Medication Assisted Treatment (MAT)

As Part Of A Comprehensive Approach to Treatment for Opioid Use Disorder (OUD)

Addiction is not a moral failing
Substance use is not a simple matter of choice.
Addiction

- A (neurobiological), psychological and behavioral disorder characterized by loss of control, craving, continuation of use despite adverse consequences, and preoccupation with obtaining and using the drug (Tanco, 2015).
- Based in brain chemistry, predetermined by genetics, triggered by stress.

Common medications used in assisted treatment. (MAT)
- Opioid use disorder as a disease model affecting neurobiology
- How medications treat substance use disorders in relation to basic brain chemistry
- Guidelines of screening for patients with SUD
- Importance of monitoring patients with SUD
- Holistic supports to reinforce treatment.

DSM V Criteria for OUD

1. Opioids are used in larger amounts or over a longer period of time than intended.
2. Persistent desire or unsuccessful efforts to cut down or control
3. > time spent trying to obtain, or use to recover from its effects.
4. Persistent craving/desire to use
5. Recurrent use resulting in failure to fulfill major role obligations
6. Contd. use despite recurrent social/interpersonal problems caused or exacerbated by use
7. Important social, work or recreational activities given up or reduced q/t use.
8. Recurrent use in physically hazardous situations
9. Contd use despite knowledge of persistent/recurrent physical or psychological problem likely caused or exacerbated by use
10. Tolerance, the need for markedly increased amounts for desired effect or diminished effect w/ same amount
11. Withdrawal, as manifested by either active w/d or contd. use to avoid w/d
Opiate or Opioid

- Opiate are alkaloid molecules derived from opium which in turn is derived from the the poppy plant (Papaver somniferum). Examples include morphine and codeine.
- Opioid refers to all compounds which have functional properties like opiates; include not only opiates, also semi-synthetic non-alkaloids and even endogenous peptides.

Opioids generate intense brain responses:
- reward, craving, withdrawal – mediated by neurotransmitters (especially dopamine) that can potently drive behavior.
- Substances impair the function of the prefrontal cortex, the brain area responsible for cognition, affecting decision-making and judging the consequences of one’s actions. (Stanbrook, 2012)
- Over time, continued opioid-substance use causes anatomic and chemical changes in the brain.

Increase in Heroin Use

1 In 15

Among People who take Non-Medical Prescription Pain Relivers Will Try Heroin Within 10 Years
Case of Vanessa

- 33 y/o woman admitted w/ fevers, weakness, pain, parasthesias and confusion,
- Diagnosed with c spinal abscess infection requiring surgical intervention and six weeks IV antbx
- Relapsed with IV drug use three months prior, was enrolled in MMTP but felt stronger and wanted to try to get by without MAT
- Past periods of unassisted abstinence lasted only a few months
- Single mother to three year old son Amari, “I am a good mother”

What was her vulnerability?

- Loss
- Trauma
- Fear
- Isolation
- Stress
- Desperation
- Opportunity
- Exploitation

A Neuro-biologic Basis for Addiction
Brain Systems Impacted By Substances and Addiction

- Opioid System-related to **reward and attachment**, endorphins (endogenous morphine) helps us to soothe physical pain and modify emotional pain. Endorphins are at the center of mother to child bonding.

Hijacking the Brain, Louis Teresi, MD

4 brain systems impacted by substances and addiction

- Dopamine System - creates motivation, dopamine firing jump starts us and is **tied into craving**, pleasure located in the middle of the brain.

Hijacking the Brain, Louis Teresi, MD
• Self Regulation- governs our impulse control, inhibits engaging in self-destructive behavior, located in the prefrontal cortex

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• Stress System- fight or flight response avoiding threats to physical survival, cortisol and adrenaline

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STOP yourself and ask, “Is It a Stick or a Snake?”
Dr. John J. Ratey

Dopamine and pleasure center

• Activated dopamine levels in pleasure center pleasure > feelings.
• Substances produce 5 x > dopamine stimulation than common sources of sex or eating satisfying food.
• Repeated using substances for pleasure on demand causes damaging brain changes and reinforcing behavioral shifts
• Substance-use behavioral memories cause susceptibility & increased cravings to cues making intake more probable.
• Directly tied to triggers- internal cues -thoughts, unconscious emotional reactions, External cues exposure to settings where substance use typically occurs and exposure to the substance-using behaviors of others- STRESS
The Opioid Disease Process

Repeated exposure to short acting opioids leads to neuronal adaptations causing changes in the brain leading to dependence.

**Tolerance**
Physiological state from regular use requiring increased dose to produce same effect as reduced effect is observed from a constant dose.

**Physical Dependence**
Physiological state of adaptation to substance and body cannot produce enough natural opioids to compensate requiring need for external sources of substance to feel normal.
Medication-assisted treatment of opioid dependence

Helps mediate tolerance, withdrawal, craving. Basis of specific pharmacotherapy to stabilize neuronal circuits & restore homeostasis.

• Recalibrate
• Repair
• Restore
• Lessen need.

How MAT Works

• Blocks or reduces drug’s effect - experience of drug is no longer pleasant (e.g., naltrexone/vivitrol).
• Substitutes for original substance/not as enjoyable but prevents highly unpleasant withdrawal symptoms from occurring (buprenorphine, methadone).

MAT Also:

• Allows for healthy neuro-physiological regeneration so addictive substance or activity will not be as appealing.
• Diminishes powerful cravings that cause people to resume drug use or an addictive activity, after a period of cessation.
Treatment Goals

• ↓ or eliminate use and minimize cravings.
• ↓ risks:
  – Overdose
  – IV use
  – Dependence
• Address:
  – Co-morbid conditions
  – Psychosocial outcomes
  – Somatic needs

MAT Targets Opioid Receptors
Mu: primarily in brainstem, responsible for supraspinal analgesia, resp depression, euphoria, sedation, gastric motility, and physical dependence.
Kappa: limbic system and diencephalic areas, brain stem, spinal cord results in analgesia, sedation, dependence, dysphoria and resp depression.
Delta: various locations in the brain and effects are not well studied.

Treatment Options
Full Agonists
Partial Agonists
Antagonists
What was our first line of treatment with Vanessa?

Based on her wishes
Openness to our recommendations
Her need for pain management,
Need for management of withdrawal
Mindfulness of her continued cravings
Consideration of her long term goals

Pharmacological Treatment

Methadone
- Full µ agonists with prolonged ½ life
- Once/day dosed
- 40-60 mg/d: sufficient to block withdrawal sx
- 60 – 100 mg/d: often sufficient to treat cravings for addiction and in RCT studies have shown evidence of < relapse to use.

Methadone Treatment

- FDA heavily regulated for maintenance programs
- Requires adequate dosing to block euphoria.
- Despite 95% relapse rates with treatment & counseling <10% of people with OUD accessed MMTP (this is > 30 years post initiation 1972-generally)
Maintenance Treatment

• With chronic & relapsing dependence
• Goals:
  1. Achieve a stable dose that
     ▪ Suppresses withdrawal
     ▪ ↓ craving
     ▪ Block effects of illicit opioids
  2. Help facilitate and promote rehabilitation

Treatment vs. Addiction

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Oral or SL</td>
<td>IV, IN</td>
</tr>
<tr>
<td>Onset</td>
<td>30 minutes</td>
<td>Immediate</td>
</tr>
<tr>
<td>Duration</td>
<td>24-36 hours</td>
<td>3-6 hours</td>
</tr>
<tr>
<td>Euphoria</td>
<td>Absent</td>
<td>Marked</td>
</tr>
</tbody>
</table>

Methadone Pharmacokinetics

How does the body handle the drug

• Absorption- is liposoluble detected in blood stream w/in 15 – 45 min (peak plasma about 2 to 4 hours post administration)
• Distribution- rapidly to tissues of brain, gut, kidney, liver, muscle, lung and saliva
• Binds- highly bound to plasma proteins including albumin and lipoproteins
• Long half life, large volume of distribution and long elimination phase
• Metabolized- mainly in liver also intestinal
• Excretion-renal and fecal excretion
Metabolism

By Cytochrome P450

- Inducers - accelerate and shorten duration effect, lower Serum Methadone Level, precipitate w/d symptoms
- Inhibitors - < metabolism, > SML, extend duration effects
- Genetic/environmental factors - affect enzymes, influence variation in response to methadone

Pharmacodynamics

- As full agonist increased doses increases effect
- Full agonists have no ceiling
- Inter-individual variability - can be related to genetic factors, glycoproteins, mood state, withdrawal
- Accumulation rate is slow and is variable in patients.
- Despite variability good evidence between dose and plasma concentrations w/in individual

Potential Drug interactions w/Methadone

**Inhibitors >**
- Cipro 3A4
- Biaxin 3A4
- Quitine 3D6 also effects QTc
- Canabis 3A4
- Paroxetine 3D6

**Inducers <**
- Rifampin
- St Johns Wort
- Meth Amphet 3D6

**Synergistic Effects**
- Benzdiazepines
- Other opioids
- Dextromathorphan

http://www.atforum.com
Methadone Induction

• Ensure patient meets criteria this includes has one year history of use
• Must be able to attend treatment daily
• Any allergic reactions?
• Cardiac history
• Concomitant history
• No signs of sedation

Risk of Methadone Effects on Cardiac Rhythm

QT prolongation is context dependent
• Associated with higher doses of methadone
• When administered with 3A4 inhibitors
• Administered with cessation of 3A4 inducers

Arrhythmia more r/t magnitude of change post induction
Recommendation is if there is a risk factor present do baseline and follow-up ECG's

Methadone Pain management

• Prescribed outpatient setting usually in TID dosing, must write “for pain.”
• Steady state and long half life make this an effective pain regimen.
Methadone discontinuation

Current clinical guidelines recommend patient first taper methadone to 30 mg or < for at least one week to obtain steady state then completely for two days, before switch is made to Choice number two for Vanessa.

Drug Abuse Treatment Act (DATA) of 2000

Allowed “Qualified” physicians to treat opioid dependence outside methadone facilities
1. Addiction certification from approved organization, or
2. Complete 8-hour course from approved organization
• DEA issues (free) to qualifying physicians a new DEA number (X number) to use medication for opioid dependence
• As of today, only one medication formulation is approved for this use

Buprenorphine
• Produces a ceiling effect at higher doses
• Has effects of typical opioid agonists—these effects are dose dependent up to a limit
• Binds strongly to opioid receptor and is long-acting
• Safe and effective therapy for opioid maintenance and detoxification
Buprenorphine Regulations

- Collaboration of govt, industry, medical societies led to development of buprenorphine as treatment for opioid use disorder with approval of FDA in 2002.
- Only physicians trained and certified can prescribe in outpatient settings.
- Originally only 30 patients, (now up to 100 with waiver)
- As of 2009 > 20,000 MD’s trained to prescribe buprenorphine.

Buprenorphine Safety

- No alteration of cognitive functioning
  - feel “normal”
- No organ damage
  - Early concern of hepatic toxicity unconfirmed
  - No evidence of QT prolongation
- Ceiling prevents respiratory depression, OD
  (Overdoses w/combining use with benzodiazepines)
- No clinically significant interactions with other drugs

Ratio of Buprenorphine to Naloxone in Tablet?

- Each tablet buprenorphine and naloxone in a 4:1 ratio
- Ratio was deemed optimal in clinical studies
- Preserves buprenorphine’s therapeutic effects when taken as intended sublingually
- If injected results in dysphoric effects so discourages misuse diminishes diversion potential
Buprenorphine/Naloxone

- Basic pharmacology, pharmacokinetics, and efficacy is the same as buprenorphine/subutex alone
- Partial opioid agonist; ceiling effect at higher doses
- Blocks effects of other agonists
- Binds strongly to opioid receptor, long acting

Assessment of Need for Treatment

- Confirm OUD
- Establish current use, when, what, how much
- Assess social supports
- Evaluate degree of motivation
- Identify co-morbid medical and psych history

and be sure to CHECK THE PMP!!!

MA PMP Overview

- MA Online Prescription Monitoring Program is a secure website supports safe prescribing/dispensing allows authorized account holder to view the prescription history of a patient for the past year. The Online PMP has been operational since December 2010.
- MA Prescription Monitoring Program (PMP) receives dispensing data on Schedule II - V (e.g., narcotic, stimulant, sedative) prescriptions dispensed by MA community, clinic and outpatient pharmacies as well as out-of-state mail order pharmacies that deliver to MA residents. The PMP has been in operation since 1992.
- Over 12 million prescription records reported to MA PMP in Calendar Year (CY) 2014.
Liberal Prescribing

- Americans — 4.6% of the world’s population

CONSUMING
- 80% of the global opioid supply
- 99% of the global hydrocodone supply

Pain Physician 2010: 13:401-435

The Prescription Monitoring Program

- Chapter 244 of the Acts of 2012 made enrollment in the PMP requirement for MD, dentists and pharmacists.
- 2013 all prescribers mandates to enroll including (APRN) (PA).
- The Public Health Council (PHC) passed regulations requiring the automatic enrollment of APRNs and PAs in November 2014.
- 100% MA licensed pharmacies submit PMP data including out-of-state mail orders to Massachusetts.
- Check before prescribing, very important for patients with SUD.
Buprenorphine Induction Phase

Consider is agent short or long acting opioid

- For shorter acting wait 8 to 12 hours after last use
- Longer acting agents require waiting longer 18-24 hours
- COWS 8 or >
- Then start 2, 4 or 8 mg monitor, pending response re-dose two hours later

Clinical Opiate Withdrawal Scale (COWS)

- Pulse
- GI upset
- Sweating
- Anxiety
- Tremor
- Restless
- Bone / Joint pain
- Runny nose / Tearing
- Gooseflesh skin
- Yawning

COWS Score are Based on Withdrawal Symptoms

Buprenorphine Research Outcomes

• As effective as moderate doses of methadone.

• Partial agonist effect make it mildly reinforcing, encouraging medication adherence.

• After a year of buprenorphine-plus counseling, 75% of patients retained in treatment compared to 0% in a placebo-plus-counseling condition.

Case of Michael

• 35-y/o father of two children
• Developed fever, weakness, confusion, worsened over course of three or four days.
• Admitted to MICU 10 days before being transferred to wards when ACT met him.
• Septic emboli to lungs, kidney and spleen, dx endocarditis - TX course – 6 wk IV AB.
• Worsening cardiac complication, cardiac surgery for AV repair
• Major cardiac surgery in early childhood.

• Longest period w/o opioids since 17
• Used prescription opioids prescribed after high-school football injury, (“I was hooked”)
• For past 15 years used heroin daily, IV use but for the past year injecting into an ulceration in his lower left extremity.
• Fear of W/D was too painful,
• Now for the first time in his adult life he felt hopeful he could stop.

What Medications might be recommended for treatment? AND what is patient’s preference for treatment?
Naltrexone

A competitive antagonist at the opioid receptors in the brain. It is metabolized in the liver to the opioid antagonist 6-B-Naltrexol.

Phase 3 clinical trials showed consistent pattern of clinical efficacy for maintaining abstinence and reducing cravings for opioids while showing good safety and tolerability.

Approved by the FDA for prevention of opioid use disorder following detoxification.

Naltrexone comes in tablet form, usual dose is 50 mg daily and should not be given for 7 to 10 days after last use of opioids.

Be prepared to manage precipitated withdrawal while taking steps to ensure this is unlikely.

Vivitrol

Initiation considerations for opioid use disorder

- Absorption is gradual
- Injectable dose vivitrol 380 mg IM 30 days
- Administered by experienced professional.
- Kits refrigerated, should be brought to room temp before injection

Patient Monitoring

- Adherence to treatment
- Ability to maintain abstinence
- Levels of craving
- Overall health status
- Continued use of illicit drugs
- Participation supportive therapies.
- Laboratory testing
- Prescription monitoring program.
- Collateral information from family/providers
- Patient and provider concerns about relapse and motivational guidance toward strategies of relapse prevention.
Psychosocial Treatment

- Specialized programs
- Cognitive behavioral therapy
- Behavioral therapy
- Psychodynamic/interpersonal
- Recovery-oriented therapies
- Group and Family therapy
- Self-help groups: NA, Al-Anon

MAT in Pregnancy

- Pregnancy- women w/OUD more susceptible to anemia, bacteremia, endocarditis, depression, gestational diabetes, HTN, STD’s
- Should be closely monitored by experienced OB/GYN
- Neonatal Abstinence Syndrome averted when women are treated during pregnancy.

- MAT w/methadone has been SOC since 1970.
- Has been evaluated thoroughly.
- Progress of Pregnancy results lower blood levels due to increased fluid volume and altered metabolism so may experience w/d sx in later stages of pregnancy.
- Subutex – appears to be as safe and effective as methadone in pregnant women.
MAT Special considerations

- Psychiatric comorbidities
- Medical comorbidities
- Hepatic disorder
- HIV/AIDS
- Pain

Co-occurring in 20 to 60% of people entering treatment, higher rates among older adults. SUD patients almost always at greater risk of disease and disorders. Require close monitoring of liver function, Hepatitis etc.

- Methadone interacts with antiretrovirals/buprenorphine less and naltrexone nearly none
- Multiple challenges to address in choice of MAT.

MAT works best when coupled with therapeutic interventions

- Individual Therapy- utilizing cognitive behavioral therapy to help identify and alleviate precipitators of use.
- Group Therapy- utilizing support, group dynamics, Dialectical behavioral therapy to engage patients in change
- Motivational interviewing- utilizing stages of change to identify patient present stage and help them move through various stages to enhance success
- 12 Step programs utilizing spirituality, connection with others suffering from AUD and working through steps to reconnect with self, others and higher power.

Governors Drug Formulary Commission working with experts toward Abuse Deterrents

1. Physical or chemical barrier that (i) prevents chewing, crushing, cutting, grinding, melting or other physical manipulations that enable abuse or (ii) resists extraction of the opioid by common solvents such as water, alcohol or other organic solvents;
2. An agonist or antagonist combination that interferes with, reduces or defeats the euphoria associated with abuse
3. An aversion quality that produces an unpleasant effect if the dosage form is manipulated or altered or a higher dose than directed is used
4. A delivery system that, under United States Food and Drug Administration guidance, offers resistance to abuse
5. A pro-drug technique that limits opioid activity until transformed in the gastrointestinal tract
6. Any other technique, as may be identified or recommended by the United States Food and Drug Administration, that offers significant abuse deterrence.
Naloxone demonstration

https://www.youtube.com/watch?v=Jis6NlZMVzc

Sarah Mackin, Program Manager at the Boston Public Health Commission explain the signs of someone who has taken an overdose and how to administer the Narcan nasal spray to hopefully save a life.