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Psychiatry and Addictions Case Conference

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HOW AND WHEN TO TRANSITION FROM METHADONE TO BUPRENORPHINE

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project ECHO

SPEAKER DISCLOSURES

- ✓ No conflicts of interest

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OBJECTIVES

1. Methadone and buprenorphine overview
2. Why and when to transition from methadone to buprenorphine?
3. How to transition?

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METHADONE

- Full agonist at mu opioid receptor (MOR)
- Peak level in 4 hours
- Half life of mean 24 hours, wide range 8-59 hours
- Usual maintenance dose: 80-120 mg daily

SAMHSA TIP 63: “Medications for Opioid Use Disorder” 2021

BUPRENORPHINE

- Partial agonist at MOR
- Ceiling effect on respiratory depression (lower risk of overdose)
- High affinity for MOR (displaces other opioids)
- Poor oral bioavailability; given sublingually or subcutaneously for OUD (transdermal or buccal for pain)
- Sublingual:
  - Peak level 3-6 hours
  - 24-48 hour duration
  - Half life >24 hours
  - Typical maintenance dose: 16-24 mg daily (typical maximum 32 mg daily)

SAMHSA TIP 63: “Medications for Opioid Use Disorder” 2021

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RISKS OF METHADONE

- Overdose and Sedation
  - Full MOR agonist
  - Risk increased when combined with other opioids or sedating medications or substances (benzodiazepines, alcohol)
- Prolonged QTc and arrhythmia risk
  - Methadone associated with QTc prolongation, increased risk of cardiac arrhythmia
  - Methadone is not recommended if QTc >500 ms
  - Buprenorphine does not cause clinically significant QTc prolongation or cardiac arrhythmia

Caplehorn 2002

ACCESS TO OUD CARE

Factor	Methadone	Buprenorphine
Treatment Setting	Opioid Treatment Program (OTP)	Office-Based Opioid Treatment (OBOT) Program (within general medical practice)
Provider	OTP provider only (for OUD)	All clinicians with current DEA registration including Schedule III authority
Pharmacy	Dispensed by OTP clinic only	Non-OTP pharmacy ok
Take-Home Doses	Per federal, state, and OTP policy. (Up to 28 days if stable per SAMHSA)	Does not require observed dosing.

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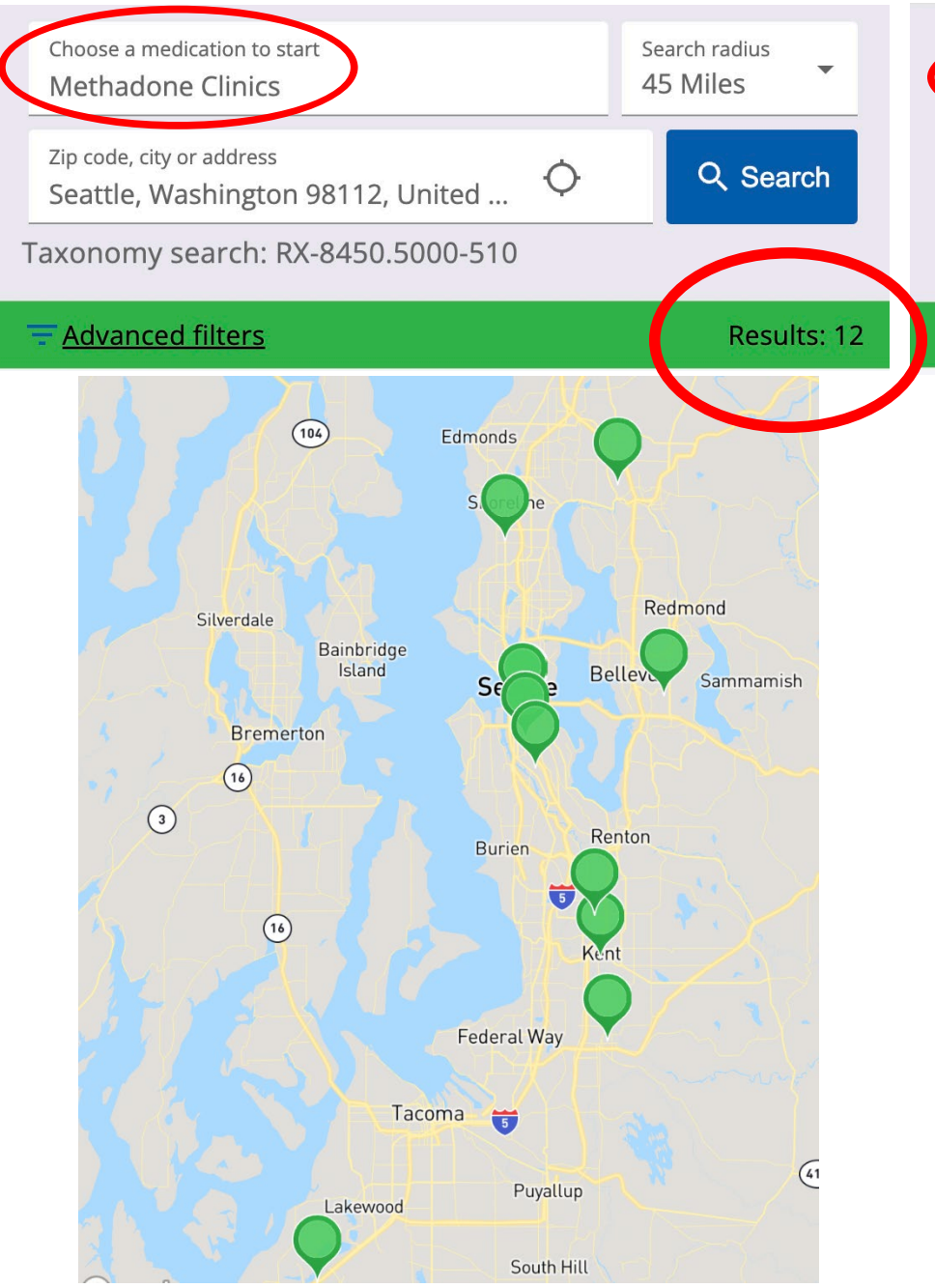

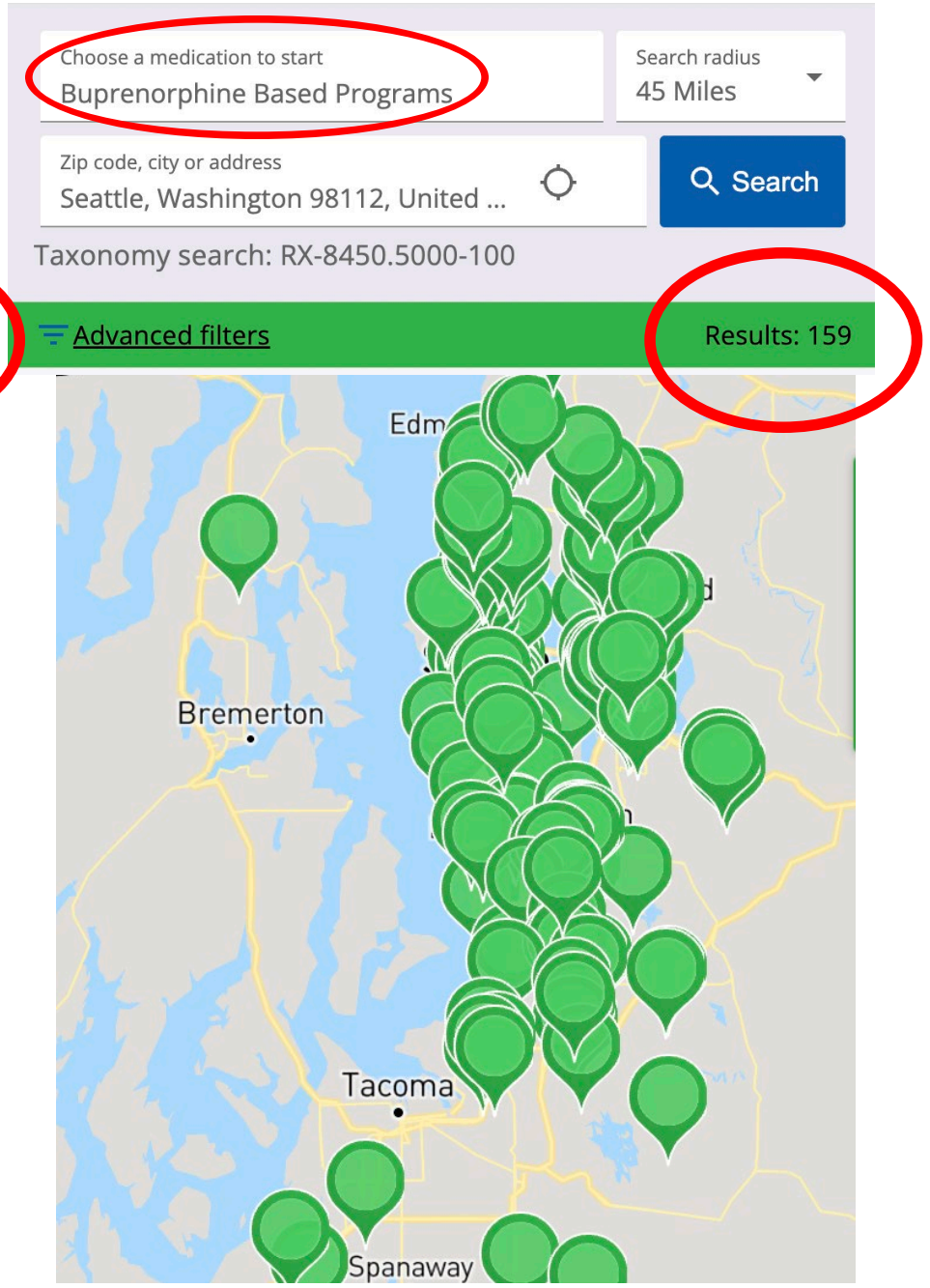

WA Recovery Helpline MOUD Locator, https://search.warecoveryhelpline.org/

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PATIENT PREFERENCES

- Desire to no longer receive treatment at OTP
  - Structured setting
  - Environment of OTP
  - Location
- Desire to receive care in integrated care setting (e.g. from PCP/OBOT program)
- Side effects of methadone
- Dosing schedule and route of administration
  - e.g. Buprenorphine XR injectable form
- Preparation for transition to antagonist treatment
- Patient-driven (rather than provider-driven) transitions to buprenorphine are associated with higher rate of success (Bhatraju 2022)

Bhatraju 2022

RISKS OF TRANSITION

- Precipitated withdrawal
- Return to use when methadone dose tapered
- Inability to quickly achieve therapeutic effect with buprenorphine

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METHADONE TO BUPRENORPHINE PROTOCOLS

- Standard initiation
- High-dose initiation
- Low-dose initiation
- Tapering methadone?
- Practical considerations

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STANDARD BUPRENORPHINE INITIATION

- Taper methadone (typically to <70 mg), then stop methadone (and any other opioids) for at least 24-36 hours
- Patient should be in opioid withdrawal (COWS>10 typically)
- Buprenorphine-naloxone started, uptitrated until withdrawal resolves (usually 1-3 days)
- Typically no more than 8-16 mg bup total on day 1
- Pro: less complex protocol
- Cons:
  - Risk for return to use after stopping methadone
  - May take days to achieve therapeutic buprenorphine level

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HIGH-DOSE INITIATION PROTOCOL

- Like conventional initiation, but higher buprenorphine dose on day 1 (16-32 mg)
- Pros:
  - Less complex protocol
  - Could be more effective in achieving therapeutic dose while minimizing withdrawal period
- Con: Limited evidence for patients on methadone (not included in study)

Herring 2021

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LOW-DOSE BUPRENORPHINE INITIATION

- Aka the “Bernese Method”
- Start buprenorphine at low doses while continuing full agonist (i.e. methadone)
- Intention is to minimize precipitated withdrawal
- Pros:
  - May be more acceptable if negative prior experiences with standard buprenorphine initiation
  - Minimizes withdrawal symptoms
- Cons:
  - More complex instructions
  - Limited evidence in outpatient setting

Hämmig 2016

LOW-DOSE BUPRENORPHINE IN THE HOSPITAL: BHATRAJU 2022

- Retrospective cohort study, n=62, hospitalized patients at Harborview Medical Center
- 42 (68%) patients on methadone at time of bup initiation
  - 14 patients on methadone prior to admission
  - 28 started on methadone during admission
- 79% (33/42) of those on methadone successfully transitioned to buprenorphine
- Unsuccessful transition significantly associated with:
  - Older age
  - Reporting any withdrawal symptoms during transition
  - Switching to buprenorphine for post-hospital placement

Bhatraju 2022

TABLE 1. Microdose with Overlap Protocol

	Dose of Buprenorphine*	Full Agonist
Day 1	0.5 mg once	Baseline dose
Day 2	0.5 mg BID	Baseline dose
Day 3	1 mg BID	Baseline dose
Day 4	2 mg BID	Baseline dose
Day 5	4 mg BID	Baseline dose
Day 6	8 mg Once	Baseline dose
Day 7*	8 mg AM/4 mg PM	Baseline dose
Day 8	8 mg BID	None

*Buprenorphine/naloxone films or tablets were utilized. Buprenorphine specific doses are reported here for simplicity.

Bhatraju 2022

LOW-DOSE BUPRENORPHINE IN THE HOSPITAL: BUTTON 2022

TABLE 2. Characteristics of Low-dose Buprenorphine Initiations

Induction Characteristic	n (%)
Unique low-dose initiation	72
Reason for low-dose initiation[*]	
Co-occurring pain	66 (91.7)
Anxiety around thought of withdrawal	50 (69.4)
Transition from high dose methadone	21 (29.2)
History of precipitated withdrawal	7 (9.7)
Opioid withdrawal intolerance	5 (6.9)
Other	13 (18.1)
Days of low-dose initiation in hospital – mean (SD)	6 (2.7)
Low-dose initiation completion status	
Completed in hospital	50 (69.4)
Scheduled to complete as outpatient	9 (12.5)
Discontinued in hospital[†]	13 (18.1)
Premature discharge during low-dose initiation	2 (2.8)

[*]Not mutually exclusive.

†One individual did not complete two low-dose initiations before the third, completed low-dose initiation.

- Retrospective cohort study, n=68, hospitalized patients at OHSU Medical Center seen by addiction consult service
- Mean prescribed MME before low-dose initiation: 198 (SD 98). (approximately methadone 25 mg dose)
- 29.2% (n=21) of patients on “high dose” methadone (not specified, but >80 mg daily dose?)

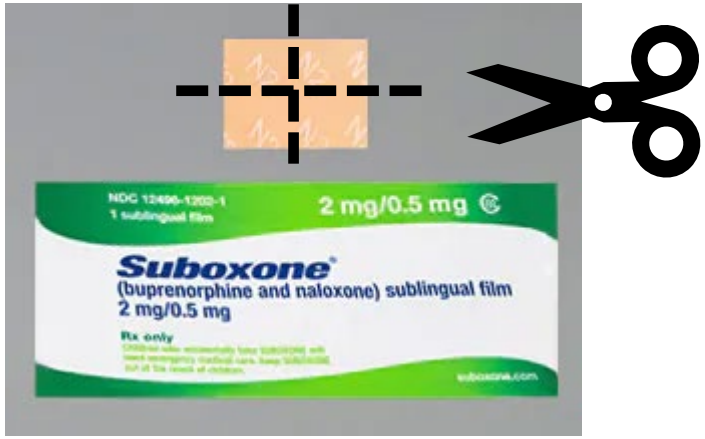
Button 2022

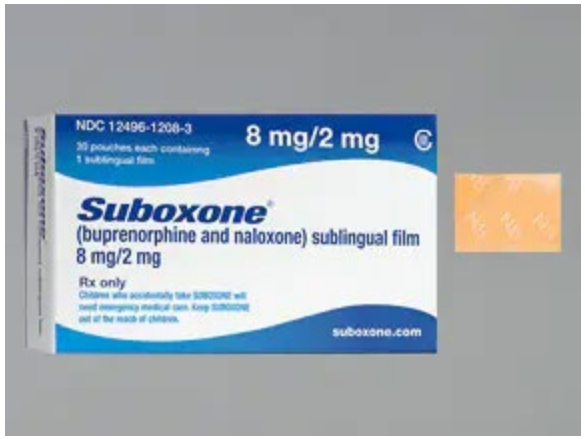
OUTPATIENT LOW-DOSE INITIATION EXAMPLE: ETS

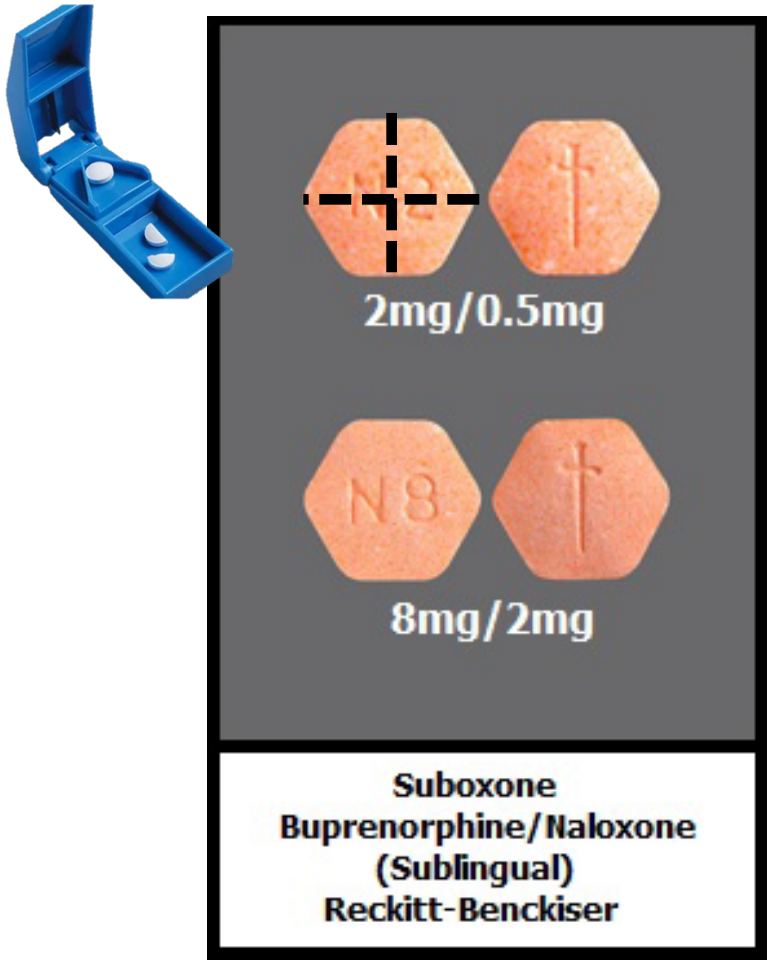
Day	Date	Actual Dose/Day	Film or SL tablets	Methadone Dose
Buprenorphine/Naloxone Film 2mg/0.5mg				
Day 1		0.5mg	¼ film once daily	Continue current dose
	See ETS Medical Provider on Day 1			
Day 2		0.5mg once daily	¼ film once daily	Continue current dose
Day 3		1mg once daily	½ film once daily	Continue current dose
Day 4		1mg once daily	½ film once daily	Continue current dose
Begin Buprenorphone/Naloxone Tablets for remainder of transition				
Day 5		2mg once daily	1 x 2mg/0.5mg daily	Continue current dose
Day 6		2mg once daily	1 x 2mg/0.5mg daily	Continue current dose
Day 7		4mg once daily	2 x 2mg/0.5mg daily	Meet with your ETS medical provider to discuss when to reduce or discontinue methadone dose.
	See ETS Medical Provider on Day 7			
Day 8		4mg once daily	2 x 2mg/0.5mg daily	
Day 9		6mg once daily	3 x 2mg/0.5mg daily	
Day 10		6mg once daily	3 x 2mg/0.5mg daily	
Day 11		8mg once daily	1 x 8mg/2mg daily	
Day 12		8mg once daily	1 x 8mg/2mg daily	
Day 13		12mg once daily	2 x 2mg/0.5mg along with 1 x 8mg/2mg daily	
Day 14		16mg once daily	2 x 8mg/2mg daily	Return to ETS
	See ETS Medical Provider on Day 14			

BUPRENORPHINE FILMS AND TABLETS

¼th of a 2/0.5 mg bup-nal film or tab = 0.5 mg buprenorphine







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COMPARISONS OF PROTOCOLS

- Most studies are observational case series with heterogeneous populations, methods, and reported outcomes
- Low-dose initiation has more evidence for efficacy
- Most data of low-dose initiation is from inpatient setting; limited generalizability to outpatient setting
- No published data on high dose transition from methadone to buprenorphine

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REVIEWS

Strategies for Transfer From Methadone to Buprenorphine for Treatment of Opioid Use Disorders and Associated Outcomes: A Systematic Review

Lintzeris, Nicholas BMedSci, MBBS, PhD, FAChAM; Mankabady, Baher MD; Rojas-Fernandez, Carlos PharmD; Amick, Halle MSPH

Author Information

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Lintzeris 2022

METHADONE TO BUPRENORPHINE TRANSFER STRATEGIES: LINTZERIS 2022

- Systematic review of 18 studies describing transfer from methadone to buprenorphine
- Conventional initiation protocols
- No low-dose initiation studies included
- Higher methadone dose was significantly correlated with lower completion rate

Lintzeris 2022

SHOULD METHADONE BE TAPERED PRIOR TO BUP START?

TABLE 4. Transfer Completion Rate* by Transfer Component

Variable	Transfer Completion Rate (Unweighted)	*F* or *t* Statistic and Corresponding *P*
Setting		
Inpatient	125/138 (90.6%)	$t = -1.41$
Outpatient	154/163 (94.5%)	$P = 0.18$
Pretransfer METH dose†		
<40 mg	108/110 (98.2%)	
40–60 mg	86/93 (92.5%)	$F = 4.23$
>60 mg	66/81 (81.5%)	$P = 0.03$
Minimum wait time before initial BUP dose		
≤24 h‡	121/129 (93.8%)	$t = 1.12$
>24 h	176/194 (90.7%)	$P = 0.28$
Degree of withdrawal at initial BUP dose		
Mild	81/86 (94.2%)	$t = 0.44$
Moderate	107/121 (88.4%)	$P = 0.66$
BUP product		
BUP monotherapy	211/230 (91.7%)	$t = 0.09$
BUP + NLX	90/97 (92.8%)	$P = 0.93$
Initial first-day BUP strategy		
Fixed dose	202/220 (91.8%)	$t = -0.17$
Flexible dose	105/114 (92.1%)	$P = 0.87$
Total first-day BUP strategy‡		
Single dose	105/111 (94.6%)	$F = 0.49$
Split dose	114/128 (89.1%)	$P = 0.62$
Mixed or flexible strategy	78/84 (92.9%)	
Overall	307/334 (91.9%)	NA

*Defined as achieving and maintaining a stable dose of BUP, unless defined otherwise by individual study.

†Transfer completion rates were identical for starting METH dose and METH dose averaged over final 5 days.

‡Does not include the study that administered a 35 μg/hr BUP patch at 12 hours after last METH dose.

BUP indicates buprenorphine; METH, methadone; NA, not applicable; NLX, naloxone.

- Pretransfer methadone daily dose weighted mean 46 mg (range 19-78)
- No methadone taper in 9 studies, with taper in 7 studies
- Higher pretransfer methadone dose correlated with lower transfer completion rate
- However, at higher methadone doses, completion rate still >80%
- Therefore lower methadone dose may lead to somewhat higher success?

Lintzeris 2022

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SHOULD METHADONE BE TAPERED PRIOR TO BUP START?

- Per SAMHSA TIP 63: recommended to taper methadone to 30-40 mg daily for at least 1 week prior to buprenorphine start (SAMHSA 2021)
- Methadone 60 mg or less generally recommended by published guidelines (Lintzeris 2022)
- Limited evidence for buprenorphine low-dose initiation without methadone taper
- However: risk of return to use with methadone taper is a concern

SAMHSA TIP 63: "Medications for Opioid Use Disorder" 2021
Lintzeris 2022

PREDICTORS OF SUCCESSFUL METHADONE TO BUPRENORPHINE TRANSITION: GONZALEZ 2021

Table 1: Characteristics of patients who successfully converted to buprenorphine maintenance treatment (BMT) and who discontinued treatment or returned to methadone maintenance treatment (MMT)

Table 1 (part 1): Demographic and treatment factors of 26 patients from an opioid agonist treatment clinic who were in opioid agonist treatment from January 2018 until February 27, 2019

Characteristics	Successfully converted to BMT n=15 (57.7%)	Discontinued Tx or returned to MMT n=11 (42.3%)	p value
Mean age (SD)	40.5 (9.4)	36.1 (4.9)	t (24) =2.5, p<0.05
Sex, n (%)			0.17
Males	7 (46.7)	6 (54.5)	
Females	8 (53.3)	5 (45.5)	
OAT duration over 2years n (%)			<0.05
Yes	12 (52.2)	11 (47.8)	
No	3 (47.8)	0 (0.0)	
Starting dose buprenorphine n (%)			<0.05
<1mg	11 (73.3)	5 (45.5)	
1mg or higher	4 (26.7)	6 (54.5)	
Days to titration n (%)			0.21
7 days or less	1 (6.7)	1 (9.1)	
over 7 days	14 (93.3)	10 (90.9)	
Positive urines at 3 months n (%)			<0.05
Yes	9 (60.0)	9 (86.7)	
No	6 (30.0)	2 (13.3)	
MMT cessation n (%)			0.08
Abrupt	6 (30.0)	3 (27.3)	
Titrated	9 (60.0)	8 (72.7)	

**Tx = treatment*
**BMT = buprenorphine/naloxone maintenance treatment*
**MMT = methadone maintenance treatment*
**n = number of patients*
**SD = standard deviation*
t(degrees of freedom) =the t-statistic

Gonzalez 2021

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PRACTICAL CONSIDERATIONS

- OTP versus OBOT-based transition?
- Inpatient versus outpatient transition?
- Symptomatic medications
- Advice for patients

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OTP-BASED TRANSITION

- Start methadone daily dosing at clinic (no take-home) to provide daily support
- Write for buprenorphine-naloxone order
- Prescribe comfort medications PRN
- Plan for day 1 on Monday (to allow for provider support PRN)
- Schedule provider visit on days 1, 7, and 14
- At days 7 and 14:
  - Review progress
  - Assess for opioid withdrawal
  - Consider adjusting buprenorphine uptitration schedule
  - Start methadone taper or discontinue methadone (when at therapeutic buprenorphine dose)

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OBOT-BASED TRANSITION

- Collaboration with OTP provider (have ROI signed to allow for communication with OTP)
- Prescribe buprenorphine-naloxone and PRN comfort medications with instructions on home initiation
- Schedule provider visits starting on day 1 of initiation protocol, at least weekly and PRN
- Follow-up via telephone as needed (with RN or other clinic staff)

INPATIENT METHADONE TO BUPRENORPHINE TRANSITION

- Could consider inpatient detoxification to assist in transition from methadone to buprenorphine, if available
- Closer monitoring of patient
- Managing complicated dosing schedule
- Ability to adjust protocol more quickly in response to clinical status

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ADJUNCTIVE MEDICATIONS FOR OPIOID WITHDRAWAL

Symptom	Medication	Typical Dose Range
Anxiety, restlessness, insomnia	Clonidine	0.1-0.2 mg q2H PRN, NTE 1.2 mg daily (avoid if hypotensive), taper by 0.1-0.2 daily
	Gabapentin	300 mg TID PRN
	Hydroxyzine	25-50 mg q6H PRN
Muscle spasms	Methocarbamol	500 mg TID PRN
Muscle aches, joint pain, headache	Ibuprofen	400-800 q6H PRN
	Acetaminophen	500-1000 mg q6H PRN
Nausea, vomiting	Ondansetron	4-8 mg q8H PRN
Abdominal cramping	Dicyclomine	20 mg 4x daily PRN
Diarrhea	Loperamide	2 mg 4x daily PRN

Srivastava 2020

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OTHER PRACTICAL CONSIDERATIONS

- Advise patient to consider reducing work, other obligations as able during transition (likely 1-2 weeks)
- Ensure clinical support (e.g. access to clinic RN via telephone) available for patient PRN during transition

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METHADONE TO BUPRENORPHINE TRANSITIONS: SUMMARY

- The decision to transition may be based on risks of methadone, adherence concerns, access to MOUD, and patient preferences
- Risks of transition include risk of return to use or precipitated withdrawal during transition period
- Low-dose bup initiation has evidence for efficacy; most evidence comes from hospital setting

CASE EXAMPLE: HOSPITALIZED PATIENT

- 65M history of OUD, gastric adenocarcinoma s/p resection complicated by severe anastamosis stricture, presenting with recurrent stricture resulting in acute on chronic abdominal pain and malnutrition.
- Smoking 10 fentanyl "blues" daily previously.
- Methadone started at 30 mg daily, increased to 35 mg daily
- However complicated by intermittently prolonged QTc >500
- Risk/benefit discussion with patient:
  - Patient willing to transition to buprenorphine
  - Motivated by desire to travel, felt monthly visits to clinic more feasible than frequent OTP clinic visits
  - Risks of precipitated withdrawal discussed

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CASE EXAMPLE: HOSPITALIZED PATIENT

Day	Buprenorphine	Methadone	Notes
0	None	35 mg daily	No withdrawal symptoms
1	Buprenorphine 450 mcg buccal once	35 mg daily	“Irritability”
2	Buprenorphine 450 mcg buccal BID	35 mg daily	No change in symptoms
3	Buprenorphine 900 mcg buccal BID	35 mg daily	No change in symptoms
4	Buprenorphine-naloxone 2-0.5 mg SL BID	35 mg daily	No change in symptoms
5	Buprenorphine-naloxone 4-1 mg SL BID	35 mg daily	Restlessness, rhinorrhea
6	Buprenorphine-naloxone 8-2 mg SL BID	None	Irritability, anxiety, restlessness, rhinorrhea
7	Buprenorphine-naloxone 8-2 mg SL BID	None	Nausea, diarrhea, but otherwise better

Patient ultimately transitioned to XR buprenorphine 300 mg SC injection by day 10
Discharged with OBOT clinic follow-up for buprenorphine monthly injections

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Thank you!

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