

Substance Use Disorder in Pregnancy: Opioids

Project RESPECT

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Outline

- Opioid Epidemic: Heroin and the scope of the problem
- Substance Use Disorder / Opioid Addiction
- Equation for Addiction

- Project RESPECT: the treatment program
 - Methadone
 - Buprenorphine

Heroin

leading cause of death ages 25-49



Phillip Seymour Hoffman. 1967-2014

Opioids in US

2013: National Institute on Drug Abuse

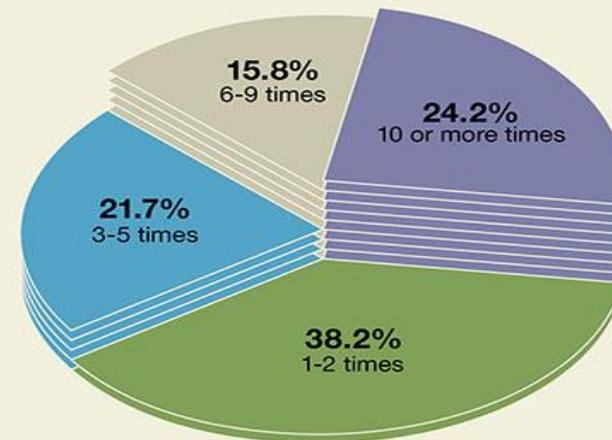
WHO 2013

2 million Americans
addicted to
prescription opioids



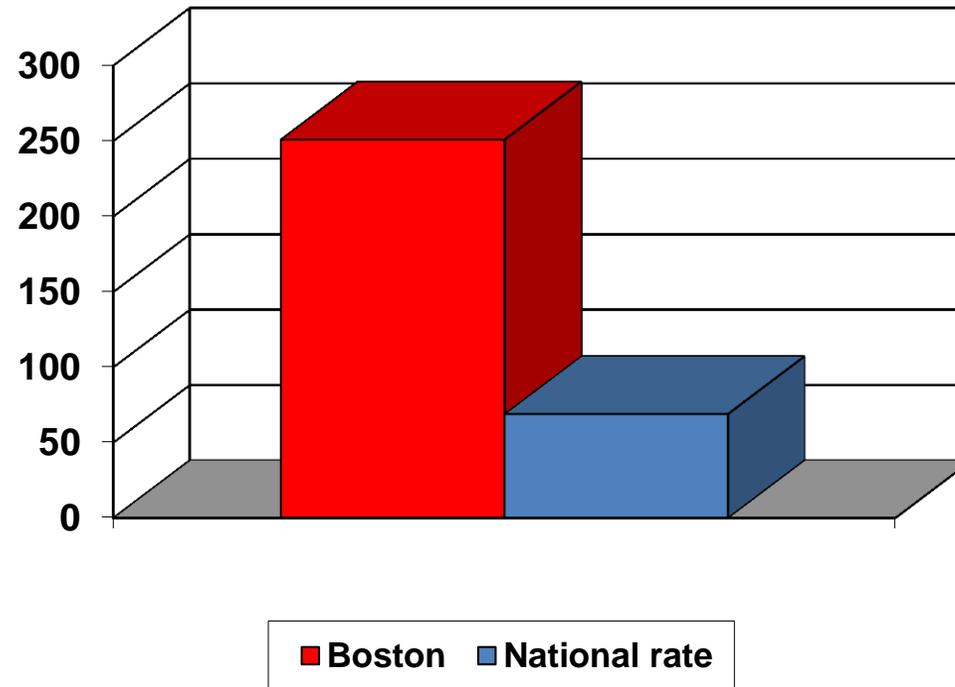
high school seniors surveyed reported nonmedical prescription opioid use in the past year.

**Past-Year Nonmedical Use of Prescription Opioids
by High School Seniors**



Substance Abuse and Mental Health Services Administration 2011 report

- Boston ranked first in ER treatment for heroin overdoses
- 4 times the national rate



The Boston region includes Suffolk, Middlesex, Norfolk, Plymouth and Essex counties plus two New Hampshire counties

Treatment Works

Addiction Treatment

Opioid maintenance therapy reduces opioid-related mortality by 70%



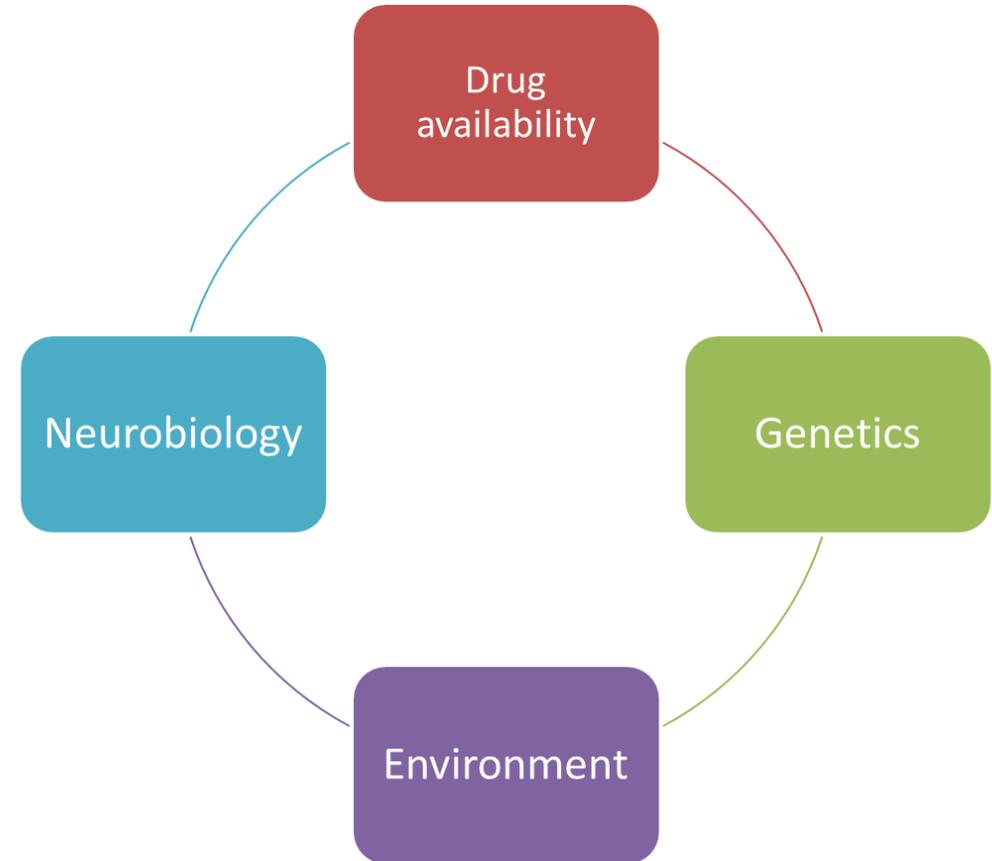
Overdose Prevention

Since 2007, MA Narcan Program reversed over 3,200 overdoses



Understanding Addiction

- American Medical Association
- Substance Use Disorder: DSM V
- Definition of addiction



American Medical Association 1956

The Disease of Addiction

- Predictable and progressive
- Primary
- Permanent
- Terminal



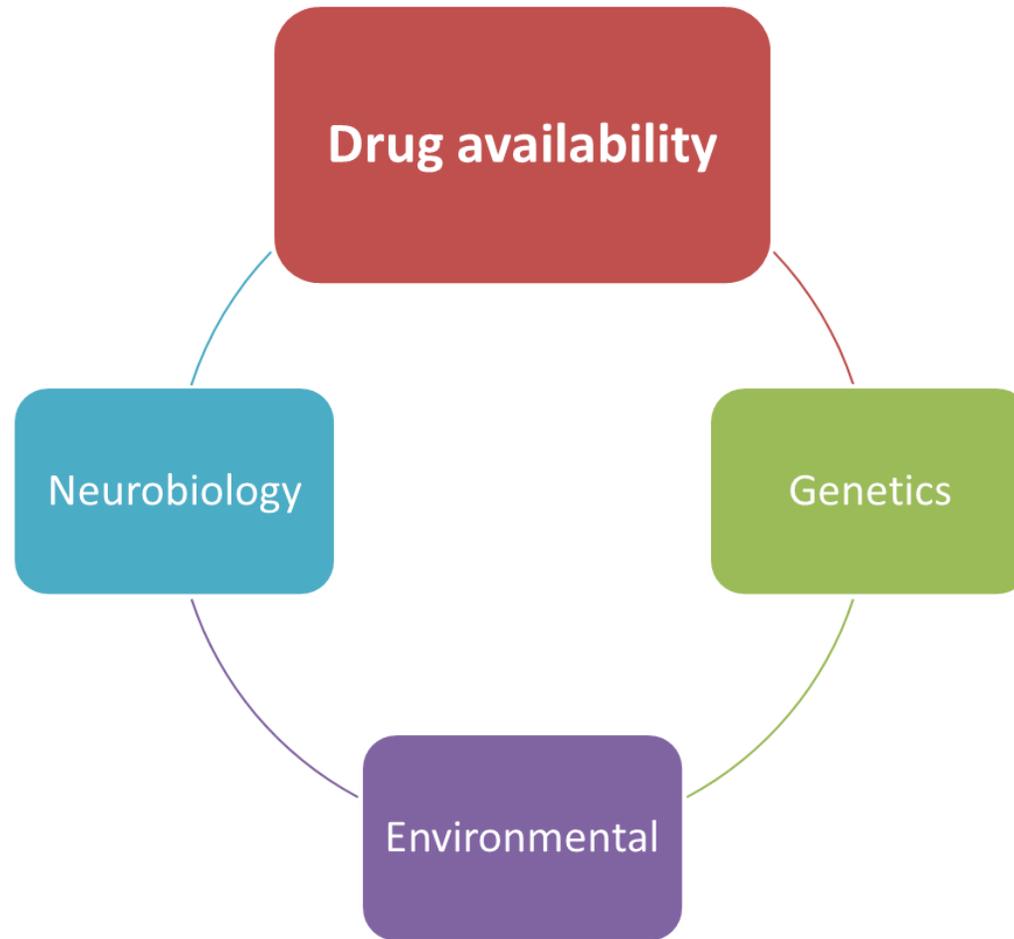
DSM V: Substance Use Disorder: patterns of symptoms resulting from use of a substance which the individual continues to take, despite experiencing problems as a result

- Taking the substance in **larger amounts** or for longer than the you meant to
- Wanting to **cut down** or stop using the substance but not managing to
- Spending a lot of **time getting, using, or recovering** from use of the substance
- **Cravings** and urges to use the substance
- Not managing to do what you should at **work, home or school**, because of substance use
- Continuing to use, even when it **causes problems** in relationships
- Giving up important **social, occupational or recreational activities** because of substance use
- Using substances again and again, even when it puts the you in **danger**
- Continuing to use, even **when the you know** you have a physical or psychological problem that could have been caused or made worse by the substance
- Needing more of the substance to get the effect you want (**tolerance**)
- Development of **withdrawal symptoms**, which can be relieved by taking more of the substance

Addiction: definition

- The state in which a person engages in compulsive behavior and pursuit of a reward despite the hazards or consequences
- The compulsion is rewarded and reinforced by neurobiological **pathways**
- Ultimately: loss of control in limiting the intake/exposure

Equation for Opioid Addiction



Historical

1830: Stickney and Poor's marketed *Paragoric*



46% ETOH + one and three-sixteenth "grains of opium per ounce"

Dosage chart for newborns, children and adults

1870: Bayer synthesized and marketed as analgesic

Not addictive
To treat
Morphine
addiction



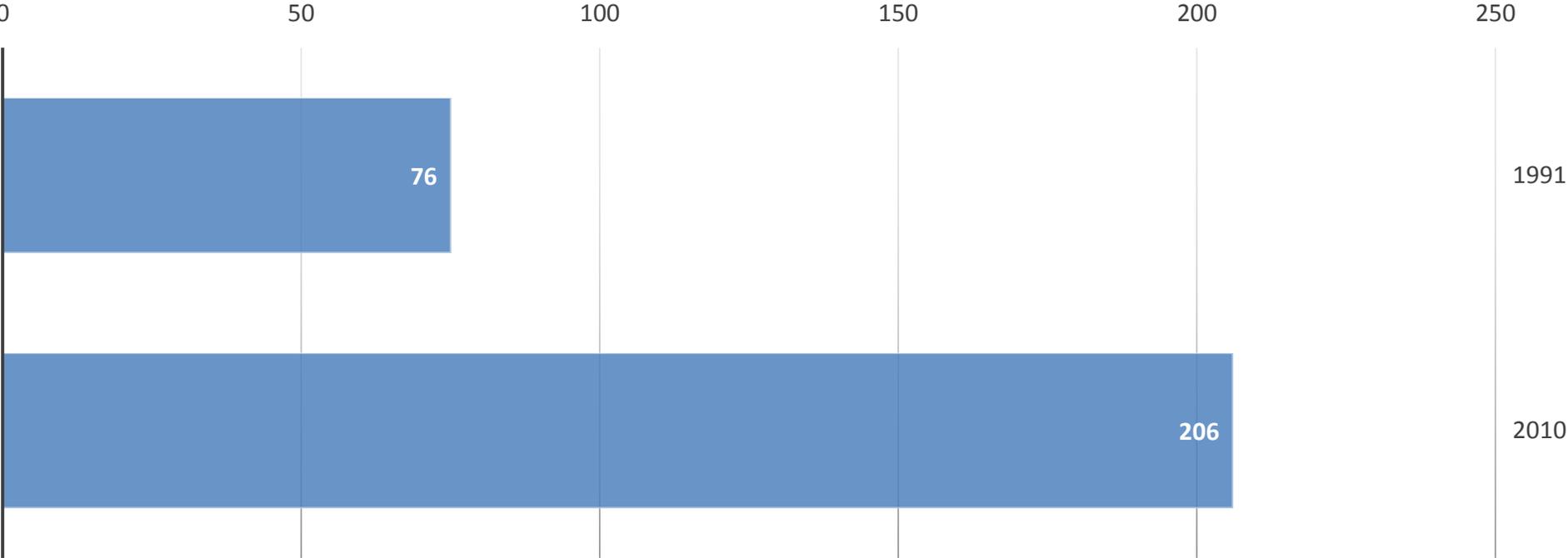
FDA NEWS RELEASE: October 25, 2013

Zohydro ER

- Extended-release/long-acting (ER/LA) opioid analgesics
- Manufactured by San Diego-based Zogenix, Inc.

Drug Availability: Prescription Opioid Statistics in US

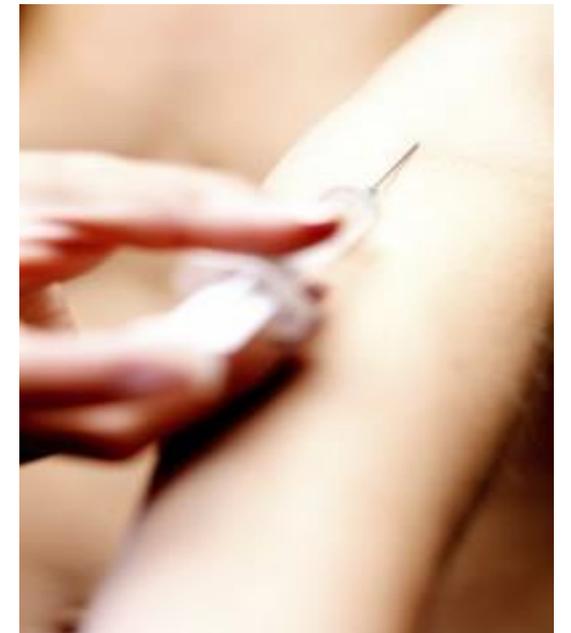
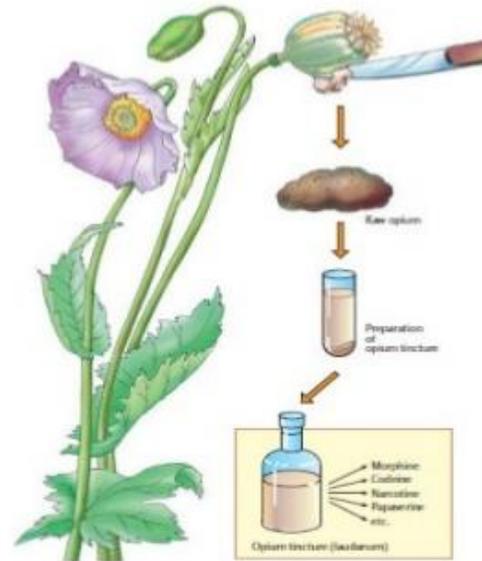
Number of Opioid Prescriptions (in millions)
1991, 2010



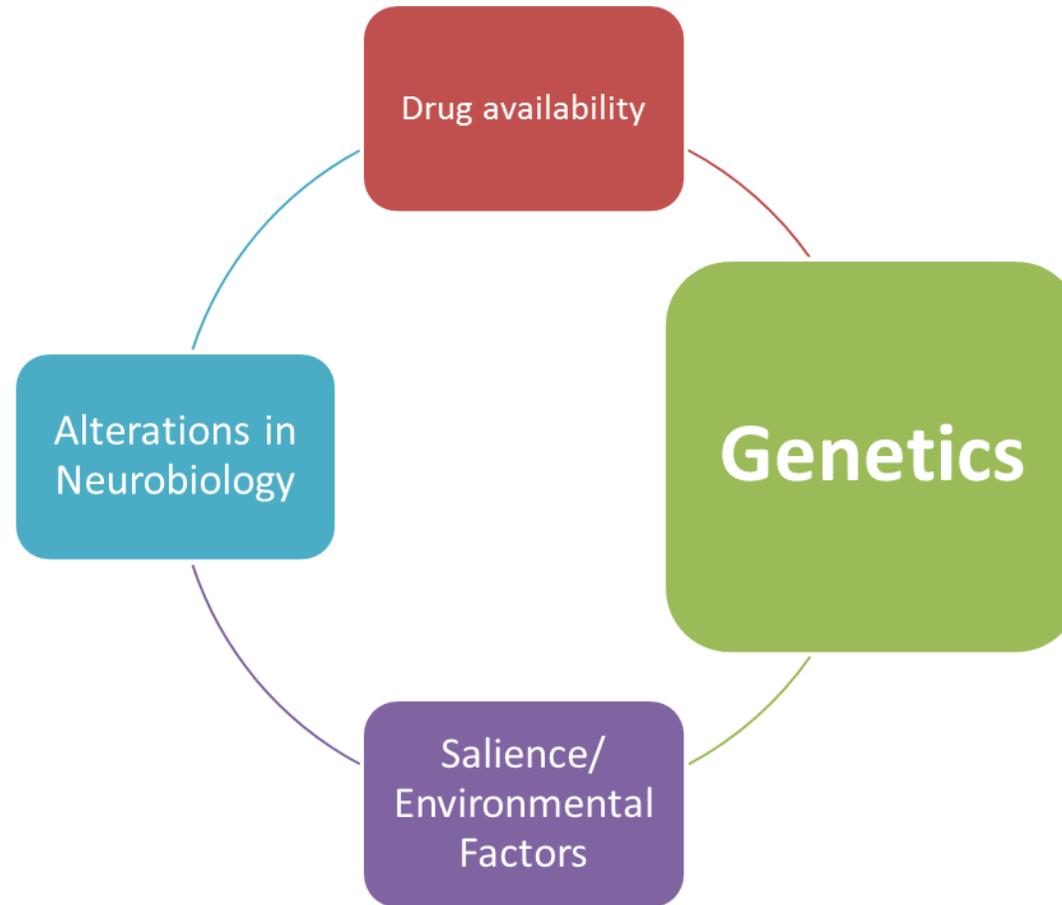
Diacetylmorphine: *Heroin*

- 2010: Afghanistan supplied 80% of the world's opium
- US heroin supply from Mexico, Columbia

Poppy to Opioids



Equation for Opioid Addiction

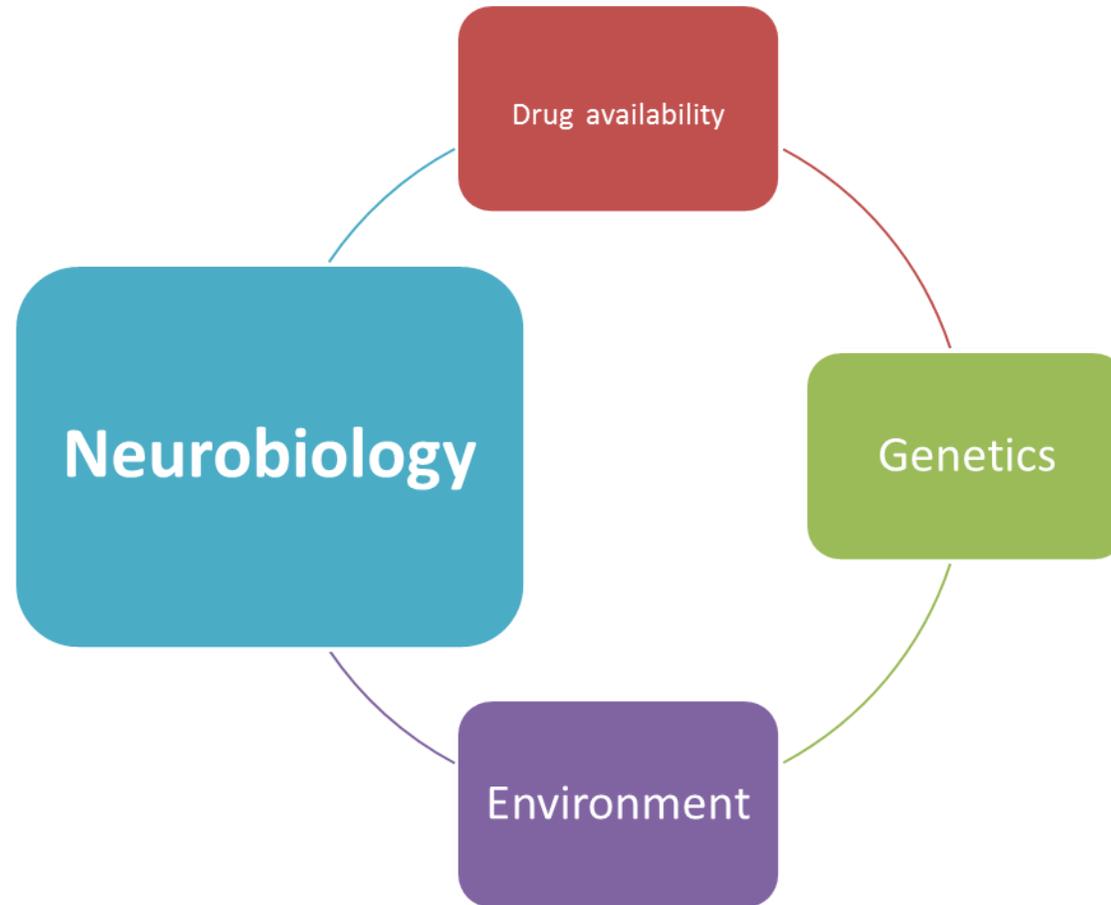




**40%-60% attributable to
genetic vulnerability**

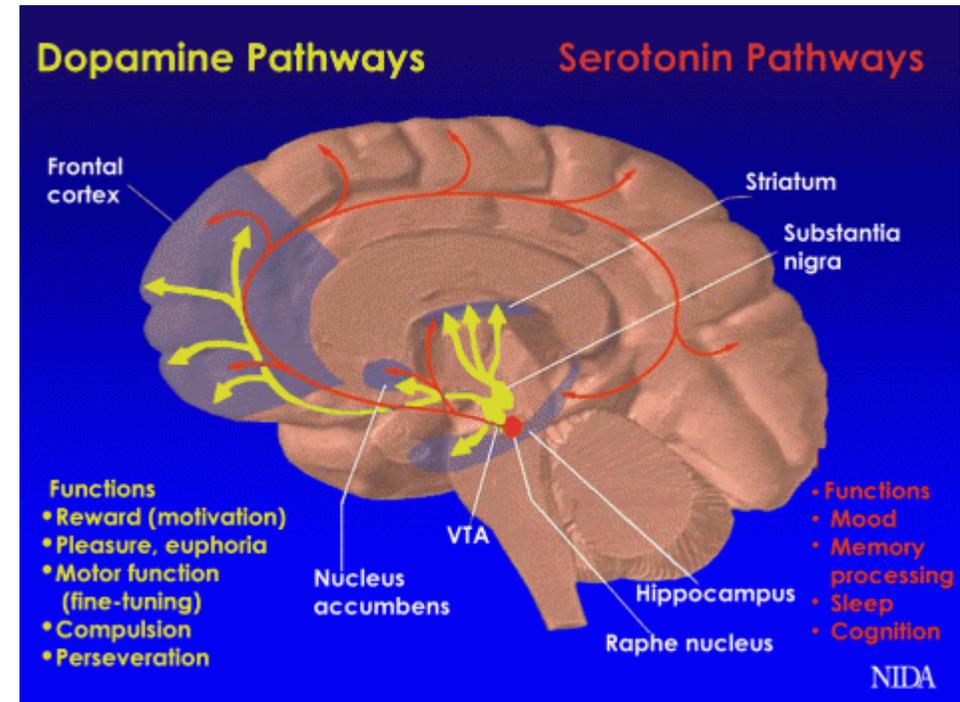
- P450 2A6 : protective against nicotine addiction
- P450 2D6 : protective against codeine abuse
- GABA type A: predisposes to ETOH abuse

Equation of Opioid Addiction



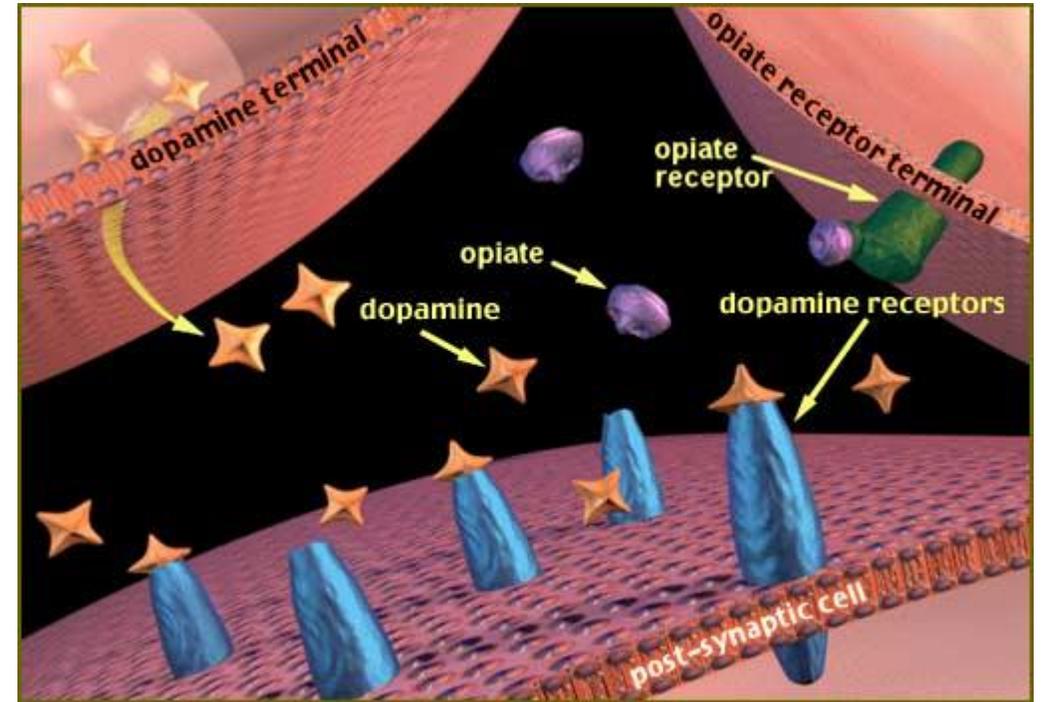
Neurobiology of Addiction

- Limbic System: emotion, memory, impulse
 - 8 main regions: including amygdala, basal ganglia, hippocampus and olfactory cortex
 - g-protein coupled opioid receptors (μ , k , delta)
- Prefrontal Cortex: center of executive function
 - 3 main regions: decision making, execution of actions and reward pathways



Dopamine reward pathways

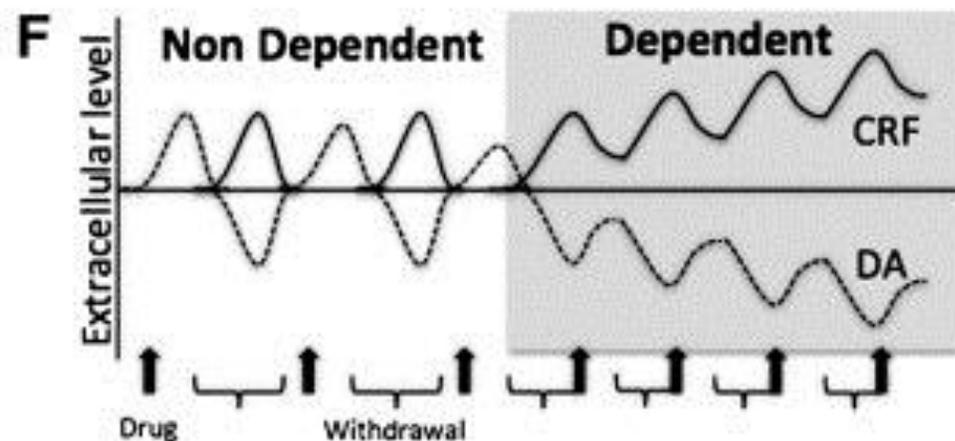
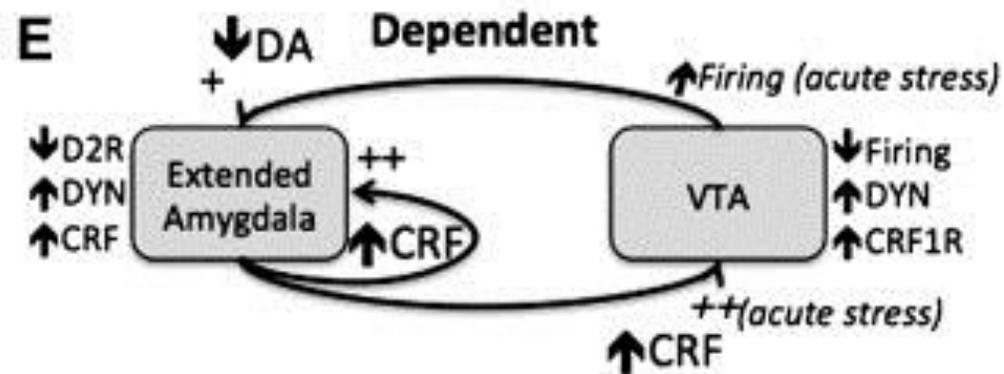
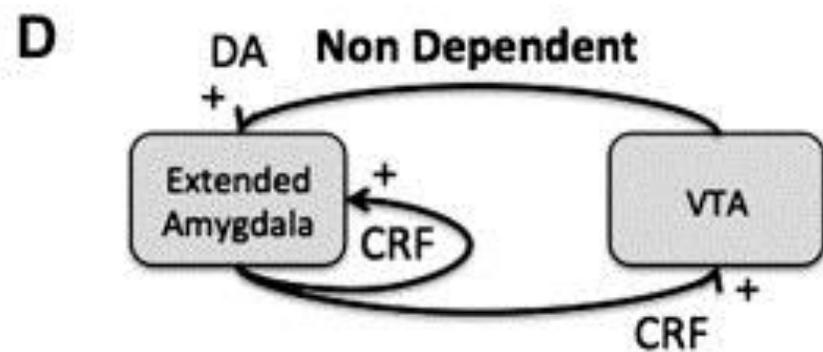
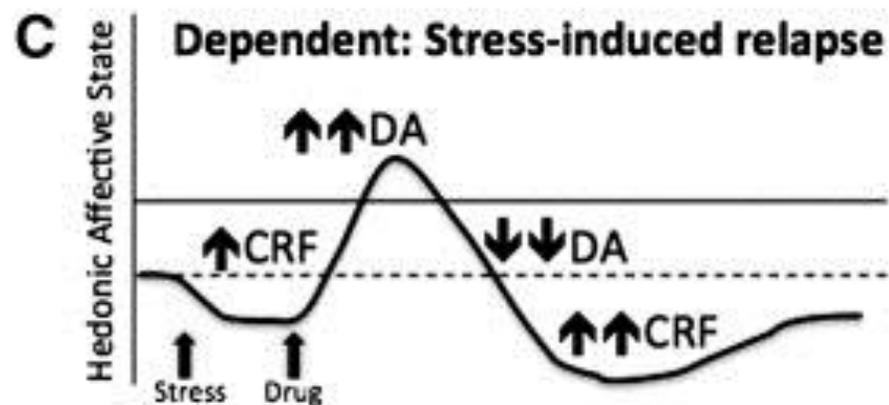
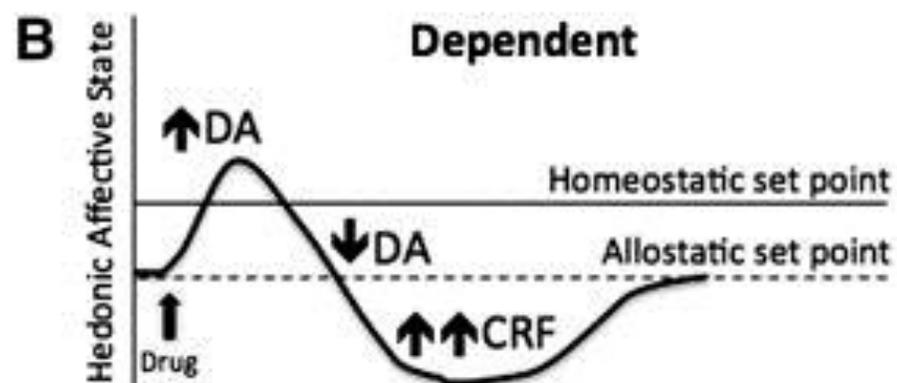
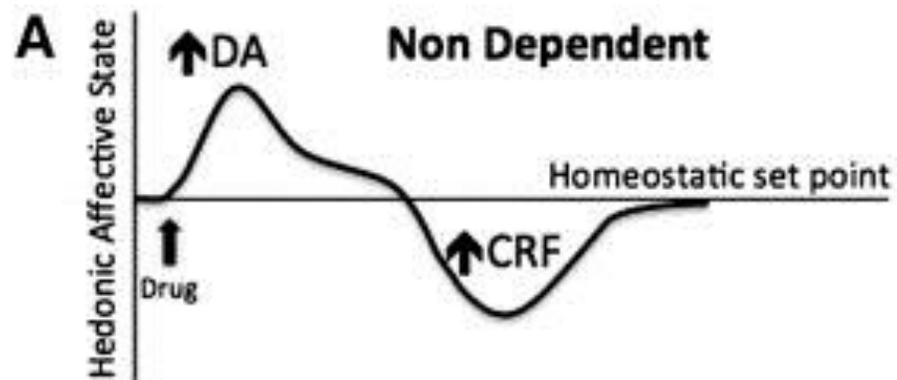
- Drugs of abuse increase the extracellular dopamine in Limbic regions
- 5-10 fold sustained increases in dopamine release
- Reuptake inhibitors:
 - Cocaine, amphetamines, methamphetamines, ecstasy: dopamine
- Alterations in receptor function
 - Opioids, nicotine, alcohol and marijuana



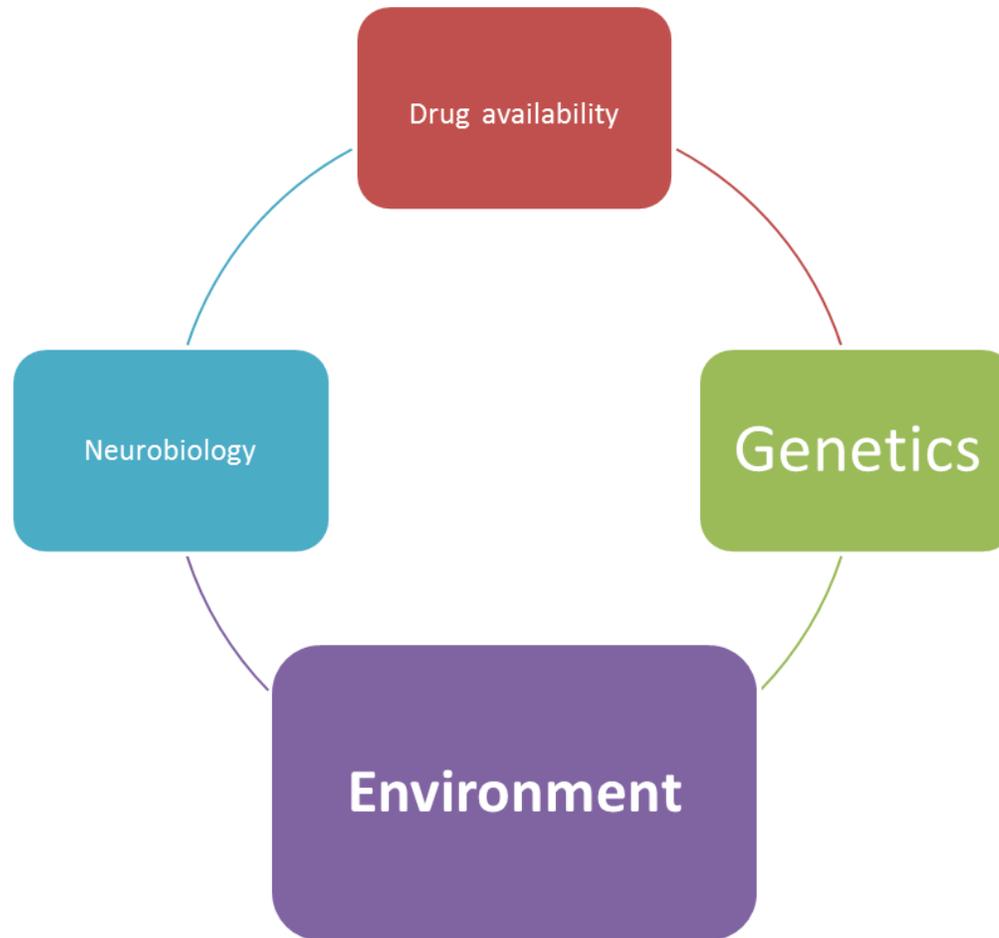
Chronic use changes Dopamine receptor

- D2 receptors: five types of receptors that bind dopamine in the brain
- D2 receptors in striatum shows up as bright red and yellow





Equation of Opioid Addiction



Trauma

- **178 women in treatment for Substance Use Disorder**
 - **84%** reported history of childhood sexual abuse or neglect

Frederick S. Cohen and Judianne Densen-Gerber J.D., M.D

- Adolescents who had experienced physical or sexual abuse/assault were **three times more likely** to report past or current substance abuse

National Survey of Adolescents 2003



- **Over 70% of adolescents** receiving treatment for substance abuse reported a history of trauma exposure

Funk RR, McDermeit M, Godley SH, Adams L. *Child Maltreat* 2003

Environment

Social factors

- Low socioeconomic status
- Unhealthy or Unstable support network
- Housing instability
- High drug availability

New stressors





Project RESPECT: Substance Use Disorder Treatment in Pregnancy

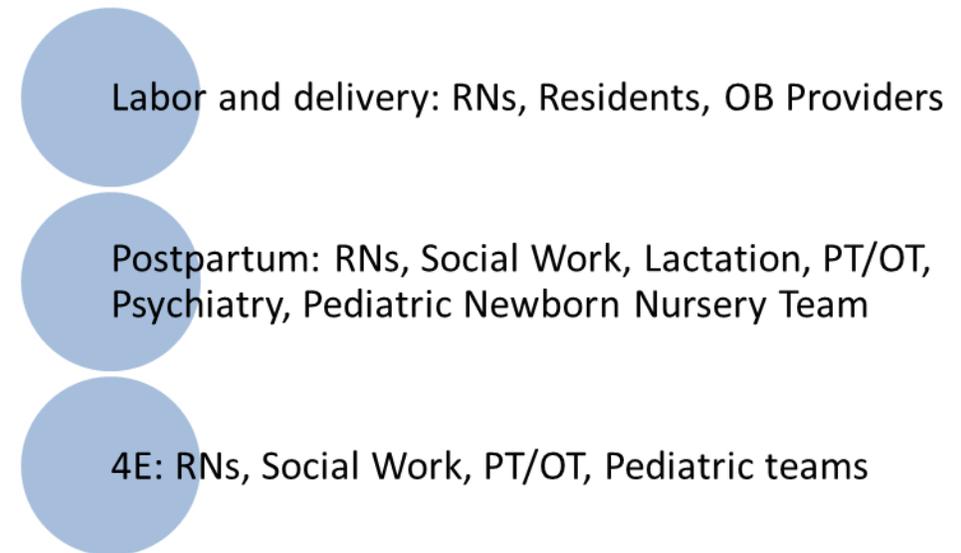
- **Recovery**
 - **Empowerment**
 - **Social services**
 - **Prenatal Care**
 - **Education**
 - **Community**
 - **Treatment**
- **150 patients annually**
 - 2006-2010: > 600 women
 - 2010: increased volume by 30%
 - **60% Methadone**
 - Average dose 68mg/day
 - **40 % Buprenorphine**
 - Average dose 12mg/day

Project RESPECT: the program

Out-patient team



In-patient team



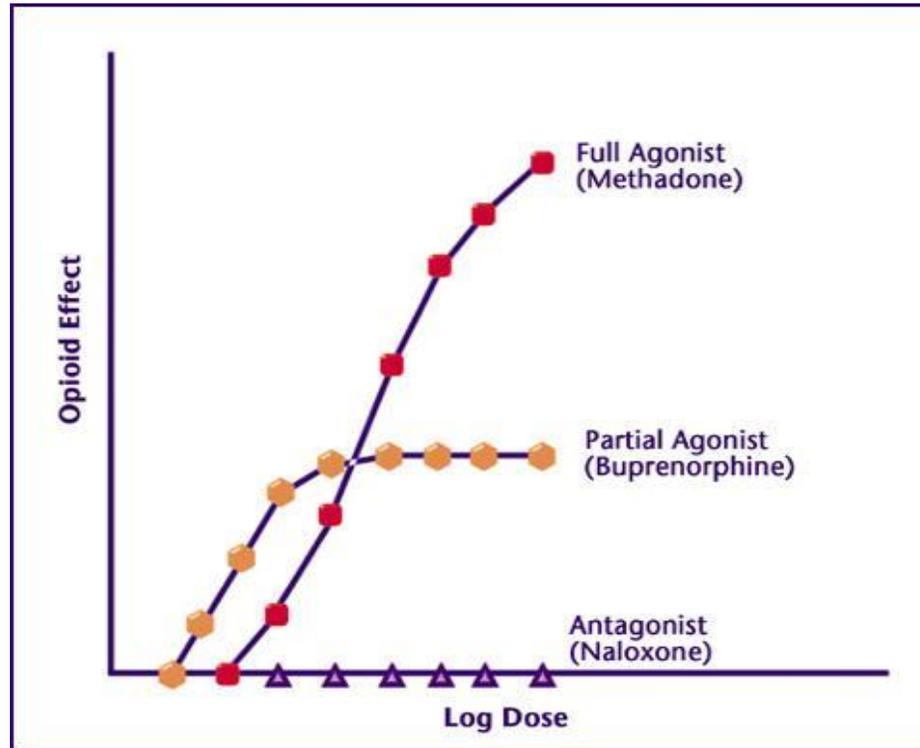
How do women enter RESPECT?

- Self referral, provider referral, transfer from a detox program



Opioid Maintenance Therapy

Methadone



Buprenorphine

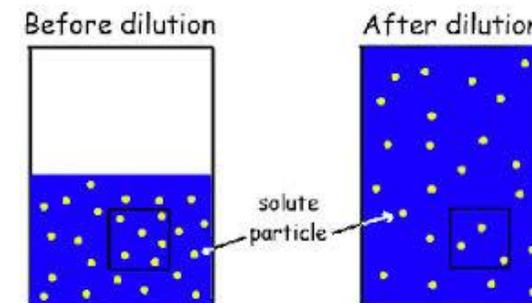


Pregnant Physiology :

- **Total blood volume:** 45% increase by 28wks
- **Cardiac Function:**
 - HR 10-15 bpm
 - CO 30-50% increase by 2nd
- **GFR** increases

Maintenance Dose

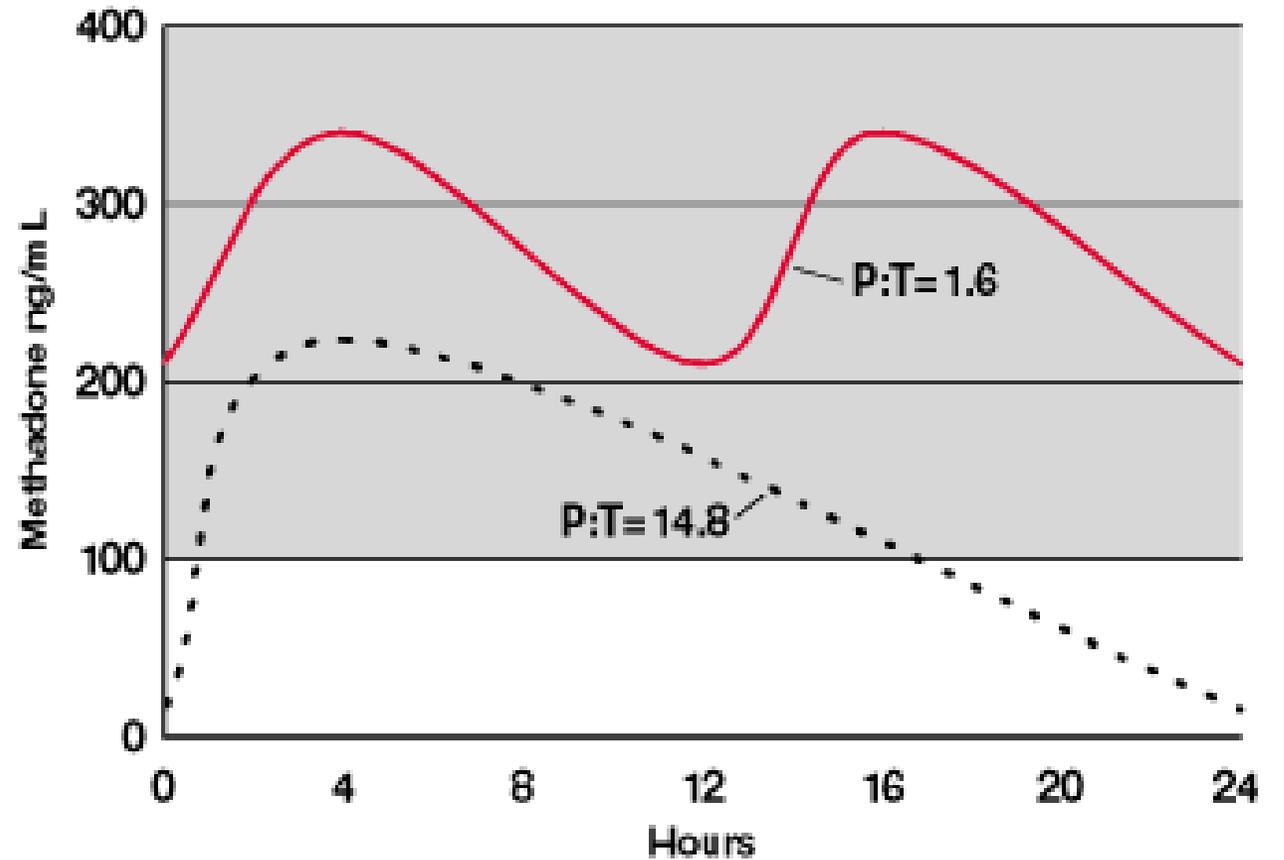
- Terminal **half-life decreases** in 2nd and 3rd trimesters
- **Lower trough levels**
- **Withdrawal symptoms**



Opioid Maintenance in Pregnancy

- Dosing changes
- Split dosing

Figure 3:
Split dose
resolves drug
interaction
problem.



Maternal Dose and NAS Severity

NO CORRELATION



Detoxification

- **Zuspan 1975:** cortisol levels
 - N=1
- **Rementeria 1973:** 5 fold increase stillbirth
 - High risk pregnancies

Detox Programs

Manage the *symptoms* of withdrawal.

depression	suicide
tremors	nausea
seizures	weakness
anxiety	diarrhea
vomiting	irritability
headaches	cravings
insomnia	muscle aches
sweating	bone aches
chills	sweating
paranoia	delirium

Substances: CoMeth, Marijuana, pills, alcohol, pain killers, Heroin

COMPLETED under the supervision of a DOCTOR

Opioid Detox. Studies in Pregnancy

- **Maas et al: 1990:** 2-8 wks outpt detox: 59 women
 - 17 completed detox, no relapse
- **Dashi et al: 1998** 12-day MTD detox: 34women
 - 59% completed, no relapse (out pt pnv, did not do urines)
- **Luty et al: 2003:** 101 women, only 50 women booked for PNC
 - 1 of 50 “drug free” at delivery
- **Jones et al: 2008:** treatment retention, PNVs, hospital delivery

Pregnancy:

Induction of Maintenance Therapy

- ❖ Goal is to reach the dose just high enough to stop use and block cravings
- ❖ Management of dose should be individualized and based on patients' symptoms
- ❖ Dose adjustments are often necessary with advancing gestational age based on pregnant physiology (see next slide)
- ❖ Split dosing, when available, is ideal in pregnancy to meet the accelerated metabolic clearance of pregnancy
 - ❖ Split dosing with methadone can help to avoid peak dose sedation and pre-dose withdrawal symptoms

Managing Maintenance Therapy through Pregnancy

Methadone

- ❖ Risk of Prolonged QTc Syndrome:
 - ❖ Obtain baseline EKG
 - ❖ Repeat with dose increase > 100mg
 - ❖ May be mitigated with split dosing

Buprenorphine

- ❖ Evaluation of liver function
 - ❖ Obtain Baseline LFTs: follow through pregnancy, may require dose adjustments
 - ❖ Elevated LFTs may complicate diagnosis of pre-eclampsia >20wks
- ❖ Monotherapy: higher risk of diversion

Opioid Maintenance: Improved outcomes

- Maternal:
 - Relapse prevention
 - Reduces polysubstance use
 - HBV, HCV, HIV
 - Increases engagement with prenatal care/ health care
- Neonatal:
 - Decreases preterm delivery and IUGR
 - Decreases NICU admissions
 - Decreases morbidity/ mortality



Postpartum: critical



- Fatigue / Stress
- Physical / Emotional Changes
- Breastfeeding
- Postpartum/ Postoperative Pain
- NAS Anxiety
- DCF Anxiety
- Family Stressors
- Demands of Recovery Program
- Postpartum Visit QI
- RESPECT team rounding 4E
- 4E Drop-in Support Group
- Social Work Communication

Managing Maintenance Therapy through labor and Delivery

- ❖ Labor Pain: Epidural only!
 - ❖ Commonly used intrapartum opioid agonist/antagonists will precipitate withdrawal
- ❖ Maintain Dose Through Labor and Delivery
 - ❖ For scheduled or unscheduled C-sections, continue maintenance therapy at same dose into the postpartum period
- ❖ Post C-Section Pain: use IV NSAIDS and Opioids as needed
 - ❖ Women on maintenance therapy will require higher doses than opioid naïve women to treat post-operative pain (Meyer et al 2007, Jones et al 2009)
- ❖ Tapering Post-Partum Dose: any adjustments should be individualized
 - ❖ Rapid postpartum taper is not recommended
 - ❖ Relapse prevention, support and stabilization should be the goal

Breastfeeding Benefits in General Population

- ❖ Benefits for all mother-infant pairs:
 - ❖ Decreased risk of SIDS, diabetes, and obesity for children
 - ❖ Decreases risk of breast and ovarian cancer for women
 - ❖ Improved infant cognitive development
 - ❖ Improved mother-infant bonding
 - ❖ Financial benefits

- ❖ Additional benefits for preterm infants:
 - ❖ 50% reduction in necrotizing enterocolitis
 - ❖ Better feeding tolerance and attainment of full enteral feedings
 - ❖ Decreased rates of late onset sepsis
 - ❖ Improved developmental outcomes

Opioid Use Disorder and Breastfeeding

- ❖ The transfer of methadone and into human milk is minimal
- ❖ Concentrations of methadone in breast milk are unrelated to maternal doses and are particularly low in infant plasma, therefore unlikely to cause any adverse effects on the infant
- ❖ Buprenorphine has poor oral bioavailability and is also compatible with breastfeeding
- ❖ The amount of buprenorphine in human milk is small and unlikely to have negative effects on the infant
- ❖ Both are considered Category L3

McCarthy JJ 2000, Begg EJ 2001, Jansson LM 2007 & 2008,
Hale 2008, Grimm 2005, Lindemalm 2008, Ilett 2012

Breastfeeding and NAS

- ❖ Benefits of breastfeeding for newborns with NAS
 - ❖ 30% decrease the development of NAS
 - ❖ 50% decrease in neonatal hospital stay
 - ❖ Improved mother-infant bonding
 - ❖ Positive reinforcement for maternal recovery

Breast feeding

- ❖ Breastfeeding is recommended for women with HCV infection
 - ❖ Unless she develops cracked or bleeding nipples
 - ❖ Recommend to pump/ dump until healed
- ❖ **Contraindications** to breastfeeding
 - ❖ Maternal HIV infection
 - ❖ Current maternal substance use
 - ❖ mother currently under the influence of illicit substance
 - ❖ Recent heavy marijuana use
 - ❖ lipophilic, concentration in breast milk

Project RESPECT Team



- **Kelley Saia, MD**
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- **Jordana Price, MD**
- **Andrea Hutcheson, Addiction Psychiatry NP**
- **Sarah Katherman, LICSW**
- **Daniel Shaw, MD Psychiatry**
- **Ingrid St. Hill: Clinic Coordinator**
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Thank you!

Maternal Opioid Treatment Human Experimental Research (MOTHER)

NEJM 12/2010

- Double-blind, double-dummy, flexible-dosing, parallel-group clinical trial
- Comparing MMT and Buprenorphine

- 73 MMT
- 58 Buprenorphine

- Shorter Hospital Stay (10 days vs. 17 days)
- Lower Mean Dose of Morphine (1.1mg vs 10.4mg)
- Shorter Duration of Treatment (4 days vs. 9 days)

Table I. Maternal Characteristics by Prenatal Opioid Agonist Treatment for 435 Pregnancies.

Characteristic	No Opioid Agonist Treatment (N=103)	Buprenorphine (N=82)	Methadone (N=245)	Buprenorphine and Methadone (N=5)
Maternal Age, Years	30.2 ± 6.4	28.1 ± 5.1	27.7 ± 5.1	27.2 ± 3.3
No Prenatal Care	16 (15.6)	0 (0)	3 (1.2)	0 (0)
Gestational Age at Presentation for Care, Weeks	16.8 ± 8.8	16.4 ± 8.9	17.2 ± 8.9	11.8 ± 8.6
Number of Prenatal Care Visits	6.5 ± 5.3	11.5 ± 4.7	8.7 ± 4.3	11.6 ± 2.2
Initial Daily Dose of Opioid Agonist Therapy (mg)	-	12.0 ± 6.5	68.3 ± 37.4	12.0 ± 4.0
Stopped Agonist Therapy During Pregnancy	-	2 (2.4)	0 (0)	0 (0)
Daily Dose of Opioid Agonist Therapy at Delivery (mg)	-	15.1 ± 7.5	89.3 ± 41.7	77.0 ± 28.9
Prescribed Psychiatric Medications				
SSRIs	7 (6.8)	14 (17.1)	38 (15.5)	2 (40.0)
Benzodiazepines	3 (2.9)	14 (17.1)	51 (20.8)	0 (0)
Antipsychotics	3 (2.9)	1 (1.2)	18 (7.4)	0 (0)
Other	4 (3.9)	9 (11.0)	15 (6.1)	2 (40.0)
≥1 Urine Screen	58 (56.3)	78 (95.1)	233 (95.1)	5 (100)
≥1 Positive Urine Screen	42 (72.4)	31 (39.7)	123 (52.8)	5 (100)

Characteristic	Unexposed (N=103)	Buprenorphine (N=82)	Methadone (N=245)	Buprenorphine & Methadone (N=5)
Pharmacologically Treated for NAS	6 (5.8)	57 (69.5)	221 (90.2)	4 (80.0)
Length of Hospitalization, Days	7.3 ± 12.1	16.0 ± 10.5	24.8 ± 11.3	21.4 ± 9.1
Age at NAS Treatment Initiation, Days	1.7 ± 1.2	2.4 ± 1.5	2.2 ± 2.3	1.8 ± 1.0
First-line NAS Treatment				
Morphine	5 (83.3)	43 (75.4)	103(46.6)	2 (50.0)
DTO	1 (16.7)	14 (24.6)	118 (53.4)	2 (50.0)
Total Morphine Used to Treat NAS, Mg per Kg Birth Weight**	3.1 ± 2.7	4.4 ± 4.1	8.8 ± 7.8	9.2 ± 4.0
Additional NAS Treatment with Phenobarbital or Clonidine	1 (16.7)	7 (12.3)	66 (29.9)	1 (25.0)
Length of NAS Treatment, Days	17.2 ± 12.2	14.3 ± 7.0	20.3 ± 9.5	20.0 ± 7.0
Peak Finnegan Score Among Neonates Treated for NAS	11.8 ± 3.8	11.1 ± 2.1	12.9 ± 3.0	13.3 ± 3.0
Gestational Age at Birth, Weeks	38.0 ± 3.1	39.2 ± 1.9	38.1 ± 2.4	38.5 ± 2.0
Preterm birth, <37 Weeks	17 (22.7)	6 (7.3)	51 (20.8)	1 (20.0)
Birth Weight, Grams	2919.3 ± 705.5	3146.1 ± 558.9	2792.8 ± 610.4	2968.0 ± 359.5