the matrix, triggering polymerization. Buprenorphine trapped inside the polymer formed in situ is gradually released over a one-month period as the polymer biodegrades

1. Indivior, Annual Report 2017

Average Plasma Concentration of Buprenorphine[1]

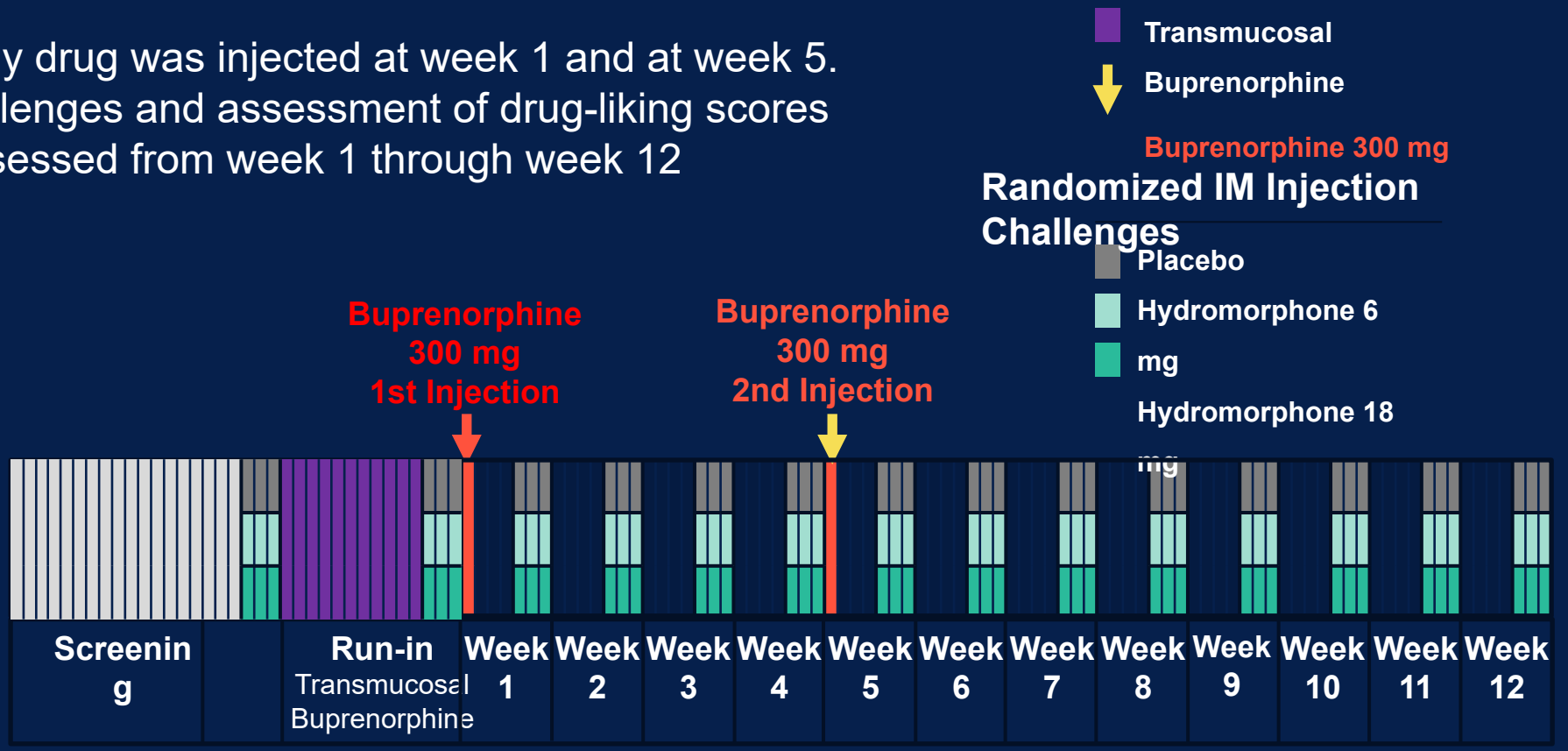
SL 12 mg	Steady state	1.71 ng/mL
SL 16 mg	Steady state	2.31 ng/mL
SL 24 mg	Steady state	2.91 ng/mL
300 mg	1st injection	2.19 ng/mL
100 mg	Steady state*	3.12 ng/mL
300 mg	Steady state**	6.54 ng/mL

Monthly dose (mg) regimen:
*300-300-100-100-100-100
**300-300-300-300-300-300

1. Indivior, Sublocade Prescribing Information

Blockade of Subjective-Liking Effects of Mu-Opioid Full Agonist[1]

The study drug was injected at week 1 and at week 5. The challenges and assessment of drug-liking scores were assessed from week 1 through week 12



1. Indivior, Sublocade Prescribing Information

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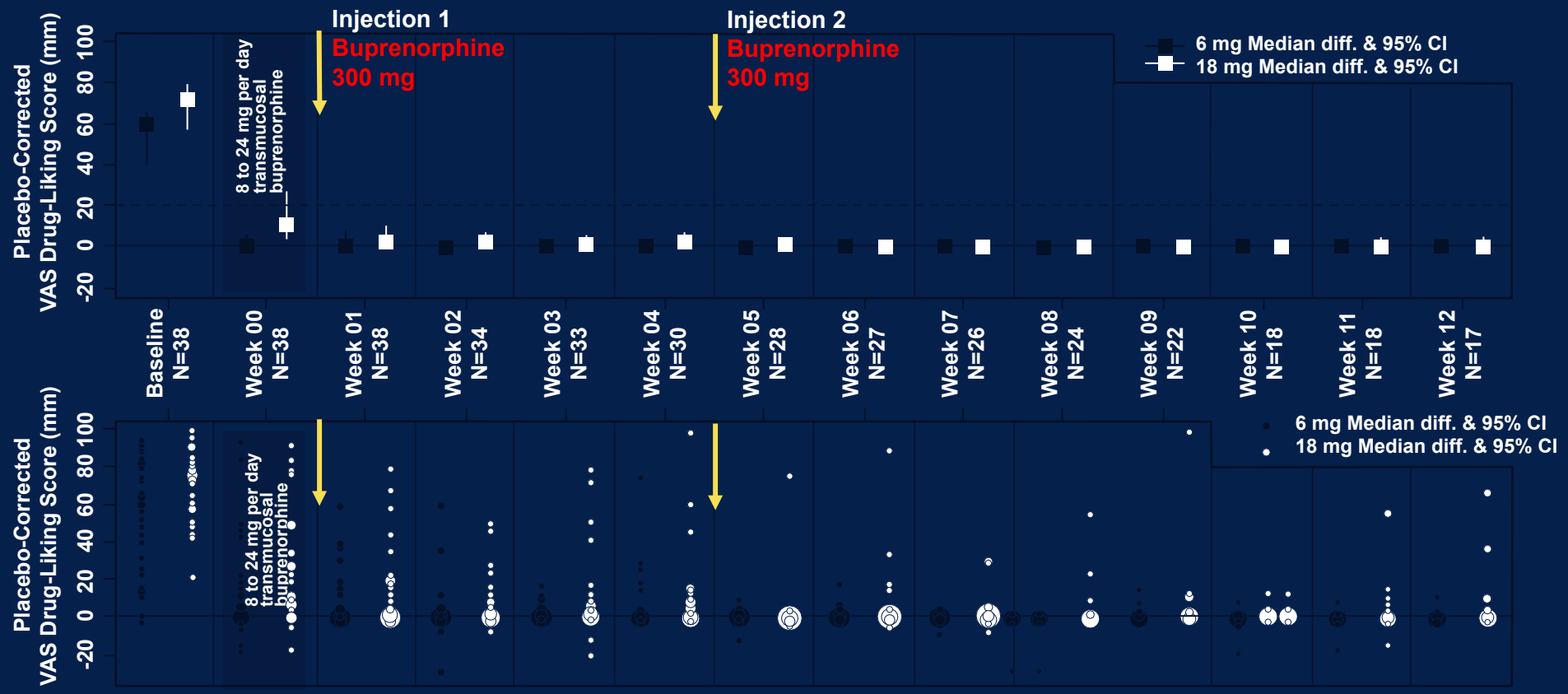
Likability of Drug By Week[1]



1. Indivior, Sublocade Prescribing Information

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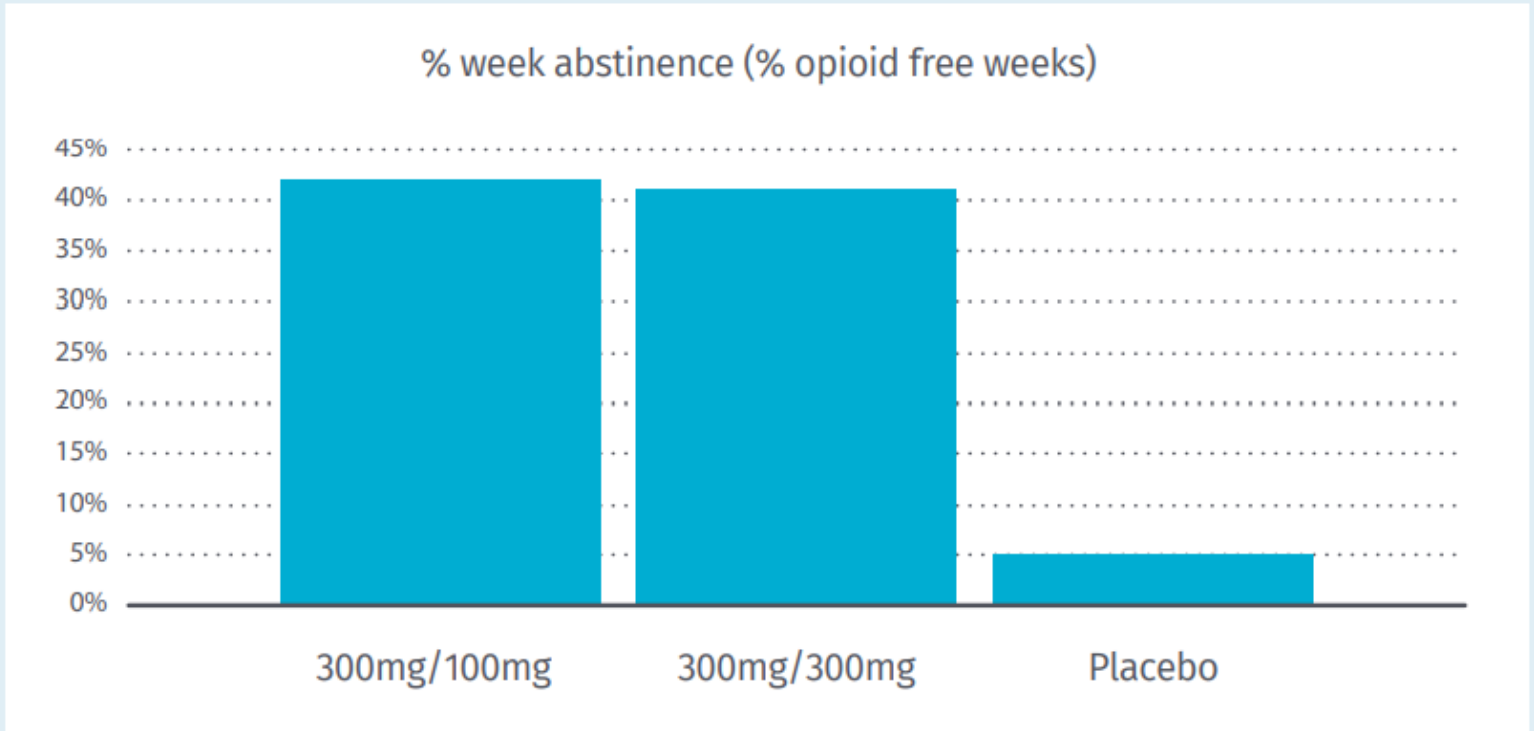
Effectiveness[1]



The primary efficacy endpoint (% abstinence from Week 5 through Week 24) was statistically significantly superior (P<0.0001) for both the 300 mg/100 mg and 300 mg/300 mg groups compared with the placebo group, with mean percentages as shown in the figure above.

1. Indivior, Annual Report 2017

Effectiveness – Clinical Trials

- "In this population it is more difficult to initiate patients to XR-NTX than BUP-NX, and this negatively affected overall relapse. However, once initiated, both medications were equally safe and effective. Future work should focus on facilitating induction to XR-NTX and on improving treatment retention for both medications."[1]
- "Participants' percentage abstinence was significantly higher in both BUP-XR groups than in the placebo group. Treatment with BUP-XR was also well tolerated. The availability of this monthly formulation . . . reduces risks of current buprenorphine products" [2]
- "Extended-release naltrexone was as effective as buprenorphine-naloxone in maintaining short-term abstinence from heroin and other illicit substances and should be considered as a treatment option for opioid-dependent individuals."[3]

1. Lee, 2018
2. Haight, 2019 (funded by Indivior)
3. Tanum, 2018

Initiation

- Choosing the right patients
  - Consider extended-release buprenorphine in certain scenarios . . .
- Transitioning from methadone[1]
- Insurance pitfalls
  - We haven't found many issues; most cover it
  - Utilize the co-pay assistance program for high co-pays
  - Sometimes needs to be billed under patient's "medical" insurance, not pharmaceutical plan
  - Sometimes it's not covered (often Medicare) . . . Oh well

1. Soyka September, 2021.

Storage

- Stored in refrigerator, lasts usually 6-12 months[1] (see expiration date)
  - Case: someone got first one, lost to follow-up, came back 6 months later in withdrawal, got the injection right away
  - PEARL: if space allows, hold onto it until expires (or you have no room)
- Once thawed, needs to be given within 7 days[1]
  - PEARL: staff should not thaw extended-release buprenorphine unless patient is physically at appointment and clearly will get the injection

1. Indivior, Sublocade Prescribing Information

Anesthesia

- PEARL: off label administration of numbing agent to minimize discomfort
- Our protocol
  - 2 cc bupivacaine (or lidocaine) SQ given
  - Provider visit (allow time for anesthesia)
  - Medication injection

Administration[1]

STEP 6: PINCH THE INJECTION SITE

Pinch the skin around the injection area. Be sure to pinch enough skin to accommodate the size of the needle. Lift the adipose tissue from the underlying muscle to prevent accidental intramuscular injection.

Figure 6

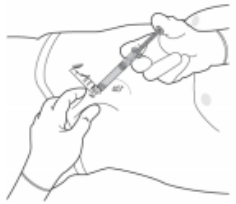
STEP 7: INJECT THE MEDICATION

SUBLOCADE is for subcutaneous injection only. Do not inject intravenously, intramuscularly, or intradermally *[see Warnings and Precautions (5.1, 5.6)]*.

Insert needle fully into the abdominal subcutaneous tissue. Actual angle of injection will depend on the amount of subcutaneous tissue.

Use a slow, steady push to inject the medication. Continue pushing until all of the medication is given.

Figure 7

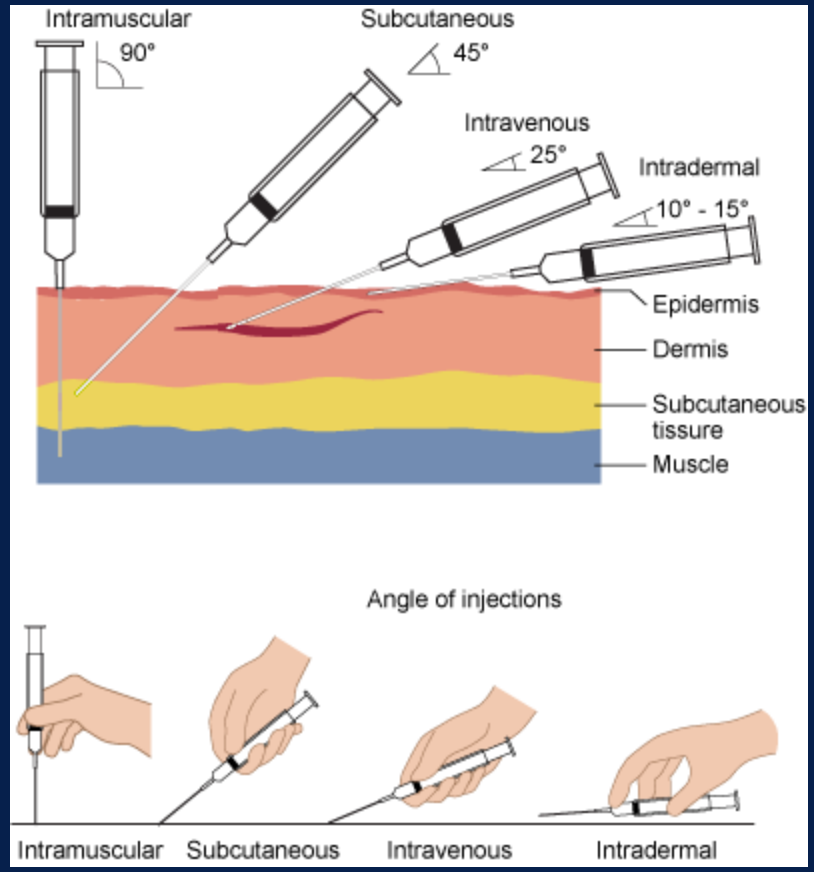


STEP 8: WITHDRAW THE NEEDLE

Withdraw the needle at the same angle used for insertion and release the pinched skin.

1. Indivior, Sublocade Prescribing Information

Subcutaneous (not Intradermal)



Wikimedia Commons, Needle Insertion Angles

Sample Administration

Clinical Conundrums

Image courtesy of https://pxhere.com/en/photo/1403209

Extended-Release Buprenorphine vs. SL

Potential Advantages

- Improved adherence
- Less diversion
- Patient comfort/preference (flexibility, logistics, taste)
- Smoother taper/discontinuation

Potential Disadvantages

- Costs, insurance coverage
- Limited provider experience/confidence
- Unique usage challenges (dosing/timing issues, perceived too low/high a dose, injection complications)
- Role in “novel” populations?
- Challenges when patients move/seeing new providers

Dosing Considerations

- Usual: 300 mg monthly X 2 then 100 mg monthly
- Minimal interval is q26 days
  - Could theoretically give sooner “off-label”
  - However, insurance won’t pay for that
- Same price
  - 100 mg vs. 300 mg
- Goal: control cravings/comfort balanced with adverse effects

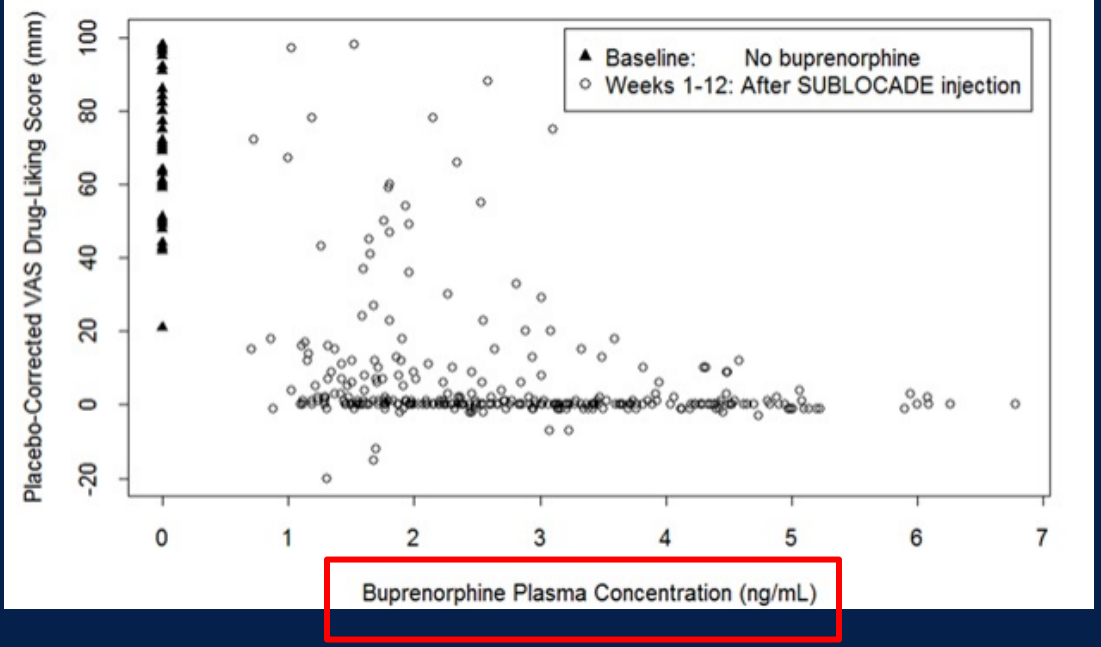
Dosing Pearls

Problem	Withdrawal symptoms early on	Fine first few weeks, withdrawal symptoms last week (most common challenge)	Tired throughout the month	100 mg is too low, 300 mg is too high
Solution	Options: • Proper administration • Increase the dose (max dose=300 mg)	Options: • Reassurance (if first 1-2 injections) until blood levels therapeutic • Supplemental SL last few days of month (temporary only) • Same dose, increase frequency (recall, minimal frequency q26 days) • Increase dose (to 300 mg?)	Lower the dose	Off-label dosing (ex, approximately 200 mg)

“2 ng/mL” and Opioid Blockade Study[1]

- “The observed plateau for maximal response was reached at buprenorphine plasma concentrations of approximately 2-3 ng/mL for illicit opioid use and 4 ng/mL for opioid withdrawal symptoms.”
- “Figure 10 illustrates the relationship between buprenorphine plasma level and drug liking after 18 mg hydromorphone IM”

Figure 10 Drug Liking VAS vs. Plasma Buprenorphine Concentration Following 18 mg Hydromorphone Challenges



1. Indivior, Sublocade Prescribing Information

Serum Buprenorphine Levels

- CPT 80348
- Example
  - Quest Diagnostics - Test Code is 93031
  - Charge (to patient's insurance, 2/2022): $146.30.
- From a list-serve: "My colleague has been seeing that the 2 ng level that is listed in the brochure & often reported as working well for pts, is no longer true with the highly potent Fentanyl analogues. Levels in the 7-8 ng range are often necessary for these pts & he maintains them on the 300 mg injection."
- PEARL: Levels are RELATIVE, but usually 4, 5 and higher are needed

Case Intro: KV

- KV was on extended-release buprenorphine a few months
- Always felt in terrible w/d
- Went to 300 mg monthly . . . same

Substance Monitoring Report

Test Ordered	Result	Cutoff		Lab
BUPRENORPHINE AND METAB, LC/MS/MS, SERUM			*Endnote 1*	SLI
BUPRENORPHINE	6.9	ng/mL	See Note 1 See Note 2	
NORBUPRENORPHINE	<0.6	ng/mL	See Note 3 See Note 2	
BUPRENORPHINE GLUCURONIDE	<5.0	ng/mL	See Note 2	
NORBUPRENORPHINE GLUCURONIDE	<5.0	ng/mL	See Note 2	

Endnote 1 This drug testing is for medical treatment only. Analysis was performed as non-forensic testing and these results should be used only by healthcare providers to render diagnosis or treatment, or to monitor progress of medical conditions.

Note 1
Reference Range
Maximum buprenorphine concentrations in patients maintained on varying buprenorphine doses were:

2 mg/day 0.2-0.4 ng/mL
16 mg/day 5.4-7.2 ng/mL
32 mg/day 8.8-17.2 ng/mL

- Buprenorphine: 6.9
- Norbuprenorphine: <0.6

Note 2 This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by the FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

Note 3 Reference Range Maximum norbuprenorphine concentrations in patients maintained on varying buprenorphine doses were: 2 mg/day 0.5-0.9 ng/mL 16 mg/day 4.1-6.7 ng/mL 32 mg/day 11.1-16.9 ng/mL

PERFORMING SITE:

Potential Next Steps?

KV – Options?

- Continue current treatment?
- Supplement with sublingual buprenorphine?
- Change to sublingual buprenorphine?
- Go to 400 mg monthly?

- Buprenorphine: 6.9
- Norbuprenorphine: <0.6

- Rapid metabolizer? Went back to SL and did fine

Case Intro: RM

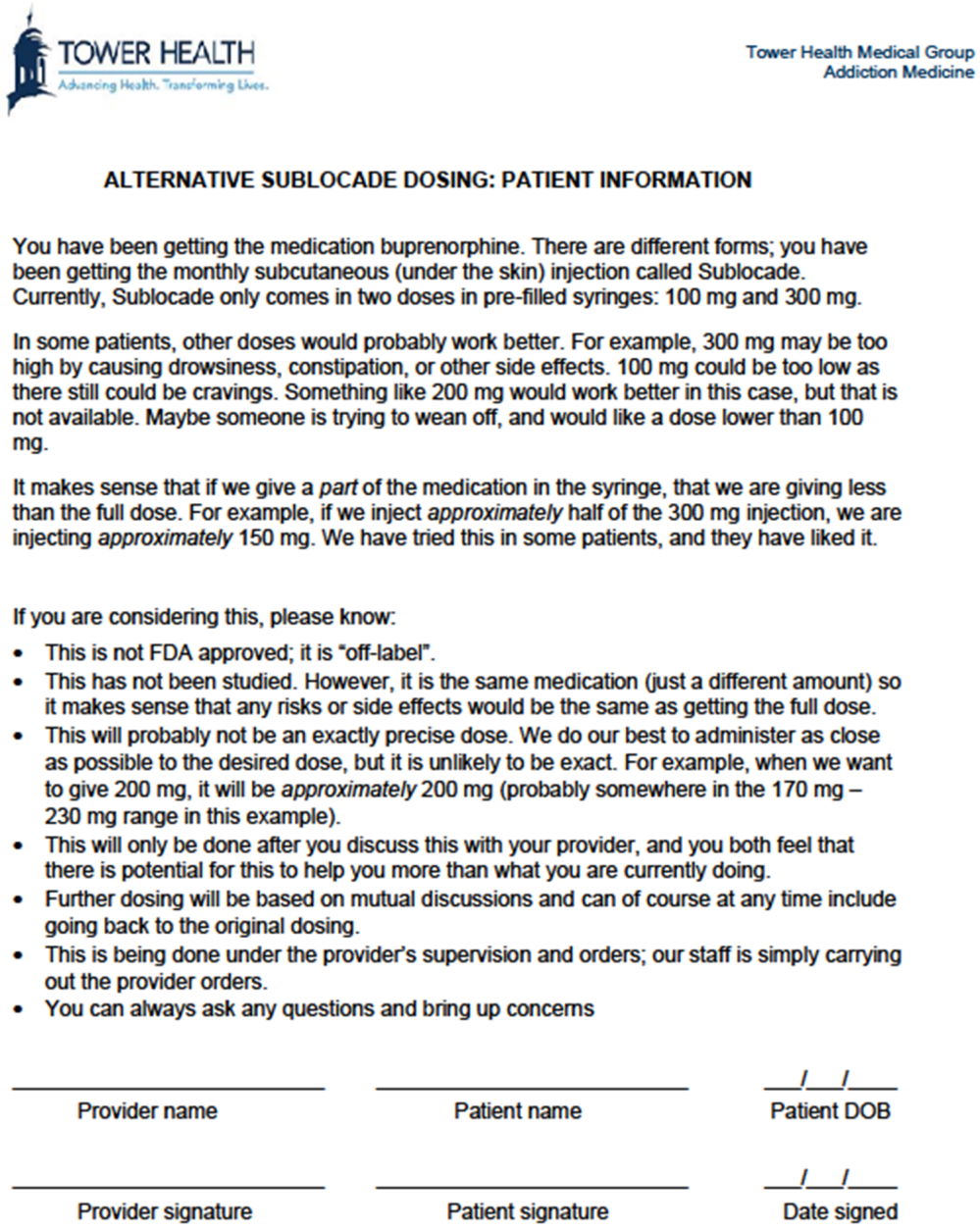
- 29 yo female
- Started monthly extended-release buprenorphine 6/2019
- Went to 100 mg 8/2019
- By 11/2019, few days before injection “yawning, nausea, aching joints, and runny nose”
- PEARL: Levels would not have changed management
- 12/2019 back to 300 mg, did great

Case Continued: RM

- But by 10/2021 – spotting; happened on previous opioids
- Options reviewed
  - Lower dose? But “does not want to go back to 100 mg as that did not work in the past.”
- 11/2021 did off-label 200 mg
- Feels great since

Off-Label Dosing

- Review the logic with patients
- Make clear: off-label
- Provider – not nurse – decision
  - We eyeball the line
- Utilize "patient information" document
- Our experience:
  - Patients very appreciative
  - Don't feel like guinea pigs



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ALTERNATIVE SUBLOCADE DOSING: PATIENT INFORMATION

You have been getting the medication buprenorphine. There are different forms; you have been getting the monthly subcutaneous (under the skin) injection called Sublocade. Currently, Sublocade only comes in two doses in pre-filled syringes: 100 mg and 300 mg.

In some patients, other doses would probably work better. For example, 300 mg may be too high by causing drowsiness, constipation, or other side effects. 100 mg could be too low as there still could be cravings. Something like 200 mg would work better in this case, but that is not available. Maybe someone is trying to wean off, and would like a dose lower than 100 mg.

It makes sense that if we give a *part* of the medication in the syringe, that we are giving less than the full dose. For example, if we inject *approximately* half of the 300 mg injection, we are injecting *approximately* 150 mg. We have tried this in some patients, and they have liked it.

If you are considering this, please know:

- This is not FDA approved; it is "off-label".
- This has not been studied. However, it is the same medication (just a different amount) so it makes sense that any risks or side effects would be the same as getting the full dose.
- This will probably not be an exactly precise dose. We do our best to administer as close as possible to the desired dose, but it is unlikely to be exact. For example, when we want to give 200 mg, it will be *approximately* 200 mg (probably somewhere in the 170 mg – 230 mg range in this example).
- This will only be done after you discuss this with your provider, and you both feel that there is potential for this to help you more than what you are currently doing.
- Further dosing will be based on mutual discussions and can of course at any time include going back to the original dosing.
- This is being done under the provider's supervision and orders; our staff is simply carrying out the provider orders.
- You can always ask any questions and bring up concerns

Provider name	Patient name	___/___/____ Patient DOB
Provider signature	Patient signature	___/___/____ Date signed

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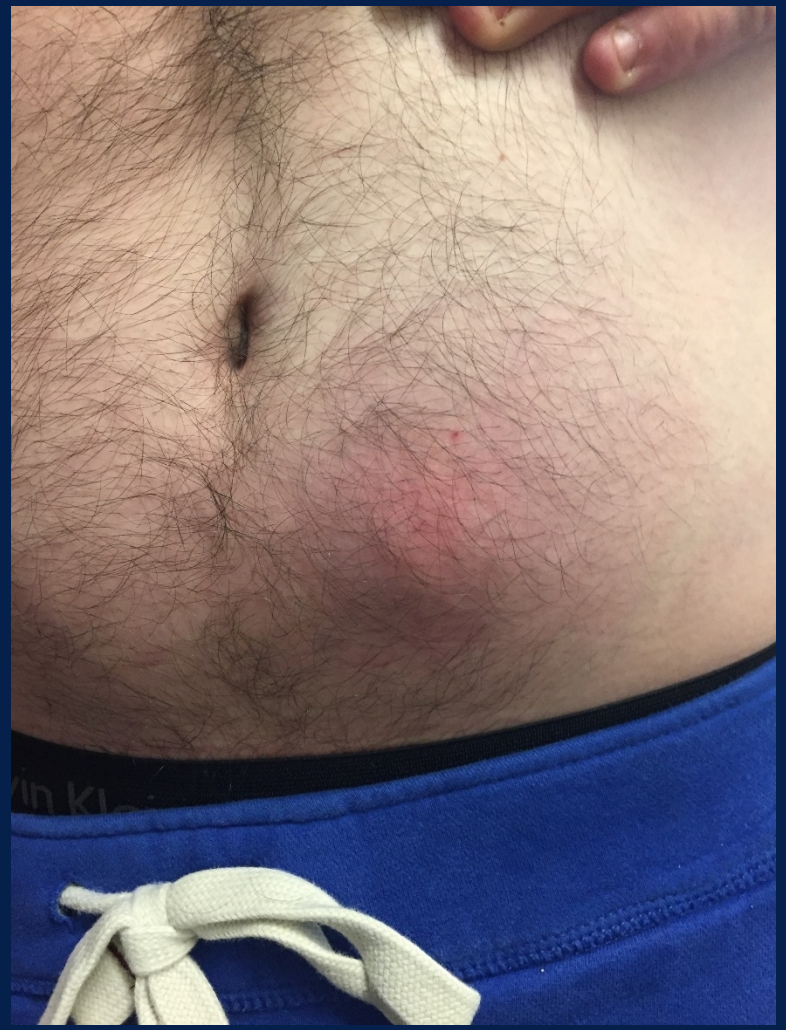
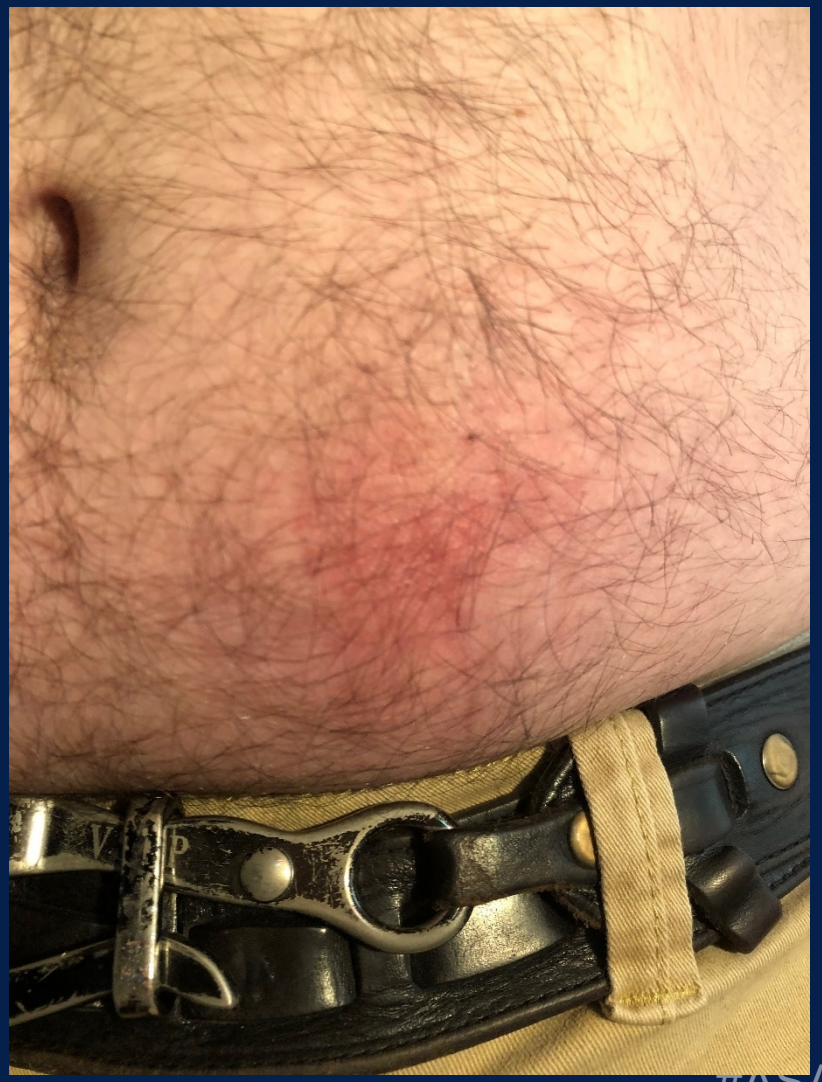
Redness/Adverse Reactions

- Infection (rare) vs. ecchymosis/other reaction
- Common causes
  - Administering too superficial (or too deep)
  - Maybe that it was not yet at room temperature
- From a list-serve:
  - "[Patient had redness/ulceration] and we talked to the nurse - she had given intradermal and eventually it resolved over 1 week . . . On review she admitted to not going deep enough and never had an issue again."
- "Injection-site [reactions],13.2% of participants, were mostly mild or moderate in severity. . . They were lower in the second 6 months of treatment versus the first 6 months"[1]
- PEARL: Treatment often is just reassurance

1. Andorn, 2020

Reassurance Prevails





Other Adverse Reactions (Can Also Get on SL)

- Sweats
  - Dose adjustment?
  - Off-label oxybutynin?
  - Reassurance (benefits vs. SE)
- Restless legs
  - Reassurance (benefits vs. SE)
- Constipation
  - Aggressive bowel regimen
  - Bulking agents/fiber, stool softeners, etc.

Image courtesy of https://freesvg.org/img/1526415126.png

Case Intro: JA

- 29 yo female, stable on SL buprenorphine since 12/2020
- Wanted convenience of monthly injectable
- 5/25/2021: 1st injection
- 6/8/21:
  - "Nodding out - so tired/fatigued that she will be dozing throughout the day . . . agreeable to obtaining a buprenorphine plasma level. We will also go ahead and order the 100 mg dose for her as she is concerned about feeling drowsy for another additional month."
  - She never did the BW

JA: Timeline

- 6/15: Now, symptoms wearing off! Supplemented with SL
  - Too much before, now not enough?
- 6/22: Got 100 mg injection
- 7/21: Mild drowsiness past month, but got 100 mg again
- 7/24: “Still occasional nod-off and falls asleep for about 20 minutes at a time; irritable and is having memory fog” – tried supplemental SL after BW done
- 8/3: Buprenorphine levels from 7/26 available
  - Norbuprenorphine, 5.5 ng/mL
  - Buprenorphine, 1.9 ng/mL
- Side effects despite low dose, but (relatively) low therapeutic levels

Potential Next Steps?

JA: Options?

- 100 mg every 26 days?
- 50 mg with supplemental sublingual?
- Change back to sublingual?

- Back to sublingual, doing well
- Just not a good fit!
- “If it ain’t broke, don’t fix”
- However, as always for sublingual, “trust but verify”
  - Wrapper and/or strip and/or tablet counts

Prolonged Positive Drug Test Results

- PEARL: Can be a year out
  - "After steady-state has been achieved (4-6 months), patients discontinuing SUBLOCADE may have detectable plasma and urine levels of buprenorphine for twelve months or longer"[1]
- We have had several patients like this
- Others on list-serves have noted this

1. Indivior, Sublocade Prescribing Information

Case: SP

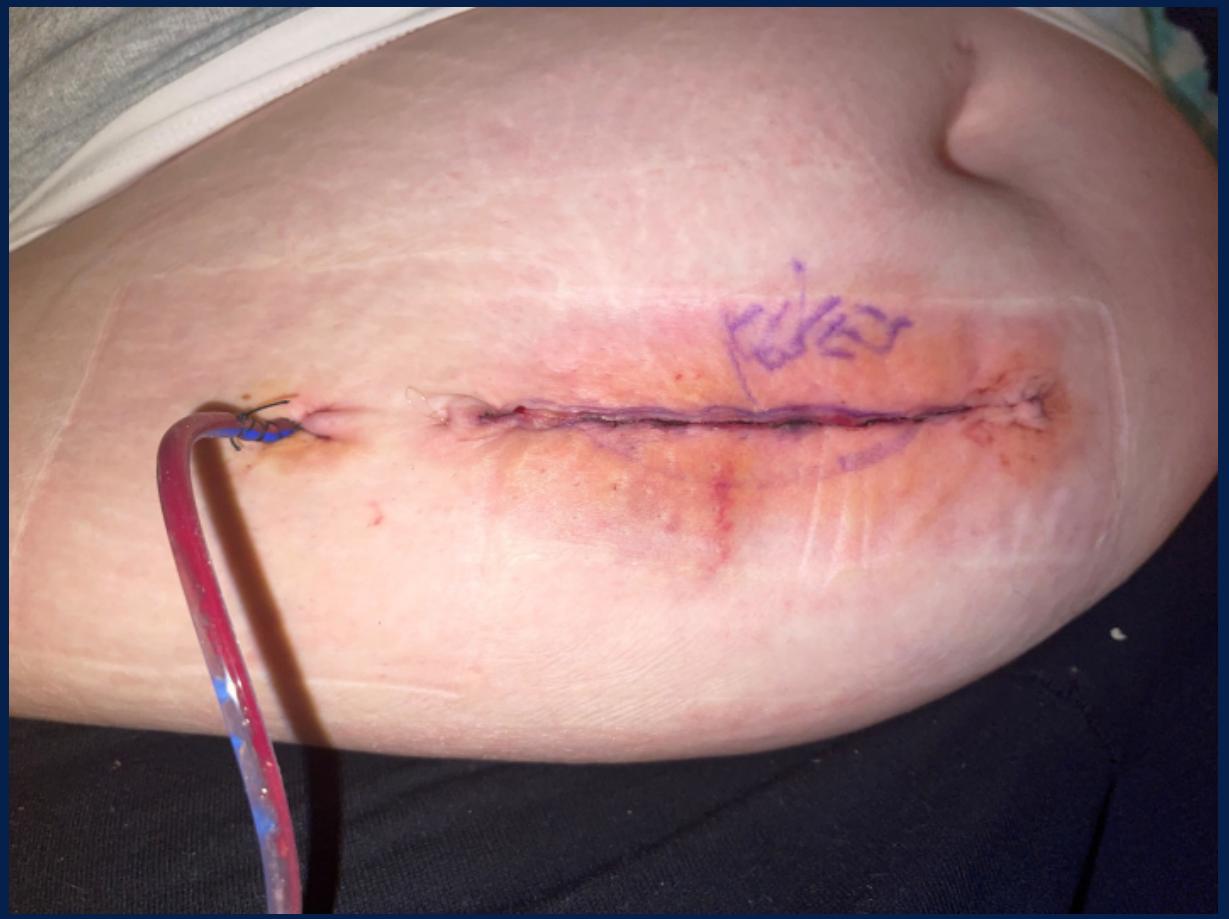
- SP, 66 yo male, on SL buprenorphine for years
- Extended-release buprenorphine starting 9/2018
- Last injection: 2/11/2021
- As of 2/3/2022 – UDS (rapid, in office) *still* positive
- 11/30/2021 serum levels
  - Buprenorphine: <0.6
  - Norbuprenorphine: <0.6
- PEARL: Patients may be falsely accused of still using buprenorphine

Case Intro: BW

- BW, 26 yo woman, did not tolerate any sublingual forms
  - Nausea and vomiting after each dose
  - Thought “taste” was the issue
- Wished to try extended-release buprenorphine
  - Understood could be the med itself causing N/V, not the taste
- Received extended-release buprenorphine
  - Within a few hours developed unrelenting nausea and vomiting
- Symptoms did not subside; worsened after 24 hours
  - Did not respond to oral antiemetics

Potential Next Steps?

BW: Outcome



- Decision made to undergo surgical removal of depot
- Can be surgically excised under local anesthesia within 14 days of injection[1]
- Only most recently injected depot should be removed[1]

1. Indivior, Sublocade Prescribing Information

Alternative Applications

Image courtesy of https://pxhere.com/en/photo/1447713

Other Uses

- Pregnancy
- Chronic pain
- Weaning off SL

Pregnancy

- Most recommendations based on buprenorphine exposure (in general), not specific extended-release buprenorphine
- Concerns regarding extended-release stem primarily from the delivery system (Atrigel ®) [1]
  - 50:50 mixture of poly (D, L-lactate-co-glycolide) and N-methyl-2-pyyrolidone (NMP)
- Poly (D, L-lactate-co-glycolide) is unlikely to cross placenta, but NMP would likely cross the placenta [1]
  - NMP exposure by inhalation in pregnant rats resulted in preimplantation losses, reduced fetal body weight, and delayed ossification
- Animal versus human studies do not often correlate
- May be reasonable to use in pregnancy

1. Towers, 2020
2. Cleary, 2020

Case Intro: SF

- SF, 34 yo woman, wished to try extended-release
- Started on extended-release buprenorphine about two months prior to finding out she was pregnant
- Extensive discussion
  - Continuing extended-release vs. transitioning back to SL
- Severe nausea during her first trimester
- Chose to stay on ‘what was working for her’
- Gave birth to a healthy baby boy

Chronic Pain: Coverage

- Increasing use of buprenorphine for chronic pain
- Extended-release buprenorphine not approved for pain
  - What to do?
- Approved for moderate to severe opioid dependence
- Usually, patients with chronic pain who are considering buprenorphine are on – and physiologically dependent – on traditional opioids
- Thus, should be covered (ICD-10 code F11.2)

Case Intro: MB

- MB, 45 yo woman, on oxycodone for many years due to chronic back pain
- Had issues with taking more than prescribed and needing early refills
- Referred to us by her family doctor

Potential Next Steps?

Case Resolution: MB

- Transitioned to sublingual buprenorphine
- Struggled with dosing and waking up with pain
- Transitioned to extended-release buprenorphine
- Significant improvement in her back pain
  - Found the ‘around the clock’ nature provided consistent relief

Extended-Release to Wean Off Sublingual

- Typical SL tapering process involves gradually decreasing dose over period of months to years
- Can get “stuck” at a dose where the patient physiologically and/or psychologically is unable to taper further down
- As extended-release buprenorphine gradually dissipates, it can provide an alternative method

Tips on Stopping The Injectable

- Simply stop[1]
- Gradually decrease dose
  - 300 mg -> 200 mg -> 100 mg -> 50 mg -> ?
- Space injections further apart?
  - But too long an interval can cause ups and downs
- Combo of gradually decreasing dose and spacing injections apart
- Can use sublingual supplementation if needed
  - Occasionally patients experience mild withdrawal symptoms 2 – 3 months after stopping injection
- "Comfort" medications if needed

1. Indivior, Sublocade Website

Innovative Settings

- Prisons
- Prior to discharge from rehab
- Mobile units[1]

1. Wenzel, 2021

Extended-release vs Sublingual in Prisons

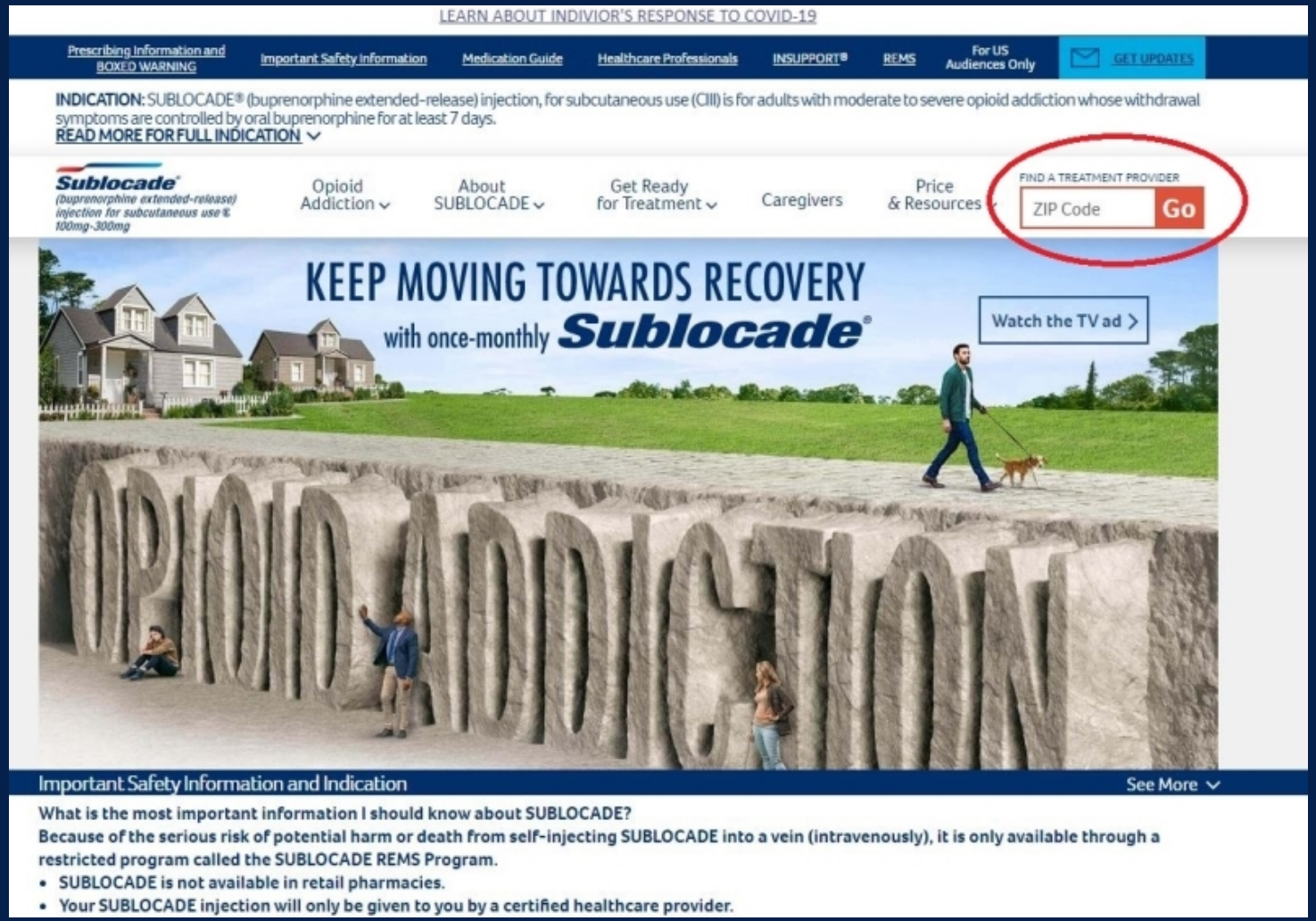
- 52 incarcerated adults in NYC observed for 8 weeks post release between June 2019 to May 2020[1]
  - 26 randomized to receive sublingual and 26 randomized to receive extended-release
- Extended-release continued 8 weeks after release
- Patients in the extended-release arm had fewer jail medical visits
- At 8 weeks post release, 18 retained in the extended-release arm compared to 9 in the sublingual arm
  - Opioid-negative UDS - 72/130 in the extended-release vs. 50/130 in the sublingual
- No difference in rates of serious adverse events, no overdoses, and no deaths

1. Lee, 2021

When Patients Transition Away From Your Practice

- Unfortunately, there are less providers for injectable buprenorphine than sublingual
- Counsel patients on challenges
- Consider having 1-2 contacts in large areas
  - Example: surrounding counties, large metropolitan areas
- Assist a new practice in logistics of ordering?
- Transition back to sublingual?

Find a Provider[1]



1. Indivior, Sublocade Website

Future?

- Further research
  - Additional comparison research?
  - Cost-effectiveness?
- Potential future interventions/ideas to facilitate increased use of long-acting buprenorphine products
  - No refrigeration
  - Increased options[1] – doses, frequencies, implants, etc.
  - Varied injection sites
  - Availability – local pharmacies vs. shipped to office? “Buy & bill”?
  - Costs/regulations

1. Soyka January, 2021.

Final Takeaways/Summary

- Extended-release buprenorphine may have some advantages over sublingual
- Usually well-tolerated, but when issues arise, they can be easily addressed
- Some “tricks of the trade” can make offering and managing this much easier

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