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Review

Tapering and withdrawing opioids: guidance informed by fundamental principles to minimise withdrawal symptoms

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***Abstract*:** Formal guidelines recommend that opioids should be stopped when risks outweigh benefits. These guidelines generally recommend gradual dose tapering at a rate tolerable to the patient. However, there is considerable variation regarding the pattern of dose tapering recommended, with some suggesting linear tapers (with a fixed reduction of dose at each step), while others recommend increasingly small dose reductions as the total dose gets lower. No biological rationale has been put forward for these recommendations. We examined the pharmacodynamic properties of opioids to derive pharmacologically rational principles for tapering. As dictated by the law of mass action, the relationship between dose of opioid and effect on its principal target, the mu-opioid receptor, is hyperbolic, with diminishing incremental effects for increasing doses. This suggests that in order to mitigate withdrawal symptoms, opioid doses should be tapered according to a corresponding hyperbolic pattern, with dose reductions becoming increasingly small as total dose reduces. This can be approximated by proportional decreases (e.g. 1%–10% reduction of the most recent dose every 1–2 weeks). Dose reductions should be titrated to withdrawal symptoms throughout the process, and final doses before complete cessation will need to be very small (such as 0.1 mg of buprenorphine or 1 mg of methadone, or less). The duration required for this strategy of tolerable tapering after long-term use may require many months or years for some patients. The theoretical proposals in this paper offer a pharmacologically rational strategy that should prompt review of clinical practice and guidelines. Gradual, hyperbolic tapering should be evaluated in randomised controlled trials.

Plain language summary

How to minimise withdrawal effects when reducing opioids

Many patients would benefit from reducing or stopping opioid medication when the harms outweigh benefits. There are numerous current guidelines making recommendations on how to reduce doses of opioids. Many recommend that doses are reduced in a linear manner – that is, by the same dose every week or two (e.g. 4 mg of buprenorphine per week). A few guidelines recommend reducing by smaller and smaller sized doses every period. We reviewed studies that have looked at how opioids affect the brain to determine which approach is most advisable for patients.

The relationship between dose of an opioid and its effect on the brain, as revealed by brain imaging, is not linear (where doubling the dose doubles the effect). Rather, it is curved (called hyperbolic): small doses have out-sized effects and as the dose gets larger the effect flattens out. As a result, it makes sense to reduce the dose in such a way that

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reflects this relationship. This means reducing dose by smaller and smaller amounts (known as hyperbolic tapering) may reduce the risk of withdrawal effects.

We develop examples for reduction regimens for commonly used opioids like methadone and buprenorphine from these principles. For any opioid, reducing at 1-10% of the most recent dose every 1-2 weeks is an example of application of these principles. Formulations other than widely available tablets or capsules may be required in order to implement this in clinical practice. The rate of reduction should be adjusted to the withdrawal effects experienced by the patient. This approach may allow patients who were unable to cease their opioid with traditional linear approaches to do so safely thereby reducing unnecessary harm to patients.

Keywords: hyperbolic tapering, law of mass action, opioid withdrawal, receptor occupancy, mu-opioid receptor

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> I had one sixteenth of an ounce of junk with me. I figured this was enough to taper off, and I had a reduction schedule carefully worked out. . . I had the junk in solution, and in another bottle distilled water. Every time I took a dropper of solution out to use it, I put the same amount of distilled water in the junk solution bottle. Eventually I would be shooting plain water. This method is well known to all junkies.
>
> -William Burroughs (1953), Junkie, p. 72

Introduction

Opioids are valuable medications which can relieve pain and reduce suffering.[1] They also have an established role as opioid agonist treatment (OAT) in maintenance treatment for opioid use disorder. However opioid use can sometimes pose serious risks in the short- as well as long-term, including overdose, dependence, addiction and reduced quality of life, as well as increased pain and emergent psychiatric symptoms.[1,2] A dose-dependent association between long-term opioid treatment and an increased risk of myocardial infarction, fractures, falls and even all-cause mortality has been suggested from observational studies.[3,4] Guidelines recommend that opioid treatment should be stopped when risks outweigh benefits, and that, in the long-term, stopping often improves function, sleep, anxiety and mood, and generally does not worsen (and may improve) pain.[5] Nevertheless, most longitudinal studies have found that patients on opioid agonists are not able to successfully complete tapering attempts.[6–8]

In this paper we examine the recommendations proposed in influential guidelines for the pattern of opioid tapering and identify some pharmacological principles that might help to rationalise the process of tapering and thereby improve the outcomes of discontinuation by minimising withdrawal symptoms. The principles outlined relate both to tapering opioid medications used for opioid use disorder and those prescribed for pain, as the principles of tapering (related to pharmacological laws) are the same. However, for opioid use disorder: there are aspects beyond the pharmacology of opioids that influence cessation, and, in general, the current standard of care for opioid use disorder is ongoing maintenance of opioids, such as methadone and buprenorphine, rather than tapering. Nevertheless, a substantial number of patients strive for abstinence from all opioids notwithstanding the challenge and the risk of relapse.

Approaches to tapering opioids

There is consensus on a number of principles regarding tapering opioids in influential guidelines.[5,9–11] No guideline recommends abruptly stopping opioids because of the severe withdrawal symptoms that result, including serious psychological distress, anxiety, restlessness, insomnia, intestinal cramps, severe craving, increased pain and suicidal thoughts.[5] Instead, most guidelines espouse the core principle that dose tapering be undertaken in order to minimise withdrawal symptoms,[5,9] as emphasised in a recent label change by the Federal Drug Administration (FDA).[12] The rationale for tapering is to reduce

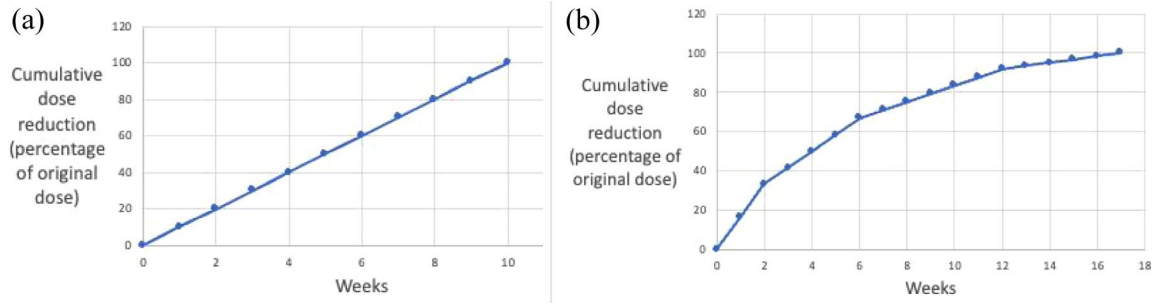

Figure 1. (a) Linear dose reductions recommended in a fast taper by the Centres for Disease Control (CDC).[1] The graph shows cumulative dose reductions over time expressed as a percentage of the starting dose. (b) Stepped linear dose reductions recommended by the Royal College of General Practitioners, which approximates an exponentially decreasing pattern of dose reduction.[10] The graph shows cumulative dose reductions over time expressed as a percentage of the starting dose.

the intensity of withdrawal symptoms and thereby to improve the chance of dose reduction or cessation.[5,11] In order for the process to be successful, patients require a clear commitment to stop opioids and need considerable support;[5] incautious tapering can do harm, shaking patient confidence and reducing the chance of successful deprescribing and should not be imposed.[12,13]

Guidelines recommend that tapering rates should be individualised according to withdrawal symptoms and the goals and concerns of the patient, with shared decision-making central throughout,[5,9,12] including ongoing communication about difficulties experienced.[1,14] Guidelines also emphasise the importance of patients learning non-pharmacological approaches to managing pain, distress and withdrawal symptoms.[5] There is also consensus on the observation that the time taken for patients to taper off opioids is highly variable, with some patients requiring months or years to successfully stop opioids, especially when use has been prolonged.[5,13]

Recommended patterns of tapering

Despite this, consensus guidelines are inconsistent with respect to the pattern of dose tapering they recommend. In a linear reduction pattern, the dose of opioid is reduced by a fixed amount (e.g. 5 mg or 10% of the original starting dose) in each step (or period) of reduction. The influential Centres for Disease Control (CDC) Guideline for Prescribing Opioids recommends a linear reduction of opioid doses: 'A decrease of 10% of the original dose per week' or 'slower tapers (e.g. 10% per month)' for longer term users (Figure 1(a)).[1] More recent guidance from the United States Department of Health and Human Services (HHS) recommends dose reductions that decrease in size as the total dose becomes lower: 'A decrease of 10% of the original dose per week or slower (until 30% of the original dose is reached, followed by a weekly decrease of 10% of the remaining dose)'.[5] This is effectively a two-stage linear process. Previous NICE guidance in the UK also recommended linear reductions of methadone (5 mg every 1–2 weeks, irrespective of the dose) but suggests a two-stepped linear approach for dose reductions of buprenorphine: '2 mg around every two weeks, with final reductions of around 400 micrograms'.[9]

The Burroughs quotation at the beginning of this paper illuminates a rather different, nonlinear method of tapering; a method of exponential dose reduction (where each reduction in dose becomes smaller and smaller) – that had also been suggested in 1990.[15] In fact, some existing guidelines do recommend similar patterns of tapering. For example, UK and Australian guidelines recommend the regimen in Table 1.[10,11,16] This schedule is composed of several steps of linear reductions which approximates an exponential reduction (Figure 1(b)). However, no pharmacological rationale has so far been proposed to justify one regimen over another. We outline a clear pharmacological rationale for exponential over linear tapering below.

Methods

We outline a conceptual overview of pharmacologically rational principles for tapering opioids based on a narrative review examining the pharmacodynamic properties of opioids. We

Table 1. Recommended dose reduction pattern for buprenorphine from Royal College of General Practitioners (UK).[10].

Daily buprenorphine dose	Reduction rate
Above 16 mg	4 mg every 1–2 weeks
8–16 mg	2–4 mg every 1–2 weeks
2–8 mg	2 mg every 1–2 weeks
Below 2 mg	0.4–0.8 mg every 1–2 weeks

examined published studies investigating occupancy of the mu-opioid receptor (MOR) by opioids using positron emission tomography (PET) scanning in clinical subjects, as well as studies examining the relationship between occupancy and clinical effects, including withdrawal effects, searched via Google Scholar. There was a single study by Greenwald et al.[17] (as reported in Greenwald et al.[18]) that reported occupancy data for mu-opioid occupancy for buprenorphine. From this study we developed pharmacologically rational schedules for dose reduction. We also briefly review existing evidence for rate of taper, the utility of adjunctive treatment and nonpharmacological aspects of opioid dose reduction and cessation.

Results

Neurobiology of opioid tapering

Opioids produce their analgesic and dependency-forming effects through agonism of opioid receptors, and, most importantly, the MOR, with downstream effect on GABAergic and dopaminergic neurotransmission.[2,19,20] Tolerance develops with repeated use whereby, as a result of changes at the metabolic or cellular level, the same dose produces less effect, or higher doses are required to achieve the same effect.[2,20] At the cellular level tolerance occurs because of the drive to homeostatic balance,[2] involving de-sensitisation and down-regulation of MORs, as well as modifications to the mu-signalosome, neuronal proteome, transcriptome and neuronal morphology,[20] with consequent downstream effects on mesolimbic dopaminergic neurons.[19,20]

Withdrawal symptoms occur when opioids are reduced or stopped because the raised homeostatic set-point of the mu-opioid system registers reduced doses as 'under activation'.[2,20] This concept is supported by the ability of MOR antagonists to induce withdrawal symptoms in individuals with physiological opioid dependence.[19] The time taken for withdrawal symptoms to resolve probably reflects the time taken for neuro-adaptations of the mu-opioid system, and its downstream effects, developed during use to 're-tune' to lower levels of agonism and establish a new homeostatic set-point.[20] This process of re-setting of neurons and networks has been estimated to take between hours and years (although research is lacking in this area).[20,21]

The pivotal importance of the MOR in the effect of opioids is borne out by studies that find that opioid agonist effects are linearly related to occupancy of this receptor.[18] A linear relationship is also evident between occupancy of MORs and subjectively measured withdrawal symptoms, with greater withdrawal symptoms correlated with lower MOR occupancy in subjects with opioid use disorder.[18] This suggests that tapering opioids in a manner that reduces MOR occupancy in a linear fashion will produce less severe, 'evenly spread' withdrawal symptoms.

In order to achieve a pattern of tapering that achieves even reductions in effect at the MOR, a regimen consisting of progressively smaller decrements at each step is required (as shown in Figure 2 and Table 2), similarly to other psychotropic medications.[22–31] While the relationship between occupancy and subjective effect is linear, the relationship between dose of opioid and occupancy of the MOR is hyperbolic, as exemplified by the partial agonist, buprenorphine (Figure 2). This hyperbolic relationship is dictated by the law of mass action, where initial doses have the greatest effect but each additional gram of a drug has less and less effect as receptors become saturated.[32] These curves are captured by E_{max} equations of the form $E = E_{max} * \text{dose}/(\text{dose} + \text{ED}_{50})$, where ED_{50} is the dose required to produce half the maximal effect (E_{max}). The hyperbolic nature of this relationship is often obscured by the habit of plotting dose–response curves on logarithmic *x*-axes which creates the illusion of a sigmoidal or linear dose–response relationship, especially at intermediate doses.[32]

We derived a curve of best fit for buprenorphine from dose-occupancy data in Greenwald et al.[17] (as reported in Greenwald et al.[18]) where occupancy was measured 4 h after 12 days of maintenance treatment with doses ranging from 1 to

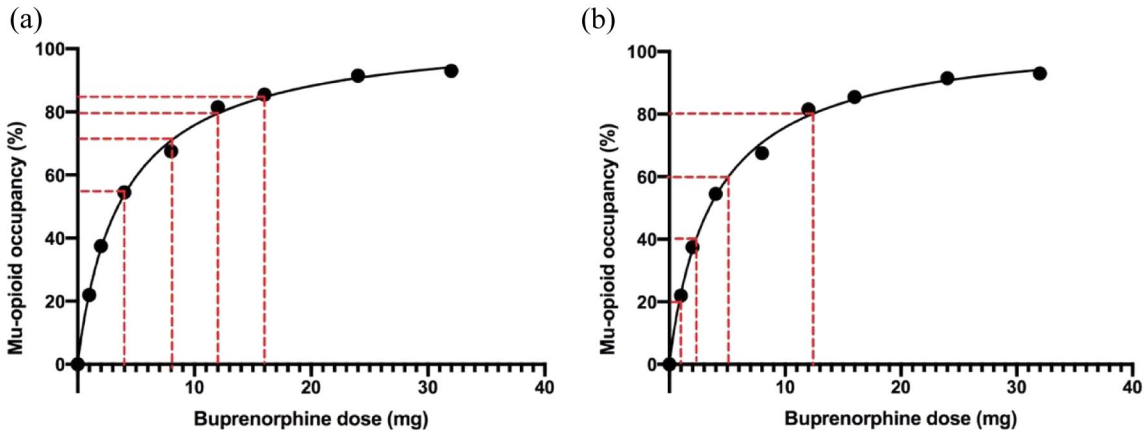

Figure 2. (a) Linear reductions of dose produce increasingly large reductions in effect on the MOR. (b) Hyperbolically reducing doses are required to produce equal-sized reductions in effect on the MOR (in this case 20 percentage points). Note how small final reductions before zero will be required to be to prevent a greater decrease in effect than has been tolerable for previous steps.
MOR, mu-opioid receptor.

Table 2. Dose reduction schedule required to produce even reductions of effect at MOR (in this case by 10 percentage points).

Dose (mg)	MOR occupancy (%)
21.1	90
11.7	80
7.5	70
5	60
3.5	50
2.4	40
1.5	30
0.9	20
0.4	10
0	0

Source: The data are derived from a curve of best fit generated from the data in Greenwald et al.[17] (as reported in Greenwald et al.[18]).
MOR, mu-opioid receptor.

Table 3. MOR occupancy produced by linear reductions of dose of buprenorphine.

Dose (mg)	MOR occupancy (%)
32	95.1
28	93.7
24	91.8
20	89.3
16	85.7
12	80.5
8	71.6
4	53.9
0	0

Source: The data are derived from a curve of best fit generated from the data in Greenwald et al.[17] (as reported in Greenwald et al.[18]).
MOR, mu-opioid receptor.

32 mg (Figure 2 and Table 3). Plasma levels 4 h after dosing do not correspond to either trough or peak levels – however the relationship between dose and receptor occupancy will be hyperbolic at any given fixed sampling time given the law of mass action.[32] From this data, it can be seen that the recommended linear reductions of dose can be seen to give rise to increasingly large reductions in MOR activity (Figure 2(a)). In the case of buprenorphine, reducing dose by 4 mg from 16 mg will cause 5.2 percentage points reduction in MOR activity but the same-sized reduction from 4 to 0 mg will cause a 53.9 percentage point reduction, ten times the size of the former. This may explain why patients find it particularly difficult to reduce doses when at low total dose.[33] One systematic review found that withdrawal

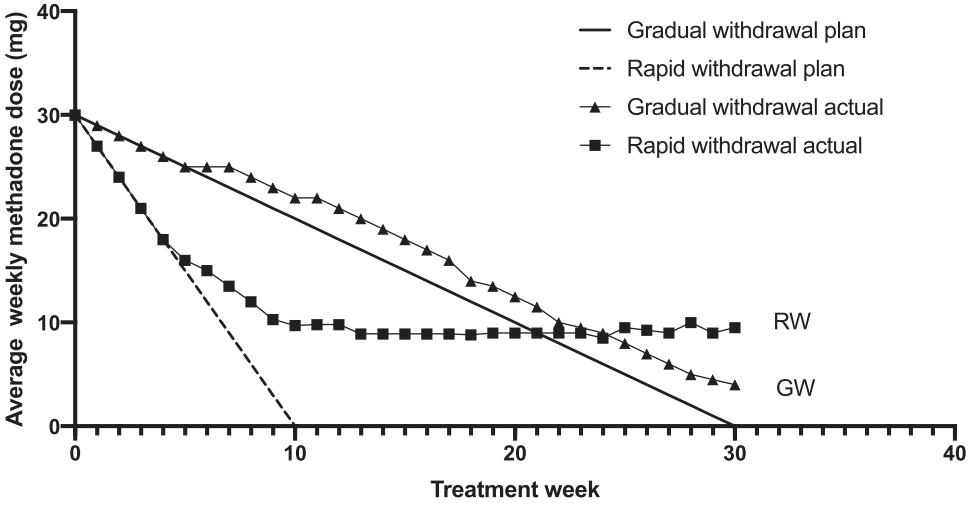

Figure 3. Average dose of methadone in groups assigned to different tapering protocols of methadone. There were small deviations from protocol for the gradual withdrawal (GW) group (3% original dose/week). There were much greater deviations from protocol for the rapid withdrawal (RW) group (10% of original dose/week) that increased as total doses became smaller. This is consistent with the notion that fixed reductions of dose at lower doses have increasingly larger aversive withdrawal effects because they transduce increasingly large reductions in MOR occupancy.
Source: Figure adapted from Senay et al.[35]
MOR, mu-opioid receptor.

symptoms commonly peaked after buprenorphine dose had been tapered below 2 mg.[34]

This hyperbolic relationship between dose and activity may explain why in studies that have employed linear tapers (e.g. 10% of the original dose per week) patients do not comply with the dose tapering regimen, and instead modify the process to more readily fit a hyperbolic pattern (Figure 3).[35] Deviation from the protocol did not occur at high doses (greater than 2 mg/day of methadone) but started to occur when doses approached 2 mg/day of methadone, with most patients refusing a linear rate of reduction completely at 1.5 mg/day of methadone.[35]

A linear reduction in MOR activity can be achieved by hyperbolic tapering in which the reductions in dose become increasingly small as the total dose decreases (Figure 2(b) and Table 3). For example, a reduction in dose of buprenorphine from 20 to 16 mg will cause less of an effect on target receptors than a reduction in dose from 0.4 to 0.2 mg. Exponentially reducing regimens (reducing by a proportion of the most recent dose, e.g. 10% of the last dose, with reductions decreasing in size at each step) are good approximations to these hyperbolic regimens. This is the principle encapsulated by the William Burroughs quotation above (which involves making increasingly small reductions in dose), and reflected to differing degrees in existing guidance,[5,9] particularly in UK and Australian guidance, in which the recommended pattern of cumulative dose reduction resembles the dose-occupancy of buprenorphine (note the similar shape of Figure 1(b) and Figure 2).[10,11] More explicit application of these principles to tapering regimens might improve the ability of patients to achieve cessation, particularly during the challenging final dose reductions, especially given that fear of withdrawal symptoms is one of the most common barriers to discontinuation.[6,36] A simplified summary of a regime that follows hyperbolic principles is given in Tables 4 and 5 that corresponds to receptor occupancy and also takes into account widely available formulations. Some deprescribing services which taper opioids have developed an exponential approach to dose reduction through trial and error. This roughly approximates hyperbolic tapering by making reductions by a fixed proportion of the most recent dose, so that the size of reductions becomes smaller as total dose reduces.

Table 4. An example tapering regime that uses easily available doses of buprenorphine and does not cause greater than 5% reductions of MOR occupancy at any step.

Dose (mg)	MOR occupancy (%)	Dose (mg)	MOR occupancy (%)	Dose (mg)	MOR occupancy (%)
32	95.1	5	59.8	1	21.7
28	93.7	4	53.9	0.8	18.1
24	91.8	3.6	51.1	0.6	14.1
20	89.3	3.2	47.9	0.5	12.1
16	85.7	2.8	44.4	0.4	9.87
14	83.4	2.4	40.5	0.3	7.57
12	80.5	2	36	0.2	5.17
10	76.7	1.8	33.5	0.1	2.65
8	71.6	1.6	30.9	0	0
7	68.4	1.4	28.1		
6	64.5	1.2	25		

Source: The data are derived from a curve of best fit generated from the data in Greenwald et al.[17] (as reported in Greenwald et al.[18]).
MOR, mu-opioid receptor.

Application to methadone

Along with buprenorphine, the most commonly used medication for opioid use disorder is methadone, a full agonist of the MOR.[37] Unfortunately, imaging of the relationship between methadone and opioid receptors has been difficult with two studies finding no relationship between dose and occupancy of opioid receptors.[38,39] This has been attributed to either the insensitivity of the radiotracers used, or to their inability to label receptors internalised by methadone agonism.[38] However, the relationship between dose and several effects of methadone, both behavioural and molecular, demonstrates a hyperbolic relationship, as would be expected of an agonist that conforms to the law of mass action.[32] For example, the relationship between dose of methadone and analgesic effects in mice is hyperbolic (Figure 4(a)), mirroring the relationship between dose of methadone and in vitro binding of MORs in mouse brain membranes (Figure 4(b)). Similar hyperbolic dose–response relationships are found for both objective measures (pupillary constriction, Figure 4(c)) and subjective measures (reported 'drug effect', Figure 4(d)) in humans.[40]

The presence of a hyperbolic dose–response relationship between dose and both behavioural and biological effects of methadone suggests that hyperbolic dose reduction regimen will be required to produce linear reductions in effect on target receptors (and the consequent behavioural effects, including withdrawal effects). Although methadone is a full agonist at the MOR, while buprenorphine is a partial agonist (meaning that methadone will produce greater agonist effects for a given level of MOR occupancy), the shared hyperbolic pattern of the curves will mean that similar patterns of tapering will produce approximately 'evenly-spaced' effects on receptor occupancy for both drugs.

It has been determined that approximately 56 mg of buprenorphine weekly is equivalent to 60 mg of methadone per day,[42] meaning 1 mg/day of buprenorphine is approximately equal to 7.5 mg/day of methadone. This allows conversion of the regimen shown in Tables 4 and 5 into an equivalent for methadone to provide a pharmacologically informed tapering regimen (Tables 6 and 7). This regimen could be made more precise using data directly from PET imaging of MOR

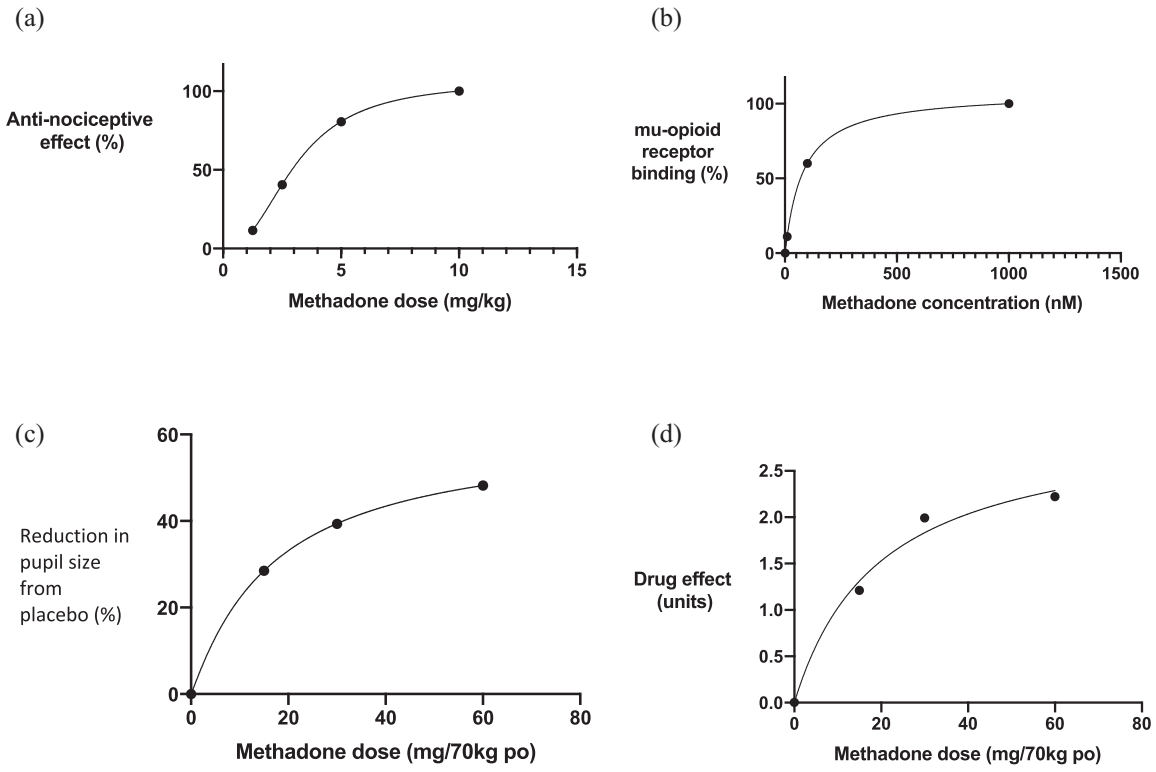

Figure 4. (a) The relationship between dose of methadone in mice and its anti-nociceptive effect is hyperbolic, derived from data in Doi et al.[41] (b) The relationship between in vitro concentration of methadone and proportion of MOR binding (measured by displacement of radio-labelled DAMGO) in membranes of mouse is hyperbolic, derived from data in Doi et al.[41] (c) The relationship between oral dose of methadone and reduction in pupil size compared with placebo in humans, derived from data in Eissenberg et al.[40] (d) The relationship between oral dose of methadone and reported drug effect ('Do you feel any drug effect?') in humans, derived from data in Eissenberg et al.[40]
MOR, mu-opioid receptor.

Table 5. A shorthand guide for tapering buprenorphine.

Daily buprenorphine dose	Reduction rate	MOR of lowest dose in step (%)
Above 16 mg	2–4 mg every 1–2 weeks	85.7
8–16 mg	1–2 mg every 1–2 weeks	71.6
4–8 mg	0.5–1 mg ever 12 weeks	53.9
2–4 mg	0.2–0.4 mg every 1–2 weeks	36.0
0.6–2 mg	0.1–0.2 mg every 1–2 weeks	14.1
Below 0.6 mg	0.1 mg every 1–2 weeks	0

Source: This guide is based on data derived from a curve of best fit generated from the data in Greenwald et al.[17] (as reported in Greenwald et al.[18]).
The maximum reduction in each option will produce less than a 6% point reduction in MOR occupancy; the smallest will produce less than 3% point reduction. MOR occupancy indicates each of the six dose ranges are approximately evenly distributed along MOR occupancy.
MOR, mu-opioid receptor.

Table 6. An example tapering regimen for methadone, calculated from the regimen for buprenorphine, using dose equivalence conversion.

Period	Dose (mg)	Period	Dose (mg)	Period	Dose (mg)
1	240	12	37.5	21	7.5
2	210	13	30	22	6
3	180	14	27	23	4.5
4	150	15	24	24	3.75
5	120	16	21	25	3
6	105	17	18	26	2.25
7	90	18	15	27	1.5
8	75	19	13.5	28	0.75
9	60	20	12	29	0
10	52.5	21	10.5		
11	45	22	9		

occupancy for varying doses of methadone if this became technically feasible with more appropriate radiotracers. The greatest uncertainty comes with the final reduction to zero – if there is imprecision in the calculations derived to establish this lowest dose before cessation, the reduction in effect on MOR may be greater than the other steps, in which case it might cause greater withdrawal symptoms, necessitating more incremental steps before cessation. Pharmacologically rational tapering regimens could be calculated for other opioids, such as codeine, tramadol, fentanyl, hydrocodone and oxycodone, from primary neuroimaging (where it has been conducted) or from dose conversions. These regimens should be implemented flexibly, guided by the ability of an individual to tolerate the process, rather than imposed rigidly.

Table 7. A shorthand schedule for tapering methadone, based on dose equivalent conversion from the buprenorphine schedule.

Daily methadone dose	Reduction rate
Above 120 mg	10–20 mg every 1–2 weeks
60–120 mg	5–10 mg every 1–2 weeks
30–60 mg	2.5–5 mg ever 1–2 weeks
15–30 mg	1–2.5 mg every 1–2 weeks
4.5–15 mg	0.5–1 mg every 1–2 weeks
Below 4.5 mg	0.25–0.5 mg every 1–2 weeks

Gradual tapers versus shorter tapers

One last element to consider in optimising tapering regimens for opioids is the duration of the taper. In general, the success rates of medically supervised opioid withdrawal are low.[6,7,33] One study examining almost 15,000 patients on opioid maintenance treatment for opioid dependence attempting a taper found that only 4.4% of patients were able to stop altogether or to reduce their opioids to a low dose (<5 mg/day of methadone).[33] It is possible that too rapid or linear patterns of tapering may contribute to the poor outcomes of opioid tapering, although there are likely to be a variety of variables involved.[33] In another analysis, only 13.7% of patients tapering opioids achieved complete cessation in a 9-year window.[43] In patients prescribed long-term opioid therapy for pain, success rates are better – 20% to 91% depending on the intervention used (although some of these interventions involved switching patients to buprenorphine rather than opioid cessation per se).[44]

Gradual tapers generally have better outcomes than shorter tapers. Long tapers (12–52 weeks)

and very long tapers (>52 weeks) were 3.6 times and 6.7 times, respectively, more likely to succeed (defined as sustaining less than 5 mg/day of methadone without complication) than short tapers (<12 weeks).[33] Small reductions in dose (<1% of the original dose as mean weekly change) were more likely to lead to successful outcomes than bigger reductions (1%–4% or >4% mean weekly change).[33] In another study population, tapering at a rate <5%/week doubled the chance of stopping opioids compared with tapering at a rate of 5%–10%/week.[45] Patients who tapered at less than 5 mg of methadone per week had a 5-fold increased chance of a positive outcome (in this case, heroin abstinence) compared with people who tapered at more than 10 mg of methadone per week.[45]

This is consistent with the findings of an older study that found reduced dropout rates, less illicit drug use, lower withdrawal symptom scores and fewer requests for study interruption in patients tapered by 3% of their original dose per week (53% achieved opioid cessation) compared with 10% of their original dose per week (24% achieved opioid cessation).[35] Overall, the rapid withdrawal group ended at a higher total methadone dose for the group, a finding consistent with Aesop's fable, 'The Tortoise and the Hare'.[35] As 47% of patients were still unable to achieve opioid cessation at a reduction rate of 3%/week, it may be that an even slower reduction schedule might improve cessation rates further.[35]

Evidence suggests that physiological adaptations to opioid dependence might take months or years to resolve. One line of evidence in support of this notion is the existence of long-lasting withdrawal symptoms, following opioid de-toxification, that persist for months and years sometimes called 'protracted withdrawal' or 'post-acute withdrawal syndrome'.[2,21,46,47] As withdrawal symptoms are thought to be produced by the mismatch between the raised homeostatic set-point of the mu-opioid system following long-term opioid dependence and levels of opioid agonism produced by medication,[48] these periods of time likely reflect the time period required for adaptations of the opioid system to resolve.[2,20,46,47] These time periods are consistent with the finding that tapers that occur over longer than 52 weeks are the most likely to succeed.[33] It may therefore be reasonable to expect people to take many months or years to taper off opioids (depending on duration of use) at a rate that produces tolerable withdrawal symptoms, so allowing underlying adaptations enough time to resolve.

In practice many patients are tapered much faster than the rates identified as optimal by these studies. A study of almost 100,000 patients found that the average rate of tapering was 34.0% of the original dose per month and more than a quarter of patients were tapering at a rate faster than 40% of their original dose per month,[43,49] even higher than the maximum rate recommended by the CDC.[1] Another study in China had similar findings: with 50.4% of patients tapered faster than guidelines recommend (>10% of the original dose/week), with only 38.7% of patients tapered in the 5%–10%/week range and only 10.9% tapered at <5% of the previous dose per week (the rate most likely to produce heroin abstinence at study end).[45]

A vitally important aspect to consider is the experience of the individual patient. Imposing too rapid a rate of taper for an individual with opioid use disorder may lead to a resumption of illicit use, a strong reason for a reduction regimen to be guided by the person's subjective experience of withdrawal symptoms, rather than being imposed based on a published regimen.

Limitations

Individual differences

One aspect to emphasise is the existence of inter-individual differences in both pharmacodynamic (evident in imaging studies, with identical doses producing different levels of receptor occupancy) and pharmacokinetic characteristics. The pharmacodynamic relationships explored above represents the averages across a population – whereas an individual may deviate from this (while still demonstrating a hyperbolic pattern, according to the law of mass action).[32] This means that the reduction regimens devised from average data should be approached cautiously. The best guide for an individual is the degree of withdrawal they experience, and this feedback should trump any derived regimen (while still conforming to a hyperbolic pattern). Additionally, the elimination half-lives of opioids can relate to both genetic (e.g. variations in CYP P450 iso-enzymes) and nongenetic factors (such as other interactions with other medications or substances),[50] and this can influence withdrawal effects. Aspects such as the greater lipophilicity of buprenorphine and its re-circulation from adipose

tissue may play some role in the tapering process by providing, in effect, a longer elimination half-life – which might have a beneficial effect on withdrawal effects (see below).[51] Further research may help elucidate these individual factors and help to develop personalised risk profiles to guide reduction regimens.

Approximations

In the preceding discussion, we have relied on opioid receptor occupancy derived from imaging 4 h post dose (neither representing peak or trough plasma levels) whereas there will be peak and trough variations each day in clinical practice, when the drugs are dosed once daily. This does not alter the overall principles but some patients may experience inter-dose withdrawal at trough plasma levels – this is more likely for fast metabolisers of methadone (half-life of 8–59 h, average 24 h) than for buprenorphine (half-life 25–70 h after sublingual administration, average 38 h). Inter-dose withdrawal may be ameliorated by more frequent dosing.

The other relevant approximation in this work is the principle proposed to extrapolate tapering regimens for a wide variety of opioids via equivalent dose conversions from the known relationship between dose of buprenorphine and mu-opioid occupancy. Given a lack of primary data of MOR occupancy for other opioids, this is the most feasible way of developing relevant regimens. As above for methadone, extrapolation from a partial agonist to a full agonist will involve 'scaling' whereby a higher dose of a partial agonist will be needed to have the equivalent effect on target receptors as a full agonist. Nevertheless, the shared hyperbolic pattern of the curves will mean that similar patterns of tapering will produce approximately 'evenly-spaced' effects on receptor occupancy for all opioids. There will be some variations based on binding and dissociation kinetics, and functional efficacy (intrinsic activity), among pharmacological properties, but due to the organising principle of the law of mass action, all drugs will follow a hyperbolic pattern of action. So while further primary imaging studies would be helpful in order to develop more precise tapering regimens for each opioid in the absence of such studies, extrapolation from buprenorphine's regimen is likely to be a workable approximation.

Other considerations

Pharmacokinetics and tapering

Any tapering scheme that minimises the change in occupancy per unit time is likely to minimise withdrawal effects. There are two major strategies to achieve this (within the constraints of the hyperbolic principles outlined). One strategy is to utilise longer acting opioids which will help to buffer the lowering of receptor occupancy, as, for example, methadone or depot medications, as outlined below. The second approach is that smaller dose reductions made more often are likely to cause less withdrawal effects than larger reductions made less often.[25] An analogy could be made to descending a stair well: in the same way as it will cause less impact on the knees to jump down one stair a day as compared with jumping down 30 stairs in one go and then waiting 30 days before repeating the process, smaller reductions of dose made more often are likely to produce less withdrawal effects because of smaller perturbations of the equilibrium.[25] This is often called 'micro-tapering' and generally requires a liquid version of a drug. For example, rather than reducing by 3 mg each month, reductions could be made by 0.1 mg per day. In this way, a short-acting drug can more easily simulate the gradual reductions of occupancy of longer acting drugs.

Nonpharmacological aspects of stopping opioids

In addition to the pharmacological aspects of tapering that have been the focus of this manuscript, there are additionally psychological factors that play an important role in tapering and cessation which we mention briefly here. This is particularly true for patients with opioid use disorder where compulsive use, loss of control over intake and craving for the drug add significant barriers to reduction and cessation above and beyond those people who are just physically dependent on the drug. For example, in opioid use disorder, hedonic homeostatic dysregulation - manifesting as elevated reward thresholds and aversive, anxiety-like states during withdrawal - has been proposed to drive relapse and drug-seeking behaviour.[52] Addressing these issues are beyond the scope of this paper, which has mainly focused on people with physical dependence to opioids. However, a hyperbolic, gradual taper is likely to

minimise withdrawal effects which adds an extra drive towards drug resumption.

For those patients prescribed for pain the underlying pain disorder may present difficulties, despite it being now clear that opioids are largely ineffective for chronic non-cancer pain[53] and can even make pain worse. In the short term however, an increase in pain, potentially a withdrawal effect, can present a barrier to reduction – which can potentially be ameliorated by slower, pharmacologically informed tapering. Other important aspects that have been noted to increase cessation are patient willingness, motivation, level of engagement and personal circumstances.[54]

Lastly, expectancy effects have been shown to play a role in tapering.[35] Patients who are provided with maintenance treatment but blinded (so they do not know whether they are reducing or maintaining) show drop-out rates almost as high as those who are gradually withdrawing from medication,[35] suggesting that expectations of withdrawal (nocebo effects) may contribute to patients' difficulties. This is supported by another study which demonstrated that patients with opioid use disorder who were receiving methadone maintenance treatment showed more symptoms when they were blinded to a taper schedule rather than informed about dose reductions, suggesting that blinding led to greater anxiety and uncertainty for the participants.[55] However, in this study and others,[56] blinded or open tapers have not demonstrated significant differences in rates of opioid cessation. There are substantial limitations to these studies however with participants continuing to use heroin in some cases, very small sample sizes, contradictory findings, missing details about blinding procedures (e.g. whether there were any visual or olfactory clues that would have indicated timing of reduction), likely too-fast rates of reduction and, in the case of Ralphs et al., nonrandomisation to condition.[56] Given the limitations in these studies, further research in this area may be required to determine the role of blind tapers. This should be considered within the principle of shared decision-making and the understanding that gradual, hyperbolic tapering is likely to be a key aspect in safe tapering. Indeed, other commentators have suggested that psychological factors can be minimised by undergoing a slow taper and ensuring the patient knows that the rate can be adjusted if need be: this contributes to a less anxiety-provoking process.[57]

For patients prescribed opioids for pain, it is important to inform them that generally speaking tapering off opioids does not increase pain and, in fact, may lead to a reduction in pain intensity over time: 80% of such patients show a reduction in pain, 15% have no change to their pain and only 3% have an increase in pain intensity.[58] The patients most likely to have a reduction in pain severity are those with mild to moderate pain.[58]

Use of adjunctive medications

The use of other medications during tapering has been associated with successful cessation,[59] including various antidepressants, antipsychotics, gabapentin and pregabalin. However, these medications themselves can cause physical dependence and withdrawal effects though apart from gabapentin and pregabalin have not been implicated in abuse or use disorders. Use of technically nonaddictive medication may be preferable for some patients. However, NICE explicitly recommends against using adjunctive medication with dependence forming properties when tapering off opioids.[60] In some cases, use of adjunctive medications in the long term can mean that one dependency-forming medication has been traded for another: not ceased but rather switched. Rather than concealed with additional medication, withdrawal effects in general should be seen as an important signal that the rate of reduction is too great for the person's physiology to accommodate and be an indication that rate of tapering should be slowed down. Analogically, altitude sickness on rising altitude (akin to an 'air pressure withdrawal syndrome') too rapidly is best treated by maintaining altitude and slowing the rate of incline rather than continuing at the same rate and using adjunctive medication to conceal the effects. Occasional, limited use of symptomatic adjunctive medication, such as alpha α2-adrenergic receptor agonists, may be a reasonable strategy.

Suggested tapering practice

We have outlined a tapering regimen that is consistent with the pharmacodynamic properties of opioid agonists. In order to produce even reductions in effect of opioids on their principal target, the MOR, opioids should be tapered according to

a hyperbolic pattern. These regimens may minimise the severity of withdrawal symptoms with every step of a reduction, potentially contributing to more successful outcomes for opioid cessation. These regimens can be approximated by exponentially reducing regimens (reduction by a proportion of the last dose), outlined in simple form in Tables 5 and 7.

The guidance provided in this paper should be regarded only as a useful framework, as neurobiological and psychological sensitivity will differ between individuals. Patients should taper at a rate that is tolerable to them, dictated by the emergence of withdrawal symptoms. This is not to abandon the principles outlined above regarding hyperbolic tapering (it is useful to have a map of the territory) but to suggest that it may need to be adjusted to the individual. Gradual tapering may be required, which may mean the complete process of withdrawal can take months or years. A suggested approach, involving shared decision-making, may be an initial step of reducing patients by 1%–5% of their current dose with subsequent monitoring of withdrawal symptoms for 2 weeks (or as long as it takes for withdrawal symptoms to resolve). The tolerability of this experience can be used to determine the size of the next dose reduction (based on a proportional reduction of the patient's most recent dose). This process can be re-iterated, titrating rate to the patient's experience of withdrawal symptoms, acknowledging that there is a wide variety in the ability of patients to tolerate reductions, and that some patients may reduce less than 1% of their dose per week.[33] These reductions should continue until patients reach a dose from which a reduction to zero does not cause a greater reduction in MOR occupancy than previously tolerated reductions. For buprenorphine, the final daily dose required may be 0.1 mg or less, and for methadone 1 mg or less. Further research may allow stratification of patients based on recognised risk factors to determine which tapering regimen may be most appropriate, but we currently lack this level of understanding.

Formulations for tapering

Although buprenorphine and methadone are available in either small tablet formulations or liquid solutions, the lack of graduated dosages in tablet form can be one barrier to simple application of pharmacologically rational hyperbolic tapering[61] which requires small changes in dose and very small final doses before complete cessation. Indeed, 28% of physicians working in addiction cited difficulties with tapering opioids because of a lack of tablets at lower doses.[36] Both opioids examined here have relatively long plasma elimination half-lives (37 h for buprenorphine and 29 h for methadone)[16] which can facilitate gradual tapers, especially as these plasma half-lives may be shorter than receptor binding half-lives. In the US, the smallest available dose for sublingual buprenorphine is 2 mg, but buccal film is available in as small as a dose of 75 ug, equivalent to 150 ug of sublingual buprenorphine,[62] potentially facilitating some of the regimens outlined here. The use of liquid versions of opioids (produced by their manufacturer or by compounding pharmacies) or compounded smaller dose tablets (or capsules) specially compounded are potential solutions when convenient formulations are not available.[63,64] Manufacturers might facilitate this process by producing smaller dose drug formulations.

Another option (perhaps most useful at higher doses) may be the use of the recently introduced long-acting injectable formulations of opioids. There are formulations with terminal half-lives of 19–25 days in the UK and Europe[65] and 43–60 days in the US and Australia.[66] Sequential lowering of the doses of these long-acting formulations or extending the dosing interval[67] might provide a smoother transition in tapering dose, making the process more tolerable. However, as previously demonstrated for antipsychotic depots,[68,69] even slow tapering of depot preparations by extending the dosing interval and lowering to the smallest available dose may present too fast a reduction in MOR for some patients to tolerate (e.g. those who require 1% reductions per week). It is likely that abrupt cessation of even the smallest dose of depot may entail too rapid a reduction in MOR for some patients and so will require a switch to oral medication to complete the taper.[68] There are pros and cons to such an approach: relative simplicity on the one hand, but also a lack of control for the patient, with difficulty varying the rate of decrease (such as can be achieved with shorter acting oral medications) recognised to be a helpful element in the discontinuation process.[69] Another option may be presented by use of the very long-acting buprenorphine implant (Sixmo),[70] which exhibits flip-flop pharmacokinetics (where the absorption half-life predominates over the elimination half-life to determine duration of drug action)[71] and might allow gradual tapering by reducing the number of implants used. An examination of the

effectiveness of these approaches in clinical trials may be useful.

Further research

The principles outlined in this paper might be explored in randomised controlled trials comparing linear tapers with hyperbolic tapers, or by correlation of withdrawal symptoms with size of dose reductions. A prospective RCT may compare tapering linearly (e.g. 10% per month as per CDC guidelines) with tapering gradually and hyperbolically over 2 years, either open-label or even using double-blinded schedules, to see if hyperbolic tapering achieves superiority in terms of cessation of opioid use (or drop-outs) by study end. Such a trial might exclude the use of ancillary medication to remove a confounder, or might regard use of more than minimal use of ancillary medication as a proxy for failure of the prescribed regimen.

It would be useful to create opioid tapering nomograms which would agglomerate the average rate of opioid tapering (as well as the standard deviations), which might be related to characteristics such as age,[33] duration of use, dose[10] and type of opioid, and other individual characteristics, including pharmacokinetic characteristics, which might provide a guide to predict the average duration of tapering for an individual, while acknowledging individual idiosyncratic differences.

Conclusion

The pharmacological rationale for hyperbolic tapering has been outlined so that it might encourage and inform physicians and guidelines to adhere more closely to a hyperbolic pattern of taper with the objective of improving successful completion of opioid cessation by minimising withdrawal symptoms.

Declarations

Ethics approval and consent to participate

No ethics approval was required for this paper because no subjects were involved.

Consent for publication

Not applicable.

Author contributions

Mark Abie Horowitz: Conceptualisation; Formal analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Adele Framer: Writing – review & editing.

John Strang: Supervision; Writing – review & editing.

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Competing interests

MAH is a co-applicant on the RELEASE and RELEASE+ trials in Australia, funded by the Medical Research Future Fund and the National Health and Medical Research Council, evaluating hyperbolic tapering of antidepressants against care as usual. MAH reports being a co-founder of and consultant to Outro Health, a digital clinic which provides support for patients in the US to help stop no longer needed antidepressant treatment using gradual, hyperbolic tapering. MAH receives royalties for the Maudsley Deprescribing Guidelines: Antidepressants, Benzodiazepines, Gabapentinoids and Z-drugs. AF is founder of the Psychotropic Deprescribing Council, a non-profit organisation for research and education, and SurvivingAntidepressants.org, a peer support website, and does not receive any compensation, monetary or otherwise, for serving in these capacities. DT has received investigator-initiated research grants, and spoken at events for AstraZeneca, Eli Lilly, Janssen, Lundbeck, Otsuka, Servier, Sunovion, Viatris and Recordati and has shares in Myogenesg, Saladax and

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Availability of data and materials

All relevant data are contained in this manuscript.

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