NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Novel Buprenorphine Induction Strategies

July 6, 2021

James J. Gasper, PharmD, BCPP
National Clinician Consultation Center
University of California San Francisco

This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) under grant number U1OHA30039-04-00 (AIDS Education and Training Centers National Clinician Consultation Center) in partnership with the HRSA Bureau of Primary Health Care (BPHC) awarded to the University of California, San Francisco.

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Brief History of Buprenorphine Inductions

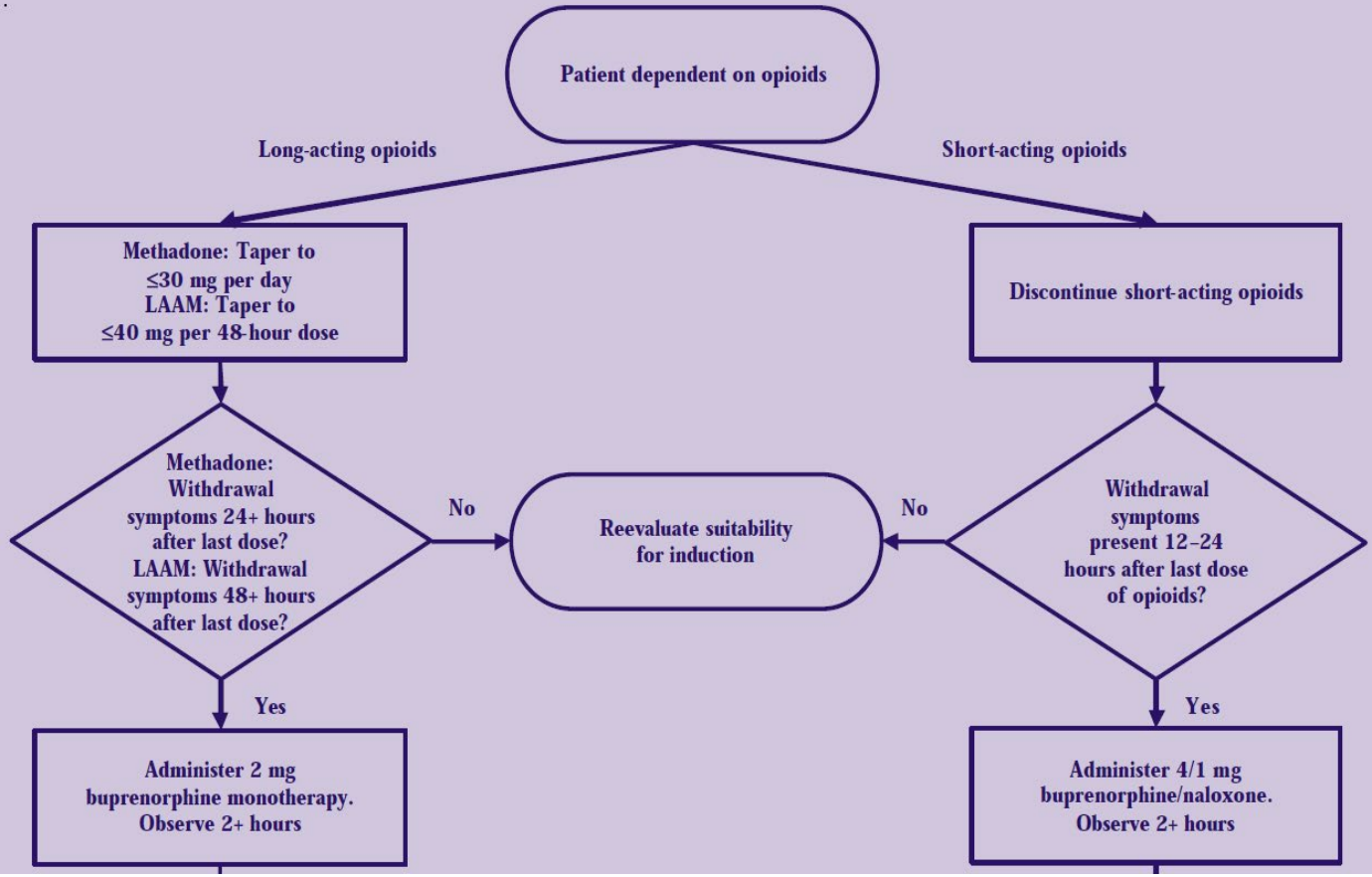
A Treatment Improvement Protocol

TIP 40

Center for Substance Abuse Treatment. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004.

Figure 4–1

Induction Days 1–2



TREATMENT IMPROVEMENT PROTOCOL

TIP 63

Induction

Patients who are currently physically dependent on opioids

Patients should begin buprenorphine when they are exhibiting clear signs of opioid withdrawal. Induction typically starts with a 2 mg to 4 mg dose of buprenorphine or a 2 mg/0.5 mg to 4 mg/1 mg dose of buprenorphine/naloxone.[329] Depending on the formulation used and whether a given patient has a dry mouth, the dose can take between 3 and 10 minutes to dissolve fully. After approximately 2 hours, an additional 2 mg to 4 mg dose of buprenorphine/naloxone can be given if there is continued withdrawal and lack of sedation.

Before initiating buprenorphine, carefully taper methadone to lower the risk of return to illicit opioid use during transition. Patients who take methadone for OUD should taper to 30 mg to 40 mg methadone per day and remain on that dose for at least 1 week before starting buprenorphine.[334] With patients' permission, OTPs can confirm the time and amount of patients' last methadone dose.

Do not start buprenorphine until the patient manifests signs of opioid withdrawal. At least 24 hours should pass between the last dose of methadone and the first dose of buprenorphine. Waiting 36 hours or more reduces risk of precipitated withdrawal. Lower doses of buprenorphine/naloxone are less likely to precipitate methadone withdrawal.[335] For example, once opioid withdrawal is verified, an initial dose of 2 mg/0.5 mg can be given. If patients continue to have unrelieved opioid withdrawal after the first 2 mg dose, administer another 2 mg/0.5 mg dose approximately every 2 hours as needed (holding for sedation). Induction should be conducted slowly; consider palliating unrelieved withdrawal with nonopioid therapies for the first few days of transition to buprenorphine. Be alert to any increase in withdrawal symptoms, as this may suggest precipitated withdrawal.

Substance Abuse and Mental Health Services Administration. *Medications for Opioid Use Disorder.* Treatment Improvement Protocol (TIP) Series 63. Publication No. PEP20-02-01-006. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2020.

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Why Don't These Always Work?

- Require a period of abstinence for an illness that is defined by loss of control
  - "Come back when you are in withdrawal"
- Long painful tapering protocols with high risk of relapse
- Fear of pain and withdrawal defeat even the best attempts
- Low motivation/external forces for treatment or transition

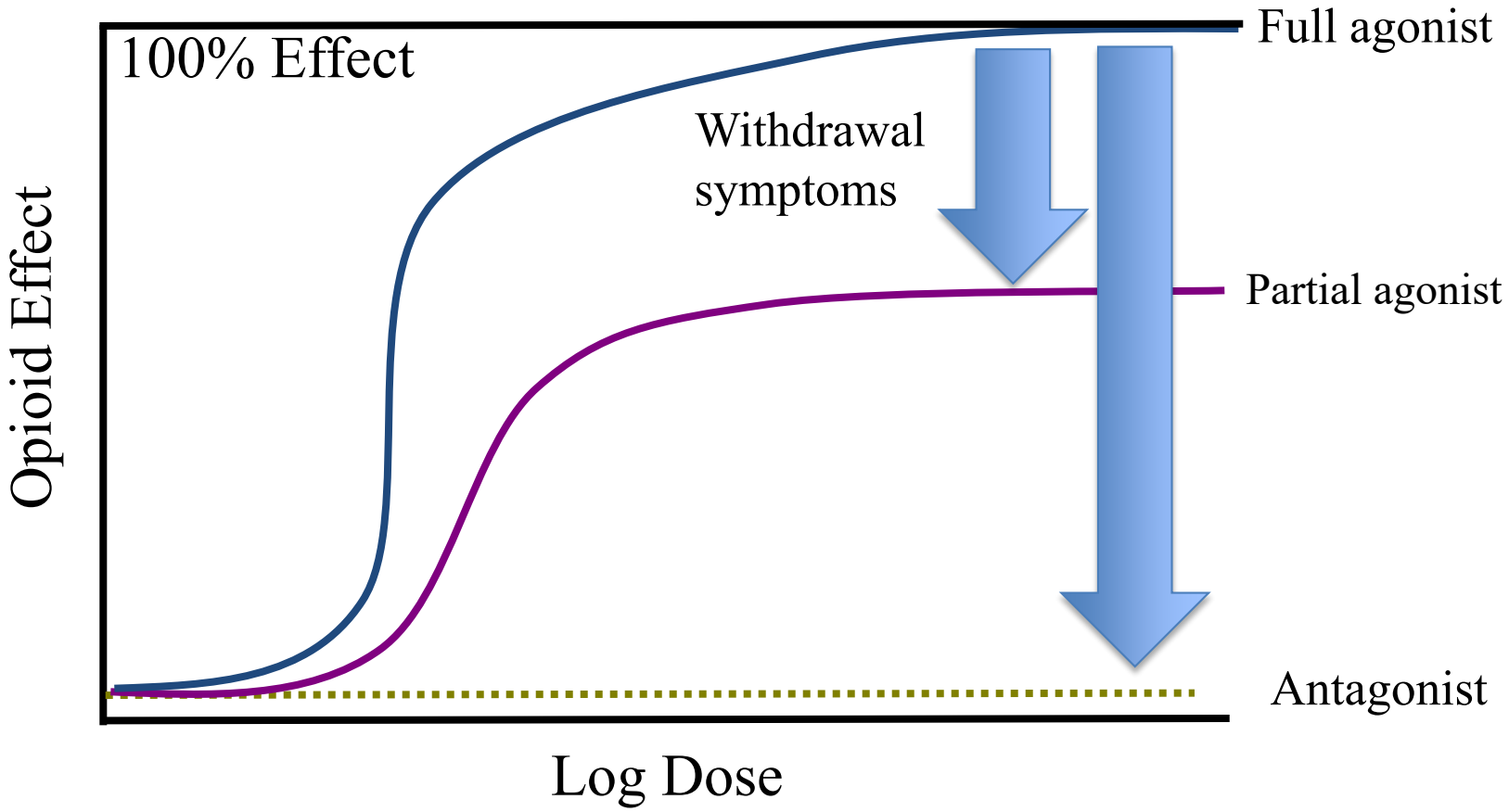
NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

The Patient Centered Approach

- Allow ongoing opioid use/minimize opioid free period
- Reduced withdrawal severity
- Prevent precipitated withdrawal

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

The Problem



NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

The Approach

- Give doses of buprenorphine below the threshold for precipitated withdrawal
- Slowly replace unbound MOR with buprenorphine
- Slowly displace full agonist from bound MOR
- Restore opioid tone with buprenorphine titration

Net outcome: no perceptible withdrawal

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Establishing the Dose Threshold

Methadone Maintenance (45-60mg)

- Buprenorphine 0.2mg IV
- Naloxone 0.1mg IV
- Buprenorphine 0.2mg IV Naloxone 0.1mg IV

N = 5

Mendelson J et al. Biol Psych 1997;41:1095-1101

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Establishing the Dose Threshold

Intervention	Bad Drug	Sickness
Buprenorphine	15	13
Buprenorphine/naloxone	73*	49*
Naloxone	64*	56*
Placebo	6	7

Mean VAS at peak, comparisons vs buprenorphine, * = $p < 0.05$

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

What about Repeated Doses

- 16 pts on MMT 100mg per day
- Phase 1
  - Dose finding for precipitated withdrawal
    - Established by Four at 4mg, Two at 8mg, One at 16mg, Three had none up to 32mg
- Phase 2
  - Dose in Phase 1 split and given 2 hours apart
    - Minimal precipitated withdrawal reported

Rosado et al. Drug Alcohol Depend 2007;90:261-269

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Why Does this Work?
Dose vs MOR

Dose (SL)	μ Receptor Occupancy
2 mg	27-47%
16 mg	80-92%
32 mg	89-98%

Greenwald et al. Neuropsychopharmacology 2003;28:2000-2009

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

What Have We Learned

- There is substantial variability in how patients tolerate and experience buprenorphine precipitated withdrawal
- Doses ≤ 0.5mg SL are unlikely to produce noticeable symptoms in MMT patients
- Repeated lower doses decreases reports of withdrawal

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Low Dose Transitions
“Microdosing”
“Microinductions”

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Bernese Method

Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method

Einleitung einer Substitutionsbehandlung mit Buprenorphin unter vorübergehender Überlappu Heroinkonsum: ein neuer Ansatz („Berner Methode")

Induction of a Buprenorphine Substitution Treatment with Temporary Overlap of Heroin Use: A New Approach ("Bernese Method")

Autor R. Hämmig

Institut Funktionsbereich Sucht, Universität und Poliklinik für Psychiatrie (UPD

Table 1 Buprenorphine dosing and use of street heroin in case 1

Day	Buprenorphine (sl)	Street heroin (sniffed)
1	0.2 mg	2.5 g
2	0.2 mg	2 g
3	0.8+2 mg	0.5 g
4	2+2.5 mg	1.5 g
5	2.5+2.5 mg	0.5 g
6	2.5+4 mg	0
7	4+4 mg	0
8	4+4 mg	0
9	8+4 mg	0

Abbreviation: sl, sublingual.

Robert Hammig, MD
University Psychiatric Services Bern
Bern, Switzerland

Suchttherapie 2010;11:129-132
Substance Abuse and Rehab 2016:7:99-105

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Sublingual Transitions

Citation	N	Agonist	Starting/target Dose	Duration
Hammig 2016	1 1	Heroin DAM/Methadone	0.2mg to 12mg 0.2mg to 24mg	9 days 28 days
Klaire 2019	1 1	Heroin/Hydromorphone OD/Hydromorphone	0.25mg q4h to 16mg 0.5mg q3h to 12mg	5 days 3 days
Vogel 2019	1	DAM	0.2mg to 48mg	111 days
Terasaki 2019	3	Methadone	0.5mg to 12mg	8 days
Rozylo 2020	1	Heroin	0.25mg to 12mg	7 days
Becker 2020	6	Analgesic morphine, oxycodone, methadone	0.5mg BID to 4mg TID	5 days
Brar 2020	7	Fentanyl/heroin, morphine, methadone	0.5mg to 16-32mg	8 days
Caulfield 2020	1	iOAT (hydromorphone/ morphine)	0.5mg to 16mg	24 days

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Sublingual Transitions (cont)

Citation	N	Agonist	Starting/target Dose	Duration
Hamata 2020	1	Fentanyl infusion 200mcg/min	0.25mg q3h to 12mg	4 days
Azar 2020	1	Illicit fentanyl	0.5mg q3h to 8mg day 3 then Bup-XR 300mg	4 days

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Other Route Transitions

Citation	N	Agonist	Starting/Target Dose	Duration
Hess 2011	11	Methadone	35 mcg/h TDS to 24mg SL	5 days
Cortina 2017	1	Methadone	20 mcg/h TDS to 24mg SL	4 days
De Aquino 2020	1	Methadone	5 mcg/h TDS x 3 day 0.5mg BID to 12mg	12 days
Weimer 2020	1	Morphine PCA	225 mcg buccal QD 225 mcg buccal BID 450 mcg BID 2mg SL BID	7 days
Thakrar 2021	1 1	Methadone Multiple oral	0.15 mg IV q6h to 12mg SL BID 0.15mg IV q6h to 8mg SL BID	5 days 5 days

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Systematic Review

- 20 studies and 57 patients
- 16 North America, 4 Europe
- 15 studies published in 2019-2020

Moe et al. Addictive Behaviors 2021;114:106740

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Systematic Review

- No precipitated withdrawal reported in 54/57 patients
- Studies without precipitated withdrawal
  - Median starting dose 0.5mg, duration 6 days, maintenance dose 16mg, rate of dose change to 8mg was 1.36mg/day
- All 3 with precipitated withdrawal were methadone transitions

Moe et al. Addictive Behaviors 2021;114:106740

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

University of BC Vancouver Outpatient Protocol

Outpatient Microdosing Induction Schedule

- Day 1 0.5mg once a day
- Day 2 0.5mg twice a day
- Day 3 1mg twice a day
- Day 4 2mg twice a day
- Day 5 3mg twice a day
- Day 6 4mg twice a day
- Day 7 12mg (stop other opioids)

Randhawa et al. CMAJ 2020;192:E73

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Patient Selection

- Fear of withdrawal
- Past failed induction
- Unable to stop using
- High level of physical dependence
- Transition from long-acting lipophilic drugs (methadone, fentanyl)

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Take Home Points

- Initial doses should be ≤ 0.5 mg SL or equivalent
- Continue full agonist until patient achieves at least 8mg of SL*
- Choose a convenient available formulation and dosing schedule
- Target 8mg by day 7 (KEEP GOING TO 16mg!)

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Getting to a low dose*

Sublingual	Analgesic** Buccal	IV/IM**	Transdermal**
0.5 mg	225 mcg	0.15 mg	15 mcg/hr-20 mcg/hr
1 mg	450 mcg	0.3 mg	(>> 20mcg/hr switch to SL)
2 mg	900 mcg	0.6 mg	(>>20mcg/hr switch to SL)

*All doses are approximations based on available formulation, only to be used for microdosing until SL doses are achieved (SL *F~29%*, Buccal *F= 46-65%, TD F~40%, IV/IM F ~ 100%)*

** Not indicated for addiction. Only for use inpatient or for chronic pain

Weimer et al. J Addict Med. Epub ahead of print
Thakrar et al. J Addict Med. Epub ahead of print

NATIONAL CLINICIAN CONSULTATION CENTER
Translating science into care

Thank you! For more information, please visit nccc.ucsf.edu

Substance Use Warmline 855-300-3595
Substance use evaluation and management

Perinatal HIV Hotline 888-448-8765
Pregnant women with HIV or at-risk for HIV & their infants

HIV/AIDS Warmline 800-933-3413
HIV testing, ARV decisions, complications, and co-morbidities

PrEPline 855-HIV-PrEP
Pre-exposure prophylaxis for persons at risk for HIV

Hepatitis C Warmline 844-HEP-INFO 844-437-4636
HCV testing, staging, monitoring, treatment

PEPline 888-448-4911
Occupational & non-occupational exposure management