

A Summary of Evidence to Optimize the use of Extended Release-Buprenorphine in Opioid Use Disorder

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Potential for conflict(s) of interest:

Presenter is a former employee of Indivior

I have no financial or professional ties to Indivior or any other pharmaceutical company and have not received honorarium or funding for this presentation. I will only use generic names to describe medications, unless appropriate to mention the brand name.

Learning Objectives and Outline

After this presentation participants will gain awareness of evidence to explain current opioid-use disorder management methods with BUP-XR

Topics include

- BUP-XR pharmacokinetics
- Buprenorphine vs Fentanyl interaction
- Dose equivalence of BUP-SL vs BUP-XR
- Rapid initiation of BUP-XR

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Buprenorphine Fundamentals¹

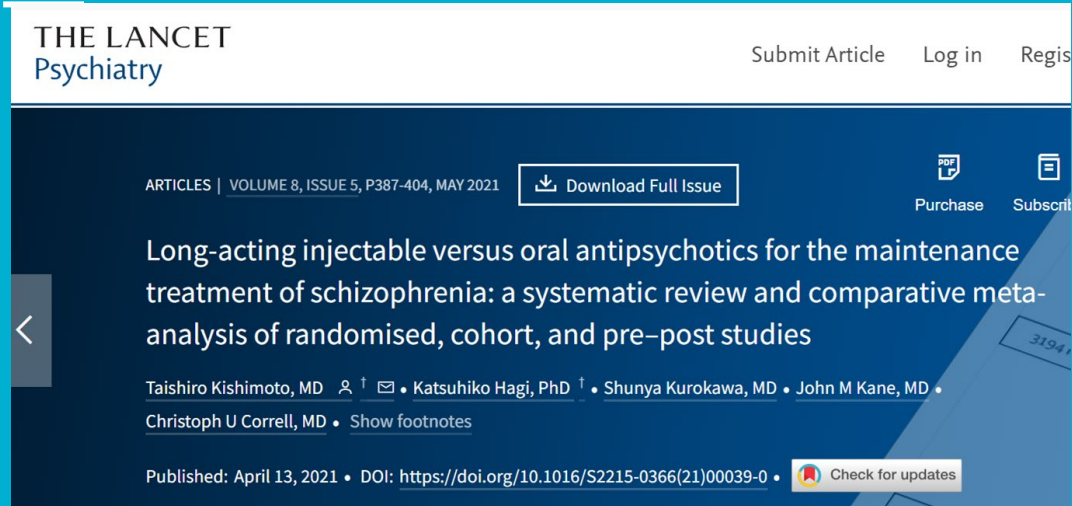
1. Partial Agonist (ceiling effect)
2. High affinity for the receptor
3. Slow dissociation from the receptor

Buprenorphine dose effect relationship²

Plasma [BUP]	Mu-Opioid receptor availability *	Outcome*
1ng/ml	<50%	Relief of opioid withdrawal
2ng/ml	<30%	Control of withdrawal and cravings
3ng/ml	<20%	Blockade of non-medical typical doses of opioids

*These findings come from a review publication and sources data originates prior to the prevalence of powdered fentanyl

Why LAI to your patients?

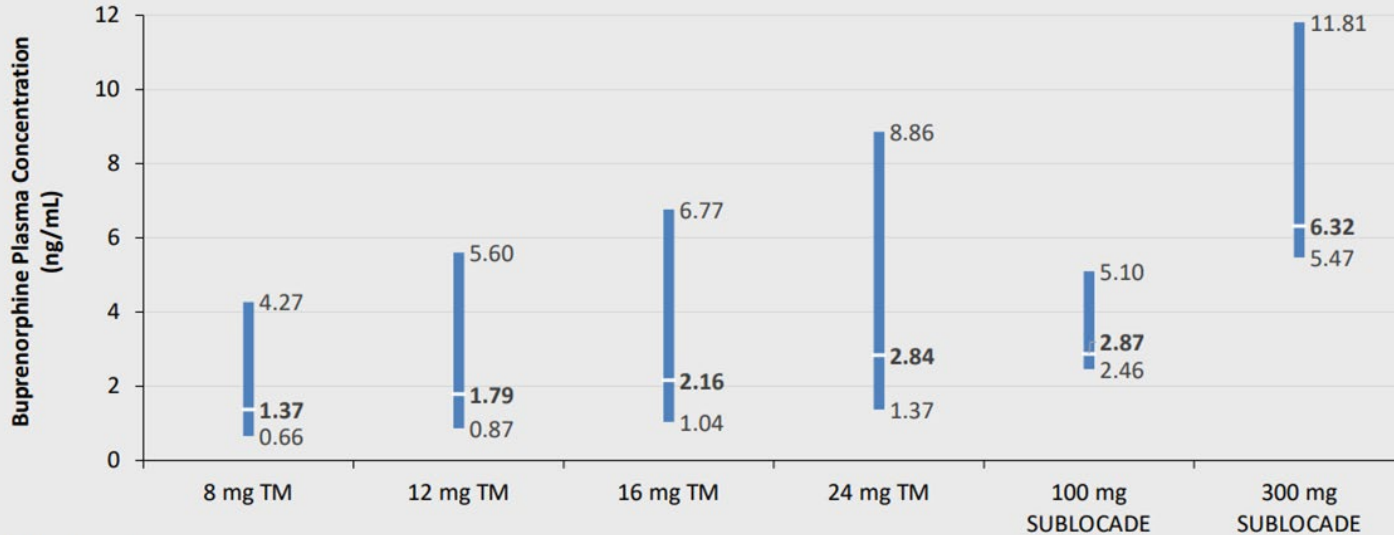
A screenshot of a Lancet Psychiatry article page. The header shows 'THE LANCET Psychiatry' on the left and 'Submit Article', 'Log in', and 'Regis' on the right. Below the header, there are navigation options: 'ARTICLES | VOLUME 8, ISSUE 5, P387-404, MAY 2021', a 'Download Full Issue' button, 'Purchase', and 'Subscri'. The main title of the article is 'Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies'. The authors listed are Taishiro Kishimoto, MD, Katsuhiko Hagi, PhD, Shunya Kurokawa, MD, John M Kane, MD, and Christoph U Correll, MD. At the bottom, it says 'Published: April 13, 2021 • DOI: https://doi.org/10.1016/S2215-0366(21)00039-0 • Check for updates'.

- Systematic-review³ and meta analysis showed that LAI's (long acting injectables) demonstrated significant benefit in the domains of preventing hospitalizations and relapse
- possible reasons for this include patient discontinuation of treatment from oral options

Key differences: Daily BUP-SL vs BUP-XR

	BUP-SL ^{4,5}	BUP-XR ⁶
Dosing Frequency	Daily (every other day)	Monthly
Peak	~1.5 hours	~24 hours
Half-Life	24-42 hours	43-60 DAYS
Time to steady state	~1 week	4-6 injections (months)
Induction	2-12mg on day 1, and may increase to 16 mg on day 2	Minimum 7 days treatment with SL-BUP at 8-24mg before 2 monthly 300mg injections of BUP-XR

Figure 2. Comparison of Steady-State Buprenorphine Plasma Exposure Between Daily Transmucosal Buprenorphine and Once-Monthly SUBLOCADE



TM: transmucosal

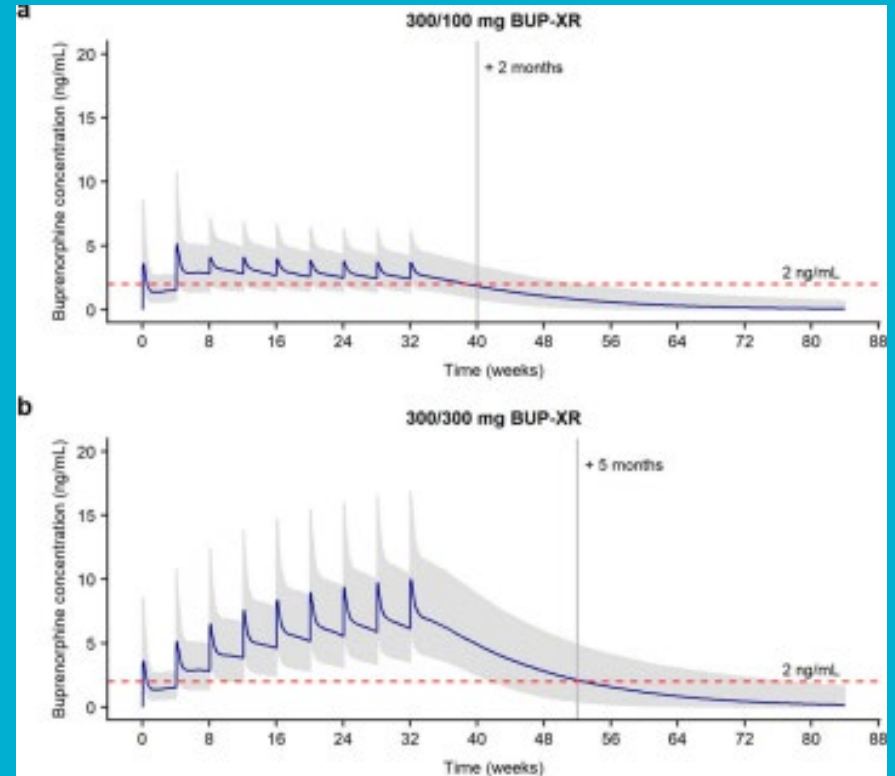
Each bar shows the geometric mean for buprenorphine trough plasma concentration (bottom), average plasma concentration (white mark), and peak plasma concentration (top).

BUP-XR evidence

Population Pharmacokinetics of BUP-XR

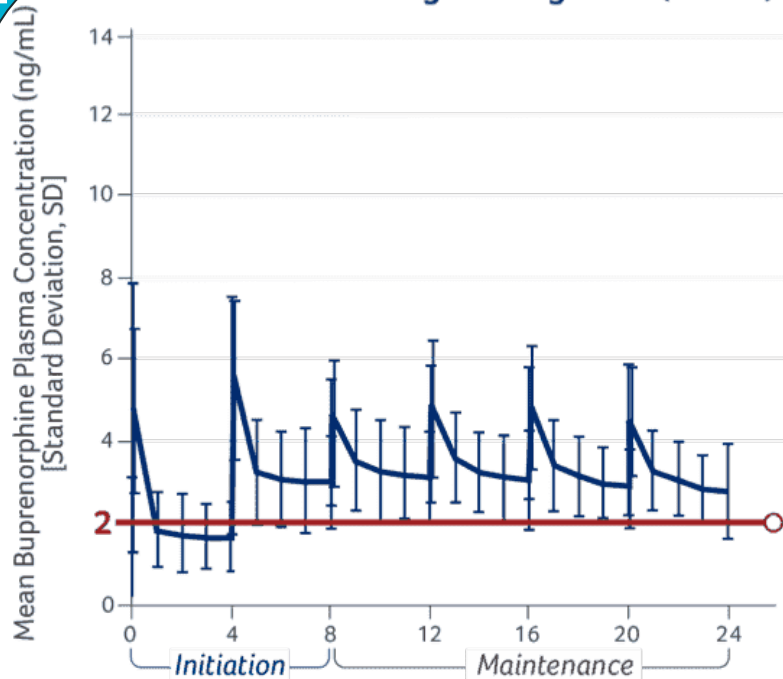
Jones et al 2021⁸

1. Steady state depends on dose (time and plasma level)
2. Discontinuation after steady state is steady
3. Benefits of treatment are prolonged long after discontinuation (relative to oral OAT options)

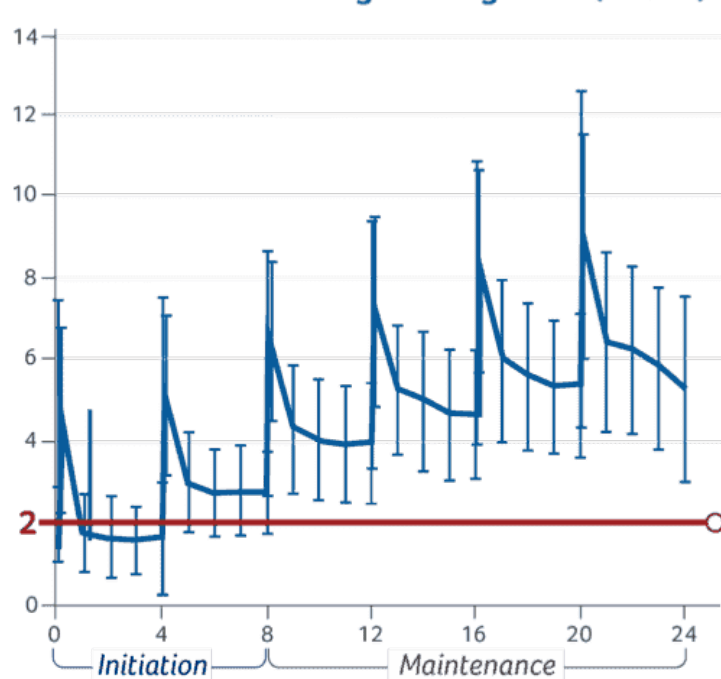


Weekly plasma levels

SUBLOCADE 300 mg/100 mg + IDC (n=203)



SUBLOCADE 300 mg/300 mg + IDC (n=201)



Time (weeks)

Transitioning from SL to XR-BUP

- The following table¹⁰ informs clinicians the relative difference between SL-BUP and XR-BUP
- Flexibility with BUP-XR dosing which contrasts the original product monograph
- XR-BUP for those stabilized on SL-BUP<8mg is off-label
 - discretion should be exercised if proceeding with BUP-XR in these cases

Table 1. Relative Simulated Exposure Between 100-100 mg SUBLOCADE (Scenario 1) and Transmucosal Buprenorphine

SUBOXONE dose	SUBLOCADE Injection 1 100 mg			SUBLOCADE Injection 2 100 mg		
	C _{trough}	C _{max}	C _{avg}	C _{trough}	C _{max}	C _{avg}
2 mg/day	1.82	1.10	1.08	3.44	1.37	1.88
4 mg/day	1.15	0.75	0.71	2.17	0.86	1.19
6 mg/day	0.88	0.61	0.56	1.66	0.66	0.91
8 mg/day	0.73	0.53	0.48	1.37	0.54	0.75
12 mg/day	0.56	0.44	0.38	1.05	0.42	0.57
16 mg/day	0.46	0.39	0.32	0.86	0.34	0.47
24 mg/day	0.36	0.34	0.26	0.66	0.26	0.36

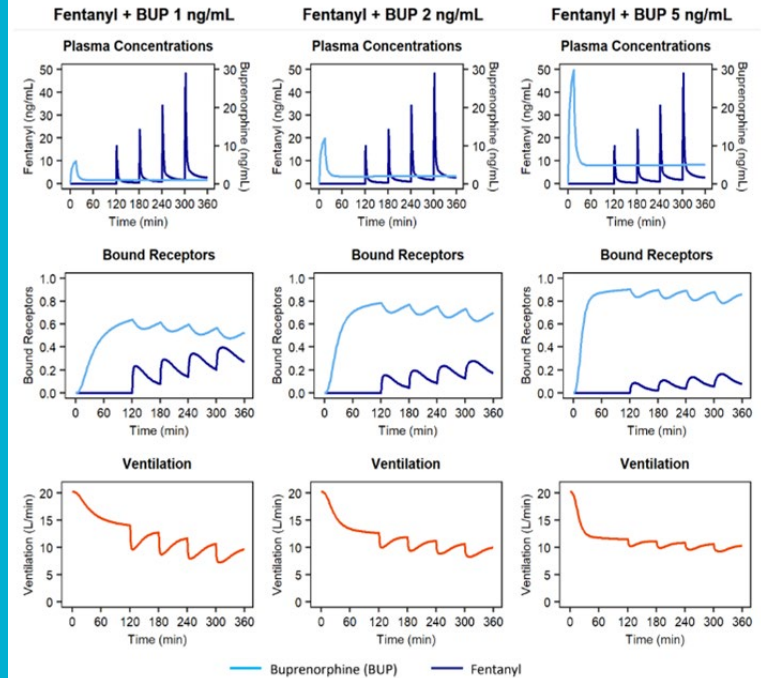
Table 2. Relative Simulated Exposure Between 300-100 mg SUBLOCADE (Scenario 2) and Transmucosal Buprenorphine

SUBOXONE dose	SUBLOCADE Injection 1 300 mg			SUBLOCADE Injection 2 100 mg		
	C _{trough}	C _{max}	C _{avg}	C _{trough}	C _{max}	C _{avg}
2 mg/day	5.50	3.02	3.11	6.61	2.15	3.62
4 mg/day	3.48	1.96	1.99	4.19	1.36	2.28
6 mg/day	2.66	1.53	1.54	3.20	1.04	1.74
8 mg/day	2.18	1.29	1.28	2.64	0.86	1.44
12 mg/day	1.68	1.02	1.00	2.02	0.66	1.10
16 mg/day	1.39	0.87	0.84	1.67	0.54	0.91
24 mg/day	1.07	0.70	0.66	1.28	0.41	0.70

Buprenorphine vs Fentanyl

1. Open label, crossover study (n=8 opioid tolerant participants) comparing fentanyl induced respiratory depression with or without the presence of buprenorphine¹⁰
2. BUP-XR or BUP-SL were not used, instead IV BUP was given at concentrations that reflect BUP-XR
3. BUP appears to have a dose dependent “protection” effect against fentanyl induced respiratory depression

Figure 4. Simulations of a Typical OT Subject Under the Study Design



Rapid Initiation (same day start)

Initiating Monthly Buprenorphine Injection After Single Dose of Sublingual Buprenorphine - Wiest et al, 2021 ¹¹

- Not without adverse events, however all severe adverse events occurred in the first 48 hours only, & no deaths
- Starting BUP-XR is possible as early as the first day, provided risk of precipitated withdrawal can be avoided

Safety Results

Table 3 Summary of Treatment-Emergent Adverse Events (TEAEs)

Parameter	Participants Receiving SUBLOCADE (N=24)	
	All TEAEs	TEAEs within 48h
Any TEAE	20 (83.3%)	19 (79.2%)
Treatment Related TEAEs	5 (20.8%)	4 (16.7%)
Serious TEAEs	0 (0.0%)	0 (0.0%)
Treatment Related Serious TEAEs	0 (0.0%)	0 (0.0%)
Severe TEAEs	5 (20.8%)	5 (20.8%)
Injection site reaction TEAE	3(12.5%)	1 (4.2%)
TEAE resulting in study treatment withdrawal or interruption	0 (0.0%)	0 (0.0%)
TEAE resulting in death	0 (0.0%)	0 (0.0%)

The TRANSFORM trial is currently underway comparing rapid vs traditional induction methods

New in 2023

Real-world Evidence for Impact of Opioid Agonist Therapy on Nonfatal Overdose in Patients with Opioid Use Disorder during the COVID-19 Pandemic - Lee et al, 2023 ¹²

- Canadian wide study comparing overdose outcomes between methadone, BUP-SL and BUP-XR
- Retrospective observational trial (baseline characteristics of patient populations were unbalanced)
- When risk adjusted BUP-XR was found to be superior to methadone for prevention of NF-OD
- Given these findings a future RCT could provide clinicians with robust evidence of which modality is superior

Summary and recommendations

- BUP-XR is a distinct treatment option from SL-BUP
 - Less “highs and lows,” sustained plasma concentrations
- BUP-XR is a useful tool for treating patients with OUD
 - Interferes with other opioids from binding and appears to have a protection effect
 - Those who desire the drug liking effects of opioids may find that this is not the right option for them
- BUP-XR may provide a smoother OAT discontinuation process than traditional taper methods
 - There is currently a study underway assessing this
- Higher BUP-XR maintenance dose (300mg) is a better option than 100mg for those who use fentanyl
- If safe and necessary, BUP-XR can be initiated as early as Day 1

Thank You!

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