

# Pharmacological treatment and intervention

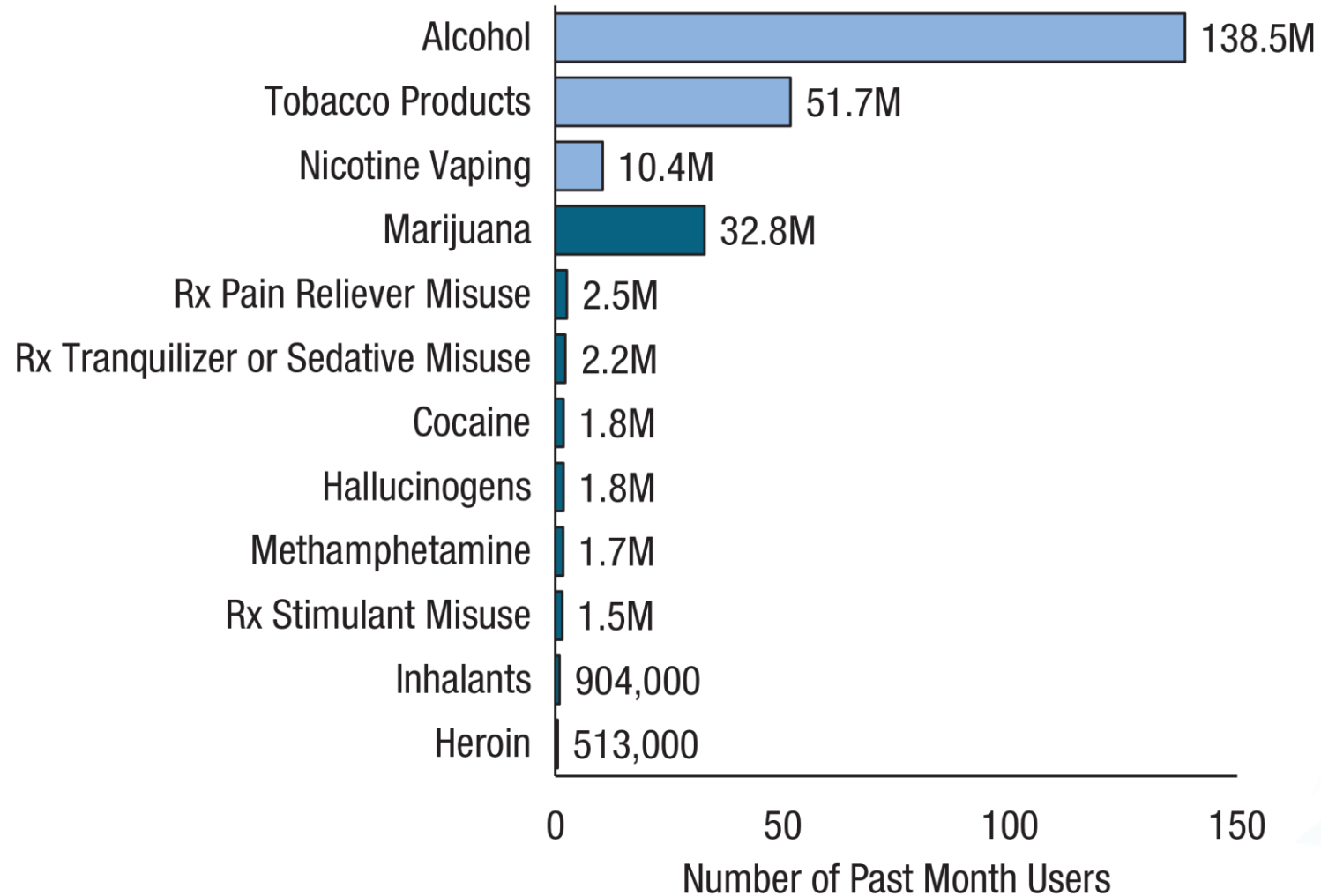


# Learning objectives

- For each substance class, recognize its primary effects and pharmacological treatment options.



# United States past month substance use among people aged 12 or older, 2020<sup>1</sup>



# Pharmacological treatments for alcohol use disorder

- FDA approved for alcohol use disorder
  - Disulfiram (Antabuse)
  - Naltrexone (Vivitrol, Revia)
  - Acamprosate (Campral)
- Off label use
  - Gabapentin (Neurontin)
  - Varenicline (Chantix)



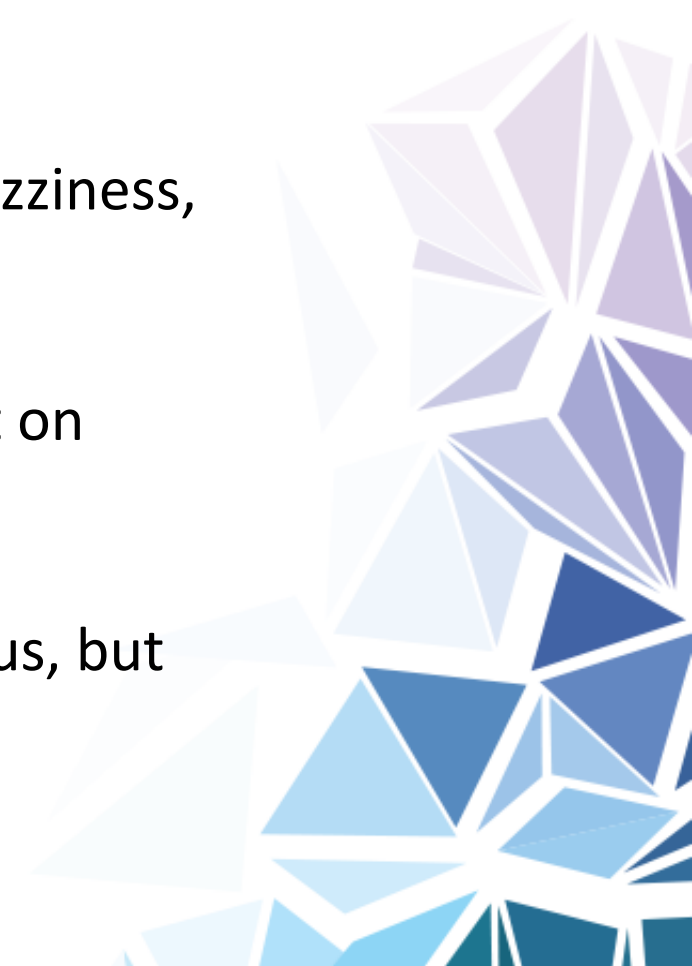
# Historical treatments for alcohol use disorder: conditioned reflex treatment

- Amphetamine administration to produce euphoria and obviate the need for alcohol<sup>2,3</sup>
- Aversive conditioning or aversion therapy
  - Apomorphine administration with vodka<sup>4</sup>
  - Emetine administration paired with alcoholic drinks<sup>5</sup>
  - Remains a mainstay of several addiction treatment centers despite lack of evidence



# Disulfiram (Antabuse)

- Inhibits acetaldehyde dehydrogenase (ALDH) causing acetaldehyde to build up in the liver when alcohol is metabolized
- Acetaldehyde causes flushing, nausea, vomiting, headaches, dizziness, tachycardia, hypotension, and dyspnea
- Relies on fear of negative consequences for its effect; no effect on cravings
- Open-label studies with supervision find it is safe and efficacious, but studies that are blinded or unsupervised show no efficacy<sup>6</sup>



# Disulfiram (Antabuse) caveats

- The reaction to alcohol consumption can prove fatal<sup>7,8</sup>
- FDA approval obtained in the 1950s
- **Side effects:** headaches, drowsiness, peripheral neuropathy, optic neuritis, hepatotoxicity, psychosis
- **Contraindications:** cardiovascular disease, hypertension, personality disorder, suicidality, psychosis, pregnancy, breast-feeding
- **Not recommended for use in primary care settings**



# Naltrexone (Vivitrol, Revia)

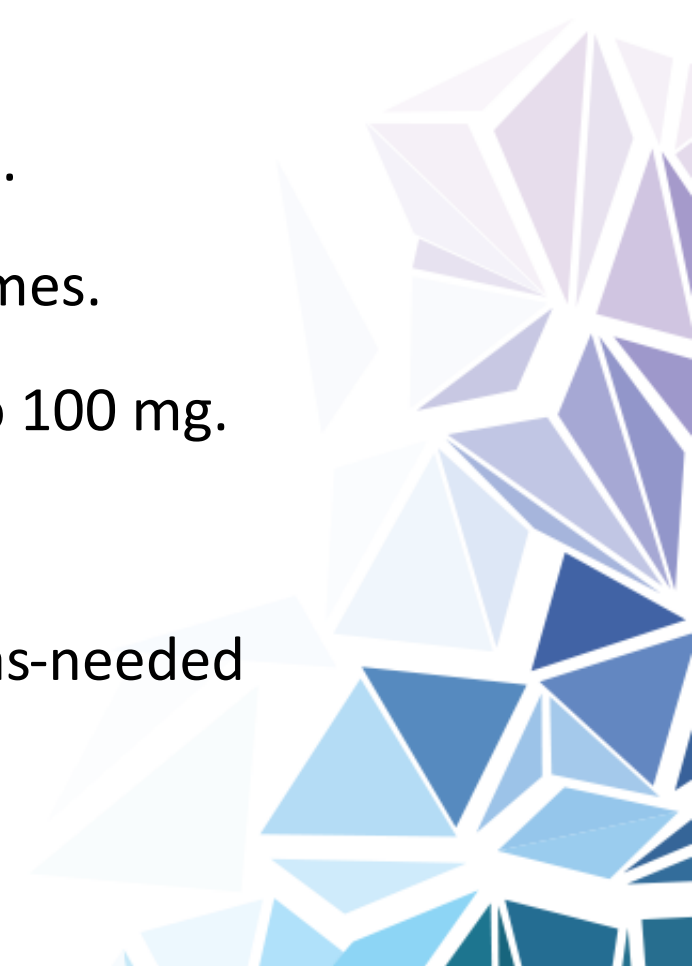
- $\mu$ -opioid receptor antagonist (as is the active metabolite 6 $\beta$ -naltrexol)
- Improves outcomes by about a third<sup>9</sup>
- Thought to reduce the pleasurable aspects of drinking





# Naltrexone (Vivitrol, Revia) prescribing

- Opioid blockade persists 48-72 hours after the last dose. Stop opioids 7-10 days before initiation.
- Can be started while patients are still drinking or in withdrawal.
- Primarily renal excretion; not much interaction with liver enzymes.
- Start at 25 mg daily for 2 weeks, then 50 mg daily. Can go up to 100 mg.
- Available as a long-acting injection.
- Treatment duration should be at least 6 months. Can be used as-needed rather than daily.<sup>10</sup>



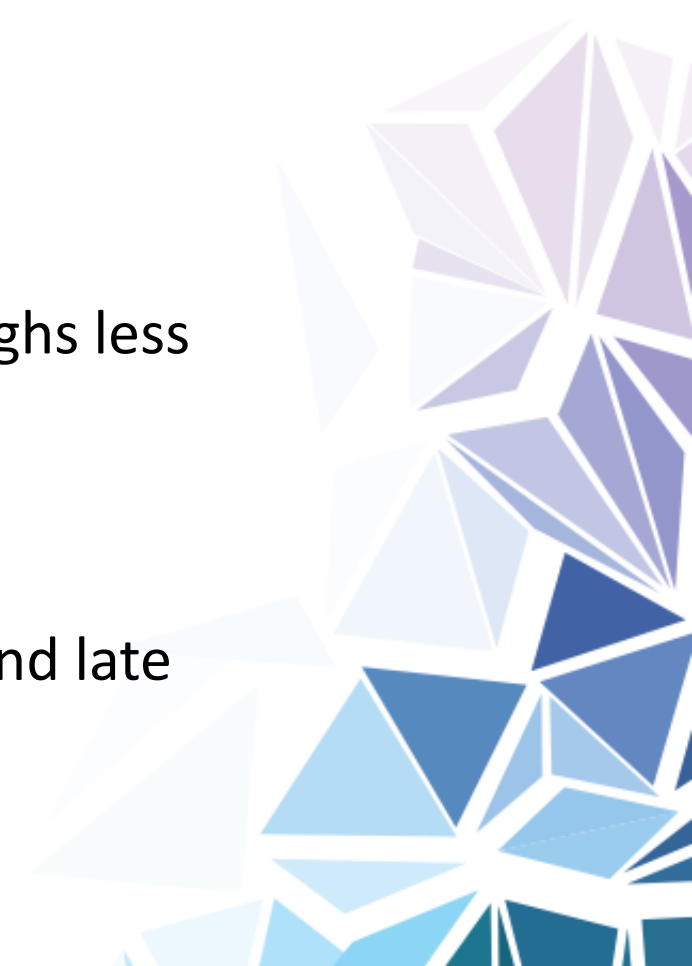
# Acamprosate (Campral)

- Calcium salt of N-acetyl-homotaurine
- Mechanism is unclear and usually ascribed to modulation of glutamate and/or GABA<sup>11</sup>
- Calcium may actually be the active ingredient<sup>12</sup>
- A preponderance of RCTs have shown efficacy in combination with psychosocial support
  - Abstinence rates improve from 23.4% to 36.1%<sup>13</sup>
  - Other drinking outcomes also improve<sup>14</sup>



# Acamprosate (Campral) prescribing

- Renal excretion with no liver metabolism, so safe with liver disease
- Also does not interact with many medications
- Generally well-tolerated, but commonly causes GI problems
- Dose is 666 mg three times daily, or half that if the patient weighs less than 130 pounds.
- Recommended treatment duration is at least 6 months
- Seems to work best in anxious women with no family history and late onset of alcoholism<sup>15</sup>



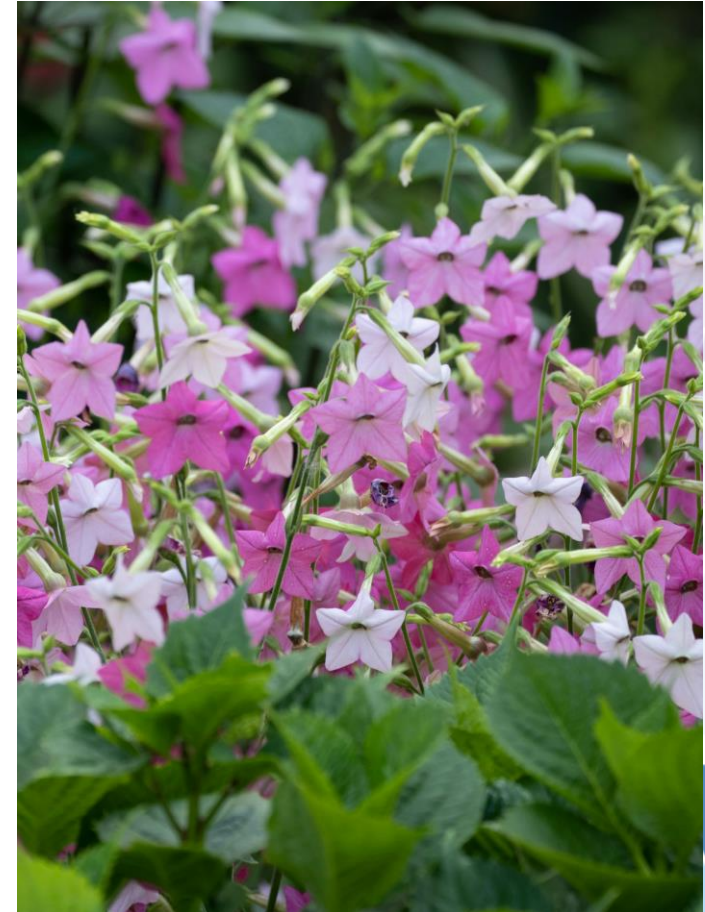
# Off label treatments for alcohol use disorder

- **Gabapentin**: anticonvulsant that stimulates GABA-B
  - Reduces EtOH consumption and improves sleep (Myrik 2009; Mason 2009; Mason 2014)
  - Can be combined with naltrexone for improved sleep outcomes (Anton 2011)
  - Higher doses (1800 mg daily) produce better outcomes
- **Varenicline**: decreases cravings and drinking in smokers and non-smokers<sup>16-19</sup>



# Nicotiana tabacum (Tobacco)

- Native to Mesoamerica
- Used mainly for ceremonial purposes
- Introduced to Europe by Columbus
- Major cash crop in the early colonies
- Remains an important industry in the South



# Systemic effects of nicotine

- Sympathomimetic: tachycardia, vasoconstriction, hypertension<sup>20</sup>
- Reduces insulin sensitivity<sup>21</sup>
- May interfere with endothelial cell function<sup>22</sup>
- Impairs wound healing due to vasoconstriction
- Not a direct carcinogen
- Is a neuroteratogen<sup>23</sup>



# Potential health benefits of nicotine

- Reduces malaria risk
- Increases survival if caught in a fire
- Smoking reduces risk of Parkinson's disease by ~70%<sup>24</sup>
- Improves sensory gating by activating  $\alpha 7$  nAChRs<sup>25</sup>
- Inhibits MAO A and B and releases dopamine, serotonin, and norepinephrine
- Desensitizes nAChRs, which has been postulated to stabilize mood



# Pharmacological treatments for nicotine use disorder

- FDA approved for nicotine
  - Nicotine replacement therapy
  - Varenicline (Chantix)
  - Bupropion (Zyban, Wellbutrin)
- Approved in other countries
  - Cytisine (Tabex, Cravv)
- Off label use
  - Nortriptyline (Pamelor)



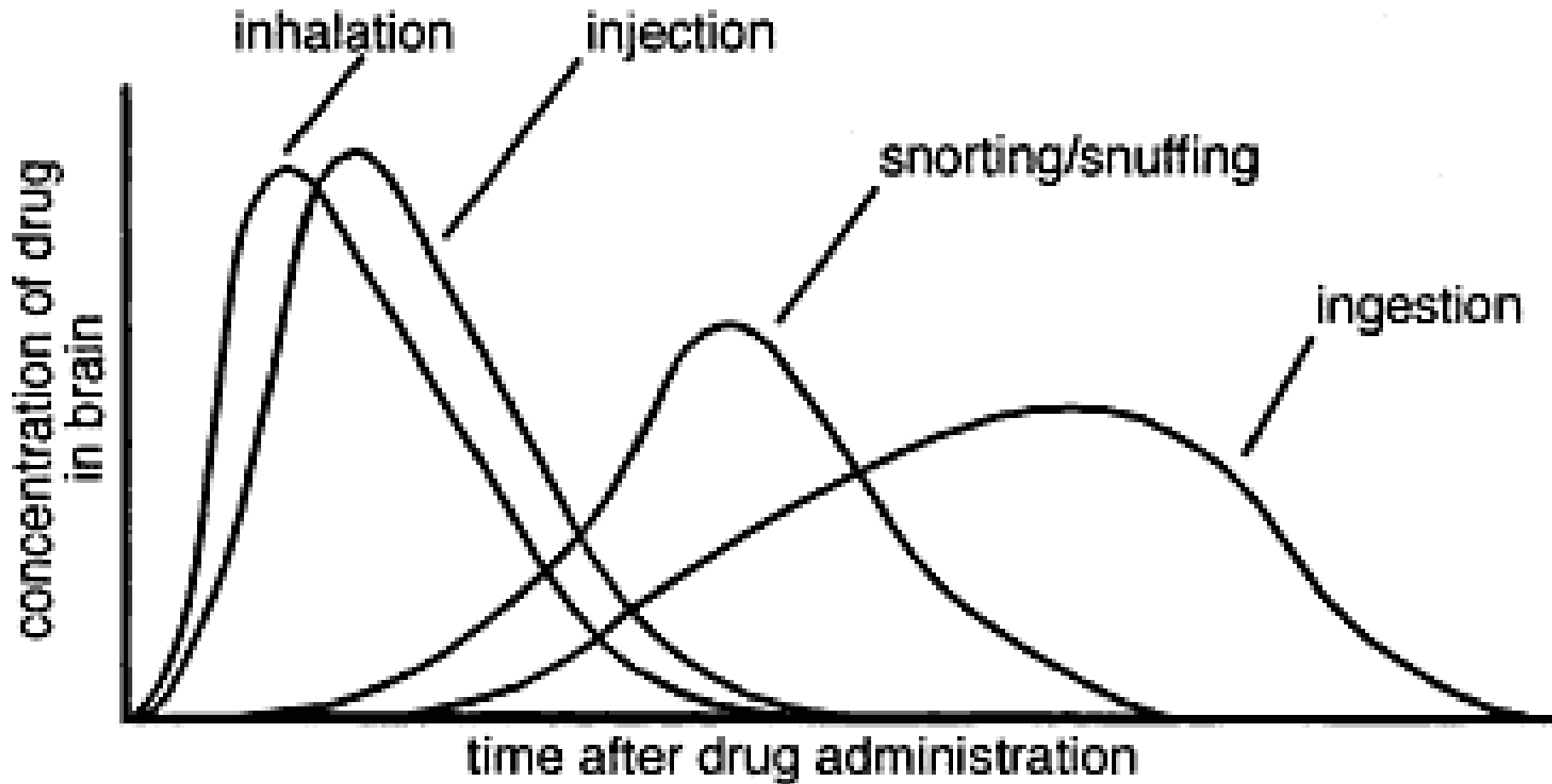


# Nicotine replacement therapy

- Available in transdermal patches, gum, nose spray, inhalers, and lozenges
- Increases smoking cessation success rates from 10% to 22%<sup>26</sup>
- Even better efficacy with a patch plus some form of immediate release<sup>27</sup>
- Adverse effects are uncommon but can include GI upset, headaches, and local irritation



# Addiction pharmacokinetics<sup>28</sup>



# Varenicline (Chantix)

- High-affinity nAChR partial agonist
- Increases smoking cessation success rates 2 to 3-fold<sup>29</sup>
- Treat for at least 12 weeks; evidence that even longer treatment improves outcomes<sup>30</sup>
- Combining with nicotine replacement may improve efficacy<sup>31</sup>
- Insomnia and vivid dreams are common, but reports of suicidality and other psychiatric side effects have not been substantiated<sup>32</sup>



# Cytisine (Tabex, Cravv)

- Alkaloid found in the SE European Laburnum golden rain tree
- Same mechanism as varenicline (which is actually a derivative).
- Initial reports indicated poor bioavailability, but subsequent studies have shown 4-fold increases in quit rates.<sup>33</sup>
- Available in Europe (Tabex), but not the US



# Bupropion (Wellbutrin)

- Norepinephrine and dopamine reuptake inhibitor
- Noncompetitive NACHR antagonist<sup>34</sup>
- Increases quit rates ~2 fold
- Combining with nicotine replacement may improve efficacy<sup>35</sup>
- May reduce weight gain associated with quitting<sup>36</sup>



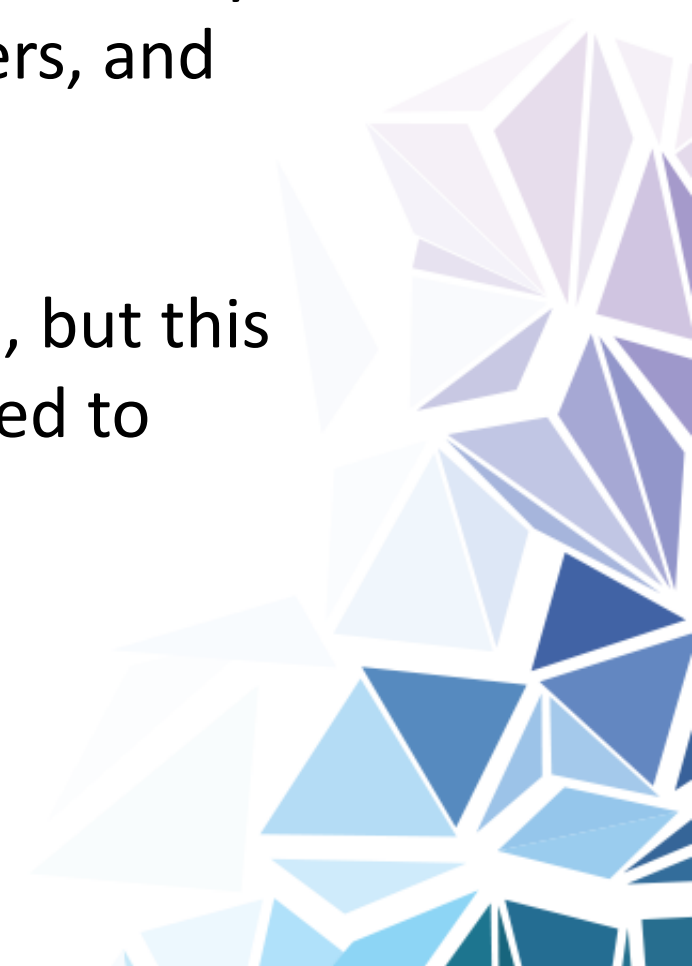
# Nortriptyline (Pamelor)

- Tricyclic antidepressant
- Equivalent efficacy to bupropion<sup>37</sup>
- Rarely used due to anticholinergic side effects and overdose risk



# Electronic nicotine delivery systems

- Less toxins than conventional cigarettes<sup>38</sup> but often contain by-products from metals, plastics, rubbers, ceramics, fibers, and foams<sup>39</sup>
- Some RCTs have shown efficacy for smoking cessation, but this is offset by adolescent non-smokers who are introduced to nicotine through these products.<sup>40</sup>



# Treating nicotine use disorder during pregnancy and lactation



- Adverse effects of smoking: low birth weight, prematurity, miscarriage, decreased milk production, increased sudden infant death syndrome
- Known risks of nicotine<sup>41</sup>
- Probable risks of bupropion
- Paucity of data on varenicline and nortriptyline
- Don't forget non-pharmacological interventions
- Up to 45% quit “spontaneously”<sup>42</sup>






# Cannabis misinformation

*Beware!* Young and Old—People in  
All Walks of Life!

This  may be handed you   
by the friendly stranger. It contains the Killer Drug  
“Marihuana”—a powerful narcotic in which lurks  
**Murder! Insanity! Death!**

**WARNING!**  
Dope peddlers are shrewd! They may  
put some of this drug in the  or  
in the  or in the tobacco cigarette.


WRITE FOR DETAILED INFORMATION, ENCLOSED 12 CENTS IN POSTAGE—MAILING COST

**Address: THE INTER-STATE NARCOTIC ASSOCIATION**  
*(Incorporated not for profit)*  
**53 W. Jackson Blvd. Chicago, Illinois, U. S. A.**

AMERICAN POLICE IN POINT TO THE FEDERAL BUREAU OF INVESTIGATION, U. S. DEPARTMENT OF JUSTICE, AS THE LEADING AUTHORITY IN THE FIELD OF NARCOTIC INVESTIGATION. THE FEDERAL BUREAU OF INVESTIGATION IS THE LEADING AUTHORITY IN THE FIELD OF NARCOTIC INVESTIGATION. THE FEDERAL BUREAU OF INVESTIGATION IS THE LEADING AUTHORITY IN THE FIELD OF NARCOTIC INVESTIGATION.

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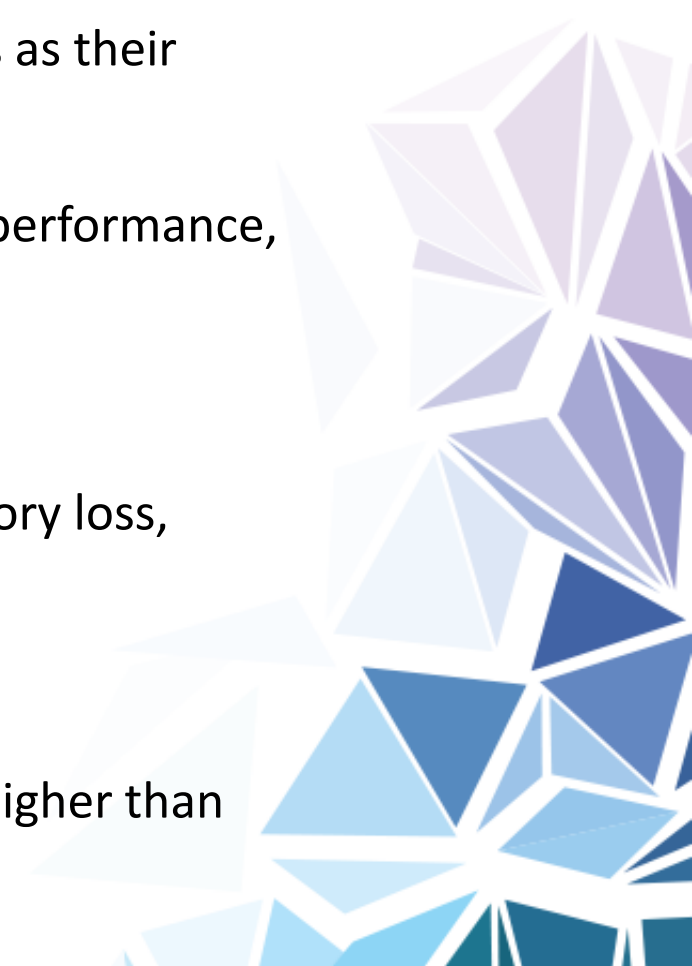
**34 Medical Studies  
Proving Cannabis  
Cures Cancer**



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# Is Cannabis addictive?

- People readily respond to ads for treatment, and the majority do not abuse other drugs<sup>43, 44</sup>
- ~25% of people admitted for any type of drug treatment reported cannabis as their primary drug
- Social impairment: loss of relationships, financial difficulty, impaired work performance, legal problems<sup>45</sup>
- Psychiatric distress: somatization, depression, anxiety, irritability, paranoia
- Adverse consequences: guilt, procrastination, loss of self-confidence, memory loss, withdrawal
- Inability to quit with multiple failed attempts
- Lifetime prevalence of cannabis dependence is estimated at 6%, ~3 times higher than any other illicit drug<sup>46</sup>



# Treatments for Cannabis use disorder

- Psychotherapeutic interventions, including CBT, DBT, motivational enhancement, and contingency management are effective in reducing cannabis use<sup>47</sup>
- Agonist therapy with dronabinol (synthetic THC)
  - 30-120 mg/day dose-dependently reduces withdrawal symptoms<sup>48,49</sup>
  - Does not reduce self-administration or relapse<sup>50,51</sup>
- Antidepressants have generally been unimpressive
- N-acetylcysteine 1200 mg twice daily ~doubled abstinence rates in adolescents in one RCT<sup>52</sup>

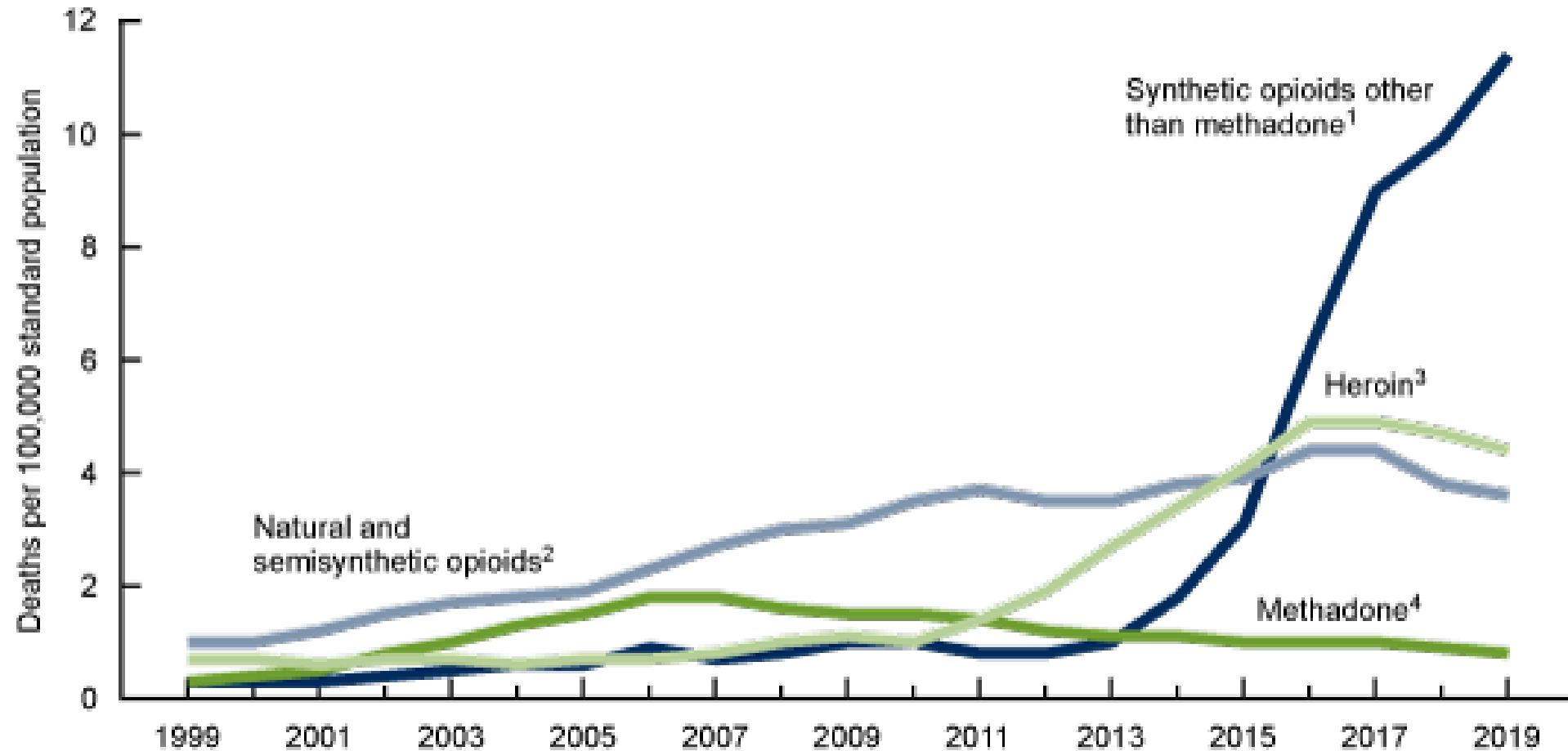


# Opioids

- Originally from the poppy plant
  - First cultivated in Mesopotamia
  - Initially used for euphoric mind-altering effects
  - Long history of medicinal use in the Old World
- Morphine isolated in 1806
- Heroin synthesized in 1898
- Several historical spikes of opioid dependence, e.g., the 1960s (Vietnam)
- Backlash in the 1980s among physicians; pain was undertreated



# Age-adjusted rates of drug overdose deaths involving opioids, by type of opioid: United States, 1999–2019<sup>53</sup>

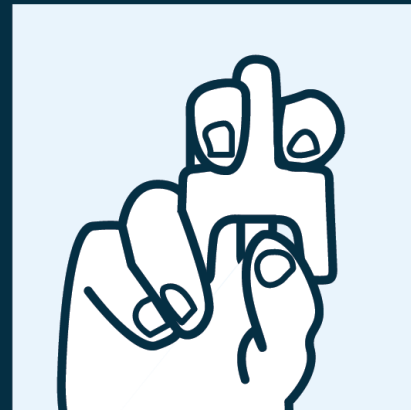


# Rescue medication: Naloxone (Narcan)

## How to Administer Narcan



Remove Narcan from box



Hold with your thumb,  
first and middle finger



Insert tip into  
either nostril

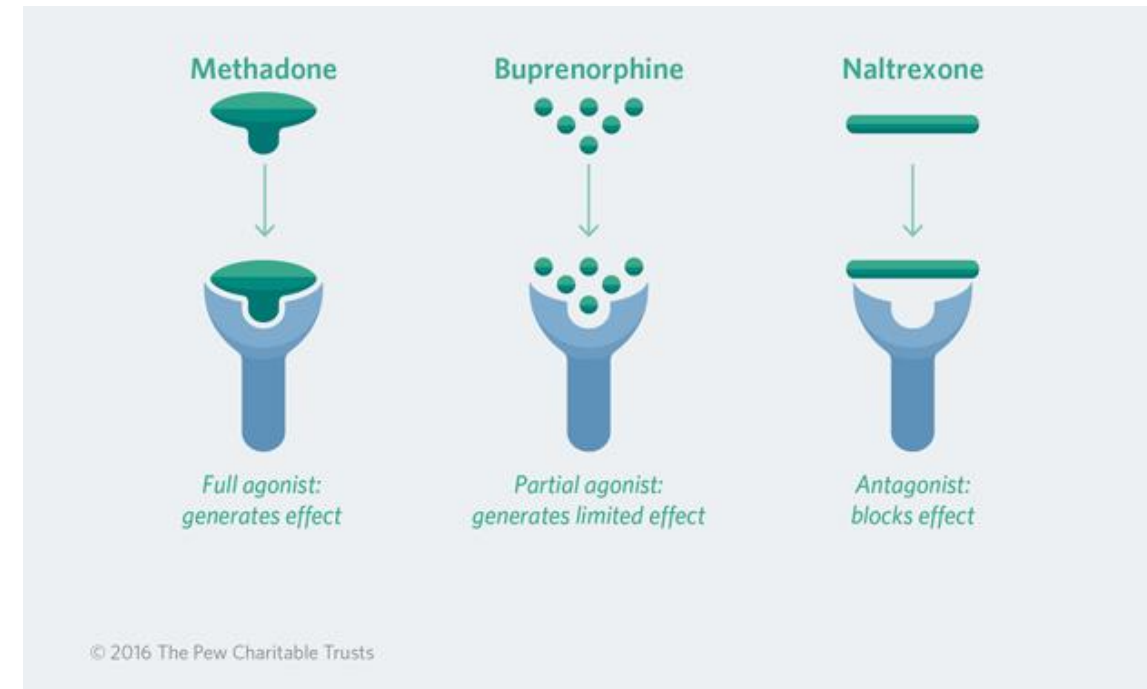


Press the plunger firmly

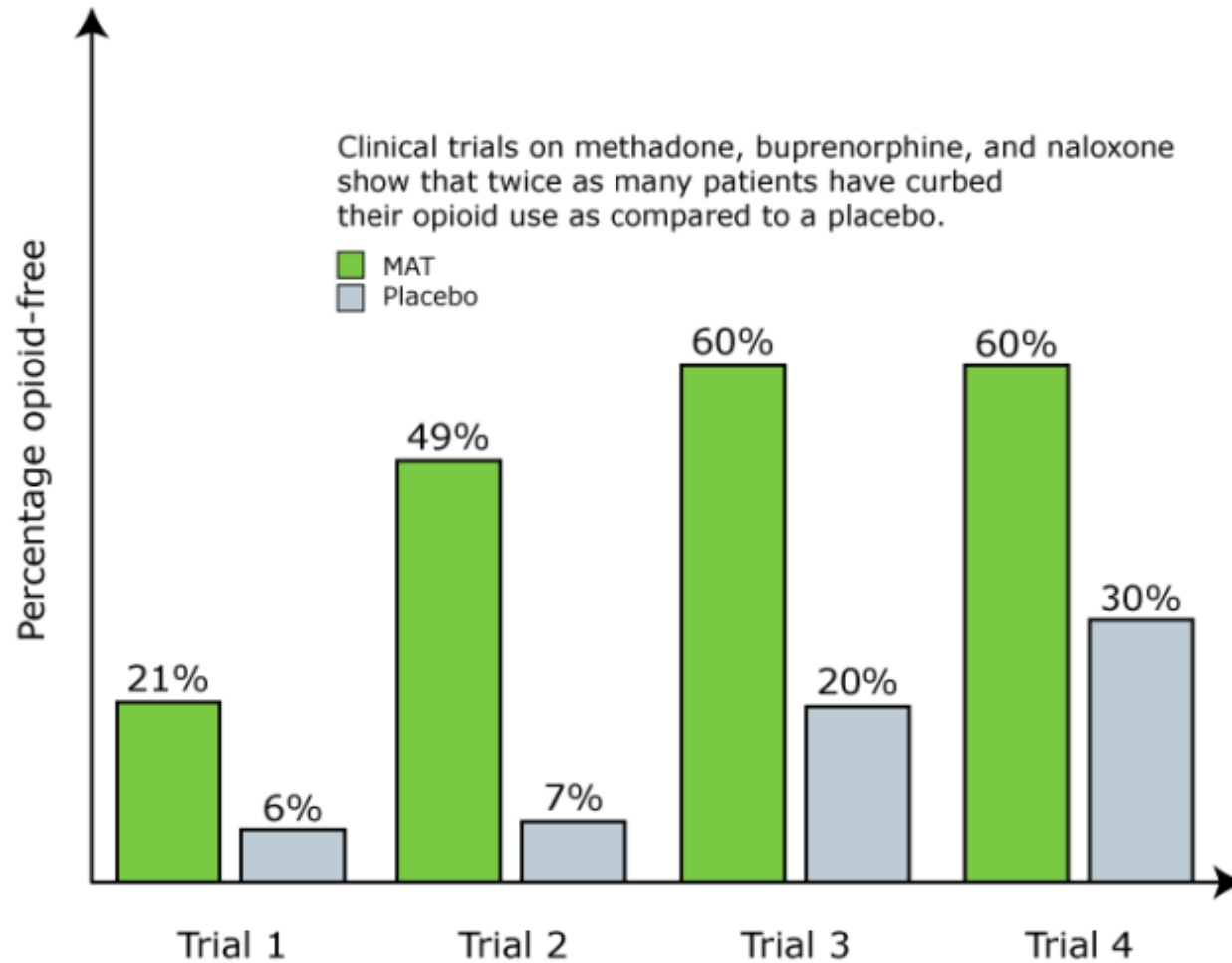
If you suspect an overdose is occurring, **call 911**. Administer rescue breathing and naloxone (Narcan).

# Medications for opioid use disorder (MOUD)

- **Methadone**- full  $\mu$ -opioid agonist
  - Long half-life, high binding affinity
  - Became more widely used in the 1970s
  - Addictive, deadly in overdose
  - Strictly regulated due to public backlash
- **Buprenorphine**- partial  $\mu$ -opioid agonist
  - High binding affinity
  - Usually combined with naloxone
  - Not lethal (unless combined with benzos)
  - Less severe restrictions
- **Naltrexone**- opioid antagonist
  - Not addictive
  - Effective for those who take it, but high drop out rate (< 10% retention at 6 months)



# MOUD works<sup>54</sup>





# Treatments for psychostimulant use disorder

- Contingency management
- Antipsychotics don't work
- Antidepressants don't work
- Agonist therapy (ADHD only)



# Challenges for addiction pharmacotherapy

- Poor compliance rates
- Large placebo effects
- Low rates of adoption among providers
  - Lack of training
  - Historical hostility toward medications in the treatment community<sup>55</sup>
  - Misconceptions about the tractability of addiction to treatment
- Lack of interest from pharmaceutical industry
  - Low insurance coverage
  - Low prescription rates



# Drug screens

- Consensual diagnostic test used to monitor treatment
- Testing schedules must be individualized (not one-size-fits-all)
- Beware of creating additional barriers to treatment
- Potential Benefits
  - Can improve communication
  - Provides objective data about patient's drug use
  - Provides an assessment of response to treatment
  - Advocate for patient or family in third party issues



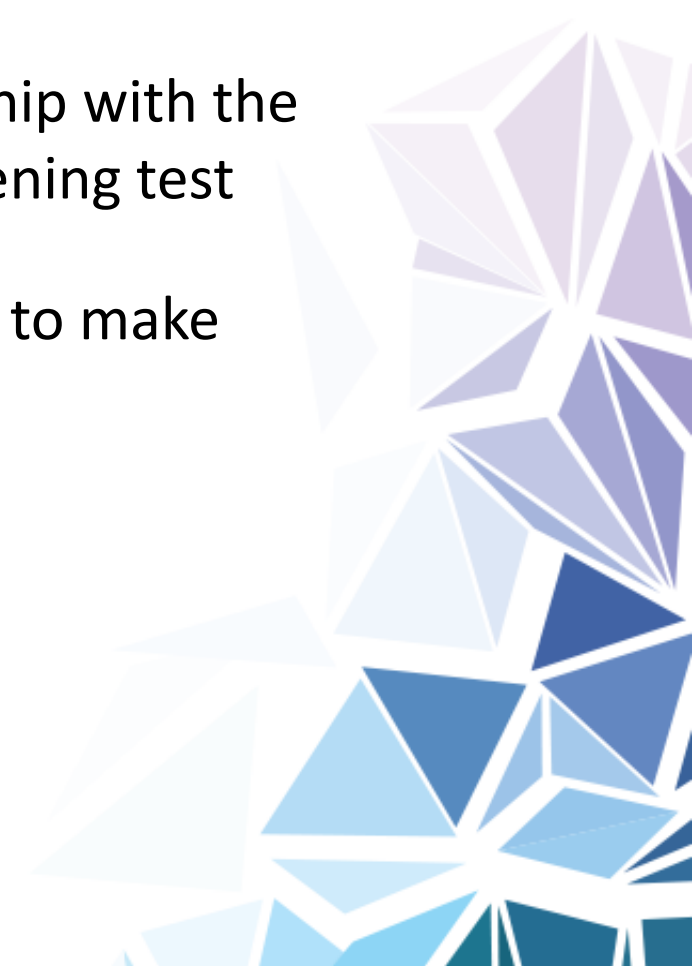
# Managing unexpected drug screen results

## Do

- Use results as a conversation starter
- Send confirmatory testing
- Get to know your test as cut off values vary by manufacturer

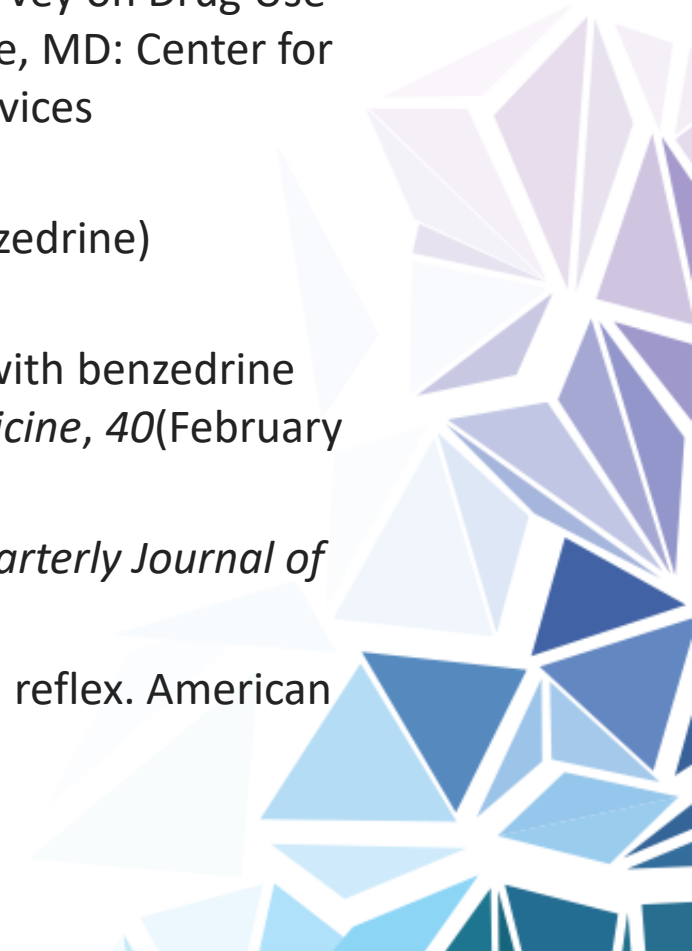
## Don't

- Ruin your relationship with the patient over a screening test
- Use screening tests to make clinical decisions



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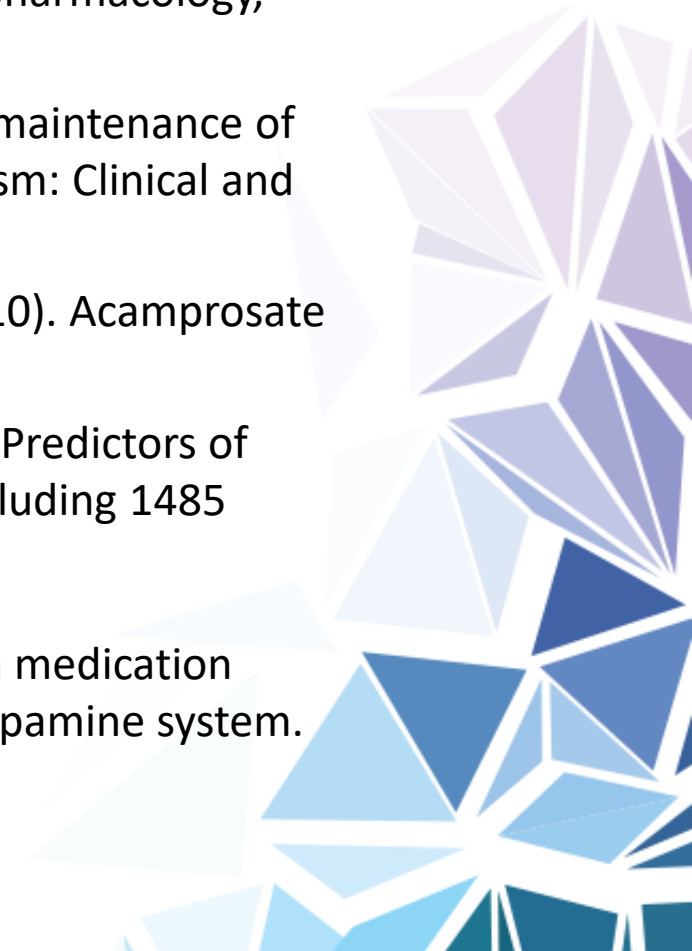


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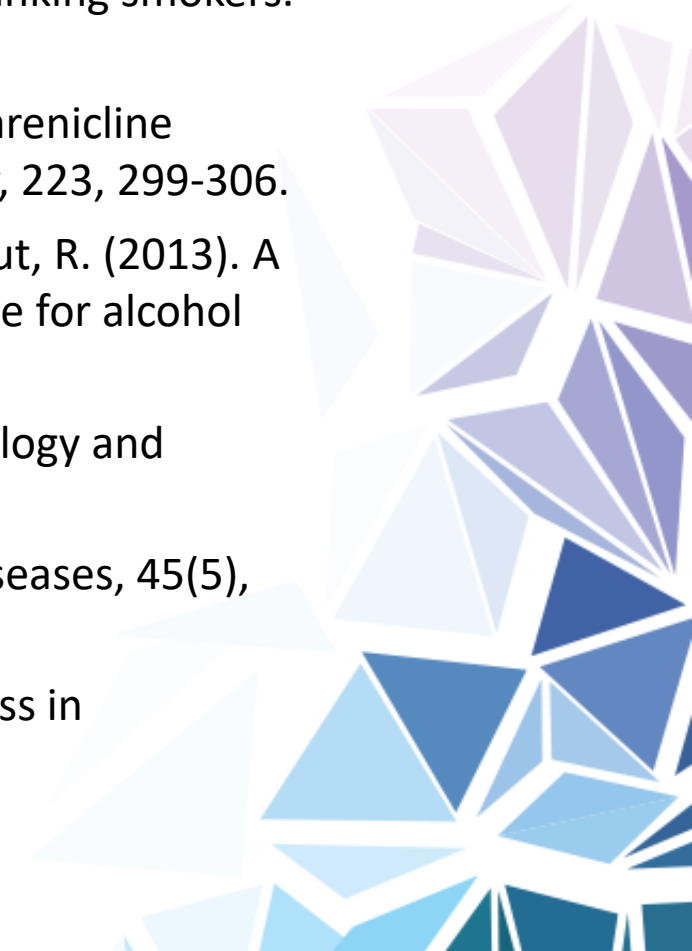
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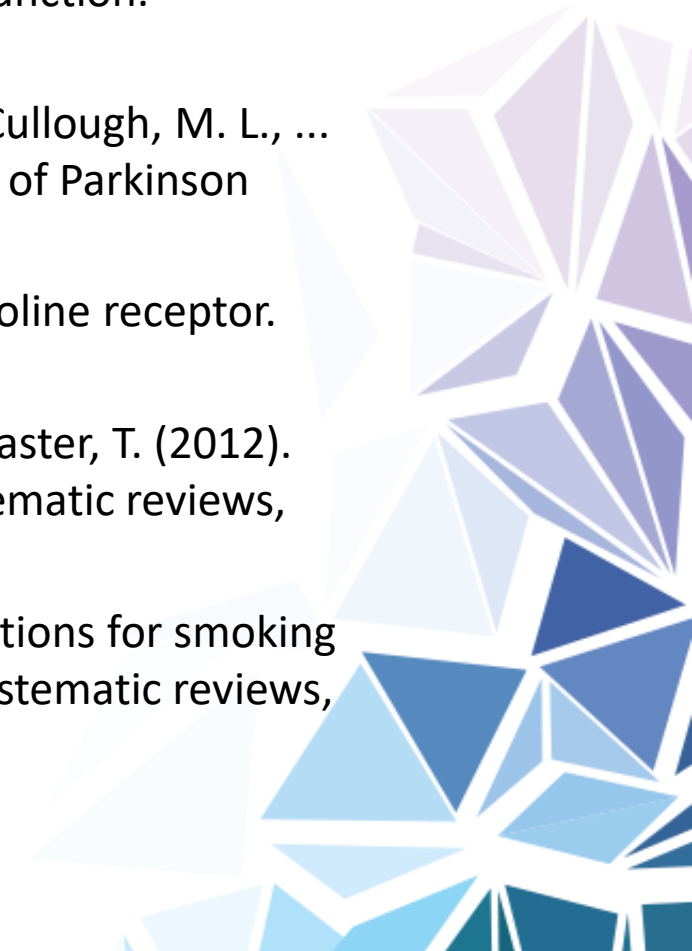
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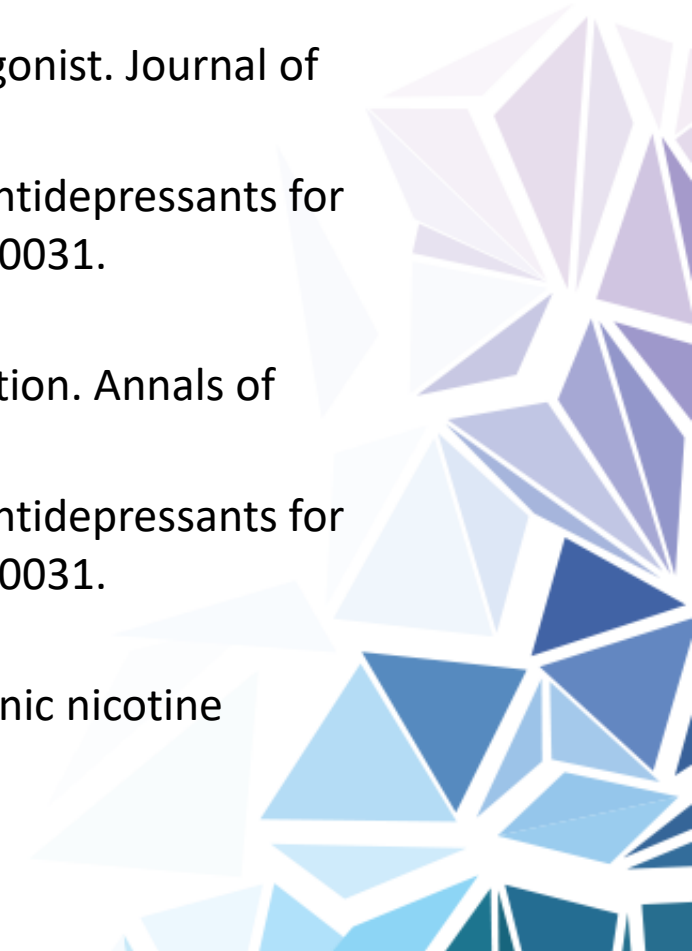


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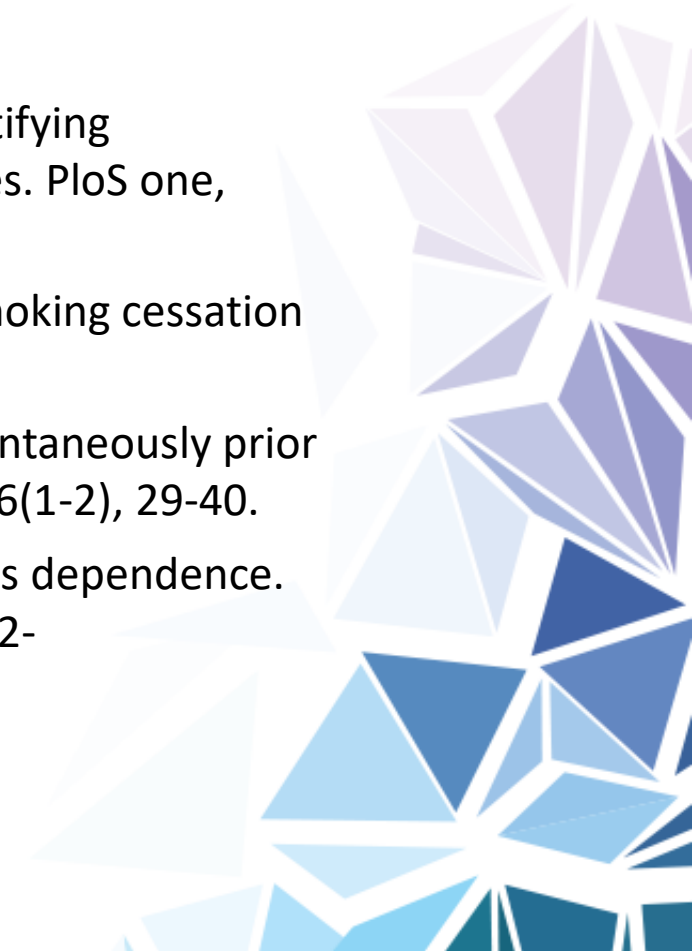
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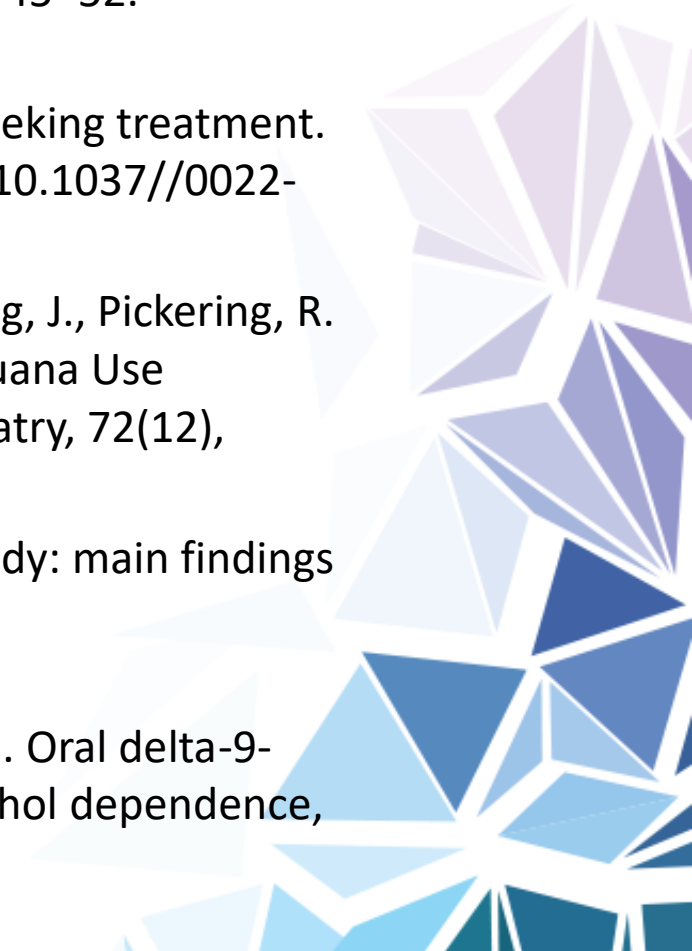
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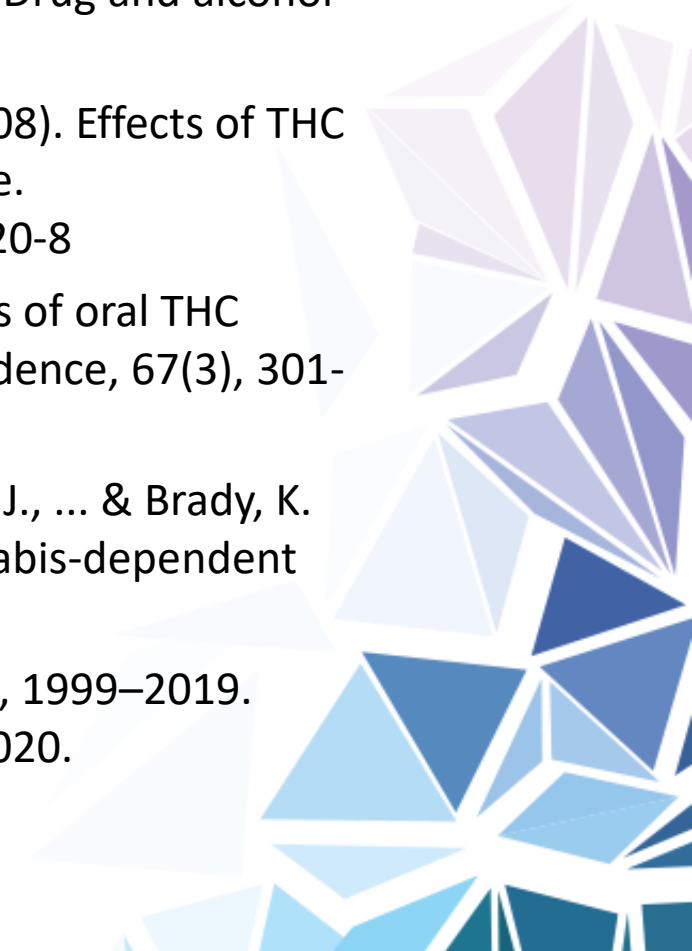
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# Additional support from PRISM

## Advanced training

- <https://micmt-cares.org/upcoming-trainings>
  - Implementing Collaborative Care with Perinatal Patients
  - Implementing Collaborative Care with Adolescent and Pediatric Patients
  - Treating Substance Use in Collaborative Care Settings

## Upcoming webinars

- <https://micmt-cares.org/events?type%5B4639%5D=4639>

## BHCM monthly discussion group

- 3rd Thursday of the month from 12:00pm–1:00pm ET

## Ongoing implementation support

- Discuss scheduling with your Implementation Specialist





# CEU and CME reminders

## CEU

- Allow up to 24 hours to receive the evaluation e-mail from MICMT
- Follow the link in the email to complete the evaluation within 5 business days

## CME

- Login to your account at MiCME at <https://micme.medicine.umich.edu/>
- Attendance must be registered by **July 8, 2024**



# Contact us

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