Parallel Pharmaceutical & Alternative Opioid Agonist Therapies to Treat Opioid Use Disorder

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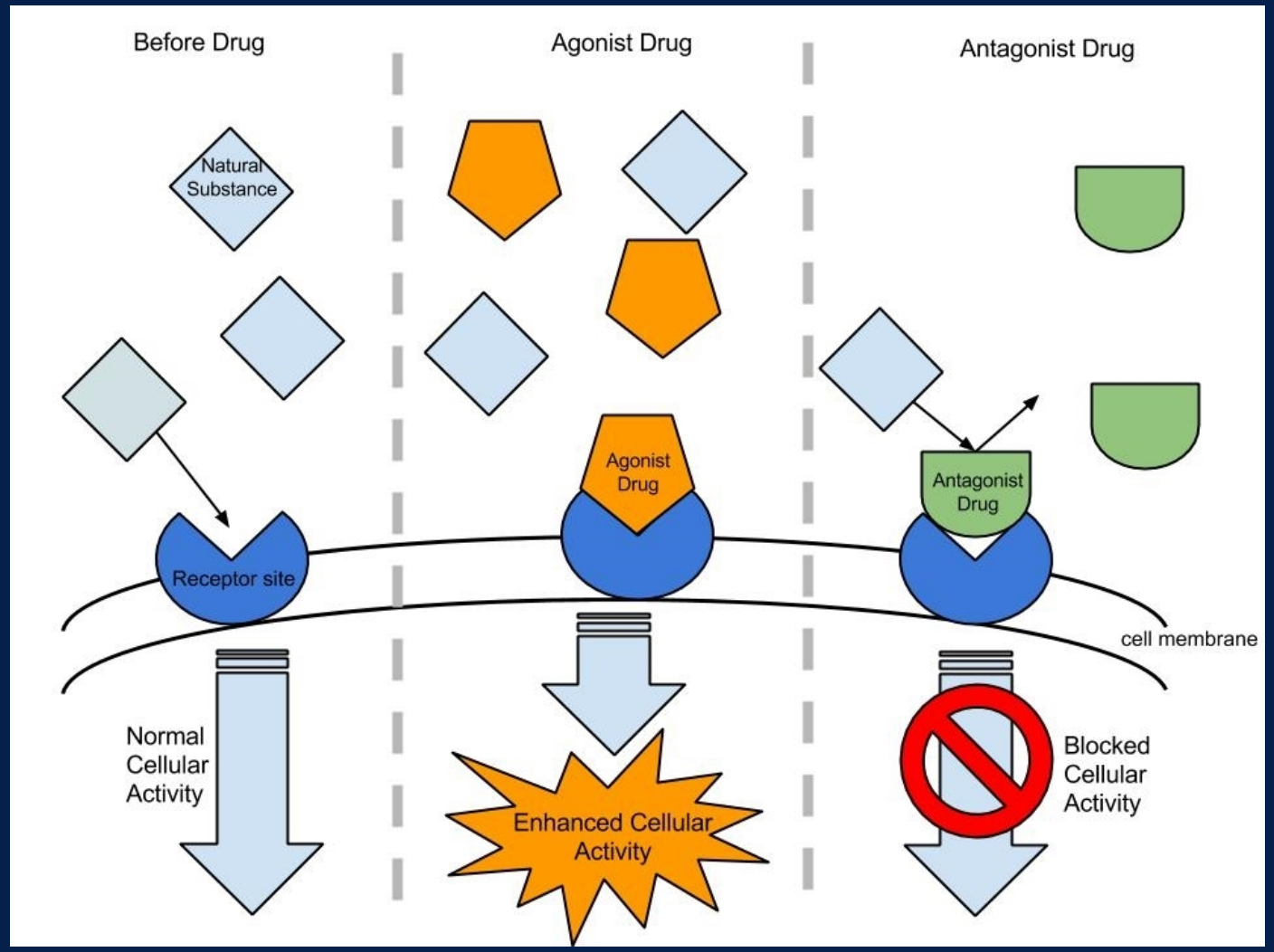
Disclosure Information

- Stephanie T. Weiss, MD PhD
  - No Disclosures
- Lewis S. Nelson, MD
  - No Disclosures

Learning Objectives

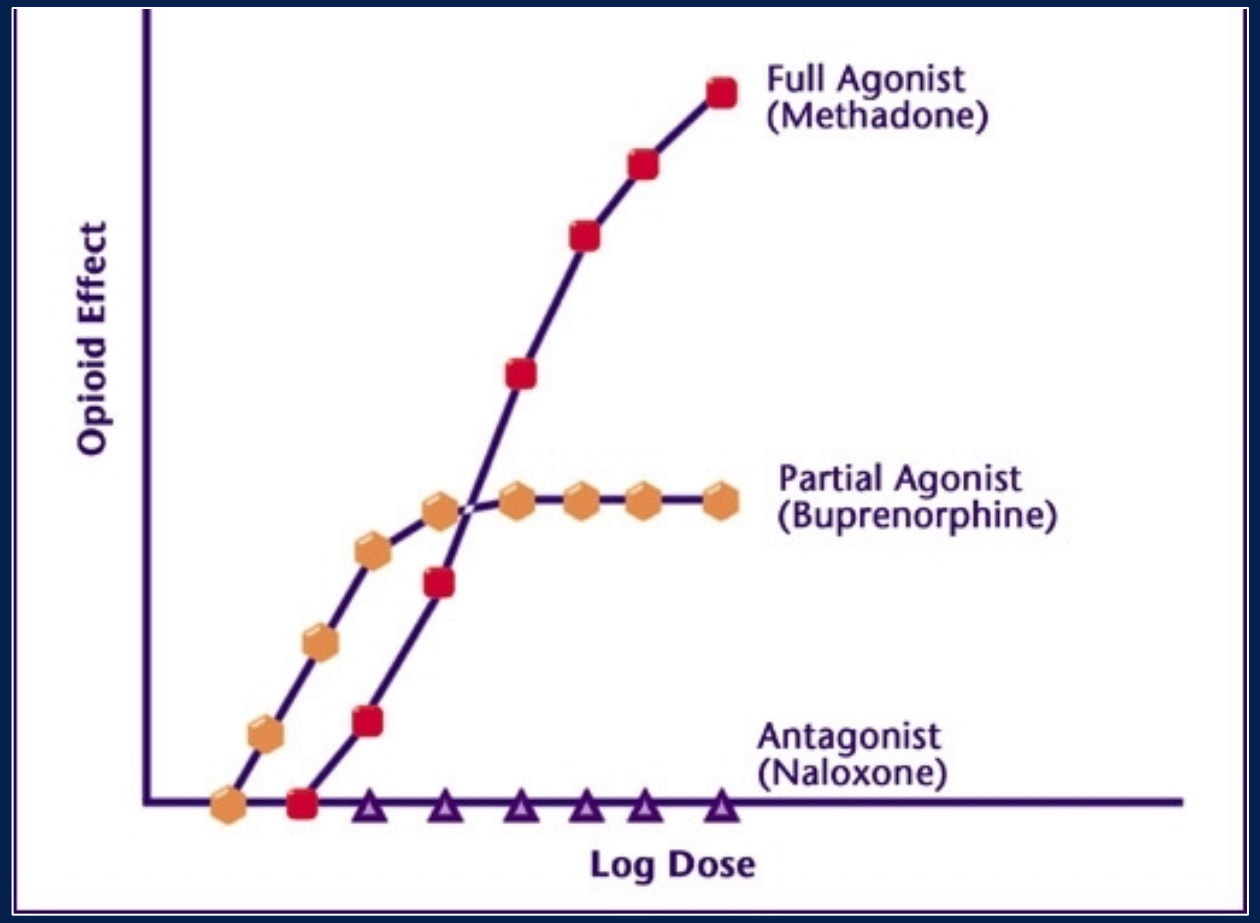
- Define the difference between a full versus a partial opioid agonist
- List the two Food and Drug Administration (FDA)-approved opioid agonists (methadone, buprenorphine) and two alternative opioid agonists (loperamide, mitragynine) that are used to treat opioid use disorder
- Describe the similarities and differences between the two full opioid agonists (methadone and loperamide) and the two partial opioid agonists (buprenorphine and mitragynine) used to treat opioid use disorder
- Discuss the risks and benefits of using FDA-approved opioid agonist therapy drugs as well as alternative opioid agonist therapies with a patient or client

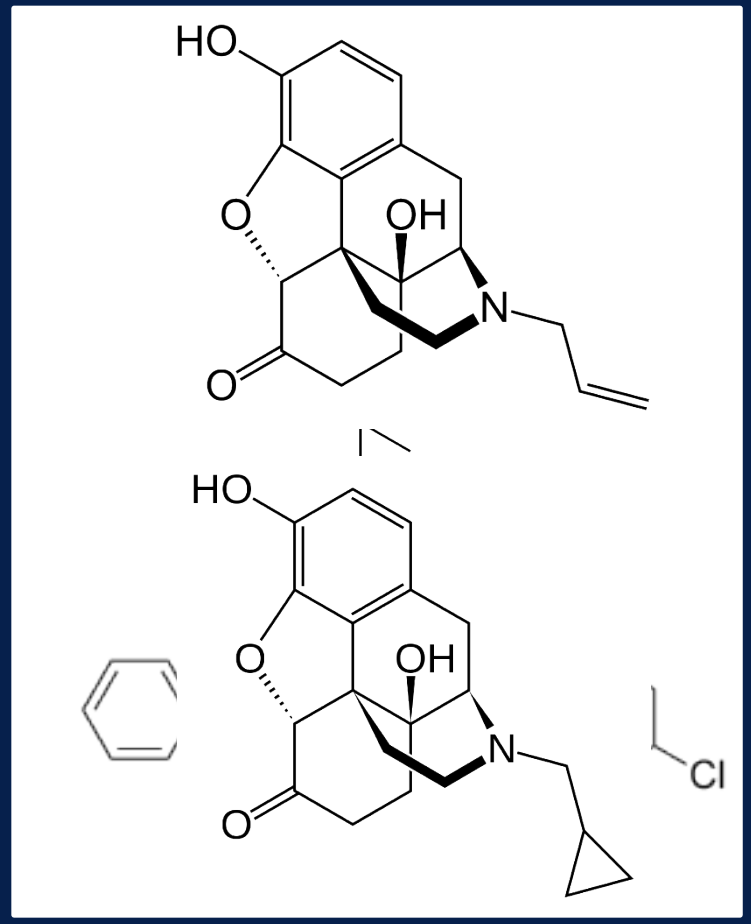
Quick Pharmacology Review



https://en.wikipedia.org/wiki/Agonist-antagonist

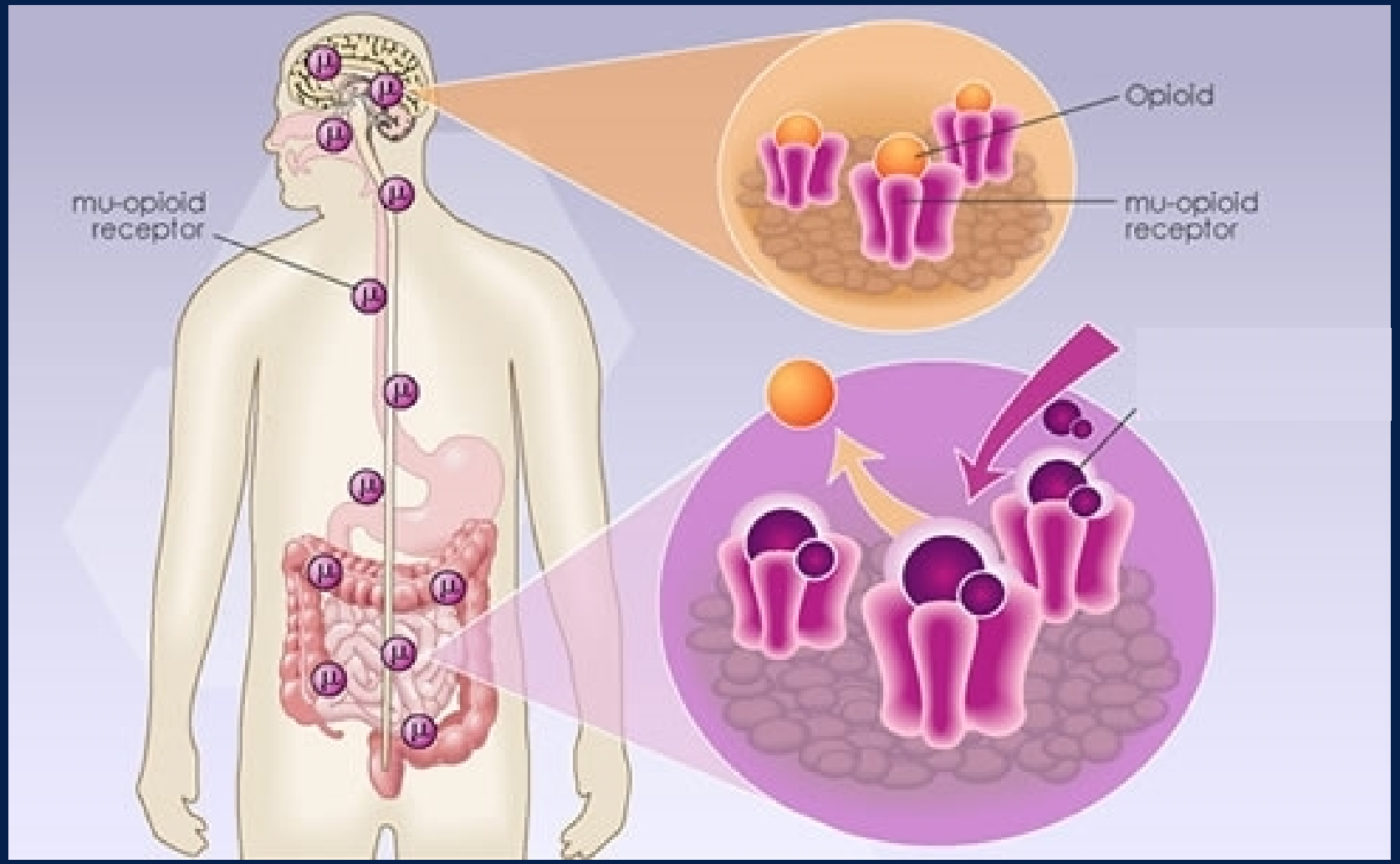
Quick Pharmacology Review





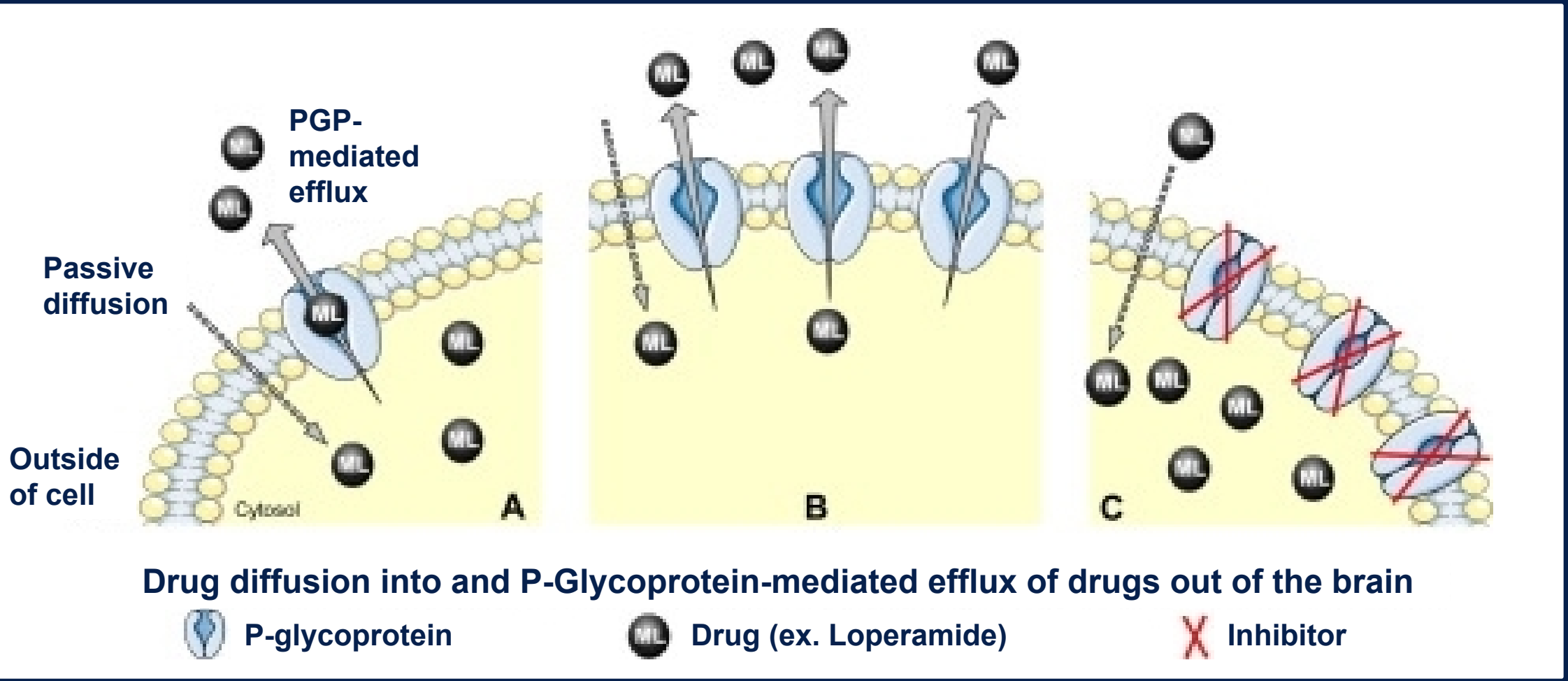
https://www.naabt.org/education/technical_explanation_buprenorphine.cfm

Opioid Receptors Are Widespread



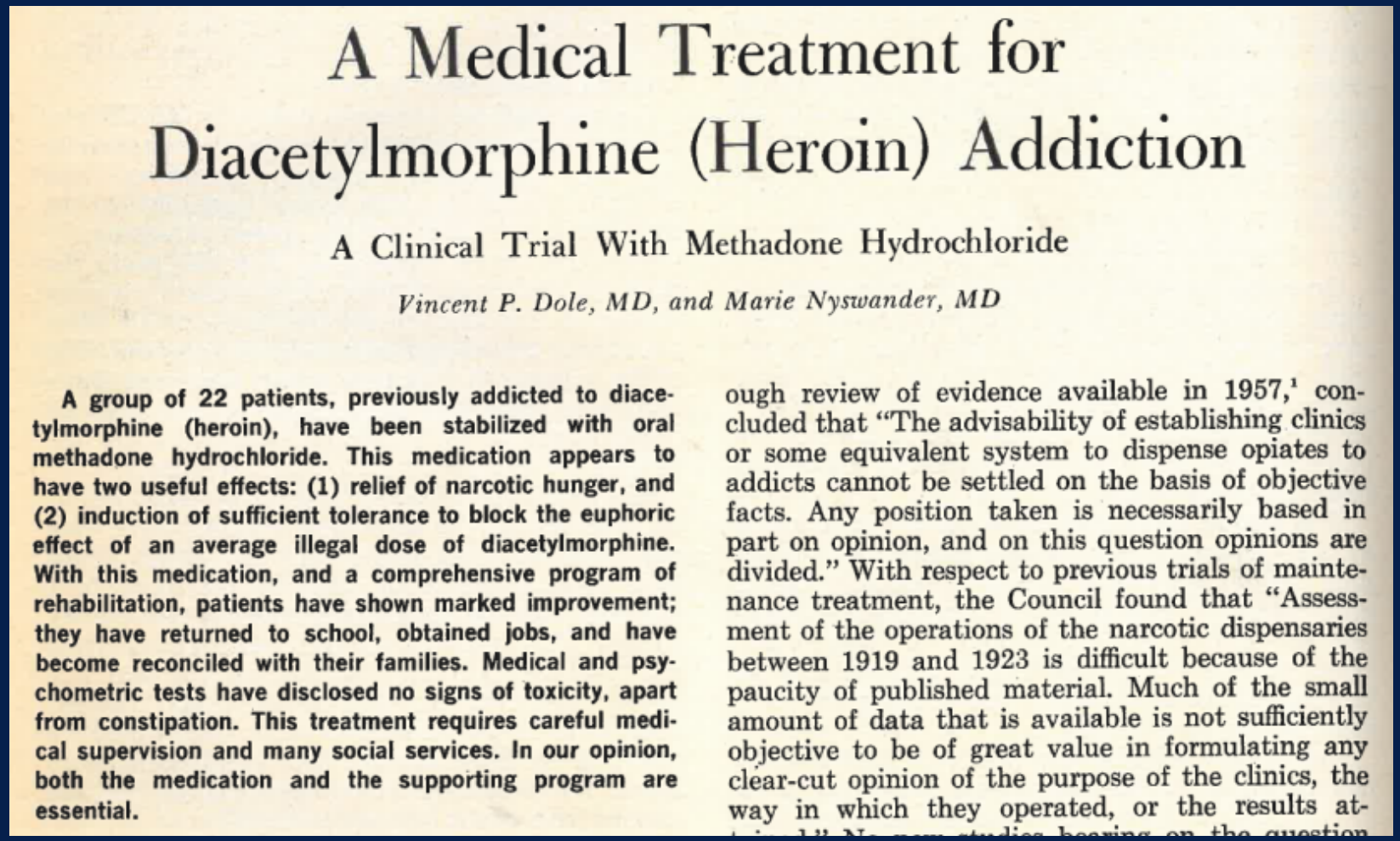
http://www.peritonealmesotheliomawiki.info/peritoneal-mesothelioma/

Opioid Transport into the Brain



Lespine A *et al*. International Journal for Parasitology: Drugs and Drug Resistance. 2012 Dec 1;2:58-75.

FDA-Approved Opioid Agonist Therapies



A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A Clinical Trial With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

A group of 22 patients, previously addicted to diacetylmorphine (heroin), have been stabilized with oral methadone hydrochloride. This medication appears to have two useful effects: (1) relief of narcotic hunger, and (2) induction of sufficient tolerance to block the euphoric effect of an average illegal dose of diacetylmorphine. With this medication, and a comprehensive program of rehabilitation, patients have shown marked improvement; they have returned to school, obtained jobs, and have become reconciled with their families. Medical and psychometric tests have disclosed no signs of toxicity, apart from constipation. This treatment requires careful medical supervision and many social services. In our opinion, both the medication and the supporting program are essential.

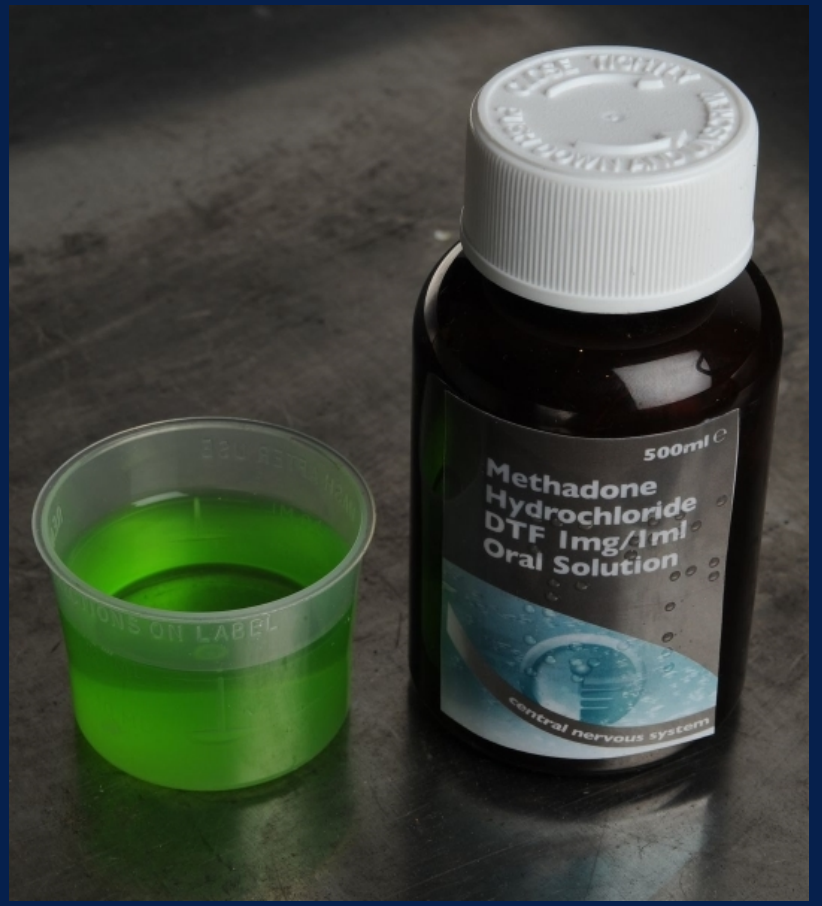
ough review of evidence available in 1957,[1] concluded that "The advisability of establishing clinics or some equivalent system to dispense opiates to addicts cannot be settled on the basis of objective facts. Any position taken is necessarily based in part on opinion, and on this question opinions are divided." With respect to previous trials of maintenance treatment, the Council found that "Assessment of the operations of the narcotic dispensaries between 1919 and 1923 is difficult because of the paucity of published material. Much of the small amount of data that is available is not sufficiently objective to be of great value in formulating any clear-cut opinion of the purpose of the clinics, the way in which they operated, or the results at-

Dole, V.P. and Nyswander, M., 1965. *JAMA*, *193*(8): 646-650.

FDA-Approved Opioid Agonist Therapies

- Methadone History
  - 1937: developed by IG Farben (Germany)
  - 1947: approved for use in US (pain)
  - 1960s: opioid use disorder treatment

- Approved Methadone Uses in 2021
  - Opioid use disorder
  - Chronic pain



https://www.methadonecenters.com/methadone-treatment/when-does-methadone-treatment-end/

FDA-Approved OATs (Methadone)

- 51 y/o male with history of HIV admitted to hospital with shakiness, diaphoresis, body aches, abdominal pain, blurred vision, and hypotension x 5 hours
- Other medical history: OUD, hypertension, GERD
- Medications (all unchanged x 2-3 years): methadone 90 mg/day, Bactrim (PCP prophylaxis), fosinopril 20 mg/day, cimetidine 400 mg BID
- What do you want to know?

Geletko SM, Erickson AD. The Journal of Human Pharmacology and Drug Therapy. 2000 Jan;20(1):93-4.

FDA-Approved Opioid Agonist Therapies

Human Pharmacology and Abuse Potential of the Analgesic Buprenorphine

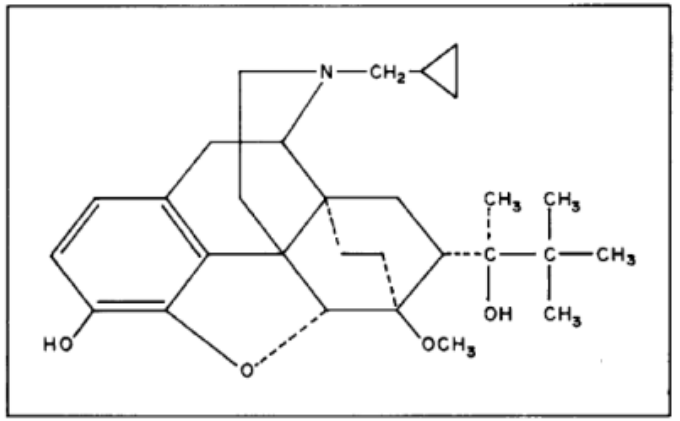
A Potential Agent for Treating Narcotic Addiction

Donald R. Jasinski, MD; Jeffrey S. Pevnick, MD; John D. Griffith, MD

• **Buprenorphine was evaluated for its abuse potential and utility in treating narcotic addiction. The drug was morphine-like but was 25 to 50 times more potent than morphine and was longer-acting. Little if any physical dependence of clinical significance was produced by buprenorphine. The effects of morphine to 120-mg doses were blocked by buprenorphine, a blockade that persisted for 29½ hours. In man, buprenorphine has less intrinsic activity than morphine, and as such, has a low abuse potential. Moreover, the drug has potential for treating narcotic addiction since it is acceptable to addicts, is long-acting, produces a low level of physical dependence such that patients may be easily detoxified, is less toxic than drugs used for maintenance therapy, and blocks the effects of narcotics.**

(*Arch Gen Psychiatry* 35:501-516, 1978)

Buprenorphine hydrochloride is a clinically effective analgesic some 25 to 40 times more potent than morphine sulfate.[1] The drug is a highly lipophilic oripavine derivative containing a cyclopropylmethyl substitution (Fig 1) similar to that in the narcotic antagonists cyclazocine and naltrexone.[2] In rats, mice, and monkeys, bupre-



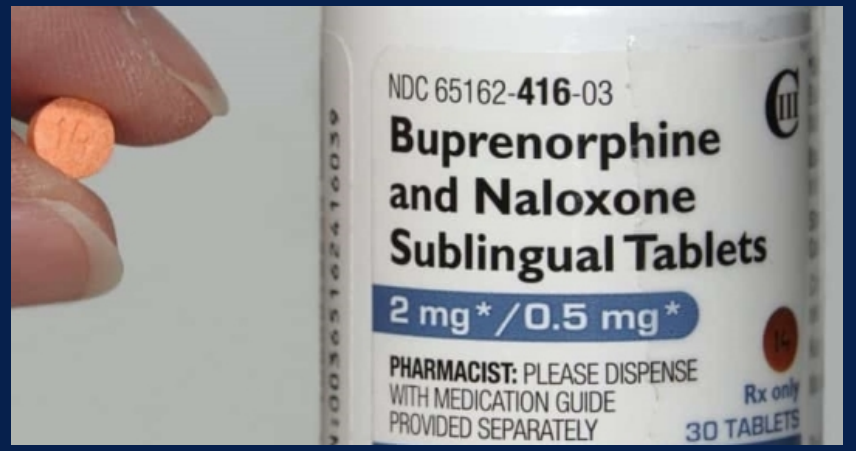
Accepted for publication Oct 15, 1977.
From the National Institute on Drug Abuse, Division of Research, Addiction Research Center, Lexington, Ky. Dr Pevnick is now with St Louis

Jasinski DR, Pevnick JS, Griffith JD. Archives of General Psychiatry. 1978 Apr 1;35(4):501-16.

FDA-Approved Opioid Agonist Therapies

- Buprenorphine History
  - 1969: synthesized by Reckitt and Colman
  - 1978: pain treatment in Britain
  - 2002: US approval for opioid use disorder

- Approved Buprenorphine Uses in 2021
  - Opioid use disorder
  - Pain, including chronic pain



https://www.therecoveryvillage.com/treatment-program/addiction-medications/buprenorphine/
https://www.clearbrookinc.com/news/facts-suboxone-didnt-know-need-to/man-holding-suboxone-strip/

FDA-Approved OATs: Buprenorphine

- 35 y/o female pharmacist admitted to inpatient treatment center with OUD after attempting to self-treat her migraine headaches with buprenorphine/naloxone films
- Other medical history: ADHD
- Medications: amphetamine/dextroamphetamine since high school
- What do you want to know?

Norton M, *et al.* Mental Health Clinician. 2016;6(3):127-30.

Alternative Opioid Agonist Therapies

"I Just Wanted to Tell You That Loperamide WILL WORK": A Web-Based Study of Extra-Medical Use of Loperamide

Raminta Daniulaityte[1], **Robert Carlson**[1], **Russel Falck**[1], **Delroy Cameron**[2], **Sujan Perera**[2], **Lu Chen**[2], and **Amit Sheth**[2]

[1]Center for Interventions, Treatment, and Addictions Research (CITAR) Department of Community Health, Boonshoft School of Medicine, Wright State University

[2]Ohio Center of Excellence in Knowledge-Enabled Computing (Kno.e.sis), Wright State University: http://knoesis.org

Abstract

Aims—Many websites provide a means for individuals to share their experiences and knowledge about different drugs. Such User-Generated Content (UGC) can be a rich data source to study emerging drug use practices and trends. This study examined UGC on extra-medical use of loperamide among illicit opioid users.

Methods—A website that allows for the free discussion of illicit drugs and is accessible for public viewing was selected for analysis. Web-forum posts were retrieved using web crawlers and

Daniulaityte, R., *et al*., 2013, *Drug and alcohol dependence*, *130*(1-3), pp.241-244.

Alternative Opioid Agonist Therapies

- Loperamide History
  - 1969: synthesized by Janssen (Belgium)
  - 1976: US approval for diarrhea
  - 1988: available over-the-counter
- Approved Loperamide Uses in 2021
  - Diarrhea

https://ahmedipharm.en.made-in-china.com/product/bszmiVjJrCkB/China-Loperamide-Hydrochloride-Capsule-2mg-GMP-Medicine.html

Alternative OATs: Loperamide

- 19 y/o male with a history of SUD found dead in bed by family
  - No other psychiatric or medical history, no medications
  - Autopsy found a distended bladder and bloody froth around the mouth

- Initial post-mortem toxicology results positive for the following:
  - Alprazolam
  - Fluoxetine
  - Marijuana (THC)

- What else do you want to know?

Dierksen J, *et al*. The American journal of forensic medicine and pathology. 2015 Dec 1;36(4):268-70.

Alternative Opioid Agonist Therapies

Self-Treatment of Opioid Withdrawal with a Dietary Supplement, Kratom

Edward W. Boyer, MD, PhD,[1] Kavita M. Babu, MD,[1] Grace E. Macalino, PhD,[2] Wilson Compton, MD, MPH[3]

[1]Division of Medical Toxicology, Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, Massachusetts
[2]Tufts-New England Medical Center, Boston, Massachusetts
[3]National Institute on Drug Abuse, Rockville, Maryland

We examined the use of Kratom (Mitragyna sp.*), a dietary supplement with mu-opioid agonist activity, by members of a cybercommunity who self-treat chronic pain with opioid analgesics from Internet pharmacies. Within one year, an increase in the number of mentions on Drugbuyers.com, a Web site that facilitates the online purchase of opioid analgesics, suggested that members began managing opioid withdrawal with Kratom. This study demonstrates the rapidity with which information on psychoactive substances disseminates through online communities and suggests that online surveillance may be important to the generation of effective opioid analgesic abuse prevention strategies.* (Am J Addict 2007;16:352–356)

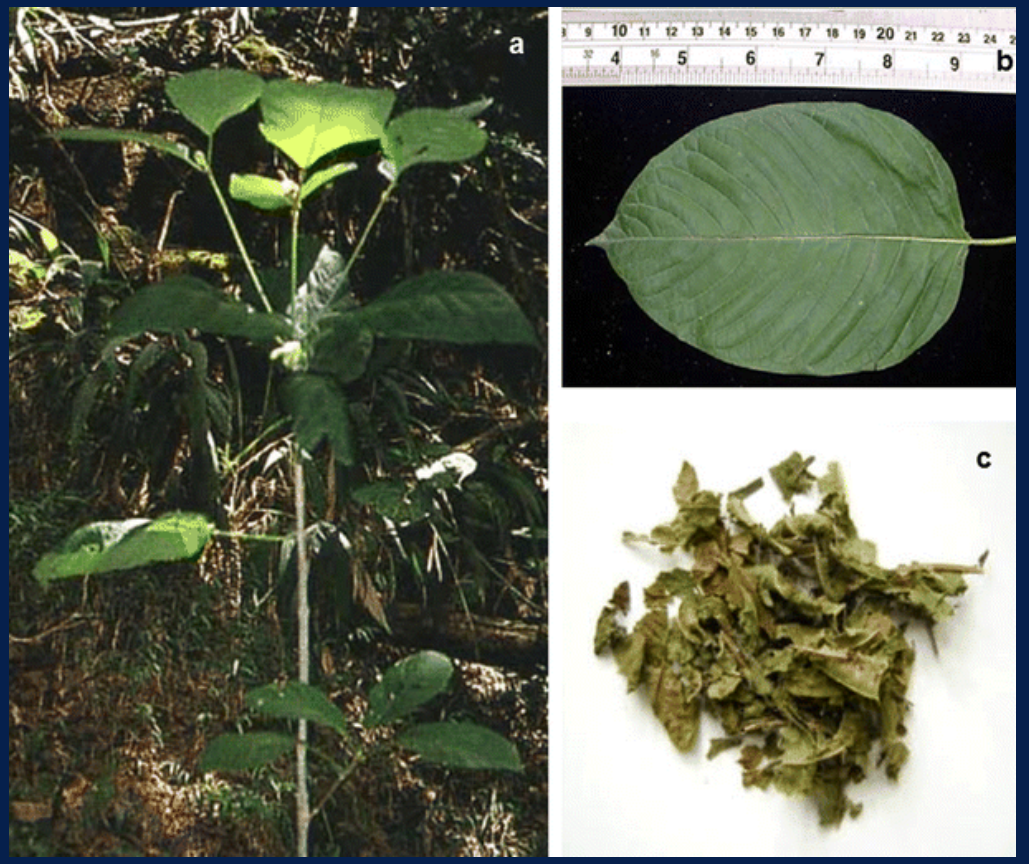
Recent increases in the use of opioid analgesics (e.g., to opioids, and management of withdrawal using opioid replacement therapy or herbal products.

One such herbal product is Kratom (*Mitragyna speciosa Korth*), a tree native to southeast Asia and Africa.[5] Mitragynine, the most prevalent alkaloid isolated from Kratom, and its congeners possess agonist activity at mu- and delta-opioid receptors and are responsible for the drug's opioid-like effects.[6–8] Additional animal studies suggest that mitragynine, a non-opioid indole alkaloid, may also stimulate post-synaptic alpha-2 adrenergic receptors and/or antagonize stimulation of 5-HT_{2A} receptors.[9] Kratom was traditionally used in Thailand and Malaysia by manual laborers to enhance productivity and for its euphoric effects; its indication

Boyer EW, *et al*.. American Journal on Addictions. 2007 Jan 1;16(5):352-6.

What Is Kratom?

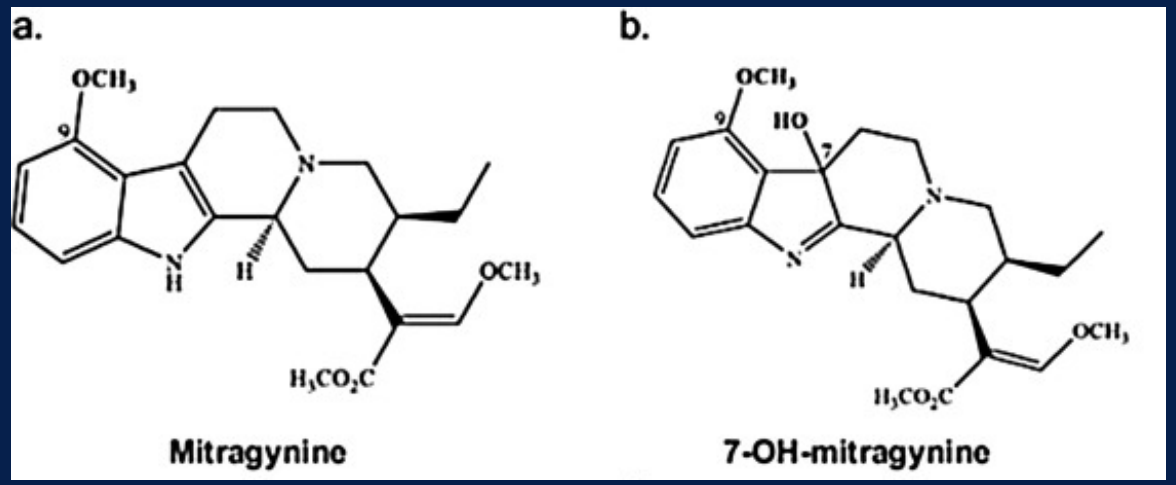
- Tropical tree indigenous to southeast Asia
- Kratom leaves are chewed or prepared as a powder or juice
  - Low dose (1-5 g): stimulant effects used to reduce fatigue in laborers
  - Moderate dose (5-15 g): opioid effects
  - High dose (>15 g): severe opioid effects including stupor

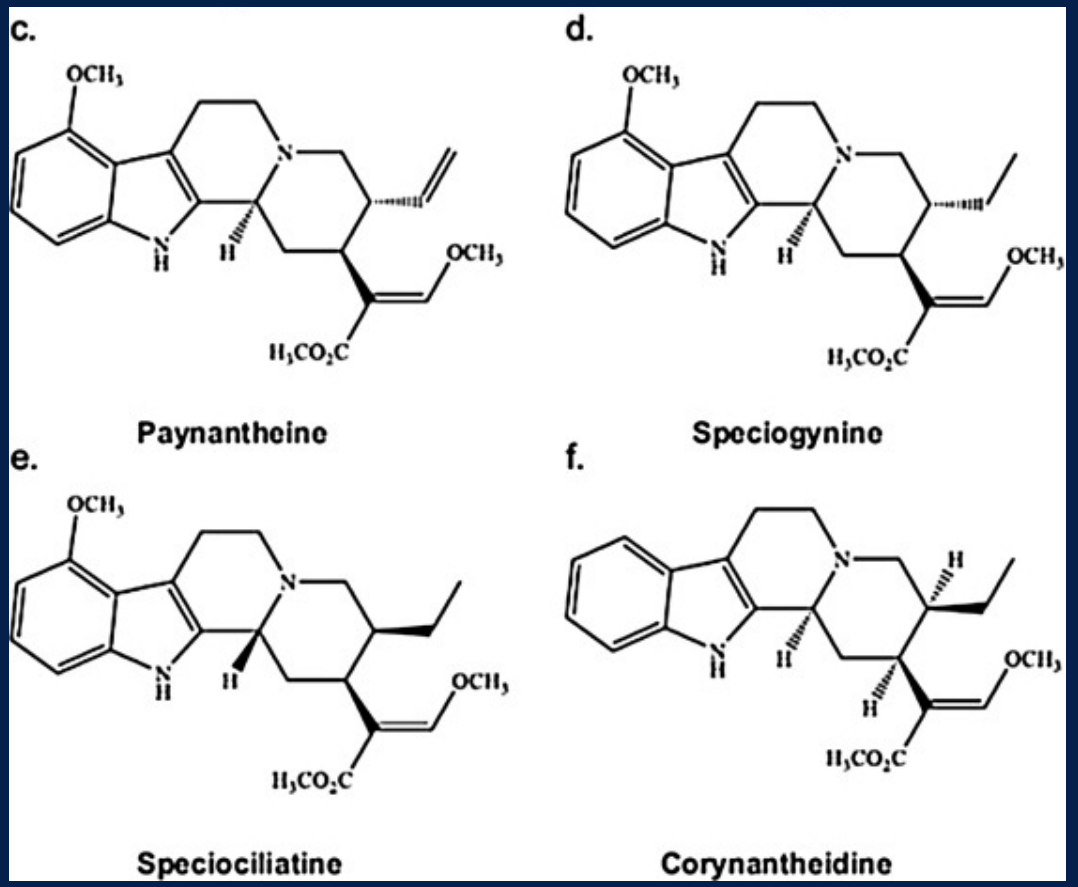


Warner ML, *et al*. International journal of legal medicine. 2016 Jan;130(1):127-38.

Kratom Alkaloids

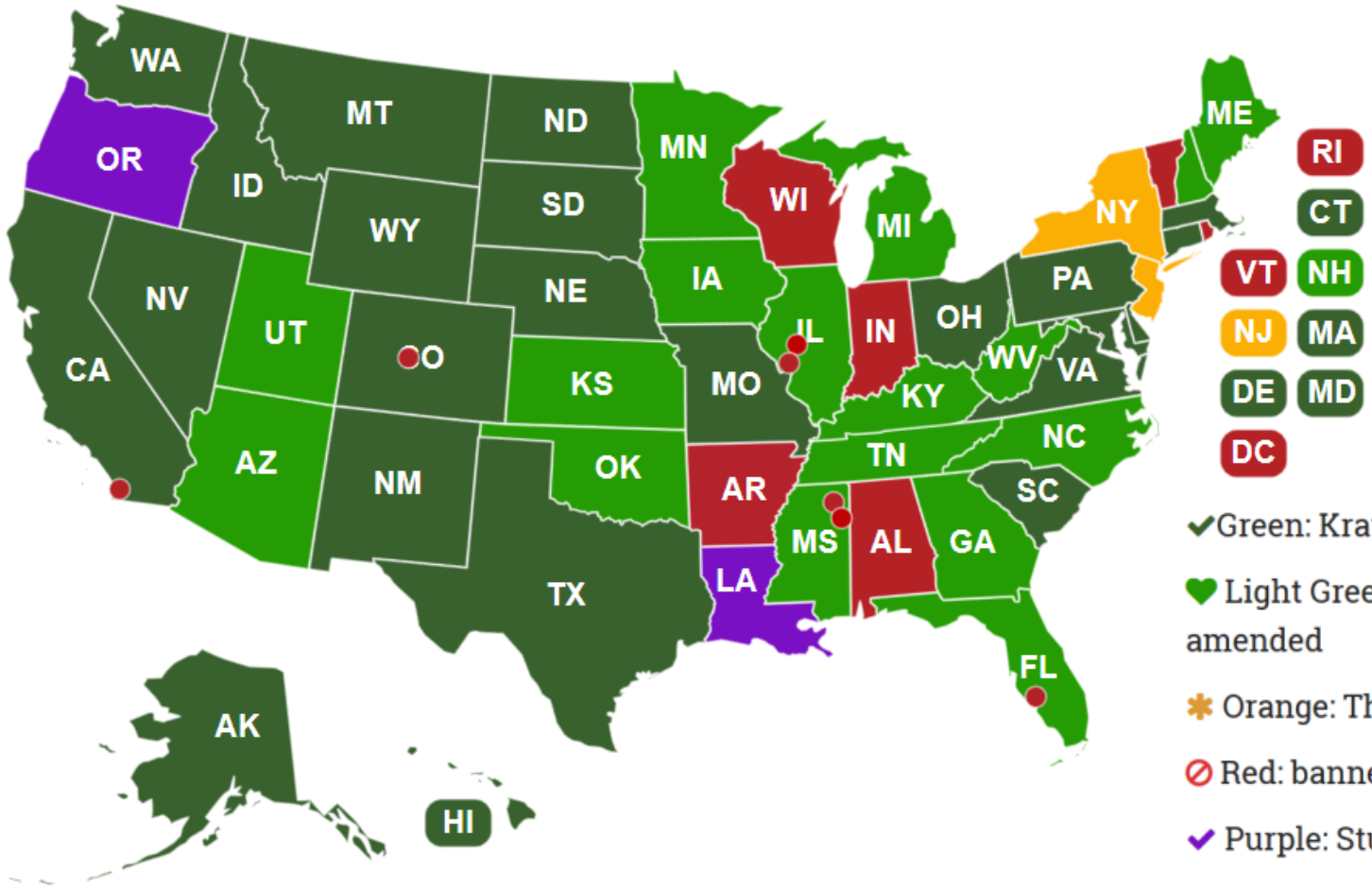
- Mixture of >40 alkaloids





Suhaimi F, *et al*. Brain research bulletin. 2016 Sep 1;126:29-40.

Kratom Legality in the United States



✔Green: Kratom is legal and no restrictions

Light Green : Legislation in these state has failed or has been amended

✱ Orange: There is pending legislation on Kratom in these states

⊘ Red: banned states schedule 1 for Kratom

✔ Purple: Study involving Kratom

● Red Dot: banned city for Kratom

http://speciosa.org/home/kratom-legality-map/

Alternative Opioid Agonist Therapies

- Kratom History (US)
  - 8/30/2016: DEA announced plan to schedule kratom alkaloids as Schedule I
  - 10/12/2016: DEA withdrew intent-to-schedule after public outcry
  - 11/2017: No FDA-approved therapeutic uses of kratom

- Approved Kratom Uses in 2021
  - None

https://www.aegislabs.com/resources/clinical-update/kratom-correlation

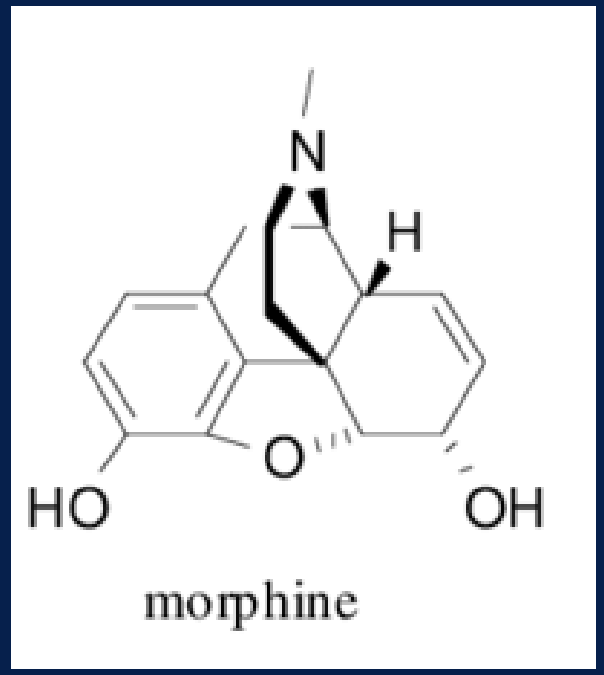
Alternative OATs: Mitragynine (Kratom)

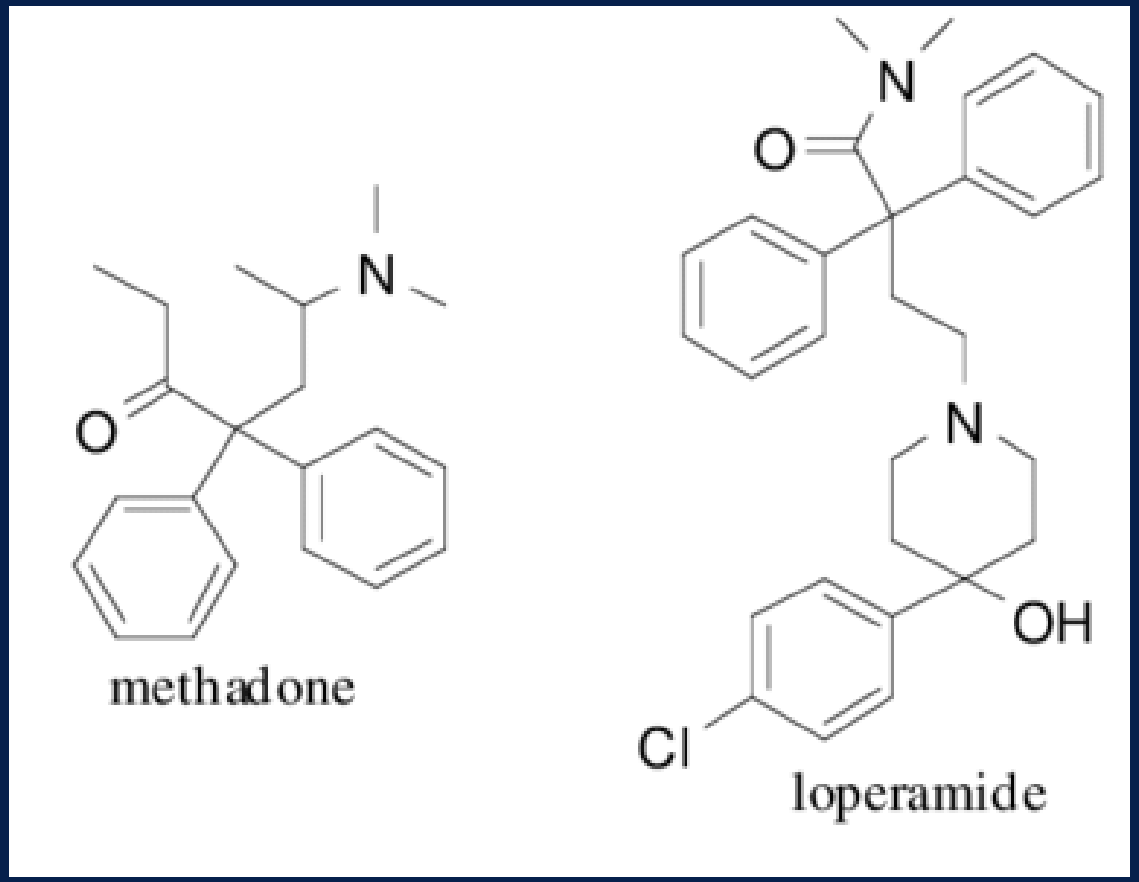
- 37 y/o male with history of anxiety, depression, and OUD initiated on buprenorphine/naloxone therapy for kratom use disorder after using kratom to self-treat his heroin dependence
- Medications: sertraline 100 mg qday, trazadone 25-50 mg QHS
- Drug use history: heroin, marijuana, kratom
- What else do you want to know?

Weiss ST, Douglas HE. Journal of Addiction Medicine. 2020 Aug 26.

Methadone vs. Loperamide Similarities

- Synthetic Opioids
  - Not opiates!



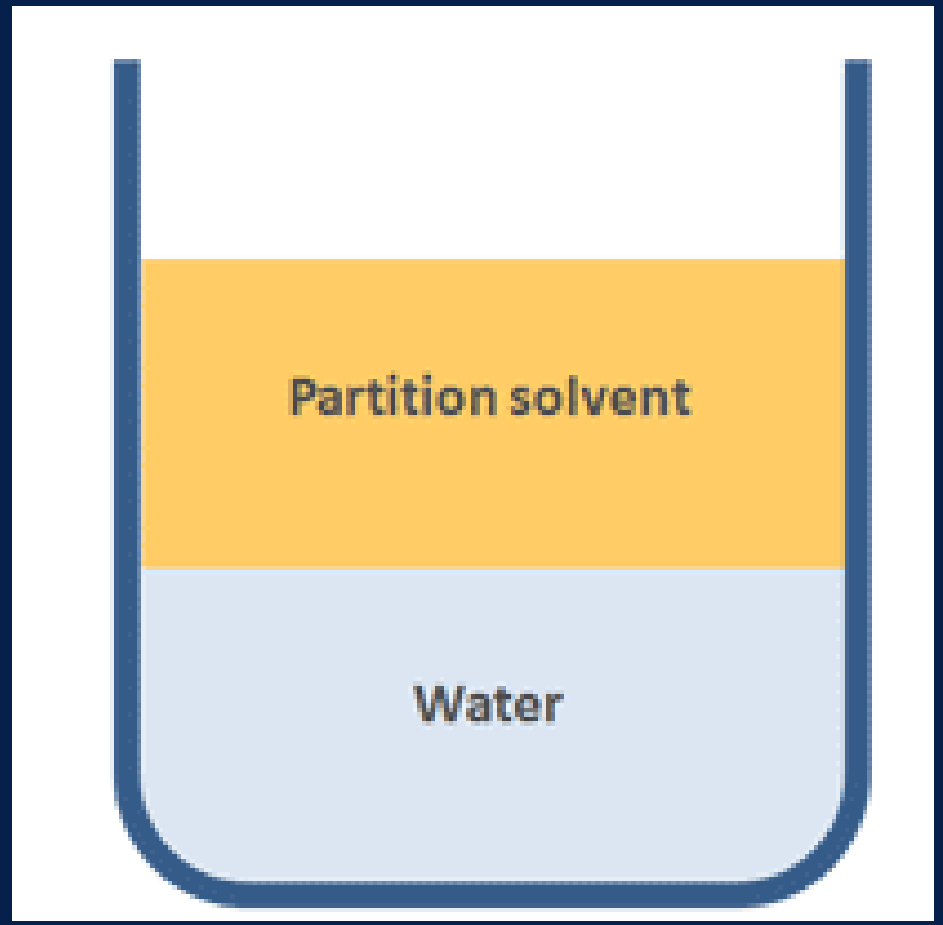


L Mercer S, Coop A.. Current topics in medicinal chemistry. 2011 May 1;11(9):1157-64.

Methadone vs. Loperamide Similarities

- Both lipophilic
  - Loperamide log P = 5.15-5.5
  - Methadone log P = 3.93

$$P = \frac{(\text{conc dissolved in partition solvent})}{(\text{conc dissolved in water})}$$

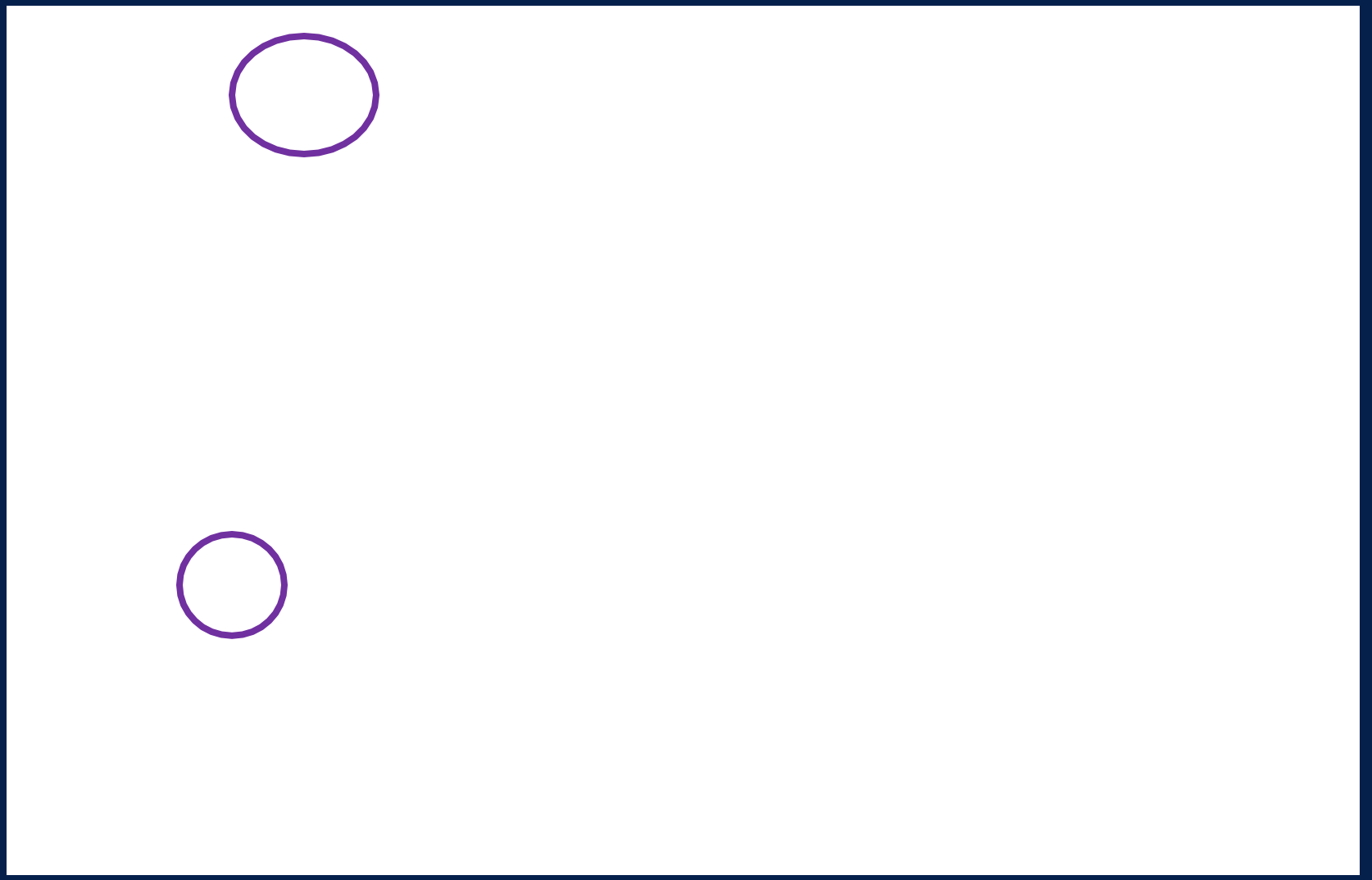


https://m.pion-inc.com/science/lipophilicity-logp/logp-definitions/

https://pubchem.ncbi.nlm.nih.gov/

Methadone vs. Loperamide Similarities

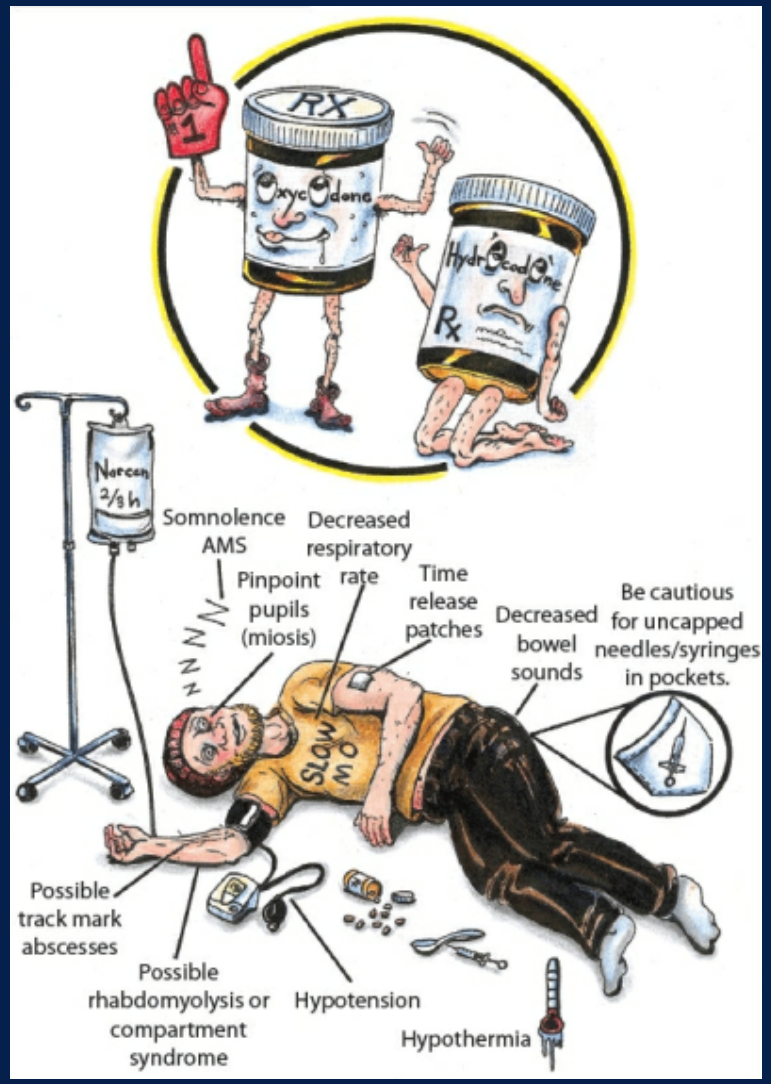
- Both are CYP3A4 substrates



Dilmaghanian S. *et al*. Chirality. 2004;16(2):79-85.
Lin QM, *et al*. Infection and drug resistance. 2019;12:2809.

Methadone vs. Loperamide Similarities

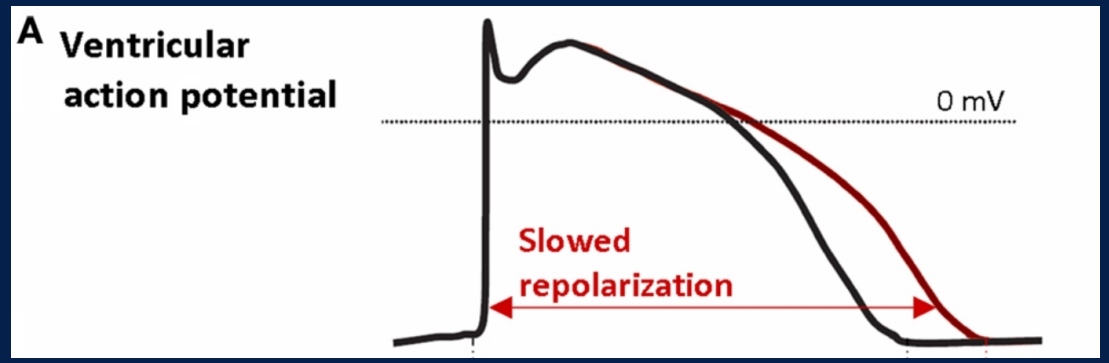
- Peripheral opioid effects
  - Constipation
- Central opioid effects*
  - Euphoria
  - Decreased respiratory rate
  - Somnolence

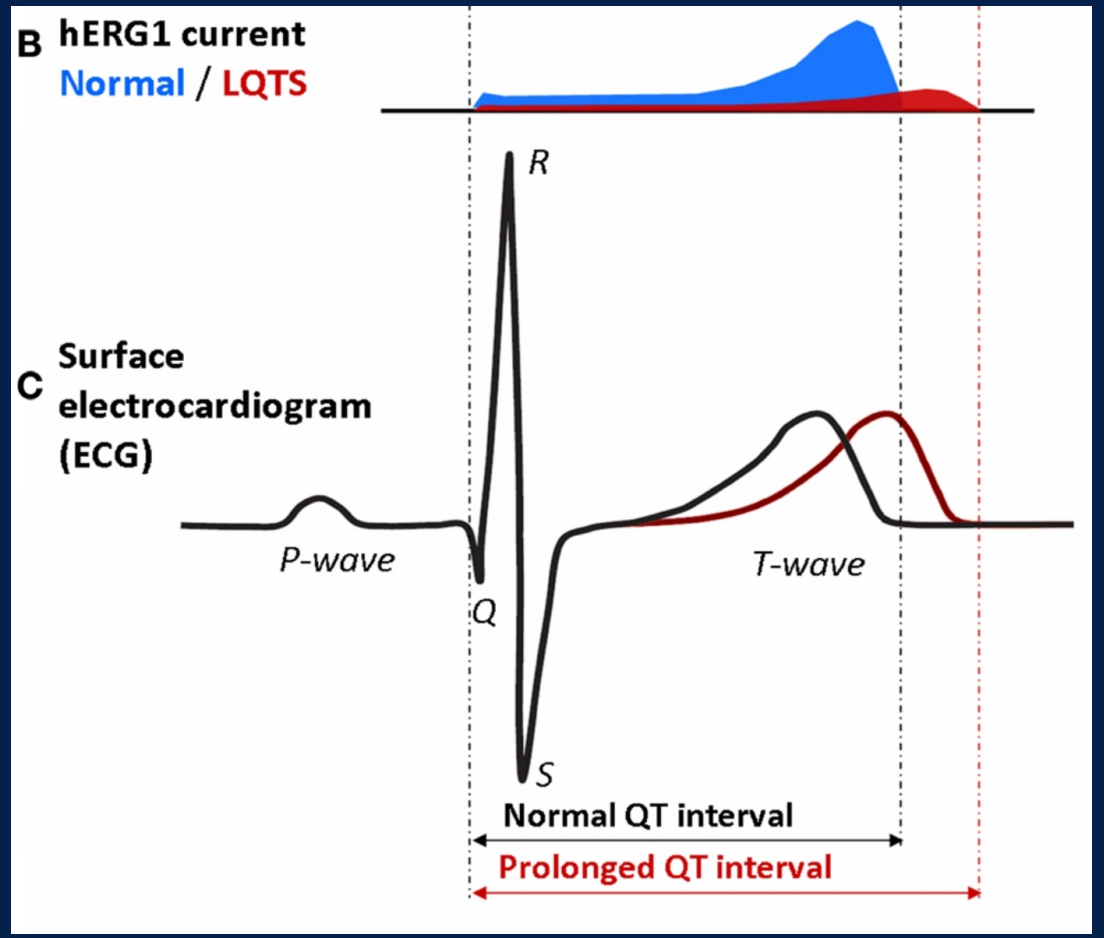


Kloss B, Bruce T. Toxicology in a Box. New York, NY: McGraw-Hill Education; 2014.

Methadone vs. Loperamide Similarities

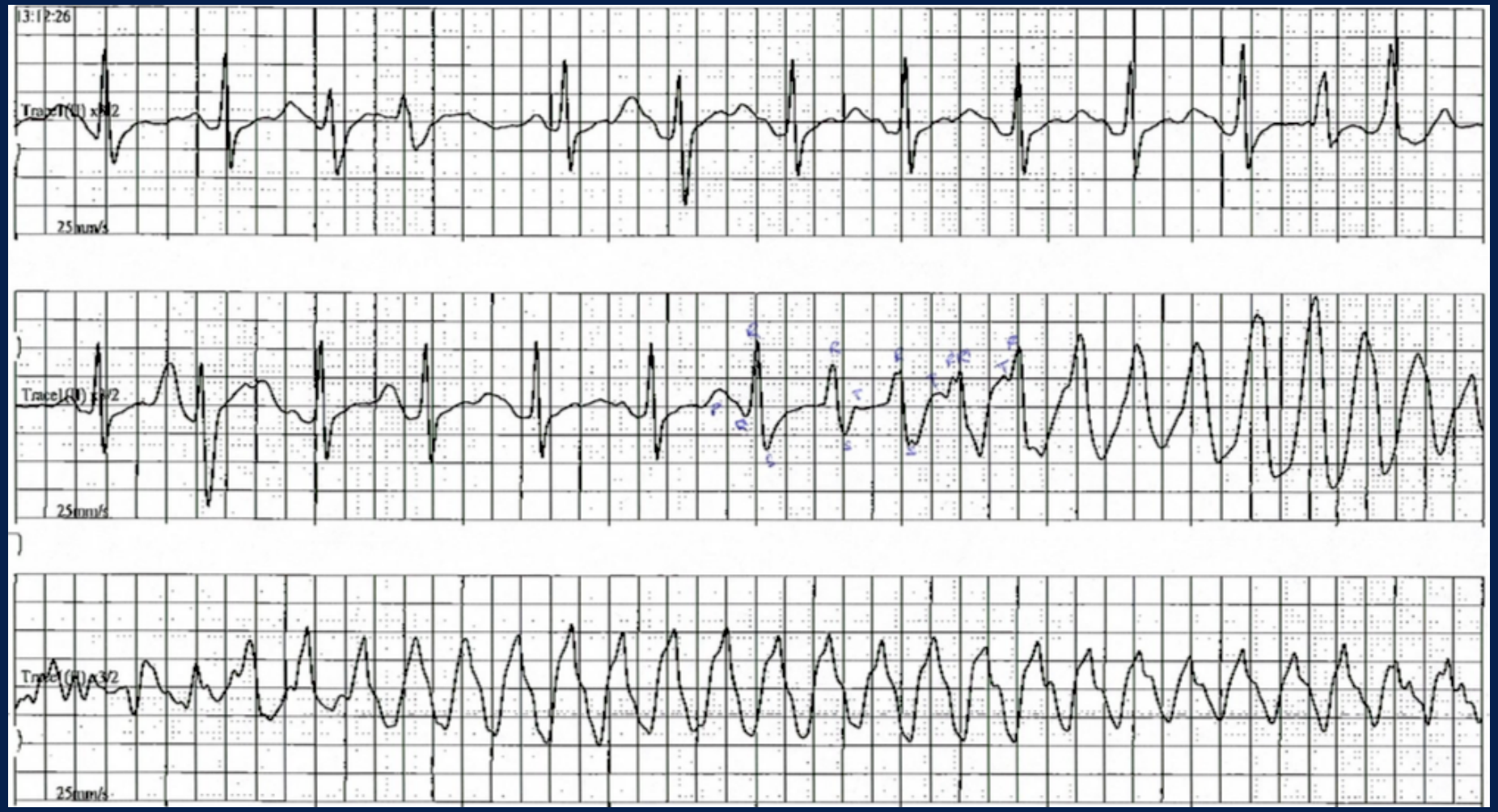
- Inhibition of hERG K^+ channel
  - Most common cause of acquired prolonged QT
  - Can cause drug-induced torsades and sudden death





Sintra Grilo *et al*. Frontiers in pharmacology. 2010 Nov 22;1:137.

Methadone vs. Loperamide Similarities



https://www.aliem.com/2016/08/cardiotoxicity-loperamide-overdose-toxicologist-mindset/

Methadone vs. Loperamide Differences

- Methadone has a long (highly variable) elimination half-life
- Caveat: half-life of other drugs is increased in overdose!

Opioid	Elimination Half-Life
Morphine	2-3 hours
Loperamide	9.1-14.4 hours
Methadone	13-47 hours (avg. 23-25 hours)

https://pubchem.ncbi.nlm.nih.gov/

Methadone vs. Loperamide Differences

- Loperamide has much greater P-glycoprotein efflux
  - This efflux prevents it from being centrally acting at usual doses
  - Methadone is centrally acting since it is not effluxed as effectively

Initial Brain Uptake Clearance of Opioids During In Situ Perfusion in Mice

Compound	Receptor	Wild Type Mice	PGP Knockout Mice	Net PGP Effect
Morphine	μ	1.04 ± 0.03	1.29 ± 0.08	1.24 ± 0.08
Methadone	μ	41.7 ± 5.8	109 ± 17	2.61 ± 0.55
Loperamide	μ	9.86 ± 1.73	103 ± 6	10.4 ± 1.9

L Mercer S, Coop A.. Current topics in medicinal chemistry. 2011 May 1;11(9):1157-64.

FDA-Approved OATs (Methadone)

- Started a new HIV medication regimen seven days prior
  - Ritonavir 400 mg BID (no titration)
  - Saquinavir 400 mg BID
  - Stavudine 40 mg BID

- Labs:
  - LFTs mildly elevated but at pt's baseline
  - Plasma methadone level: 210 ng/mL (normal range 50-1000 ng/mL, baseline unknown)

- What happened, and what should be done?

Geletko SM, Erickson AD. The Journal of Human Pharmacology and Drug Therapy. 2000 Jan;20(1):93-4.

FDA-Approved OATs (Methadone)

- Pt is now on two medications that affect CYP3A4
  - Cimetidine 400 mg BID (CYP3A4 inhibitor, unchanged x 2 years)
  - Ritonavir 400 mg BID (CYP3A4 inducer, newly started 1 week prior)

- Diagnosis: methadone withdrawal
  - Methadone dose increased (90 mg/day => 100 mg/day => 130 mg/day)

- **Clinical Pearl: drug-drug interactions can occur between methadone and other medications that affect CYP3A4 activity**

Geletko SM, Erickson AD. The Journal of Human Pharmacology and Drug Therapy. 2000 Jan;20(1):93-4.

Alternative OATs: Loperamide

- Based on autopsy and initial testing, opioid OD was suspected
  - Further testing was positive for loperamide
  - Blood [loperamide]: 63 ng/mL (therapeutic range <10 ng/mL)

- **Clinical Pearl: P-glycoprotein efflux can be overwhelmed by taking large amounts of loperamide, or by using a PGP inhibitor**
  - Typical dose might be 100-400 mg loperamide (usual dose 2-4 mg)
  - Fluoxetine is a known PGP inhibitor, and this information is freely available on drug user websites

Dierksen J, *et al*. The American journal of forensic medicine and pathology. 2015 Dec 1;36(4):268-70.

Erowid recipe for using loperamide to help with opioid withdrawal symptoms

A decade-long abuser of opioids, I had recently run out of supplies, which happens more often than I'd like, and wanted to stave off withdrawal symptoms as I work nearly every night.

Normal dose of 50 mg oxycodone three times a day for a total of 150 mg oxycodone was stopped completely after a four-month binge. Typical withdrawal symptoms appeared after 12 hours of stoppage. SAWS (sudden acute withdrawal symptoms) manifested within 24 hours. These included severe discomfort, sweating without exercise, cold and hot flashes and waves, cramps, nausea, RLS-type symptoms, over-emotional sympathies, crying, muscle tremors and spasms, headache, supreme dysphoria, longing, loneliness, and more.

32 hours into SAWS, I took this cocktail of drugs. I will first list the dosages and then why I took them.

0:00: 32 mg loperamide hcl
0:00: 20 mg paroxetine hcl
0:00: 500 mg acetaminophen (APAP, Tylenol)

Loperamide is an opioid that has an extremely difficult time crossing the blood-brain barrier (BBB). Therefore it is available over-the-counter as an anti-diahrreal agent at 2 mg per tablet. There are shady ways of increasing the amount of loperamide that crosses the BBB - Loperamide is kept from crossing the BBB via P-glycoprotein(P-gp). P-gp essentially sweeps away things like loperamide as soon as they attempt to cross the BBB. Paxil (paroxetine hcl) is a P-gp inhibitor that I was already taking previous to this at 20 mg/day for anxiety.

Already mentioned was how I take Paxil 20 mg/day. This is relevant as Paxil is a P-gp inhibitor, allowing more loperamide to cross the BBB.

https://www.erowid.org/experiences/exp.php?ID=98136

Methadone vs. Loperamide Risks

- **Both methadone and loperamide** can
  - Cause respiratory depression
  - Prolong QT => torsades and sudden cardiac death
  - Have drug-drug interactions with CYP3A4 substrates/inhibitors/inducers

- **Methadone** can also be:
  - Very long-lasting and “stack”
  - Associated with stigma, difficult to obtain, or illegal in some countries
  - Difficult to dose due to large variation in individual patient factors

- **Loperamide** is not studied or approved for opioid use disorder

Methadone vs. Loperamide Benefits

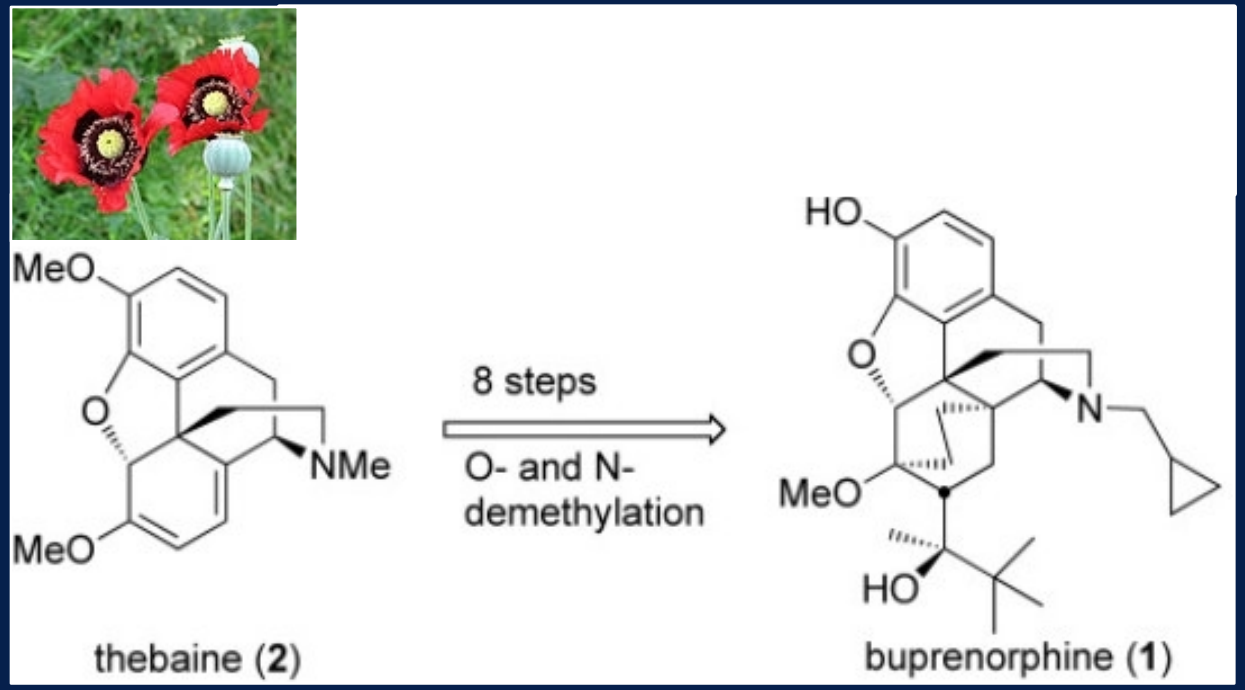
- **Both methadone and loperamide** can
  - Be obtained cheaply
  - Be obtained reliably and are produced under regulated conditions

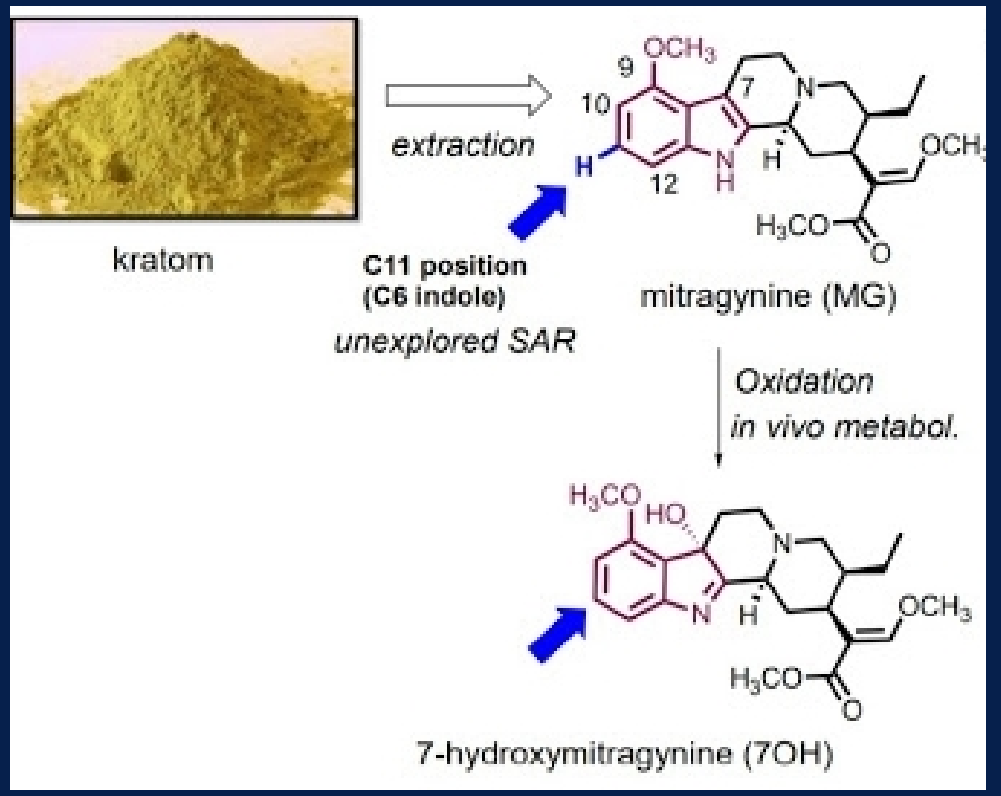
- **Methadone** has also been:
  - Well studied for treatment of opioid use disorder
  - Shown to be effective for OUD with well-established dosing protocols

- **Loperamide** can also be purchased over-the-counter

Buprenorphine vs. Mitragynine Similarities

- Natural products and semisynthetic derivatives



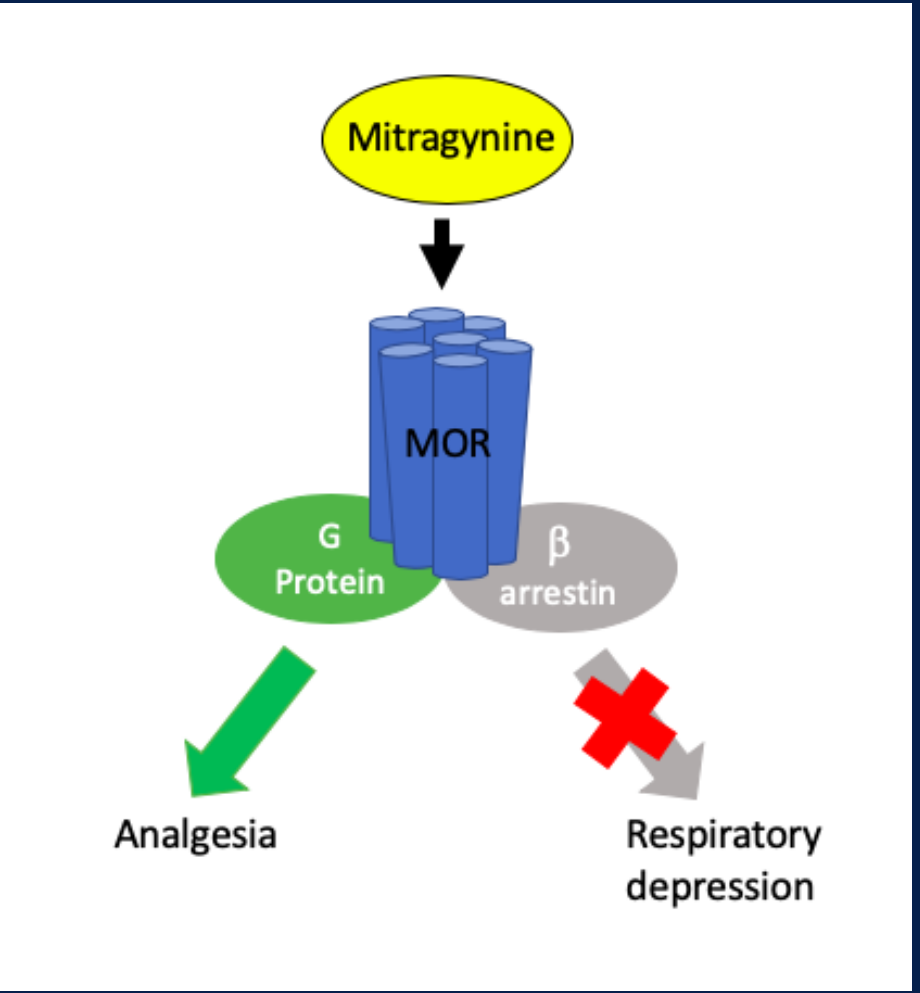


Machara A, *et al*. Advanced Synthesis & Catalysis. 2012 Mar;354(4):613-26.

http://www.columbia.edu/cu/chemistry/groups/sames/news.html

Buprenorphine vs. Mitragynine Similarities

- Both are lipophilic
  - Buprenorphine log P = 4.98
  - Mitragynine log P = 1.73
- Both are partial agonists
- Both appear to be biased agonists
  - Activate G-protein coupled path
  - Less activation of β-arrestin path



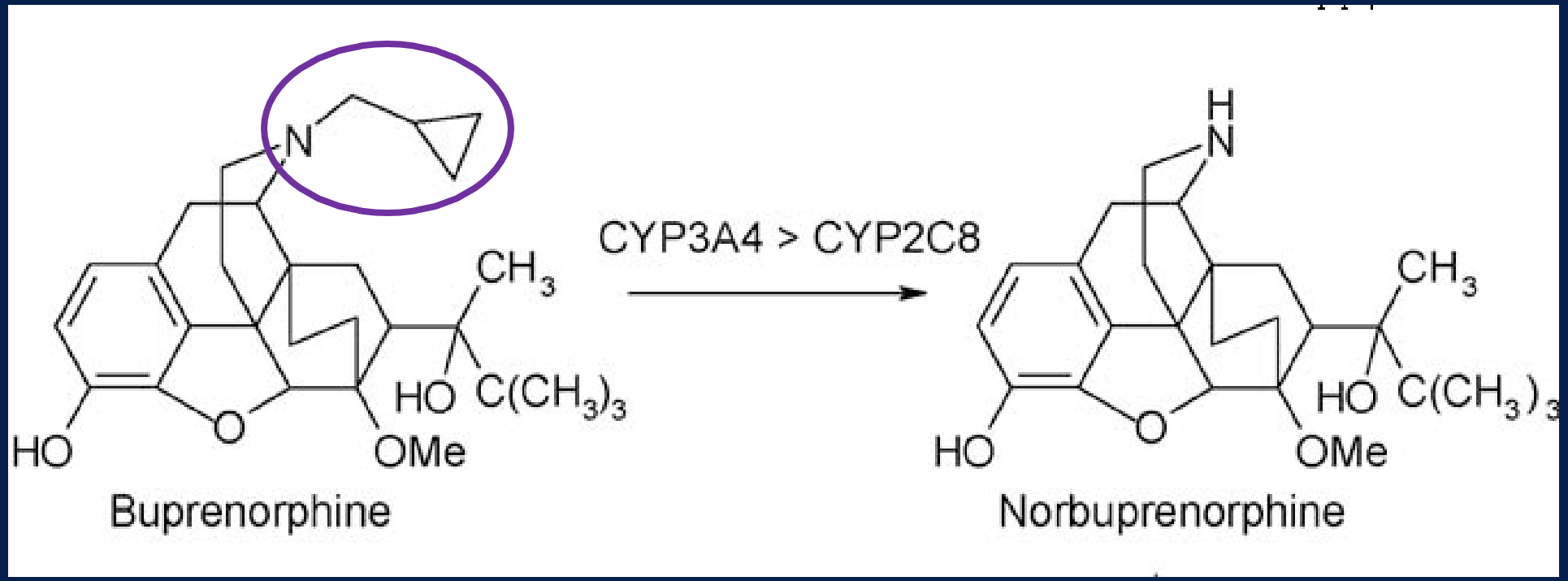
https://pubchem.ncbi.nlm.nih.gov/

Ramanathan S, *et al*. Molecules. 2015 Mar;20(3):4915-27.

https://www.wikiwand.com/en/Mitragynine

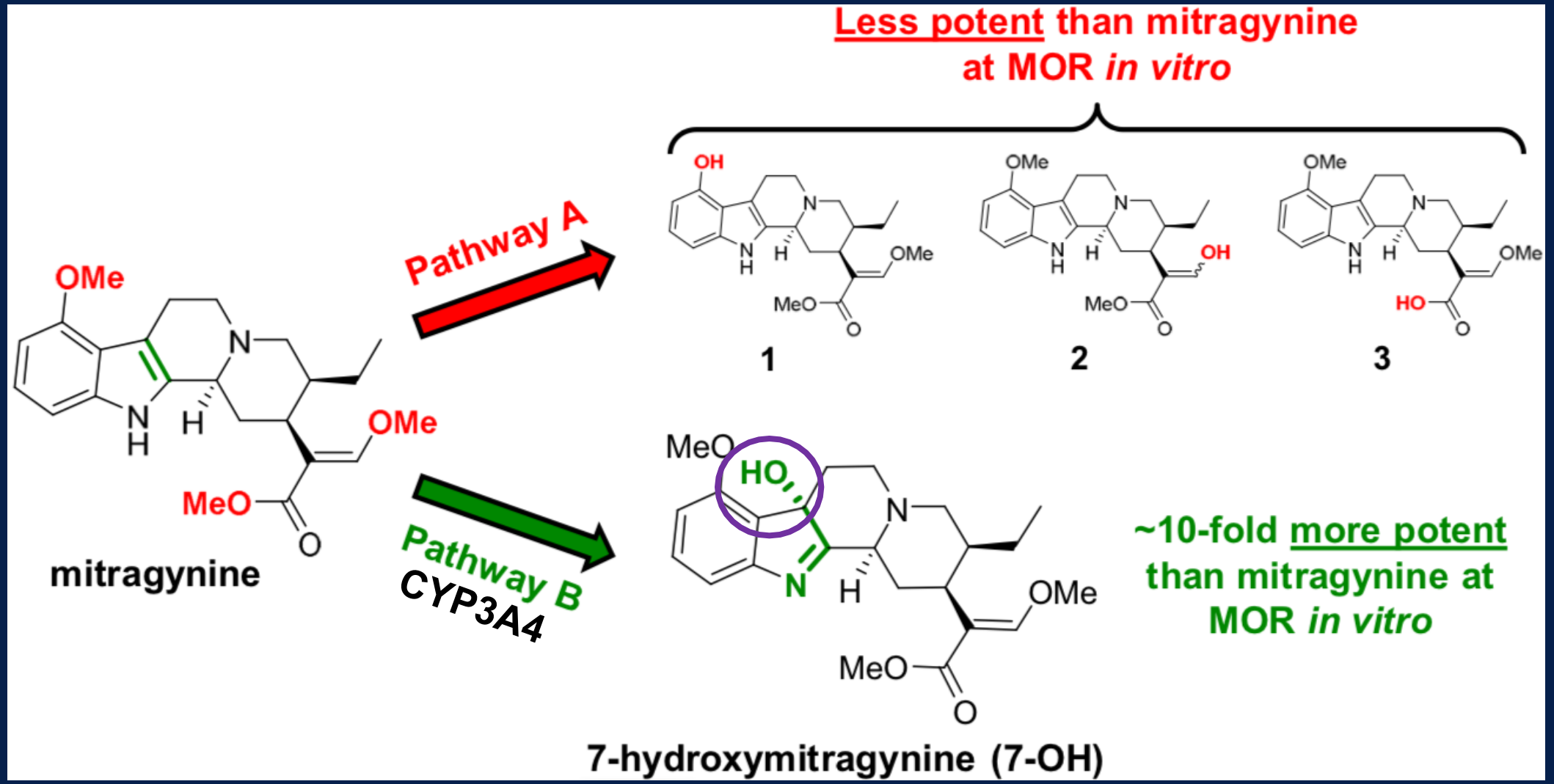
Buprenorphine vs. Mitragynine Similarities

- Metabolism: both primarily by CYP3A4



Oechsler S, Skopp G. Forensic science international. 2010 Feb 25;195(1-3):73-7.

Kratom Metabolism



Kruegel AC, *et al*. 2019 May 29;5(6):992-1001.

Buprenorphine vs. Mitragynine Differences

- Formulation
  - Kratom is a natural product
  - Buprenorphine is a pharmaceutical product
- Elimination half lives
  - Buprenorphine: 31-42 hours
  - Mitragynine: 3.85 hours (in rats)

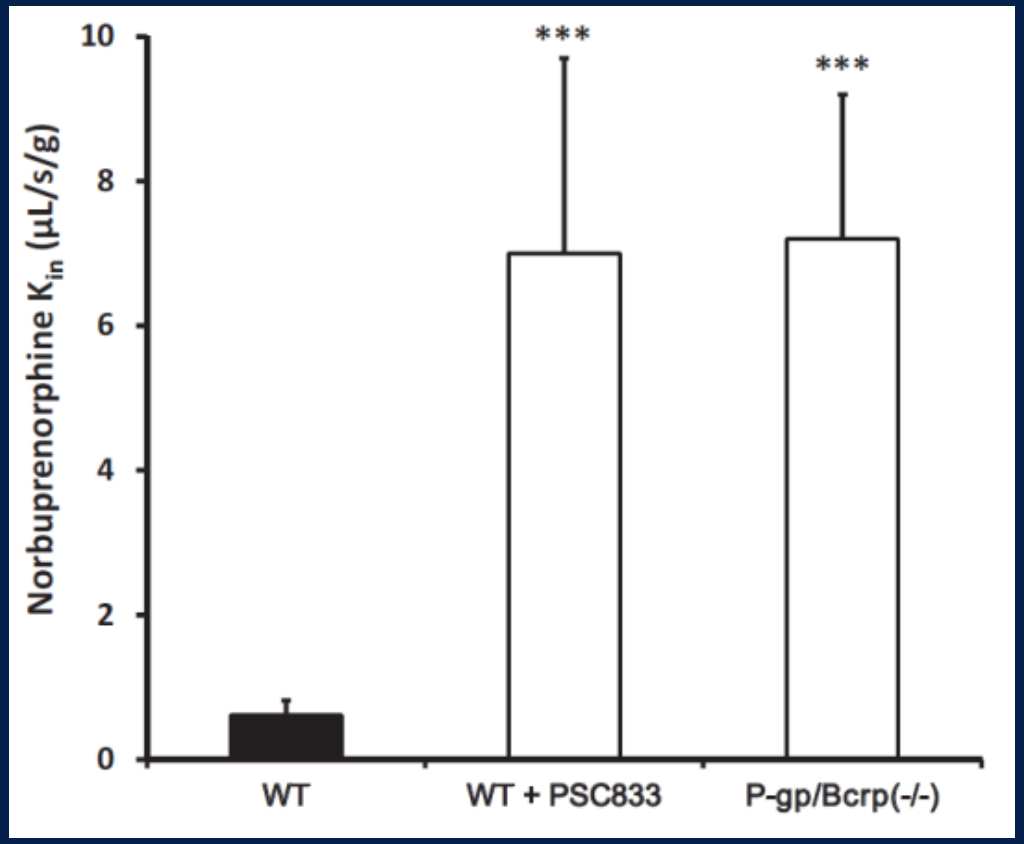
https://www.wuft.org/news/2020/10/28/uf-study-suggests-kratom-could-treat-opioid-addictions/

https://pubchem.ncbi.nlm.nih.gov/

Buprenorphine vs. Mitragynine Differences

- Neither parent drug is a P-glycoprotein substrate

- BUT:
  - Norbuprenorphine metabolite is a PGP substrate in rats
  - Mitragynine and its metabolite 7-hydroxymitragynine are both PGP inhibitors in cells



Alhaddad H, *et al*. Critical care medicine. 2012 Dec 1;40(12):3215-23.

Manda VK, *et al.* Planta Med. 2014 May 1;80(7):568-76.

Rusli N, *et al*. Naunyn-Schmiedeberg's archives of pharmacology. 2019 Apr;392(4):481-96.

Buprenorphine vs. Mitragynine Differences

- Mitragynine blocks potassium channels *in vitro*
  - hERG potassium channels
  - Rapid delayed rectifier potassium channels

- Buprenorphine blocks hERG channels *in vitro* too, but not clinically significant

Drug	IC_{50} for hERG	Plasma C_{max}	Ratio (IC_{50}/C_{max})
Methadone	9.8 µM	3.6 µM	2.7
Buprenorphine	7.5 µM	0.036 µM	208

Lu J, *et al*. PLoS One. 2014 Dec 23;9(12):e115648.
Wedam EF, *et al.* Archives of internal medicine. 2007 Dec 10;167(22):2469-75.
Katchman AN *et al*. Journal of Pharmacology and Experimental Therapeutics. 2002 Nov 1;303(2):688-94.

FDA-Approved OATs: Buprenorphine

- Pt was buying buprenorphine/naloxone 4/1 mg films from a friend
  - Improvement of pt's headaches w/ initial PRN use
  - Escalation to 2-4 mg buprenorphine qday after discovery that she felt better in general on the medication

- Problem: pt was not prescribed buprenorphine!
  - She attempted to wean herself from buprenorphine and was not successful due to intolerable opioid withdrawal
  - Routine drug test at work: positive for buprenorphine

- What should be done next?

Norton M, *et al.* Mental Health Clinician. 2016;6(3):127-30.

FDA-Approved OATs: Buprenorphine

- Patient was diagnosed with OUD and had her license suspended
  - Sent for 21 day detox and remained sober for a month but then relapsed
  - Admitted for inpatient treatment followed by IOP and NA
  - Started sumatriptan injections for her migraines

- **Clinical Pearl: health care professionals, especially pharmacists, are at high occupational risk for substance use disorder**
  - Strong pharmacologic knowledge, high-stress job, easy workplace access
  - Treatment is essential => high rate of success (up to 85%)

Norton M, *et al.* Mental Health Clinician. 2016;6(3):127-30.

Alternative OATs: Mitragynine (Kratom)

- Prior SUD clinic patient who had declined OAT previously in favor of self-treating with kratom
  - Using 7-14 g kratom/day PO for the past six months
  - Was unable to stop using kratom due to intolerable withdrawal
  - Patient reported ongoing craving for heroin

- Started on buprenorphine/naloxone 8/2 mg/day but wanted to discontinue buprenorphine/naloxone

- What should be done next?

Weiss ST, Douglas HE. Journal of Addiction Medicine. 2020 Aug 26.

Alternative OATs: Mitragynine (Kratom)

- Patient goal is to completely stop using all opioids
  - Counseling of patient regarding risk of relapse due to premature discontinuation of OAT
  - Patient buprenorphine/naloxone taper begun at patient request

- **Clinical Pearl: kratom users run a risk of developing dependence on kratom in turn, with signs/symptoms of kratom withdrawal being similar to opioid withdrawal signs/symptoms**
  - Physical symptoms: rhinorrhea, goosebumps, mydriasis, nausea and vomiting, diarrhea, abdominal cramping, sweating, fatigue, restlessness, myalgias
  - Psychiatric symptoms: irritability, anxiety, depression, hallucinations, inability to stop using kratom, cravings for the drug

Weiss ST, Douglas HE. Journal of Addiction Medicine. 2020 Aug 26.

Buprenorphine vs. Mitragynine Risks

- **Both buprenorphine and mitragynine** can potentially:
  - Have drug-drug interactions with CYP3A4 substrates/inhibitors
  - Cause dependence and opioid use disorder themselves

- **Buprenorphine** can potentially cause respiratory depression when co-administered with a P-glycoprotein inhibitor

- **Kratom (mitragynine)** can also potentially:
  - Have unknown effects or risks due to limited study in humans
  - Be contaminated or of uncertain provenance
  - Cause sudden cardiac death or have drug-drug interactions with PGP substrates

Buprenorphine vs. Mitragynine Benefits

- **Both buprenorphine and mitragynine** potentially have:
  - Reduced risk of respiratory depression compared to full agonists
  - Less tolerance and fewer other side effects versus full agonists

- **Buprenorphine** has also been:
  - Well studied for treatment of opioid use disorder
  - Shown to be effective with well-established dosing protocols

- **Kratom (mitragynine)** can also be bought on the internet or in head shops, potentially lessening stigma

Final Takeaways/Summary

- **Two sets of parallel opioid agonist treatments are used for OUD**
  - FDA-approved opioid agonists: methadone, buprenorphine
  - Alternative opioid agonists: loperamide, mitragynine

- **Two types of opioid agonist drugs exist**
  - Full opioid agonists: methadone and loperamide
  - Partial (biased?) opioid agonists: buprenorphine and mitragynine

- Patients and providers should be aware of the risks and benefits of both FDA-approved and alternative opioid agonist therapy drugs

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