

Medications for Substance Use Disorders



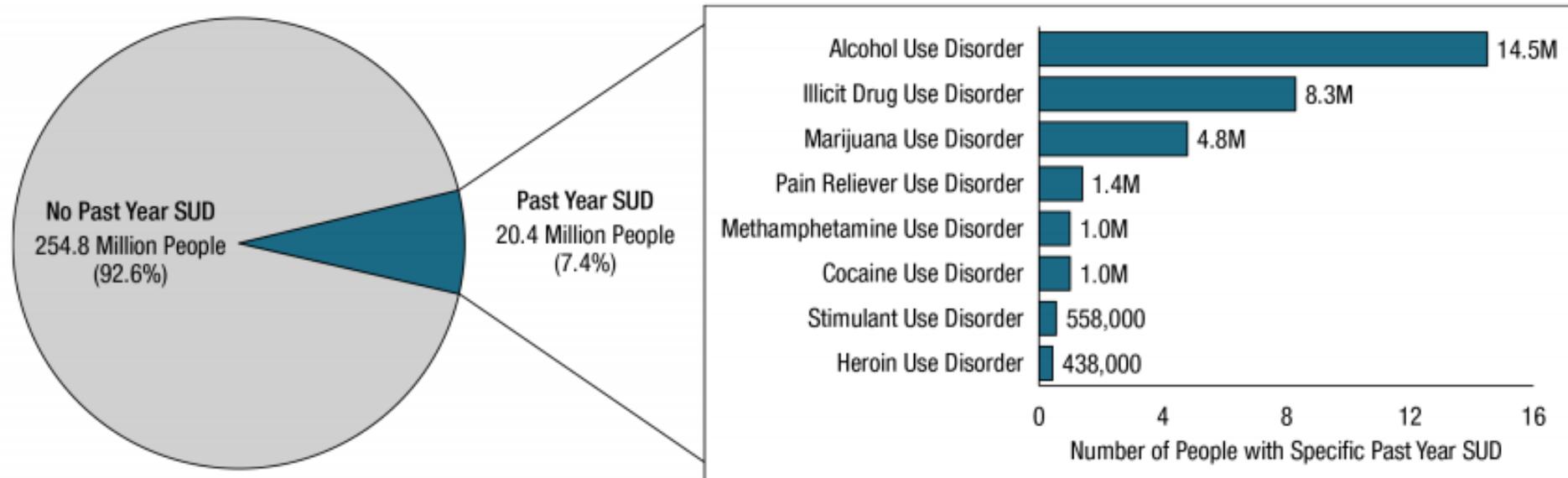
Changing What's Possible | [MUSChealth.org](https://www.musc.edu/health) >

Karen Hartwell MD Associate Professor

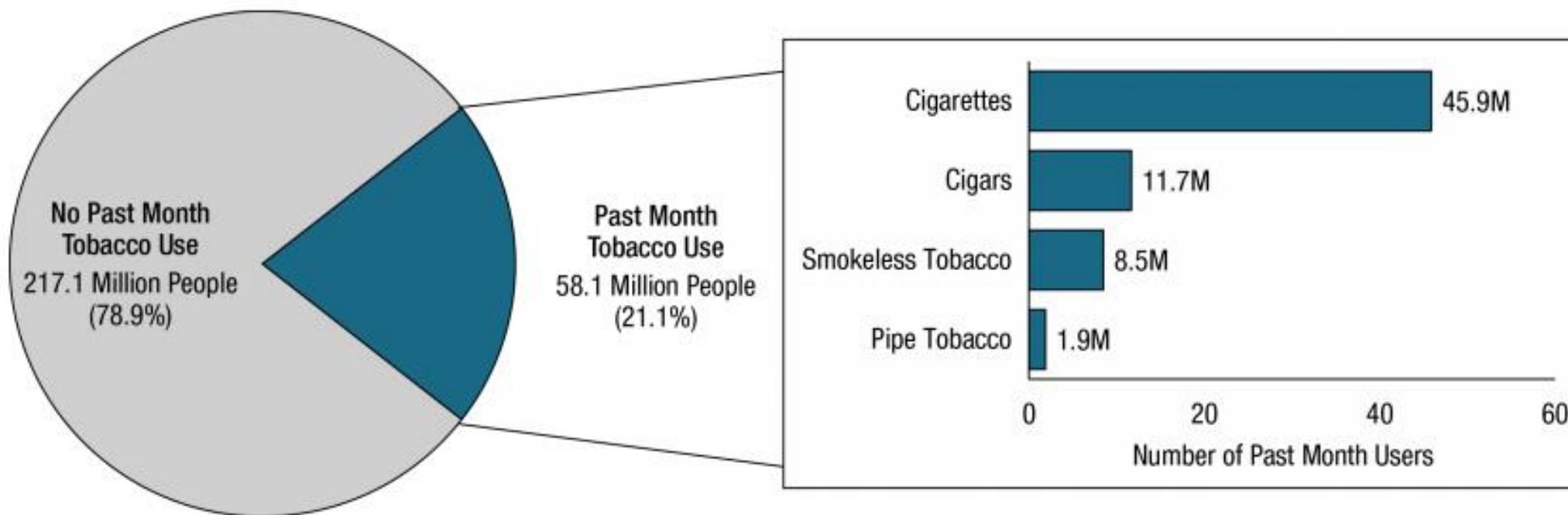
No conflicts of interest relevant to today's topic

Off label medications will be discussed and identified

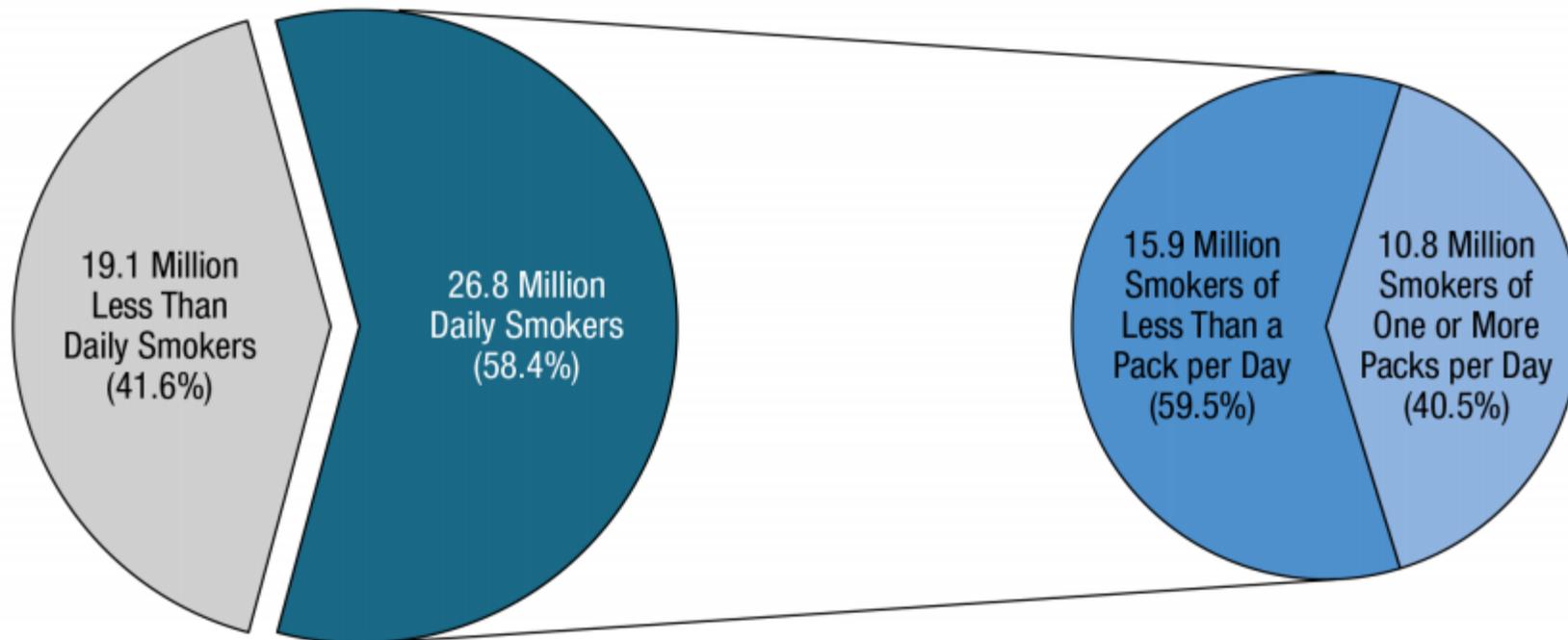
2019 Past Year Substance Use Disorder Aged 12 or older

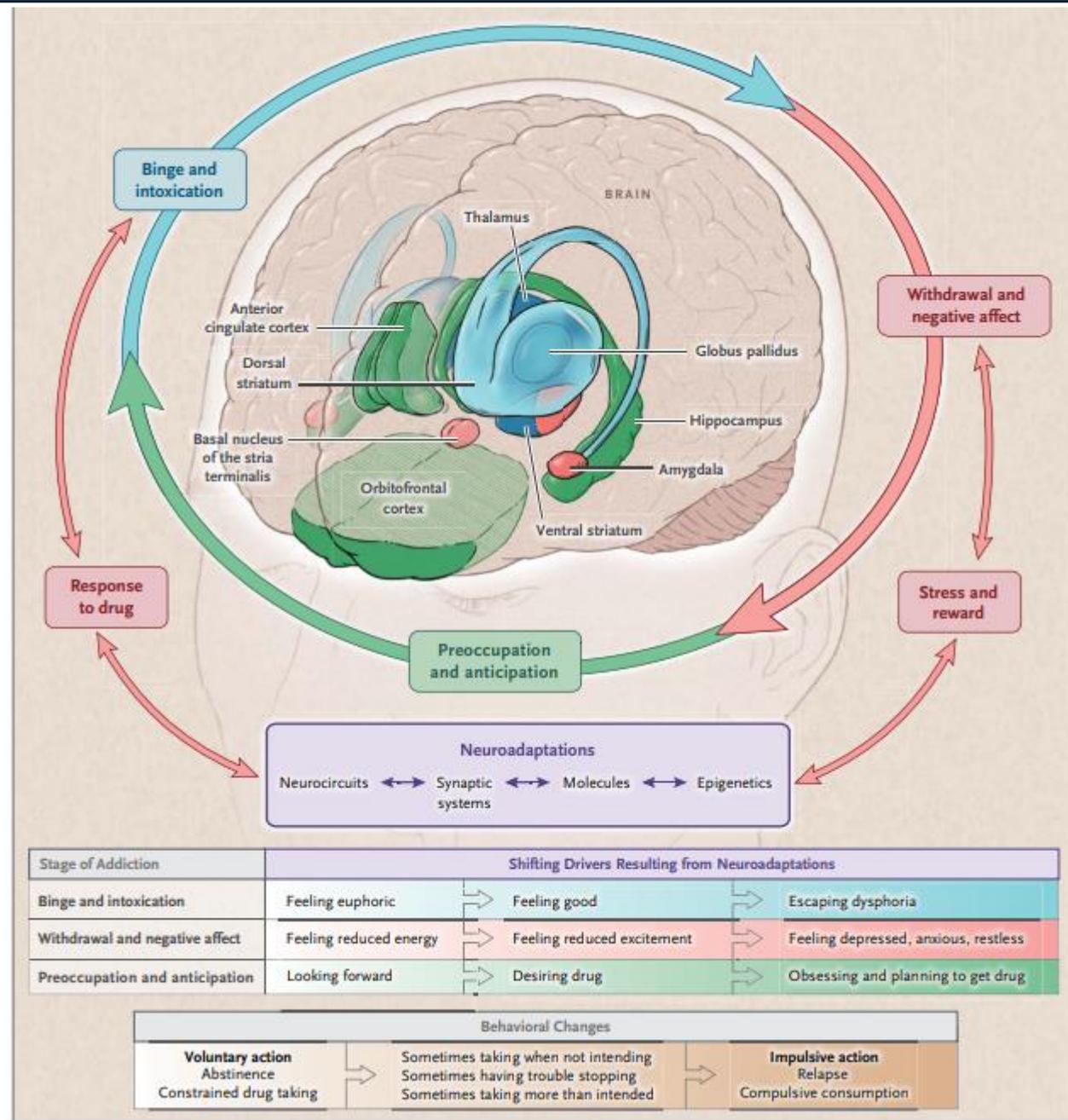


2019 Past Month Tobacco Use \geq 12 years of age



2019 Current Smokers \geq 12 yr.-old





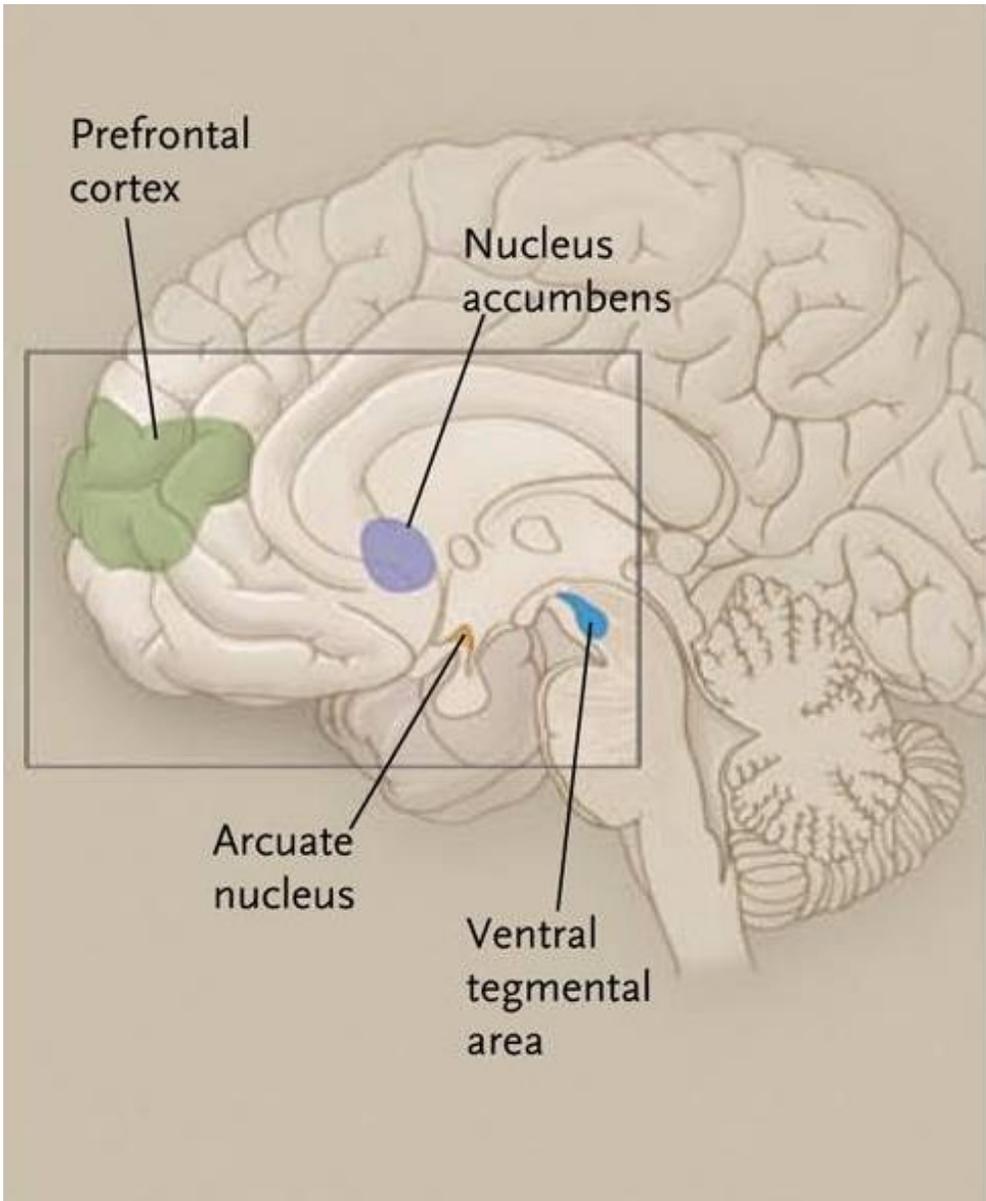
Volkow, Koop & McLellan.
NEJM. 2016; 374:363-71.

FDA-Approved Medications for Alcohol Use Disorders

1. Naltrexone: can help people reduce heavy drinking
2. Disulfiram: unpleasant effects if drink while taking
3. Acamprosate: makes it easier to maintain abstinence

Naltrexone

- Opioid antagonist
- Alcohol \uparrow release of dopamine in the nucleus accumbens, part of the brain reward pathway
- Naltrexone inhibits dopamine release in response to drinking and blocks reward from drinking
- Can reduce effects of environmental cues and craving
- Can reduce alcohol intake
- AEs: somnolence, nausea/vomiting, \downarrow appetite, abdominal pain, insomnia, dizziness, injection site reactions



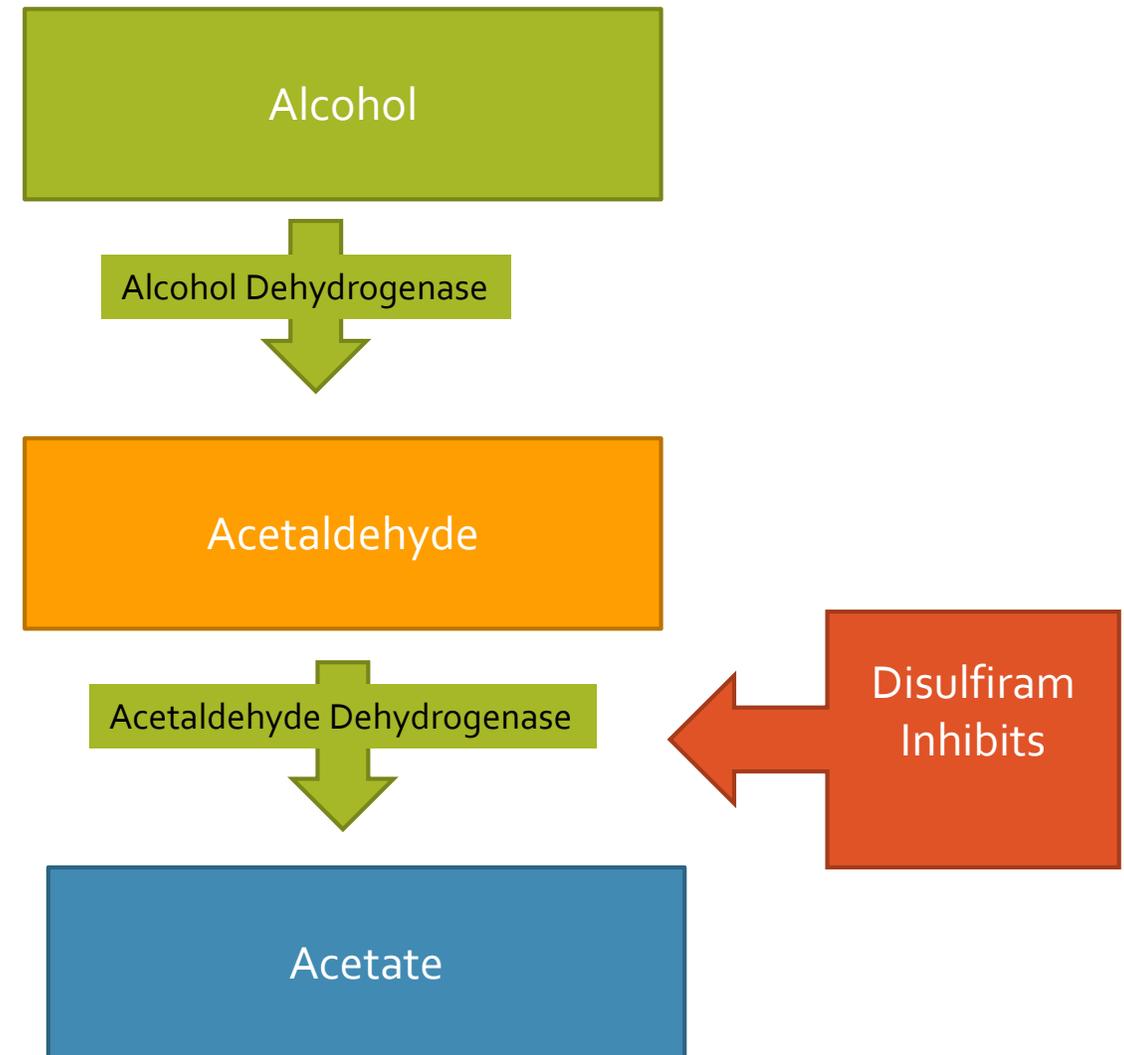
Naltrexone

- Available by once-a-day tablet (50mg tab) or monthly injection (380mg)
- Can start while still drinking
- Can cause elevation in liver functions
- Blocks action of opioids so useful for combo AUD and OUD
- Meta-analyses and a Cochrane review have shown
 - Oral naltrexone superior to placebo
 - Preventing relapse to heavy drinking after an initial period of abstinence
 - Increasing the percentage of abstinent days
 - Injectable extended-release naltrexone
 - Reduced heavy drinking days by 25% with men > women
 - Greater effect with at least 4 days of abstinence before starting
 - <https://www.vivitrol.com/content/pdfs/emergency-pain-management-card.pdf>

Anton RF. *NEJM*. 2008; 359:715-721.

Disulfiram

- 1st approved in 1949 to treat AUD
- Inhibits aldehyde dehydrogenase which breaks down the toxic acetaldehyde metabolite
- If drink, ↑ acetaldehyde → disulfiram-alcohol reaction
 - Nausea/vomiting, flushing, sweating, rapid heartbeat, ↓ BP and rarely serious rxn (CV collapse)
- Avoid hidden alcohol: e.g., cough syrup, sauces
- Once enzyme blocked must wait about 2 weeks for liver to make new enzyme



Disulfiram

Use for abstinent individuals who want to maintain abstinence

Dosage: 250-500mg/day by mouth

Requires informed consent

Baseline and follow-up LFTs
Drowsiness in ~ 8%

Compliance is poor without observed administration

Disulfiram associated with better response than control condition when disulfiram was supervised but not when it was unsupervised

Acamprosate

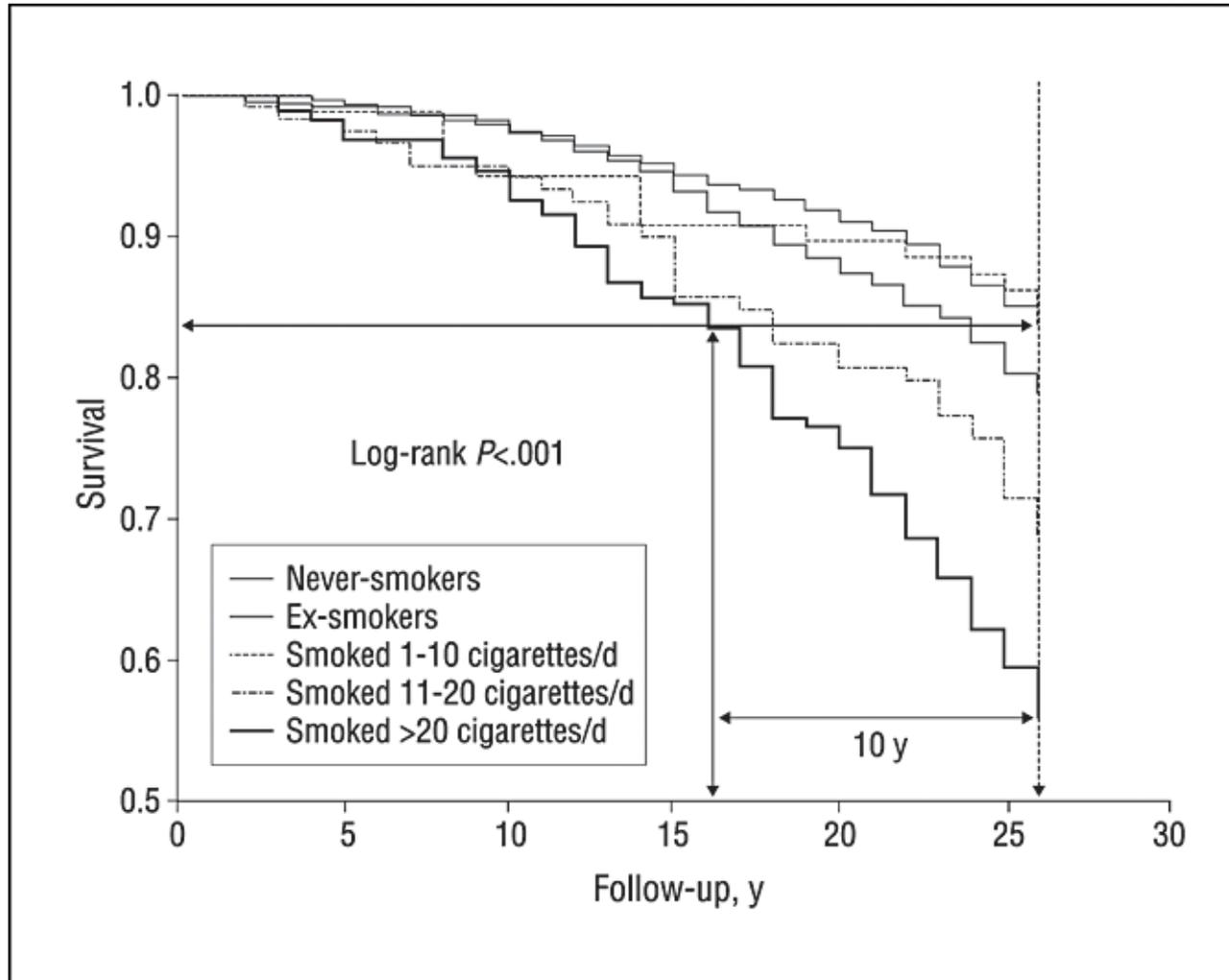
- Thought to regulate balance of excitatory and inhibitory systems in the brain
- **Maintenance of abstinence in patients with AUD who are already abstinent**
- 666mg three times a day so adherence is an issue
- Primarily excreted by the kidneys so can use in people with liver disease
- Meta-analysis of 16 studies, acamprosate associated with ↓risk of drinking among abstinent patients but not ↓ in the likelihood of binge drinking
- Only side effect more common than placebo was diarrhea (~25%)

Kranzler & Soyka. *JAMA*. 2018; 320:815-824

Non-FDA approved medications used in research and occasionally off-label

- Nalmefene –opioid antagonist used in Europe. Not approved in US
- Topiramate- currently used for seizures, migraine prophylaxis, weight loss in combo with phentermine. Transient mental dulling and word finding difficulty among side effects. Requires gradual dose titration.
 - Meta-analysis of 7 RCTs small to medium effect on abstinent days & binge drinking days
- Baclofen – used to treat spasticity from neurological disorders
 - Meta-analysis of 13 trials greater time to first lapse and likelihood of abstinence during treatment
- Gabapentin – Results mixed. potential bias due to high drop out rate.

The unadjusted association of smoking status and the number of cigarettes smoked daily at baseline in 1974 and mortality during the 26-year follow-up period



**Shortened
Life Span**

Strandberg, A. Y. et al. Arch Intern Med
2008;168:1968-1974.

Unaided Quit Attempts

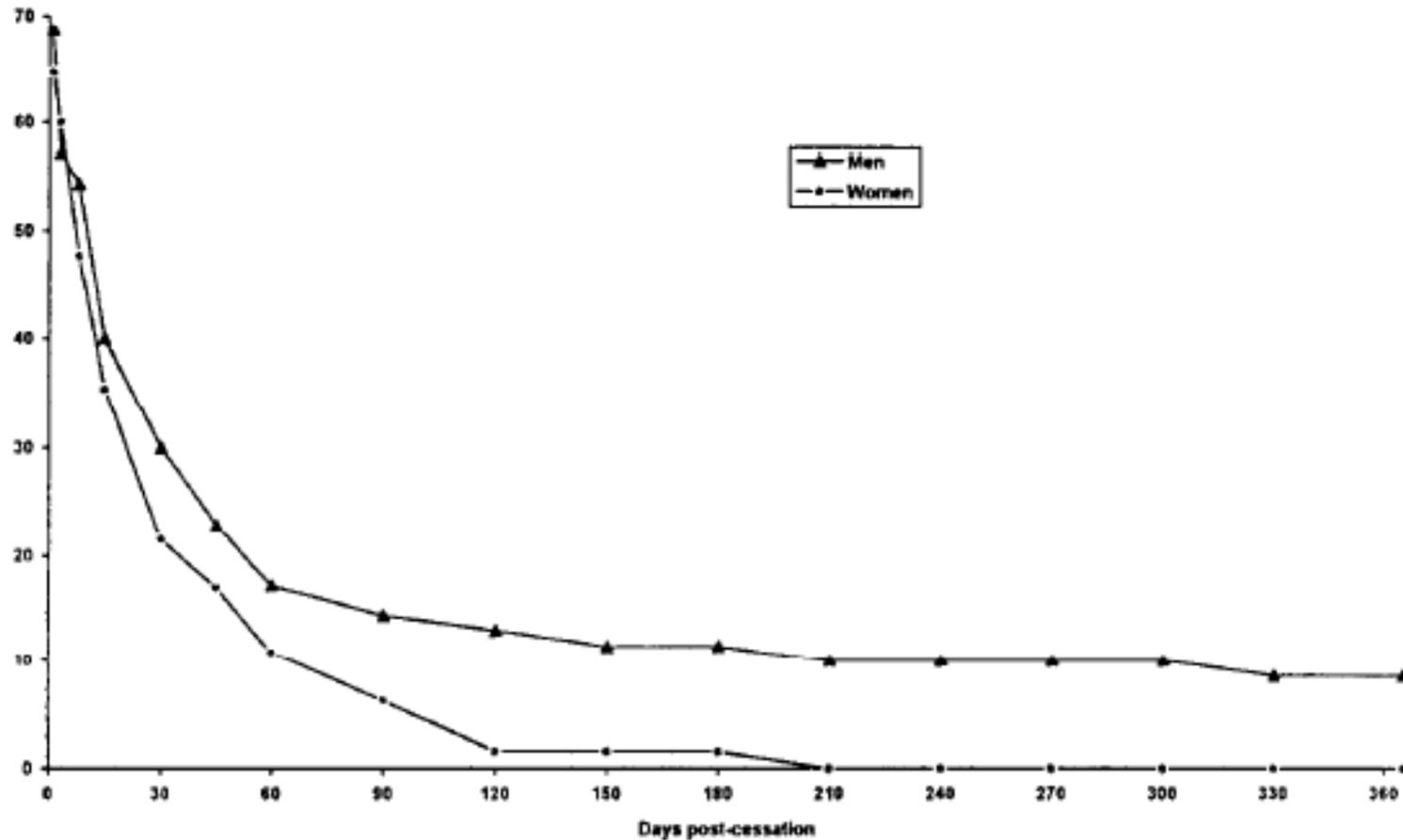


Fig. 1. Incidence rates of relapse for men and women across 1 year of follow-up ($n=135$).

FDA Approved Medications for Smoking Cessation

1. Nicotine Replacement

- Gum (OTC)
- Lozenge (OTC)
- Patch (OTC)
- Inhaler
- Nasal Spray



2. Bupropion

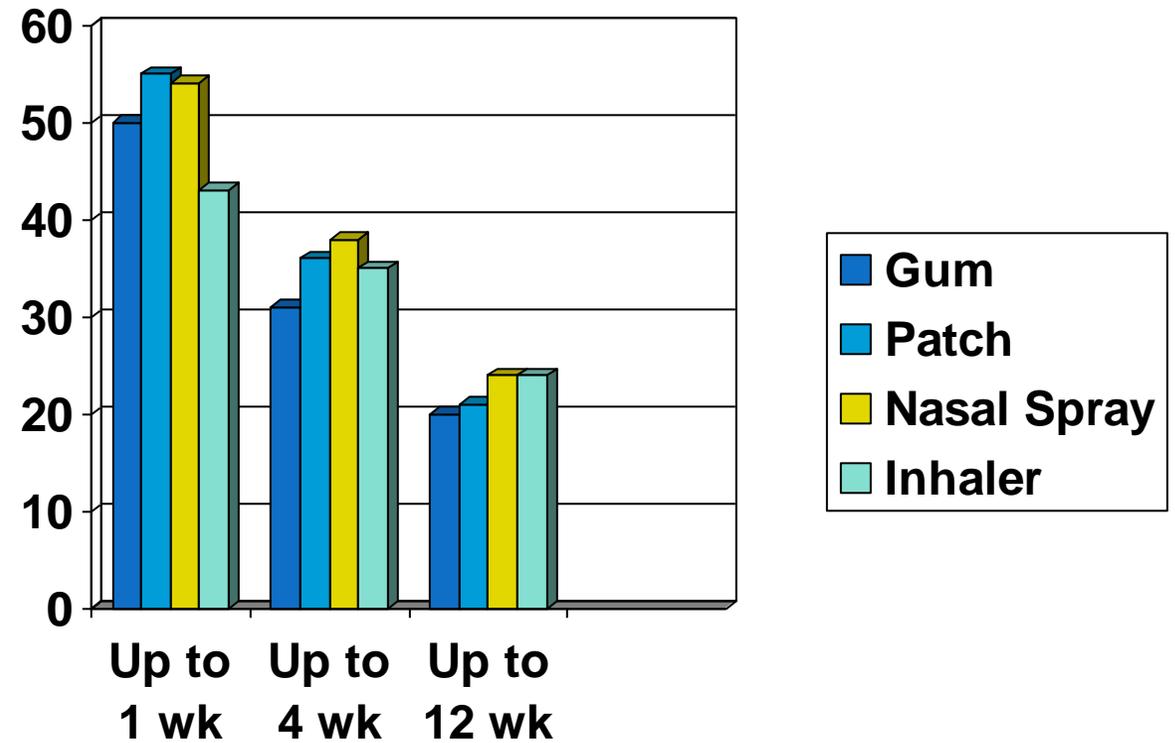
3. Varenicline



NRT

- NRT acts by partially replacing nicotine
- Decreased withdrawal symptoms and alleviates craving
- All forms ↑increase quit rates by 1.5 - 2.5-fold compared to placebo
- Compliance: patch highest, low for gum, & very low for inhaler & spray Silagy 2004. Cochrane DR

Percent Abstinent by NRT Type (n=504)



NRT Adverse Effects

- Common Adverse effects: headache, dizziness, sleep disturbances, vivid dreams, nausea, vomiting, indigestion, local irritation at administration site.
- Rare: Irregular heart rhythms, rapid heartbeat, palpitations, chest pain, BP changes.
 - Increased blood insulin levels & insulin resistance
 - Dizziness, lightheadedness, insomnia, & irritability 1-25%

Cardiovascular Disease

- NRT not independent risk factor
- Use with caution 1st 2 wks after a heart attack, heart rhythm irregularities, & chest pain

Bupropion SR (Zyban, Wellbutrin SR)

- Action:
 - weak inhibitor of norepinephrine reuptake
 - Weak inhibitor of dopamine reuptake
- Doubles odds of quitting
- Nearly 20 RCT relatively less withdrawal symptoms and craving compared to placebo
- Weight gain less during active treatment.
Tends to disappear in long term follow-up

Bupropion SR

- Precaution: Risk of seizures, mania/mixed state in bipolar disorder
- Early trials excluded pts with personal or family hx seizures, active alcohol or other substance abuse, head trauma lead to absence of seizures
- Seizure risk: on 300 mg/d incidence of 0.1%
 - In depression studies predisposing factors were alcohol with possible alcohol abuse, history of head trauma Dunner 1998. JCP

Adverse Effects

- 300mg/d 8-12% discontinuation rates due to side effects
 - Most common tremor, rash, h/a, hives
 - Insomnia & dry mouth more likely than placebo

Varenicline (Chantix)

- Appropriate first line treatment
- Action: nicotine ($\alpha_4\beta_2$ nAChR) partial agonist
 - Mimics nicotine → moderate & sustained dopamine release
 - Blocks subsequent nicotine dopamine release
- Triples odds of quitting compared to placebo
- Excreted in urine (92% unchanged), $t_{1/2}=24h$
- Precautions
 - Significant renal disease or on dialysis. Reduce dose
 - May experience impaired driving ability or operate heavy equipment
- Side effects: nausea (30-40%), insomnia (20%), vivid/abnormal dreams(9-13%), headaches (15-19%)

Varenicline

- FDA warning February 2008: Depressed mood, agitation, behavioral changes, suicidal ideation, & suicide reported during smoking cessation attempts with varenicline.. Clinicians monitor for changes in mood and behavior.
- FDA warning lifted in 2017 w additional data analysis of 17 placebo RCT (n=8027) DOD data
 - In RCTs, varenicline ↑ risk of nausea (OR=3.69) but not rates of depression, suicidal events, or aggression/agitation. Current or past psych disorder ↑ risk neuropsych AEs equally in both groups. Gibbons & Mann. *AJP*. 2013; 170:1460-7.
- EAGLES Trial: Large multisite trial (placebo controlled & blinded) compared nicotine patch, varenicline & bupropion for 12 weeks in 16 countries (n=8144 w).
 - Did not show significant increase in neuropsych AEs from varenicline or bupropion compared to nicotine patch or placebo
 - Varenicline more effective than bupropion, nicotine patch or placebo. Patch and bupropion more effective than placebo. Anthenelli et al. *Lancet*. 2016;387:2507-20.

Methamphetamine Clinical Trials

No FDA-Approved Medications

Bupropion XL 450mg and naltrexone-XR IM.

- Weighted average response ~14% vs. placebo 2.5%. Overall tx effect ~11%

Trivedi et al. *NEJM*. 2021; 384:140-153

Stimulants (dextroamphetamine, methylphenidate)

- Mixed/positive signal with most studies underpowered and low treatment completion rates

Siefried et al. *CNS Drugs*. 2020; 337-365

- Topiramate: some promise. Mixed results. Rezaei found ↓ in meth use, craving, severity

Rezaei et al. *Fundam Clin Pharm*. 2016; 30:282-289.

Watch June 18th Project Echo OUD Didactic

Cocaine Clinical Trials

No FDA-Approved Medications

- Antidepressants most widely studied (38 RCTs)
 - No effect on cocaine use or treatment retention
- Bupropion (2 RCTs), Topiramate (2 RCTs), psychostimulants (14 RCTs)
 - Increased abstinence
 - Strength of evidence low
- Antipsychotics (8 RCTs) improved treatment retention

Chan et al. *J Gen Intern Med.* 2019; 34:2858-2873

Cannabis Clinical Trials

No FDA-Approved Medications

- Review 21 RCTs (n=1755), predominantly male (75%)
- Abstinence at end of treatment no more likely
 - THC preparations (e.g. dronabinol): some evidence for decreased withdrawal
 - SSRIs
 - Mixed action antidepressants
 - Anticonvulsants
 - Buspirone
 - N-acetylcysteine

Nielson et al. *Cochrane Database Syst Rev.* 2019; 1:CD008940

Agents with promise currently under investigation: varenicline, extended-release naltrexone, quetiapine, dronabinol & Lofexidine and many others

Questions?



Kindly complete the brief post session survey! Your feedback is invaluable!

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**2nd & 4th Tuesday/Month
noon – 1:00 pm**

Unique Challenges of Peers

Date	Topic	Presenter
7.13.21	Working with Families	Rich Jones

1.0 CEU is awarded for this activity approved and accepted by NAADAC



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