OPIOID TAPERING

Is it time for a definitive randomized controlled trial of opioid tapers?

Joseph L. Grossman

Author's interests on last slide

What is the status of opioid tapering in the midst of an opioid epidemic?

- Deaths from opioids increasing
- More opioid use
- More patients projected to be in pharmacotherapy.[1]
- Some MAT patients elect to taper.
- 9 (nine) % succeed in desisting from pharmacotherapy[1]

1. Rao IJ, Humphreys K, Brandeau ML. Effectiveness of Policies for Addressing the US Opioid Epidemic: A Model-Based Analysis from the Stanford-Lancet Commission on the North American Opioid Crisis. Lancet Reg Health Am. 2021 Nov;3:100031. doi: 10.1016/j.lana.2021.100031. Epub 2021 Jul 31. PMID: 34790907; PMCID: PMC8592267.

CDC opioid taper option

"Experts noted that tapers slower than 10% per week (e.g., 10% per month) also might be appropriate and better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations (e.g., for years)."[2]

[Parentheses original]

2. CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016; "Considerations for Tapering Opioids."

Veterans Health Administration opioid taper option

- VHA taper recommendation: 10% per month reduction to as slow as a 2% reduction is 8 weeks, for long-term users.[3]

3. Opioid Taper Decision Tool. U.S. Department of Veterans Affairs

Mayo Clinic opioid taper option

❖ Mayo Clinic: “Rate [of reduction], based on tolerability: slower preferred with long-term use.”

❖ “There is no established best way to reduce or eliminate opioids, and evidence to support a particular taper rate is weak.” [4]

4. Covington EC, Argoff CE, Ballantyne JC, Cowan P, Gazelka HM, Hooten WM, Kertesz SG, Manhapra A, Murphy JL, Stanos SP Jr, Sullivan MD. Ensuring Patient Protections When Tapering Opioids: Consensus Panel Recommendations. Mayo Clin Proc. 2020 Oct;95(10):2155-2171. doi:

CDC, VHA and Mayo Clinic Taper Guidelines Are In Agreement:

- CDC, VHA, and Mayo Clinic Option: 10% per month decrement.
- If that taper rate is not successful, try a 5% per month decrement, or slower.
- VHA has an option for 2% in 8 weeks.

Monthly vs Weekly Decrement

❖Unanswered question in
10% monthly decrement:

Which is likely to effectively treat more patients?

1) 0.20 mg decrement *all at once*: I.e.: On day 30, daily dose is 2.00 mg and on day 31 dose is 1.80 mg, or;
2) 0.04 mg decrease *per week :*
   (0.2mg/5wks = 0.04 mg/wk)

Centers for Disease Control and Prevention states that tapers are poorly studied

- CDC Guideline, notes, “evidence on the comparative effectiveness of opioid tapering or discontinuation versus maintenance, and of different opioid tapering strategies, was limited to small, poor-quality studies.” [5]

5. CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016

Tapering is complex. Not simply dosage reduction.

- Tapering is a complex medical task
- Intensive social interactions.
- Guidelines review risks and precautions.
- *Team support* of patients
- *Family support* of patients.

Comprehensive Stanford-*Lancet* Report

Treatment of OUD Requires:

1) Evidence-based systems
2) Innovations

2022 Report: "Responding to the opioid crisis in North America and beyond: recommendations of the Stanford–*Lancet* Commission"[6]

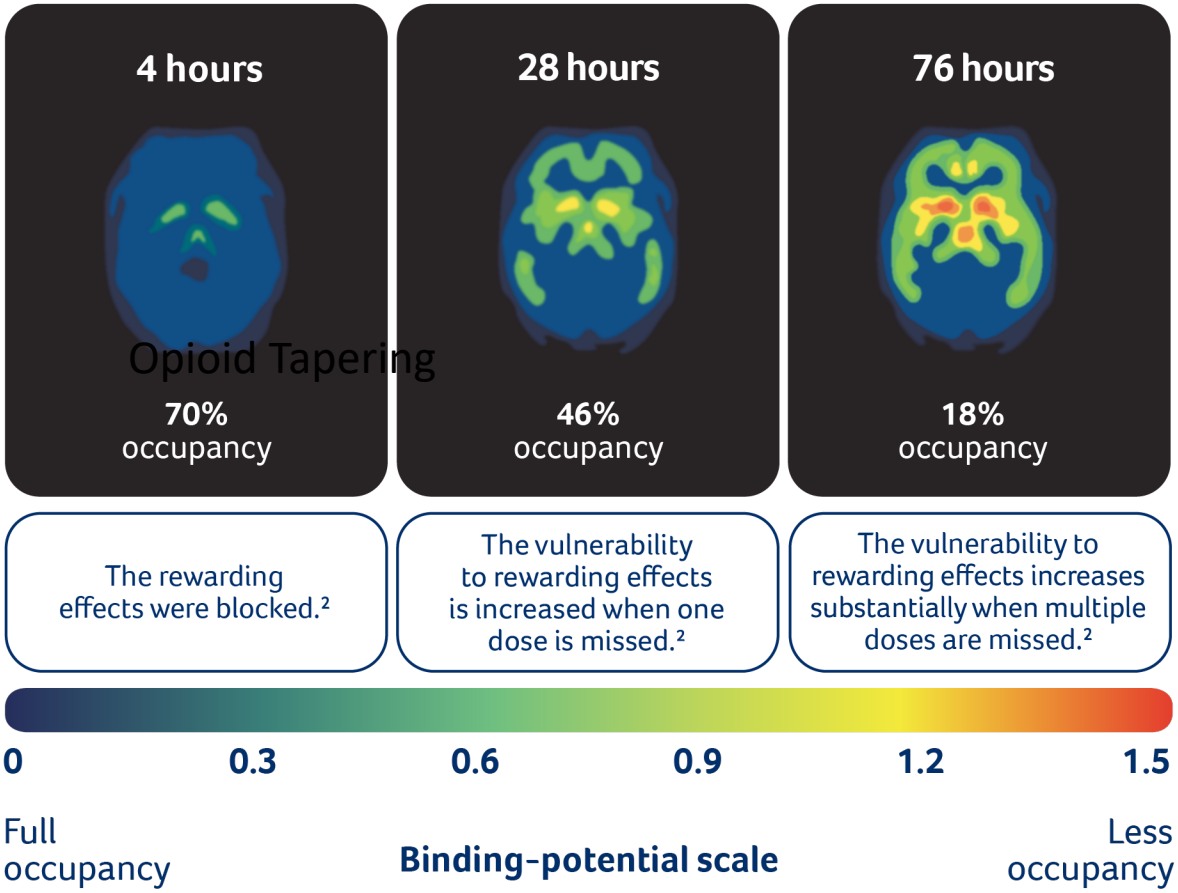
- 6. Humphreys K, Shover CL, Andrews CM, Bohnert ASB, Brandeau ML, Caulkins JP, et al. Responding to the opioid crisis in North America and beyond: recommendations of the Stanford-Lancet Commission. Lancet. 2022 Feb 5;399(10324):555-604. doi: 10.1016/S0140-6736(21)02252-2. Epub 2022 Feb 2. PMID: 35122753.

Medication-assisted treatment reduces cravings

- Buprenorphine occupies opioid receptors in brain
- When sufficient percentage of opioid receptors occupied, then craving reduced
- Level in brain related to blood serum level
- Opioid receptor occupancy is temporary
- Dosing interval varies among patients

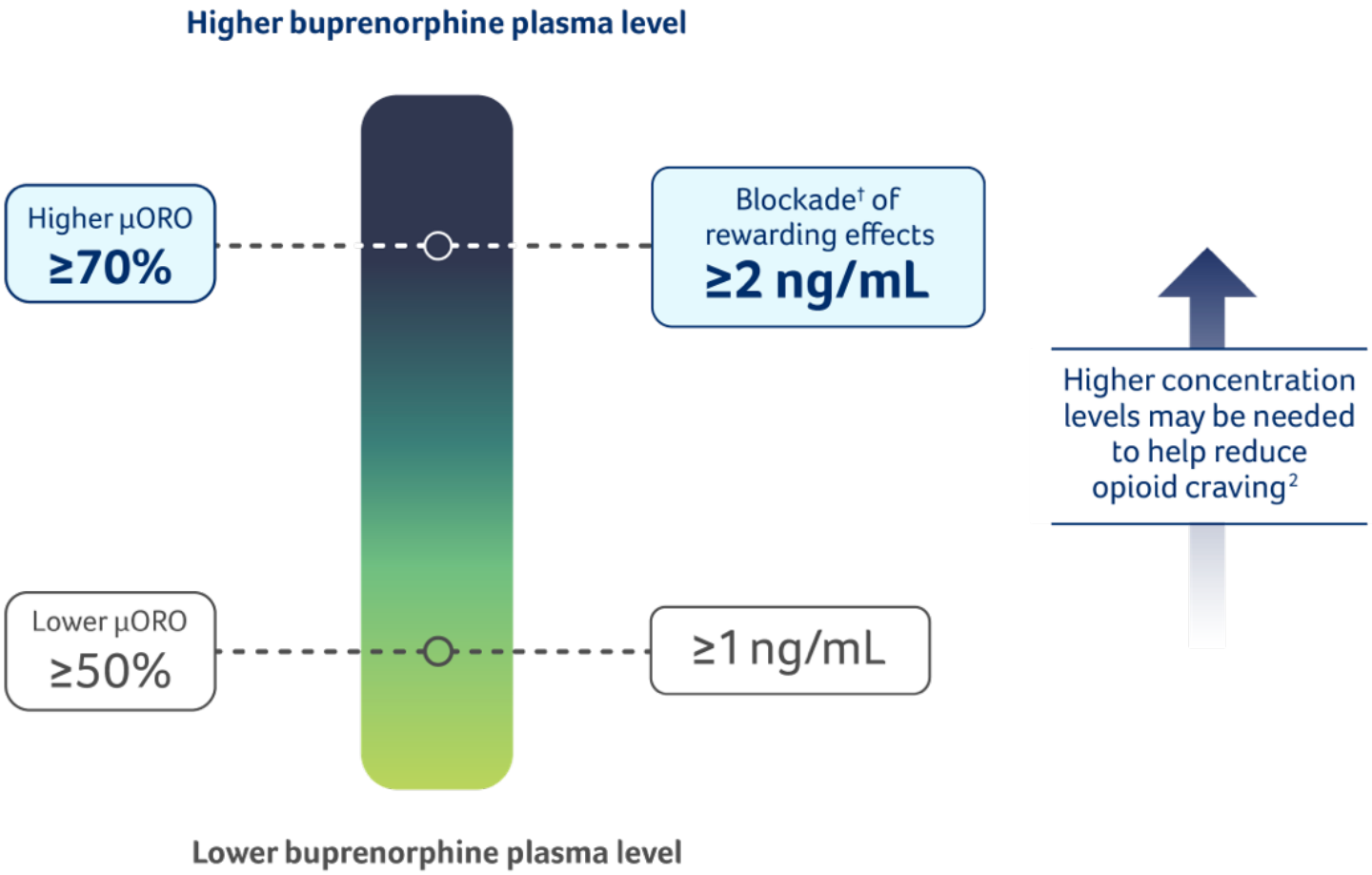
Analyzing Whole-Brain mu-opioid receptor occupancy (μORO) in a Patient Following Maintenance Administration of 16 mg of transmucosal buprenorphine [7] [1 of 2 slides]

7. ***www.sublocadehcp.com/opioid-receptor-occupancy***



≥70% μ OPIOID RECEPTOR OCCUPANCY (μORO) WAS CORRELATED WITH BUPRENORPHINE PLASMA LEVELS OF AT LEAST 2 ng/mL

As buprenorphine plasma levels increased, some OUD symptoms, such as craving, decreased. [2 of 2 slides]



Buprenorphine options in U.S. for medication-assisted treatment

- ***Sublingual/buccal film,*** with buprenorphine:naloxone in 4:1 ratio in **2, 4, 8, and 12 mg** strips. (Suboxone)
- ***Sublingual tablets,*** **2** and **8 mg; *without* naloxone**.(Subutex)
- ***Sublingual tablets,*** with **0.7, 1.4, 2.9, 5.7, 8.6 and 11.6 mg** of buprenorphine in 4:1 ratio with naloxone. (Zubsolv)
- **Subcutaneous injection**, **1 x month.** (Sublocade)

There are no commercial tapers available for prescription.

All taper regimens are off-label.

Opioid tapering can involve significant levels of risk for some patients

*Tapering off opioids causes loss of tolerance.

* Fatal overdose more likely if opioid use after reaching abstinence.

* Previous low-risk “recreational” dose can be fatal.

Who is a candidate for an opioid taper?

Need for some uniformity for screening

- Patient understands risks of opioid exposure following reduction/abstinence
- Stable patient in MAT.
- Is adequately motivated to reduce dose.
- Absence of opioids in urine tests.
- Capacity to reduce at higher doses.
- Understands a taper may take years.
- No significant history of severe depression.
- No history of suicidal gestures or activity.

What do the CDC, VHA, Mayo Clinic 10% per month tapers look like *in terms of milligrams?*

Example of 10% per month guidelines: Table below of the *daily dosages*, for 24 months, of a patient *who has already tapered to 2 mg* of buprenorphine per day and then elects to taper to a lower dose, or to opioid abstinence, at a rate of ***10% per month***:

Month 36: Daily dose:0.05 mg

Month	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Dose mg/day	**2.00**	**1.80**	**1.62**	**1.46**	**1.31**	**1.18**	**1.06**	**0.96**	**0.86**	**0.77**	**0.70**	**0.63**
Month	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*
Dose mg/day	**0.56**	**0.51**	**0.46**	**0.41**	**0.37**	**0.33**	**0.30**	**0.27**	**0.24**	**0.22**	**0.20**	**0.18**

Variation among patients during dose reduction:

Greenwald: “[T]here is large variation in opioid-dependent individuals’ sensitivity to withdrawal symptoms during dose reduction.” [8]

8. Greenwald, M. K., Comer, S. D., & Fiellin, D. A. (2014). Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug and alcohol dependence*, *144*, 1–11. https://doi.org/10.1016/j.drugalcdep.2014.07.035
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252738/

Variation to buprenorphine sublingual medication

- From 0.67 to 3.50 hours to peak serum concentrations
- Terminal elimination half-life from 3 to 44 hours.[9]
- Impact on tapering?

9. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet. 2005;44(7):661-80. doi: 10.2165/00003088-200544070-00001. PMID: 15966752.

Related Topics Not Discussed

- Adherence.
- Divided doses
- Depression as confounder when withdrawal symptoms emerge.
- Methods for determining need

SLIDES 20 through 28 are an addendum designed to provide a basis for detailed discussion and contain significant detail and some advanced topics. Information about buprenorphine as an antidepressant and the pharmacological basis of an exponential taper are the main topics past this point.

Statement of Interest
Patent granted Joseph Grossman, on February 22, 2022, for
"Opioid Taper Regimen."
U.S. Patent 11,253,512 B2

Joseph Leon Grossman, is a science and medical writer. He is a graduate of *Universidad del Noreste* Medical School with an MD degree. He has an MSW from Rutgers University, New Brunswick, NJ
Telephone/text: (831) 247-7294

Addendum

The following slides are for additional study and discussion after the above PowerPoint has been viewed.

Buprenorphine is used as an anti-depresent. What is the potency of buprenorphine? How small a dose can have an effect?

The following demonstrates the potency of small doses of buprenorphine and is intended to show how small reductions might be capable of having large effects when a certain critical level is reached. The authors describe the cautious introduction of buprenorphine in treating depression, writing, "Given the efficacy at very low doses, BUP administration may be started at 0.1 – 0.2 mg daily and — if possible — it should be recommended to slowly titrate the drug, in order to avoid its side effects until a personalized dosage may allow a sufficient clinical response." If researchers find that an introduction of amounts as small as 0.1 – 0.2 mg of buprenorphine can represent the point at which depression responds therapeutically, then, conversely, should it be assumed that as doses are *lowered*, symptoms could emerge following a similarly small reduction at some patient-specific critical point, such as found in a taper.

1. Serafini G, Adavastro G, Canepa G, De Berardis D, Valchera A, Pompili M, et al.. The Efficacy of Buprenorphine in Major Depression, Treatment-Resistant Depression and Suicidal Behavior: A Systematic Review. Int J Mol Sci. 2018 Aug 15;19(8):2410. doi: 10.3390/ijms19082410. PMID: 30111745; PMCID: PMC6121503.

Buprenorphine as anti-depressant

Serafini et al.:Start administration at 0.1 – 0.2 mg daily and increase slowly

Implications for sensitivity during reduction?

1. Serafini G, Adavastro G, Canepa G, De Berardis D, Valchera A, Pompili M, et al.. The Efficacy of Buprenorphine in Major Depression, Treatment-Resistant Depression and Suicidal Behavior: A Systematic Review. Int J Mol Sci. 2018 Aug 15;19(8):2410. doi: 10.3390/ijms19082410. PMID: 30111745; PMCID: PMC6121503.

Decrement amounts in a 10% per month taper

Month	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***
Dose mg/day	**2.000**	**1.800**	**1.620**	**1.458**	**1.312**	**1.181**	**1.063**	**0.957**	**0.861**	**0.775**	**0.697**	**0.628**
Decrement mg	0.200	0.180	0.162	0.146	0.131	0.118	0.106	0.096	0.086	0.077	0.070	0.063
Month	***13***	***14***	***15***	***16***	***17***	***18***	***19***	***20***	***21***	***22***	***23***	***24***
Dose mg/day	**0.565**	**0.508**	**0.458**	**0.412**	**0.371**	**0.334**	**0.300**	**0.270**	**0.243**	**0.219**	**0.197**	**0.177**
Decrement mg	0.056	0.051	0.046	0.041	0.037	0.033	0.030	0.027	0.024	0.022	0.020	

UNKNOWNS

***What percentage of MAT patients would benefit from tapers that follow the CDC, VHA, Mayo Clinic guidelines?**

***To what degree does the hyperbolic reduction apply at different dosage levels? E.g.:At 2.00; 1.00; 0.50; 0.25 mg?**

***Can a diagnostic taper can be made?**

***How to consistently detect the dosage level in an individual below which it may be physiologically impossible to further reduce opioid dosages without inducing subjectively intolerable withdrawal symptoms.**

To what degree does the hyperbolic reduction chemistry apply at different dosage levels?

For example:

2.00 to 1.80 (0.20) mg is 10% reduction.

0.50 to 0.45 (0.05) mg is 10% reduction.

Can it be that many patients will fail in a taper attempt if their monthly decrement exceeds ***0.05 mg*** of buprenorphine? Is there a difference between 0.01 mg/week and 0.05 mg all at once after 5 weeks?: Not known.

Hyperbolic expression has been closely studied with SSRIs: Here is an example of sensitivity change at different dosage levels in SSRIs:

The Lancet June 2019 ***Table 2*** *and Figures 3 and 4 pgs 542-543*:

Reduced serotonin transporter occupancy (with an SSRI) leads to withdrawal symptoms.

Comparing **serotonin occupancy** when reducing daily dosing with the SSRI citalopram. See next slide for description:

Dose reduction **Transporter occupancy**

A) **60.0 to 40.0** mg/day = 2.0% reduction.

B) **1.5 mg to 0.8** mg/day = 10.0% reduction.

When going from, e.g., **60 to 40 mg/day** of the **SSRI** citalopram, there is an approximately 2 (two) % reduction in serotonin transporter occupancy. That is: a 20 mg **dose** reduction results in 2% reduction of serotonin transporter **occupancy**. A reduction in occupancy associated with withdrawal. (0.1% occupancy reduction *per mg* dose reduction) When going from **1.5 mg to 0.8 mg/day**, there is approximately 10 (ten) % reduction in serotonin occupancy. That is: 0.7 mg **dose** reduction results in 10% reduction of serotonin transporter **occupancy.** (14% occupancy reduction *per mg* of dose reduction) Compare 0.1 (one-tenth) % with 14 (fourteen) % reduction. The ratio is 1 to 140. Similar specificity to dosages assumed for opioids when using serial percentage reductions.

Is it time for a randomized clinical trial of an opioid taper?

- Is it time to compare several opioid tapers?
- Is there some reason to not try an RCT of an opioid taper?
- Do the technical problems of making a slowly decreasing sequence of dosages pose a challenge to pharmaceutical production?
- How would the potential need for a taper or tapers be determined?

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