

Medication-Assisted Treatment of Substance Use Disorders

RADACT
2024 Fall Academy
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Acknowledgements

- Bakti, S. (date?). Addiction pharmacotherapy, UCSF School of Medicine.
- NYS Office of Alcoholism and Substance Abuse Services (date?), Addiction Medications.
- Peterson, K. (2014-15). Biomarkers for alcohol use and abuse: A summary, *Alcohol Research & Health*, 28(1), 30-37.
- SAMHSA. (2015). *Medication for the treatment of alcohol use disorder: A brief guide*.
- Saxon, A. (date?), Pharmacotherapy for alcohol use disorders, UW School of Medicine.
- RADACT Trainees, Nov. 1, 2023

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Assessment – Candidacy for Medication-Assisted Therapy (MAT)

- Readiness to change (Importance and Confidence)
- Relapse potential
- Severity of comorbid medical & psychiatric problems
- Ability to tolerate medications
- Medication adherence issues
- Pregnancy or pregnancy risk in childbearing women

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Assessment – Candidacy for MAT (Cont'd)

- Medical and Psychiatric History
- Substance use history
- Evaluation of family and psychosocial supports
- Prescription drug use history
 - Alaska Prescription Drug Monitoring Program
 - NABP PMP InterConnect (interstate)

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Assessment – Candidacy for MAT (Cont'd)

- **Physical Exam**
 - Include neurocognitive function
 - Identify sequelae of alcohol use
 - Evidence of hepatic dysfunction
- **Examples:** cirrhosis, encephalopathy, B-complex vitamin deficiencies, tachycardia, hand or tongue tremor, HTN, hepatosplenomegaly, peripheral neuropathy, spider angiomas, conjunctival injection, unexplained trauma

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Assessment – Candidacy for MAT (Cont'd)

Laboratory Testing (for alcohol patients)

- BAL
- Carbohydrate Deficient Transferrin (CDT)
- Gamma-glutamyl transpeptidase (GGT) (5-40 U/L ref)
- Aspartate aminotransferase (AST) or SGOT (5-40 U/L ref)
- Alanine aminotransferase (ALT) or SGPT (7-56 U/L ref)
- AST/ALT ratio (2:1 or > suggests alcoholic liver disease)
- Ethyl glucuronide (ETG) (Detects ETOH at low levels (+/-); cutoff 500 ng/mL)

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Ethyl Glucuronide (EtG) & Ethyl Sulfate (EtS)

- Detect ETOH at low levels (+/-)
- EtG or EtS alone does not confirm drinking or abstinence
 - Sensitive to incidental exposure to alcohol (-> false positive)
 - Advise client to avoid ETOH-containing products - including “non-alcoholic” beer and wine & kombucha
 - Urinary tract infection degrades EtG (false-negative) but doesn't affect EtS

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Assessment – Candidacy for MAT (Cont'd)

Laboratory Testing (for alcohol patients) – Continued

- LFT – other enzymes or factors (PT-PTT; Prothrombin Time and Partial Thromboplastin Time)
- CBC and MCV (Mean Corpuscular Volume)
- Test for vitamin deficiencies (thiamine, folic acid, pyridoxine) **RATHER**, usually give vitamin supplements assuming vitamin deficiency
- Other liver and renal testing (most medications are metabolized by liver and/or excreted through kidneys)

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Assessment – Candidacy for MAT (Cont'd)

Laboratory Testing (for all patients)

- Drug urine toxicology screen
 - Thin layer chromatography
 - Enzyme immunoassay
 - Gas chromatography - mass spectrometry
- Issues
 - Sensitivity (avoid false negative) and specificity (avoid false positive)
 - Cutoff scores
 - Pharmacokinetics

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Assessment – Candidacy for MAT (Cont'd)

Other factors to consider

- Client's attitude about medication-assisted tx
- Client's family's attitude about medication-assisted tx

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Treatment Planning for MAT

COMPONENTS

- Medication and other therapies with rationale
- Schedules for F-U visits and lab testing
- Reasons for participation in mutual self-help groups
- Family/significant-other involvement in tx
- Plan for tx of co-occurring medical, psychiatric and other SUDs – including smoking
- Criteria for D/C'ing medications and other txs

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Patient Education and Informed Consent

- Info re. SUD as a chronic medical disorder
- What to expect from tx
- Info re. medication; why selected; potential risks/benefits; side effects, even info re. pharmacology
- Importance of informing physicians and dentists
- Sxs that should be reported
- Plan for ensuring medication adherence
- Importance of concurrent psychosocial tx
- Plan for F-U

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Pharmacotherapy

- Efficacious but less available
 - Philosophy
 - Payment
 - Prescribers
 - Over-the-counter
- **COMBINATION** of psychosocial and pharmacological tx crucial for adherence and success

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Pharmacotherapy

- Agonists
 - Activate receptor site
 - Enhance activity of neurotransmitter system
 - E.g., Methadone
- Antagonists
 - Block or reverse effects of drug
 - Inhibit activity of neurotransmitter system
 - E.g., Naloxone
- Partial Agonists
 - E.g., Buprenorphine

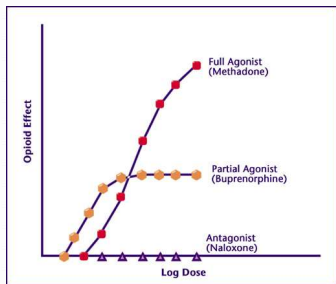
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Medication-Assisted Treatment of Opioid Dependence



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Medications for Treating Opiate Addiction



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Medication for Opiate Addiction Tx – Methadone

- Agonist
 - Activates receptors
 - Produces drug effect, has potential for abuse
 - Slow onset, long half-life
 - Reduces opiate use, crime, infectious disease
- Detoxification
- Maintenance

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Medication for Opiate Addiction Tx – Naltrexone

- Opioid receptor antagonist
- Blocks receptors for 48-72 hours
- No euphoria
- Treating overdose
- Maintaining abstinence
- Poor adherence except in select populations & combined with sanctions &/or behavioral treatment
- Address with Vivitrol® (depot version of naltrexone)

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Medication for Treating Opiate Overdose – Naloxone (Narcan®)

- Opioid antagonist
- High receptor affinity
 - Opioid effects immediately reversed
- Rapid pharmacokinetics
 - Requires repeated administrations until opioids completely metabolized

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Medication for Treating Opiate Overdose – Nalmefene (OPVEE®)

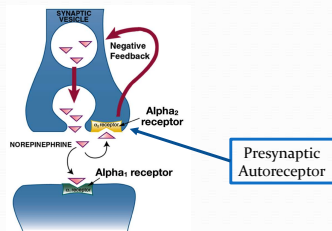
- Opioid inverse agonist (reduces receptor activity BELOW basal level)
- High receptor affinity
 - Opioid effects immediately reversed
- Longer pharmacokinetics
 - Lasts longer than naltrexone or naloxone

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Xylazine (Tranq) – new additive to street fentanyl

- Potent Alpha₂ Receptor agonist



<https://servingnature.blogspot.com/2013/03/ans-receptors.html?m=1>

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Naloxone vs. Fentanyl with Xylazine

- Fentanyl – synthetic opioid
 - As a potent MOR antagonist, Naloxone effective
- Xylazine - Alpha2 receptor agonist – NOT an opioid
 - Thus, Naloxone will NOT reverse Xylazine effects
 - Tx is supportive: Atropine, low-dose epinephrine, oxygen/intubation, fluid, and/or norepinephrine
- Yet, STILL give naloxone to reverse opioid respiratory suppression (NIDA)

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Medication for Opiate Addiction Tx – Buprenorphine

- Mixed agonist-antagonist (partial agonist)
- Approved for general practice settings
- Reduces opiate craving 24-36 hours
- No withdrawal symptoms on discontinuation
 - Contested by some
- Low risk of overdose when combined with other opiates

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Buprenorphine

- Subutex® contains only buprenorphine hydrochloride
- Suboxone® contains naltrexone to prevent misuse
- Subutex® given during first few days of treatment, while Suboxone® is used for maintenance treatment
- First narcotic drugs available under Drug Abuse Treatment Act (DATA) of 2000 for treatment of opiate dependence prescribed in physician's office

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Buprenorphine – Role in Tx

- Medication-Assisted Withdrawal
 - Goal – total abstinence from all opioids, therapeutic or otherwise
 - Abstinence Model
- Medication-Assisted Maintenance
 - Goal – total abstinence from all illegal and nonprescribed opioids
 - Harm-Reduction Model
 - Superior to Medication-Assisted Withdrawal (see handout Fiellin et al., 2014)

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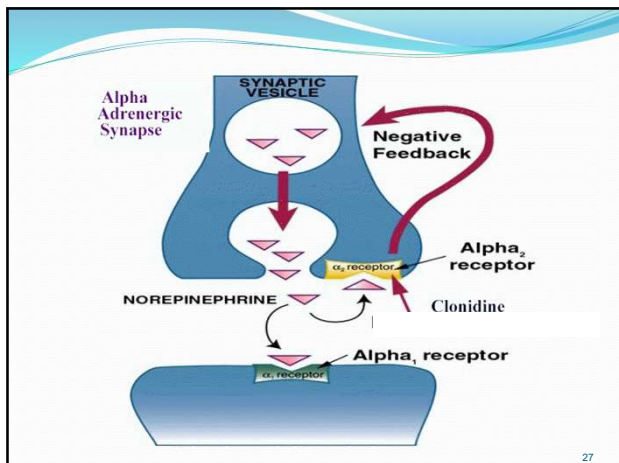
Clonidine

- Alpha₂ receptor agonist used to treat HTN, suppresses NE release
- Adding to buprenorphine extends opioid abstinence
- Even in absence of withdrawal signs, it “decouples” stress from craving in everyday life
- Alpha₂ receptor agonist used to treat HTN, suppresses NE release
- (Also used to minimize withdrawal Sxs from LT use of opioids, ETOH, benzodiazepines, nicotine)

Kowalczyk et al., 2014

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Discussion

What factors would lead you to choose the following and why?

- Methadone
- Buprenorphine
- Naltrexone
- None

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Kratom (*Mitragyna speciosa*)

- Leaves from tree in SE Asia
- Stimulating at low doses; sedating at high doses
- Novel μ , δ , and κ opioid receptor agonist
- Mytraginine (major alkaloid) *partial* agonist
- 7-hydroxymitragynine (minor alkaloid) more potent than morphine

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Kratom (*Mitragyna speciosa*)

- Used by opioid users to ameliorate opioid withdrawal Sxs
- μ -opioid agonism averts withdrawal sxs, while κ agonism attenuates reinforcement and produces aversion
- Mitragynine, as an α_2 adrenergic agonist, may also mimic adjunctive therapies for opioid withdrawal such as clonidine
- Thus, may exert several convergent pharmacological effects that could attenuate opioid withdrawal sxs and blunt cravings

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Kratom (*Mitragyna speciosa*) Cont'd

- Politics, money behind efforts to schedule kratom
- Efforts to place kratom as Schedule I
 - DEA 2016
 - FDA 2017
- Pharmaceutical companies applied for patents of kratom alkaloids
- Panel of leading scientists write to Congress to oppose scheduling kratom (*see handout*)

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Medication- Assisted Treatment of Alcohol Use Disorders



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Medications for Treating Alcohol Dependence

- Disulfiram (Antabuse®; 1970s)
 - Vomiting, flushing, headaches following alcohol ingestion
 - Well-supervised patients
- Naltrexone (1999)
 - Blocks stimulation of endogenous opioids
 - Blunts “high” effects of alcohol
- Acamprosate (2004)
 - Alcohol-blocking agent
 - Blocks craving

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Indications for Medications for Treating Alcohol Dependence

- **Acamprosate** – Patients dependent on alcohol who are abstinent at treatment initiation
- **Disulfiram** – Select patients who want enforced sobriety to optimize efficacy of other treatment
- **Oral naltrexone** - Treatment of alcohol dependence
- **Extended-release injectable naltrexone** – Patients who have been able to abstain from alcohol in outpatient setting

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FDA Approved Medications for Treating Alcohol Dependence

Medication	Target	Year Approved
Disulfiram	Aldehyde Dehydrogenase	1949
<p>Research from animal models over the past 25 years has provided promising targets for pharmacotherapy</p>		
Naltrexone	Mu Opioid Receptor	1994
Acamprosate	Glutamate and GABA-Related	2004
Naltrexone Depot	Mu Opioid Receptor	2006

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Disulfiram (Antabuse®)

- On market since 1948 (originally as an antihelminthic – antiparasitic medicine)
- Deters consumption by making people ill if they drink
- Interferes with metabolism of alcohol
- Aversion therapy to deter person from drinking

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Alcohol Metabolism

(1) Alcohol $\xrightarrow{\text{Alcohol dehydrogenase}}$ Acetaldehyde

(2) Acetaldehyde $\xrightarrow{\text{Acetaldehyde dehydrogenase}}$ Acetic Acid

(3) Acetic Acid $\xrightarrow{\text{o}_2}$ $\text{CO}_2 + \text{H}_2\text{O} + \text{Energy}$

About one ounce of alcohol eliminated every 3 hours

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Disulfiram-Alcohol Reaction

- Related to acetaldehyde buildup
- Flushing
- Sweating
- Nausea and Vomiting
- Headache
- Tachycardia
- Sometimes hypotension
- Sometimes dyspnea

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Disulfiram Side Effects

- Sedation
- Tingling in extremities
- Metallic taste
- **Hepatotoxicity**
 - Occurs 1/25,000 patient-years of tx
 - Mechanism unknown
 - Potentially fatal

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Naltrexone (Revia®)

- Acts on opioid receptors to reduce pleasurable aspects of drinking
- Taken daily
- Safe (although metabolized by liver)
- Cannot be abused, does not produce any dependence
- Blocks euphoric effects of alcohol
- Abstinence OR Harm-Reduction Model

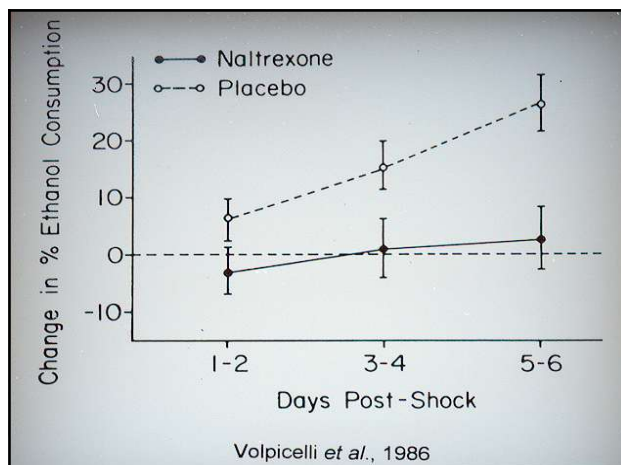
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Naltrexone Pre-clinical Effects

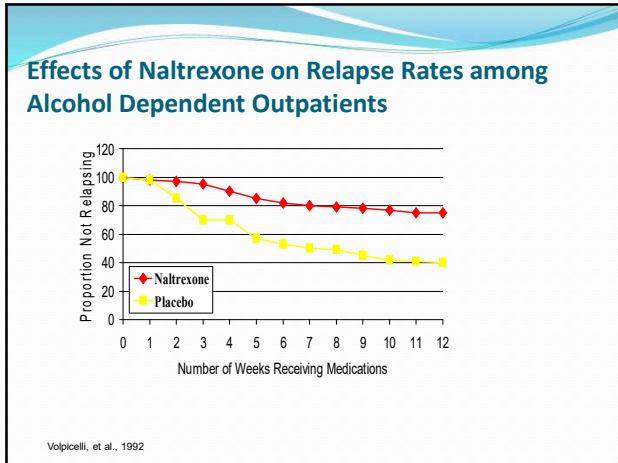
Volpicelli *et al.*, 1986

- 32 male rats with free access to H₂O and ETOH
- Received inescapable shocks
- Randomly assigned to naltrexone or placebo injections after the shocks

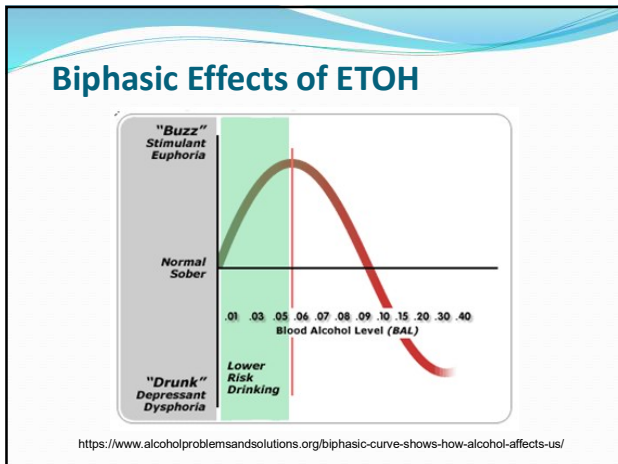
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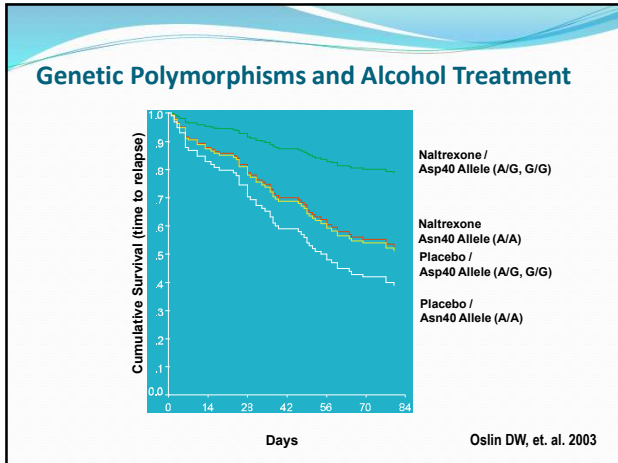
Naltrexone Human Lab Effects

Swift *et al.*, 1994

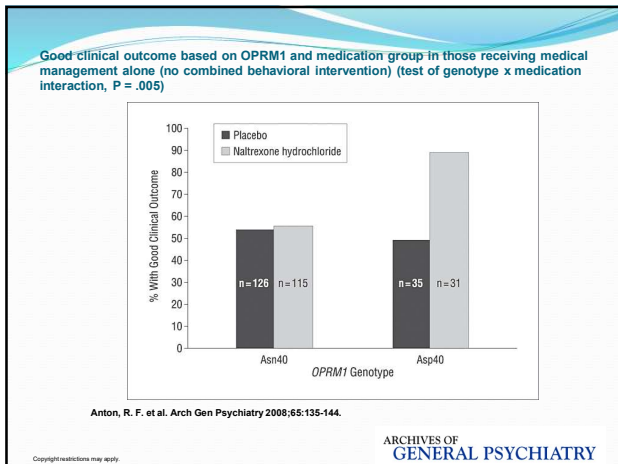
- 19 non-alcoholic subjects
- Double Blind crossover study
- Subjects received naltrexone 50 mg or placebo followed by an intoxicating dose of alcohol
- Completed Biphasic Alcohol Effects Scale

	NTX	Placebo	p
Mean Stimulant Score	2.5±2.1	3.4±2.2	<.04
Mean Sedative Score	4.1±2.6	3.2±2.2	<.03

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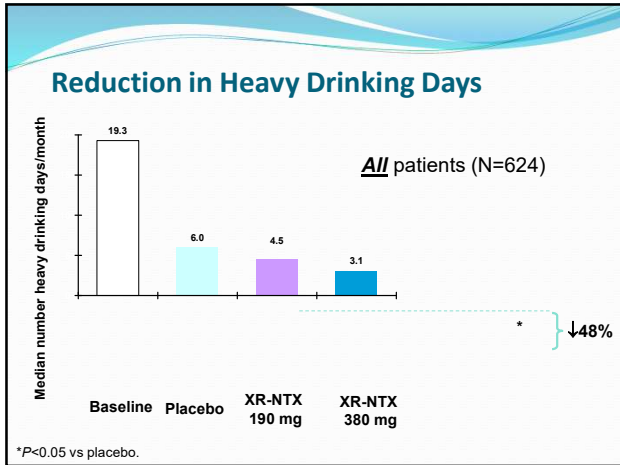
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Long-Acting Injectable Naltrexone Clinical Trial

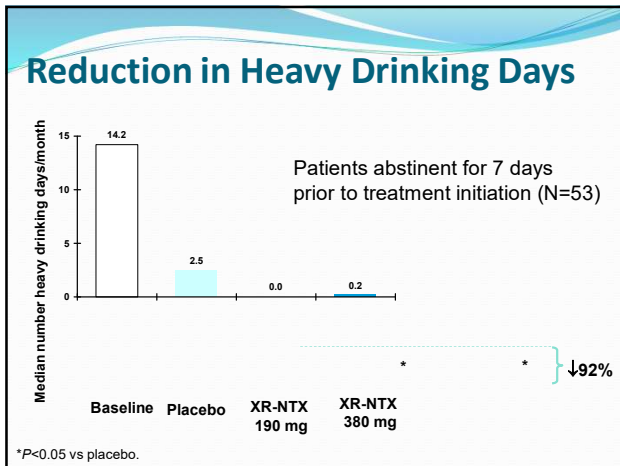
- 24-week multicenter, randomized, double-blind, placebo-controlled study
- 624 alcohol-dependent patients (DSM-IV)
 - Subgroup abstinent prior to treatment initiation
 - 82 patients (13.1%) abstinent for 4 days
 - 53 patients (8.5%) abstinent for 7 days
- Treatment – 12 sessions of low-intensity psychosocial intervention plus 6 monthly IM injections of either:
 - Placebo, XR-NTX 190 mg, or XR-NTX 380 mg

Garbutt et al., 2005

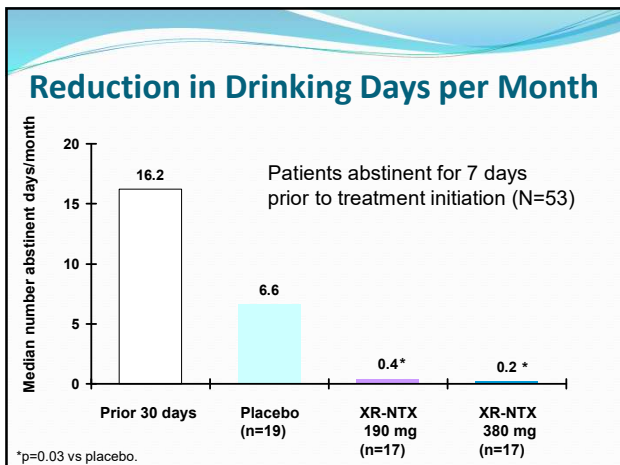
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Nalmefene (Revex[®])

- Analog of naltrexone
- Soyka, Friede, & Schnitker (2016) compared nalmefene with naltrexone for treatment of Alcohol Dependence and found:
 - Nalmefene performed better than naltrexone in reducing quantity and frequency of drinking
 - Both had benign side effect profiles
- Studies needed to see if OPRM gene polymorphisms moderate effect of nalmefene (as found with naltrexone)

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Acamprosate (Campral[®])

- ETOH inhibits NMDA receptors (a type of glutamate receptor)
- Chronic alcohol consumption leads to overproduction (upregulation) of NMDA receptors
- Sudden alcohol abstinence causes excessive NMDARs to be overactive and produce DTs and excitotoxic neuronal death – a surge in release of glutamate, which activates NMDARs
- Acamprosate reduces glutamate surge

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Acamprosate (Campral[®]) – (Cont'd)

- Also works by indirectly stimulating GABA_A receptors
- Dysphoria in early recovery is partially result of GABA depletion
- Used after person has stopped drinking
- First anti-relapse medication that normalizes alcohol-induced changes in brain function after alcoholic stops drinking
- May take drug up to a year after quit drinking

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Acamprosate

- Calcium acetyl homotaurinate (Campral®)
- Available 1/2005
 - Delayed release tablets
 - Daily dose – two 333mg tabs tidEnhances abstinence and reduces drinking days
- **Very important factor:** Not metabolized in liver
- No significant drug-drug interactions

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Acamprosate

- May restore receptor tone that usually can take up to 12 months to normalize on its own
- Thus, attenuates symptoms of acute **and** protracted alcohol withdrawal (Post-Acute Withdrawal Syndrome)

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Acamprosate

- Whitworth et al. showed relapse rate of 19% in 12-week study period
 - (23% with naltrexone)
- Patients report they “seemed to lose interest in alcohol”

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Acamprosate vs. Naltrexone

Meta-analysis by Maisel et al. (2012) showed:

- Acamprosate better than naltrexone for maintaining abstinence
- Naltrexone better than acamprosate on reducing heavy drinking and craving
- For naltrexone, requiring prior abstinence better for abstinence maintenance and reduced heavy drinking compared with placebo

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Acamprosate vs. Naltrexone (Cont'd)

- For acamprosate, prior detox resulted in better abstinence than placebo
- Conclusions:
 - Acamprosate slightly better in promoting abstinence and naltrexone slightly better in reducing heavy drinking and craving.
 - Detox before treatment or a longer prior abstinence before treatment associated with larger medication effects for acamprosate and naltrexone respectively

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Varenicline (Chantix®) and Med Mgmt of AUD with comorbid cigarette smoking

- High comorbidity of smoking in individuals with AUD
- Randomized, double-blind, placebo-controlled trial
- Participants met criteria for AUD and smoked
- Varenicline (1 mg b.i.d.) with med mgmt results:
 - Decreased heavy drinking among men (but not woman)
 - Increased smoking abstinence in overall sample

O'Malley, S. et al. (2018). JAMA Psychiatry, 75(2), 129-138.

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Topiramate (Topamax®)

- Novel molecule – tx for seizures and off-label for bipolar disorder, now **Alcohol Use Disorder**
- Mechanism(s) still uncertain, appears to suppress ETOH-induced DA release
- Reduced drinks per day, number of heavy drinking days
 - No difference in early or late onset alcoholics
 - Measured abstinence initiation not persistence
 - Perhaps different pharmacotherapies could be used for initiation, maintenance and prolonged abstinence

Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: A randomized controlled trial. *Lancet*. 2003;361:1677-1685.

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Topiramate vs. Naltrexone

- Open-label – Topiramate or Naltrexone
- Assessed at intake, 3 months, 6 months
- Measured ETOH intake, cravings, disability, quality of life
- Topiramate **better than** Naltrexone at reducing alcohol intake and cravings, functioning and quality of life

NOTE: All studies used topiramate as an adjunct to behavioral therapies

Florez G, Saiz PA, Garcia-Portilla P, Alvarez S, Nogueiras L, Bobes J. Topiramate for the treatment of alcohol dependence: comparison with naltrexone. *Eur Addict Res*. 2011;17:29-36.

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Topiramate and Cocaine

Week	Placebo	Topiramate
1	45	45
2	35	40
3	15	40
4	30	45
5	30	45
6	30	40
7	30	35
8	30	35
9	25	35
10	25	35
11	25	35
12	15	45
13	15	45

Group	% Abstinent
Placebo	26%
Topiramate	59%

More patients in topiramate group

- Abstinent than in placebo group
- Achieved 3 or more continuous weeks of abstinence from cocaine

(Kampman, K.M., et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug and Alcohol Dependence* 75(3):233-240, 2004.)

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Medications for Treating Alcohol Dependence – Under Investigation

Medication	Target (action)
Topiramate	GABA/Glutamate (multiple, agonist)
Valproate	GABA/Glutamate (multiple, agonist)
Ondansetron	5-HT ₃ Receptor (antagonist)
Nalmefene	Mu Opioid Receptor (antagonist)
Baclofen	GABA _B Receptor (agonist)
Antalarmin	CRF1 Receptor (antagonist)
Rimonabant	CB1 Receptor (inverse agonist)

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Examples of NIAAA-Supported Clinical Pharmacotherapy Trials for AUDs and Comorbid Psychiatric Conditions

Comorbidities	Medication(s)
AD/Depression	naltrexone; sertraline
AD/Bipolar	valproate; naltrexone
AUD/anxiety disorders	venlafaxine (Effexor)
AD/schizophrenia	clozapine (Clozaril)
AD/tobacco dependence	bupropion (Zyban)
AD/cocaine dependence	topiramate (Topamax)

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Glucagon-Like-Peptide 1 (GLP1)

- Released in small intestine
- Promotes blood glucose homeostasis, slows gastric emptying, reduces appetite
- GLP1 agonists (Ozempic®) Used to treat Type II Diabetes Mellitus and Obesity
- Mechanism appears to involve ghrelin suppression
- GLP1 agonists – show decrease in alcohol and drug intake – even at low, subclinical doses

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Medication-Assisted Treatment of Tobacco Dependence



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Co-occurrence of Alcohol and Tobacco Use



- Alcohol-dependent people 3 Xs more likely than general population to be smokers
- Tobacco-dependent people 4 Xs more likely than general population to be alcohol-dependent

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Medications for Nicotine Dependence Tx Nicotine replacement therapy (NRT)

- Reduces reinforcing effects of tobacco-delivered nicotine
- Reduces withdrawal sx's
- Delivers "positive effects" of nicotine
- Sustains desirable mood and attention
- Helps handle stressful or boring situations
- Manages hunger and weight gain
- Breaks "connection" between context, smoking and reinforcing effect

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Medications for Nicotine Dependence Tx

Nicotine Replacement Therapy (NRT)

- Passive dosing
 - Transdermal patch (7-, 14-, & 21-mg/day dose)
- PRN dosing
 - Gum, lozenge, sublingual tablet, nasal spray
- Needs
 - Higher dosing
 - Use while continued smoking
- Use Fagerström Nicotine Dependence Scale to titrate dosing

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Medications for Nicotine Dependence Tx

Bupropion (Zyban®)

- Antidepressant
- Indirect DA and NE reuptake inhibitor and antagonist on select nicotinic receptors
- Alters reinforcing properties of nicotine
- Reduces withdrawal sx's (depression, irritability, difficulty concentrating)
- Can combined with NRT

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Medications for Nicotine Dependence Tx

Varenicline (Chantix®)

- Partial agonist of nicotine receptors
 - Reduces craving for nicotine
 - Reduces pleasurable effects of nicotine
- Does not greatly increase downstream release of DA
- Competitive binding blocks nicotine from binding and stimulate mesolimbic dopamine pathway (like buprenorphine in tx of opioid addiction)

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Medications for Nicotine Dependence Tx

Nicotine vaccine

- Under development – (Use Google Scholar to see articles)
- Induces antibodies that prevent nicotine molecules from reaching receptors
- Smoking cessation, perhaps prevention

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Treatment of Comorbid Psychiatric Disorders to Enhance SUD Recovery

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Poor Mental Health Linked to increased Drug Use

Rate of drug use among people aged 18 years or older

Mental Health Category	Rate of Drug Use (%)
All	~28%
No mental illness	~20%
Any mental illness	~45%
Serious mental illness	~55%

Samantha, A. & Rekito, M.S. (2025). Mental Health and Substance Use Linked in New Survey. JAMA, published online September 26, 2025. doi:10.1001/jama.2025.15338

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Odds of Co-Occurrence of Current (12-month) DSM-IV Alcohol Dependence and Selected Psychiatric Conditions

Disorder	Odds
Anxiety Disorders	2.6x
Mood Disorders (especially Major Depression)	4.1x
Personality Disorders	4.0x
Antisocial Personality Disorder	7.1x
Drug Dependence	36.9x
Nicotine Dependence	6.4x

NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2004.

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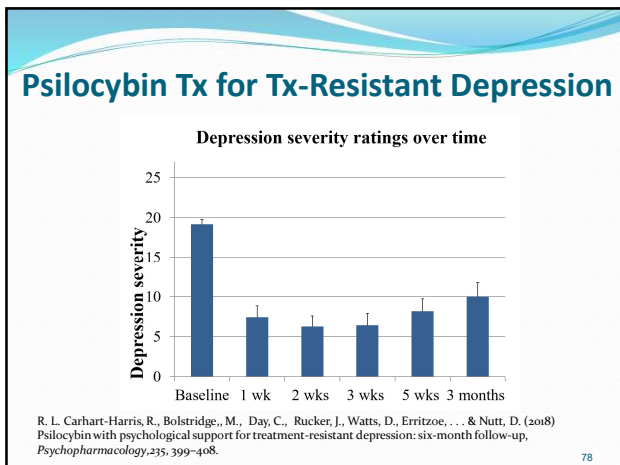
Combined Naltrexone and Ketamine – Depression and AUD

Ketamine

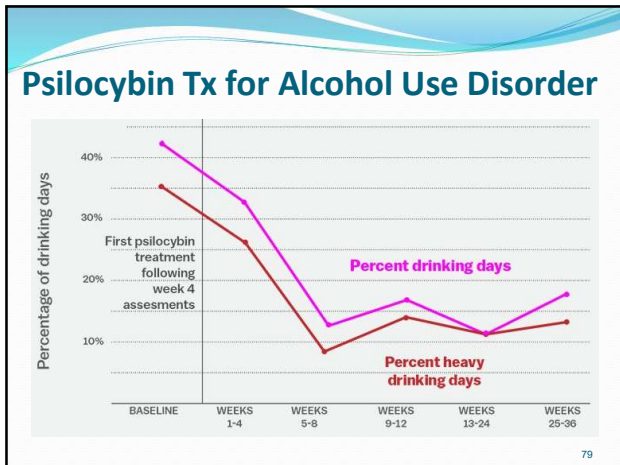
- Rapid, robust antidepressant effects
- Concerns about abuse liability
- Antidepressant effects
 - Might depend on opiate receptor stimulation
 - Not attenuated by naltrexone pretreatment
- Combined opiate receptor antagonism with ketamine may reduce addiction risk among depressed patients at risk for substance abuse

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Treatment of Pain as an Adjunct to SUD Treatment

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- ### Discussion
- How do you distinguish between legitimate complaints about pain vs. “just drug-seeking?”
 - How do you address legitimate pain issues without compromising recovery?
 - What role (if any) does harm reduction play in this issue?

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References / Handouts

Mehendale, A., Goldman, M., Cizerle, K., & Parvin, T. (2016). The problems of outcomes in addiction treatments, the inconvenient truths. *Journal of Addiction and Preventive Medicine*, 1, 1-6.

Strain, E., Kampman, K., & Weiss, R. (2021). Moving Beyond Medications That Act at the μ Receptor in the Treatment of Opioid Use Disorder. *JAMA Psychiatry*, 78, 701-702.

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Questions, Discussion

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TED Talk – “Rat Park” (Johann Hari)



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