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

- Marijuana, 70.3%
- Pain Relievers, 12.5%
- Inhalants, 6.3%
- Tranquilizers, 5.2%
- Stimulants, 2.7%
- Hallucinogens, 2.6%
- Sedatives, 0.2%
- Cocaine, 0.1%

2.8 million initiates of illicit drugs

National Survey on Drug Use & Health (NSDUH), 2013
Past-Month Use of Selected Illicit Drugs

- Marijuana
- Hallucinogens
- Illicit Drugs
- Cocaine
- Prescription Drugs

Percent Using in Past Month vs Year (2002-2013)

NSDUH, 2013
PAST MONTH MARIJUANA USE AMONG PREGNANT AND NONPREGNANT WOMEN

Brown et al., JAMA 2017
PAST MONTH MARIJUANA USE AMONG PREGNANT WOMEN BY AGE

Volkow et al., Annals Int Med 2017
INCREASING POTENCY OF MARIJUANA

Potency of Seized Marijuana in the U.S.

Source: University of Mississippi, National Center for Natural Products Research, Potency Monitoring Project Quarterly Report 107 (January 2010)
INCREASING POTENCY OF MARIJUANA
LEGALIZATION OF MARIJUANA

A look at marijuana laws in the U.S.
updated 12:34 PM ET, May 6, 2014

Two states -- Colorado and Washington -- have legalized marijuana for recreational use. Nineteen other states and the District of Columbia allow legal use of marijuana, primarily for medicinal purposes.

Click on each state for more details.

Concerns grow about state's medical marijuana regulations
Massachusetts' possession limit ranks third highest among 21 states and the District of Columbia

Yet Another State Wants To Legalize Marijuana
The States Where It's Legal To Smoke Marijuana
Laws on recreational and medical marijuana use in the US*

Legalized for recreational & medical use
- Washington
- Washington D.C.
- Oregon
- Alaska
- Colorado
- California
- Massachusetts
- Nevada
- Maine

Medical use only

* 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
The States Where It's Legal To Smoke Marijuana

Laws on recreational and medical marijuana use in the US*

- **Legalized for recreational & medical use**
- **Medical use only**

Legalized recreational marijuana:
- Alaska
- California
- Colorado
- District of Columbia
- Maine
- Massachusetts
- Nevada
- Oregon
- Vermont
- Washington

* As of July 01, 2018. Some states not highlighted allow limited medical marijuana access

Sources: NY Times, Business Insider
CHALLENGES IN STUDYING PRENATAL MARIJUANA EXPOSURE

• Theoretical model
• Assessment of exposure
• Assessment of outcomes
• Assessment of covariates
• Evaluating prenatal vs. current environmental influences
CHALLENGES IN STUDYING PRENATAL MARIJUANA EXPOSURE

- Theoretical model
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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

NIAAA
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
Endocannabinoids bind to cannabinoid receptors (CB1 and CB2)

CB1 receptors are GPCRs and are G_i/o coupled

Activation of CB1 typically decreases vesicular neurotransmitter release

Guzman (2003), *Nat. Reviews Cancer*
Brain regions that express the CB₁ cannabinoid receptor

Red = abundant CB₁ receptor expression  Black = moderately abundant CB₁ receptor expression
NEUROBIOLOGY OF MARIJUANA

DA in Nucleus Accumbens

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).
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 Ross¹, Devon L Graham², Kelli M Money³ and Gregg D Stanwood⁴,⁵
¹Chemical & Physical Biology Program, Vanderbilt University, Nashville, TN, USA; ²Department of Pharmacology, Vanderbilt University, Nashville, TN, USA; ³Neuroscience Graduate Program, Vanderbilt University, Nashville, TN, USA; ⁴The Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, TN, USA
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.
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!
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-INT-mediated feedforward and feedback inhibition

Altered social behavior
Pittsburgh Maternal Health Practices & Child Development Project Cohorts

Alcohol Use During Pregnancy
NIAAA
N. Day

Core Data Sets
Instruments
Personnel
Analyses

Prenatal Marijuana Exposure
NIDA
N. Day

Teenage Prenatal Tobacco Use
NIAAA/NIDA
M. Cornelius

Prenatal Cocaine Use
NIDA
G. Richardson
PRENATAL PHASES

4th prenatal month
1st trimester

7th prenatal month
2nd trimester

24-48 hrs post-delivery
3rd trimester
STUDY DESIGN

- 22 YEARS
- 16 YEARS
- 14 YEARS
- 10 YEARS
- 6 YEARS
- 3 YEARS
- 18 MONTHS
- 8 MONTHS
- DELIVERY (N = 763 combined cohort)
- 7TH PRENATAL MONTH
- 4TH 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
DETECTION OF MARIJUANA USE

- 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

<table>
<thead>
<tr>
<th></th>
<th>Usual</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>37%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>47%</td>
<td></td>
<td></td>
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</tbody>
</table>

Richardson, Huestis, Day, 2006
## IMPORTANCE OF QUESTION FORMAT

<table>
<thead>
<tr>
<th></th>
<th>Usual</th>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>37%</td>
<td>45%</td>
<td>17%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>47%</td>
<td>50%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Richardson, Huestis, Day, 2006
PATTERN OF MATERNAL MARIJUANA USE

PERCENT

Year prior 1st trim. 3rd trim. 18 mos 6 yrs 14 yrs 22 yrs

None: 0 joints/day Light: <1 joint/day Heavy: 1+ joints/day
PATTERN OF MATERNAL ALCOHOL USE

YEAR
Prior
1st trim.
3rd trim.
18 mos
6 yrs
14 yrs
22 yrs

PERCENT

None: 0 drinks/day
Light: <1 drink/day
Heavy: 1+ drinks/day
PATTERN OF MATERNAL TOBACCO USE

- None: 0 cigarettes/day
- Light: < 1 pack/day
- Heavy: 1+ packs/day
WHAT IS ASSOCIATED WITH PRENATAL MARIJUANA USE?
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Use</th>
<th>Heavy Use*</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (yrs)</td>
<td>22.9</td>
<td>23.2</td>
<td>ns</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>12.0</td>
<td>11.8</td>
<td>ns</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>53.8</td>
<td>22.3</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>% Married</td>
<td>37.6</td>
<td>18.4</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>Family income (% &lt; $400/month)</td>
<td>56.1</td>
<td>71.3</td>
<td>p &lt; .05</td>
</tr>
</tbody>
</table>

*≥ 1 joint/day

Day et al., 1991
USE OF OTHER SUBSTANCES BY FIRST TRIMESTER MARIJUANA USE

PERCENT

1st trimester drug use

Alcohol
Tobacco
Other Drugs

No PME
Heavy PME*

*≥1 joint/day
# Effects of Prenatal Marijuana Maternal Health Cohort

<table>
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<tr>
<th>Age</th>
<th>Birth</th>
<th>3 years</th>
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**Growth**

**Behavior**

**Cognitive**
EFFECTS ON COGNITION
RELATION BETWEEN PME & 6 YEAR IQ

Goldschmidt et al., 2008
IMPORTANCE OF CONTROL OF COVARIATES
10-year PIAT reading comprehension

<table>
<thead>
<tr>
<th></th>
<th>No marijuana use</th>
<th>Light(^a) marijuana use</th>
<th>Heavy(^b) marijuana use</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adjustments</td>
<td>95.9</td>
<td>93.6</td>
<td>89.0</td>
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\(^a\) < 1 joint/day; \(^b\) ≥ 1 joint/day

Goldschmidt et al., 2004
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<td>95.6</td>
<td>93.7</td>
<td>90.2</td>
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Goldschmidt et al., 2004
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<td>90.2</td>
<td>.01</td>
</tr>
<tr>
<td>HOME, education</td>
<td>95.5</td>
<td>93.9</td>
<td>90.1</td>
<td>.01</td>
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<sup>a</sup> < 1 joint/day;  <sup>b</sup> ≥ 1 joint/day

Goldschmidt et al., 2004
importance of control of covariates

10-year PIAT reading comprehension

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<td>90.1</td>
<td>.01</td>
</tr>
<tr>
<td>HOME, education, race</td>
<td>95.1</td>
<td>94.1</td>
<td>91.5</td>
<td>ns</td>
</tr>
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\textsuperscript{a} < 1 joint/day; \textsuperscript{b} \geq 1 joint/day

Goldschmidt et al., 2004
EFFECTS ON BEHAVIOR
RELATION BETWEEN PME & 10 YEAR BEHAVIOR

Teacher Reported Behavior

- Delinquent
- Aggressive

Percent above borderline clinical cutoff

- No PME
- Heavy PME* ≥1 joint/day

Goldschmidt et al., 2000
OFFSPRING SUBSTANCE USE ACROSS TIME

% use

- Alcohol
- Tobacco
- Marijuana

10 years
14 years
22 years
RELATION BETWEEN PME & 22 YEAR OFFSPRING MARIJUANA USE

% use at 22 yrs

No PME

Any PME

No use

≥ 3 times/wk

P < .001

Sonon et al., 2015
RELATION BETWEEN PME & PSYCHOTIC SYMPTOMS AT 22 YEARS

Day et al., 2015
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

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<tbody>
<tr>
<td>GROWTH</td>
<td>length</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>BEHAVIOR</td>
<td>sleep changes</td>
<td>impulsivity</td>
<td>activity, inattention, impulsivity, delinquency, depression</td>
<td>delinquency, marijuana use</td>
<td>marijuana use, psychotic sx, arrests</td>
<td></td>
</tr>
<tr>
<td>COGNITIVE</td>
<td>IQ, memory</td>
<td>IQ, memory</td>
<td>memory, achievement</td>
<td>achievement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
<table>
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<tr>
<th>3 years</th>
<th>6 years</th>
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</table>
| Overall IQ  
- Short term memory  
- Verbal  
  Day et al., 1994 | Overall IQ  
- Short-term memory  
- Verbal  
- Quantitative  
  Goldschmidt et al., 2008 | Achievement:  
- Reading  
- Spelling  
  Memory – overall;  
- visual  
  Goldschmidt et al., 2004; Richardson et al., 2002 | Achievement:  
- Reading  
- Total  
  Goldschmidt et al., 2012 |
# EFFECTS OF PRENATAL MARIJUANA EXPOSURE ON BEHAVIOR

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