# THE DEVELOPMENTAL EFFECTS OF PRENATAL DRUG EXPOSURE: MARIJUANA

FSU Grand Rounds 12/13/2018

**Funded by NIDA, NIAAA** 

#### First Specific Drug Associated with Initiation of Illicit Drug Use 2013



National Survey on Drug Use & Health (NSDUH), 2013

#### Past-Month Use of Selected Illicit Drugs



NSDUH, 2013

#### Past-Month Use of Selected Illicit Drugs



NSDUH, 2015

#### **Past-Month Use of Selected Illicit Drugs**



**NSDUH, 2017** 

### PAST MONTH MARIJUANA USE AMONG PREGNANT AND NONPREGNANT WOMEN



Percent

Brown et al., JAMA 2017

### PAST MONTH MARIJUANA USE AMONG PREGNANT WOMEN BY AGE



Volkow et al., Annals Int Med 2017

Percent

### **INCREASING POTENCY OF MARIJUANA**



### **INCREASING POTENCY OF MARIJUANA**



### LEGALIZATION OF MARIJUANA



# Concerns grow about state's medical marijuana regulations

Massachusetts' possession limit ranks third highest among 21 states and the District of Columbia

UPDATED 11:49 PM EDT May 08, 2014

wcvb.com

#### Yet Another State Wants To Legalize Marijuana

The Huffington Post | by Kim Bellware
Posted: 04/29/2014 11:02 am EDT | Updated: 04/30/2014 5:59 pm EDT



### **INCREASING LEGALIZATION OF MARIJUANA**



© () = @StatistaCharts \* As of Nov 10, 2016 - laws in some states have not yet taken effect. Some states not highlighted allow limited medical marijuana access



Source: NY Times

### **INCREASING LEGALIZATION OF MARIJUANA**





### CHALLENGES IN STUDYING PRENATAL MARIJUANA EXPOSURE

- Theoretical model
- Assessment of exposure
- Assessment of outcomes
- Assessment of covariates
- Evaluating prenatal vs. current environmental influences

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# HOW TO MEASURE DRUG USE?

# PARAMETERS FOR MEASURING SUBSTANCE USE

- Quantity
- Frequency
- Duration

## HOW MUCH ALCOHOL IS IN A DRINK?



12 oz beer = 5 oz wine = shot of liquor

Each contains 0.5 oz of alcohol

# WHAT IS MARIJUANA?

**Cannabis Sativa plant** 

500+ compounds; 100+ cannabinoids

Main psychoactive ingredient is  $\Delta 9$ -tetrahydrocannabinol ( $\Delta 9$ -THC)

Mechoulam & Hanuš, 2000

# JOINTS



# **BLUNTS**



# **CIGARS, CIGARILLOS**



# PIPES, BONGS



# MARIJUANA WAX



#### Image courtesy of the Weed Street Journal



# MARIJUANA INTOXICATION

- Initially, increase in arousal, excitement, vasodilation, tachycardia, heightened senses
- Later, euphoria, sedation, relaxation; at high doses, perceptual changes, paranoia, anxiety attacks
- Post-intoxication involves low energy, decreased motivation, binge eating, sedation
- Side effects include memory impairments, impaired motor coordination, poor judgment, erratic behavior, reduced reaction time

# **NEUROBIOLOGY OF MARIJUANA**



Endocannabinoids bind to cannabinoid receptors (CB1 and CB2)

CB1 receptors are GPCRs and are G<sub>i/o</sub> coupled

Activation of CB1 typically decreases vesicular neurotransmitter release

Guzman (2003), Nat. Reviews Cancer

#### Brain regions that express the CB<sub>1</sub> cannabinoid receptor

**Red = abundant CB**<sub>1</sub> receptor expression Black = moderately abundant CB<sub>1</sub> receptor expression



# **NEUROBIOLOGY OF MARIJUANA**



Elliot Gardner - Neuroscience Letters, 1991, 129: 1872-79

# CANNABINOID EFFECTS ON DOPAMINE TRANSPORT

Stanwood group has described protective effects of GLP-1 receptor agonists on cocaine reward.

This is due to GLP-1 receptors blocking the endocannabinoid 2-AG, which then retrogradely alter the trafficking dynamics of the

dopamine transporter (the substrate for cocaine).



Transl Psychiatry. 2016 May; 6(5): e809

# ENDOCANNABINOIDS AND NEURODEVELOPMENT



**Figure 2**. Proposed developmental roles of the endocannabinoid system. Top panel shows temporal changes in available quantities of the two major endocannabinoids, 2-AG and AEA, at the indicated developmental stages. Concentrations of 2-AG generally exceed those of AEA in the developing brain [15,16]. Bottom panels illustrate the major events of embryogenesis that are regulated by endocannabinoid signaling through the CB<sub>1</sub> receptor (shown in orange). Only the actions of known endocannabinoids and THC are shown. The term 'td-eCBs' refers to target-derived endocannabinoids potentially released from putative postsynaptic target cells during axon guidance. For further details, see Refs [2,5,15–18,24,27,31–34,36,38].

TRENDS in Pharmacological Sciences Vol.28 No.2

#### In human, CB1 receptors are detectable by week 14 of gestation

Many possible mechanisms through which drugs can alter fetal neurodevelopment

Developmental Consequences of Fetal Exposure to Drugs: What We Know and What We Still Must Learn

Emily J Ross<sup>1</sup>, Devon L Graham<sup>2</sup>, Kelli M Money<sup>3</sup> and Gregg D Stanwood\*<sup>,2,4</sup>

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#### Polypharmacy exposure (alcohol, tobacco, marijuana) Prenatal substance use

- Insomnia
- Memory loss
- Hallucinations
- Abnormal behavior

#### Lungs

- Pulmonary edema
- Breathing problems

#### Breastfeeding

- Continued exposure
- Decreased prolactin release and supply

#### Amniotic fluid

- Possible accumulation of
- intact drugs

#### Umbilical cord

- Drugs are passed directly to fetus
- Tissue can be used to detect drugs

#### Additional risk markers (maternal and paternal age, education, stressors) Increased risk Blood, heart, and skin infections Arrhythmias Infectious diseases Seizures Stroke Hypothermia Mother's blood

- Increased levels of CO<sub>2</sub> CO, and blood pressure
- Anemia
- Pre-eclampsia

#### Placenta

- Vasoconstriction
- Placental insufficiency
- Placental abruption

#### Uterus

- Premature birth
- Contractions

# ANIMAL MODELS OF PRENATAL MARIJUANA / THC / CANNABINOIDS

- Generally speaking, the animal literature has been poorly developed!
- Multiple doses, duration, and routes of administration have been used with little consistency.
- Nevertheless, several recent studies of note.

# Prenatal exposure to cannabinoids evokes long-lasting functional alterations by targeting CB<sub>1</sub> receptors on developing cortical neurons

Adán de Salas-Quiroga<sup>a,b,c,1</sup>, Javier Díaz-Alonso<sup>a,b,c,1,2</sup>, Daniel García-Rincón<sup>a,b,c</sup>, Floortje Remmers<sup>d</sup>, David Vega<sup>a,c</sup>, María Gómez-Cañas<sup>a,b,e</sup>, Beat Lutz<sup>d</sup>, Manuel Guzmán<sup>a,b,c</sup>, and Ismael Galve-Roperh<sup>a,b,c,3</sup>

PNAS | November 3, 2015 | vol. 112 | no. 44 | 13693-13698



Impaired performance on a skill pellet-reaching task

Transiently altered CB1 receptors during prenatal development

Deficits restored by normalization of CB1 receptors on excitatory neurons!

#### ORIGINAL ARTICLE Persistent inhibitory circuit defects and disrupted social behaviour following *in utero* exogenous cannabinoid exposure

GA Vargish, KA Pelkey, X Yuan, R Chittajallu, D Collins, C Fang and CJ McBain

#### Molecular Psychiatry (2017) 22, 56-67



#### Reduced hippocampal CCK-INT number and complexity

Compromised CCK-INTmediated feedforward and feedback inhibition

Altered social behavior





### Pittsburgh Maternal Health Practices & Child Development Project Cohorts



# **PRENATAL PHASES**

4<sup>th</sup> prenatal month

7<sup>th</sup> prenatal month

24-48 hrs post-delivery

1<sup>st</sup> trimester

2<sup>nd</sup> trimester

#### 3<sup>rd</sup> trimester







STUDY DESIGN 22 YEARS 16 YEARS 414 YEARS **\*10 YEARS** 3 YEARS 18 MONTHS ✤8 MONTHS DELIVERY (N = 763 combined cohort)

◆7<sup>TH</sup> PRENATAL MONTH

◆ 4<sup>TH</sup> PRENATAL MONTH 1982-1985

# METHODS OF DETECTION

- Biological markers
- Interviews
- Self-report questionnaires



# **BIOLOGICAL MARKERS**

Window of detection varies with:

- Type of assay
- Drug
- Chronicity of use



# **DETECTION OF MARIJUANA USE**

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 Substantial evidence of greater detection of marijuana use by self-report/interview methods than by biological assays



Fendrich et al., 2004; Gray et al., 2010; Richardson et al., 2006

# **DETECTION OF MARIJUANA USE**

### Positive urine screen, reported use on interview:

95%

### Reported use on interview, negative urine screen:

**40%** 

### **IMPORTANCE OF QUESTION FORMAT**

	Usual	
Marijuana	37%	
Cocaine	47%	



Richardson, Huestis, Day, 2006

### **IMPORTANCE OF QUESTION FORMAT**

	Usual	Maximum	Minimum
Marijuana	37%	<mark>45%</mark>	17%
Cocaine	47%	<mark>50%</mark>	3%



Richardson, Huestis, Day, 2006

### PATTERN OF MATERNAL MARIJUANA USE



### PATTERN OF MATERNAL ALCOHOL USE



### PATTERN OF MATERNAL TOBACCO USE



# WHAT IS ASSOCIATED WITH PRENATAL MARIJUANA USE?



### CHARACTERISTICS ASSOCIATED WITH 1<sup>ST</sup> TRIMESTER MARIJUANA USE

	<u>No Use</u>	<u>Heavy Use*</u>	Significance
Maternal age <sub>(yrs)</sub>	22.9	23.2	ns
Education (yrs)	12.0	11.8	ns
% Caucasian	53.8	22.3	<i>р</i> < .01
% Married	37.6	18.4	<i>р</i> < .01
Family income (% < \$400/month)	56.1	71.3	р < .05



Day et al., 1991

# USE OF OTHER SUBSTANCES BY FIRST TRIMESTER MARIJUANA USE



1<sup>st</sup> trimester drug use

PERCENT

### EFFECTS OF PRENATAL MARIJUANA MATERNAL HEALTH COHORT

Birth <u>3 years</u> <u>6</u>

<u>6 years 10 years 14 years</u>

22 years

GROWTH

**BEHAVIOR** 

COGNITIVE

# **EFFECTS ON COGNITION**



### **RELATION BETWEEN PME & 6 YEAR IQ**



	No marijuana use	Lightª marijuana use	Heavy <sup>ь</sup> marijuana use	Significance
No adjustments	95.9	93.6	89.0	.001

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HOME, education	95.5	93.9	90.1	.01

	No marijuana use	Light <sup>a</sup> marijuana use	Heavy <sup>ь</sup> marijuana use	Significance
No adjustments	95.9	93.6	89.0	.001
Adjust for: Home environment (HOME)	95.6	93.7	90.2	.01
HOME, education	95.5	93.9	90.1	.01
HOME, education, race	95.1	94.1	91.5	ns

a < 1 joint/day;  $b \ge 1$  joint/day

# **EFFECTS ON BEHAVIOR**





# RELATION BETWEEN PME & 10 YEAR BEHAVIOR



### **OFFSPRING SUBSTANCE USE ACROSS TIME**



### RELATION BETWEEN PME & 22 YEAR OFFSPRING MARIJUANA USE



Sonon et al., 2015

### RELATION BETWEEN PME & PSYCHOTIC SYMPTOMS AT 22 YEARS



Day et al., 2015

#### At the Tip of an Iceberg: Prenatal Marijuana and Its Possible Relation to Neuropsychiatric Outcome in the Offspring

Alán Alpár, Vincenzo Di Marzo, and Tibor Harkany

Biological Psychiatry April 1, 2016; 79:e33-e45



**Figure 2.** Major dopaminergic pathways of the brain. In adolescence, mesocortical dopamine (DA) influence peaks in the prefrontal cortex (PFC) but dopamine activity becomes lower in the nucleus accumbens (Acc). The increased inhibition of PFC pyramidal cells results in a decreased excitatory glutamatergic output onto the subcortex, further amplifying the increased inhibitory dopaminergic tone on the PFC. Compared with nigrostriatal input, mesolimbic but especially mesocortical afferents are sensitive to environmental stressors/drug abuse that may escalate the dopamine imbalance between the cortical and subcortical integration centers in adolescent marijuana abuse. Altered line thickness across the named conditions denotes changes in strength of expression/effects. Glu, glutamate; SN, substantia nigra; Str, striatum; THC,  $\Delta^9$ -tetrahydrocannabinol; VTA, ventral tegmental area.

Adolescent marijuana exposure increases susceptibility to develop psychosis and other neuropsychiatric conditions. Even earlier exposures may do the same (or worse?).

### EFFECTS OF PRENATAL MARIJUANA MATERNAL HEALTH COHORT



# CONCLUSIONS

- Effects of prenatal marijuana exposure on behavior and cognition consistent across phases (and studies)
- Increased risk of marijuana use in offspring
- Pattern of effects consistent with teratologic model and mechanisms

### **IMPLICATIONS**

- Different types/patterns of prenatal marijuana use
- Co-use of marijuana and tobacco is common
- Consider other characteristics associated with prenatal drug use
- Non-judgmental communication is important
- Understand woman's belief system

### MATERNAL HEALTH PROJECT



### EFFECTS OF PRENATAL MARIJUANA EXPOSURE ON COGNITIVE DOMAINS

<u>3 years</u>	<u>6 years</u>	<u>10 years</u>	<u>14 years</u>
Overall IQ - Short term memory - Verbal	Overall IQ - Short-term memory -Verbal	Achievement: - Reading - Spelling	Achievement: - Reading - Total
	-Quantitative	Memory – overall; - visual	
Day et al., 1994	Goldschmidt et al., 2008	Goldschmidt et al., 2004; Richardson et al., 2002	Goldschmidt et al., 2012

### EFFECTS OF PRENATAL MARIJUANA EXPOSURE ON BEHAVIOR

<u>6 years</u>	<u>10 years</u>	<u>14 years</u>	<u>22 years</u>
Impulsivity	Inattention Impulsivity Activity		Psychotic symptoms
	Delinquency	Delinquency	Maladaptive adult roles
	Depression	Marijuana use	Marijuana use
Leech et al., 1999	Goldschmidt et al., 2000; Gray et al., 2005	Day et al., 2006, 2011	Day et al., 2015; Goldschmidt et al., 2016; Sonon et al., 2015