Emerging Trends and Medical Responses in Substance Use Disorders

Andrea G. Barthwell, MD, DFASAM

WISAM Annual Conference

September 29, 2016 – September 30, 2016

Disclosures

- Braeburn Pharmaceuticals
- Encounter Medical Group, P.C.
- The Manor
- Millennium Health
- Treatment Partners LLC
- Two Dreams
- U. S. DOJ

Presentation Objectives

- Describe therapeutic approaches to contemporary views of substance use disorders
- Evaluate the impact of existing responses on outcomes in substance use disorders
- Describe the emerging treatments for and treatment targets in substance use disorders

Outline

- Current understanding of substance use disorders
- Current treatment approaches
- Existing responses
  - Psycho-social therapies
  - Medication therapies
  - Combination therapies
- Emerging Treatments
  - Facilitate abstinence/ address sensitization
  - Relapse prevention/ address reinstatement

Understanding Substance Use Disorders

- Initiation
- Maintenance
- Interruption- therapies
- Reinstatement and/or relapse

The Neural Basis of Addiction

- Early stages-dopamine
  - Release is triggered by reinforcing substances (and/or stress)
  - Critical for acute reward
  - Critical for initiation of substance use disorder

1: Am J Psychiatry. 2005 Aug;162(8):1403-13. The neural basis of addiction: a pathology of motivation and choice. Kalivas PW, Volkow ND

Pathology of Motivation and Choice

- Primary behavioral pathology in drug dependence is overpowering motivational strength and decreased ability to control desire to obtain drugs
- Understanding cellular and circuitry underpinnings of addiction predict novel pharmacotherapeutic targets

Dopamine

- Dopamine release is triggered by reinforcing substances and/or stress
  - Critical for acute reward and initiation of disease state
- End-stage dependence results primarily from cellular adaptations in anterior cingulate and orbitofrontal glutamatergic projections to NA
- Pathophysiological plasticity in excitatory transmission reduces the capacity of the prefrontal cortex to initiate behaviors in response to biological rewards (loss of salience)

Executive Controls

- Executive controls are LOST
  - Drug seeking more salient that other drives
  - Prefrontal cortex is hyperresponsive to stimuli predicting drug availability (craving is opportunistic disease)
- Cellular adaptations in prefrontal glutamatergic innervation of the accumbens promote compulsive character of drug seeking
  - Decreased value of natural rewards (salience)
  - Diminished cognitive control (choice)
  - Enhanced glutamatergic drive in response to drug associated stimuli (cues trigger behavior)

Translation

- Dopamine release feels good and changes the brain. Because it feels good, the actions that we take to stimulate its release are repeated. While dopamine creates changes in many areas of the brain, changes in certain areas are common to all types of substance use and lead to disorders.
- In the end, changes in function that support drug use are more powerful than the drive to do almost anything else.

Disease Progression

- Overpowering motivational strength which reduces or eliminates the ability to control the desire, leaving us with a…
- Pathology of motivation and choice, and
- Disease of learning and memory

Stress and Cues

- Stress
  - Mediated by CRF (corticotrophin releasing factor)
- Cues/Triggers
  - Impact neural circuitry in drug seeking
  - Impact the final common pathway

Stress, Cues, and Priming

- Adverse life events can increase impulsivity
  - Conflicts, incarceration, homelessness, etc.
- Reversal learning problems are in evidence
  - Addicts don't know they are doing it wrong, perseverate
  - "Doing the same thing over and over expecting different results."
- Findings
  - Inferior frontal gyrus gray matter deficits worsen conflicts in motivation and choice, impulse control
  - Drugs damage frontal lobe inhibitory systems

Stress, Cues, and Priming

- Increase drug seeking
- Increase impulsivity
- Medications and other treatments may affect these mechanisms
  - Modulate dopamine system to yield therapeutic effects
  - Dampen the power of stress to create response
    - Change perception of stress
    - Block CRF

Sensitization v. Reinstatement (Animal Models)

- Non-contingent / experimenter administered treatments may not predict the neuroplasticity associated with contingent / self-administered drug administration
- Differentiation of findings are being elucidated

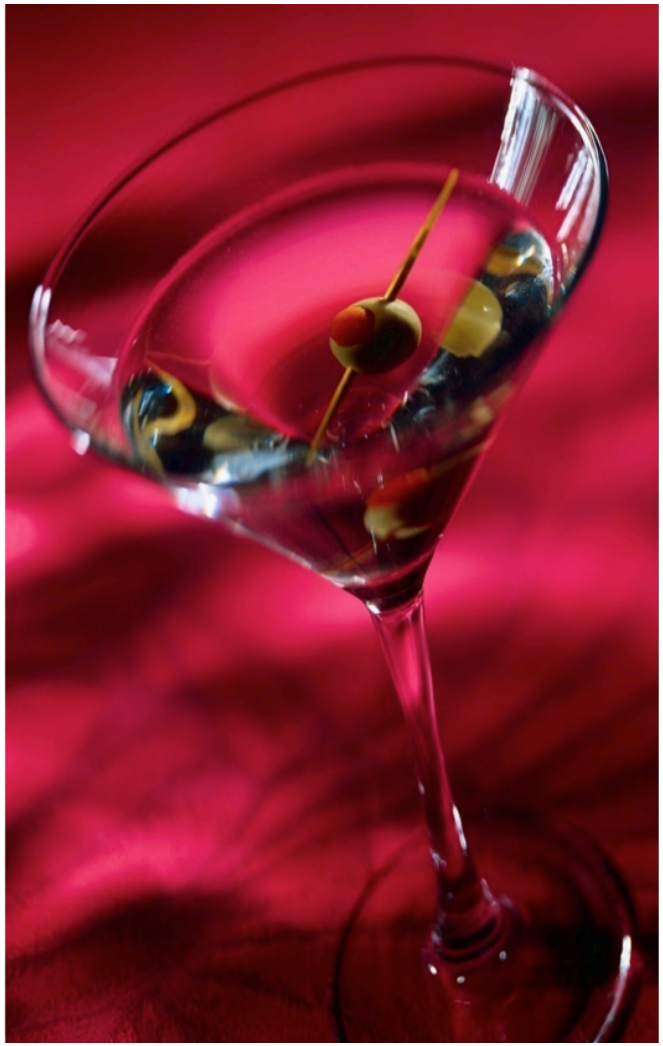
Sensitization

- Enhanced response to repeated exposure
  - Cross- sensitization described
  - Initiation- immediate neural events (VTA)
    - Environment important
  - Expression- long-term consequences of exposure (NA)
  - Lesion studies implicate medial prefrontal cortex in behavioral sensitization
  - Results in behaviors, conditioned place preference, drug reinforcement (escalating time and amount)

Neurotransmitters: Sensitization

- Dopamine- changes in release
- Dopamine Receptors- binding plays key role, reduced sensitivity
- Glutamate-generally, increases in levels
- CRF- released in VTA in response to stress potentiates NMDA receptor mediated transmission and communication

Reinstatement and Relapse



- Dependence and withdrawal cannot explain the characteristic persistence of relapse risk long after detoxification
- Incentive motivation hypothesis posits that repeated use increases salience of drugs and cues

Reinstatement and Relapse

- Reinstatement of drug self-administration after drug cessation is more potently motivated by re-exposure to the drug than by withdrawal
- This is a “cue” v. “state” issue

Hyman SE: Addiction: A Disease of Learning and Memory. Am J Psychiatry 162:1414-1422, August 2005.
http://ajp.psychiatryonline.org/cgi/content/full/162/8/1414

Reinstatement and Relapse

- Availability predicting stimuli (people, places, paraphernalia) precipitates relapse after detoxification more often than bodily feelings associated with prior drug use (euphoric recall or detox) and stress

Reinstatement

- Reinstatement behavior models relapse
  - Between session v. within session v. in-between session
  - Drug priming leads to resumption of use
  - Shared circuit for reinstatement exists: stress, cues, and context affect via additional inputs
- Neuro-circuitry of reinstatement involves measurement of Fructo-oligosaccharides (Fos) synthesis in the VTA, caudate nucleus, central nucleus of the amygdala and other areas
- Most studies of cocaine, heroin studies newer

Reinstatement Translation

- Animals are given drug in response to lever pressing
- Drug is taken away
- Lever pressing extinguishes
- Drug is reintroduced, priming involved
- Lever pressing returns at high intensity

Relapse and Priming

- Using a drug once or in small amounts can prime the response to drugs and lead to relapse
- “One drink is too many and a thousand is not enough…”
- Chemicals can selectively block cue-induced, but not stress-induced, priming
- Anti-priming medications could keep a “lapse” from becoming a relapse
- Naltrexone has anti-priming features

Neurotransmitters: Reinstatement

- Dopamine- mixed results
- Glutamate- primarily involves enhanced transmission from dorsal areas to NA, activate AMPA receptor
  - Changes can be blocked

Relationships between Sensitization and Relapse

- Basal glutamate levels in NA are reduced
- Re-exposure to drug increases glutamate in this region
  - Increases act on AMPS to promote behavioral responses
- Both contingent and non-contingent drug administration induce neurotransmitters
- In contrast, DA responses do not mirror
  - DA important in initiation rather than sensitization
- Glutamate circuits key to linking sensitization to relapse

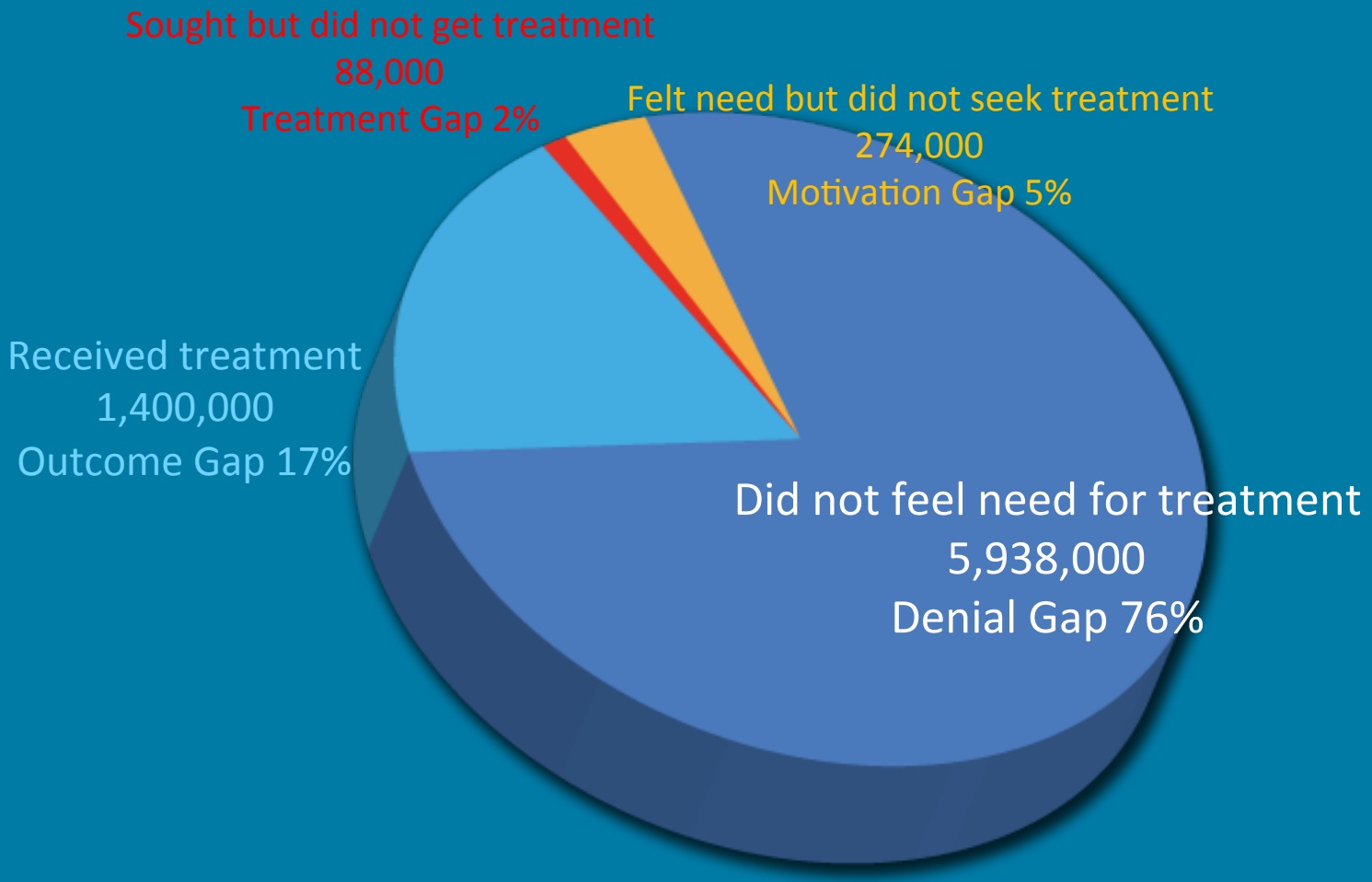
Therapeutic Implications

- Imaging research in agreement with animal research
- Tremendous overlap in systems
- Basal glutamate in NA after cocaine self-administration
  - Restored levels reduce relapse to drug-seeking in animals and humans
  - Other validation studies underway

Incubation of Craving

- Time-dependent increases in drug seeking after withdrawal
- But may work only to a certain point
  - In molecular and neuroanatomical studies, amygdala ERK (extracellular signal-regulated kinase) and glutamate are involved in the incubation of cocaine craving
- Cue-induced craving increases over time in abstinence
- “The disease progresses even when you are not using.”

Treatment Gap



Improve Treatment: Basis of Strategy

- Create desire for those who do not know they have a problem (76%)
- Harness desire for those who know but do not seek services (5%)
- Treat use for those who seek but are unable to receive treatment (2%)
- Support recovery for those who enter treatment (17%)
  - 17% enter; 25-31 % leave improved; 50% are abstinent at one year

Tools for Treatment Improvement

- Abstinence- understand and practice universal abstinence
- Medications- for primary CD and co-morbid conditions
- Peer Support- to create cohesion and identification; support the ability to identify, own, and express ones feelings
- Professional Guidance- bond, practice surrender, and gain insight
- Exercise- for restoration and protection
- Diet- for restoration and protection
- Ritual- wide range of activities and schedule to support change and normalize circadian and Ultradian rhythms

Can we strengthen these systems with medications and/or therapies?

Specific Examples of Drug Development Considerations and Targets

Non-Medication Treatments

- Many therapies are effective, helpful
- Need to target the non-rational survival brain, not just the cortex

Potential Treatments for Brain Recovery

- Exposure and Response Prevention/ Blocking
  - Vaccines
  - Receptor occupancy- agonist, antagonist, mixed
- Psychosocial Therapies:
  - 12-Step Facilitation Therapy
  - Cognitive-Behavioral Therapy
  - Motivational Enhancement Therapy
  - Others
- Medications
  - Restorative and protective

Psychosocial Therapies

- Support abstinence
  - Tones down the drive of the pleasure-reward pathway
- Retrains the brain
  - Provides healthier structure and ritual
  - Offers specific suggestions on a new way of living and behaving
- Retools the emotional brain
  - Modulates emotions
  - Works through connections with other people
  - Provides safe structure for emotional expression

A Special Note on 12 Step Recovery

- Offers a range of interventions
  - Simple (slogans)
  - Complicated (in-depth Step work)
  - For different stages of brain healing and recovery
- Builds responsibility and better judgment
  - Provides a blueprint for living sober (Steps)
  - Exercises the prefrontal cortex in working through problems
  - Provides constant reminders of needed behavior changes, and reinforcement of changes
- Is (almost) always available

Combination Treatments

- Medications in combination with counseling and psychotherapies may be the best addiction treatment we have at this point
  - Treat the survival/pleasure system abnormalities with medications to facilitate abstinence and prevent relapse
  - Treat the cortical decision-making system with counseling and therapies
- Whenever possible, provide access to ritual and soothing balms

Medication and Treatment Targets: Sensitization

- Block initiation (blunt or reduce using behaviors)
  - Address pre-morbid state
  - Manage effect of environment (reduce power of stress, cues with increased ability to identify, own, and express feelings)
- Interrupt expression (undergird decision to stop)
  - Manage long term consequences/complications of exposure
    - Restore and support homeostasis using detoxification, maintenance, or blockade
    - Reduce or eliminate inducements to use (treat co-morbidity)
  - Re-establish free will (impulse control)
  - Reduce salience of conditioned place preference (blunt response to cues, context)
  - Block drug reinforcement (substitute healthy rituals)

Medication and Treatment Targets: Reinstatement

- Suppress priming (block effect, avoid first use)
- Address secondary facilitators (blocks facilitators)
  - Manage stress
  - Stop or avert cue induced use
  - Reduce salience of context
- Calibrate Neurotransmitters (creates stability)
  - Manage basal amount and receptor sensitivity
- Balance state (encourages impulse control)

N-Acetylcysteine Postsynaptic Effect Limits Efficacy

- NAC pushes intracellular glial cell glutamate into extracellular space to increase the depleted reward system neurotransmitter
- Depletion promotes response to cues and inability to change despite consequences
- NAC in NA: low dose stimulates presynaptic receptors on neurons; higher doses add postsynaptic stimulation
  - Pre-S stimulation dampens neuronal activity and reduces cue response in rats
  - Post-S intensifies activity and offsets response to cues
  - Suggest that paired Pre-S stim with Post-S inhibition may be most effective

Kupchik, YM, Moussawi K, Tang XC, Wang X, Kalivas BC, Kolokithas R, Ogburn KB, Kalivas PW. The effect of N-acetylcysteine in the nucleus accumbens on neurotransmission and relapse to cocaine. Biological Psychiatry 71(11):978–986, 2012.

Methylphenidate for Comorbid Cocaine Abuse, ADHD

- Methylphenidate (MPH) is CNS stimulant used to treat ADHD and narcolepsy
  - Usual initial dose 10 mg BID or TID; maintenance dose 60 mg QD
- Sustained release methylphenidate (SR-MPH) in 40-60 mg/day reduced ratings on scales of “feel high” and “good drug effect” (drug liking) of cocaine in a sub set of 7 individuals with ADHD from a study of 14 non-treatment seeking volunteers
- Increased CV effects of cocaine, not to clinically significant levels
- Parallel concept of methadone- slow/long acting stimulant reduces salience of and craving for cocaine in subset of users
- Did not evaluate for effects on ADHD

Drug and Alcohol Dependence 82(2):158-167, 2006

Medication Reduces Rats' Return to Methamphetamine Seeking

- AV411 (ibudilast) is approved and used in Asia to treat asthma and post-stroke dizziness, clinical trials in Europe for MS, US for neurological conditions
- MOA at glial cells, rather than neurons, therefore, different SE profile
- Early studies suggest it may relieve pain with low abuse potential, reduces rewards associated with morphine
- Tests of relapse prevention underway: contingent methamphetamine administering rats, extinguished reward, reduced rates of lever pressing observed
  - Control- apply stress or prime with methamphetamine high rates of pressing resumed
  - Test subjects- administer AV411 when drug access denied drug seeking was reduced in both conditions

European Journal of Pharmacology 637(1-3):102–108, 2010.

Brain Responds to Marijuana Cues in Familiar Manner

- Cue triggered craving to marijuana creates brain waves similar to those from other drugs in similar areas
- F-MRI 3 days post MJ use while handling pipe evoked craving > pencil in N=38 regular users
- VTA, NA, prefrontal cortex similar to those with alcohol, nicotine, and cocaine
- Extent of cue-induced activity correlated with problem set in subject

Proceedings of the National Academy of Sciences 106(31):13016–13021, 2009.

Dr. Kevin M. Gray Q&A: A Potential Medication for Marijuana Dependence

- N-acetylcysteine (NAC) as adjunct to behavioral therapy (contingency management weekly) increases likelihood of submitting cannabis negative urine samples
- OTC nutritional supplement protects liver in acetaminophen OD, mucous clearing. Not FDA approved for this indication

https://www.drugabuse.gov/news-events/nida-notes/2014/10/dr-kevin-m-gray-q-potential-medication-marijuana-dependence

Gabapentin Tested to Treat Marijuana Dependence

- N=50 tx seeking adults, 12 week trial, DSM-IV dx cannabis dependence, weekly counseling with ME and CBT and gabapentin 25 mg or placebo
- 1/3 completed trial, mean time 6.4 weeks,
- Gabapentin v. placebo
  - 8 gm MJ v. 6 gm at outset
  - Days per week lower in gabapentin group, fewer c/o sleep disturbance, craving, depression
- Study significant as it employs NIDA strategy of testing FDA approved medications in clinical trials to fast track added indications

Mason, B.J., et al. A proof-of-concept randomized controlled study of gabapentin: Effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults. Neuropsychopharmacology 37(7):1689-1698, 2012.

Dual Regimen Aims to Shorten Medication-Assisted Therapy

- Exposure to buprenorphine in young people with still developing brain creates concerns but often requires repeated and extended exposure
- Dual TX of glutamate antagonist (with indirect mu effects) and buprenorphine/nx stabilization/taper over 9 weeks led to greater abstinence (measured for one month) in dual tx group > mono-tx
- N=80, ages 18-25 years
- Memantine 30 mg, 15 mg, or placebo week 2-13, Bp/Nx stable 8 weeks, taper week 9
- Post taper daily use/week varied: 30 (0), 15 (3-4), 0 (3-4) with milder withdrawal at higher dose
- High drop out rates noted, needs further study

Gonzalez, G.; DiGirolamo, G.; Romero-Gonzalez, M. et al. Memantine improves buprenorphine/naloxone treatment for opioid dependent young adults. Drug and Alcohol Dependence 156:243-253, 2015.

Study Points to Individualized Therapy for Opioid Addiction

- START trial shows opioid medication without injection of heroin stayed in tx longer and had better outcomes than those addicted to heroin or injecting
- N= 1,289, f/u 24 weeks; medication v. heroin users at end
  - 70 v. 56% completed
  - 78 v. 54% abstinent x 30 days
  - Injectors : non-injectors drop out rates 44%: 34%
- N=731 completed full course
  - Bp/Nx v methadone – 60% more likely to drop out
  - Agitation associated with Bp/Nx not understood

Potter, J.S.; Marino, E.N.; Hillhouse, M.P., et al. Buprenorphine/naloxone and methadone maintenance treatment outcomes for opioid analgesic, heroin, and combined users: findings from Starting Treatment with Agonist Replacement Therapies (START). Journal of Studies on Alcohol and Drugs 74(4):605-613, 2013.

Long-Term Follow-Up of MAT for Addiction to Pain Relievers Yields "Cause for Optimism"

- Prescription Opioid Addiction Treatment Study (POATS) two phase study
  - 653 Bp/Nx 2 week stabilization, 2 week taper, 2 month f/u
  - If reverted to use- 12 week stabilization, 4 week taper, 2 month f/u
- 50% abstinent at 18 months, 61 % at 3.5 years, <10% dependent
- Bp/Nx predicted abstinence; heroin use history lowered odds of abstinence
- Taper drop-off: 49 to 8% 2 months after tape
  - Success with initial short taper predicted overall success
  - Higher initial pain scores predicted prescription opioid dependence at 18 months (contravenes belief that pain is not a predictor of addiction tx outcome)

Potter, J.S.; Dreifuss, J.A.; Marino E.N. et al. The multisite prescription opioid addiction treatment study: 18-month outcomes. Journal of Substance Abuse Treatment (48)1:62-69, 2015. Abstract

Weiss, R.D.; Potter, J.S.; Griffin, M.L. et al. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. Drug and Alcohol Dependence 150:112-119, 2015.

ED-Initiated Buprenorphine Outperforms Referral or SBIRT for ED Patients with Opioid Addiction

- ED initiation of Bp/Nx capitalizes on opportunity
- 71,000 screened, 329 eligible, 34% in ED for help with opioid dependence, 8.8 with OD. 75% used heroin, remainder used prescription opioids. Co-occurring use of tobacco, cocaine, MJ and sedatives high
- 3 groups: tx referral (37%), MI and facilitated tx referral (45%), add Bp/Nx x 3 days (78%)
- Use: 2.3 days v. 2.4 days v. 0.9 days
- Costly in patient admission: 37 v. 35 v. 11%

D'Onofrio, G.; O'Connor, P.G.; Pantalon, M.V. et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: A randomized clinical trial. The Journal of the American Medical Association 313(16): 1636-1644, 2015.

Varenicline (Chantix®)

- **Name:** Varenicline (Chantix®)
- **Approved Indications:** Smoking cessation
- **Dose:** Chantix comes as a white tablet (0.5 mg) and a blue tablet (1 mg). You start with the white tablet and then typically move to the blue tablet
  - Days 1-3: Take 1 white tablet each day
  - Days 4-7: Take 1 white tablet in the morning and 1 in the evening
  - Days 8-End of treatment: Take 1 blue tablet in the morning and 1 in the evening
- **Evidence for Use:** Varenicline was found in a recent 200-patient clinical trial conducted by NIAAA's Clinical investigations Group (NCIG) to reduce alcohol consumption and craving among people who are alcohol-dependent. Varenicline may work by partially stimulating receptors for nicotinic acetylcholine, a promising molecular target implicated in both nicotine and alcohol use disorders.

https://www.niaaa.nih.gov/news-events/news-releases/anti-smoking-medication-alcohol-dependence

Gabapentin

- **Name:** Gabapentin
- **Approved Indications:** Generic anticonvulsant used to treat pain conditions and epilepsy
- **Dose:** 900 mg, or 1800 mg/d
- **Evidence for Use:** Gabapentin has shown promise as an effective treatment for alcohol dependence, based on the results of a recent 150-patient clinical trial of the medication. The study found that alcohol dependent patients using gabapentin were more likely to stop drinking or refrain from heavy drinking than those taking placebo.

https://www.niaaa.nih.gov/news-events/news-releases/gabapentin-alcohol-dependence

Topiramate

- **Name:** Topiramate
- **Approved Indications:** Generic anticonvulsant used to treat seizures and prevent migraine headaches, targets the neurotransmitters GABA and glutamate.
- **Dose:** Up to 200 mg/day
- **Evidence for Use:** Clinical trials conducted by Johnson, et al in 2007 has shown that it appears to be effective in reducing drinking in alcohol-dependent patients.

https://www.niaaa.nih.gov/news-events/news-releases/statement-national-institute-alcohol-abuse-and-alcoholism-topiramate

Ondanestron

- **Name:** Ondansetron
- **Approved Indications:** Used to treat nausea and vomiting
- **Dose:** 4 microg/kg b.i.d. for cravings
- **Evidence for Use:** Ondansetron has shown promise in reducing drinking in patients who developed alcohol dependence early in life. In addition, a recent 300-patient clinical trial has shown that ondansetron works better in individuals who possess specific combinations of genes that regulate the function and binding of serotonin, a brain chemical affected by the treatment. Ondansetron is thought to work by blocking serotonin-3 receptors.

https://www.niaaa.nih.gov/news-events/news-releases/gene-combinations-alcoholism-medication

Nalmefene (Selincro®)

- **Name:** Nalmefene (Selincro®)
- **Approved Indications:** Used to treat acute opioid overdose and in the management of alcohol dependence
- **Dose:** 1 tablet per day
- **Evidence for Use:** Nalmefene, an opioid receptor antagonist, was recently approved by European Medications Agency (the FDA-equivalent in Europe) for use in the European Union to treat alcohol dependence. In two main studies involving 1,322 men and women with alcohol dependence, Selincro® was shown to reduce the number of heavy drinking days and daily alcohol consumption.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002583/human_med_001620.jsp&mid=WC0b01ac058001d124

Baclofen

- **Name:** Baclofen
- **Approved Indications:** $GABA_B$ agonist medication used to treat muscle spasms
- **Dose:** 30-270 mg/day
- **Evidence for Use:** Clinical trials have indicated that high-dose Baclofen may have beneficial effects in encouraging abstinence, especially in alcoholic patients with cirrhosis.

http://journal.frontiersin.org/article/10.3389/fpsyt.2014.00143/full

Thank You

Questions?