Hennepin Healthcare

Long-acting depot buprenorphine

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Disclosures

- I have no financial conflicts of interest.

- I will not be discussing off-label use of medications

Learner objectives

1. Describe pharmacology of subcutaneous depot buprenorphine (Sublocade)
2. Apply clinical pharmacology to prescribing practice
3. Describe clinical situations when depot buprenorphine may be indicated and contraindicated

Pharmacology Review: Buprenorphine

- Buprenorphine:
  - High MOR affinity (but similar to methadone, fentanyl, hydromorphone)
  - Partial agonism: reduced signal activation per receptor binding event
  - Slow dissociation
  - Long half-life

- Action at the mu-opioid receptor (MOR)
  - Competitive with high affinity opioid agonists at the MOR
  - Decreased downstream signaling per MOR binding event relative to full opioid agonists

Therapeutic goals & the mu opioid receptor

- Withdrawal suppression and some cravings: 40-50% saturation
  - ≥1 ng/mL serum buprenorphine
- Euphoria blockade from oral opioid agonists: 70-80% mOR saturation
  - ~2-3 ng/mL serum buprenorphine
- Blockade for high affinity opioids: 90% mOR saturation

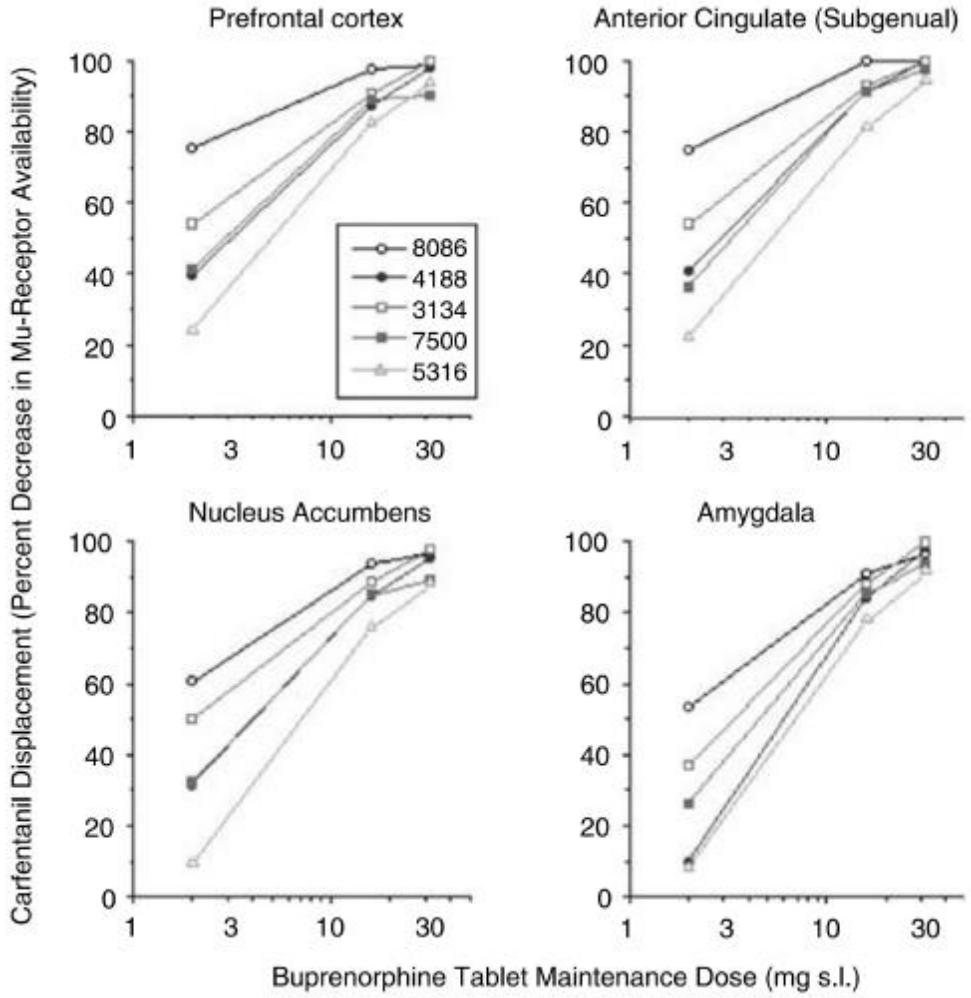
Whole brain mOR availability reduction

- 2mg SL bup: 41%
- 16mg SL bup: 85-92%
- 32mg SL bup: 94-98%

Greenwald et al, 2003

Inter-individual variability

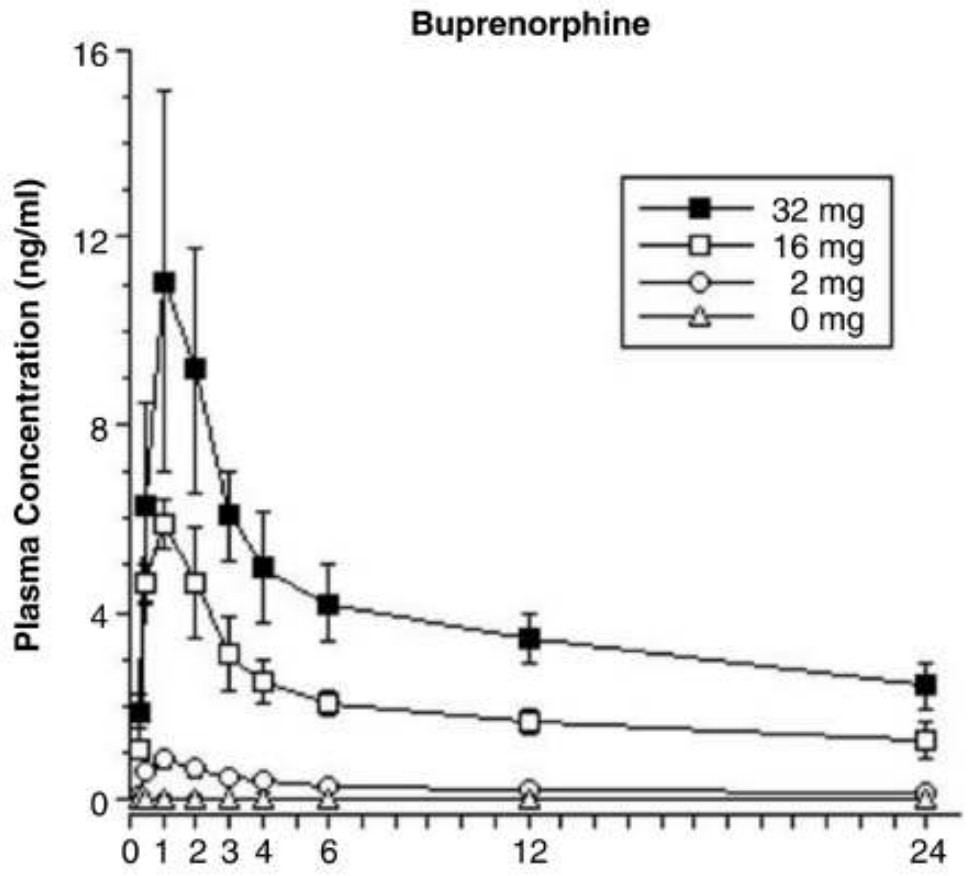
mOR availability at 8mg SL bup (inverse of graph)	
Prefrontal cortex	10-40%
Anterior cingulate	10-40%
Nucleus accumbens	20-50%
Amygdala	25-50%

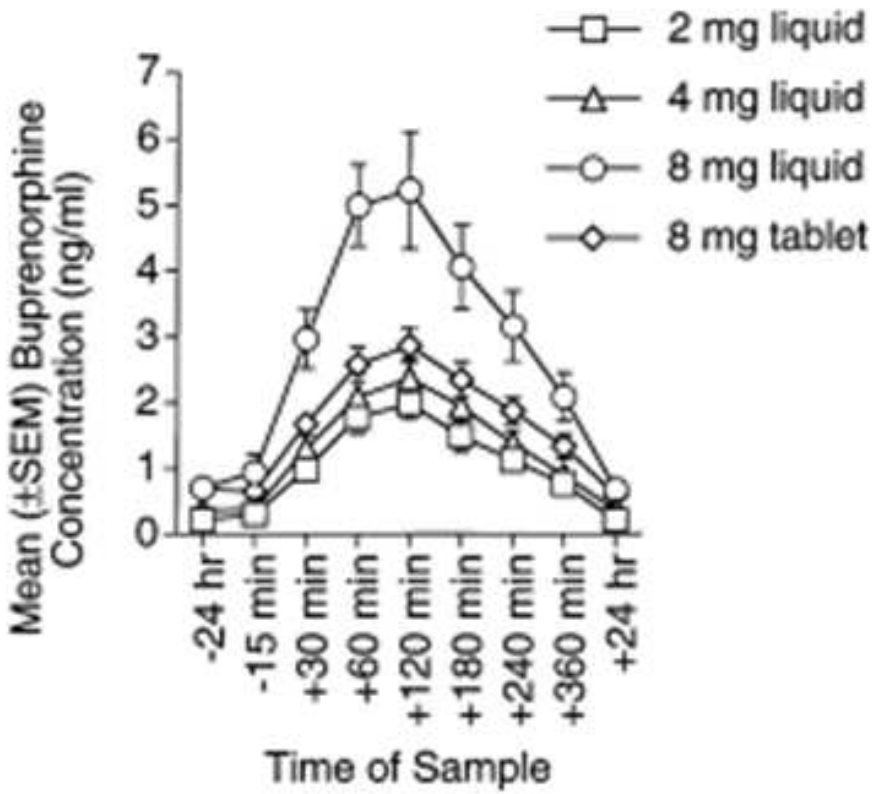


Variability narrows at higher buprenorphine doses

Greenwald et al., 2003

Time since administration matters





Greenwald et al., 2003
Schuh & Johanson, 1999

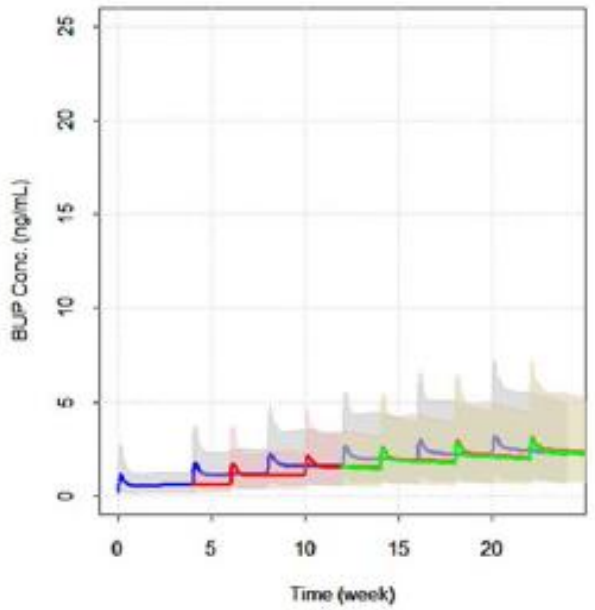
Buprenorphine level reduces euphoria

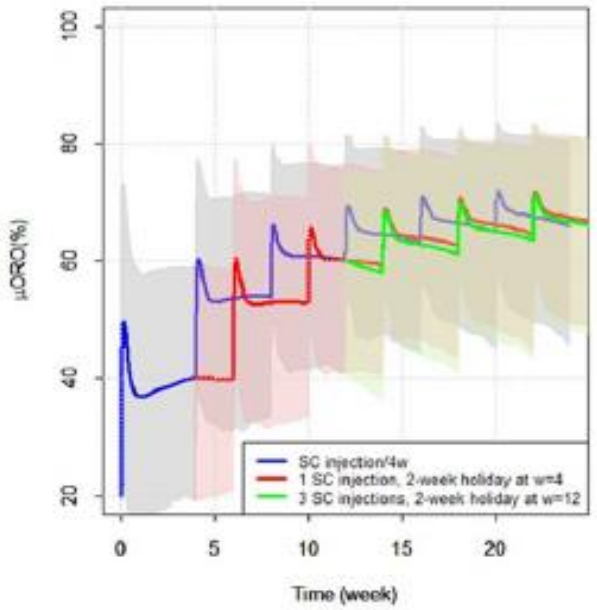
Measure	BUP 0 mg	BUP 2 mg	BUP 16 mg	BUP 32 mg	Dose–effect
Withdrawal (day 1)	17.1 (1.8)[a]	10.0 (1.5)[ab]	4.0 (0.9)[b]	3.6 (0.7)[b]	$F(3,12) = 5.01$, $p < 0.02$
Agonist (days 1–2)	6.1 (0.4)	7.5 (0.5)	8.1 (0.6)	9.2 (0.6)	$F(3,12) = 3.31$, $p < 0.08$
Δ Agonist	14.8 (2.6)[a]	13.0 (1.6)[a]	3.5 (1.3)[b]	4.0 (1.7)[b]	$F(3,9) = 8.77$, $p < 0.005$
Δ High	57.0 (8.3)[a]	69.0 (10.3)[a]	19.0 (10.5)[b]	37.3 (9.5)[ab]	$F(3,9) = 5.14$, $p < 0.03$
Δ Good Effect	55.8 (15.0)	49.0 (20.0)	15.8 (9.5)	9.8 (6.5)	$F(3,9) = 3.41$, $p < 0.07$

Sublocade (RBP-6000)

Serial 100mg dose administrations

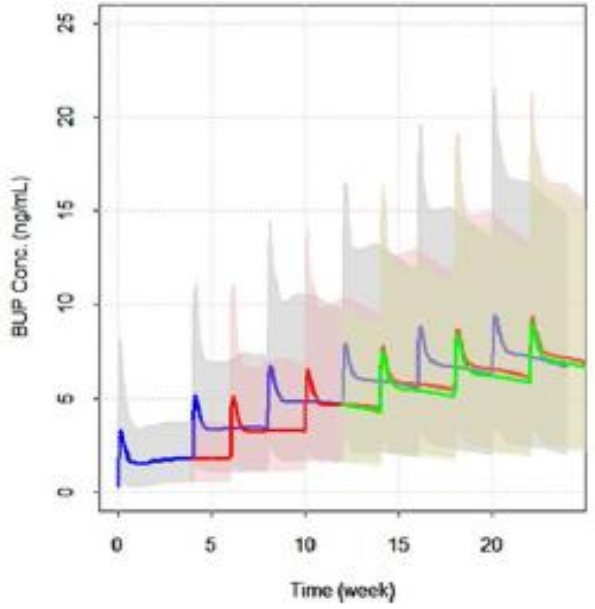
- 1st dose ~2-4mg SL bup
- 2nd dose ~4-6mg SL bup

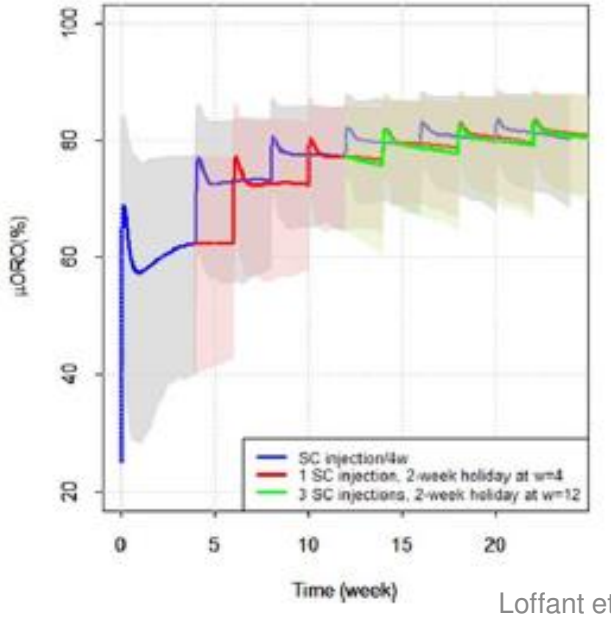




Serial 300mg dose administrations

- 1st dose ~8-12mg SL bup
- 2nd dose ~16-24mg SL bup

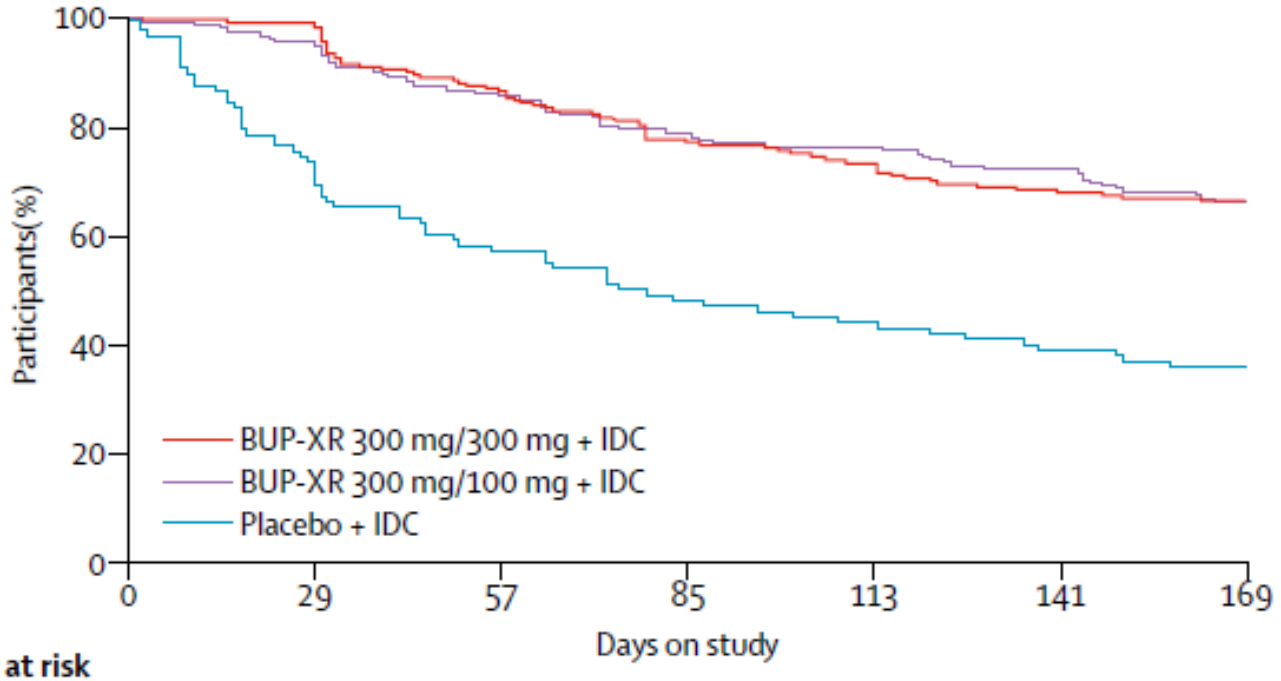




Loffant et al, 2016

Stability increased retention in care

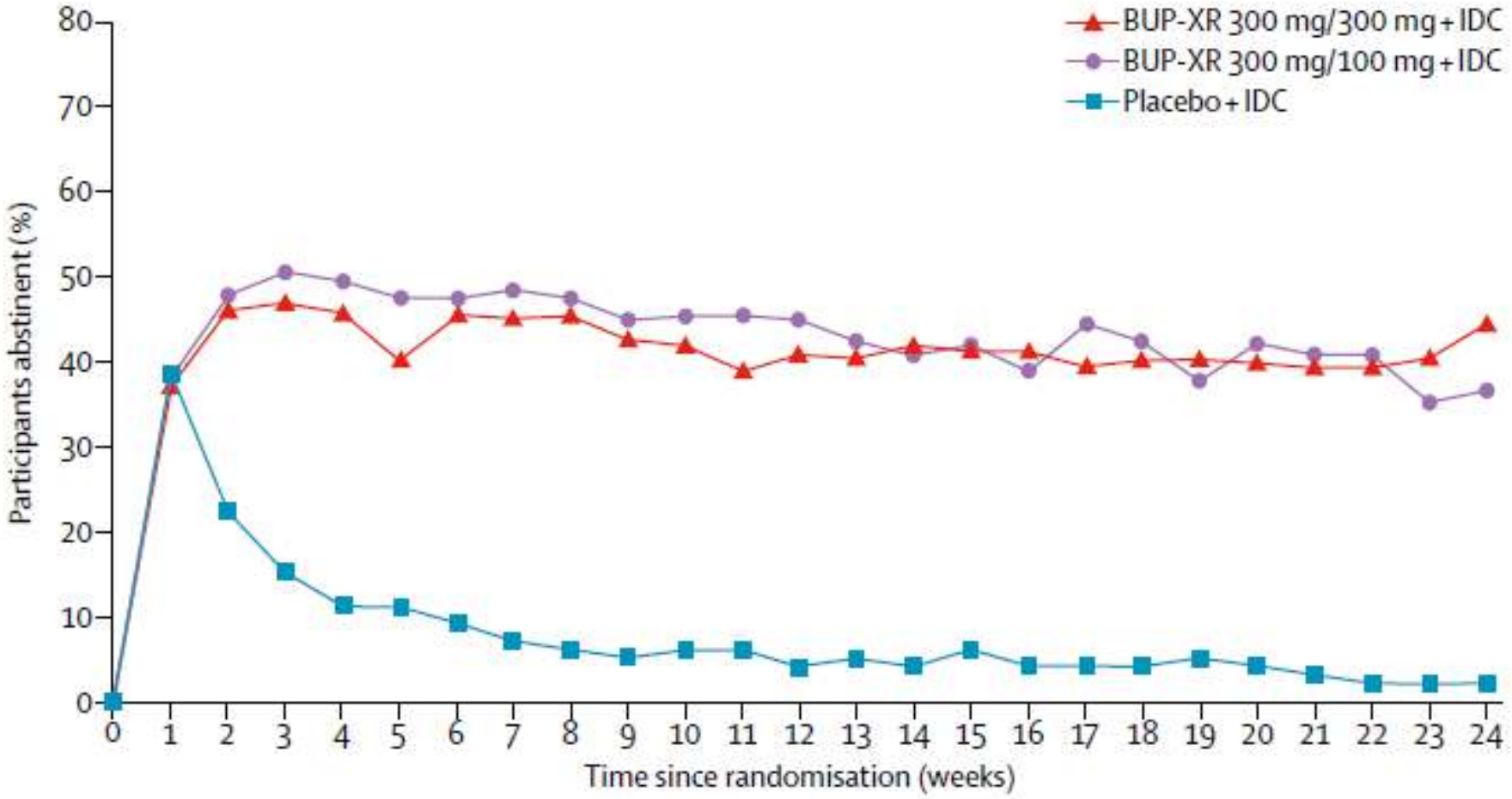
	Total (N)	Discontinued (n)	Censored (n)	25th percentile days	Median days	Log-rank test p value
BUP-XR 300 mg/300 mg + IDC	196	65	131	104	N/A	<0·0001
BUP-XR 300 mg /100 mg + IDC	194	65	129	120	N/A	<0·0001
Placebo + IDC	99	63	36	26	78	NA



Number at risk							
BUP-XR 300 mg/300 mg + IDC	196	193	170	152	144	134	95
BUP-XR 300 mg/100 mg + IDC	194	185	167	153	148	141	80
Placebo + IDC	99	69	57	48	44	39	23

Haight et al, 2019

Illicit opioid use improved, often intermittent



Haight et al., 2019

Results independent of other drug use

	BUP-XR 300 mg/300 mg plus individual drug counselling (n=196)		BUP-XR 300 mg/100 mg plus individual drug counselling (n=194)		Placebo plus individual drug counselling (n=99)	
	Screening	Weeks 5–24	Screening	Weeks 5–24	Screening	Weeks 5–24
Amphetamines*	15%	7–12%	25%	12–22%	19%	5–19%
Barbiturates	1%	0–1%	2%	0–2%	0	0–3%
Benzodiazepines	10%	4–9%	12%	4–10%	13%	3–20%
Cocaine†	40%	27–39%	47%	25–33%	42%	28–45%
Cannabinoids	47%	30–38%	55%	28–36%	53%	31–43%
Phencyclidine	1%	1–4%	0	0–2%	1%	0–6%

Use of other substances at weeks 5–24 is shown as the range of observed values for percentage of participants with positive urine drug screen, positive self-report in timeline follow-back interviews, or concomitant medication per visit during weeks 5–24. Confirmatory testing was not done. Numbers of participants in each group reflect the number in the intent-to-treat population; this number fluctuated between weeks 5 and 24. *Defined as amphetamines and methamphetamines. †Based on assay for benzoylecgonine, a cocaine metabolite.

Haight et al, 2019

No significant increase in adverse events

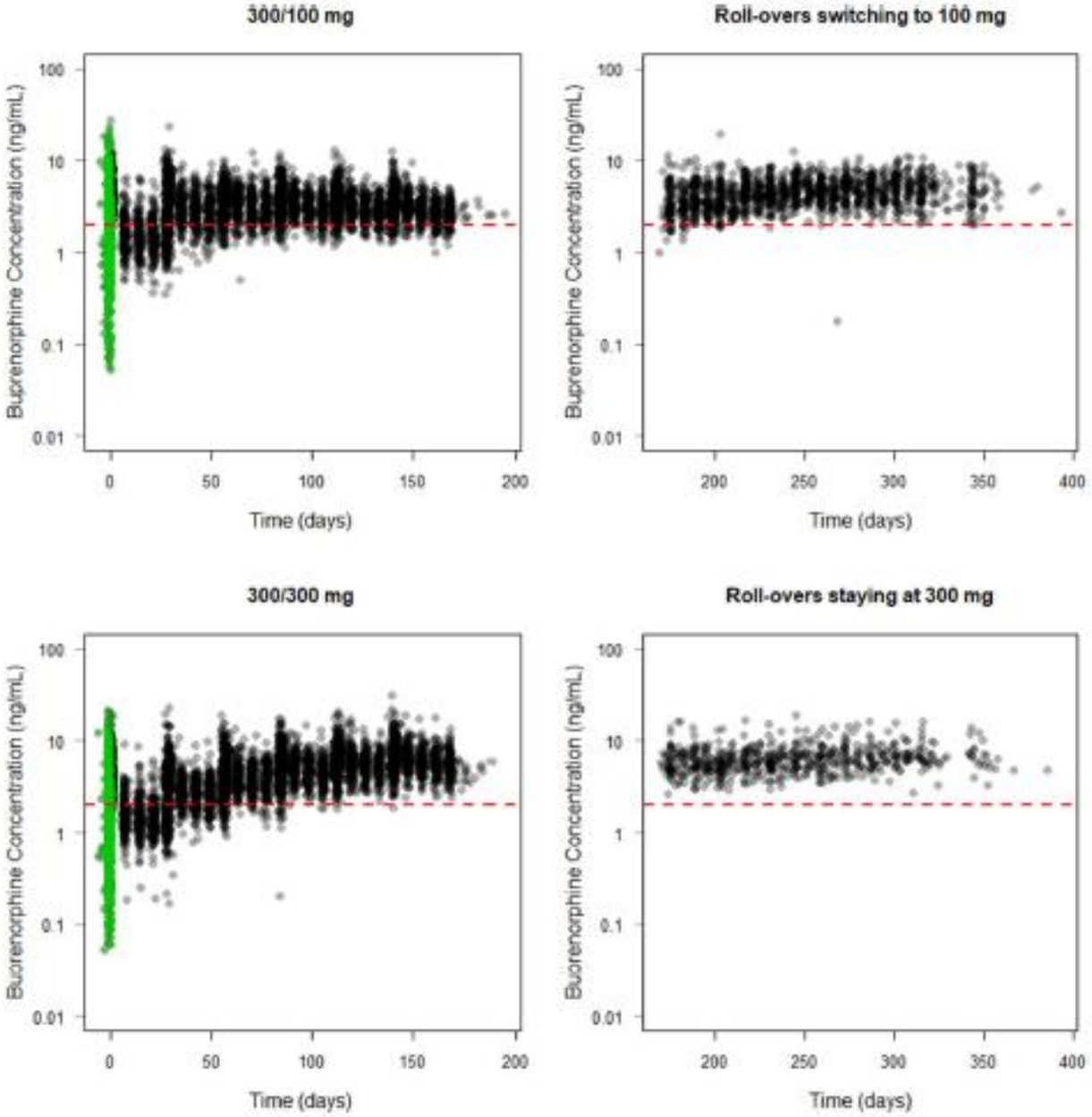
	BUP-XR 300/300 mg plus individual drug counselling (n=201) (n=201)	BUP-XR 300/100 mg plus individual drug counselling (n=203) (n=203)	Placebo plus individual drug counselling (n=100)
Any treatment-emergent adverse event	134 (67%)	155 (76%)	56 (56%)
Any serious treatment-emergent adverse event	7 (3%)	4 (2%)	5 (5%)
Any severe treatment-emergent adverse event	13 (6%)	15 (7%)	4 (4%)
Any treatment-emergent adverse event leading to discontinuation	10 (5%)	7 (3%)	2 (2%)
Any treatment-emergent adverse event leading to death	1 (<1%)	0	0

Haight et al, 2019

Clinical exceptions

- Some people remain below 2 ng/mL after two (2) 300mg q4 week injections

- None remained below therapeutic level after 4th 300mg injection



Jones et al, 2021

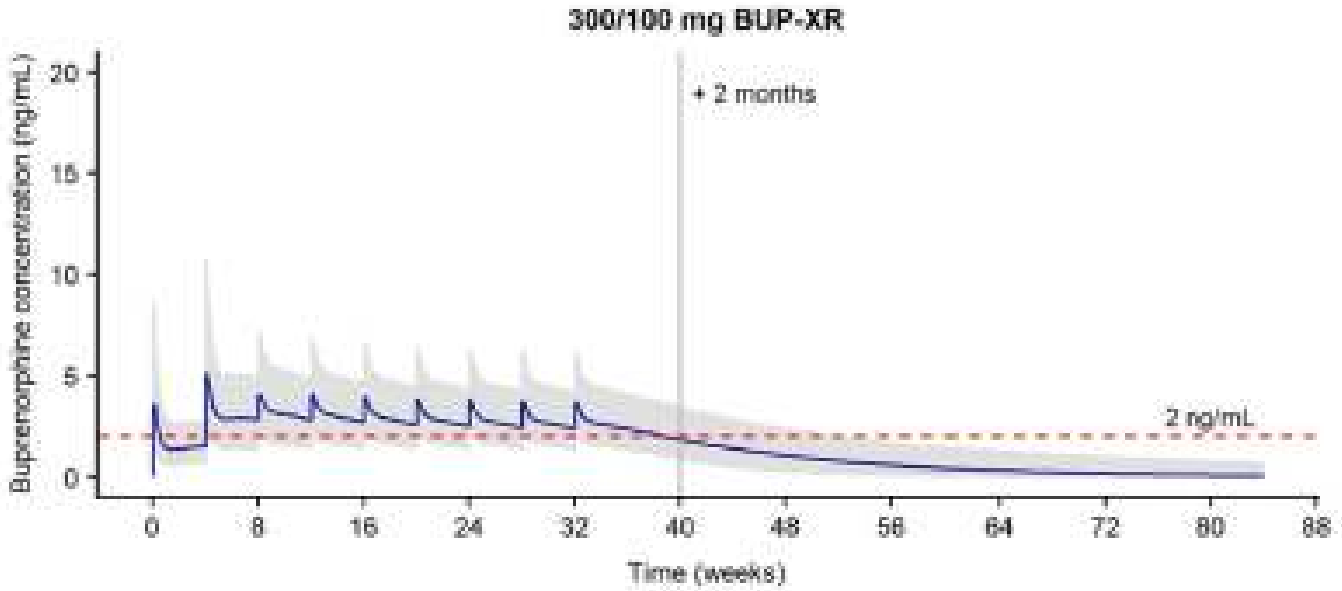
Areas of exploration

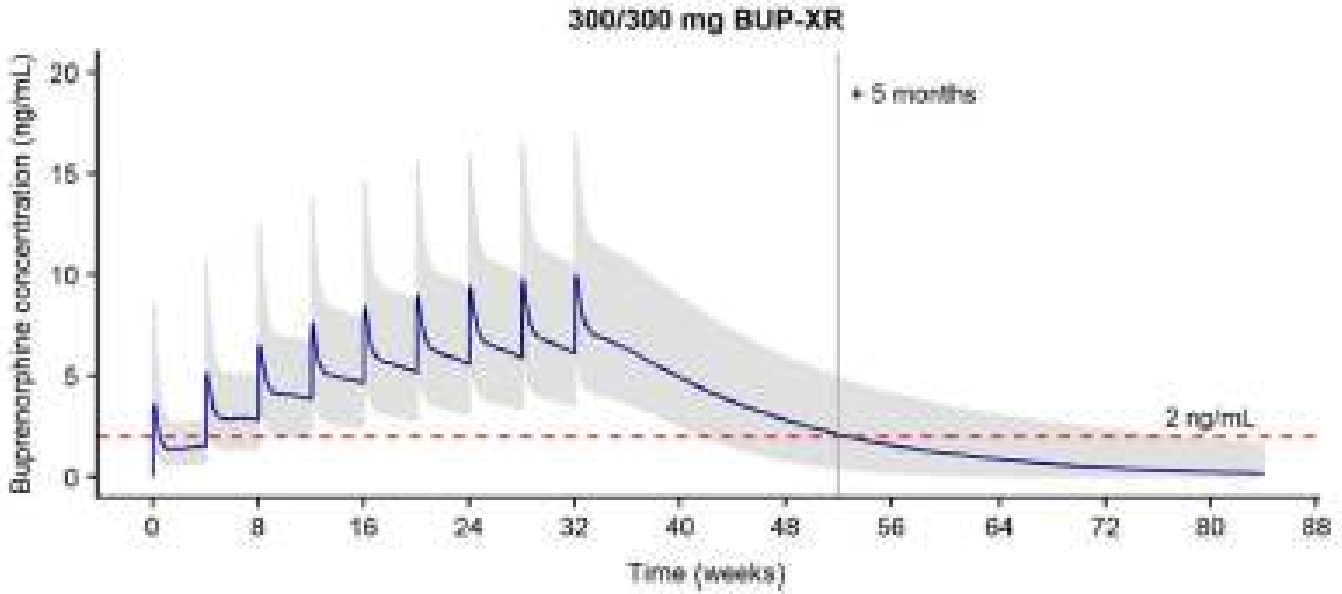
- Pregnancy
  - Case reports exist of people maintained on Sublocade for duration of pregnancy and through either vaginal or cesarean section delivery without complication
- Adolescence and emerging adulthood
  - Nonadherence is commonplace
- Management of Sublocade for people with other moderate-severe SUDs
  - Loss of contingency management
  - Loss of medication safety monitoring
- Acute pain management in people on stable high dose (≥2 doses 300mg Sublocade) depot buprenorphine
- Buprenorphine taper/cessation approach

Taper option?

Anecdotally, some people who have wanted to taper off, but struggled with SL stepoffs below 2mg total daily, have successfully* tapered using Sublocade

*Long-term abstinence unknown





Jones et al, 2021

Considerations

- Sublocade may be indicated in these settings:
  - Medication non-adherence
    - Cognitive impairment
    - Psychosocial instability
  - Difficulty scheduling clinic follow-up
  - Convenience

- Questions
  - Given loss of contingency management, appropriate for people with active stimulant, sedative, or severe alcohol use disorders?
  - In what situations is counseling more important than medication adherence?

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Questions?

References

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