TOGETHER
Maine
Substance Use Disorders
Learning Community

Switching Between Methadone and Buprenorphine

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Jonathan C Fellers, MD

Disclosures

- Nothing to disclose

Outline

- Pharmacologic differences between methadone and buprenorphine
- Efficacy comparisons and dose-equivalence
- Strategies for switching

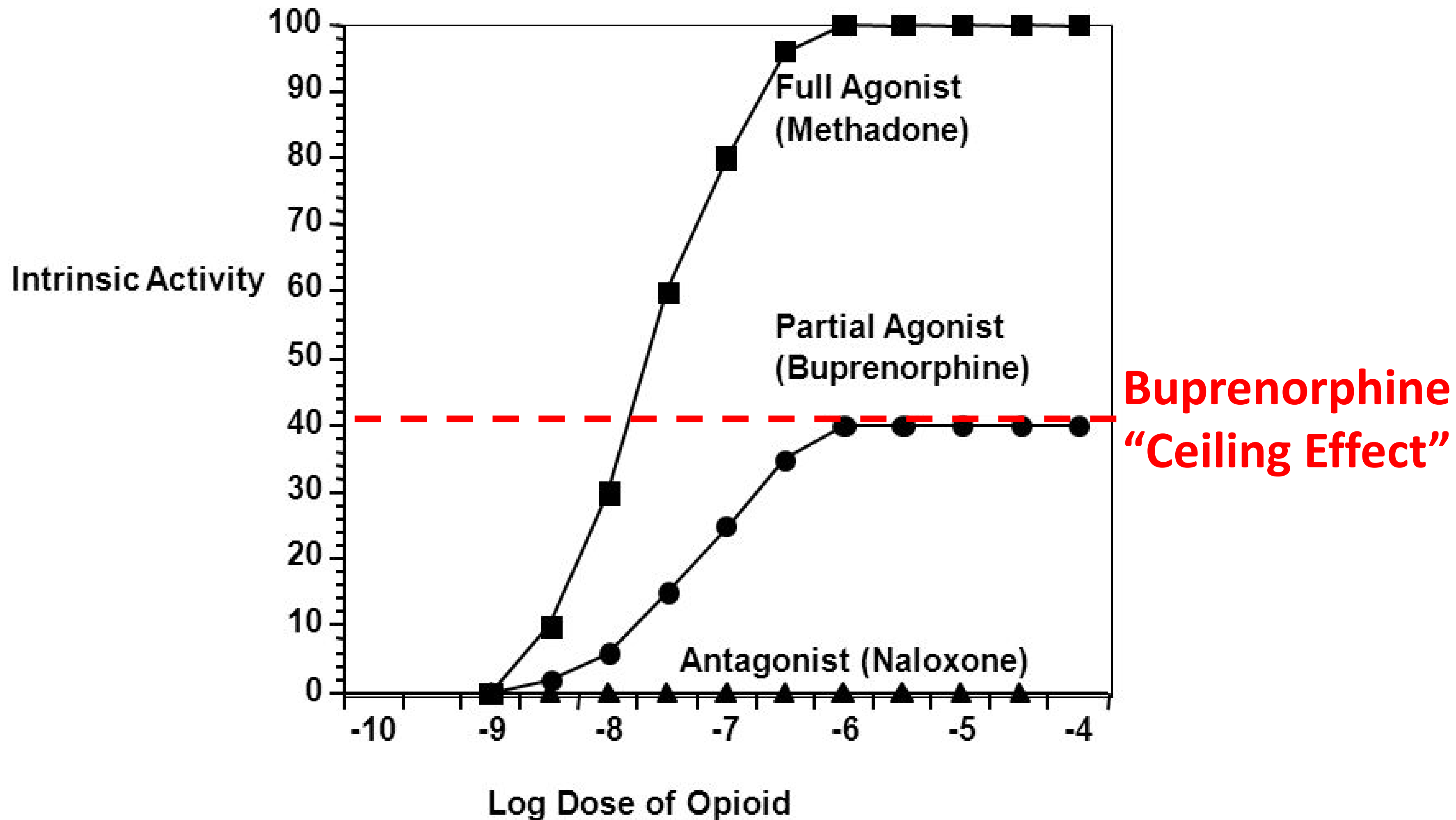
Pharmacology Comparison

Opioid	30 MME dose	100 MME/day (oral)
Hydrocodone	30 mg (oral)	100 mg (oral)
Oxycodone	20 mg (oral)	65 mg (oral)
Methadone (oral)	10 mg (oral)	30 mg (oral)
Hydromorphone (oral)	7.5 mg (oral)	24 mg (oral)
Buprenorphine	0.4 mg (sublingual) 0.3 mg (parenteral)	3 mg (sublingual) 50 ug/hr (transdermal)
Fentanyl	100-200 ug (parenteral)	50 ug/hr (transdermal)

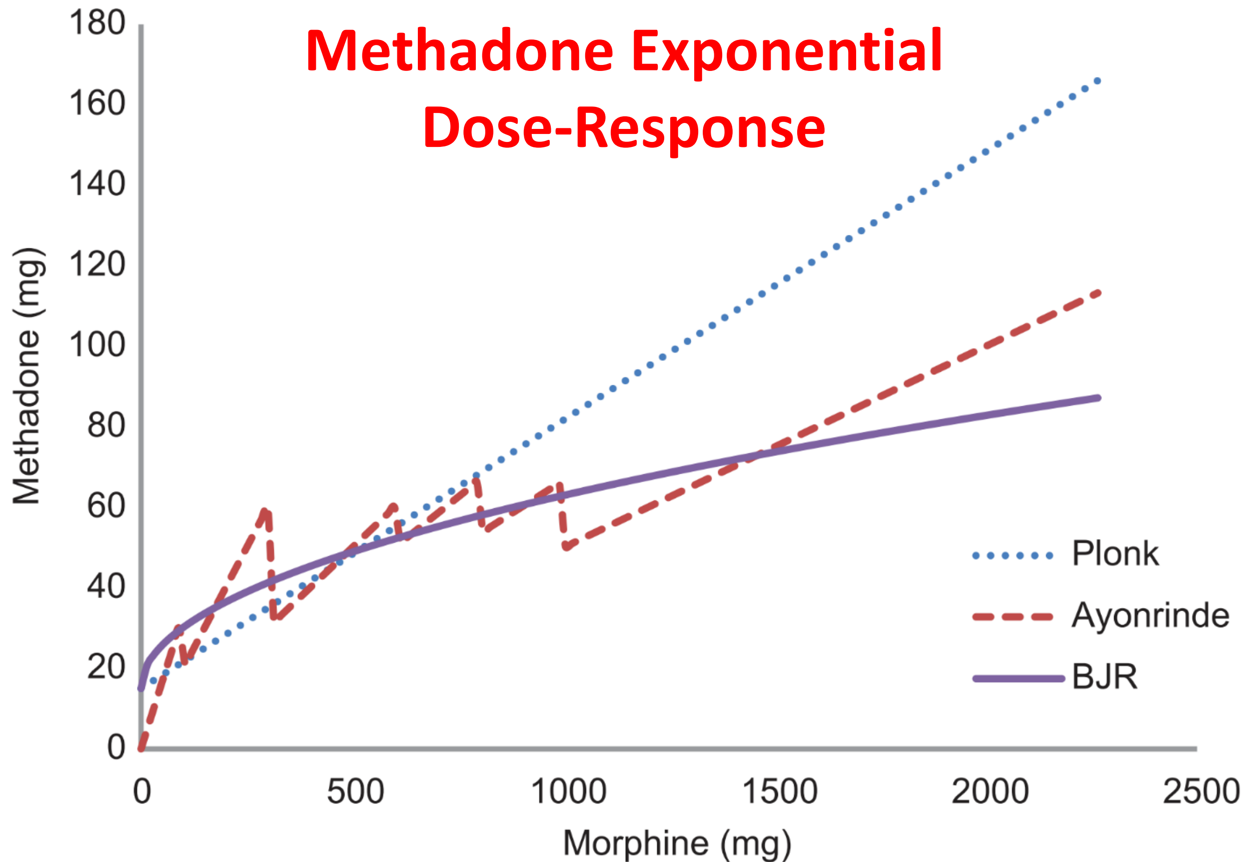
[illegible]
MAT doses easily exceed 100 MME
[illegible]

- National Center for Injury Prevention and Control. *CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2018 version*. Atlanta, GA: CDC; 2018.
- McPherson ML. *Demystifying opioid conversion calculations: A guide for effective dosing, Second edition*. Bethesda, MD: American Society of Health-System Pharmacists, 2018.

Pharmacology Comparison



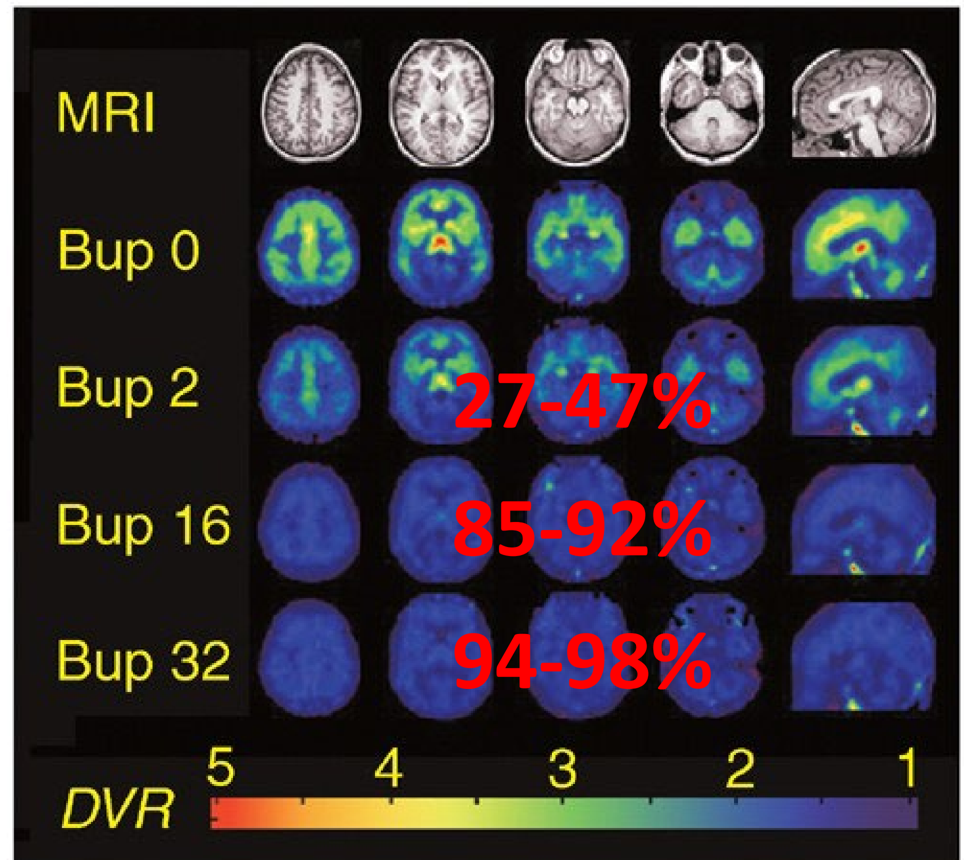
Pharmacology Comparison



- Baumrucker SJ, Jbara M, Rogers RM. (2016). A new mathematical approach to methadone conversion. *Journal of pharmacology & pharmacotherapeutics, 7*(*2*), 93–5.

Buprenorphine

- High potency binding to μ-opioid receptors
- At therapeutic doses, saturation of μ-opioid receptors



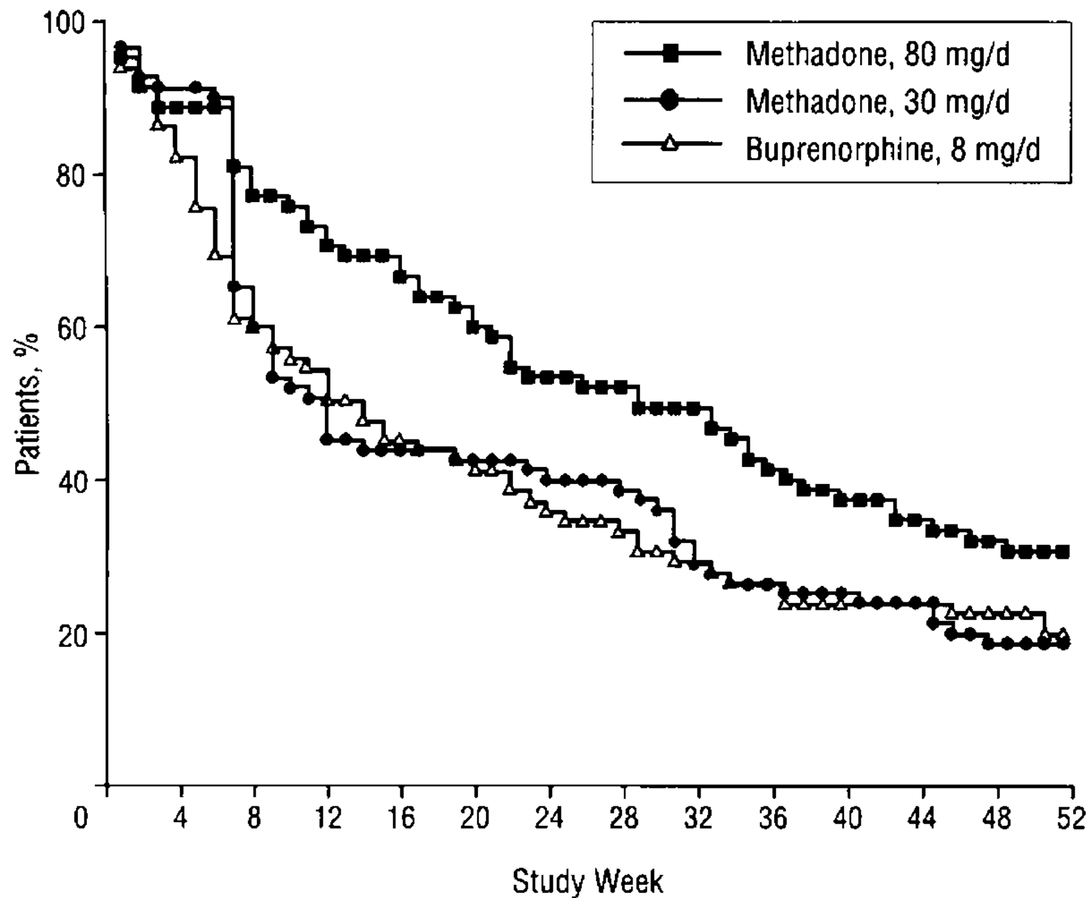
- Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK. (2003). Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology*, 28(11), 2000–9.

Methadone

- Good potency binding to µ-opioid receptors
- At therapeutic doses, **19–32%** reduction in µ-opioid receptors
  - Caveat: ligand used in this PET study binds k-receptors as well

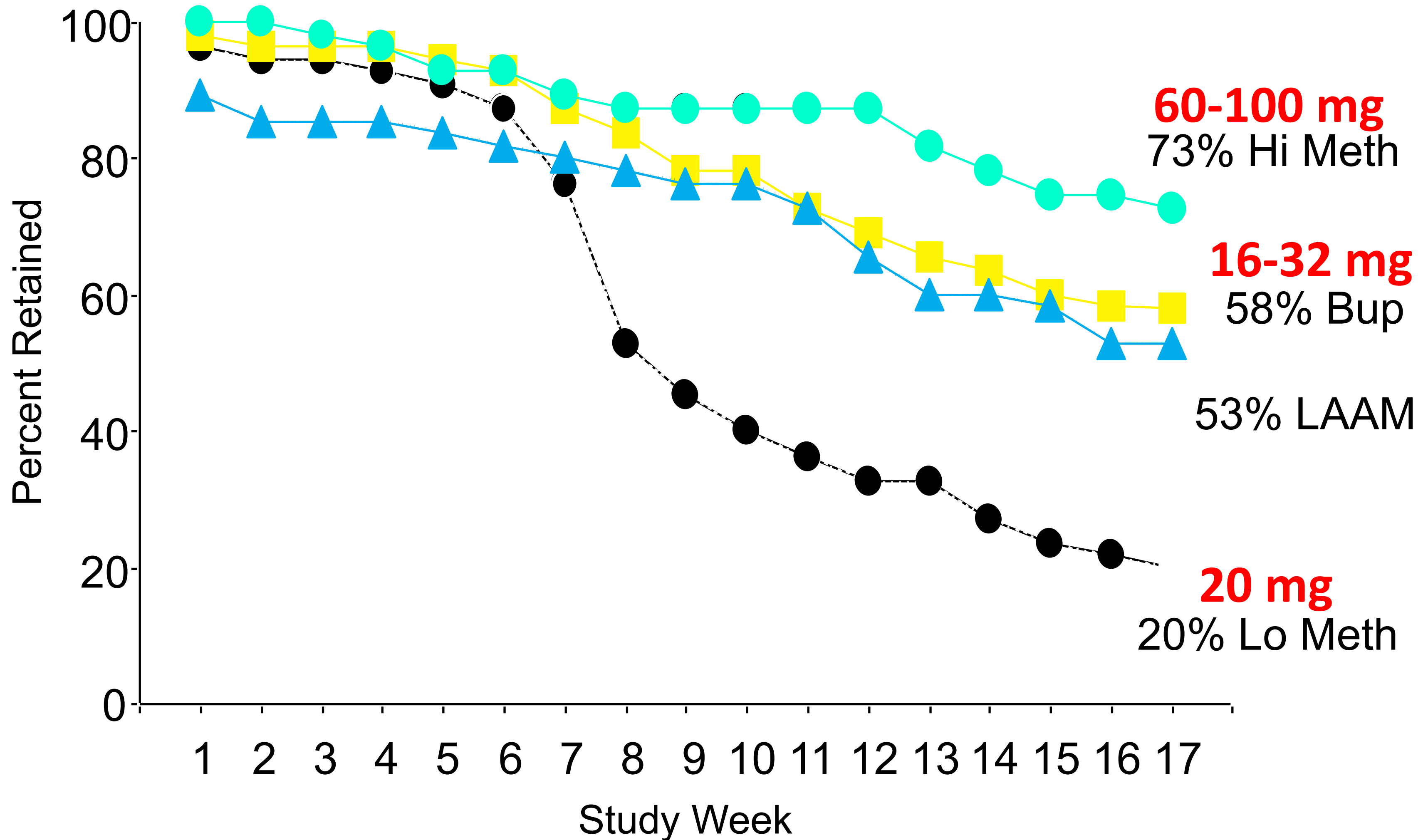
- Kling MA, Carson RE, Borg L, Zametkin A, Matochik JA, Schluger J, Herscovitch P, Rice KC, Ho A, Eckelman WC, Kreek MJ. (2000). Opioid receptor imaging with positron emission tomography and [(18)F]cyclofoxy in long-term, methadone-treated former heroin addicts. *J Pharmacol Exp Ther*, 295(3), 1070–6.

Efficacy Comparison



- Ling W, Wesson DR, Charuvastra C, Klett CJ. (1996). A Controlled Trial Comparing Buprenorphine and Methadone Maintenance in Opioid Dependence. *Arch Gen Psych*. 53:401-407.

Efficacy Comparison



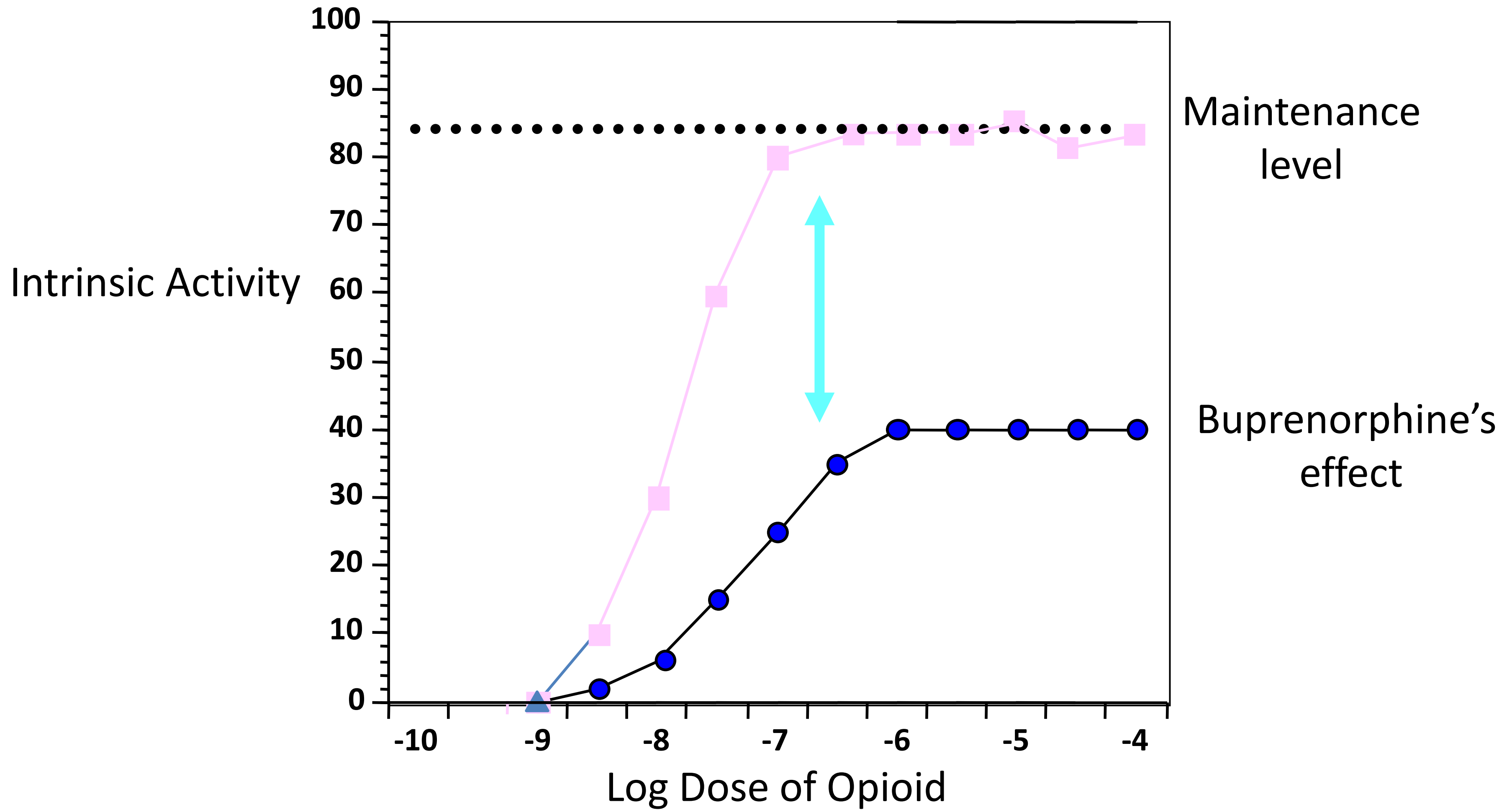
- Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. (2000). A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *NEJM*, 343(18), 1290–7.

Efficacy Comparison

- Buprenorphine placebo-controlled trials:
  - Retains those with heroin dependence in treatment at any dose above 2 mg
  - Reduces opioid use at doses of 16 mg or more
- Compared to methadone:
  - Similar to methadone at reducing opioid use at higher doses
  - Methadone is more effective at retaining people in treatment

- Mattick RP, Breen C, Kimber J, Davoli M. (2014). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2:CD002207.

Switching



Guidelines for Switching

- Carefully taper methadone to to 30-40 mg methadone and remain on that dose for at least 1 week
- Do not start buprenorphine until signs of opioid withdrawal
  - At least 24 hours, better waiting 36 hours
  - Lower doses of buprenorphine/naloxone are less likely to precipitate withdrawal

- Substance Abuse and Mental Health Services Administration. (2019). *TIP 63: Medications for Opioid Use Disorder*. Retrieved from https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder

Adjuvant Medications for Switching

- To relieve withdrawal symptoms during the transfer
  - Lofexidine, clonidine
  - Benzodiazepines
  - Nonsteroidal anti-inflammatory drugs
  - Loperamide
- No standard yet

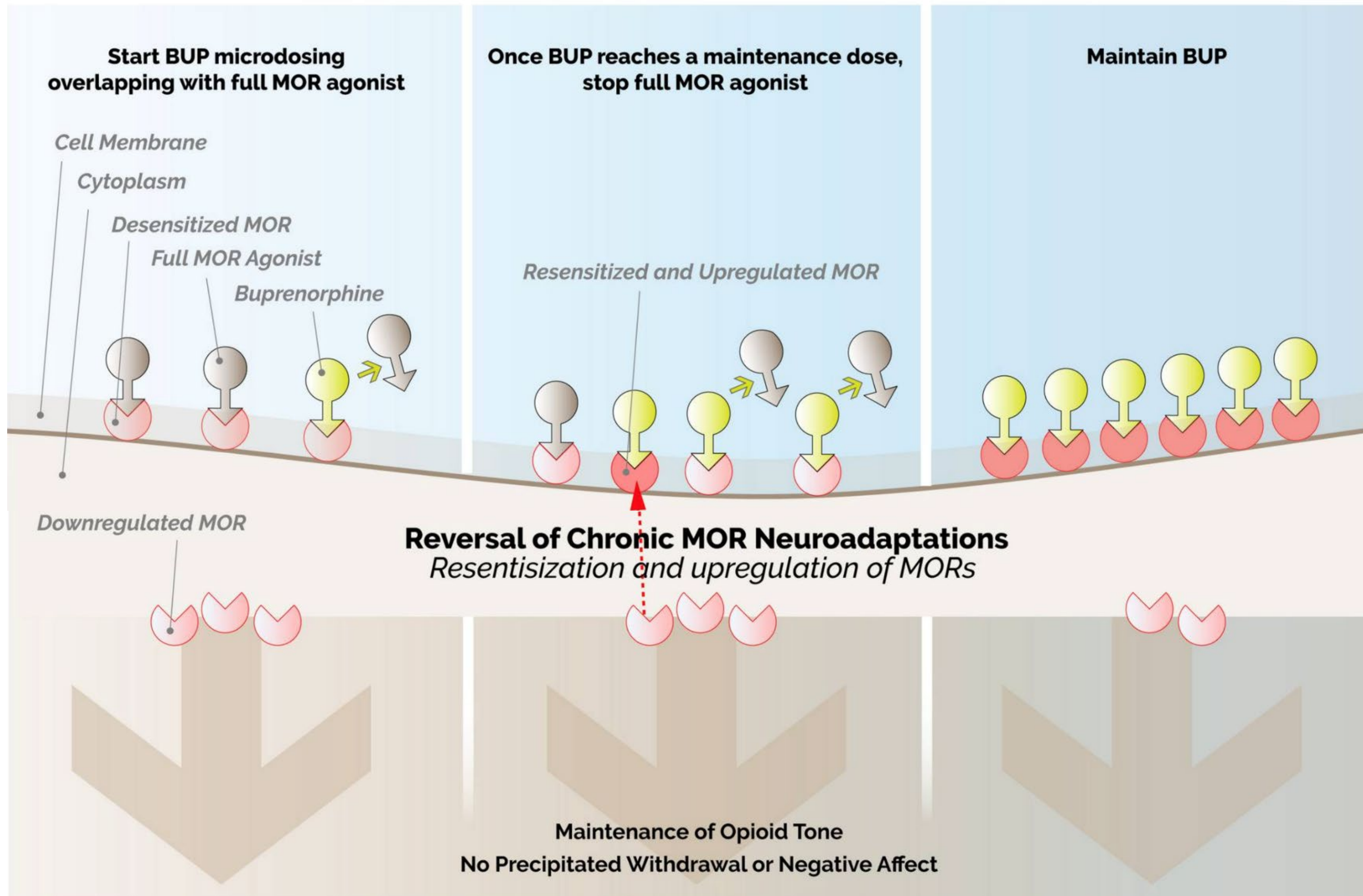
- Lintzeris N, Mankabady B, Rojas-Fernandez C, Amick H. (2022). Strategies for Transfer From Methadone to Buprenorphine for Treatment of Opioid Use Disorders and Associated Outcomes: A Systematic Review. *J Addict Med*, 16(2), 143–51.

Microdosing Induction

- To avoid withdrawal symptoms by gradually accumulating buprenorphine and replacing methadone at μ-opioid receptors
  - "Bernese method": overlapping buprenorphine micro-doses with continued full opioid use, then stop opioid when on full buprenorphine dose
  - "Bridge method": using hydromorphone or fentanyl as stepping stone
  - "Abrupt method": stopping methadone and starting micro-doses of buprenorphine

- Soyka M. (2021). Transition From Full Mu Opioid Agonists to Buprenorphine in Opioid Dependent Patients-A Critical Review. *Frontiers in pharmacology*, 12, 718811.

Microdosing Induction



- De Aquino JP, Parida S, Sofuoglu M. (2021). The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clinical drug investigation, 41*(5), 425–36.

Microdosing Induction

- Micro-dose
  - Commonly 0.5 mg (1/4 of a 2 mg film) [range 0.03-1.0 mg]
  - Typically completed in 4-8 days [range 3-112 days]
  - Typical protocol (Becker and Frank):

Day	Individual Doses	Total Dose
1	0.5 mg BID	1 mg
2	1 mg BID	2 mg
3	1 mg TID	3 mg
4	3 mg BID	6 mg
5	3 mg TID	12 mg

- Soyka M. (2021). Transition From Full Mu Opioid Agonists to Buprenorphine in Opioid Dependent Patients-A Critical Review. *Frontiers in pharmacology*, 12, 718811.
- Becker WC, Frank JW, Edens EL. (2020). Switching from High-Dose, Long-Term Opioids to Buprenorphine: A Case Series. *Ann Intern Med*. 173, 70–1.

Comparison of Switching

- Traditional and micro-dosing show equivalent success (95.6% and 96% respectively)
- Withdrawal expected (100%) with traditional method
- Withdrawal emerges in 40-60% with micro-dosing

- Spreen, L. A., Dittmar, E. N., Quirk, K. C., & Smith, M. A. (2022). Buprenorphine initiation strategies for opioid use disorder and pain management: A systematic review. Pharmacotherapy, 42(5), 411–27.

Methadone Dose on Switching

- Better outcomes with methadone dose below 60 mg

Methadone Dose	Induction Success
<40 mg	108/110 (98.2%)
40–60 mg	86/93 (92.5%)
>60 mg	66/81 (**81.5%**)

$P = 0.03$

70% of Methadone Maintenance Patients are on Dose >60 mg/day

- Lintzeris N, Mankabady B, Rojas-Fernandez C, Amick H. (2022). Strategies for Transfer From Methadone to Buprenorphine for Treatment of Opioid Use Disorders and Associated Outcomes: A Systematic Review. *J Addict Med*, 16(2), 143–51.
- D'Aunno T, Pollack HA. (2002). Changes in methadone treatment practices: results from a national panel study, 1988-2000. *JAMA, 288*(7), 850–6.

Equivalence?

- Comparing apples and oranges
- Buprenorphine 16-24 mg ≈ Methadone 30-60 mg

Medication	Buprenorphine	Methadone
Pharmacology	Partial agonist	Full agonist
Medication overdose risk	Ceiling effect	Exponential dose-response
Mechanism of blocking illicit opioids	Saturation of receptors	High tolerance