



UW PACC

Psychiatry and Addictions Case Conference

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THE TROUBLE WITH FENTANYL

TREATING OPIOID ADDICTION IN THE FENTANYL ERA



DISCLOSURES:

- None

- But... if you have some lucrative (and ethical) conflicts of interest I could add here let me know. I got loans.

GOALS

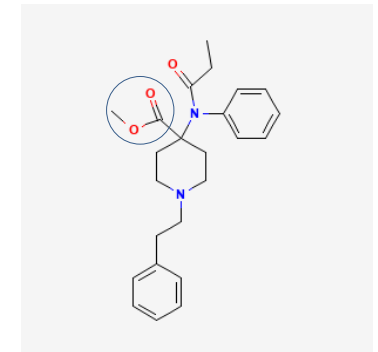
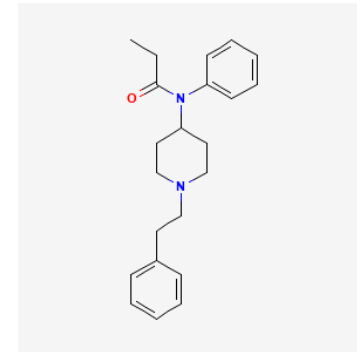
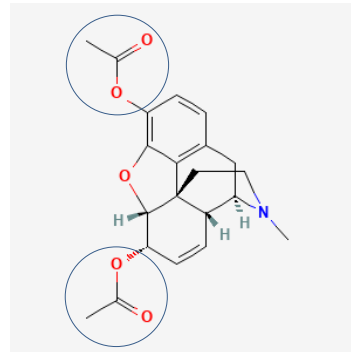
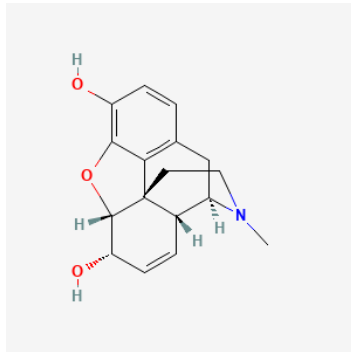
- Why is fentanyl the enormous problem it is in treating OUD?
- What do we do about it as clinicians/researchers?

FIRST: AN EXPERIENCE DISCLOSURE

- I have only ever treated opioid addiction in the fentanyl era.
- So I asked some who have experienced the contrast:
 - Naloxone for methamphetamine?
 - Deadly
 - Variable dosing (see below)
 - Less predictable withdrawal (see above)
 - Much more likely to precipitate withdrawal
 - Test strips: “get what I paid for.”
 - Microinductions? Single day induction?

THE BASICS

- Morphine equivalents per milligram¹
 - Heroin: 2-4x
 - Fentanyl: ~100x
 - Carfentanyl/carfentanil: ~10,000x



THE 'WHY' IS CLEAR...

- “It is better, in every way.”
 - Cheaper
 - Better cutting agent (levamisole or K2 anyone?)
 - No farming required
 - No import/export
 - \$4 per pill



- Much more potent
- Double trouble
- Death sells
- Look of legitimacy for the new user. ²⁻⁴



\$1.5 million in Fentanyl seized in Vancouver, BC.



Opium poppy field in Dorset, England

THE PROBLEM WITH SYNTHETIC DRUGS

- What about meth? The most American drug synthesis:^{5,6}

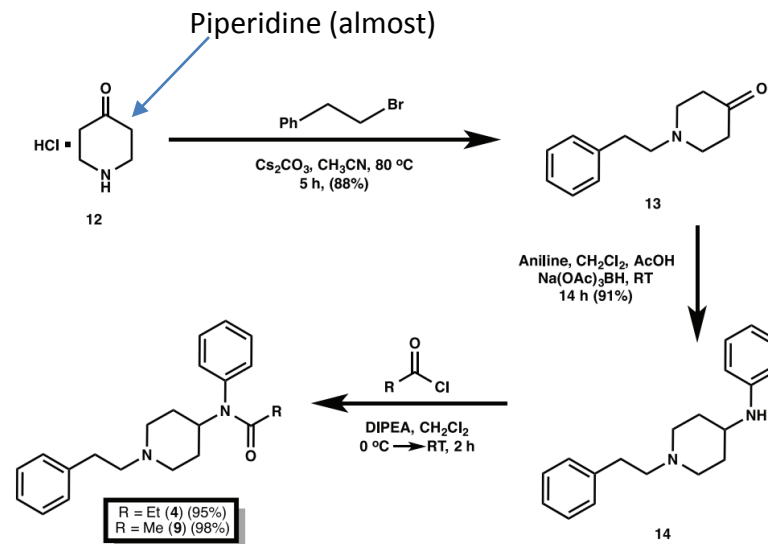


Figure 4. Synthesis of fentanyl and acetylthiofentanyl. Yields reflect the isolated materials by column chromatography after each step and using the optimized conditions (cf. Table 1). Citrate and hydrochloride salts for each analog were obtained in nearly quantitative yields by treating the free bases at the end of these routes with the corresponding acids.
doi:10.1371/journal.pone.0108250.g004

WHAT DID WE GET?

- Herein lies the problem: we're not dealing with a single drug, but a multitude, all with different (some unknown) properties. Because organic chemistry is messy – even for organic chemists.⁶

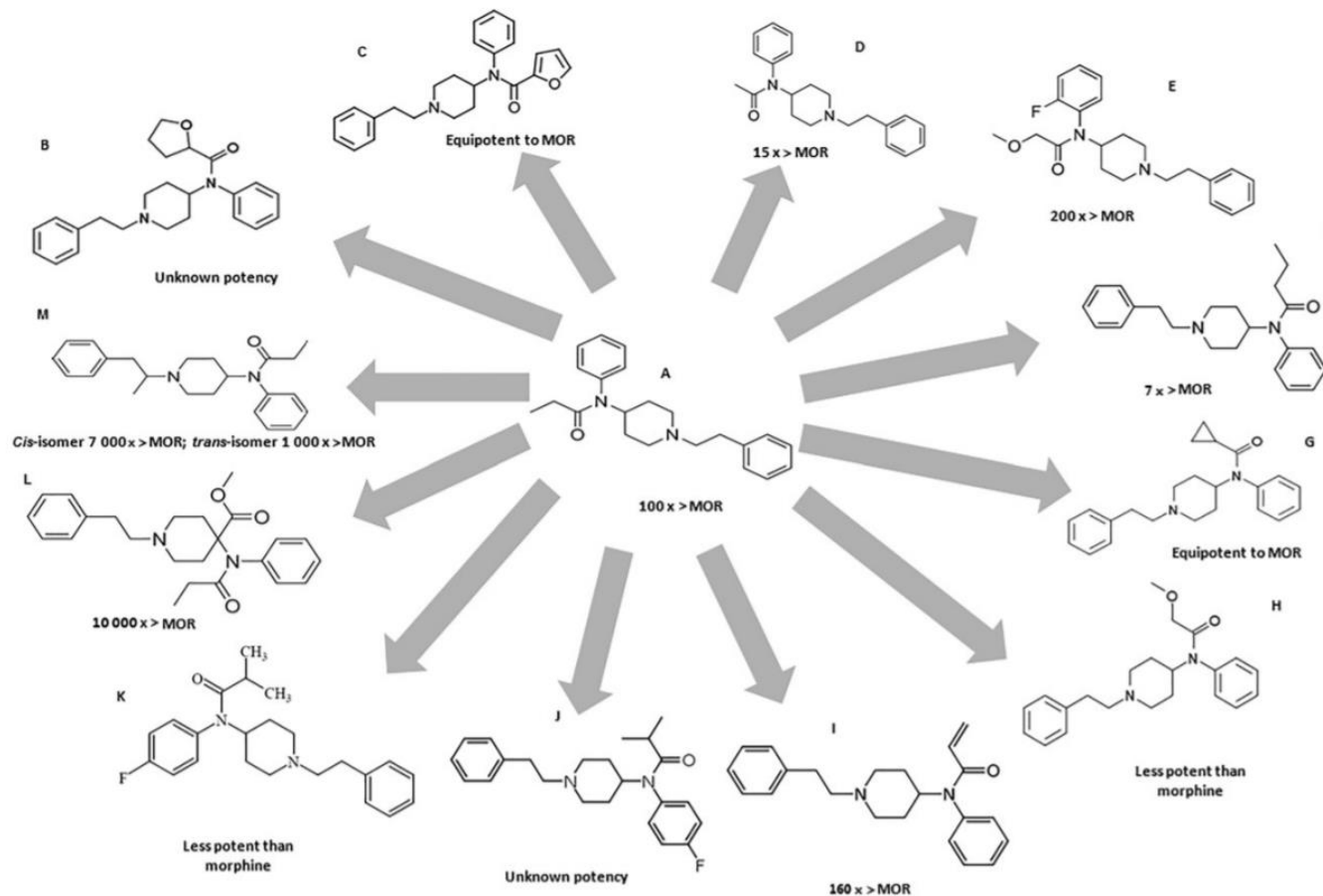


Figure 1. Chemical structure of fentanyl and their analogues: (A) fentanyl; (B) tetrahydrofuranylfentanyl (THFF); (C) furanylfentanyl; (D) acetylfentanyl; (E) ocfentanil; (F) butyrfentanyl; (G) cyclopropylfentanyl; (H) methoxyacetylfentanyl; (I) acrylfentanyl; (J) *para*-fluoroisobutyrfentanyl; (K) *para*-fluoroisobutyrylfentanyl; (L) carfentanil; (M) α -methylfentanyl. The compounds' potency has been compared to that of morphine (MOR).

SO WHAT DO WE HAVE?

- Maybe about a dozen drugs, with mixed pharmacokinetics and pharmacodynamics, widely available, cheaper and adulterating multiple different unrelated classes of illicit drugs.
- Inadequate research on the target chemical to understand its half-life.
 - Theoretical half-life of about 4 hours. In practice, perhaps a week in urine.
- ~100,000 drug related deaths so far this year in the US. Causation by substance is very challenging.
- Let's look at another issue in depth...⁷

12 Month-ending Provisional Number of Drug Overdose Deaths

Based on data available for analysis on: 11/7/2021

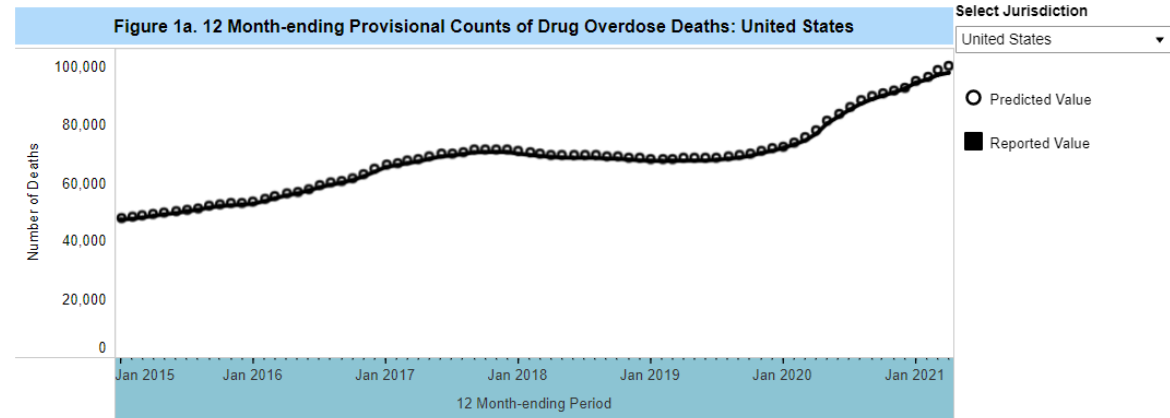
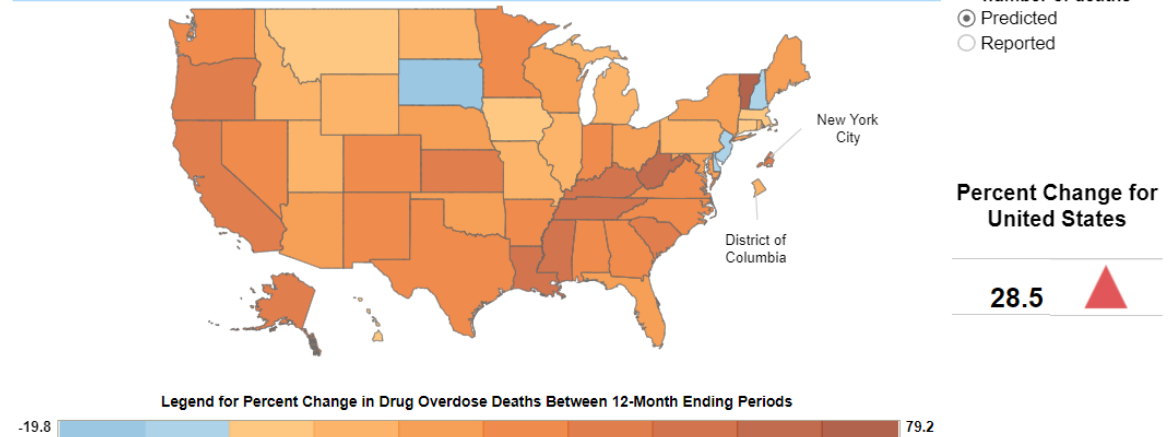


Figure 1b. Percent Change in Predicted 12 Month-ending Count of Drug Overdose Deaths, by Jurisdiction: April 2020 to April 2021



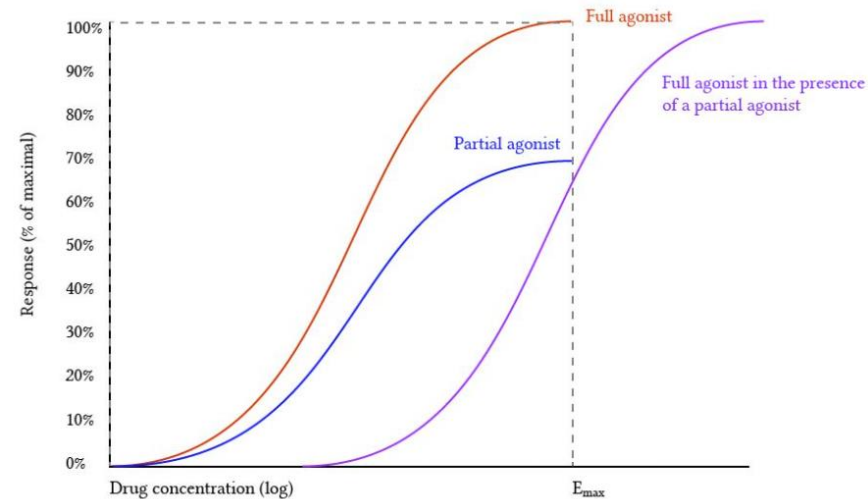
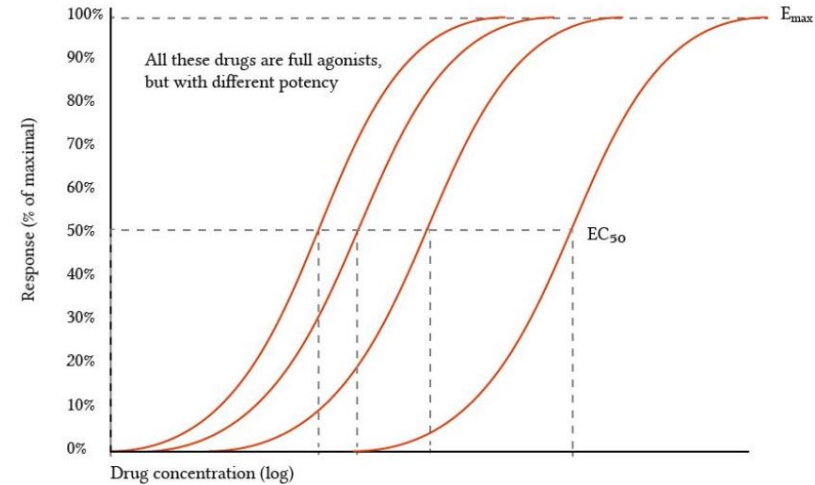
THE LIPOPHILIC PROBLEM

- Fentanyl clearance in persons with OUD is considerably longer than the typical 2-4 day clearance of other short-acting opioids. Up to 7 days renal excretion in chronic users.⁸
- Greater lipophilic properties affecting addiction...
 - Ex: benzodiazepines. Re: dose, duration, administration bioavailability, speed in crossing BBB.
- This might be the biggest problem for treatment.
- Some potential solutions...

Benzodiazepines	Diazepam Equivalent (10 mg)	Onset of action	Peak onset	Half-life [active metabolite]	Notes
Alprazolam	0.5 mg	Intermediate	0.7-1.6 hours	6-12 hours	High risk of misuse
Clobazam	20 mg			12-60 hours	
Clonazepam	~0.25 mg to 0.5 mg ^[4]	20 to 40 minutes	1-4 hours (PO)	18-50 hours	Fast onset, long acting, high potency, partial serotonin agonist
Diazepam	10 mg	Rapid (PO, IV – due to its lipophilic nature)	1 (PO) hours	IV: 33-45 hours PO: 44-48 hours PR: 45-46 hours	
Lorazepam	1 mg	Intermediate (PO) Rapid (SL/IV)	1.-1.5 (PO) hours	10-20 hours	
Oxazepam	20 mg	Slow	2-3 hours	4-15 hours	
Tamazepam	20 mg	Slow (PO 0.5-2 h) ^[5]	0.75-1.5 hours	8-22 hours	
Triazolam	0.5 mg	Intermediate	0.75-2	2 hrs	
Estazolam					
Flurazepam		Rapid	0.5-2		

A QUICK REVIEW ON PARTIAL AGONISTS

- Naloxone in suboxone does not cause the withdrawal! (if used properly).
- Buprenorphine is a partial μ -opioid agonist and κ -opioid antagonist
- **Agonist:** A ligand that binds to a receptor and alters the receptor state resulting in a biological response
 - **A full agonist** reaches the maximal response capability of the system
 - **A partial agonist** does not reach the maximal response capability of the system even at full receptor occupancy.⁹



MICROINDUCTIONS

- First described in 2010 as a case study of two patients in Bern, Switzerland. Also known as the Bernese method.
- Goal: Switch to suboxone and avoid withdrawal which will cause treatment failure.
- Allows patients to continue fentanyl use concurrent with suboxone and overcome partial agonist. Buprenorphine has 2-3x greater receptor ($K_i = 1.35$ vs 0.216) affinity than fentanyl (not potency!). Most derivatives (inc. carfentanil) are unknown.
- To be clear... patients will still likely have some withdrawal, but should be mild. This strategy does not work for high dose methadone typically.¹⁰⁻¹⁶
- Example Strategy:
 - Day 1: 0.5mg loading dose (0.5mg total)
 - Day 2: 0.5mg BID (1mg total)
 - Day 3: 1mg BID (2mg total)
 - Day 4: 2mg BID (4mg total)
 - Day 5: 3mg BID (6mg total)
 - Day 6: 4mg BID (8mg total)
 - Day 7: 12 mg (16mg and discontinue other opioids)
 - Option - Day 8: Sublocade 300mg

MICROINDUCTION EFFICACY

- Not yet well established. I'm batting around 50%.
 - Pharmacologically suspect
- >
- Two ongoing comparison RCTs.
 - Ahmed et al, 2020: 18 papers, 63 patients. Primarily inpatient settings with a variety of opioids, range of dosing all without significant withdrawal. Initial dosing 0.2-0.5 mg and time frame of 3-112 days most over 4-8 days and most completed cross titration between 8-16 mg.
 - Most recent reviews suggest available studies are low quality with highly variable dosing strategies. Inconsistent reporting, selection bias, and poor quality evidence limit conclusions regarding optimal dosing, and patient characteristics and clinical settings in which micro-induction is likely beneficial.¹⁷⁻¹⁹

Drug	Human K _i (nM) [35]	Marmoset K _i (nM) [38]	Guinea Pig K _i (nM) [13]	Average Docking Score (ADS)	Standard Deviation in Score	Predicted Conc. Regime
<i>N</i> -methyl fentanyl*			18000 ± 3000	-7.89	0.21	> 100 nM
(1R,2R)Tramadol	12,500			-7.85	0.06	> 100 nM
(1S,2S) Tramadol	12,500			-7.97	0.20	> 100 nM
Meperidine	450			-7.77	0.07	> 100 nM
Propoxyphene	120			-9.56	0.08	0-100 nM
<i>N</i> -Methyl carfentanil*			42 ± 6	-8.53	0.07	0-100 nM
Diphenoxylate	12.4			-10.1	0.47	Sub nM
Alfentanil	7.39	14.4 ± 4.2		-10.5	0.56	Sub nM
R-Methadone	3.38			-8.69	0.12	0-100 nM
S-Methadone	3.38			-8.63	0.07	0-100 nM
Fentanyl	1.35	1.32 ± 0.35	1.2 ± 0.2	-9.43	0.38	0-100 nM
Sufentanil	0.138	0.24 ± 0.05		-9.89	0.23	Sub nM
Carfentanil [^]		0.22 ± 0.08	0.024 ± 0.004	-10.8	0.30	Sub nM
Lofentanil [^]		0.055 ± 0.006	0.023 ± 0.004	-10.8	0.50	Sub nM
R30490*			0.09 ± 0.01	-10.3	0.31	Sub nM
Codeine	734			-8.23	0.16	> 100 nM
(+)-Pentazocine	118			-7.77	0.12	> 100 nM
Oxycodone	25.9			-8.78	0.27	0-100 nM
Nalbuphine	2.12			-8.47	0.29	0-100 nM
Morphine	1.14			-7.76	0.14	> 100 nM
Oxymorphone	0.406			-8.40	0.18	0-100 nM
Hydromorphone	0.365			-7.94	0.26	> 100 nM
Buprenorphine	0.216			-9.76	0.48	0-100 nM

SINGLE DOSAGE METHOD

- Mariani et al, 2021: **Open-label trial of a single-day induction onto buprenorphine extended-release injection for users of heroin and fentanyl**
 - 12-week outpatient clinical trial to test the feasibility of a single-day induction onto extended-release buprenorphine (BXR) injection treatment for five adults (N=5)
 - All 5 received all three injections, with first on first day and all maintained on injections for 3 months.²⁰

• EX:

Time	COWS	Bupe
1020		Buprenorphine 2 mg SL
1110	8	Buprenorphine 8 mg SL
1145	9	Buprenorphine 8 mg SL
1230	15	Buprenorphine 6 mg SL
1245		XR-Buprenorphine 300 mg SC

CRITIQUE

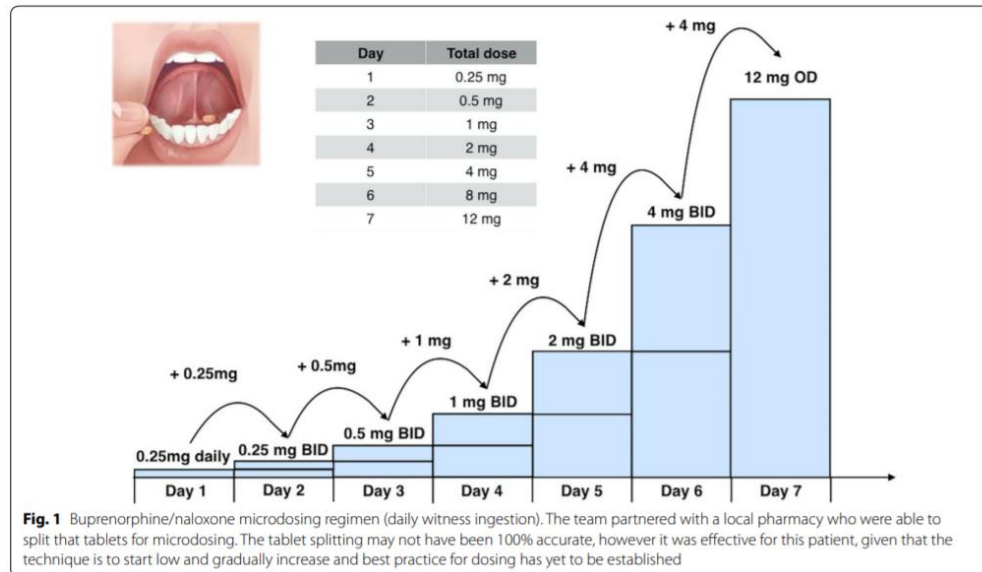
- Single dosage method may have some benefits, but current method would not be feasible in most treatment settings and would be a small, dedicated subset of our patients – much like microinductions are currently.
- 3 months is insufficient time frame to measure efficacy.

TAKE-AWAYS FOR CLINICIANS

- The fentanyl epidemic is not a problem of fentanyl alone, it is a problem with multiple known and unknown fentanyl analogues with variable receptor affinities, potencies, half-lives, lipophilicities that are created in very different concentrations from multiple different manufacturers.
- This variable affect in regards to reward is likely, in of itself, more addictive (variable number and interval). Like gambling on top of opioid addiction.
- Fentanyl analogues may be the most beneficial thing for cartels since methamphetamine and are nearly impossible to regulate or control.
- Effective ways to address this problem are not yet validated.

WELL THAT WAS DARK... HERE'S THE UPSIDE!

- More research is on the way.
- Microinductions do work²¹, from my limited experience with them and multiple case studies of short duration. Here is what we're doing at the VA (Rozylo et al, 2020):



Two quick stories...

**QUESTIONS?
THOUGHTS?
DISAGREEMENT?**

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