Disclosures

- AppleTree Partners
- Braeburn Pharmaceuticals
- Encounter Medical Group, P.C.
- Ideal Option
- Treatment Management Behavioral Health
- Treatment Partners LLC
- Two Dreams
- U. S. DOJ
Presentation Objectives

- Describe scientific understanding of substance use disorders (SUD), particularly Opioid Use Disorders (OUD)
- Apply understanding of SUD to predicting therapeutic approaches, including medications, to treat SUD, and OUD
- Evaluate the impact of existing responses on outcomes in substance use disorders, particularly OUD
- Demonstrate knowledge of the emerging treatments for, and treatment targets in, substance use disorders, particularly OUD
- Evaluate one’s bias for or against medication's in treating OUD
Outline

- Review current understanding of neuroscience underlying substance use disorders as understood through the American Society of Addiction Medicine (ASAM) definition of SUD
- Outline current treatment approaches to SUD based upon the neuroscience of addiction
- List existing responses to SUD including:
  - Psycho-social therapies
  - Medication therapies
  - Combination therapies
- Explore the basis of selection bias in developing and promoting a therapeutic response to SUD from a review of societal/cultural vs. individual considerations
ASAM Definition of Addiction

- Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

- Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.
Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry.

- **Primary** - greater underlying psychopathology not necessary
- **Chronic** - persistent, long-standing, long term
- **Disease** - interruption or cessation or disorder of bodily functions, system, or organs
  - 2/3: 1- recognizable etiology, 2- sign and symptoms, and 3- consistent anatomical alterations
Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry

- Brain reward- a group of neural structures responsible for incentive salience (motivation, wanting, desire, craving, etc.), associative learning (positive reinforcement and classical conditioning), and positive emotions (pleasure at the core- joy, euphoria, ecstasy)
- Reward is responsible for attraction and motivation to approach and consume (not avoid!)
Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry

- Survival depends upon maximizing contact with beneficial stimuli and minimizing contact with harmful stuff
- Reward evolved to help increase adaptive fitness of species
Kinds of Rewards: The Motivation

- Rewards produce association between reward and behavior (try it, you’ll like it)
- Rewards affect decision making and induce approach behavior (overcome mom’s warnings)
- Rewards elicit positive emotions, pleasure (ding, ding, ding!!!)
- Rewards are basis of wanting and liking
  - Wanting- appetitive desire, approach behaviors, preparatory behaviors, instrumental behaviors, anticipatory behaviors, and seeking
  - Liking- consuming and taking
Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry

- Reward is located in the cortico-basal ganglia-thalamo-cortical loop
- Involve the neurotransmitters Glutamate, GABA, and dopamine
- Other areas for neuroscientists
- Basal ganglia drives activity
- Dopamine pathways set up and are necessary for the reward or initiation
Types of Rewards

- **Primary rewards** - facilitate the survival of one’s self and offspring
  - Homeostatic (food, water) and reproductive (sexual and parental investment) rewards
- **Intrinsic rewards** - are inherently pleasurable (Just do it!)
- **Extrinsic rewards** - not inherently, but learned pleasure association
  - Money
  - Watching sports
  - May provide pleasure after conditioning (lottery ticket)
Dozens of sites in the brain maintain intracranial self-stimulation; response habits are similar to those established by primary rewards

- Stimulation here *both* rewarding and motivation inducing- strong, not responsive to satiation, compulsive, competes with and reduces salience of life sustaining behaviors

- Robust reward sensation due to relatively direct activation
  - Natural stimuli generally travel here through PNS
  - Associated with unmet needs or desires
  - Deprivation state drives instinctual, motivated behaviors
  - Drive reduced when state changes
Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations.

- AIW
- BM
- EM
- TAR
- RP
- RE
This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

- Pathological-
  - altered or caused by disease
  - diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and
  - being such to a degree that it is extreme, excessive, or markedly abnormal
Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional response.

- At initiation, dopamine release triggered by reinforcing substances is critical for acute reward
- Maintenance results 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)

Where to Strengthen Systems

- At initiation
- During maintenance
- To interrupt
  - Terry Rustin says, “quit and stay quit”
- To block or blunt reinstatement and/or relapse
- 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)
Executive Controls

- Executive controls are LOST
  - Drug seeking more salient than other drives
  - Prefrontal cortex is hyperresponsive to stimuli predicting drug availability (craving is opportunistic disease)
Dopamine release feels good and changes the brain. Because it feels good the things we do to get it released are repeated. While dopamine creates changes in many areas of the brain, change in certain areas are common to all types of substance use, leading to disorders.

In the end, changes in function that support drug use are more powerful than the drive to do almost anything else.
Pathology of Motivation and Choice

- Primary behavioral pathology in drug dependence is overpowering motivational strength to approach and consume (use) and decreased ability to control desire to obtain drugs
- Reduced capacity of prefrontal cortex to initiate behaviors in response to biological rewards- survive
  -and-
- Reduced capacity of prefrontal cortex to provide executive control over drug seeking- avoid danger
- Prefrontal cortex is hyperresponsive to stimuli predicting drug availability
Like other chronic diseases, addiction often involves cycles of relapse and remission.

- Relapse is NOT necessary
- Relapse only occurs if, as result of treatment, these conditions met:
  - Acknowledge addiction
  - Commit to recovery
  - Reduce, or eliminate inducements to use
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
Concepts of Stress and Cues

- Adverse life events
  - Increase impulsivity and increase “state” of deficit or need
  - Conflicts, incarceration, homelessness, etc.
- Reversal learning problems
  - Perseverate: “Doing the same thing over and over expecting different results.”
- Research findings support our observations
  - Inferior frontal gyrus gray matter deficits worsen conflicts in motivation and choice, impulse control
  - Drugs damage frontal lobe inhibitory systems
Stress and Cues

- 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 (beta-blockers, benzodiazepines, anti-psychotics, etc.)
    - Block CRF release in response to stress
Concept of Sensitization

- Non-associative learning process, with repeated exposure there is progressive amplification of the reaction to the stimulus; more sensitive to the stimulus as time passes
- Response is enhanced to a whole class of stimuli, not just the one that is repeated
- In *addiction* there is increased effect of drug following repeated doses, opposite of tolerance
- May contribute to psychological disorders such as PTSD, panic/anxiety, mood disorders
- Findings associated with a range of medical implications from pain to seizures, Kandel awarded Noble Prize for discovery
Sensitization Research

- Initiation- in VTA, with dopamine
  - 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)
- Environment and other cues or stimuli associated with drug taking may \textit{increase craving}
- Craving sets off cascade
Neurotransmitters implicated in 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, loss of feedback loop
  - Perceived anxiety also promotes using
Dependence and withdrawal cannot explain the characteristic persistence of relapse risk long after detoxification.

- People are not using just to avoid withdrawal.

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.

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.
  - NB: Gender difference
- Recall role of cues to attract, create approach
Reinstatement behavior models relapse

- Drug priming (or electrical stimuli in lab animal) 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 are studies of cocaine, heroin studies newer
Practical Reinstatement

- 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, or medications, can selectively block cue-induced, but not stress-induced, priming
- Anti-priming medications are hoped to keep a “lapse” from becoming a relapse
- Naltrexone has anti-priming features
Basal glutamate levels in NA are reduced
Re-exposure to drug increases glutamate in this region
Both contingent and non-contingent drug administration induce neurotransmitters
In contrast, DA responses do not mirror these findings
   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
- 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.”
ASAM Unpacked VI

Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

- Stop using
- Change everything about yourself
Treatment Gap

- Did not feel need for treatment
  - 5,938,000
  - Denial Gap 76%

- Sought but did not get treatment
  - 88,000
  - Treatment Gap 2%

- Received treatment
  - 1,400,000
  - Outcome Gap 17%

- Felt need but did not seek treatment
  - 274,000
  - Motivation Gap 5%
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
- Matter of OUTCOMES, not THRUPUTS
Tools for Treatment Improvement

- **Abstinence**: understand and practice universal abstinence, avoid priming
- **Medications**: for primary CD and co-morbid conditions
- **Peer Support**: to create cohesion and identification; support the ability to identify, own, and express one's 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
What is Recovery?

Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional response.

- A list of characteristics that are endorsed by > 90% of a group of 9,341 responders in long term recovery who said that these “Elements” belonged in a definition of recovery.
  - Authenticity
  - Emotional competence
  - Healthy Relationships
  - Right sizing of ego and spirituality
  - Attention to neuroadaptation
How Do You Get from Addiction to Recovery?

- Develop Authenticity
- Become emotionally competent
- Gain healthy relationships
- Practice spirituality and ego awareness
- Address neuroadaptation
- Heal developmental trauma (not listed but my addition)
What are the Measures of Authenticity?

- Guardedness -> vulnerability
- Untruthfulness -> honesty
- Cute, angry, demanding, “private,” -> real, benign, giving and open
- Avoiding feelings -> Open and vulnerable
- Applicable Step work
  - 6 & 7
What are the Measures of Emotional Competence?

- Guilt and shame -> self-acceptance
- Conditional love -> unconditional positive regard
- Repression of feelings -> expression of feelings
- Avoidance of feelings -> embrace of feelings as information
- Applicable Step work
  - 4, 5, 6, 7, 8, 9, 10
What are the Measures of Healthy Relationships?

- Conditional love -> unconditional positive regard
- Detached due to guilt and shame -> intimacy
- Confusion about boundaries -> Learning where I stop and you begin
- Guardedness -> vulnerability
- Intolerance of feelings -> embrace of feelings as information
- Overreacting to feelings -> regulation of feelings
- Fluid commitments -> reliability
- Applicable Step work
  - 4, 5, 6, 7, 8, 9, 10
What are the Measures of Spirituality?

- Being the highest authority -> accepting a higher authority
- Self centeredness -> concern for the welfare of others
- Indulgence in appetites -> moderation of appetites
- Win-lose behaviors -> win-win behaviors
- Applicable Step work
  - 6, 7, 10, 11, 12
What are the Measures of Neuroadaptation?

- Using -> not using
- Leave seductive people, places and things -> change people places and things
  - Go to meetings
  - Make friends in recovery
  - Avoid risky environments
  - Eat well
  - Exercise
- Applicable Step work
  - 1, 2, 3, 11, 12
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 for Co-morbidity
  - 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
Medications in combination with counseling and psychotherapies may be the best addiction treatment we have at this point.

- Treat the survival/pleasure system (reward) abnormalities with medications to facilitate abstinence, blunt response, block response, and prevent return to using (relapse?)
- Treat the cortical decision-making system with counseling and therapies, increase executive control.
- Whenever possible, provide access to ritual and soothing balms.
Medication and Treatment Targets

✴ Block initiation (blunt or reduce response, reward)
  ➢ 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

- 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)
Medication Therapy for OUD

- “Fix” the receptor
  - Repair impaired receptors (restore)
- “Fill” the receptor
  - Substitute a similar molecule (patch)
- “Block” the receptor
  - Competitive blockade; to impede, obstruct, stymie desire to use (arrest use)
Which Do You Choose?

Thank You!

Questions?