

Determining the parameters of efficacious opioid tapering

Agencies and providers with shared approaches to opioid tapering

There is an extensive degree of consensus regarding opioid tapering, among:

- ❖ Centers for Disease Control and Prevention (CDC)
- ❖ Private - some private providers, such as Mayo Clinic¹
- ❖ States - some state health agencies^{2,3}
- ❖ U.S. Health and Human Services (HHS)
- ❖ Veterans Health Administration (VHA)

1. Covington EC et al. Ensuring Patient Protections When Tapering Opioids: Mayo Clin Proc. 2020;95(10):2155-2171

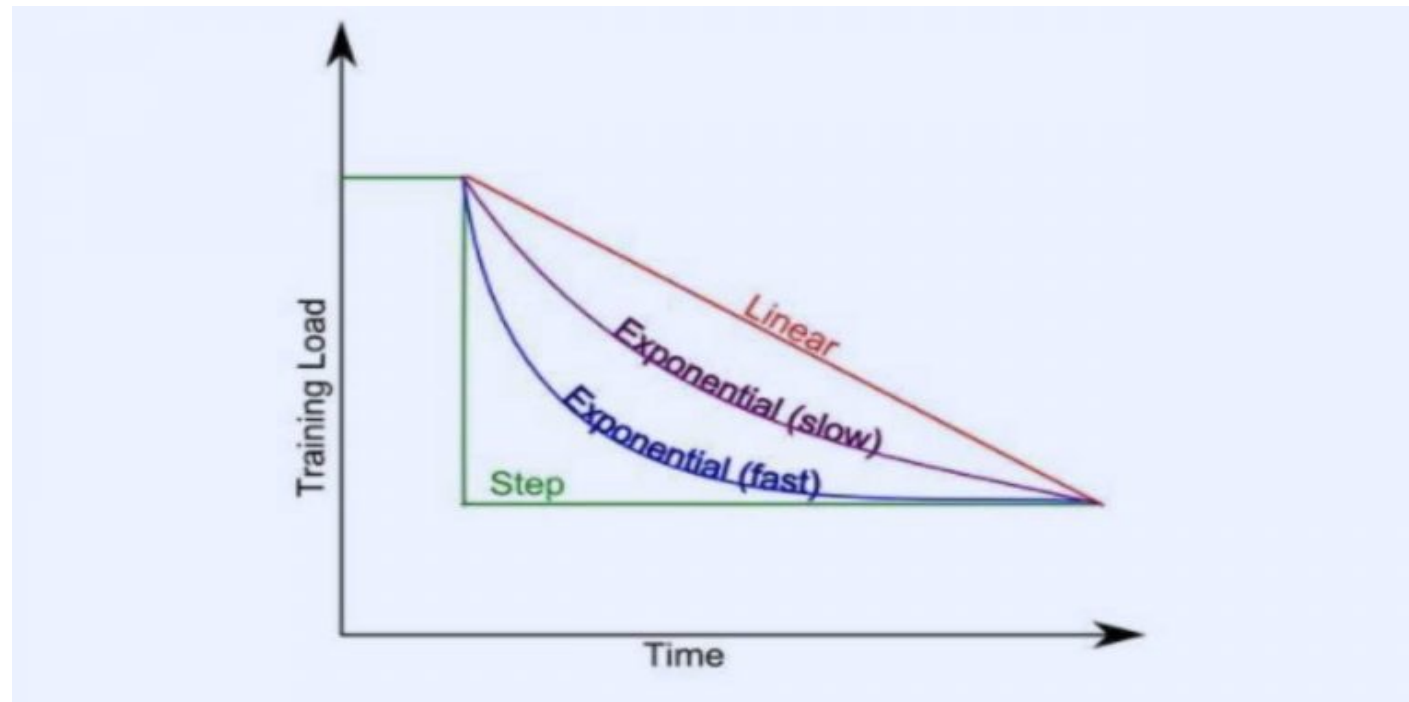
2. Oregon Health Authority, Public Health Division Oregon opioid tapering guidelines

3 Tapering and Discontinuing Opioid Use. Minnesota Department of Human Services. First Edition, 2018

Opioid tapering guideline consensus reflects shared foundational concepts

- 1) Careful patient screening for appropriate treatment
- 2) Individualized treatment and tapering for each patient
- 3) Broad range of **exponential tapering** rate options: *“Exponential tapering”* here means each successive dose is a fixed percentage of the **immediately previous dose**, e.g., 10% *reduction* per month, as opposed to *linear tapering*, when doses are a declining percentage of the **first dose** in the taper, e.g., 90%; 80%; 70% . . . of the first dose.
- 4) Finding the optimum rate of tapering for each patient
- 5) Tapering in the context and framework of a supportive and comprehensive treatment plan – dose taper is one of several parts

Graph of Exponential and Linear Steps v Time



Opioid tapering guideline consensus includes shared core tapering specifics

- ❖ **CDC** “Tapers of approximately **10% per month or slower** are likely to be better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations .”¹
- ❖ **HHS:** “Slower tapers (e.g., **10% per month or slower**) are often better tolerated than more rapid tapers”²
- ❖ **Mayo Clinic :**” **10% of previous month’s dose** (slower) have been recommended; slower preferred with long-term use”³
- ❖ **Oregon:** Directs clinicians to VHA Opioid Decision Tool.⁴ “Generally, a **5 to 20 percent taper** per month can be a helpful guide”.⁵
- ❖ **VHA:** taper options - **10% per month reduction, to as slow as a 2% taper in 8 weeks.**⁴

1. CDC Clinical Practice Guideline for Prescribing Opioids–United States, 2022 Draft accessed 9.7.22
2. HHS: Guide for Clinicians, Appropriate Dosage Reduction – Discontin. Long-Term Opioid Analgesics 10/19
3. Covington EC et al. Ensuring Patient Protections When Tapering Opioids: Mayo Clin Proc. 2020;95(10):2155-2171
4. Opioid Taper Decision Tool. U.S. Department of Veterans Affairs
5. Oregon Health Authority, Public Health Division Oregon opioid tapering guidelines

10% per month taper (exponential)

- ❖ Patient at 2.00 mg total dose per day in **Month #1**
- ❖ At end of each month, dosage reduces by 10%

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

Tapering consensus based on “sparce” evidence. *Survey: Patients support research.*

- ❖ **CDC:** *“Evidence to support specific tapering rates is **limited** . . .”*¹ (2022)
- ❖ **Mayo Clinic Proceedings:** *“. . . **little specific** and high-quality research has focused on guiding tapering from long-term opioid treatment . . .”*² (2015)
- ❖ **National Academy of Medicine webinar:** *“evidence for tapering best practices and pain management is **sparse** . . . **need for randomized controlled trials** and rigorous observational studies to compare tapering methodology, identify safe, efficacious protocols . . .”*³ (2019)
- ❖ **J Prim Care Community Health:** *“There appears to be **patient support** for future research into the effects of tapering opioid medications.”*⁴ (2019)

1. CDC Clinical Practice Guideline for Prescribing Opioids–United States, 2022 Draft accessed 9.7.22 (Revised 2016 Guidelines)

2. Berna C et al. Tapering Long-term Opioid Therapy in Chronic Noncancer Pain. Berna C et al. Mayo Clinic Proceedings 2015.04.003

3. National Academy of Medicine: Tapering Guidance for Opioids: Existing Best Practices and Evidence Standards Nat. Acad. of Medicine, Webinar July 22, 2019

4. James J, Lai B, Witt T. Patient Engagement Survey Regarding Future Double-Blinded, Randomized Controlled Trial of Tapering of Chronic Opioid Therapy. J Prim Care Community Health. 2019 Jan-Dec

All bolding above is added.

Efficacy of opioid tapering consensus guidelines now more practical to determine

- ❖ New method of precision dosage formulation
- ❖ Facilitates manufacture of tapers with close adherence to consensus opioid taper dosage recommendations.
- ❖ Randomized controlled trials of consensus recommendations can now be performed.
- ❖ There are no previous commercial taper formulations or trials.

The new method of dosage formulation

❖ Formulation method allows the consensus tapers to be precision produced in the most problematic dosage range, i.e., below two mg buprenorphine/day.

Patent at: patents.google.com/patent/US11253512

URL: <https://patents.google.com/patent/US11253512> *Author interest in patent.*

RCT can determine efficacy

- ❖ The consensus tapering regimens describe slow exponential tapers and make clear that some patients must taper very slowly.
- ❖ Consensus recommended options for long term opioid users range from 1 % to 10 % per month.
- ❖ Now possible to make these consensus tapers and to determine the degree of adherence to these guidelines that is necessary in order to maximize efficacy of the recommended tapering protocols.

New method addresses formulation of low dosages; Enables RCTs of consensus exponential tapers

- ❖ Tapering at lower dosages generally associated with dosage and withdrawal issues.
- ❖ Tapering from relatively *high* dosages to *moderate/lower* dosages associated less with the problematic withdrawal or dosage division issues encountered at lower dosage levels.
- ❖ Example: New formulation method has the precision to produce the 10%/step taper needed to get from:
 - 2.00 mg to 1.00 mg:** i.e.: 2.00; 1.80; 1.62; 1.46; 1.31; 1.18; 1.06; 0.96 mg., or, from;
 - 1.00 mg to 0.50 mg:** i.e.: 0.96; 0.86; 0.77; 0.70; 0.63; 0.56; 0.51 mg.
- ❖ Example of **Weekly** steps down at 2.3% step: 2.00; 1.95; 1.91; 1.87; 1.82 mg.

Potential specific aims of opioid taper RCTs

DETERMINE the following:

- Aim 1. Would a standardized *diagnostic* taper be useful?
- Aim 2. What is the percentage of MAT patients for whom a consensus taper approach enables a taper to abstinence.
- Aim 3. Extent to which consensus guidelines of “percentage of last dose”, that is, exponential decreases, applies at lower range of dosages, e.g., at less than 2 mg of buprenorphine/day.
- Aim 4. Can a very slow taper diagnose a patient as “physiologically unable to taper”, that is, unable to return to their pre-opioid-exposure status regardless of how slow a taper is utilized?

RCT: Would a standardized *diagnostic* taper be useful?

Does greater precision lead to an improved decision?

Aim 1, Part 1: Determining elements of standardized diagnostic taper:

Standardizes current practices.

Same medicine, new dosage precision.

- ❖ ***A diagnostic taper:*** A series of doses designed to diagnose the optimum tapering rate for a specific patient.
- ❖ ***Standardizes*** current widespread trial-and-error approach.
- ❖ ***Concept:*** a series of *increasing* tapering rates, starting slow.
- ❖ ***Challenge:*** make precision cost-effective product.
- ❖ ***Advance:*** greater diagnostic precision, improved tapering decisions.^{.13}

RCT: Would a standardized *diagnostic* taper be useful?

RCT **Aim 1, Part 2**: Determining elements of a diagnostic taper: Possible Method – Mirrors, standardizes current practice

- 1) Screen patients for taper participation.
- 2) Administer a sequence of doses that initially reduces dosages at a fixed (percentage rate)/(unit time) that the clinician believes to be ***slower*** than necessary for patient, ***e.g.*** 5%/month.
- 3) Then increase taper **rate** slowly over time, ***e.g.***, to 7%/month.
- 4) Patient feedback: ***e.g.***, withdrawal symptoms starting to emerge.
- 5) Agreement by clinician and patient on optimum tapering rate.
- 6) Observe if the taper rate then remains constant (Future RCT).

RCT Aim 2: Determine efficacy of exponential tapers

RCT AIM 2: Determine the percentage of MAT patients for which a consensus taper approach enables a taper to abstinence.

- 1) Using best practices, screen patients for taper participation.
- 2) Administer diagnostic taper to determine optimum rate.
- 3) Administer optimum rate taper.
- 4) Determine % who reach elective tapering goals.
- 5) Continue with patients who do not reach goal, but at slower rate.

RCT to determine lowest dosage range for which exponential reduction no longer necessary for efficacy

Aim 3: RCT to determine lowest dosage range in which exponential reduction no longer necessary for effective tapering

- 1) Using best practices, screen patients for taper participation.
- 2) After reaching various low total daily dosages, such as 1.0, 0.5, 0.25, 0.12, 0.05 mg of buprenorphine;
- 3A) Continue to taper some patients strictly at the taper rate used to reach that level; 3B) Taper some patients more rapidly than the taper rate used to reach that level: e.g., switch from 5% to 10% per month.
- 4) Record patients who reach dosage levels with or without symptoms of withdrawal.

Diagnosing patients who may be physiologically unable to taper below a specific dosage level.

AIM 4: Determine: Patients unable to taper below specific dosage

Determine if a very slow taper can accurately diagnose a patient who is “physiologically unable to taper”; i.e., pt is unable to return to their *pre-opioid-exposure* status, regardless of how slow a taper may be..

1. Using best practices, screen patients for taper participation.
 - Hx must include inability to taper below specific dosage range.
2. Determine, if possible, hx slowest rate of taper previously possible.
3. Prescribe slowest rate patient willing to try, e.g., 1% - ?%/month.
4. If unable to taper at 1%/month, consider Rx permanent maintenance or further individualize.

Two Underlying Hypotheses re Exponential Tapers

- ❖ Opioid tapers with formulations that adhere to the consensus exponential guidelines will enable significantly more patients to achieve their low dose, or abstinence tapering, objectives than was previously possible.
- ❖ Lack of precision in off-label approaches significantly limits efficacy.

HYPOTHESIS:

Is possible to quantify this relationship:

- 1) **degree of adherence** which a patient can achieve to an exponential, or very small step taper, and;
- 2) **efficacy** of meeting tapering goals of patients trying that taper.

Example of 10% per month taper regimen: What degree of adherence is necessary?

❖ Assuming a patient can tolerate a 10% per month taper, how closely must dosages adhere to guidelines to reach zero?
Not known.

❖ How many additional patients will be served by such adherence ? ***Not known.***

A 10% per month taper

- ❖ Patient at 2.00 mg total dose per day in **Month #1**
- ❖ End of each month, dosage reduces by 10%
- ❖ E.g.: In 12th month, daily total dosage is 0.63 mg
- ❖ E.g.: In 24th month, daily total dosage is 0.18 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

Examples of taper dosages steps down:

Month #1 at 2.00 mg daily total dose and 10% monthly taper

Total daily dosages months 1, 2, 11, 12

Month 1: 2.00 mg daily total

Month 2: 1.80 mg daily total

Per dose: 0.20 mg decrement

Month 11: 0.70 mg daily total

Month 12: 0.63 mg daily total

Per dose: 0.07 mg decrement

Total daily dosage in two divided doses

Month 1: 1.00 mg **b.i.d.**

Month 2: 0.90 mg **b.i.d.**

Per dose: 0.10 mg decrement

Month 11: 0.350 mg **b.i.d**

Month 12: 0.315 mg **b.i.d**

Per dose: 0.035 mg decrement [22]

Weekly steps down:
2.3%/week closely approximates *10%/month*

Week	1	2	3	4	5	6	7	8	9	10	11	12
Dose mg Day	2.00	1.95	1.91	1.87	1.82	1.78	1.74	1.70	1.66	1.62	1.59	1.55
Week	13	14	15	16	17	18	19	20	21	22	23	24
Dose mg Day	1.51	1.48	1.44	1.41	1.38	1.35	1.32	1.29	1.26	1.23	1.20	1.17

Weekly steps of 2.3%

Total daily dosage

Week 1: 2.00 mg daily total

Week 2: 1.95 mg daily total

Per dose: 0.05 mg decrement

Week 23: 1.20 mg daily total

Week 24: 1.17 mg daily total

Per dose: 0.03 mg decrement

Total daily in **two** divided doses

Week 1: 1.000 mg b.i.d.

Week 2: 0.975 mg b.i.d.

Per dose: 0.025 mg decrement

Week 23: 0.600 mg b.i.d.

Week 24: 0.585 mg b.i.d.

Per dose: 0.015 mg decrement ^[24]

Withdrawal symptoms as function of amount of dosage step down

Two ways to decrease by 10% per month

**Entire amount all in *one* step with entire 10% amount
or
same amount of medication in *multiple* steps**

Example of 0.20 mg reduction of a 2.00 mg dosage: *if one step* after a month, 30 days, then 0.20 mg all from Day 30 to Day 31

But if same 0.20 mg in four 0.05* mg [decrement *with one step* every 7 days, will the four steps of 0.05 mg make the 0.2 mg reduction more tolerable than all in one step of 0.20 mg?

* Actual amount of reduction is 0.046 mg, i.e., 4/1000 mg less than 0.05 mg.

HYPOTHESIS: One possible outcome of tapering that is slower than possible previously

❖ *Increased numbers of patients in medication-assisted treatment with opioids would be enabled to reach their elective tapering goals*

How closely to the consensus guidelines must an opioid taper adhere in order to be efficacious?

Is tapering efficacy a function of adherence to exponential decrease?

To what degree, i.e., how closely, must the dosages of a taper follow a consensus taper in order to have acceptable levels of efficacy?

At relatively low dosage levels, such as below 1 or 2 mg/day buprenorphine, to what extent must the taper adhere to the exponential arithmetic of tapering, in order to be efficacious?

Tapering can increase risks to patient

- ❖ Prior to consideration for a taper, an evaluation by addiction medicine specialist, or equivalent, is indicated.
- ❖ Some patients currently in MAT are not candidates
- ❖ Taper to abstinence, or very low dosage levels, causes loss of tolerance to opioids.
- ❖ After loss of tolerance, a previously well-tolerated opioid dose *can be fatal*.
- ❖ With patients with certain histories, tapering found associated with an increase in mental health episodes

How many patients taper to abstinence?

- ❖ Anecdotal reports vary
- ❖ Stanford-*Lancet* report of Rao (2021)¹ clear; conclusion is 9%, but are the results accepted?
- ❖ 61,284 desist of 669,763 patients in pharmacotherapy¹

1. Rao, Humphreys, Brandeau Stanford/*Lancet* study 2021

Percentage MAT desistance/year = 9%

Rao, Humphreys, Brandeau
Stanford/*Lancet* study 2021

U.S. population age 12 and older	276,077,200
Severe opioid use disorder prevalence (SOUD) = 0.49%	1,352,778
Severe heroin use disorder prevalence (SHUD) = 0.36%	993,878
Percent of SOUD population enrolled in pharmacotherapy = [13%]-26%	351,722
Percent of SHUD population enrolled in pharmacotherapy = [16%]-32%	318,041
Rate of desistance from SOUD in pharmacotherapy, %/month = 1.0%	3,517
Rate of desistance from SHUD in pharmacotherapy, %/month = 0.5%	1,590
Desistance SOUD+SHUD per year = 5,107 x 12 =	61,284
Total enrolled in pharmacotherapy =	669,763
Percentage desistance/year:	61,284/ 669,763 = 0.0915 = 9%

[https://www.thelancet.com/pdfs/journals/lanam/PIIS2667-193X\(21\)00023-5.pdf](https://www.thelancet.com/pdfs/journals/lanam/PIIS2667-193X(21)00023-5.pdf)

<https://doi.org/10.1016/j.lana.2021.100031>

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A major aim of RCT examining consensus tapers:

To demonstrate if causal relationship between:

1. adherence to exponential tapering guidelines and
2. tapering efficacy.

Answers the question: Do patients who closely follow a precision exponential taper reach their tapering objectives more often than patients who do not?

Bottom Line regarding value of precision tapers:

EITHER:

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1) Clinical trials will demonstrate that close adherence to the exponential consensus tapering guidelines is required for tapering success for significant numbers of patients, and therefore precision tapers can indeed make a contribution toward treatment of opioid dependent patients who elect to taper,

OR:

2) Clinical trials will show that close adherence to accepted guidelines is not required for any patients and precision tapers will not be helpful.

Statement of Interest
Patent granted Joseph Grossman, on February 22, 2022, for
“Opioid Taper Regimen.”
U.S. Patent 11,253,512 B2
Special thanks to Vincent Idemyor, Pharm.D.

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May be accessed at:
patents.google.com/patent/US11253512

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