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Direct to Inject Buprenorphine Guideline

SCOPE: This Direct to Inject (DTI) Buprenorphine Guideline is intended to offer prescribing assistance for providers, patients and the interested general public to increase the effectiveness and safety of medication for opioid use disorder (MOUD) in the ambulatory care setting. It is not intended to be comprehensive in scope. These recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient. References can be found in the Opioid Use Disorder References and Further Reading.

BACKGROUND: San Francisco Department of Public Health does not recommend the use of brand names when describing medications, however to reduce the risk of medication errors this protocol will refer to brand names of buprenorphine long-acting injectables as they have the same generic names. Buprenorphine long-acting injection is available as monthly Sublocade, weekly Brixadi and monthly Brixadi.

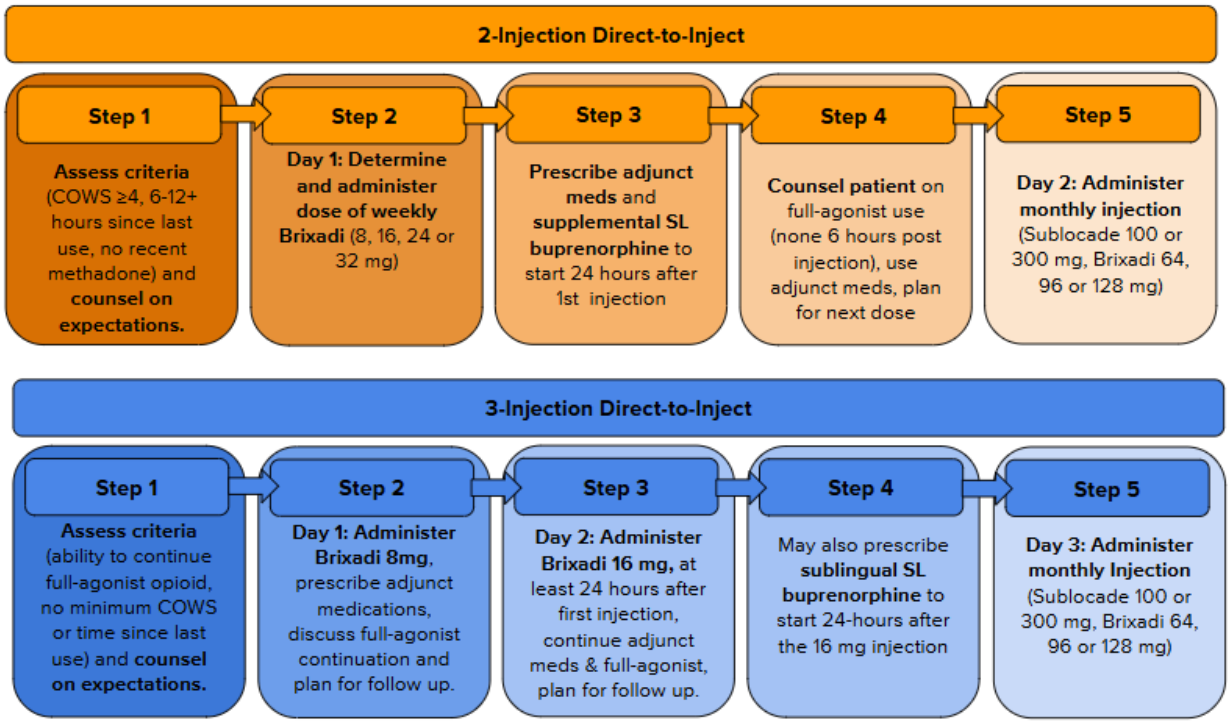
Direct to inject is a term used for initiating buprenorphine long-acting injectable in people who are not currently taking buprenorphine. Given fentanyl's prevalence in the drug market and ongoing overdose epidemic, DTI initiation using weekly Brixadi is gaining interest as one way to support patients' transition onto a life-saving medication. DTI is feasible because weekly Brixadi serum levels peak at 24 hours post-injection (Braeburn, 2023). This slow increase in buprenorphine serum levels facilitates a gradual build-up of buprenorphine while minimizing the risk of precipitated withdrawal that is seen with the quick serum peak (1-2 hours) of sublingual buprenorphine.

There are two protocols for DTI which include 2-injection DTI and 3-injection DTI. They differ in the number of injections a patient will receive and the required level of opioid withdrawal at time of injection:

- The 2 injection DTI has a lower risk of precipitated withdrawal when patients have a Clinical Opiate Withdrawal Scale (COWS) score of ³4. This requires patients to have stopped using opioids.
- The 3 injection DTI can be initiated in those who are still using opioids and thus not in opioid withdrawal.

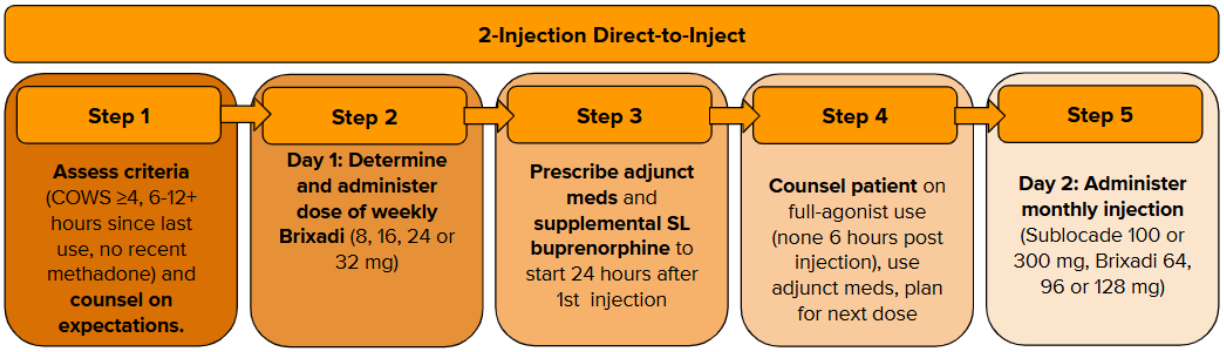
Cohort studies of both DTI protocols in the emergency department and outpatient setting have demonstrated tolerability and retention. The choice of which protocol used should be based on patient preference, severity of opioid withdrawal and patient's ability to access the medication (ex: able to receive injections 3 days in a row, close to 24 hours apart).

FIGURE 1: OVERVIEW OF 2 INJECTION VERSUS 3 INJECTION DTI PROTOCOLS



APPENDIX 1: 2 INJECTION DTI PROTOCOL

FIGURE 2: OVERVIEW OF 2 INJECTION DTI PROTOCOL



PATIENT CRITERIA

This induction method is intended for people with OUD who can be in opioid withdrawal at the time of injection (COWS $\geq$ 4) and have not used opioids in the last 6-12 hours. For people switching from methadone, will discuss on a case-by-case basis. Okay to start if no methadone in the past 2 weeks.

INITIAL VISIT WORKFLOW

Initial Visit Assessment

- Comprehensive assessment of current opioid use, last use, current goals, past OUD treatment trials (last methadone, prior buprenorphine experience, etc.)
- Any other substances used in past week
- COWS score
- Past medical history, particularly chronic pain conditions (if applicable)

Assess Patient Withdrawal and Time Since Last Opioid Use

- Assess patient COWS score and time since last opioid use
    - Ideally patient would wait until COWS $\geq$ 4 **and** at least 6-12 hours since last opioid use
    - Recent methadone: Methadone has a long half-life, especially when at steady state (e.g., given in regular daily doses for at least 3-5 days). If a patient has taken a single dose of methadone a few days prior to DTI, the risk of withdrawal is much lower than if the patient has been on regularly daily methadone within the past week. To err on the side of caution, it may be advisable to postpone DTI if a patient has taken more than one dose of methadone in the past 72 hours or been on regularly daily methadone dosing within the past week, though this should be a risk/benefit discussion with the patient.

Determine Injection Dose

- Clinicians can choose between 8, 16, 24, and 32mg doses of weekly Brixadi
    - For patients who use heroin, 16mg is often appropriate
    - For patients who use fentanyl, 24mg is often appropriate.
    - There are also cases in which 8mg or 32mg may be appropriate choices.

- Higher doses may be associated with increased withdrawal with DTI (though there is no evidence on this topic) but may be needed for patients using fentanyl with higher opioid tolerance (see Table 1 for dosing equivalents).
- It is recommended to weigh the risks and benefits of worsening withdrawal vs subtherapeutic dosing in determining which dose to give.
- See Appendix 4 for administration instructions

TABLE 1: CONVERSION FROM SUBLINGUAL BUPRENORPHINE TO WEEKLY BRIXADI

Daily Dose of Sublingual Buprenorphine	Brixadi Weekly Dose Equivalent	Brixadi Monthly Dose Equivalent
<6mg	8mg	--
8-10mg	16mg	64mg
12-16mg	24mg	96mg
18-24mg	32mg	128mg

Prescribe Opioid Withdrawal Adjuncts

- We recommend the following opioid adjunct orders (if using SFDPH Epic, can use 'Opioid Withdrawal Adjunctive' orderset):
    - Clonidine 0.1mg q6h prn withdrawal and restlessness, #12
    - Ondansetron 4mg q8h prn nausea or vomiting, #9
    - Hydroxyzine 50mg q6h prn anxiety, #12
    - Loperamide 2mg q6h prn diarrhea; #12
    - Trazodone 100mg qhs prn insomnia, #3 (if appropriate)
    - Ibuprofen or acetaminophen (if no contraindications)

Prescribe Supplemental Sublingual Buprenorphine

- Patients should not start supplemental sublingual buprenorphine until 24 hours after their injection (though they should ideally pick up the prescription on the day of the injection, along with the opioid withdrawal adjuncts).
- As a general rule, most patients need a maximum of 32mg sublingual buprenorphine equivalent per day, and the following suggested PRN total daily doses are based on providing patients a total of 32mg sublingual buprenorphine equivalence per day x 1 week.

TABLE 2. SUBLINGUAL BUPRENORPHINE OVERLAP AFTER 2 INJECTION DTI

Brixadi Weekly Dose	Goal Total Daily Dose of Sublingual Buprenorphine	Example SIG
8mg	28mg/day	8mg q6h prn withdrawal or cravings #28, do not take first dose until 24h since injection

16mg	22-24mg/day	8mg q8h prn withdrawal or cravings #21, do not take first dose until 24h since injection
24mg	16-20mg/day	4mg q6h prn withdrawal or cravings #28, do not take first dose until 24h since injection

PATIENT COUNSELING

First 24 Hours - See Appendix 4 for Patient-Facing Handout

- Mild to moderate withdrawal may continue to worsen after the injection, as time since last opioid use increases and before buprenorphine has reached adequate serum levels. For most people it is not as severe as precipitated withdrawal and self-resolves.
- It is recommended that patients avoid using any opioids after injection and rely on withdrawal adjunct medicines as much as possible. However, if a patient is going to use, we recommend waiting at least 6 hours after injection.
- WAIT to take supplemental sublingual buprenorphine for 24 hours after injection to minimize risk of precipitating withdrawal.
- Patient can safely receive monthly Brixadi or Sublocade starting 24 hours after a weekly Brixadi injection of 16mg or greater

Follow-up Appointment

24 hours after the injection, start taking additional sublingual buprenorphine, 8-32mg/day. Start with smaller doses (e.g., 2mg) at first and increase as tolerated.

FOLLOW UP

Assessment

- Any withdrawal in 24 hours after injection (yes/no). If yes, mild/moderate/severe?
- How does this compare to prior buprenorphine experiences
- Plan for next steps (note and confirm w patient plan for next buprenorphine injection)

Determine Injection Dose or Switch to Sublinguals

- Clinicians should follow up within 24-48 hours to assess patient experience and determine next dose of buprenorphine
- 24 hours after weekly Brixadi injection, the dose is at its peak, and it is safe to give more buprenorphine without concern about precipitating withdrawal.
- Patients can safely receive a monthly dose of Brixadi or Sublocade as soon as 24 hours after a weekly dose of 16mg or greater
- Patients can safely receive sublingual buprenorphine, a second weekly injectable, or a either monthly injection can be given. Factors to consider in determining dose and timing of subsequent buprenorphine:
    - Patient preference for sublingual vs. weekly vs. monthly injection

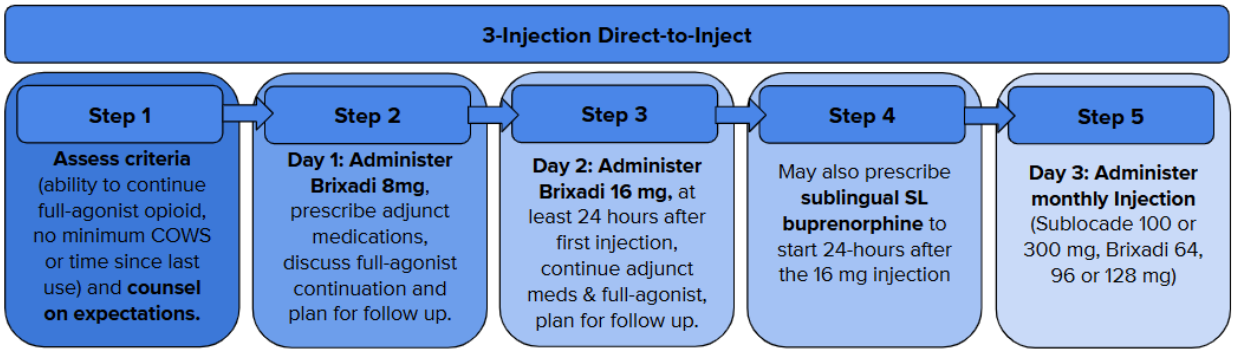
    - If there is uncertainty about the dose of buprenorphine a patient is likely to need, starting with a few days of sublingual dosing gives patients the ability to titrate to the dose they need
    - If concern for low tolerance, waiting 2+ days between injections can minimize concern for dose stacking
- The first dose of weekly Brixadi lasts for 5-9 days. If the patient is planning to continue on buprenorphine, they should receive their next dose of buprenorphine (whether sublingual or long-acting injectable) within that time frame.
    - If a patient received a weekly Brixadi dose of 16mg, it is recommended to give a monthly injection within the following 4 days
    - If a patient received a weekly Brixadi dose of 24 or 32mg, it is recommended to give a monthly injection within the following 7 days

MISSED DOSE GUIDANCE

If the patient doesn't start sublingual buprenorphine or receive another injection within 5-7 days, they will have to start the buprenorphine initiation process over again from the beginning

APPENDIX 2: 3 INJECTION DTI PROTOCOL

FIGURE 3: OVERVIEW OF 3 INJECTION DTI PROTOCOL



PATIENT CRITERIA

This induction method is intended for people with OUD who are actively using full-agonist opioids such as fentanyl or heroin. For people switching from methadone, will discuss on a case-by-case basis. Okay to start if no methadone in the past 2 weeks.

INITIAL VISIT WORKFLOW

Initial Visit Assessment

- Comprehensive assessment of current opioid use, last use, current goals, past OUD treatment trials (last methadone, prior buprenorphine experience, etc.)
- Any other substances used in past week
- COWS score
- Past medical history, particularly chronic pain conditions (if applicable)

Order Buprenorphine Injections

- Order all 3 injections together
- One will be dispensed at a time
- For the first two injections, use a ‘day supply’ of 1 day
- In ‘notes to pharmacy’ or ‘SIG’ please inform this is a 3-Injection DTI
- CAM Orders: Please utilize CAM orders for administering buprenorphine LAIs

Prescribe Opioid Withdrawal Adjuncts

- We recommend the following opioid adjunct orders (if using SFDPH Epic, can use ‘Opioid Withdrawal Adjunctive’ orderset):
    - Clonidine 0.1mg q6h prn withdrawal and restlessness, #12
    - Ondansetron 4mg q8h prn nausea or vomiting, #9
    - Hydroxyzine 50mg q6h prn anxiety, #12
    - Loperamide 2mg q6h prn diarrhea; #12
    - Trazodone 100mg qhs prn insomnia, #3 (if appropriate)
    - Ibuprofen or acetaminophen (if no contraindications)
- Prescribe Supplemental Sublingual Buprenorphine

- **Buprenorphine sublingual 8mg tablet or film PRN:** Starting 24-hours after 2nd injection, dissolve 0.5-1 tablet under tongue every 4 hours as needed for withdrawal symptoms or opioid cravings injection (Max 16 mg/day), #28

PATIENT COUNSELING

- Expectations: Per clinical experience from Seattle providers, most people experience at least mild withdrawal but generally find it tolerable and feel better in the days-weeks to come.
- Adjunct Meds: You will get medications to help treat symptoms of withdrawal including nausea, vomiting, diarrhea, anxiety, difficulty sleeping and restlessness.
- Opioid Use: Most people continue to use other opioids during the first few days while the medication level is increasing
- Sublingual PRN Buprenorphine: Starting 24 hours after the 2nd injection, you can take extra sublingual buprenorphine if you are continuing to experience cravings or withdrawal symptoms. Taking the SL buprenorphine earlier than this may cause precipitated withdrawal.
- Continuation: It is important to continue to get the monthly injection each month. The first monthly injection often feels the weakest, and after every month's injection, you'll notice fewer cravings.

FOLLOW UP

Follow-up Assessment

- Assessment of COWS and discussion of expectations
- Follow-up plan

Considerations for Selecting a Monthly Dose

- Considerations include patient preference, past SL dosing (if available), duration of opioid use, types of opioids used.
- Monthly injection options include Sublocade 100 mg, Sublocade 300 mg, Brixadi 128 mg, Brixadi 96 mg or Brixadi 64 mg.
- Sublocade 300 mg is a more suitable option for those with a history of daily fentanyl use given its higher plasma concentration and longer half-life.

TABLE 3: DAILY DOSE OF SL BUPRENORPHINE AND SUGGESTED CORRESPONDING BRIXADI DOSES (FROM PACKAGE INSERT)

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

MISSED DOSE GUIDANCE

- Subject to change with further clinical experience, current guidance from Seattle's experience with the 3-injection DTI presentations.
- Ideally to receive the 16 mg injection, they should have a plasma concentration of >1 ng/mL (Cmax of a 2 mg tablet or film is ~1 ng/mg, should also equate to ~50% receptor occupancy; Coe et al., J Addict Med 2019;13: 93–103).
- Ideally to receive the monthly injection, they should have a plasma concentration of around 1.7 ng/mL (Cmax of a single-dose 4 mg film is ~1.66 ng/mL).

TABLE 4: MISSED 2ND OR 3RD INJECTION:

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Brixadi 8 mg given	Give Brixadi 16 mg	Give Brixadi 16 mg	Restart Brixadi 8 mg					
Brixadi 8 mg given	**Brixadi 16 mg given**	Give monthly injection	Give monthly injection	Give monthly injection	Repeat Brixadi 16 mg*	Repeat Brixadi 16 mg	Repeat Brixadi 16 mg	Restart Brixadi 8 mg

*If no delay between Brixadi 8 mg and 16 mg, can consider giving monthly on day 6

Missed Monthly Injection

- Brixadi: appropriate to give if within 6 weeks from the last injection. Discuss on a case-by-case basis if beyond 6 weeks.
- Sublocade: Can be given >4 weeks late. Discuss on a case-by-case basis.

APPENDIX 3: CLINICAL OPIATE WITHDRAWAL SCALE (COWS)

Clinical Opiate Withdrawal Scale (COWS)	
Sign / Symptom	**Score**
Resting Pulse Rate (beats per minute) *Measure pulse rate after patient is sitting or lying down for 1 minute*	≤80: 0 81-100: +1 101-120: +2 >120: +4
Sweating *Not accounted for by room temperature or patient activity over the last 0.5 hours*	No report of chills or flushing: 0 Subjective report of chills or flushing: +1 Flushed or observable moistness on face: +2 Beads of sweat on brow or face: +3 Sweat streaming off face: +4
Restlessness observation during assessment	Able to sit still: 0 Reports difficulty sitting still, but is able to do so: +1 Frequent shifting or extraneous movements of legs/arms: +3 Unable to sit still for more than a few seconds: +5
Pupil size	Pupils pinned or normal size for room light: 0 Pupils possibly larger than normal for room light: +1 Pupils moderately dilated: +2 Pupils so dilated that only the rim of the iris is visible: +5
Bone or joint aches *If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored*	Not present: 0 Mild diffuse discomfort: +1 Patient reports severe diffuse aching of joints/ muscles: +2 Patient is rubbing joints or muscles and is unable to sit still because of discomfort: +4
Runny nose or tearing *Not accounted for by cold symptoms or allergies*	Not present: 0 Nasal stuffiness or unusually moist eyes: +1 Nose running or tearing: +2
	Nose constantly running or tears streaming down cheeks: +4
GI Upset *Over last 0.5 hours*	No GI symptoms: 0 Stomach Cramps: +1 Nausea or loose stool: +2 Vomiting or diarrhea: +3 Multiple episodes of vomiting or diarrhea: +5
Tremor *Observation of outstretched hands*	No tremor: 0 Tremor can be felt, but not observed: +1 Slight tremor observable: +2 Gross tremor or muscle twitching: +4
Yawning *Observation during assessment*	No yawning: 0 Yawning once or twice during assessment: +1 Yawning three or more times during assessment: +2 Yawning several times/minute: +4

Anxiety or irritability	None: 0 Patient reports increasing irritability or anxiousness: +1 Patient obviously irritable/anxious: +2 Patient so irritable or anxious that participation in the assessment is difficult:+4
Gooseflesh skin	Skin is smooth: 0 Piloerection of skin can be felt or hairs standing up on arms: +3 Prominent piloerection: +5
Total Score: 5-12=mild withdrawal; 13-24 = moderate withdrawal; 25-36=moderately severe withdrawal; more than 36 = severe withdrawal	

APPENDIX 4: RELEVANT PHARMACOKINETICS

TABLE 5: RELEVANT PHARMACOKINETICS TABLE - SINGLE INJECTION

	Cmax (ng/mL), single injection	Ctrough (ng/mL), 128 hours later for q1 week 28 days later for q4 week	Tmax (hours)	T1/2 (hours)
Brixadi 8 mg	1.71	0.3	23	70.7
Brixadi 16 mg	~3.06	~0.6	23.5	96.4
Brixadi 96 mg	5.47	0.538	10	555
Brixadi 128 mg	6.59	0.934	6.1	502

FIGURE 4: RELEVANT PHARMACOKINETICS GRAPH – SINGLE INJECTION

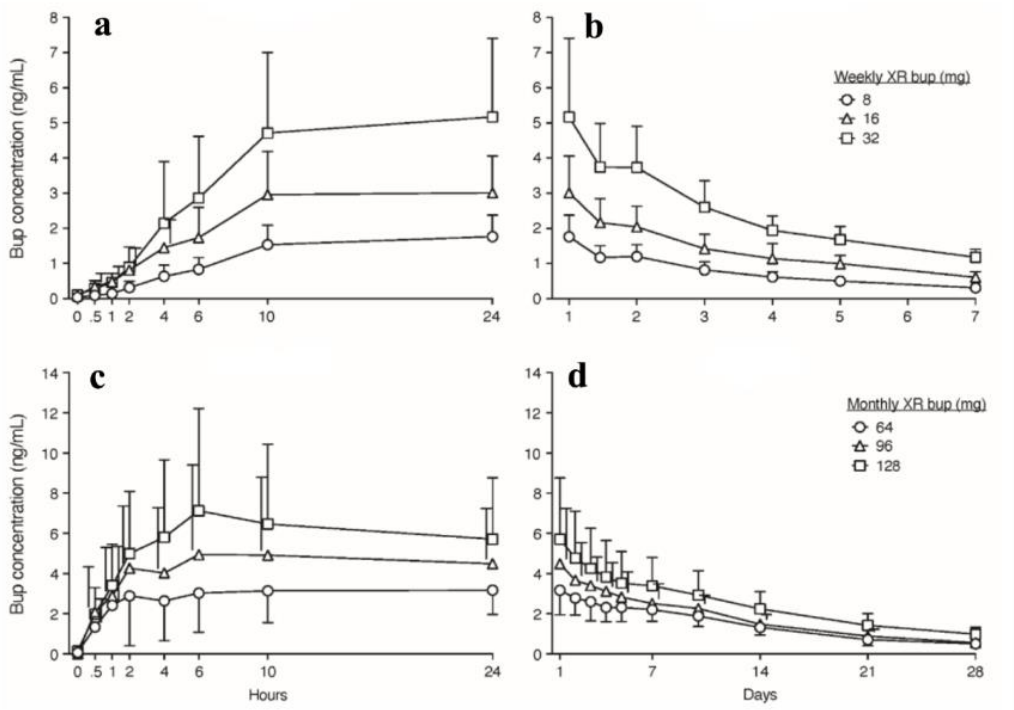


Figure 1. *Buprenorphine concentrations over time after weekly and monthly XR-buprenorphine administration. Data displayed are means with standard deviations (SDs) in one direction and staggered to the side of the mean value when needed to preserve figure clarity. (a, b) Buprenorphine (Bup) concentrations (ng/mL) over the first 24 h and 7 days, respectively, after administration of weekly XR-bup. (c, d) Bup concentrations over the first 24 h and 28 days, respectively, after administration of monthly XR-bup. CAM2038 Investigators Brochure. Braeburn Inc. Edition 17. April 5, 2023.*