Buprenorphine Dose Limits: What is the Evidence?

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ASAM 53rd Annual Conference, April 1, 2022, Hollywood, Florida

Affiliation and Disclosure Information

Buprenorphine Dose Limits: What is the Evidence?

Friday, April 1, 10:30-11:30 AM

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Psychiatric and Addiction Nurse Practitioner, Discover Recovery, Long Beach WA

- No Financial Disclosures
- Will discuss off-label use
- May mention brand names in discussion

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Buprenorphine Dose Limits: What is the Evidence?

Friday, April 1, 10:30-11:30 AM

Dave Cundiff, MD, MPH, FASAM

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Buprenorphine Dose Limits: What is the Evidence?

Friday, April 1, 10:30-11:30 AM

Lucinda A. Grande, MD

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Board Member, Washington Society of Addiction Medicine

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Buprenorphine Dose Limits: What is the Evidence?

Friday, April 1, 10:30-11:30 AM

Tricia E. Wright, MD, MS, FACOG, DFASAM

- Professor of Obstetrics, Gynecology, and Reproductive Sciences, University of California at San Francisco
- Royalties from book: "Opioid Use Disorders in Pregnancy," Cambridge Univ. Press, 2018
- Consulting income, McKesson, regarding neonatal withdrawal.
- Will discuss off-label use
- May mention brand names

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Learning Objectives

Buprenorphine Dose Limits: What is the Evidence?

Attendees will be able to:

- Discuss history and status of buprenorphine dose limits
- Discuss evidence for improved outcomes at higher buprenorphine doses
- Cite criteria for determining buprenorphine dose adequacy
- Identify special considerations for pregnant people taking buprenorphine for opioid use disorders

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- Michael M. Miller, MD, DFASAM
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- Olympia Bupe Clinic at Capital Recovery Center
- Our patients!

Issues With Dose Limits

- Prior authorizations sometimes required for doses higher than 16/4 mg or 24/6 mg per day
- Pharmacy calls: Insurer will not pay for more than 2 of any film dose (may have 8x2=16 + 12 + 4 to get dose of 32 mg)
- Many Buprenorphine prescribers refuse to prescribe doses higher than 16 mg per day
- Limits referral options for patients discharging from residential treatment, especially those in rural areas!

Case Study: 36-year-old Joe

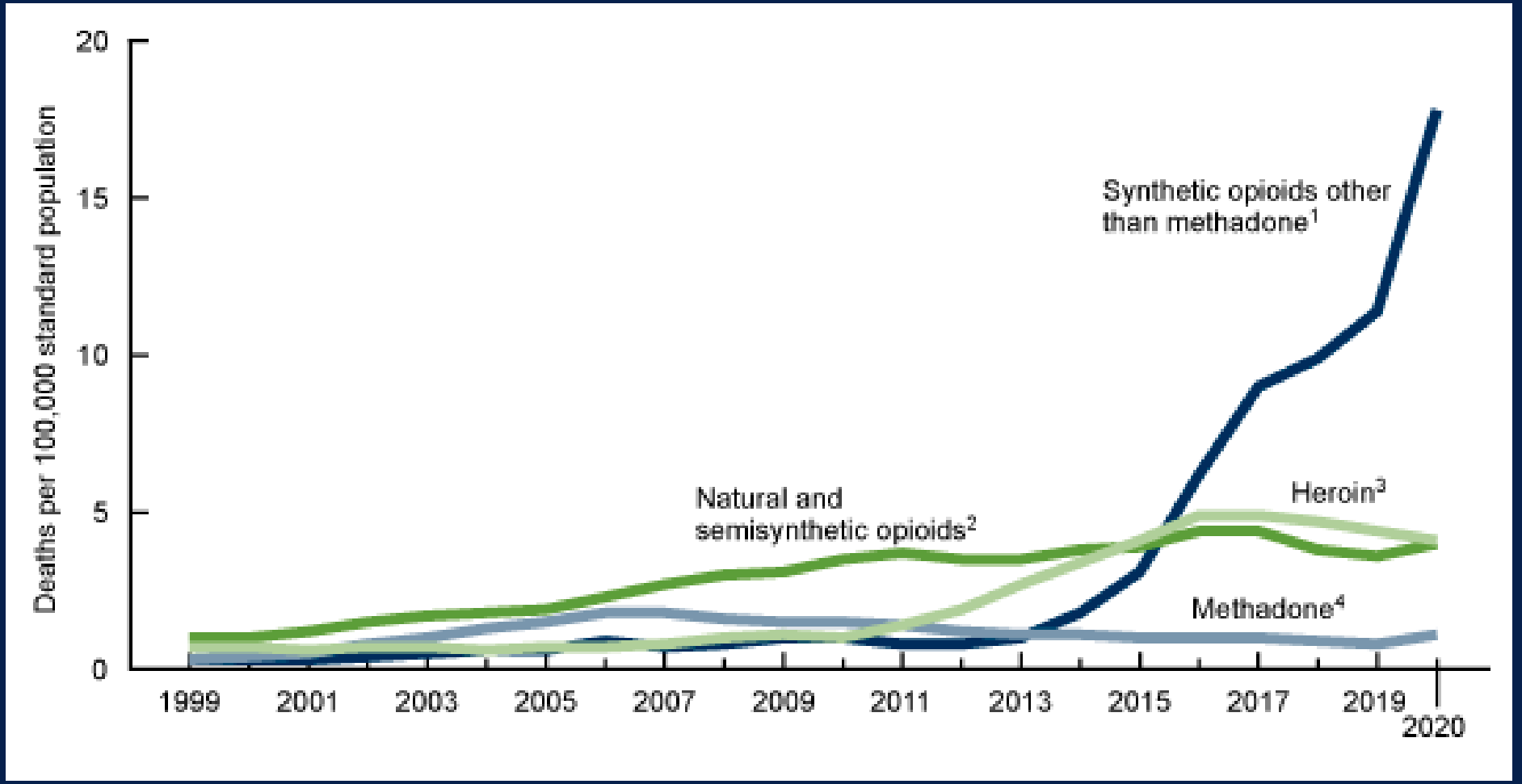
- 20 years IVDU: heroin
- Did not complete high school
- Intermittent laborer in local industry
- And then: Buprenorphine/Naloxone
  - Dose titrated upward from 8/2 Q 12 hours
  - At 32/8 able to work intermittently but always felt sick
  - At 36/9 worked full time; not sick; primary wage earner

Case Study: 28-year-old Jackie

- SUD counselor doing intake: “You need to see her NOW!”
- Cellulitis bilateral forearms, rural ED visit yesterday
- Went to different ED on my insistence
- Airlifted to population center 2+ hours away
- 4+ weeks of IV antibiotics; osteomyelitis in knee
- Phoned me in panic: Resident MDs tell me to get off bupe!
- Outcome: stable on 16/4 Q 12 hours; gait resolved in 6 mo
- Until talked about bupe/nx at NA meeting…

Why should we care about buprenorphine dose?

- Other medication options often not realistically available
- Providing effective treatment is a matter of life and death
- Fentanyl 2013 to ?



CDC, NCHS Data Brief No. 394, December 2020

Measures of OUD Treatment Success

- Death rates
- Rates of infection and other complications
- Treatment retention
- Visit reliability (“on-time visits”)
- Abstinence from non-prescribed opioids
- Abstinence from other illicit drugs
- Short-term clinical goals or “therapeutic targets”
- Long-term clinical goals or “life goals”

Arguments for and Against Dose Limits

FOR:

- FDA package insert
- Receptor occupancy interpretations (2000-2009)
- Concerns about cost
- Concerns about diversion
- "Expert opinion"

AGAINST:

- ASAM guidelines
- Individual variability
- Receptor occupancy data (2010-present)
- Improved treatment retention
- Reduced illicit drug Use
- No analgesic ceiling effect
- Kappa receptor role

FDA Buprenorphine-Naloxone Package Insert

- Dosing recommendations are based on data from trials before 2002 at doses equivalent to 6-24 mg/day.
- The recommended daily dose for maintenance is 16/4 mg.
- The maintenance dose “is generally in the range of 4/1 mg buprenorphine/naloxone to 24/6 mg buprenorphine/naloxone per day depending on the individual patient. Dosages higher than this have not been demonstrated to provide any clinical advantage.”

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022410s000lbl.pdf

ASAM 2020 Guidelines: Treatment Goals

1. Suppress opioid withdrawal
2. Block the effects of illicit opioids
3. Reduce opioid craving and stop or reduce the use of illicit opioids
4. Promote and facilitate patient engagement in recovery-oriented activities including psychosocial intervention

ASAM National Practice Guideline for the Treatment of Opioid Use Disorder, 2020 Focused Update

Is my patient meeting ASAM treatment goals?

1. Any cravings, any time of day or night?
2. Any withdrawal symptoms, any time of day or night?
3. Any night sweats?
4. Any "using dreams"?
5. Any use of any opioid that isn't prescribed for you and known to me?

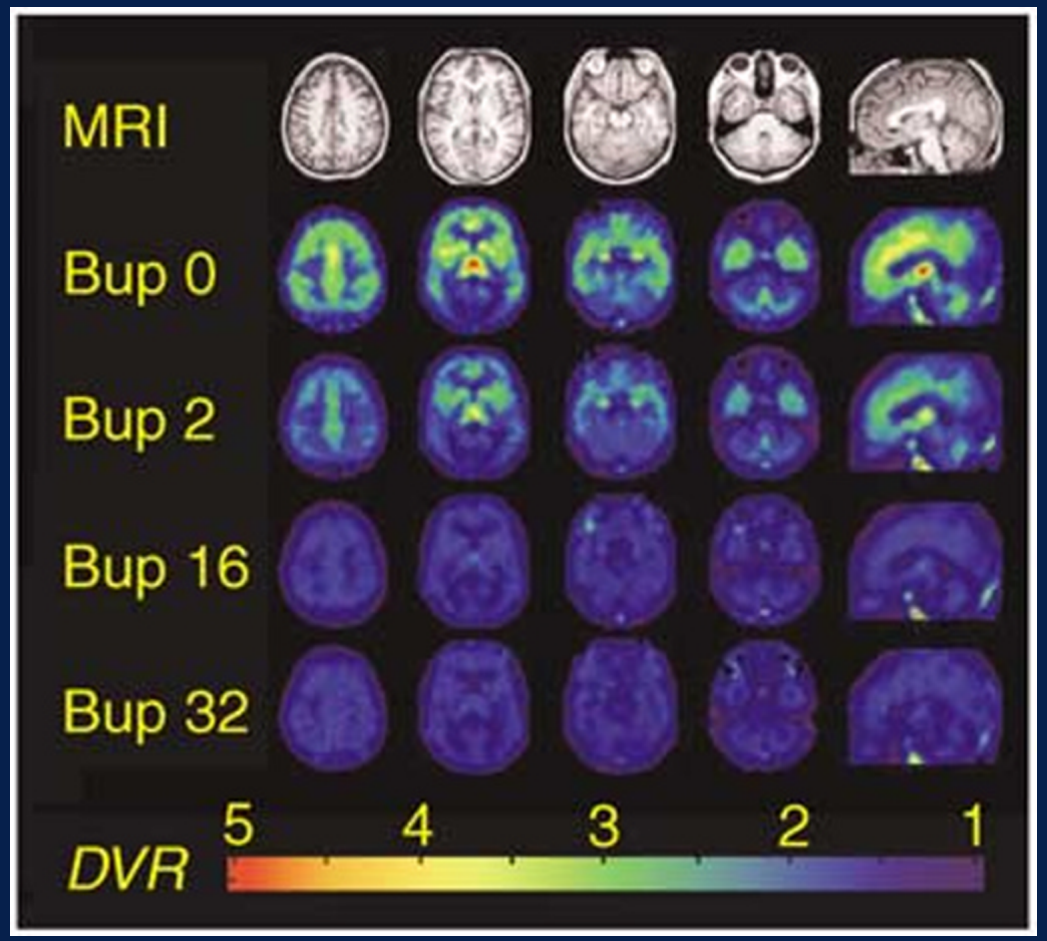
- These questions address short-term, buprenorphine-specific issues
- Additional targets depend on relationships and mutual goals
- Test urine/saliva etc. when clinically appropriate/required

Method of Dave Cundiff MD MPH. Your mileage may vary.

Buprenorphine Dose Limits: What Is The Evidence?

Dose-Response Observations in Physiology & Pharmacology Studies

Mu Receptor Occupancy (2003)



- Five heroin-dependent volunteers [no fentanyl!]
- Mu receptor occupancy (relative to placebo):
  - 2 mg/day: 27-47%
  - 16 mg/day: 80-92%
  - 32 mg/day: 89-98%

Greenwald et al, 2003

Mu Receptor Occupancy Conclusions

- Buprenorphine dose-dependently increased mu receptor occupancy
- High receptor occupancy correlated with improved therapeutic effect: decreased opioid withdrawal and reward symptoms.
- Near-maximal effect occurred at 32 mg/day

Greenwald et al, 2003

Mu Receptor Occupancy Review (2014)

- Withdrawal suppression requires >50% receptor occupancy (4 mg/day)
- Blockade of subjective opioid effects requires >80% occupancy (16 mg/day)
- Blockade of subjective effects of high opioid doses may require >90% occupancy (up to 32 mg/day)

Greenwald et al, 2014

Mu Receptor Occupancy Review (2014)

We conclude that fixed, arbitrary limits on buprenorphine doses in clinical care or limits on reimbursement for this care are unwarranted.

Greenwald et al, 2014

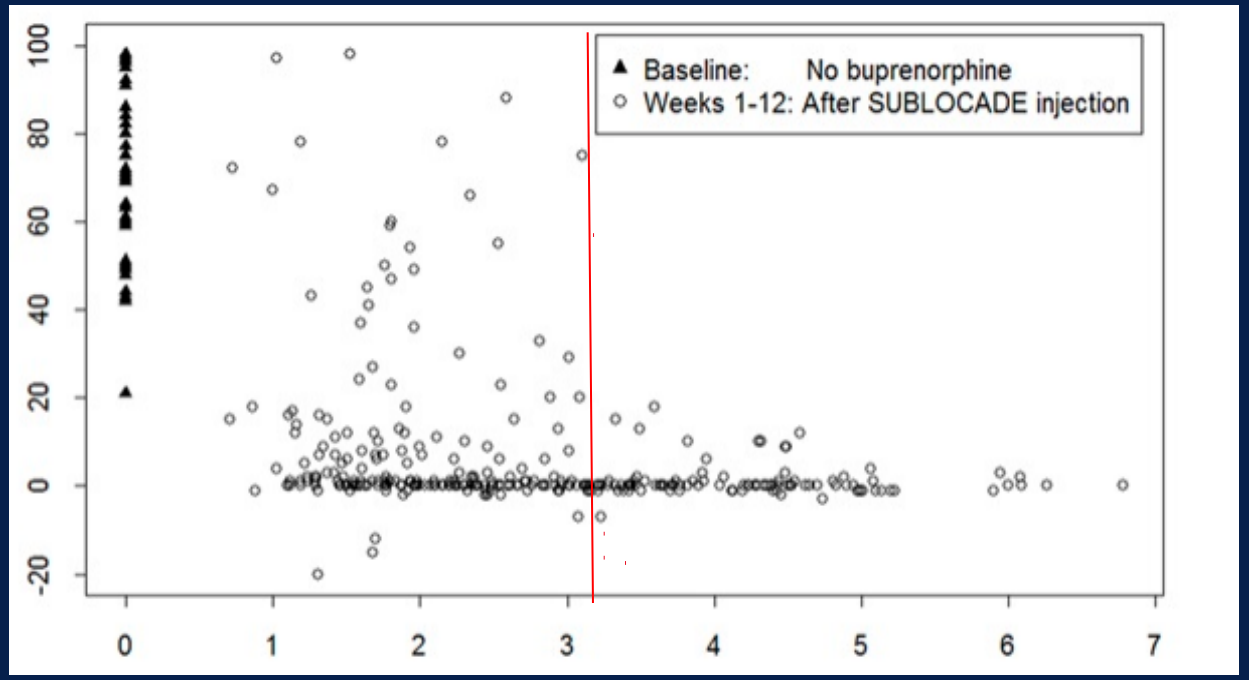
Inter-Individual Variability

"Inter-person variability in transmucosal buprenorphine pharmacokinetics (PKs) is high, with estimates of bioavailability (the amount of parent drug to reach systemic circulation) commonly ranging by 3-fold or more after both acute and chronic administration (Kuhlman et al. 1996, Strain et al. 2004, Chawarski et al. 2005, Compton et al. 2007). These differences may be partly due to individual variability in absorption."

Coe, 2019

Opioid reward suppression >24 mg/D

Drug Liking Score (VAS)



8 16 24 32 (mg/day)

Exposure:

High-dose hydromorphone (18 mg IM)

Plasma Concentration (avg ng/mL)

Equivalent SL dose avg

FDA Subcutaneous buprenorphine (as Sublocade) package insert

Role of Kappa Receptors

- Kappa receptor activation mediates dysphoria, anhedonia and aversion in animal models
- May contribute to negative affect in addiction
- Buprenorphine produces a dose-dependent kappa receptor antagonist effect **up to 1 mg/kg in rodents**

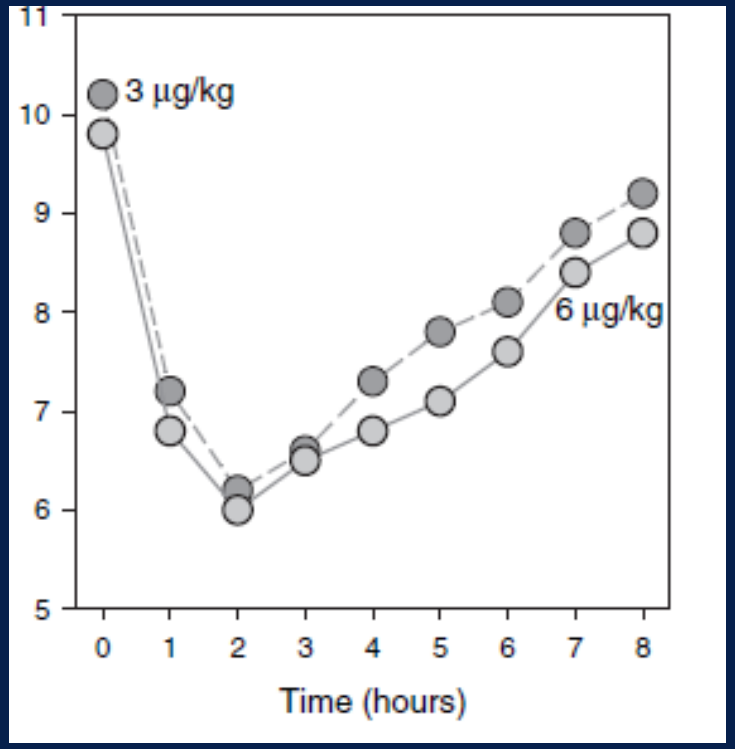
Negus, 1989

Higher Serum Levels: Are There Ceiling Effects?

YES

for respiratory depression

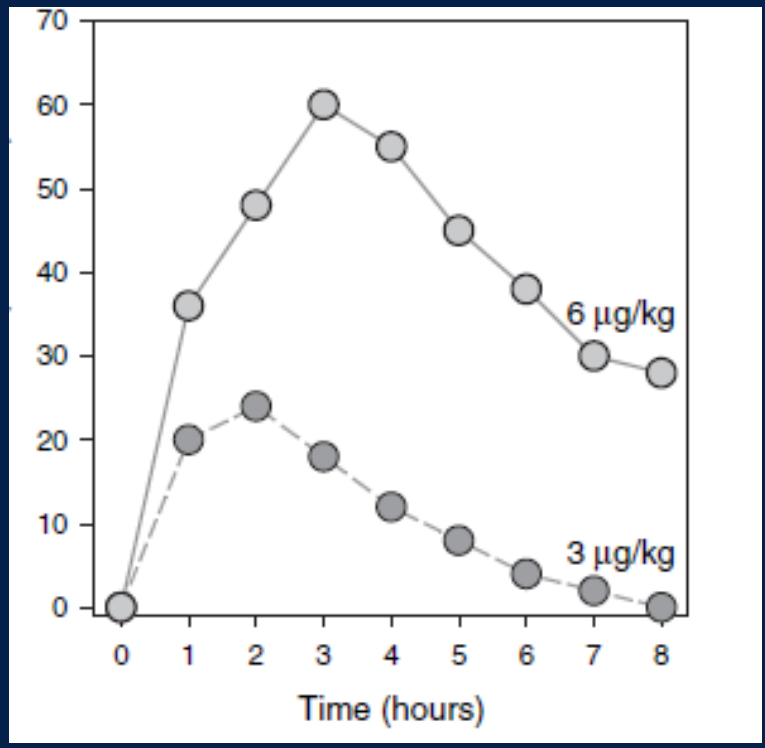
Ventilation (L/min)



… but NOT

for analgesia

Pain Tolerance



Dahan, 2006

Is There Any Ceiling Effect For Pain?

- Primary data above from Dahan, 2006 (0.2-0.4 mg IV per 70 kg)
- Lots of “expert opinion” says there’s NO ceiling effect for pain
- How high do the experimental data go? No PROVEN ceiling
- Four loci of receptor activity (Gudin, 2020):
  - Mu receptor partial agonism (analgesia, mood)
  - Delta receptor antagonism (limits GI & respiratory depression)
  - Kappa receptor antagonist (limits depression, dysphoria, suicidal tendencies)
  - ORL-1 agonist (inc. spinal analgesia, dec. supraspinal analgesia, dec. reward, dec. tolerance)

Dahan, 2006; Davis, 2012; Butler, 2013; Raffa, 2014; Khanna, 2015; Coe, 2019; Gudin, 2020

Higher Doses Work Better: Evidence From Clinical Research

Practical Measures of Treatment Success

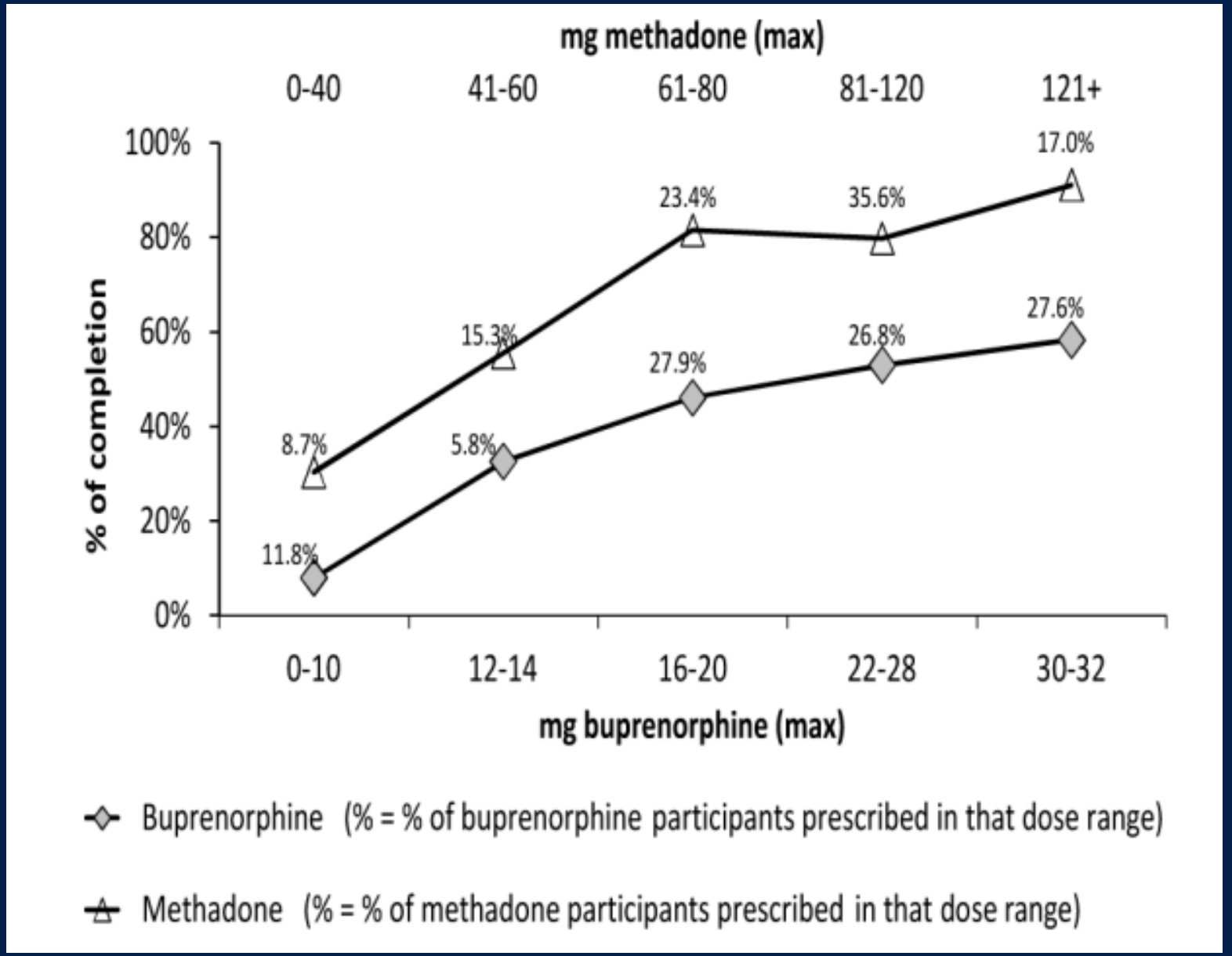
- Improved treatment retention
- Reduced illicit drug use
- Patient perception of adequate dose
- Reduce complications
- Reduced pain
- Improved visit reliability

Treatment Retention

- Open-label RCT, N=1,267 at 9 OTPs in the U.S.
- Buprenorphine (n=738) vs. methadone (n=529)
- Daily observed dosing for both groups

Hser et al., 2014

Treatment Retention Results



Hser et al, 2014

Treatment Retention: Conclusions

- Linear relationship between dose and treatment completion rate.
- 32 mg/day or even higher may be needed for optimal benefit for some patients.

Hser et al., 2014

Meta-analysis: Retention & Drug Use

- 21 RCTs, international
- 2,703 participants

- High dose group (16-32 mg/day):
  - **Better retention in treatment than low dose group**
  - **Fewer urine tests positive for opiates and cocaine**

Fareed et al., 2012

Patient Perception #1: Parameters

- 48 outpatients, Sweden
- Heroin dependence, average duration 9.4 years
- Bupe/nx dose increased as needed up to 32 mg/day, then switched to methadone if needed

Kakko et al., 2007

Patient Perception #1: Results

- Out of 48 patients:
  - 17 remained on buprenorphine
    - Mean final dose 29.6 mg/day
  - 20 switched to methadone
  - No difference between groups in retention or urine test results
  - 11 dropouts

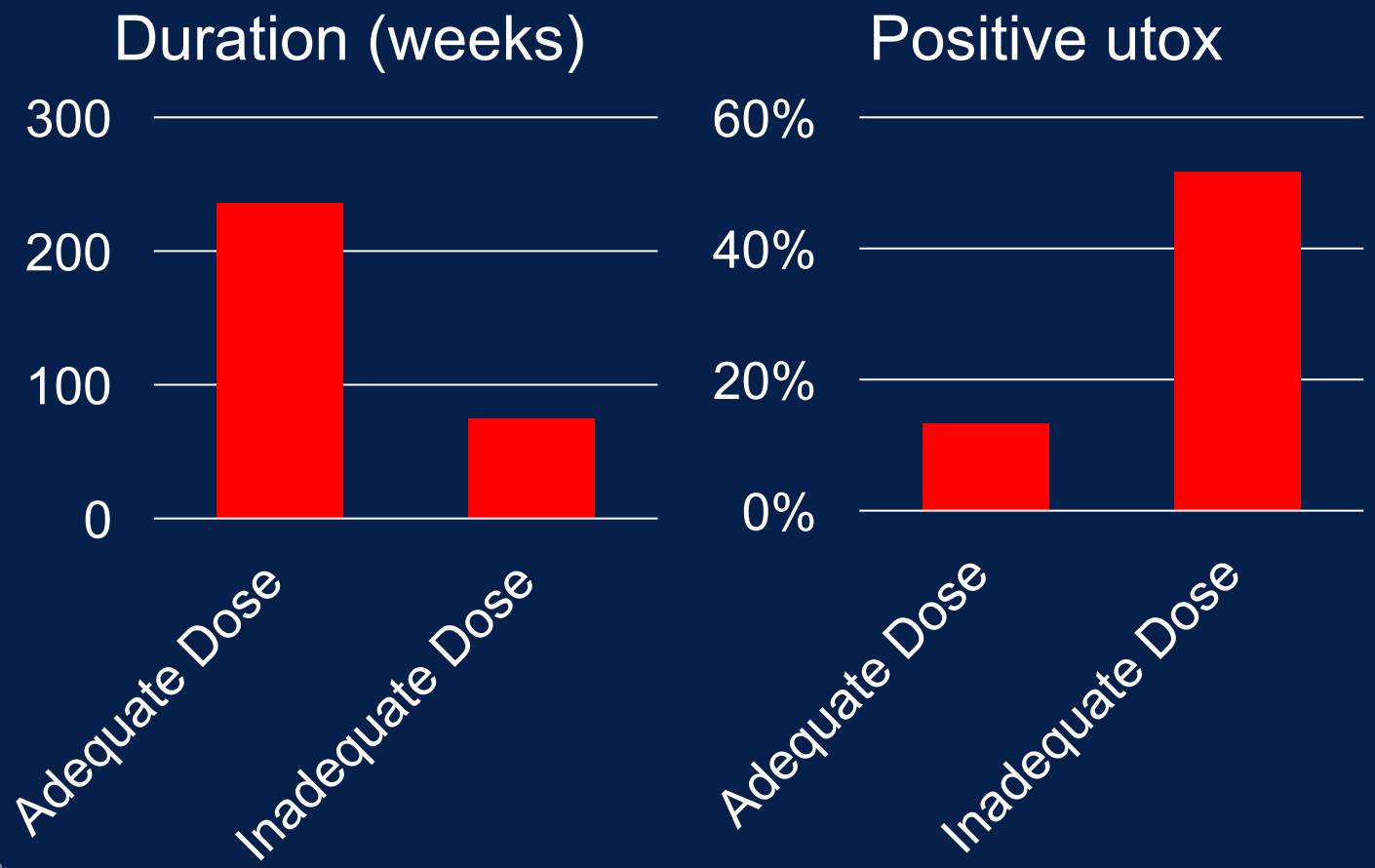
Kakko et al., 2007

Patient Perception #2: Parameters

- Addiction Psychiatry Outpatient Clinic, Finland
- Observational study
  - Methadone 65 mg/day (avg) (n=52)
  - Bupe-nx 15 mg/day (avg) (n=8)
- Inadequate Dose (n=39) vs. Adequate Dose (n=21), by patient self-report

Heikman et al., 2017

Patient Perception #2: Results



Heikman et al., 2017

Adequate Dose:

- Improved retention
- Reduced illicit drug use

Patient Perception: Chronic Pain

- Retrospective study, 35 patients with chronic pain on high-dose opioids (>200 MME)
- Transitioned to buprenorphine SL, allowed up to 32 mg/day
- Average pain score dropped from 7.2 to 3.5
- Average buprenorphine dose: 28.1 ± 5.9 mg.

Daitch et al., 2014

Reduced Complications (Hepatitis C)

- 513 HCV-negative people who inject, Canada
- Exposure 2.8 years (average)
- Comparisons:
  - Medication Dose (high vs. low vs. none)
    - Buprenorphine high dose: >=16 mg/day
    - Methadone high dose: >=60 mg/day
  - Patient perception:
    - Adequate vs. inadequate, by self-report

Artenie, 2019

Reduced Complications (Hepatitis C)

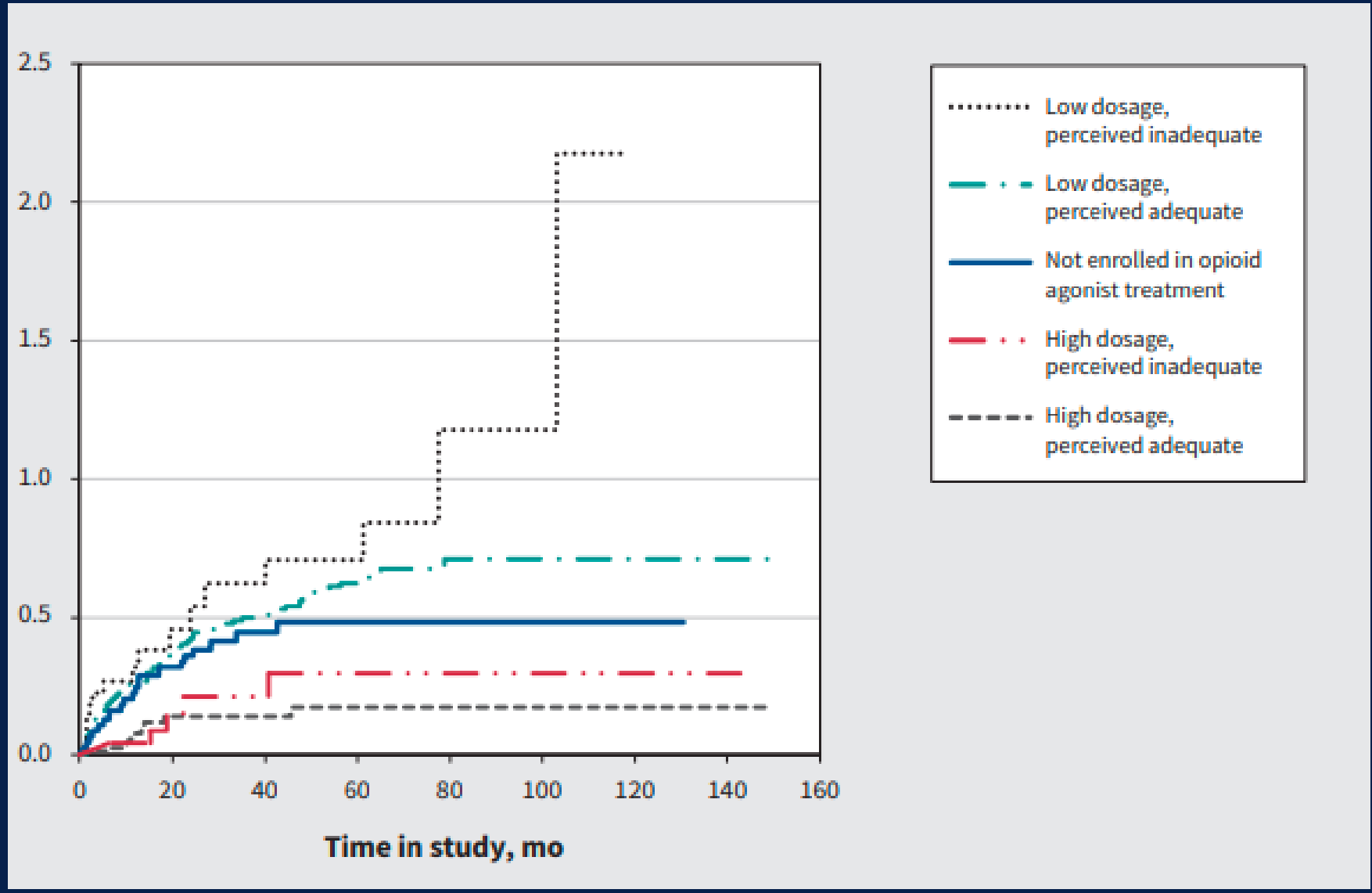
Hazard Ratio

Highest Risk:

Low dose, Inadequate

Lowest risk:

High dose, Adequate



Artenie, 2019

High Doses at a Low Threshold Clinic

- Olympia Bupe Clinic (OBC), Olympia Washington
- >1500 patients treated
- Walk-in only, no cost, medication dispensed on-site
- Team-based care, peer recovery coaches, nurse care manager
- Buprenorphine dosing to clinical effect

OBC, unpublished data

Quality Improvement Project

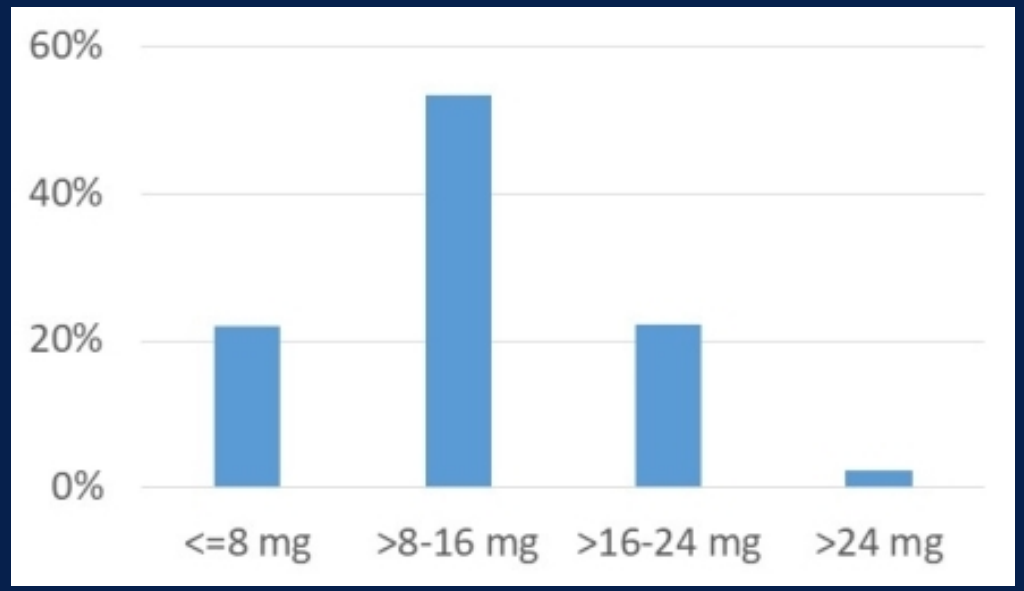
- Hypothesis: In this population, engagement consistency increases with dose up to 32 mg/day
- Data: Prescription Monitoring Program (2018-2021), Intake Database
- Measure of consistent engagement: on-time visits (+/- 1 day)
- Comparison: Prescriptions by OBC vs. non-OBC prescribers for the same patients

OBC, unpublished data

Distribution of Dose Ranges

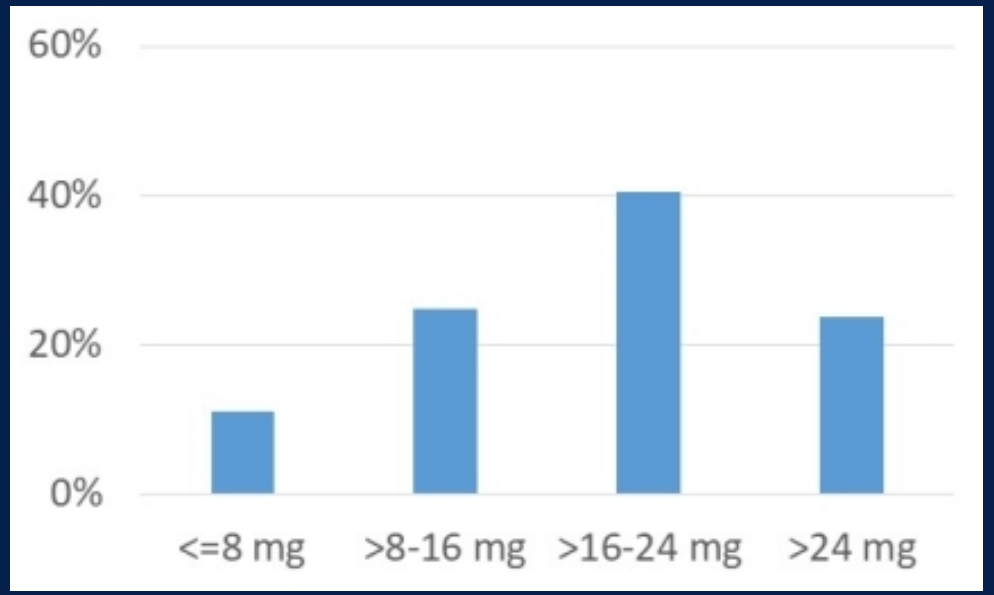
% of Rxs

Non-OBC Prescribers



2241 Rxs, 127 patients

OBC Prescribers

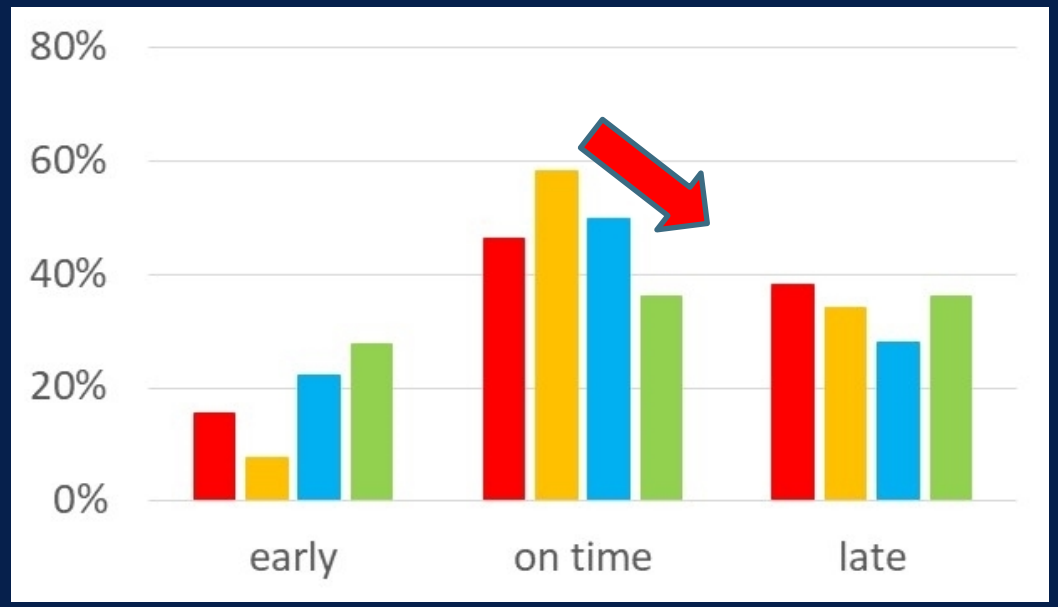


3093 Rxs, 242 patients

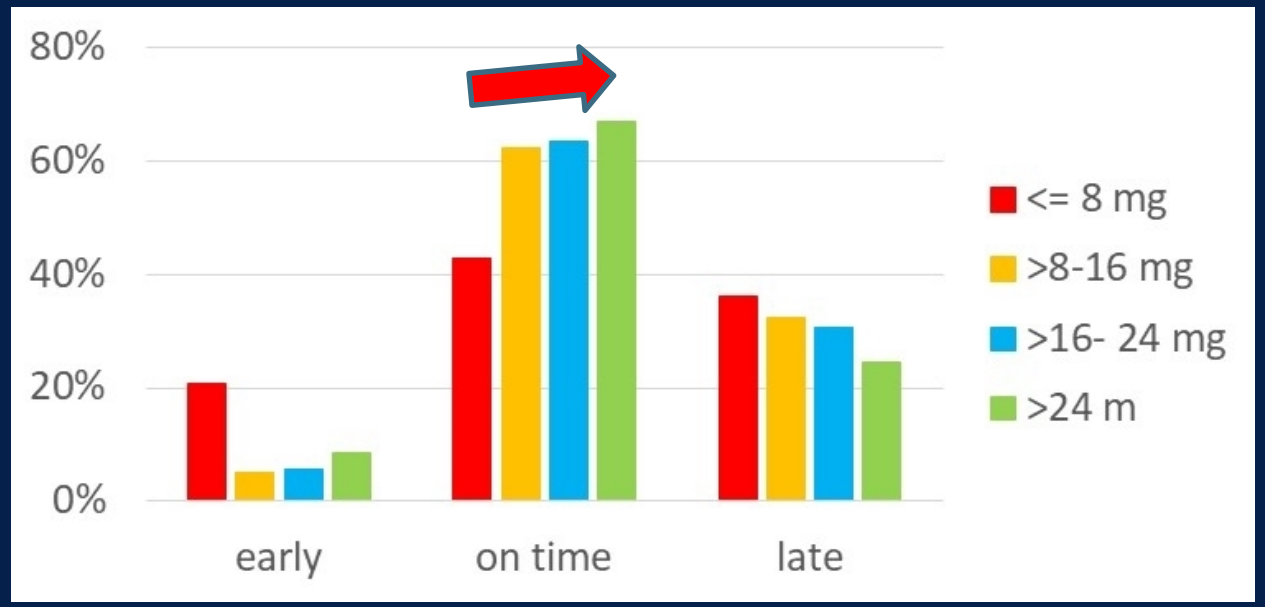
OBC, unpublished data

Timeliness of Follow-up Visits

Non-OBC Prescribers



OBC Prescribers



OBC on-time performance better overall
OBC on-time performance improves at higher doses
Why the difference?

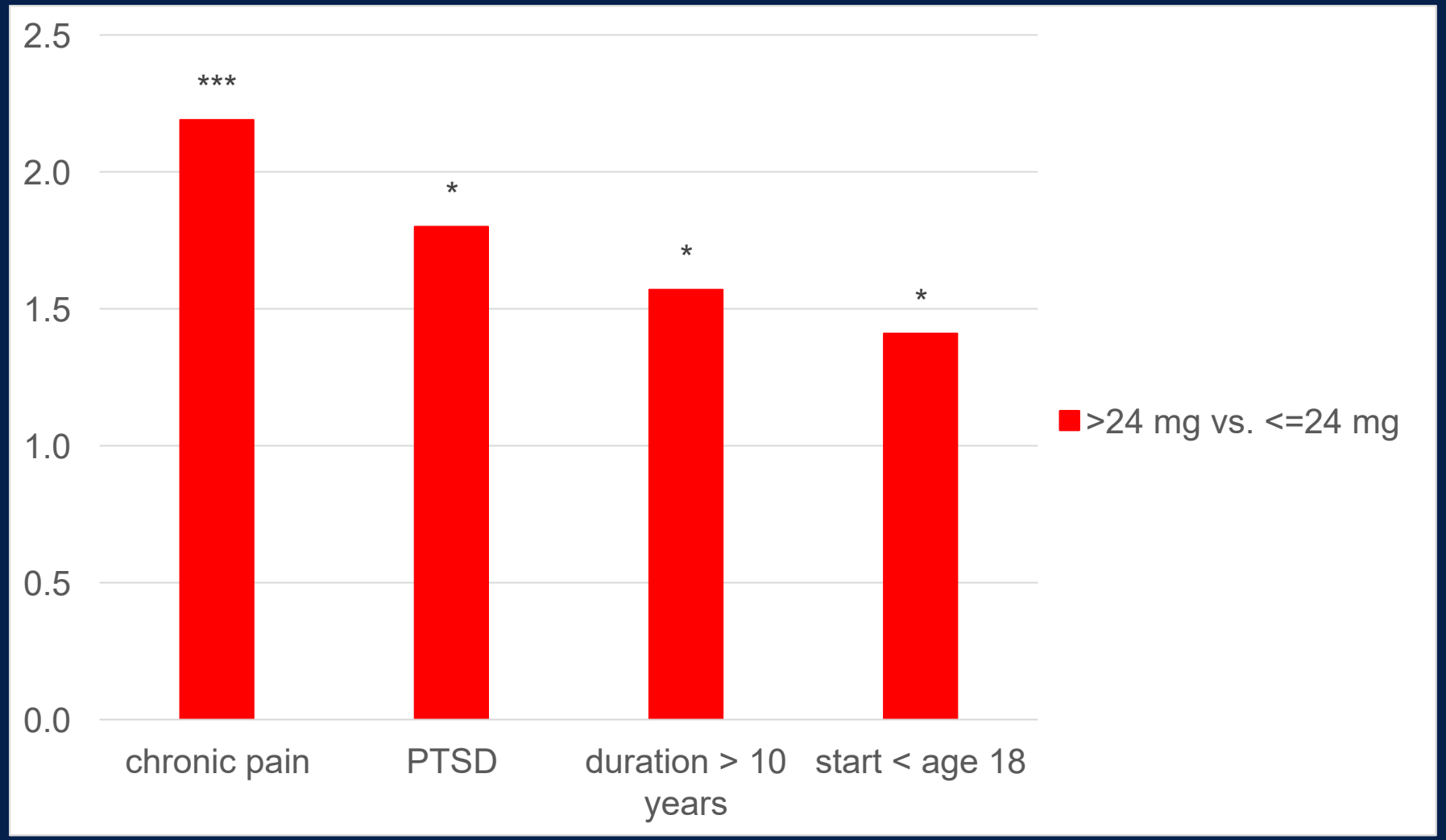
OBC, unpublished data

Relationship of Dose With Chronic Pain, PTSD & Opioid Tolerance

Relative Risk

*** p =0.0004

* p < 0.05



OBC, unpublished data

Buprenorphine dosing in pregnancy: Why 8 mg BID doesn't cut it.

Case Example

- 27 y/o pregnant female at 10 weeks gestation
- On buprenorphine 16 mg/day
- Reports increased withdrawal symptoms and cravings
- At 16 weeks, dose increased to 24 mg/day
- At 24 weeks, dose increased to 32 mg/day
- At 32 weeks, requests further increase

Case Example

- Is she diverting?
- What are the effects of pregnancy on withdrawal symptoms?
- What are the effects of buprenorphine dose on baby?

Review of Pregnancy Physiology

Table 2

Summary of gestational age associated physiological parameters incorporated into SimCyp healthy population

	Nonpregnant Female	1st trimester (≤12 gestation weeks)	2nd trimester (13–28 gestation weeks)	3rd trimester (≥ 29 gestation weeks)
Physiological and metabolic change				
Cardiac output [31]	100%	Increased 35%	Increased 40%	Increased 50%
Plasma volume [31]	100%	Increased 12.5%	Increased 32.5%	Increased 50%
Red cell volume [31]	100%	Remain same	Remain same	Increased 30%
Haematocrit [32]	100%	Decreased 3%	Decreased 4%	Decreased 5%
Albumin [32]	100%	Decrease 27%	Decrease 27%	Decrease 27%
Activity of CYP3A4 [33]	100%	Increased 35%	Increased 35%	Increased 38%
Parameter used in model				
Cardiac output scalar	1	1.35	1.4	1.5
Plasma volume scalar	1	1.125	1.325	1.50
Red blood cell volume scalar	1	1	1	1.3
Haematocrit (%)	38	35	34	33
Albumin (g l^{-1})	49	36	36	36
CYP3A4 (pmol mg $protein^{-1}$)	137	185	185	189

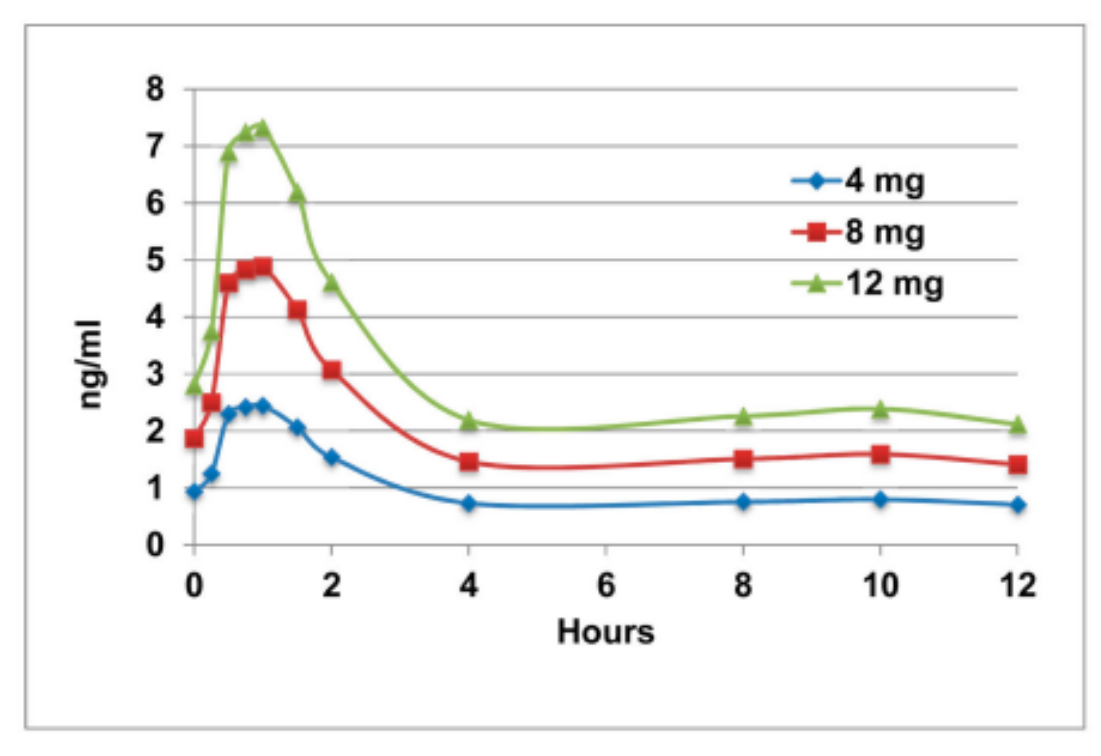
Zhang et al 2018

Pregnant Women Need Higher Doses

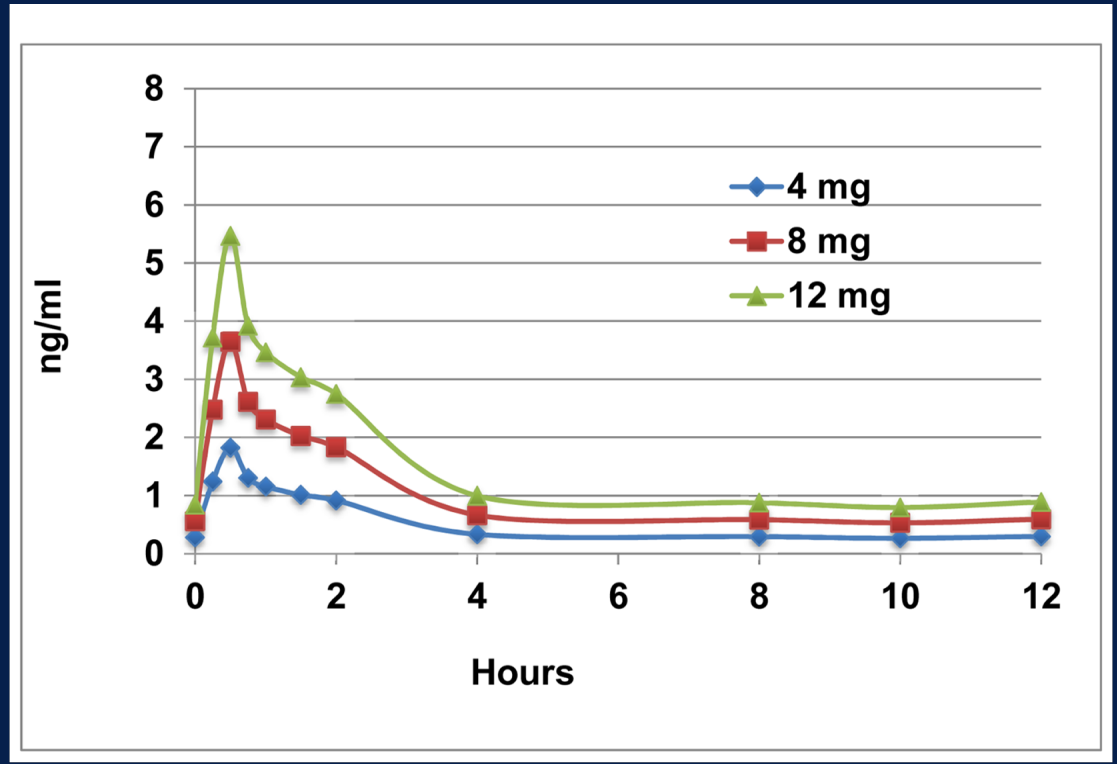
- Increased volume of distribution
- Increased clearance
- Decreased salivary pH which may decrease absorption
- Decreased time to peak concentration
- Decreased time to trough
  - Cause of nausea?
  - Relieved by split dosing?
- Plasma concentrations ~50% lower

Bastian et al 2017

Decreased Serum Concentration
Decreased Time to Trough



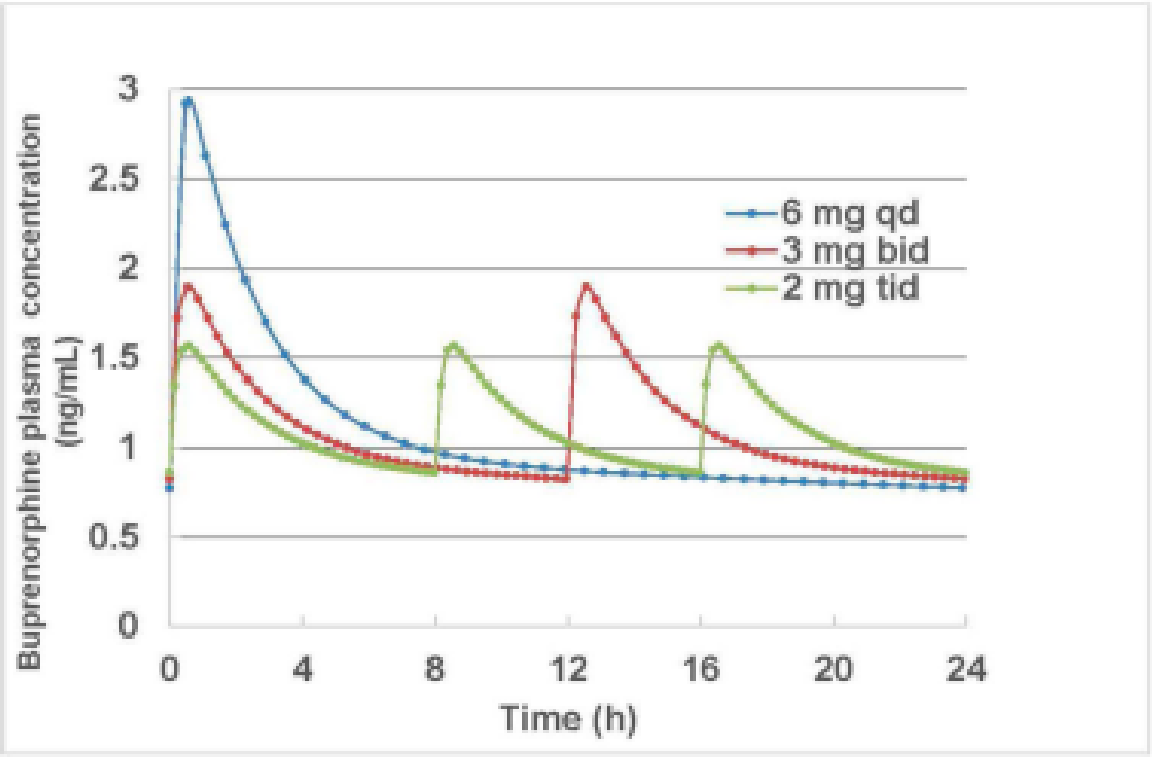
Physiologic Baseline (Postpartum)



2rd Trimester

Caritis et al 2017

Pregnant Women Need More Frequent Dosing



1 ng/mL = threshold of withdrawal symptoms

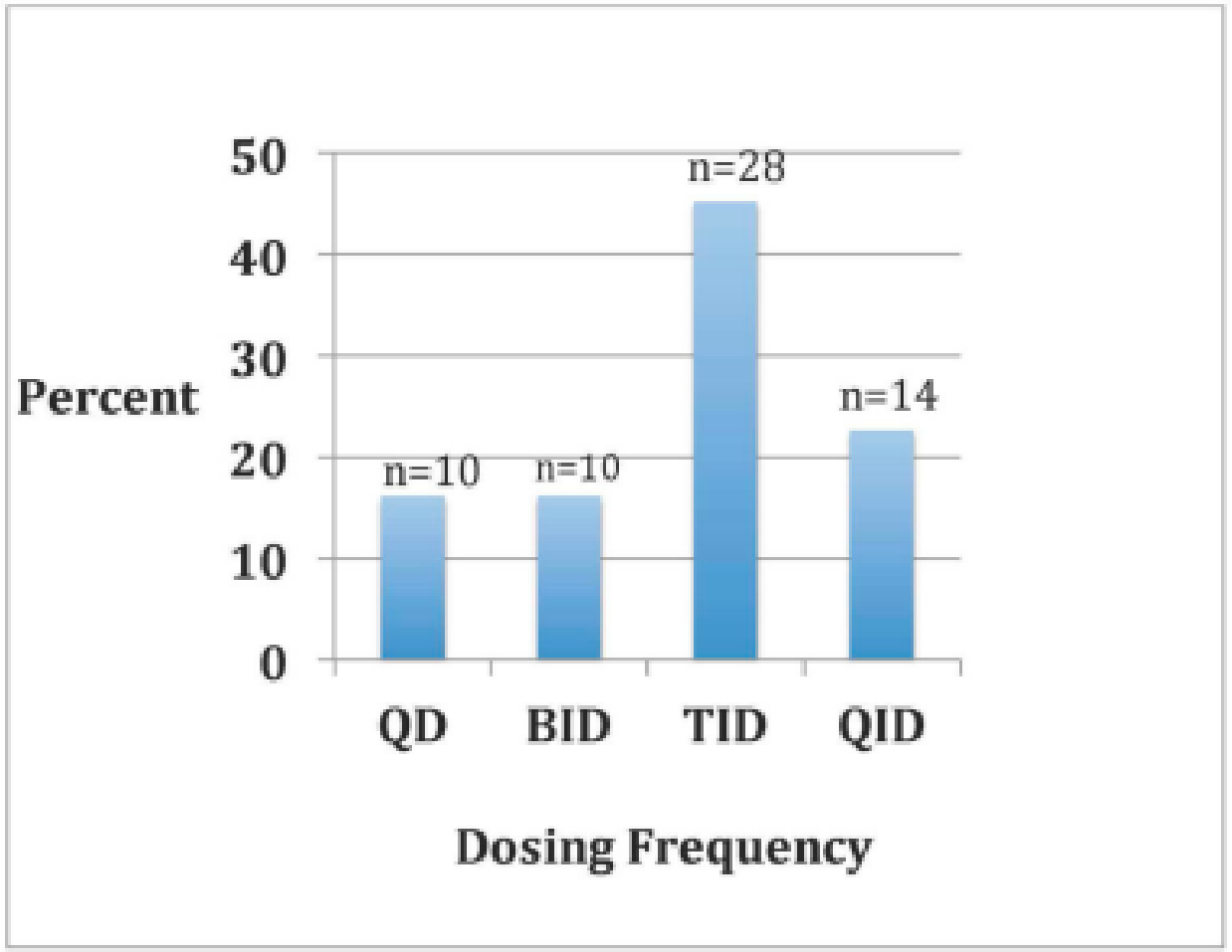
More frequent dosing results in less total time below 1 ng/mL

Dose Frequency	Time below 1 ng/mL
Once daily:	16.3h
BID:	14.4h
TID:	10.8h

Computer model of serum concentration at different dosing frequencies

Caritis et al 2017

Self-determined Dose Frequency

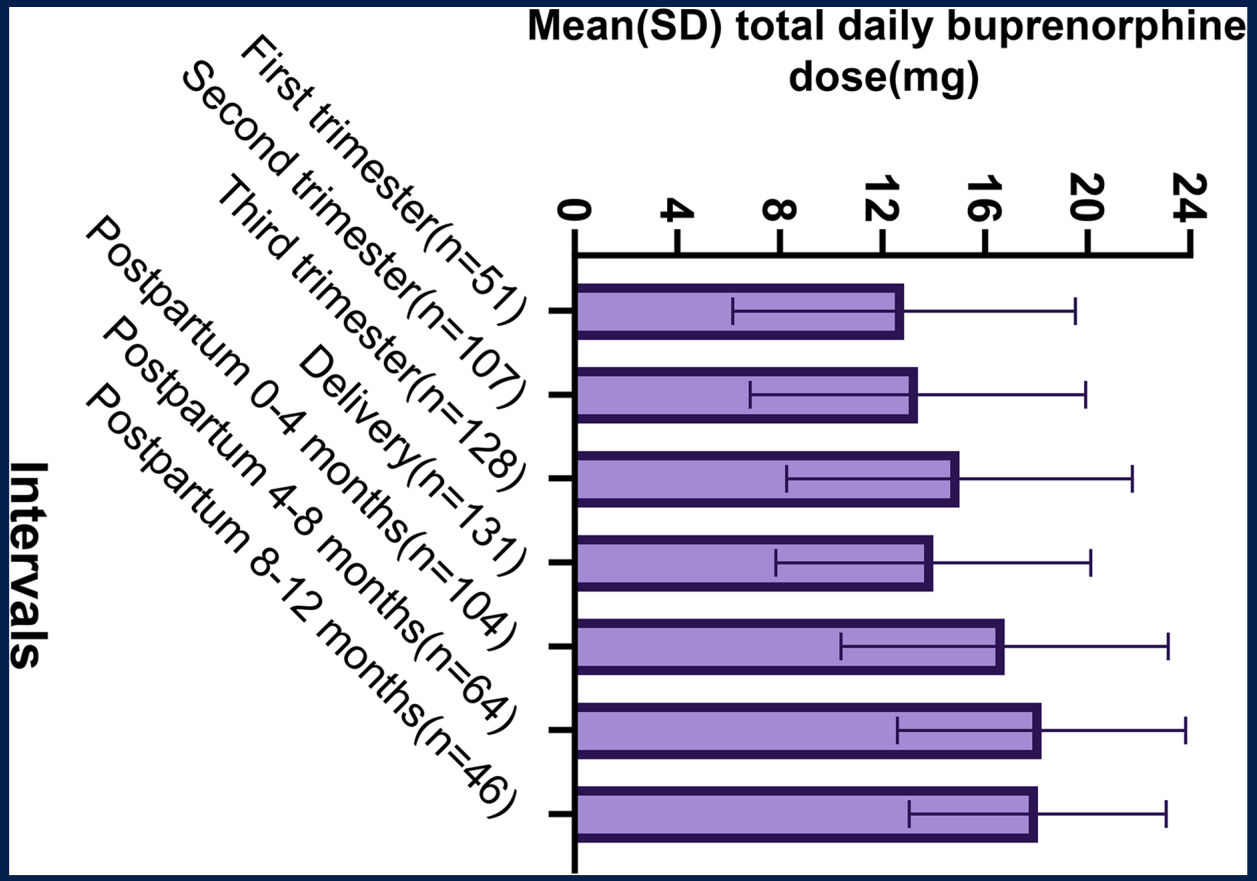


- Residential treatment facility for pregnant women.
- Most choose TID dosing.

Caritis et al 2017

Individual Dosing in Pregnancy is Needed

- Martin et al (2020)
  - Literature Review=25 studies
    - Mean dose change -12.3 to 10.5 mg/day
    - 2 studies ↓dose↓ retention
  - Prospective cohort study
    - Mean dose steadily increased
    - Maintained postpartum
    - Less split dosing postpartum
    - VA Medicaid limits dosing to 24 mg



Curr Treat Options Psychiatry. 2020 September ; 7(3): 375–399

Buprenorphine Dosing and NAS/NOWS

- No relationship between dose and risk of NAS/NOWS
- Positive relationship between meconium buprenorphine concentration and risk of NAS/NOWS

Jones et al 2013; Kacinko et al 2007; Wong et al., 2018

Summary and Take-Aways

- Buprenorphine dose is adequate if:
  - Patient perceives it as adequate, AND
  - Reduced illicit opioid use
  - Increased retention
- Clinical and preclinical evidence that 32 mg/day or higher can be helpful for some patients, particularly those with pain
- Pregnant women need:
  - Increased dose of buprenorphine
  - Increased frequency of dosing

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References

- Artenie AA et al. (2019) “Opioid agonist treatment dosage and patient perceived dosage adequacy, and risk of hepatitis C infection among people who inject drugs.” CMAJ 191:E462-8.
- Bastian, J. R., H. Chen, H. Zhang, S. Rothenberger, R. Tarter, D. English, R. Venkataramanan and S. N. Caritis (2017). "Dose-adjusted plasma concentrations of sublingual buprenorphine are lower during than after pregnancy." Am J Obstet Gynecol 216(1): 64.e61-64.e67.
- Caritis, S. N., J. R. Bastian, H. Zhang, H. Kalluri, D. English, M. England, S. Bobby and R. Venkataramanan (2017). "An evidence-based recommendation to increase the dosing frequency of buprenorphine during pregnancy." Am J Obstet Gynecol 217(4): 459.e451-459.e456.
- Ciraulo, D. A., R. J. Hitzemann, E. Somoza, C. M. Knapp, J. Rotrosen, O. Sarid-Segal, A. M. Ciraulo, D. J. Greenblatt and C. N. Chiang (2006). "Pharmacokinetics and pharmacodynamics of multiple sublingual buprenorphine tablets in dose-escalation trials." J Clin Pharmacol 46(2): 179-192.
- Coe, M. A., M. R. Lofwall and S. L. Walsh (2019). "Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations." J Addict Med 13(2): 93-103.
- Dahan A (2006) Opioid-induced respiratory effects: new data on buprenorphine. Palliative Medicine 20: s3-s8.

References

- Daitsch D et al. (2014) “Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients.” Pain Med 15(2): 2087-94.
- Fareed A et al. (2012) “Effect of Buprenorphine Dose on Treatment Outcome.” Journal of Addictive Diseases; 31; 8-18.
- Greenwald MK et al. (2003). “Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers." Neuropsychopharmacology 28(11): 2000-2009.
- Greenwald, M. K., S. D. Comer and D. A. Fiellin (2014). "Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy." Drug Alcohol Depend 144: 1-11.
- Heikman PK (2017) “Polydrug abuse among opioid maintenance treatment patients is related to inadequate dose of maintenance treatment medicine.” BMC Psychiatry 17:245-256.
- Hser YI et al. (2014) “Treatment Retention among Patients Randomized to Buprenorphine/Naloxone Compared to Methadone in A Multi-site Trial.” Addiction 109(1): 79–87.
- Indivior PLC, Sublocade Product Details, Clinical Information and Price Fact Sheet.
- Kacinko SL et al. (2008). "Correlations of maternal buprenorphine dose, buprenorphine, and metabolite concentrations in meconium with neonatal outcomes." Clin Pharmacol Ther 84(5): 604-612.

References

- Kakko J et al., (2007) “A Stepped Care Strategy Using Buprenorphine and Methadone Versus Conventional Methadone Maintenance in Heroin Dependence: A Randomized Controlled Trial.” Am J Psychiatry; 164:797–803)
- Jones, H. E., E. Dengler, A. Garrison, K. E. O'Grady, C. Seashore, E. Horton, K. Andringa, L. M. Jansson and J. Thorp (2014). "Neonatal outcomes and their relationship to maternal buprenorphine dose during pregnancy." Drug Alcohol Depend 134: 414-417.
- Negus SS et al. (1989) Kappa antagonist properties of buprenorphine in non-tolerant and morphine-tolerant rats. Psychopharmacology 98(1):141-3.
- Wong J et al., (2018) “Does Maternal Buprenorphine Dose Affect Severity or Incidence of Neonatal Abstinence Syndrome?” J Addict Med
- Zhang, H., H. V. Kalluri, J. R. Bastian, H. Chen, A. Alshabi, S. N. Caritis and R. Venkataramanan (2018). "Gestational changes in buprenorphine exposure: A physiologically-based pharmacokinetic analysis." Br J Clin Pharmacol 84(9): 2075-2087.
- Zubieta (2003). "Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers." Neuropsychopharmacology 28(11): 2000-2009

Buprenorphine Dose Limits: What Is The Evidence?

Bonus Slides

What about diversion?

- 50.5% participants reported they had shared buprenorphine
- 28.0% reported they had sold buprenorphine
- 46.5% had neither sold nor shared
- 3.0% had sold but not shared
- 25.5% had shared but not sold
- 25.0% had both shared and sold buprenorphine on the street

- 22.0% agreed or strongly agreed that it is right to share buprenorphine with dope sick friend
- 37.5% agreed or strongly agreed buying or selling buprenorphine on the street saves lives

- "Improving access to OAT by making it financially affordable is essential to further increase OAT coverage and is one of the factors that can reduce the illicit market with OAT medications." (Mravčík et al, 2018)

Kenney et al 2017

Mravčík et al, 2018

Patient Instructions: Make the dose effective!

- Stay well hydrated so films or tablets will dissolve easily.
- No nicotine use during 20-30 minutes prior to dose.
- Place film or tablet under tongue and tuck chin to chest.
- Do not swallow excess saliva (may precipitate withdrawal symptoms). Spit out excess saliva!

References, Ceiling Effect for Pain (Chronologic)

Dave Cundiff's summary: There may be a ceiling on dose-response for buprenorphine and pain, or even a decrease in pain relief at highest doses, but nobody seems to have demonstrated this ceiling in clinical studies.

1. Dahan, 2006: Dahan A, Yassen A, Romberg R, *et al.* Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth.* 2006 May; 96(5):627-32. doi: 10.1093/bja/ael051.
2. Davis, 2012: Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. *J Support Oncol.* 2012 Nov-Dec; 10(6):209-19. doi: 10.1016/j.suponc.2012.05.002.
3. Butler, 2013: Butler S. Buprenorphine – Clinically useful but often misunderstood. *Scand J Pain.* 2013 Jul 1;4(3):148-152. doi: 10/1016/j.sjpain.2013.05.004.
4. Raffa, 2014: Raffa RB, Haidery M, Huang H-M, *et al.* The clinical analgesic efficacy of buprenorphine. *J Clin Pharm Ther.* 2014 Dec;39(6):577-83. doi: 10.1111.jcpt.12196.
5. Khanna, 2015: Khanna IK, Pillarisetti S. Buprenorphine – An attractive opioid with underutilized potential in treatment of chronic pain. *J Pain Res.* 2015;8:859-870. doi: 10.2147/JPR.S85951.
6. Coe MA, Lofwall MR, Walsh SL. Buprenorphine pharmacology review: update on transmucosal and long-acting formulations." *J Addict Med* 2019;13(2):93-103.
7. Gudin, 2020: Gudin J, Fudin J. A narrative pharmacological review of buprenorphine: a unique opioid for the treatment of chronic pain. *Pain Ther.* 2020;9:41-54. doi: 10.1007/s40122-019-00143-6.

References, Buprenorphine/Death

Dave Cundiff's summary: Deaths are attributed to buprenorphine, usually in combination with "downers" but sometimes without other demonstrated toxicants, and often at doses that overlap the therapeutic doses. Is this due to individual susceptibility, or collateral causes, or attribution bias, or something else?

1. Tracqui A, Kintz P, Ludes B. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *J Anal Toxicol* 1998 Oct; 22(6):430-4. doi: 10.1093/jat/22.6.430 .
2. Kintz P. Deaths involving buprenorphine: a compendium of French cases. *Forensic Sci Int* 2001 Sep 15;121(1-2):65-9. doi: 10.1016/s0379-0738(01)00454-6 .
3. Lai SH, Yao YJ, Teck Lo DS. A survey of buprenorphine related deaths in Singapore. *Forensic Sci Int* 2006 Oct 16;162(1-3):80-6. DOI: 10.1016/j.forsciint.2006.03.037 .
4. Hakkinen M, Heikman P, Ojanpera I. Parenteral buprenorphine-naloxone abuse is a major cause of fatal buprenorphine-related poisoning. *Forensic Sci Int* 2013 Oct 10;232(1-3):11-5. doi: 10.1016/j.forsciint.2013.06.017 .
5. Paone D, Tuazon E, Stajic M et al. Buprenorphine infrequently found in fatal overdose in New York City. *Drug Alcohol Depend* 2015 Oct 1;155:298-301. doi:10.1016/j.drugalcdep.2015.08.007 .
6. Kriikku P, Hakkinen M, Ojanpera I. High buprenorphine-related mortality is persistent in Finland. *Forensic Sci Int* 2018 Oct;291:76-82. doi:10.1016/j.forsciint.2018.08.010 .
7. Mariottini C, Kriikku P, Ojanpera I. Concomitant drugs with buprenorphine user deaths. *Drug Alcohol Depend 2021 Jan 1;218:108345.* doi:10.1016/j.drugalcdep.2020.108345 .
8. Darke S, Duflou J, Larance B, et al. Characteristics and circumstances of death related to buprenorphine toxicity in Australia. *Drug Alcohol Depend* 2021 Jan 1;218:108360.
9. Wightman RS, Perrone J, Scagos R et al. Opioid overdose deaths with buprenorphine detected in postmortem toxicology: a retrospective analysis. *J Med Toxicol* 2021 Jan:17(1):10-15. doi:10.1007/s13181-020-00795-3 .
10. Bishop-Freeman SC, Friederich LW, Feaster MS, et al. Buprenorphine-related deaths in North Carolina from 2010 to 2018. *J Analytical Toxicology* 2021;45:780-791. doi:10.1093/jat/bkab073 .

Reference 1 for High-Dose Prior Authorization

Jacobs P et al, “Treatment Outcomes in Opioid Dependent Patients with Different Buprenorphine/Naloxone Induction Dosing Patterns and Trajectories”, *Am J Addiction* 2015 Oct; 24(7):667-675, https://onlinelibrary.wiley.com/doi/10.1111/ajad.12288 (Wiley, full article behind paywall).

SUMMARY: Best retention was seen in the group started at moderate dose (9-24 mg) **and advanced to 25+ mg (Figure 1).** From the Abstract: “When controlled for the baseline characteristics, bup6 participants [advanced to 25+ mg] were three times less likely to drop out the first 7 days than bup1 participants [who remained at 8 mg or below] (adjusted hazard ratio (aHR = .28, p = .03).”

Reference 2 for High-Dose Prior Authorization

Hser Y et al, “Treatment Retention among Patients Randomized to Buprenorphine/Naloxone Compared to Methadone in a Multi-site Trial”, *Addiction* 2014 Jan; 109(1): 79-87, https://doi.org/10.1111/add.12333 (Wiley, full article behind paywall).

SUMMARY: **Best 24-week completion rate (approximately 59%) was seen in patients receiving 30-32 mg/24 hours**, compared to approximately 53% in patients receiving 22-28 mg (Figure 2).

Reference 3 for High-Dose Prior Authorization

Pizzicato L et al, “Adherence to buprenorphine: An analysis of prescription drug monitoring program data”, *Drug and Alcohol Dependence*2020; 216:108317, https://doi.org/10.1016/j.drugalcdep.2020.108317 (Elsevier; full article behind paywall).

FROM FIGURE 2: **Doses 24+ mg were associated with much greater 180-day buprenorphine adherence** when compared to doses <16 mg (odds ratio 5.11) or to doses 16-23 mg (odds ratio not calculated, but appears to be around 3).

Reference 4 for High-Dose Prior Authorization

Fareed A et al, "Effect of Buprenorphine Dose on Treatment Outcome", *J Addictive Dis* 2012; 31(1):8-18, https://doi.org/10.1080/10550887.2011.642758 (Taylor & Francis, full article behind paywall).

FROM THE ABSTRACT: "**The higher buprenorphine dose (16-32 mg per day) predicted better retention in treatment compared with the lower dose** (less than 16 mg per day) ($P = .009$, R^2 adjusted = 0.40)…." [Redacted material reflects urine drug screen results, not relevant to dose.]

Reference 5 for High-Dose Prior Authorization

Gryczynski J et al, "Leaving Buprenorphine Treatment: Patients' Reasons for Cessation of Care", *J Subst Abuse Treat* 2014(March); 46(3) 356-361, https://pubmed.ncbi.nlm.nih.gov/24238714/ (Elsevier, full article behind paywall).

FROM RESULTS SECTION 3.2: "Finally, **higher buprenorphine dose was related to lower risk of leaving treatment (HR=.84; 95% CI=.78-.89; p<.001) and of discontinuing treatment within 6 months (OR=.91; 95%CI=.86-.96; p<.001).**