A STANDARDIZED OPIOID TAPER?

Is it time for a clinical trial of a standardized opioid taper based on a "new understanding" of sensitivity to opioid dose reductions at low doses?

What would be this "*new understanding*" about sensitivity to dose reductions at low doses?

The New Understanding:

- With some classes of medications: Patient sensitivity to dose reductions ***at low doses*** may be greater than previously understood by most practitioners. “Sensitivity” here means a response that includes withdrawal symptoms.

- This sensitivity to reductions at low doses appears to include SSRI’s and may include opioids.

The Lancet article on SSRI's

"Tapering of SSRI treatment
to mitigate withdrawal symptoms,"*

- At *very low doses* of SSRI, it is more difficult for a patient to tolerate the same milligram magnitude of dose reduction that the patient tolerated at *higher* doses.

- *Lancet* article makes no mention of opioids. The phenomenon of increased sensitivity to dose reduction at low doses of opioid has been widely observed and commented upon.

*Horowitz, A, Taylor, D. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry*, 2019; 6 – 538-546. [Available on request.]

The protocol in this slide presentation was developed and discussed prior to the publication on March 5, 2019, of New York Times article regarding Lancet's June 2019 publication about SSRI's

- Protocol here is for an ***opioid*** taper.
- The opioid dose reductions are small enough to be consistent with the *Lancet* article.
- May involve smaller dosage reductions than indicated in the *Lancet* article for SSRI's.

> *Lancet* article indicates a new order of magnitude, for SSRI dose reductions may be required if withdrawal symptoms are to be better avoided, i.e., smaller reductions.

> Although: Serotonin transporter (SSRIs) and the opioid receptor mechanisms that lead to withdrawal symptoms are different mechanisms.

> We can still ask: *Does the increased sensitivity to opioid dose reduction at lower doses show a similar pattern and arithmetic to that of SSRI's?*

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> To better understand opioid tapers and succeed with opioid tapers:

> Are dose reductions at low dosing levels orders of magnitude smaller than previously believed necessary?

> We know empirically, that most opioid tapers fail. Dose reduction at low doses?

> Dosing *intervals* also raise important questions. More detail later.

In this standardized opioid taper:

* Size of dose reduction is smaller than in previous trials, per unit of time.

* *Interval* of dosing is shorter than usual.

* Addresses the parameters needed to avoid the sensitivity to dose reductions at low doses.

It may not be easy to accept the degree of (hyper)sensitivity to dose reduction that occurs at low doses.

Are there elements of maintenance and taper?

This taper is designed for patients in a well-supervised maintenance program who have stabilized at a relatively low dose (2 to 4 mg/day?) and who elect, and are motivated, to try to go to abstinence. Designed with buprenorphine in mind as the opioid, in part due to half life.

An example of sensitivity change with dose with a different class of medication, SSRI's

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:

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. More than two orders of magnitude. Opioid knowledge is empirical.

The foregoing is intended to demonstrate that ultra-sensitivity to dose reduction at low doses, here *SSRI's* is possible.

Empirically, it is known that withdrawal symptoms with X mg *reduction* at low doses of *opioid* are more likely than with X mg *reduction* at higher dose of opioid.

- Once accept concept that withdrawal symptoms may be more likely with dose reduction at very low opioid doses*, the protocol described here makes sense:

*“*Very low opioid doses,” here means at 2 mg or less buprenorphine/day or less. For some, super-sensitivity could start at higher dose, e.g., 4 mg/day, total dose.*

General Elements of Opioid Taper Kit

Patient must demonstrate stability at the same relatively low dose for *at least* four weeks before starting.

· *The following information is proprietary.*
Please do not share without permission.

The novel elements of prepackaged opioid taper kit

- Amount of dose reduction per time period.
- Interval of dosing.
- Very low dose at end for 8 weeks.
- Doubly unblinded placebo at end for 8 weeks.
- Pre-packaged.
- 28-dose card.

Pre-packaged Opioid Taper Kit

Dose size and dose reduction magnitude

Assume starting at 2 mg/day buprenorphine.

(There have been suggestions that a low dose starting point for a taper might be considered to be 4 mg/day buprenorphine or equivalent opioid dose.)

Two possible regimes:

1) Reduce dose by **1/100** of *initial dose* per week.

2) Reduce dose by **1/200** of *initial dose* per week.

For example, if initial dose of 2mg/day is reduced by **1/100** of the dose, then if in ***week*** # 28 dose is 1.52 mg/day. In ***week*** #29, dose is 1.50 mg/day. This is 0.02 mg reduction per week (!) - far lower than anything (ever?) proposed.

Dosing interval observations

Putting aside individual pt. variations and factors such as metabolism, stress, diet, disease, travel, and use of other medications.

Using online half-life calculator*
Buprenorphine, using 37 hour half-life.

FOLLOWING A DOSE OF BUPRENORPHINE:

At 6 (six) hours: 89 % of buprenorphine remains.

At 12 (twelve) hours: 80 % of buprenorphine remains.

At 23 (twenty-three) hrs: 65 % of buprenorphine remains. If a patient was indeed "hyper-sensitive," [the "new understanding"], patient would have withdrawal symptoms prior to scheduled dose at 12 hrs.

If super-sensitivity is real, then would expect withdrawal to start around 6 hours , with an 11 (eleven) % drop.

Protocol taper kit doses at 6 hour doses.

***Calculator used at https://www.calculator.net/half-life-calculator.html**

A medication with *24 hour* half-life, for example, methadone for someone in maintenance program

After 4 hours, 89% remains, 11% drop.

After 6 hours, 84% remains. 16% drop.

After 12 hours, 71% remains. 34% drop.

After 23 hours, 51% remains, 49% drop.

If super-sensitivity at low doses is the norm, would dose at 4 hours.

Other dosing features; packaging and concept review

*Low dose at end for weeks..

*Double blinded placebo at end for weeks.

*Spreadsheet schedule (Provided separately).

*Packaging

This protocol has been reviewed by:

Vincent Idemyor, PharmD, co-editor of *Drug Discovery and Development, 3rd Ed*., publication scheduled for 12/19. Dr. Idemyor concluded the taper protocol is based on sound pharmacological principles and might prove effective in a clinical trial.

*Provisional Patent granted Joseph Grossman, on April 8, 2019, for “Pre-packaged opioid taper kit.”
Provisional patent *#62/919,996*.
Because of the simplicity of design, confidentiality is requested

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