Updates on the Medical Management of patients with an Opioid Use Disorder

UNC ABC ECHO
Oct 14, 2022

Stephen A. Wyatt, D.O.
Addiction Psychiatrist
UNC, Adjunct Professor of Psychiatry
MAHEC, Psychiatry Faculty
Asheville, NC

Speaker Disclosures

Dr. Wyatt: No Disclosures

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.

Objectives

1) Establish a working understanding of the pharmacology of opioids.

2) Employ your understanding of opioids to specific aspects of fentanyl.

3) Apply your understanding of fentanyl pharmacology to managing initiation of buprenorphine.

Initiation to Buprenorphine in the Patient Using Fentanyl

- Fentanyl – often sold as heroin in the street drug supply:
  - synthetic full opioid agonist
  - moderately high affinity to the opioid mu receptor
  - highly lipophilic
- Initiation to buprenorphine may be problematic due to:
  - significant tolerance developed with long-term fentanyl use.
  - persistent slow release of fentanyl from adipose cells resulting in difficult stabilization with buprenorphine.
- Patients may have tried buprenorphine on the street and experienced withdrawal symptoms and afraid of trying it again.

Neuropharmacology of Opioids

A Neuropharmacological Model to Explain Buprenorphine Induction Challenges

Mark K. Greenwald, PhD*; Andrew A. Herring, MD; Jeanmarie Perrone, MD; Lewis S. Nelson, MD; Pouya Azar, MD

- Successful buprenorphine induction requires reaching a therapeutic level of mu-opioid receptor occupancy that relieves opioid withdrawal and craving and produces full agonist blockade.[1]

- In attempting to achieve this one must account for the magnitude of the neuro-adaptations that are proportional to the duration, dose, and affinity/lipophilicity/intrinsic efficacy (ALE value) of the prebuprenorphine (residual) agonist.

- Thus, the difficulty in stabilizing a patient following prolonged fentanyl use.

Greenwald MK, et.al., Drug Alcohol Depend. 2014;144:1-11
Greenwald MK, et.al., Annals of Emergency Medicine, August 2022

Neuropharmacology of Opioids

- The acute outcome of the initial dosing depends on the;
  - preinitiation opioid balance (degree of withdrawal)
  - residual agonist (ALE).

- ALE is the product of the:
  - Ki value of **affinity**
    - logP of **lipophilicity**
      - percent maximum G protein activation of mu-opioid receptor intrinsic **efficacy**.

The authors propose the ALE value represents opioid agonist action at mu-opioid receptors enhanced by:

1. higher lipophilicity,
   a) increases rapidity of onset (passing the blood brain barrier more efficiently)
   b) extends elimination half-life;
2. higher binding affinity (increased percentage of a time in which the ligand interacts with mu-opioid receptors)
3. higher intrinsic efficacy (degree of G-protein activation, a measure of mu opioid–receptor intracellular signaling).

Greenwald MK, et.al., Annals of Emergency Medicine, August 2022

Neuropharmacology of Opioids

Heroin has a low affinity.
Fentanyl a moderately high affinity.
Buprenorphine a very high affinity.

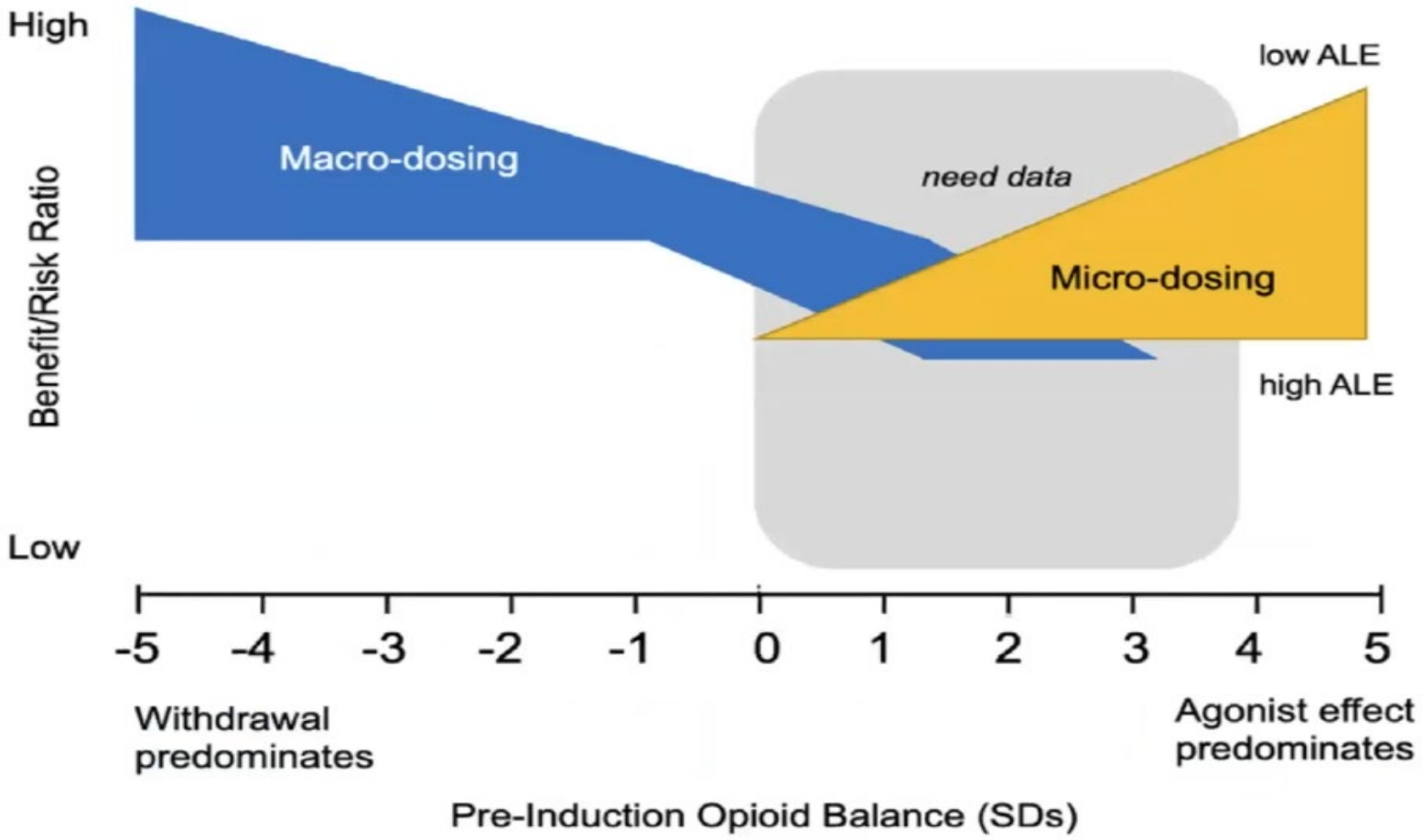
Fentanyl's high lipophilicity however results in a steady bathing of the receptors and thus a significant tolerance or desensitization of the opioid receptor.

When introduced, buprenorphine needs to re-sensitize the receptor without under activating the receptor due to its lower intrinsic activity as a partial agonist.

Ligand	Ki (Affinity) (nmol)
Hydrocodone	41.58
Oxycodone	25.87
Heroin	9.6
Methadone	3.38
Fentanyl	1.35
Morphine	1.14
Naloxone	1.1
Hydromorphone	0.6
Buprenorphine	0.21

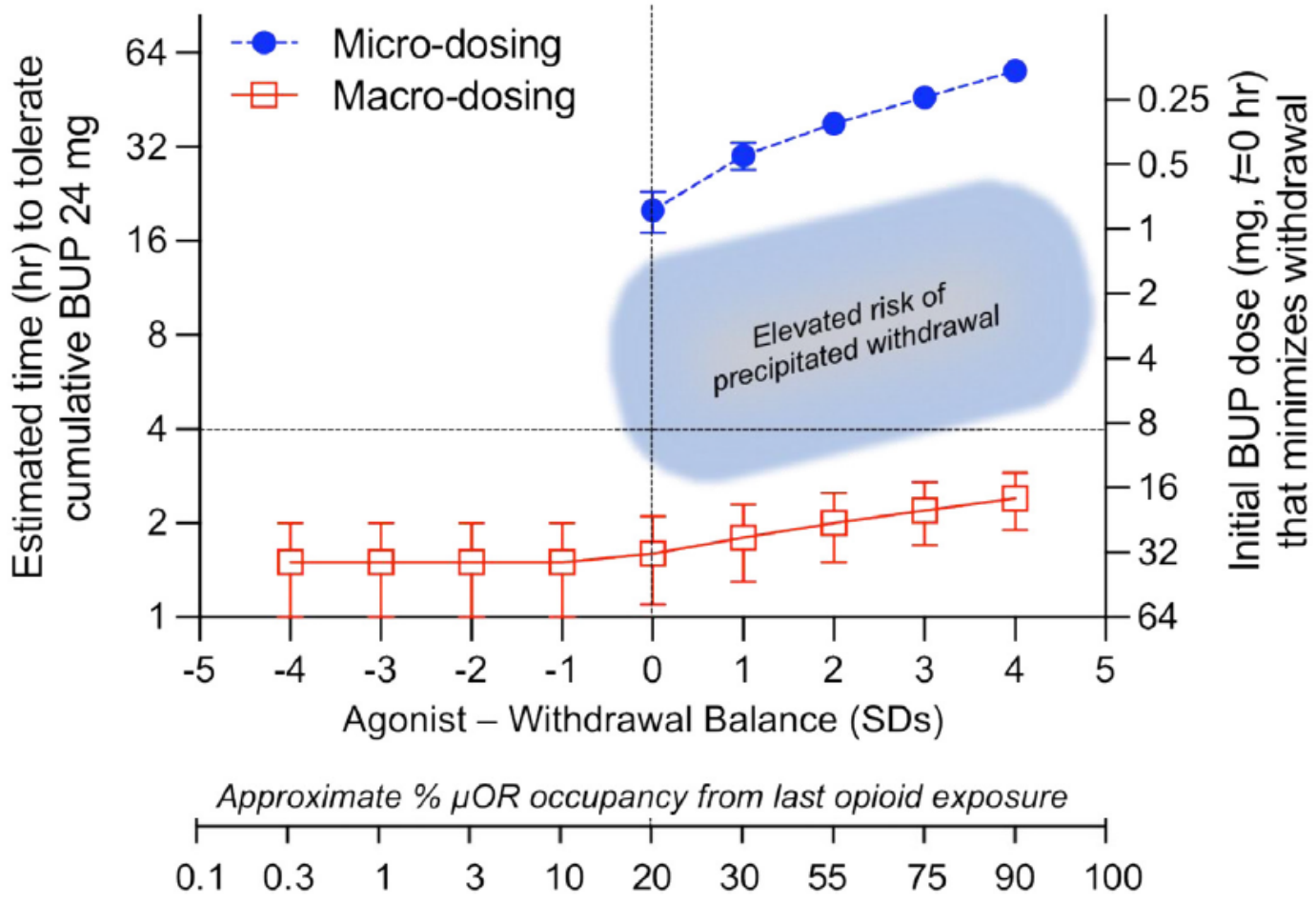
Volpe DA. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Reg Toxicol Pharmacol 2011

Neuropharmacological Model of Macro and Micro Dosing



Annals of Emergency Medicine, August 2022

Neuropharmacological Model of Macro and Micro Dosing



Annals of Emergency Medicine, August 2022

Using Alternative Methods in Transitioning Patients from Fentanyl to Buprenorphine

"High Dose Initiation"

- There is literature primarily out of emergency medicine using "high dose" buprenorphine during initiation.
  - Patients presenting in withdrawal,
    - COWS > 13,
    - known to have been using fentanyl,
  - Started right on 8 to 16mg on first dose.
  - If withdrawal continues you may increase this 8mg at a time up to 32mg as needed.
  - More frequently preformed in the ED where monitoring and adjunctive medications are available.
  - If given 24 to 32 mg, this may have the additional benefit of holding off withdrawal for greater than 24 hours to get to follow-up care, a warm hand to a follow-up is most advantageous.

Herring AA, *JAMA Network Open.* 2021;4(7):

Using Alternative Methods in Transitioning Patients from Fentanyl to Buprenorphine

"Micro or Low Dose Initiation"

- Start with a very low dose and titrates up to a standard maintenance dose.
- This protocol has been established in a variety of ways.
  - The most method conducive to use in the outpatient setting involves instructing the patient to split a 2mg BPN/NTX film or tablet in quarters initially.
  - Example:
    - Day 1: 0.5 mg once a day
    - Day 2: 0.5 mg twice a day
    - Day 3: 1 mg twice a day
    - Day 4: 2 mg twice a day
    - Day 5: 3 mg twice a day
    - Day 6: 4 mg twice a day
    - Day 7: 12 mg (stop other opioids in patients with co-occurring pain)
- Shifting away from high ALE opioids will improve the outcome.

Note: consider using alpha 2 agonist medications, clonidine or lofexidine, and other comfort medications to assist in reducing any discomfort patient may experience during the transition.

Randhawa PA, 2020

Micro-dosing Considerations/Concerns

- The potential need to write a protocol for the patient different from that sent to the pharmacy
- The suggestion to patients they continue illicit use of opioids and the potential for harm vs harm reduction.
- The co-prescribing of comfort meds, e.g. clonidine, trazodone, ondansetron.

Future Considerations:

- Approval of alternative forms of buprenorphine for OUD treatment, e.g. transdermal (Butrans) or Belbuca.