



Medication Assisted Treatment (MAT) for Opioid Use Disorder

Dr. Michael Wilson

Disclosure

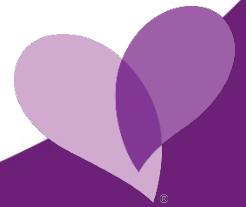
In accordance with Accreditation Council for Continuing Medical Education (ACCME) Standards of Commercial Support, Wright State University Boonshoft School of Medicine requires that disclosures be announced to activity attendees. The following fulfills that requirement.

Commercial Support

This activity has not accepted any educational grants from a commercial entity.

Conflict of Interest

All individuals in a position to influence the content of the educational material must disclose to learners any relevant financial relationships.



Disclosure

Planning Committee Disclosure

During the planning stages of this activity, all planning committee members have declared there are no relative financial arrangements or affiliations with the organization that may affect balance, independency, objectivity or scientific rigor for this continuing medical education (CME).

Planner	Relationship	Commercial Entity	Resolution
Donnica Hinkle, Kristi Carney	No relationship with a commercial entity	CareSource	No resolution needed
Dr. Christina Weston, Dr. Cameual Wright, Dr. Michael Wilson	No relationship with a commercial entity	CareSource	No resolution needed
Terry Correll and Randy Welton	Affiliation/Financial Interest	Wright State University	No resolution needed



Disclosure

Presenter Disclosure

At least one presenter has declared a relative financial arrangement or affiliation with a commercial entity. It is the policy of the CME Committee to resolve any conflicts of interest prior to the presentation. The following discloses all conflict of interest information gathered and resolutions necessary.

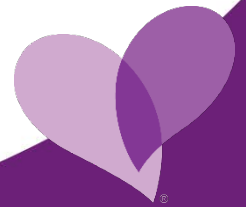
Presenter	Relationship	Commercial Entity	Resolution
Dr. Lori Desautels	Affiliation/Financial Interest	Butler University	No resolution needed
Dr. Weston, Dr. Reynolds, Dr. Wilson, Dr. Wright	No relationship with a commercial entity	CareSource	No resolution needed



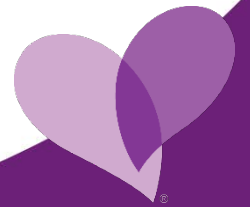
Substance Use Disorder (SUD) and Medication Assisted Treatment (MAT)

At the end of the program, the participant will be able to:

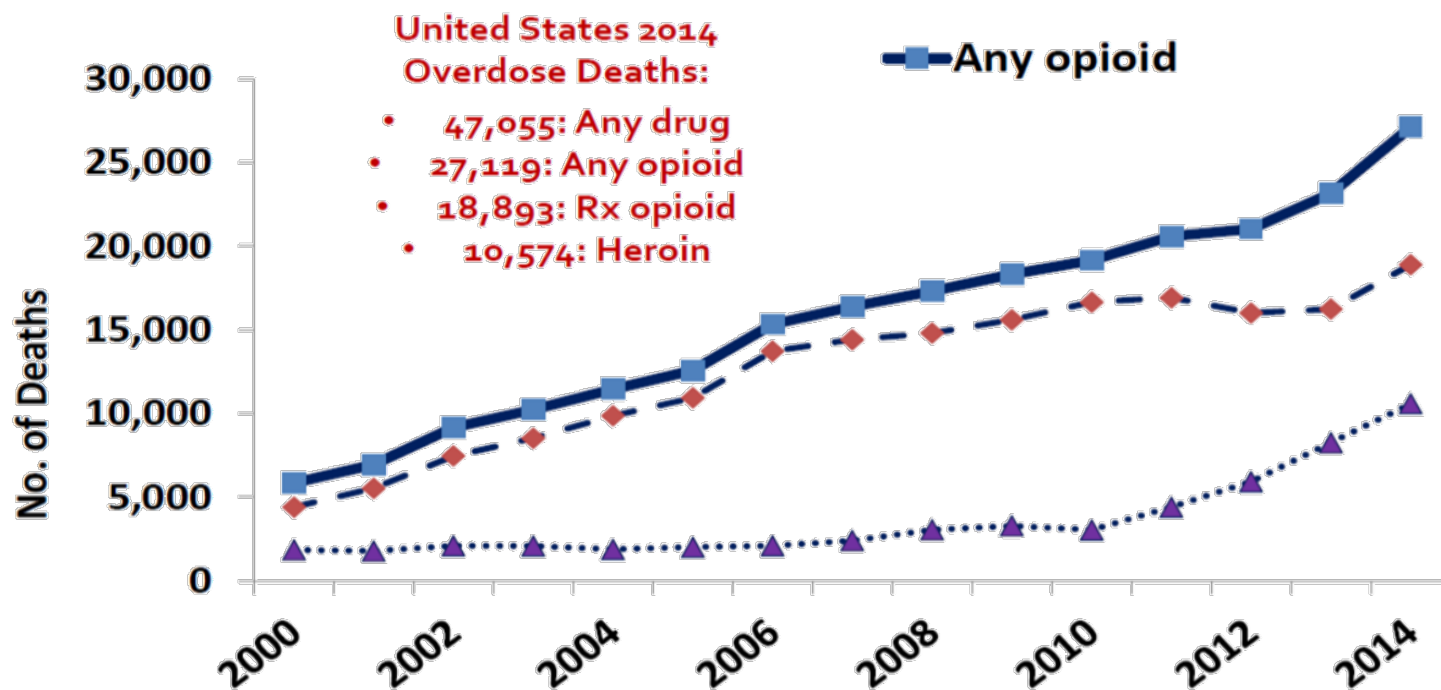
- State what SUD is
- Describe physiology changes in the brain when using substances
- Identify pharmacotherapy and non-pharmacology strategies for SUD



Knowledge Check



Marked Increases in Prescription Opioid and Heroin Overdose Deaths in the United States: 2000-2014



Centers for Disease Control and Prevention, National Vital Statistics System 2000-2014.
www.cdc.gov/nchs/data/factsheets/factsheet_drug_poisoning.htm. Accessed June 20, 2017.

Substance Use Disorder

Poor Control	1. Longer periods/larger amounts 2. Failure to reduce use 3. Excessive time 4. Cravings
Social Impairment	5. Problems with work, school, or family/social obligations 6. Interpersonal problems 7. Decrease in important social and recreational activities
Risky Use	8. Repeated use in physically dangerous situations 9. Worsening physical and psychological problems with continued use
Tolerance	10. Increased amount for same desired effect
Withdrawal	11. Response to abrupt cessation
Note: Meet ≥ 2 of these criteria to be diagnosed with SUD	
Severity: Mild 2–3, Moderate 4–5, Severe ≥ 6 Symptoms	

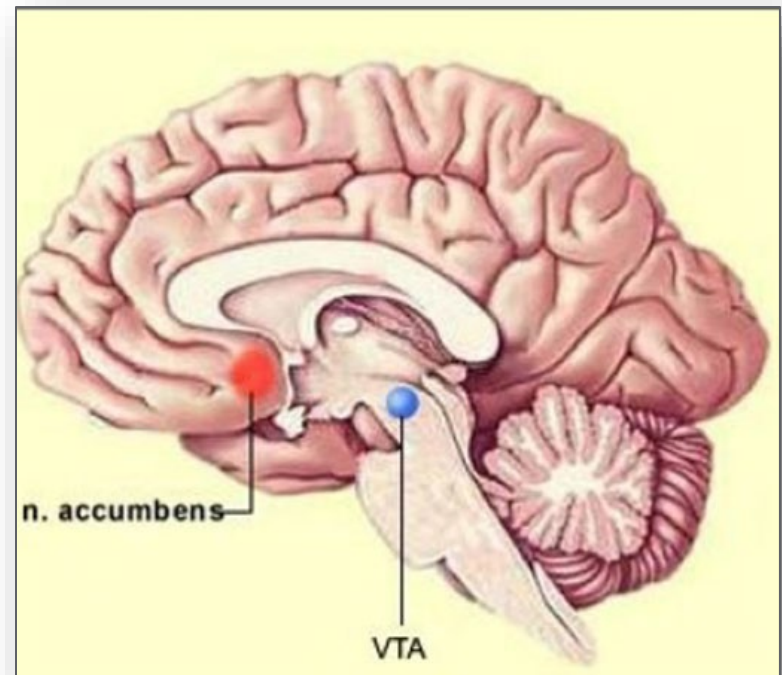
SUD = substance use disorder.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Arlington, VA: American Psychiatric Association; 2013. Hasin DS, et al. *Am J Psychiatry*. 2013;170(8):834-851.

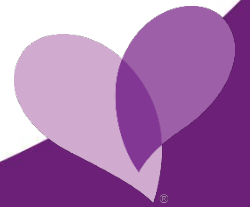
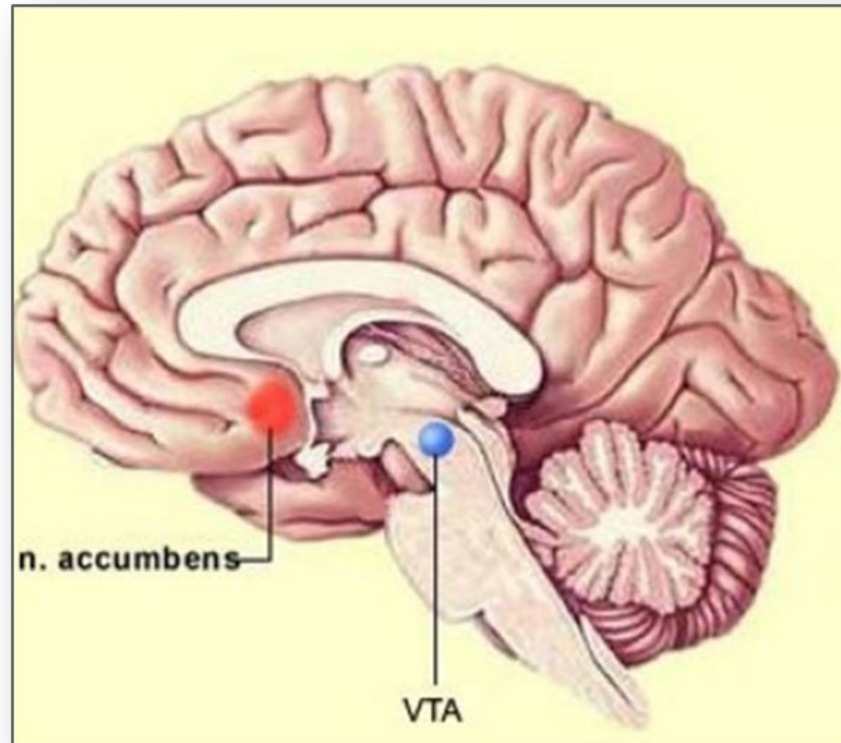


The Midbrain is the Survival Brain

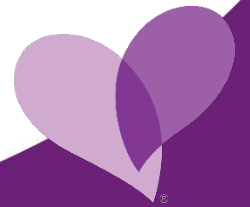
- Not conscious
- Acts immediately, no future planning or assessment of long-term consequences
- A life-or-death processing station for arriving sensory information



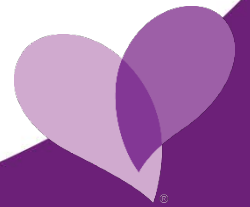
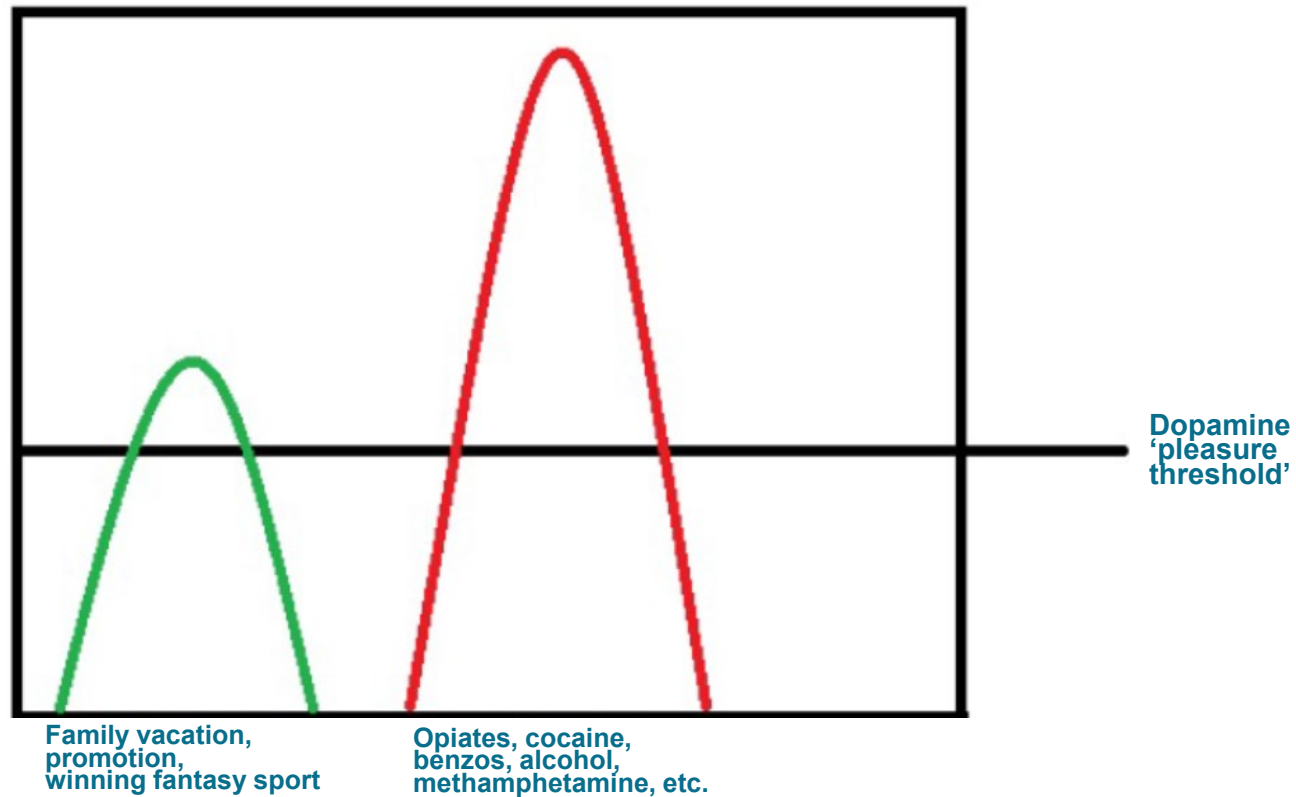
Midbrain = Instincts and Impulses



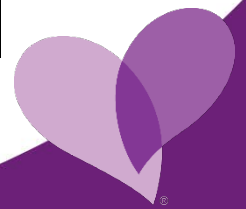
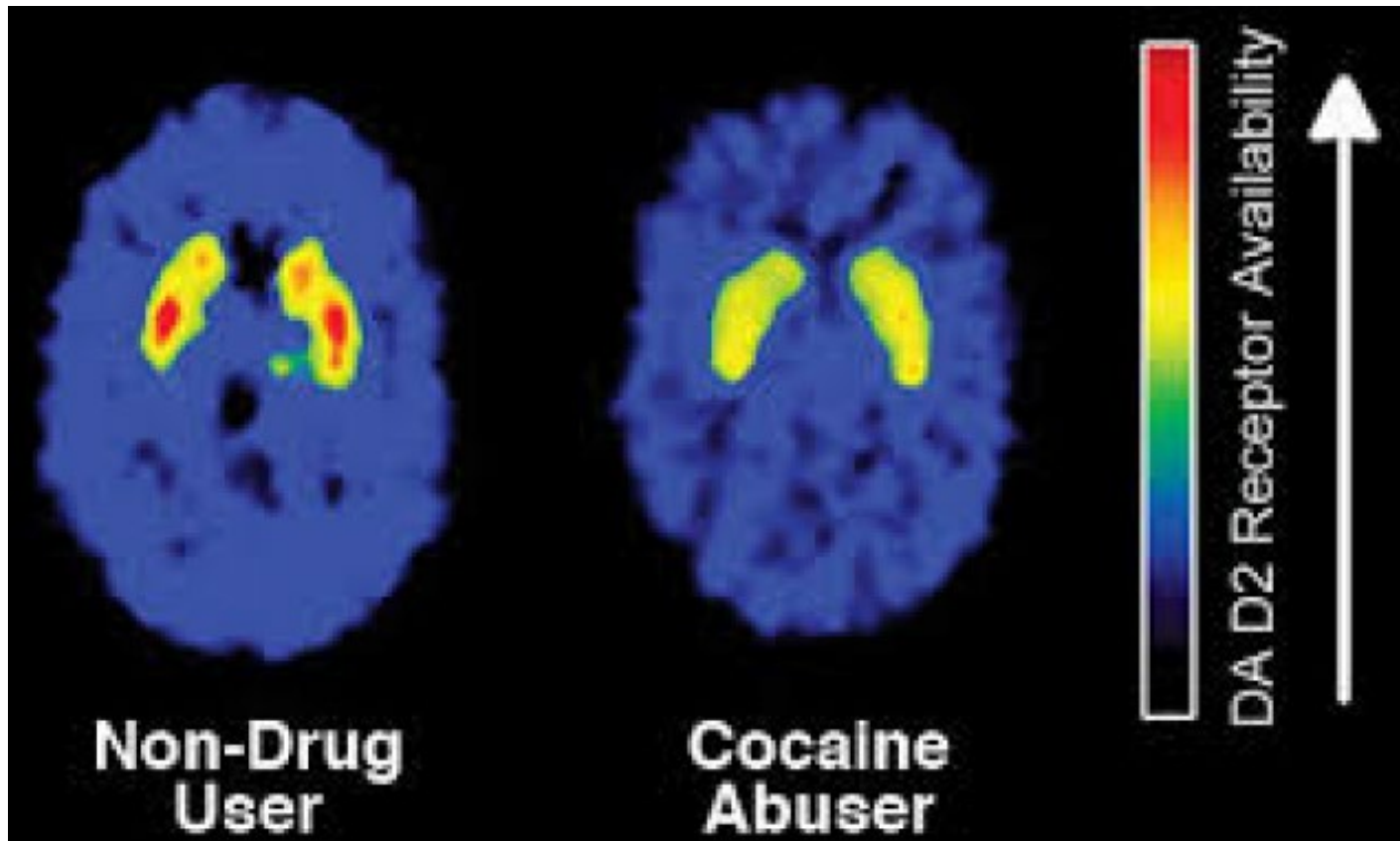
Knowledge Check



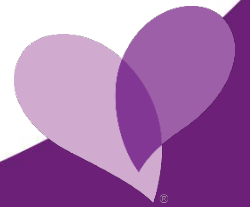
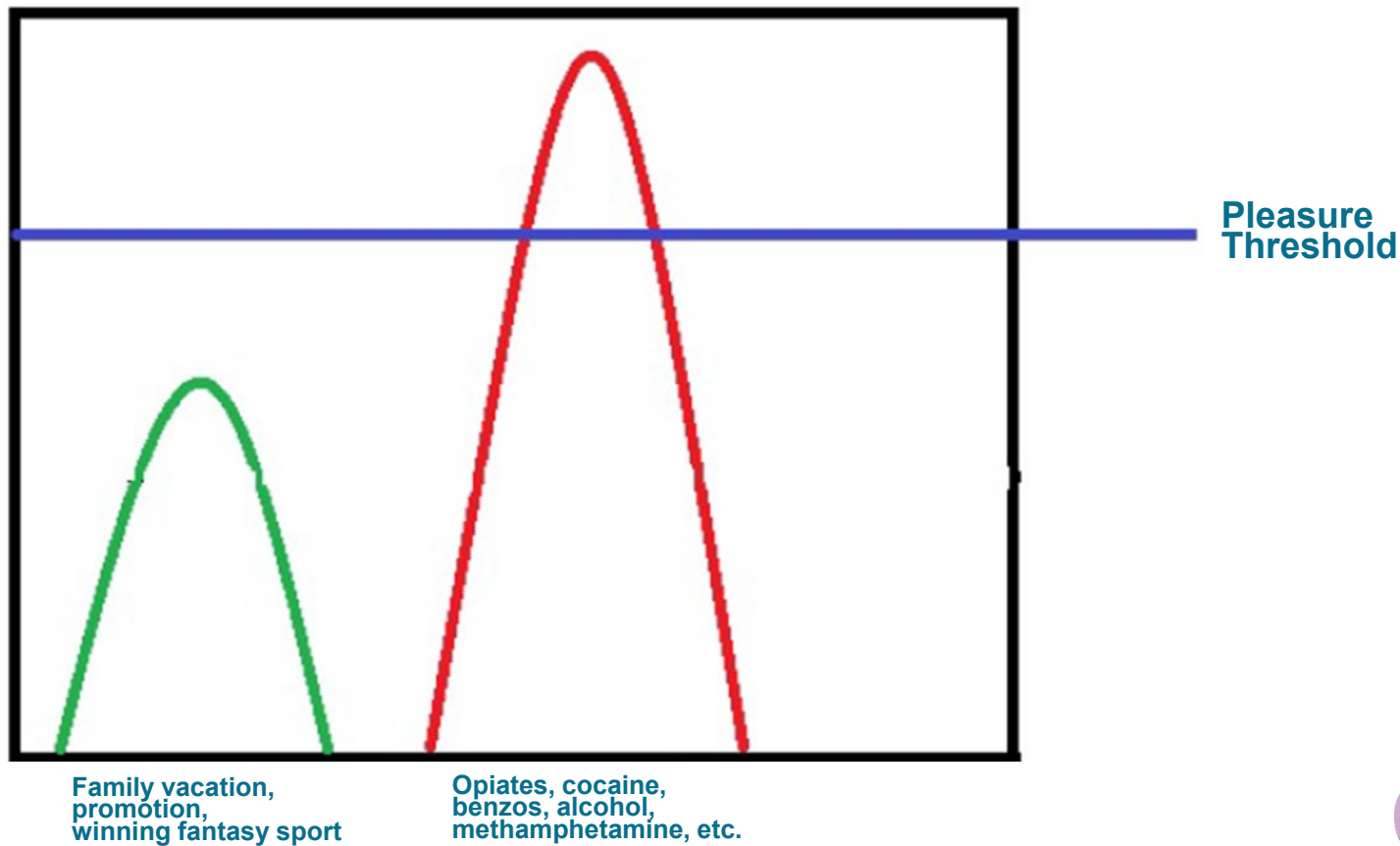
The Brain Has a Hedonic 'Set Point'



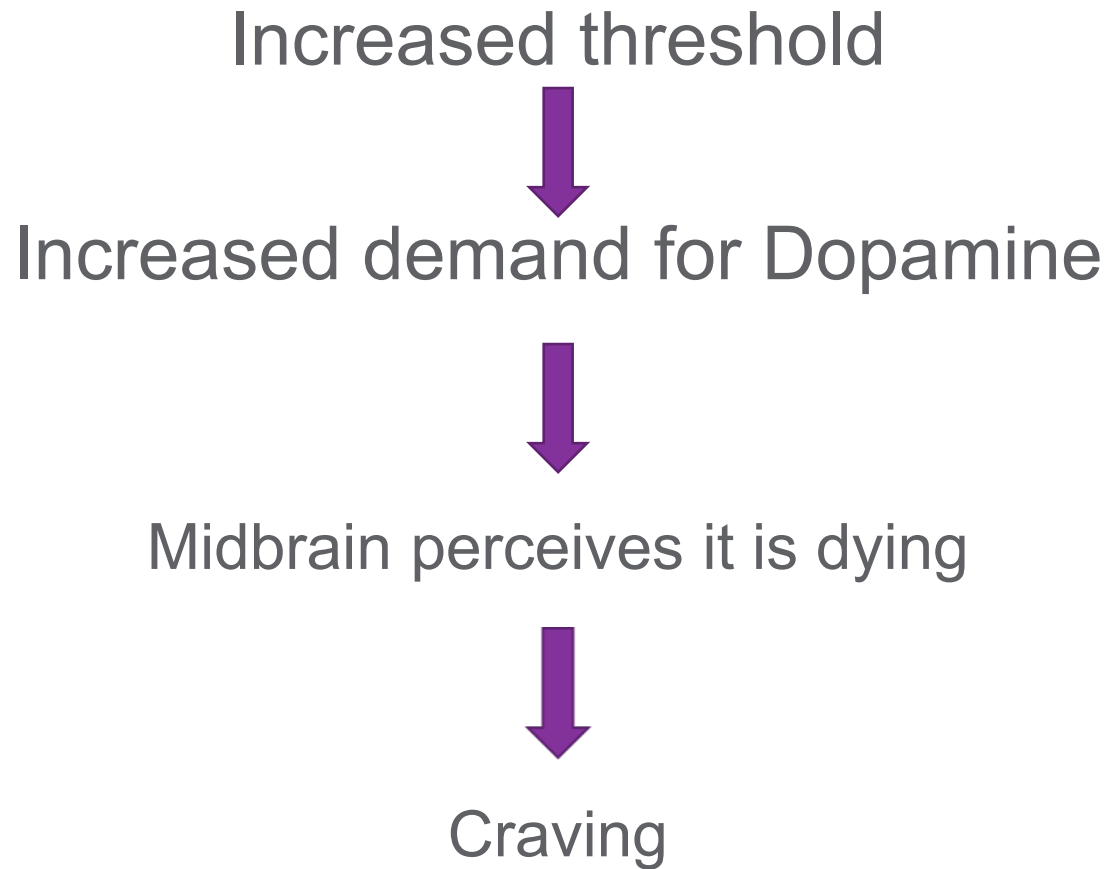
Brain Changes in SUD patients



Use Leads to Threshold Change



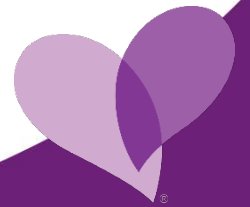
Craving



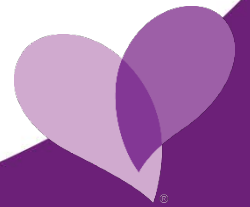
Justifications

Once there is a “perceived reason, suddenly behaviors become ‘justified’”.

- Lying
- Manipulating/stealing
- Reasoning/making excuses
- Rationalization
- Justification



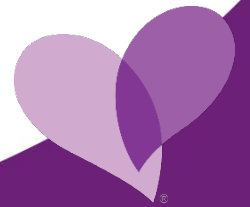
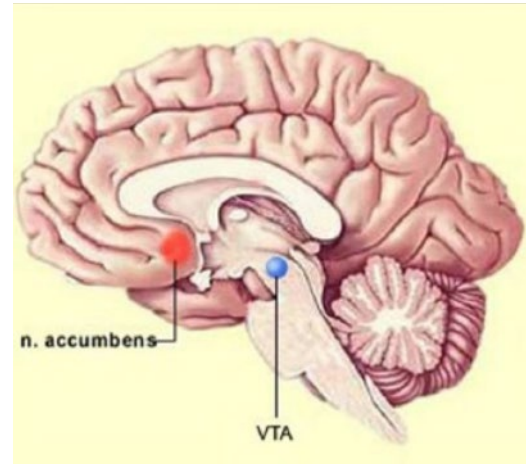
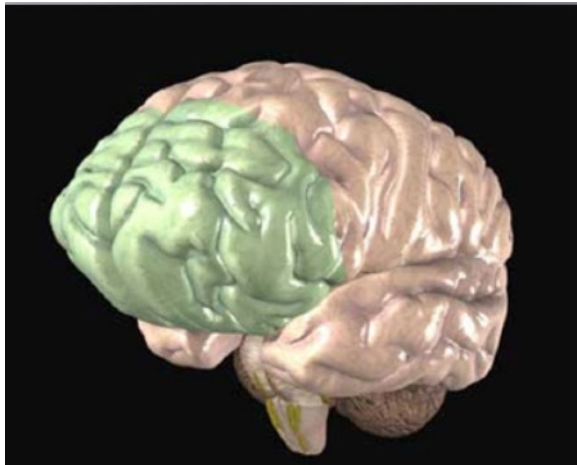
Knowledge Check



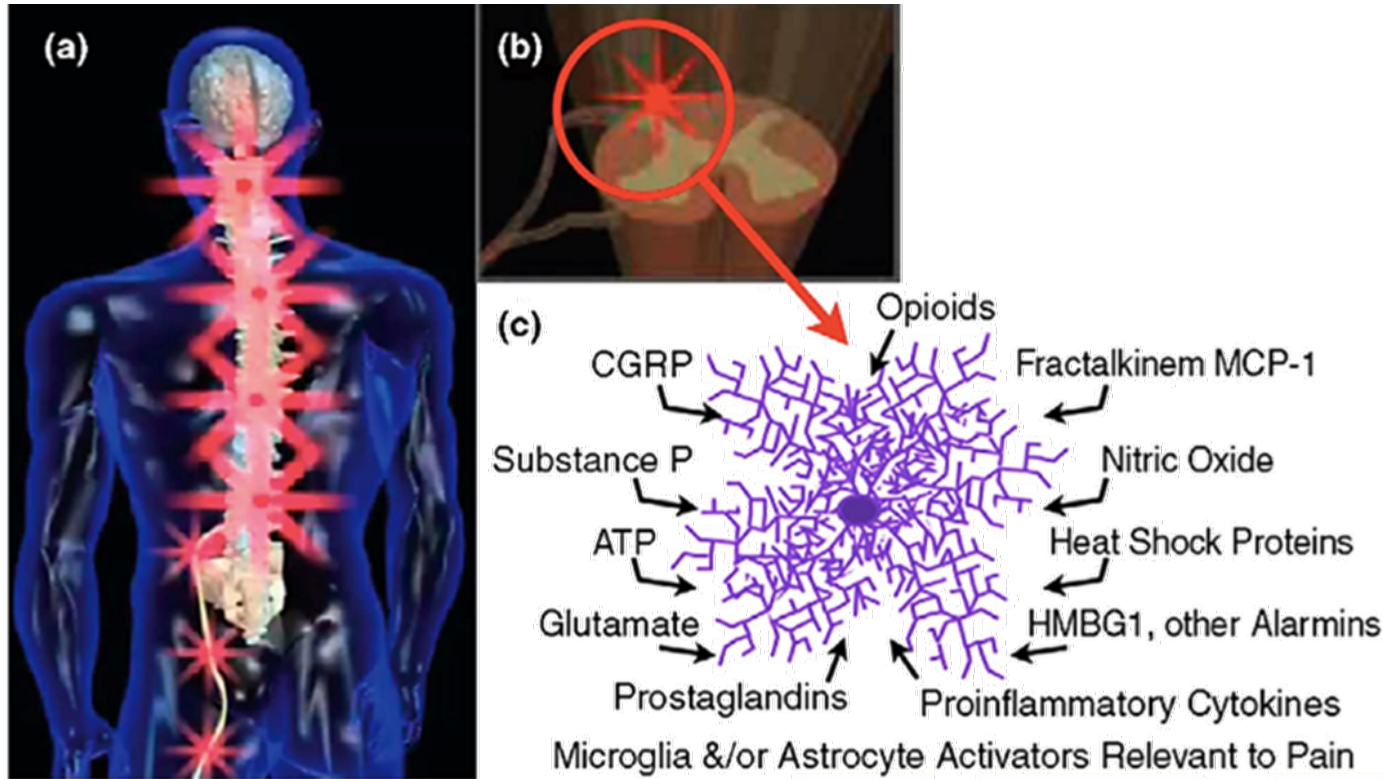
Twofold Front for Treatment

The Division of Labor

- AA/Behavioral Therapy work here
 - Frontal cortex = emotional meaning
- Drugs/Medications work here
 - Midbrain = survival/craving



Ambivalent Role: Exogenous Opioids Potentiate Neuropathic Pain Via TLR4



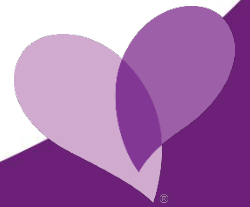
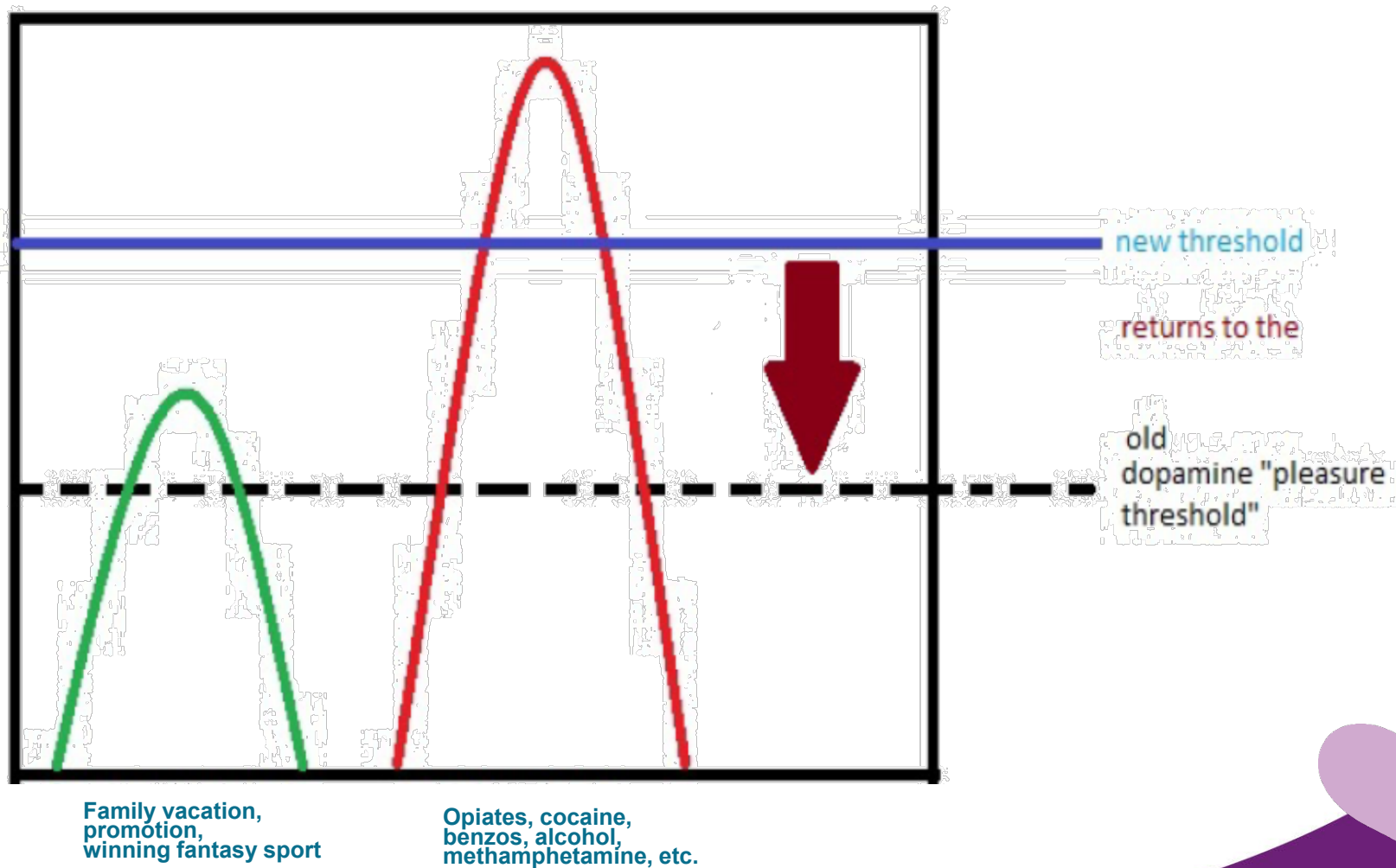
Microglial activators inducing neuroinflammation/pain.

TLR4 = toll-like receptor 4.

Watkins LR, et al. *Trends Pharmacol Sci.* 2009;30(11):581-591.

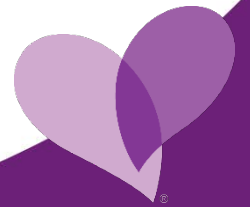


Post Treatment

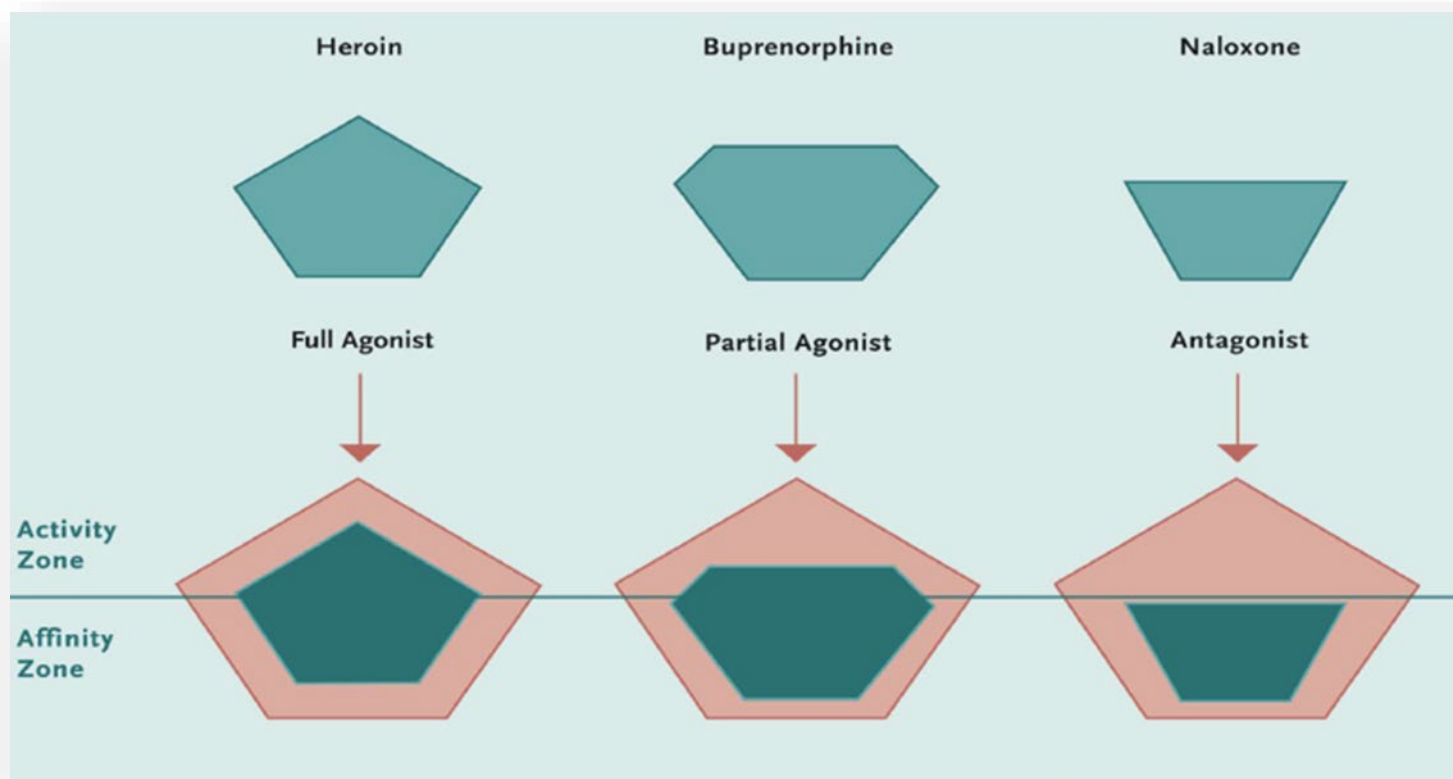


Pharmacotherapy of Opioid Use Disorder

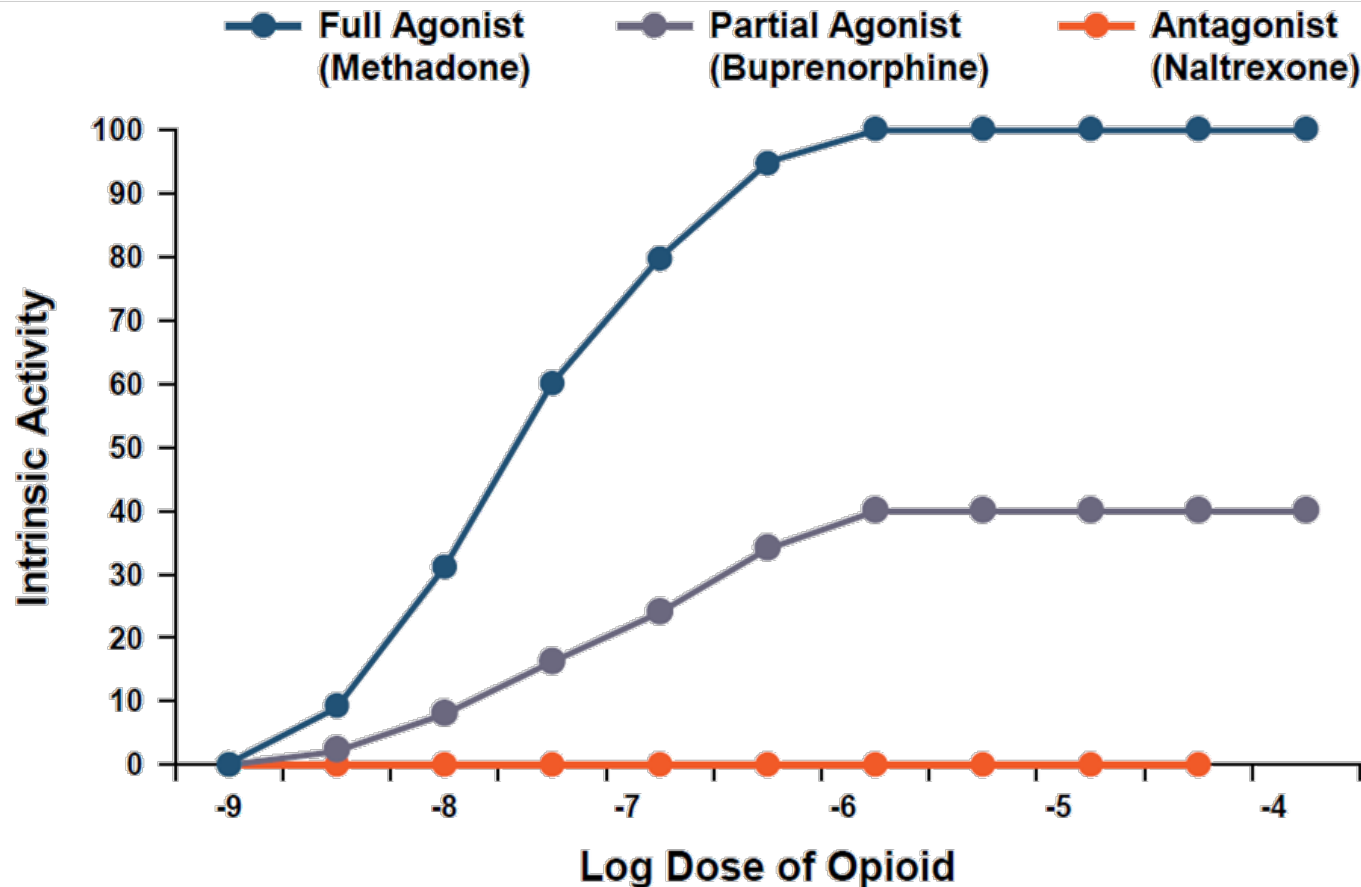
Oral Naltrexone
Methadone
Buprenorphine
Depot Naltrexone



Opioid Receptor Modulators



Intrinsic Activity: Full Antagonist (Methadone), Partial Antagonist (Buprenorphine) and Antagonist (Naltrexone)



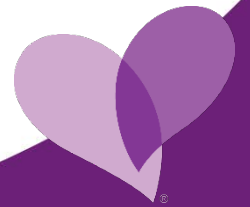
Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Rockville, MD: Substance Abuse and Mental Health Services Administration (US); 2004. Treatment Improvement Protocol (TIP) Series, No. 40.

Pharmacotherapy

New Tools For SUDs

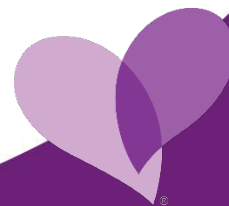
- Long-acting depot medications
 - Depot naltrexone: Opioids or alcohol
- Partial agonists
 - Buprenorphine: Opioids (including implant)
- Pharmacogenetics
 - Naltrexone and alcohol: *OPRM1* gene

OPRM1 = opioid receptor μ 1 gene.
Hulse GK. *Br J Clin Pharmacol.* 2013;76(5):632-641.



Medications in MAT for OUD

- Methadone- Full opioid; long acting
- Suboxone/Subutex- partial opioid; long acting
 - Buprenorphine in both
 - Buprenorphine- in presence of most opioids
 - Blocks them
 - Naloxone in suboxone:
 - keeps patient from injecting or snorting
- Naltrexone and Naltrexone XR (injectable)
 - Blocks all opioids



OUD Pharmacology

Methadone

- Full opioid agonist, oral tablet and liquid
- Used for detoxification and for maintenance at opioid treatment programs only (not office-based)
- FDA-indicated for pain (office-based)
- Dosing varies from 40 mg to 120 mg or higher
 - 40–60 mg “low”
 - 60–80 mg “moderate”
 - > 80 mg “high”
- Most effective for severe OUD and chronic relapsing, those who fail alternate treatments
- Not preferred first-line due to poor tolerability, need to attend opioid treatment program, daily dosing, and safety concerns (eg, cardiac, overdose), diversion



OUD Pharmacology

Buprenorphine

- Partial opioid agonist
 - Reduced overdose potential and abuse liability
 - Less-severe withdrawal than methadone when stopped
- Comparable to methadone in treatment retention and reduced heroin abuse
- Can be given in physician's office
 - Increased availability and reduced stigma



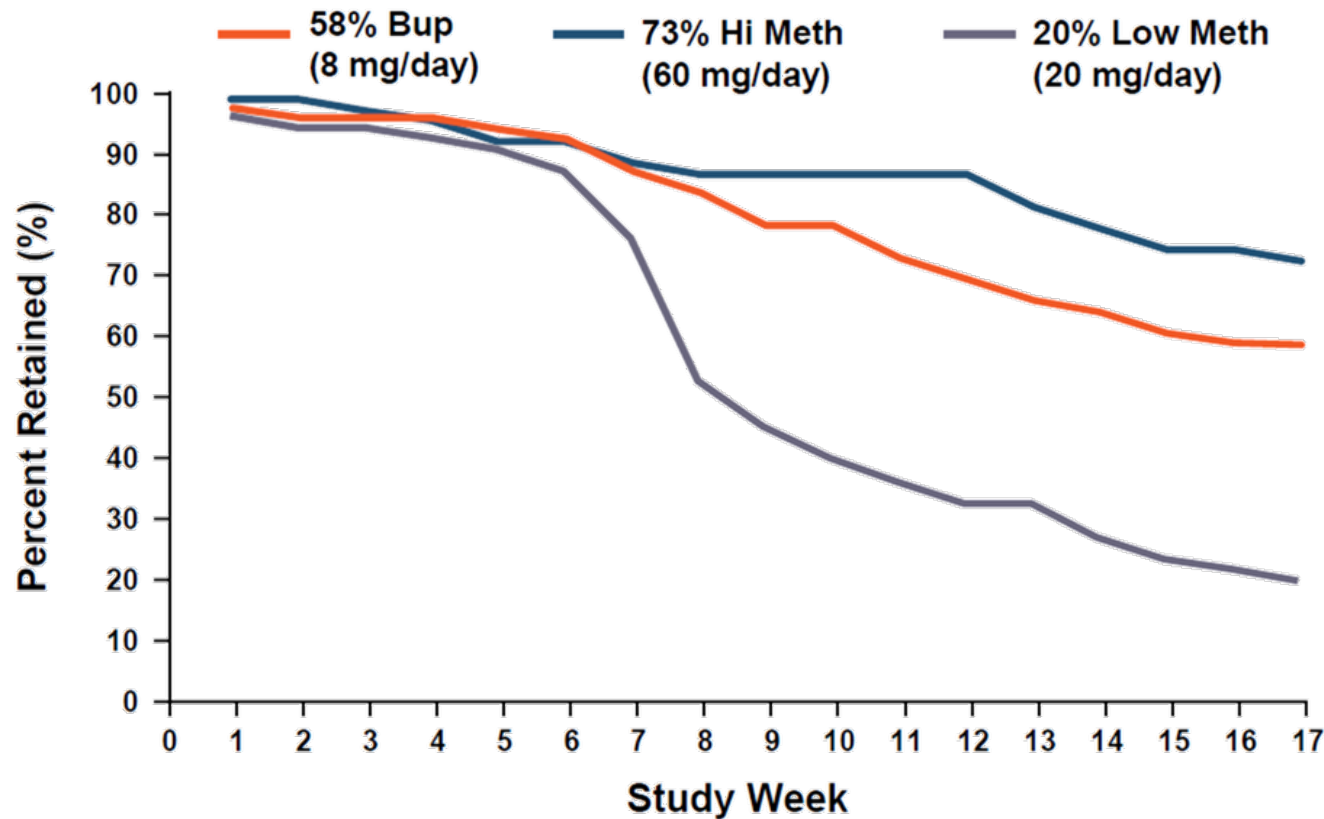
Maintenance Treatment Using Buprenorphine/Naloxone

- Naloxone added to sublingual buprenorphine maintenance formulation to deter parenteral abuse
- Naloxone has low sublingual bioavailability and combination equivalent to buprenorphine alone
- Numerous outpatient clinical trials compare efficacy of daily buprenorphine to placebo and to methadone
 - Buprenorphine is more effective than placebo
 - Buprenorphine is as effective as moderate doses of methadone (eg, 60 mg/day)



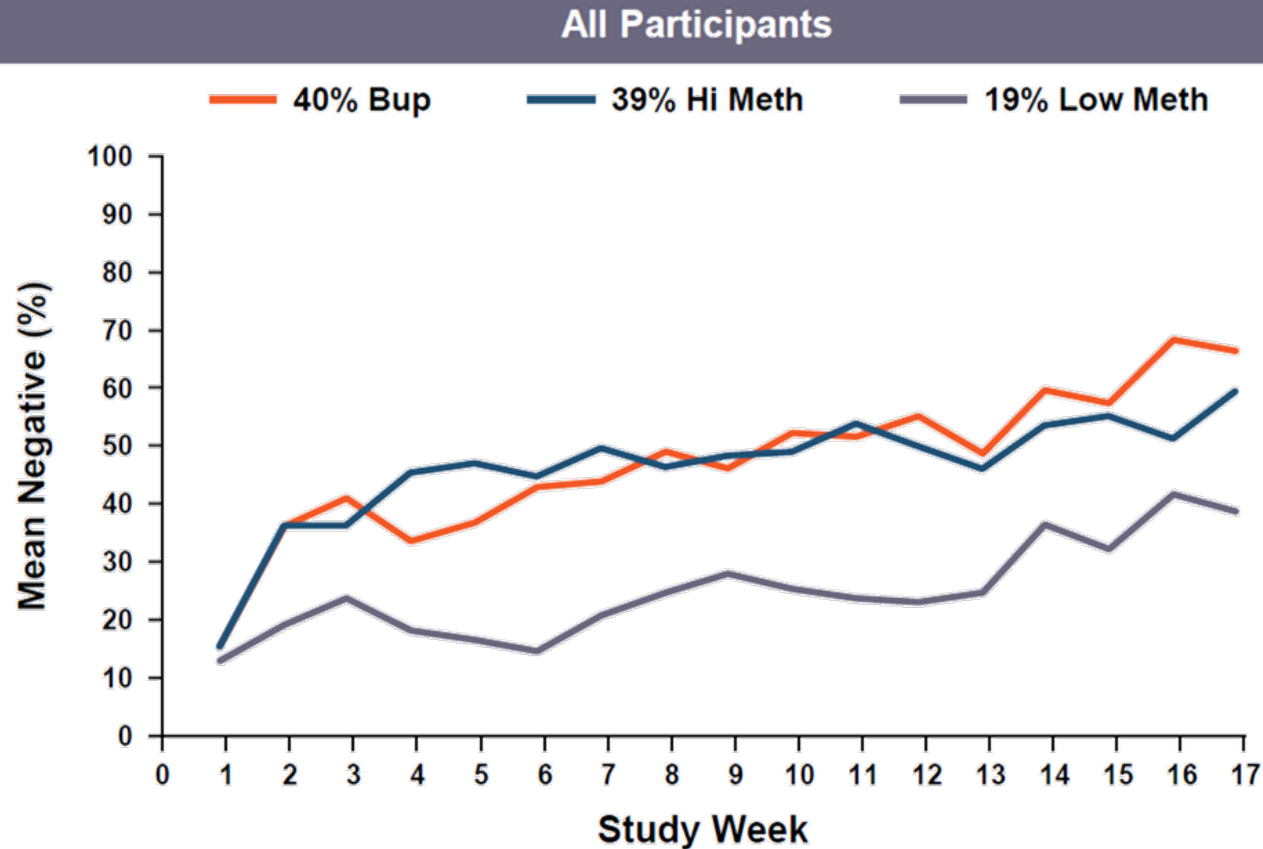
Buprenorphine vs Methadone

Treatment Retention



Buprenorphine vs Methadone

Opioid Urine Sample Results

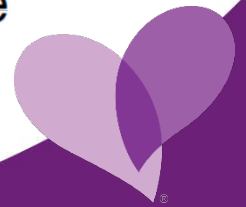


Sublingual vs Implant Buprenorphine

- Long-acting implant buprenorphine vs placebo
 - Retain 6 months (64% vs 26%) (n = 114 vs 54)
 - Opioid-free (64% vs “too many dropouts”)
- Long-acting implant vs 8-mg sublingual buprenorphine
 - Retain 6 months (64% vs 64%) (n = 114 vs 119)
 - Opioid-free (31% vs 33%)
- **Side effects of implant**
 - Implant site: Pain, itching, redness
 - Body: Headache, depression, constipation, nausea, vomiting, back pain
- **Limitations**
 - Equivalent to only 8-mg sublingual buprenorphine
 - Implanting and removal difficult

Rosenthal RN, et al. *Addiction*. 2013;108(12):2141-2149.

Ling W, et al. *JAMA*. 2010;304(14):1576-1583.



Investigational

Monthly Injectable Buprenorphine

- Two monthly formulations being developed
- **Side effects of injectable buprenorphine**
 - Injection site: Pain, itching, redness
 - Body: Headache, depression, constipation, nausea, vomiting, back pain
- **Advantages**
 - Dosing equal to 8-mg to 24-mg sublingual buprenorphine
 - Easy monthly injection
 - No removal needed (vs implant)

ClinicalTrials.gov Identifier: NCT01738503.

Sobel BF, et al. *Drug Alcohol Depend.* 2004;73(1):11-22.

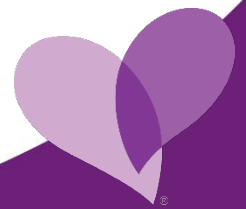


Partial Antagonists: Summary

- Buprenorphine for OUD (vs methadone)
 - Reduced overdose and abuse potential
 - Fewer withdrawal symptoms
 - Office-based practice with lower stigma
 - Higher cost
 - Long-acting 6-month implant approved and monthly injections under development
- Insufficient physician prescribing:
 - 2.5 million treatment-seeking OUD patients
 - Patients per prescriber limit expanded 100 =>
275
 - Most prescribers have < 10 patients

Kosten TR, et al. *Am J Addict.* 2004;13(suppl 1):S1-S7.

Turner L, et al. *Am J Addict.* 2015;24(1):24-29.



Oral Naltrexone for OUD

- Naltrexone is a long-acting oral analog of naloxone
 - A pure opioid antagonist (blocker)
- Binds to opioid receptors with greater affinity than opioids do
- Typical oral dose is 50 mg/day
- Taking opioids on naltrexone leads to blockade of opioid effects
- Naltrexone has no opioid properties
- Efficacy of oral naltrexone restricted by limited acceptability, except by specific populations, usually under pressure



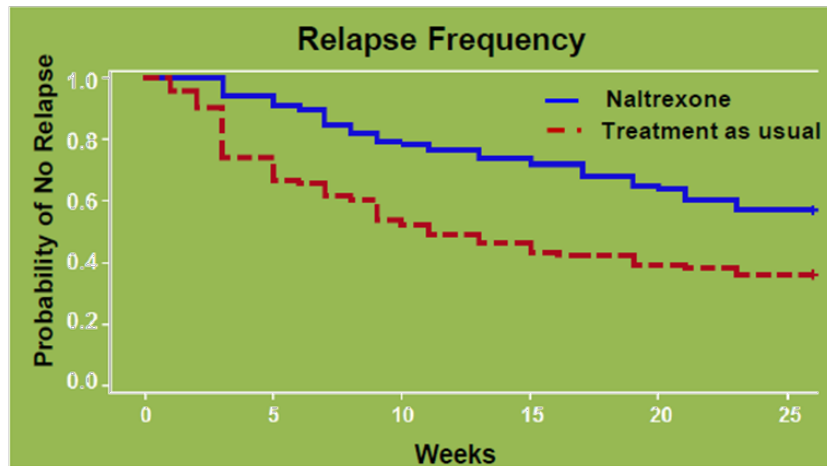
Extended-Release Injectable Naltrexone for Opioid Dependence

- Russian study (N = 250)
- Injectable naltrexone vs placebo × 6 months
- 6-month retention 53% vs 38% ($P < .02$)
- Total abstinence 36% vs 23% ($P < .03$)
- Retention rate similar to that of buprenorphine



Extended-Release Naltrexone in Criminal Justice-Involved Populations

- *Participants:* Parolees/probationers with OUD—all volunteers—received either
 - Monthly injections of extended-release naltrexone for 6 months
 - Community treatment, including methadone or buprenorphine (encouraged)



Overdoses in 78 weeks:

Control: 7

Naltrexone: 0

Lee JD, et al. *N Engl J Med.* 2016;374(13):1232-1242.

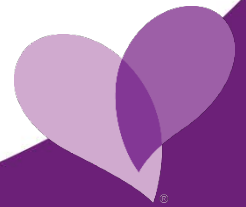
Oral vs Depot Naltrexone: OUD

- Retention and opioid-free urine compared in 2 randomized trials of naltrexone
 - Long-acting injectable (n = 42) vs oral (n = 69)
- Retention and opioid use at 8 weeks post-detoxification
- Long-acting depot vs oral naltrexone
 - **Days retained:** Depot, 42 vs Oral, 32
 - **Opioid-free urine:** Depot, 0.52 vs Oral, 0.37



Choosing a Medication for OUD

- **Methadone:** Only used in specialized opioid treatment programs
- Built-in program structure for better or worse
 - Overdose risk higher than that for buprenorphine
- **Naltrexone:** Difficult on, easy off
- **Buprenorphine:** Easy on, difficult off
- **Agonist vs antagonist:** What does the patient/family want?
 - Collaborative process



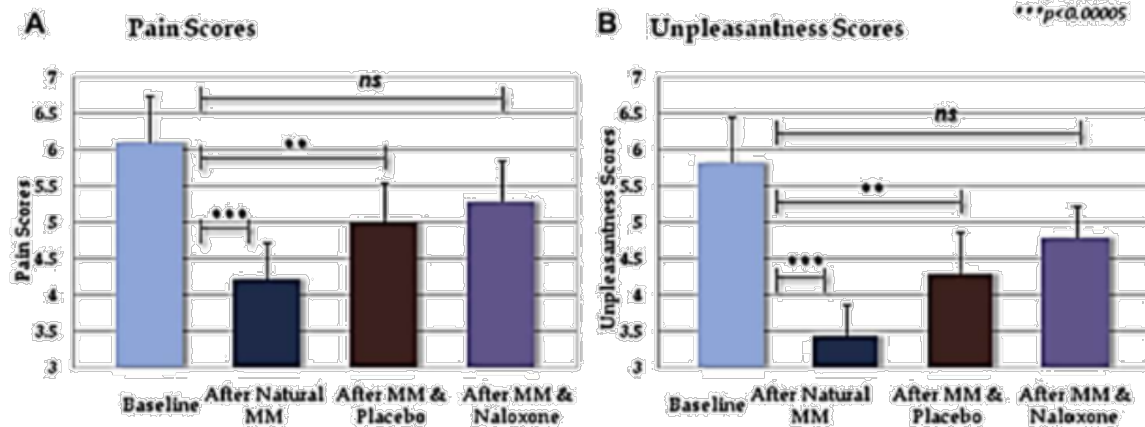
Mindfulness Meditation Modulates Pain Via Endogenous Opioids

Mean pain (A, left panel) and unpleasantness scores (B, right panel) following: a painful cold stimulus (baseline); natural meditation; meditation after placebo administration; and meditation after naloxone administration, respectively. The positive correlation of the response to intervention with years of experience suggests reduced response to placebo with increasing experience.

N = 15.

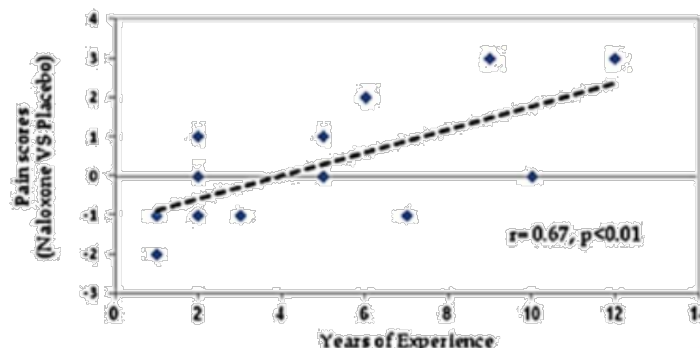
Sharon H, et al. *Am J Med.* 2016;129(7):755-758.

Pain and Unpleasantness scores

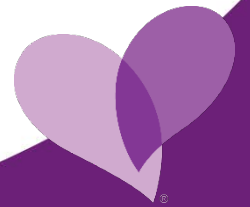


Placebo response

Correlation with Experience

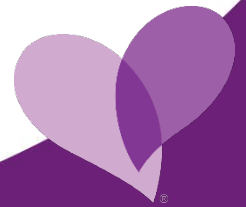


Knowledge Check



Psychotherapy/Counseling

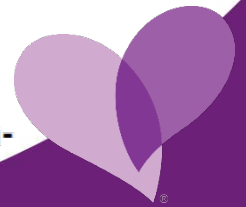
- Maximize non-pharmacologic strategies
 - Build and enhance motivation
 - Enhance self-efficacy
 - Enhance coping strategies to deal with stress, cravings
 - If receiving medication, enhance adherence strategies



Rebuilding Life Without Substances

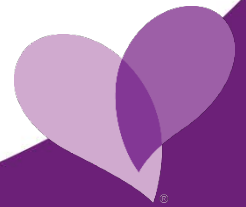
To patients with SUD, substances are an important part of life and difficult to give up

- Appropriate use of free time
- Interaction with relatives and friends now that patient is sober
- Appropriate interaction with or avoidance of substance-using friends
- Ability to say “no” to substances when offered (ie, refusal skills)



Prevention of Relapse

- Identify triggers
- Avoid high-risk situations whenever possible
- Anticipate lapses (abstinence violation effect)



Peer Support

- 12-Step (eg, AA, NA)
- Non-12-Step (eg, SMART, Women for Sobriety)
- Familiarize yourself with these
- Ask your patients about their experiences with them
 - “What’s the best thing you’ve heard this week at an AA meeting?”

AA = Alcoholics Anonymous; NA = Narcotics Anonymous; SMART = Self-Management and Recovery Training.



Naloxone Administered by Non-Medical Persons to Prevent Opioid Overdose Deaths

- **Auto-injector**
 - Take-home, hand-held, single-use
 - Has visual and voice instructions for the user to give this injection
 - Available without a prescription in some states
 - To obtain a supply of naloxone:
StopOverdose.org; ~\$100+
- **Intranasal**
 - Easier; Cost (approximately \$37.50)
- **Fentanyl deaths**
 - Fast-acting; Less time to give naloxone

Maxwell S, et al. *J Addict Dis.* 2006;25(3):89-96.

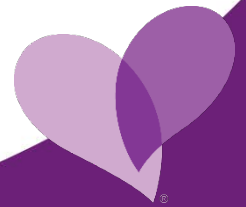
US Food and Drug Administration. www.accessdata.fda.gov/scripts/cder/daf/.



Family Disease

Addiction is a family disease

- The addict's behaviors affect everyone in the family.
- The family becomes **addicted** to the addict.
 - Family treats the addict like the addict treats drugs (Constantly thinking about them, adjusting their lives according to the addict, etc.).
 - This process occurs in the same place in the brain and needs to be treated the same
 - Alanon, Naranon, individual counseling for family members.

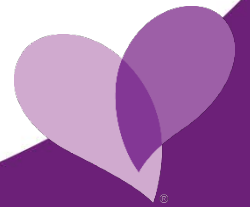




*Combining Medications to
Treat SUDs and Psychiatric
Comorbidities*

Pharmacotherapy of Co-occurring Disorders

- Typically focuses on treatment of the psychiatric disorder
 - More recent studies have focused on SUD as well
- Choice of medication is typically based on 3 considerations
 - Profile of side effects
 - Family history of medication response
 - Likelihood of medication adherence
 - No comparative effectiveness studies



Pharmacotherapy of SUD and Depression

- Tricyclic antidepressants have the most robust effect
- SSRIs are most helpful in late-onset alcoholics and may worsen early-onset alcoholics
- Sertraline (SSRI) + naltrexone particularly effective
- Less improvement in SUD (often correlated with mood improvement), but not worsening (ie, not enabling SUD)
- Buprenorphine may have efficacy for some treatment-resistant depression independent of OUD

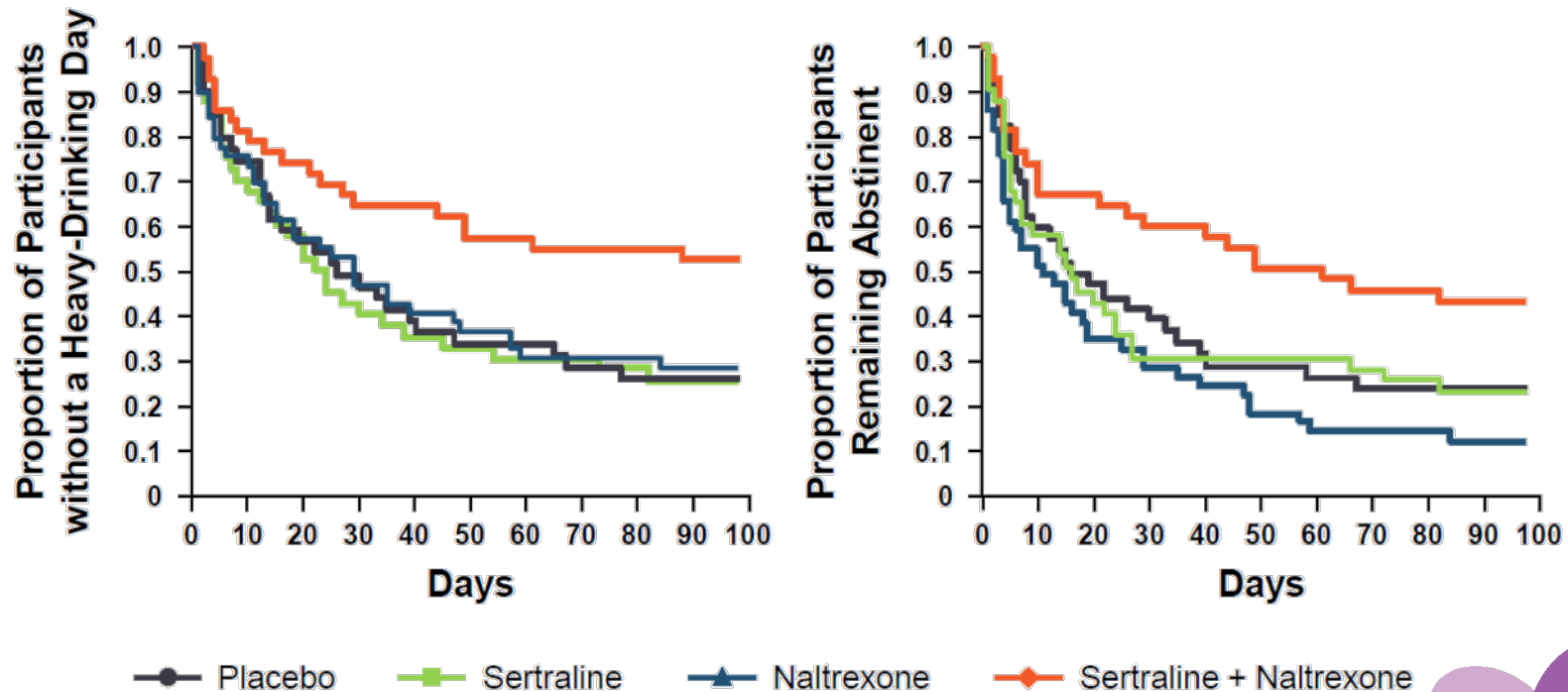
SSRI = selective serotonin reuptake inhibitor.

Nunes EV, et al. *JAMA*. 2004;291(15):1887-1896. Pani PP, et al. *Cochrane Database Syst Rev*. 2010;(9):CD008373. Fava M, et al. *Am J Psychiatry*. 2016;173(5):499-508. Nunes EV, et al. *Arch Gen Psychiatry*. 1998;55(2):153-160.



Sertraline and Naltrexone for Depressed Alcoholics

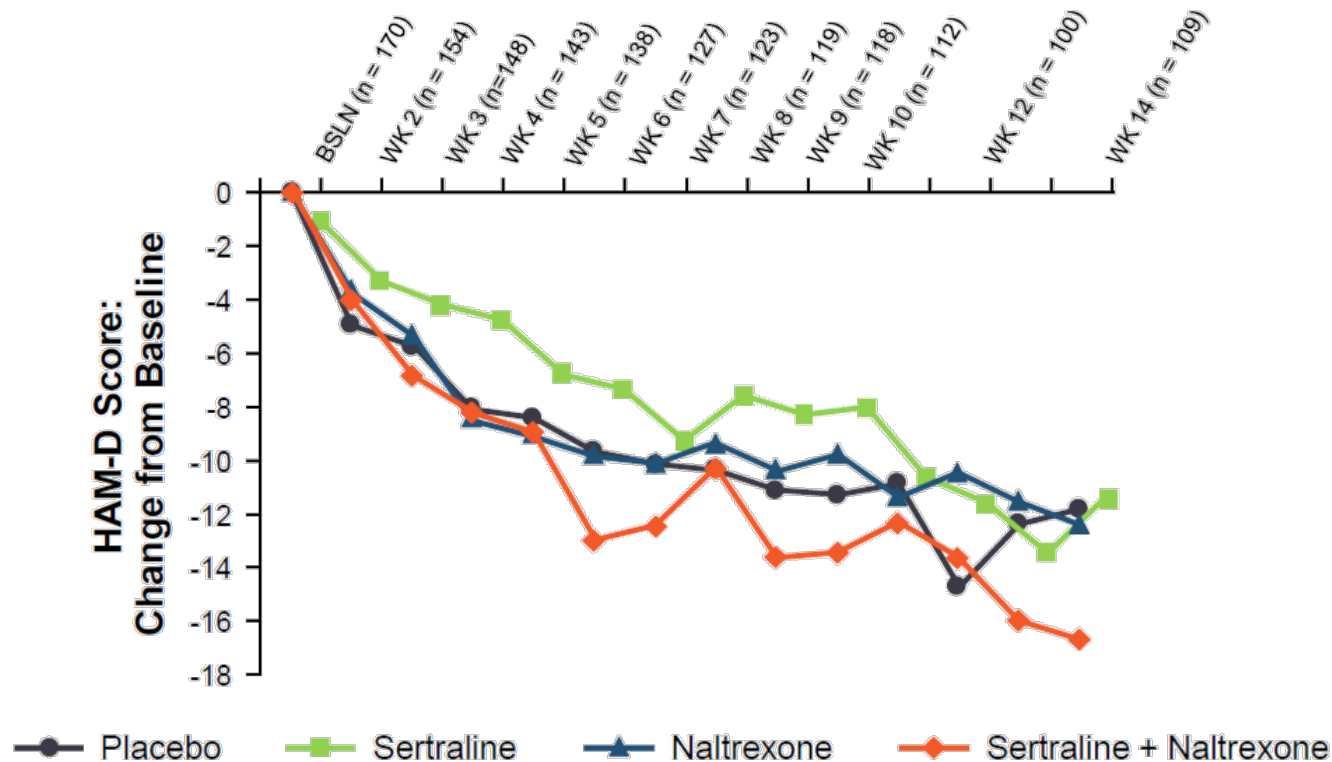
First-Drink Day and Heavy-Drinking Day



Pettinati HM, et al. *Am J Psychiatry*. 2010;167(6):668-675.

Sertraline and Naltrexone for Depressed Alcoholics

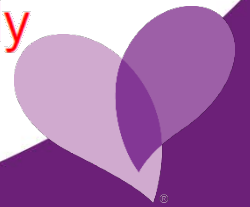
Hamilton Rating Scale for Depression



Naltrexone and Disulfiram in Patients with Alcohol Dependence and Co-occurring Axis I Psychotherapy

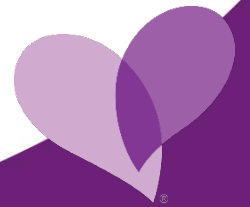
Results

- 70% reported total abstinence; 83% medication adherence
- Both active medication groups had fewer drinking days than those treated with placebo
- Disulfiram patients had less drinking compulsion than naltrexone patients
- No advantage to receiving *both* medications
- Side effects similar to those reported in non-dually diagnosed populations
- Less paranoia in active medication group vs placebo
- Naltrexone, disulfiram may be useful for motivated dually diagnosed patients



Valproate for Alcohol Dependence and Bipolar Disorder

- 24-week trial of valproate vs placebo in 59 patients receiving lithium carbonate
- Patients receiving valproate had
 - Fewer heavy-drinking days
 - Less drinking on heavy-drinking days
 - No differences in manic, depressive symptoms



Practical Takeaways

- **Intranasal naloxone** prevents opioid overdose deaths in communities
- **Depot naltrexone** has better adherence than oral naltrexone for AUD and OUD
- Partial opioid agonist **buprenorphine** has excellent safety and efficacy results with less withdrawal when stopped than methadone
 - **Long-acting depot implant available**
- **Pharmacogenetics** may be able to match AUD patients with medications such as **naltrexone**
- SUD with psychiatric illness
 - Limited data on **combination pharmacotherapies** or on **comparative effectiveness**



Managed Care Entity (MCE- CareSource, Anthem, MDWise and MHS) Buprenorphine Strategy – Implemented 12/01/17

Suspend prior authorization on preferred buprenorphine and buprenorphine/naloxone that are FDA indicated for MAT

- All MCEs to maintain the following edits:
 - Age limits of ≥ 16 years old
 - Quantity limit of 24 mg/day
 - Opioid concurrent use
- All MCEs to align buprenorphine MAT products
 - Preferred agents will be the generically available buprenorphine and buprenorphine/naloxone SL tabs for all MCEs
 - Non-preferred products will continue to be available to members through updated aligned PA criteria
 - Updated PA criteria require a trial or documented intolerance of preferred SL Tabs (similar to current brand medically necessary criteria)



Current MAT Preferred Drug List for Indiana as of 04/01/18

- **Preferred: Generic- No prior authorization required**
 - Buprenorphine tabs
 - Buprenorphine/Naloxone tabs and films
 - 24mg/day quantity limit and an age edit of 16 years for all buprenorphine products
 - Buprenorphine tabs
 - 8mg tab – allow up to 3/day
 - 2mg tab- allow up to 3/day
 - Buprenorphine/Naloxone tabs and film:
 - 12mg/3mg – allow up to 2 per day
 - 8mg/2mg- allow up to 2 per day
 - 2mg/0.5mg- allow up to 1 per day
 - 4mg/1mg- allow up to 1 per day
 - Additionally, there is a 30-day supply limit for each fill.
- **Non-Preferred: All Brand Name products.**
 - May submit a prior authorization with required documentation.
- **Vivitrol – Naltrexone Microspheres**
 - Specialty Medication; No prior authorization required



How CareSource Members Can Get Help

CareSource members can see a mental health professional or can go to any provider in the CareSource network. They don't need a doctor's referral or prior approval for most outpatient treatment. CareSource can help members find a provider close to them, by calling Member Services at **1-844-607-2829** (TTY: 1-800-743-3333 or 711).



How CareSource Members Can Get Help

If the member currently has a Care Manager, they can give him or her a call. A Care Manager can help members find the resources needed to be healthy. If a member does not have a Care Manager, they can request one. Call one of our qualified registered nurses at CareSource24® **1-844-206-5947** (TTY: 1-800-743-333 or 711).



Need Addiction Help?

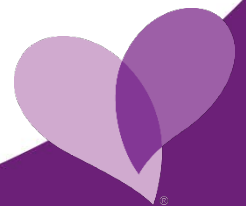
- <https://www.caresource.com/mental-health-addiction-services/>
 - 1-833-OPIOIDS
 - What to Say on the Call
 - What to Expect
 - What is Treatment
 - And More...
- <https://www.in.gov/fssa/addiction/>
 - Find Addiction Treatment in Indiana
 - Learn About Treatment Options
 - Know the O Facts
- <https://www.in.gov/recovery/know-the-o/>



How to Find a Behavioral Health Provider for CareSource Members

The CareSource Find a Doctor/Provider tool helps find a variety of health professionals including marriage and family therapists, substance use counselors, social workers, community mental health centers and more.

<https://www.caresource.com/providers/indiana/>





QUESTIONS?

RR2022-IN-P-0425a

Issue Date: 12/9/2022

OMPP Approved: 12/4/2022


CareSource™