What Hides in the Smoke

THC and Nicotine Exposure in Fetal and Neonatal Life

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Breastfeeding is nutritionally, immunologically, neurologically, endocrinologically, economically, and ecologically superior to formula…

-The Lancet 2016 McFadden et. Al.

2

No Disclosures

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Learning Objectives

- Learners will be able to describe the impact of nicotine use on fetal and infant development
- Learners will describe how nicotine enters into breast milk and expectations for postnatal exposure
- Learners will be able to educate families on importance of breastfeeding while abstaining from or reducing nicotine use
- Learners will be able to describe how tetrahydrocannabinoids (THC) interact with the endocannabinoid system and exposure's impact on the developing neural pathways

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TOBACCO AND NICOTINE

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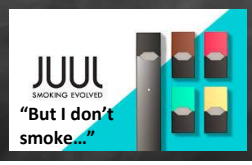
Small but Deadly

- Nicotine is the primary (but not only) psychoactive component in tobacco products
- Each Juul pod contains as much nicotine as a pack of cigarettes, around 41mg/pod
- Ingestion of 10mg can kill a child, 40mg can leave an adult comatose



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Tobacco Use during Pregnancy

- In the US approximately 11% of women use nicotine containing products while pregnant
- 5-7% of pregnant women use electronic nicotine devices
- About 55% of women decrease or stop before deliver

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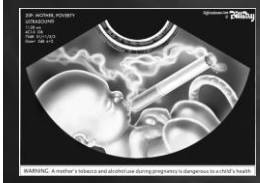
Biomechanics of Nicotine Intoxication in utero



- Mother: Inhaled from tobacco smoke or absorbed from nicotine products through mucosa or skin
- Freely crosses placenta
- Accumulates at higher concentration in amniotic fluid than maternal serum
- Permanently alters fetal development

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Effects on Fetal development

- Permanent alteration of brain biochemistry and lung mechanics
- Fetal restriction in growth and development
- Abnormalities in development of cardiovascular, immune, endocrine, gastrointestinal, craniofacial and musculoskeletal systems
- Epigenetic influences and anti-oxidative imbalance

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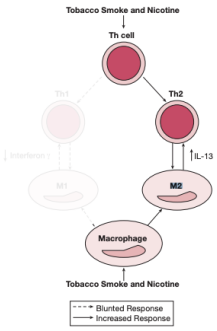

- Immune effects
  - Increased proinflammatory cytokines
  - Depressed immunoglobulin production
  - Imbalance in Th1-Th2 cell distribution towards Th2
  - Allergic phenotype, asthma like symptoms, small airway inflammation

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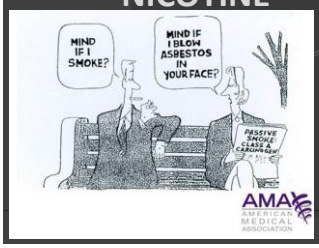
PHARMACOKINETICS OF NICOTINE



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Nicotine passes into breast milk

- Half life of nicotine and by-products is increased in milk
- Half life of nicotine and by-products in infant's is 3-4x longer than in adults
- Milk to Plasma ratio is 2.92

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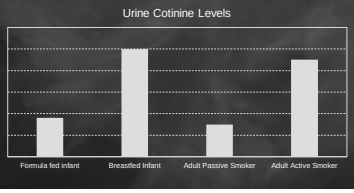
Double Shot

- Second hand exposure to tobacco smoke PLUS nicotine in mom's milk gives double or more the nicotine exposure
- Cotinine levels are 2-10 times higher in breastfed infants of smoking mothers (when compared to formula fed infants of smoking women)



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Second Hand Smoking

- Increased incidence
  - Bronchitis
  - Asthma
  - Otitis media (2.9x)
  - Upper respiratory tract infection (1.5.3x)
  - Lower respiratory tract infection (pneumonia) (8.2x)
- When mother is NOT the smoker... breastfeeding is protective

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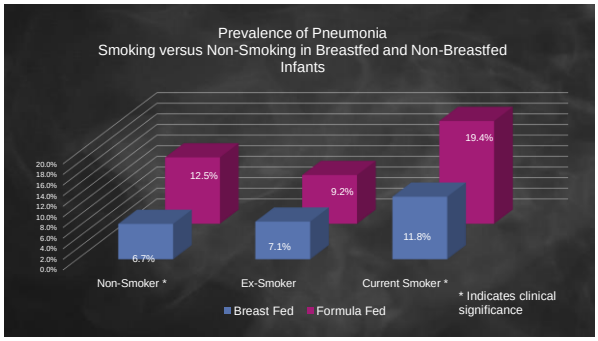

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Nicotine effect on pulmonary epithelium

- Induction of cytotoxic radicals
- Decreased anti-oxidant capacity
- Permanent fetal structural lung changes
- Altered alveolarization post-natally
- Impaired immune response
- Abnormal pulmonary capillary bed development

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Nicotine in Breast Milk

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Effect on Galactogenesis and Galactopoeisis

- Diminished prolactin during pregnancy inhibits mammary glandular growth
- Decreased production capacity
- Shorter lactation period/early weaning
- Altered neonatal feeding patterns

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Altered milk composition

- Fat
  - Decreased 19-26% total fats
  - Reduced long chain polyunsaturated fatty acids (DHA, ARA)
- Protein
  - 12% decrease in total milk protein
- Carbohydrates
  - Decreased total lactose concentration
- Micronutrients
  - Decreased calcium and phosphorus

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IUGR/SGA Infant → EUGR Infant

- Nicotine exposed infants are far more likely to be growth restricted
- 6-9x more likely to have SGA infant

Small infant + Poor feeding (low nutrient milk + low volume milk) =

EXTRAUTERINE GROWTH RESTRICTION (EUGR)

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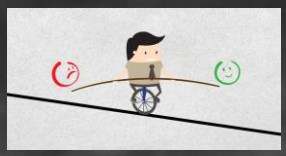
Antioxidants in the milk (or not)



- Mother's milk is rich in antioxidants
- Prevent several morbidities in preterm infants (NEC, ROP, BPD)

- Nicotine use:
  - Decreases protection from oxidative damage
  - Increases pro-inflammatory markers in milk

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Cannabis and THC

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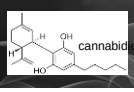
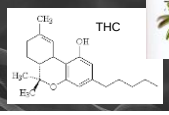
Dazed and Confused: Cannabis and its Components

- Originates from *Cannabis* plant
- Delta-9 Tetrahydrocannabinol (THC)
  - Psychoactive component
  - Derived from leaves/buds of cannabis plant
- Cannabidiol
  - Medicinal properties





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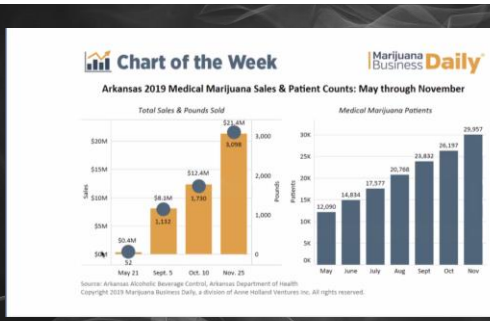

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As of end of 2021
37 licensed Arkansas dispensaries
$264.9 million dollars in sales to eligible Arkansas residents in 2021, surpassing $500 million since the first store opened in 2019

3 Proposed initiatives on the 2022 ballot involve legalizing recreational cannabis products

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THC Use in Pregnancy

- Products containing THC are third most common substance used during pregnancy
- 2019 National Survey on Drug Use indicated 5.4% of pregnant women used THC products
- 28% increase over last 10 years

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All Natural

- According to ACOG, nearly 1 in 4 women believe that there is no harm to the pregnancy or fetus through use of cannabis [for nausea and appetite stimulation] 1-2 times a week
- Higher rates of use among young, urban, socioeconomically disadvantaged women – up to 28%
- Conflicting information for pregnant women amidst a growing presence of social media support for use of cannabis products for morning sickness and "all natural" remedies for insomnia, anxiety, anorexia...

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THC Hijackers

- Normal fetal development relies on endogenous cannabidiols
- Exogenous cannabidiols from THC containing products interfere with these process and alter the expected outcomes – in some cases apparently resulting in permanent alteration in brain biochemistry

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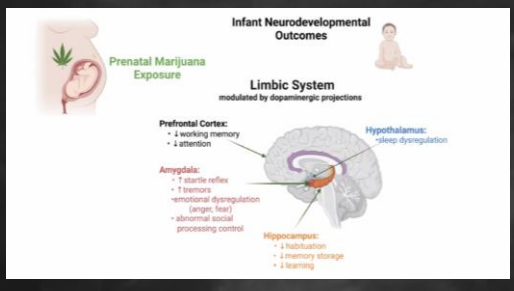

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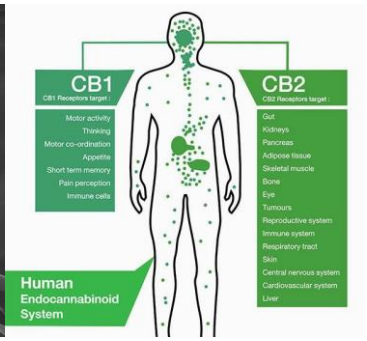
The Way We're Wired: The Endocannabinoid System

- Present at 5 week gestation
- Role in formation of
  - neural circuitry,
  - neural stem cell survival, proliferation, migration
  - differentiation of glial and neuronal lineages.
- THC acts as a partial agonist of CB1 receptors.



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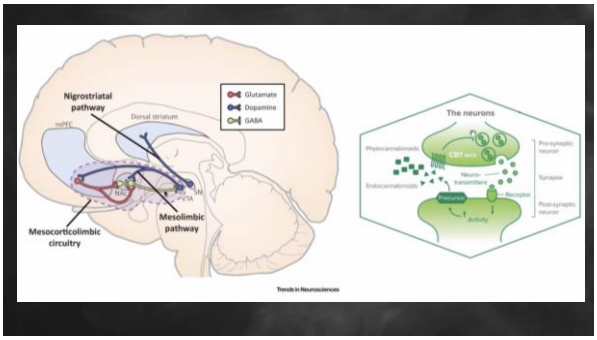

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Studies of the 70's and 80's

- Most current literature is based on fetal exposure in the 70's-early 90's
- Why this matters?

- **Potency**
- Over 300% increase in THC concentration in products for recreational cannabis since the early 90's
- Rates of daily use and quantity used are increasing along with increase in potency

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What we know and what we suspect

- We know that fetal and early childhood THC exposure alters brain biochemistry
- We know that there are alterations in behavior associated with THC use in early life

- We suspect this may become a more profound impact as potency and thus exposure increases

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Short term impact

- Fetal growth retardation causing low birth weights
- Higher chance of requiring NICU care

- Little to no evidence supporting causality in preterm birth or birth defects

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Long term implications

- Toddlers
  - Little to no alteration in behavior or outcomes
- School age
  - Increased rates of impulse control, hyperactivity and problems with attention
- Adolescents
  - Higher rates of depression, psychosis and drug/ethanol abuse

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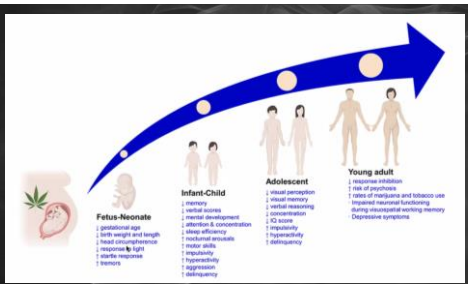

- Navarrete F. Cannabis Use in Pregnant and Breastfeeding Women: Behavioral and Neurobiological Consequences. Front Psych. 2020

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Breast milk

- THC crosses into breast milk
- Concentrations in breast milk can exceed 8x maternal serum levels

- HOWEVER
- THC has a large volume of distribution and rapidly redistributes out of maternal serum – thus maternal serum levels are often quite low
- Total exposure through breast milk is relatively low

- LOW exposure is not NO exposure

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Table 1. Summary of recommendations

Issue	Recommendations
Detection of maternal use	Antenatal drug and alcohol questions best to screen large populations Maternal and infant toxicology most likely unhelpful unless maternal history is ambiguous[56] Early detection may help implement harm-minimisation strategies
Fetal effects	No definitive link to increased spontaneous abortions[67] or congenital abnormalities[64,65] Intrauterine growth restriction, including head size of fetus, common[63]
Neonatal effects	Severe withdrawal uncommon but mild symptoms similar to an opioid-type withdrawal is recognised[69] Need for pharmacological treatment from cannabis only exposure uncommon Transient high pitched cry[69] and sleep disturbances[68] noted Increased risk of sudden infant death syndrome[66]
Effects on childhood and later life	Small head circumference may persist into teenage life Risk of long-term problems correlated with severity of prenatal exposure,[74] particularly on visual memory and executive function[74,75] that may persist to late childhood[75] and adolescence[76] Aggression and attention problems noted in toddlers (especially girls)[73]
Lactation	Cannabis and metabolites cross the milk barrier, and levels in milk may be higher than maternal plasma[69] Effects of continued use during lactation may impair early (<1 year) neurodevelopment[60]
General	Screen all pregnant women for drug use with a well-validated questionnaire Cease or decrease use as early as possible—chronic/heavy use (> 1 joint per day) increases risk of long-term adverse outcomes for the child Lactation recommendations must be taken on a case by case basis. Mother must be aware of dangers of breast feeding while intoxicated, of passage of cannabis and metabolites into milk and of possible adverse influence of continued cannabis exposure via breast milk on childhood neurodevelopmental outcomes There is insufficient current evidence to provide definitive recommendations for the use of medicinal cannabis

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Testing for THC

Table 2. **Testing for marijuana in biological samples**[a]

Biological sample	Duration of positive result	Test limitations
Maternal urine	2-3 d in occasional users; several weeks in chronic users	Chronicity of use determines duration of positive result
Maternal serum	2-3 d in occasional users; several weeks in chronic users	Chronicity of use determines duration of positive result Invasive sample Shorter half-life than urine
Maternal hair	Several weeks	Less accurate for marijuana than for other drugs False-positives from passive exposure Not clinically used because of cost and inaccuracy
Meconium	Positive result indicates second- and third-trimester exposure	Small amount of detectable THC in the samples High false-positive rate (up to 43%) Send out to reference laboratory Costly and impractical at many sites
Neonatal hair	Positive result indicates third-trimester exposure	Costly and impractical at many sites Less sensitive than meconium

Abbreviation: THC, Δ9-tetrahydrocannabinol.
[a]From Metz and Stickrath.[13] Used with permission.

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SIDS: Impact of nicotine

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Societal Burden

- $122 million in healthcare costs for infant hospitalization after delivery were attributable to prenatal smoking

- According to 2014 CDC report over 1,000 infant deaths each year are attributable to prenatal nicotine exposure

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SIDS Risk

- First associated with LACK of breastfeeding

- 0.9 per 1,000 live births

- ANY Breastfeeding is protective
  - More than 6 months OR 0.25
  - No statistically significant benefit <2 months breastfeeding

- Smoking during pregnancy more than doubles the risk of SIDS

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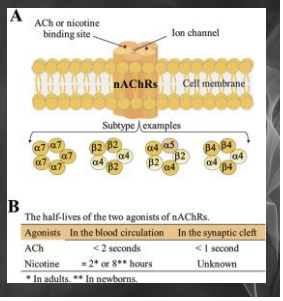
Nicotine Action in Brain: Nicotinic Acetylcholine Receptors

- Nicotine
  - Easily crosses the blood brain barrier
  - Tightly binds receptors in the brain and doesn't let go
  - Binding causes persistent depolarization of neuron leading to permanent brain function and chemistry alterations



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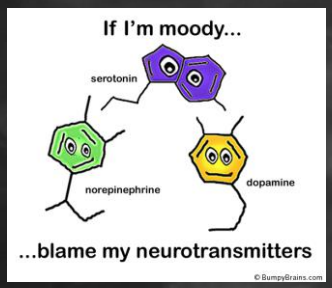
Neurotoxicity of Nicotine: Serotonin System



- Nicotine decreases serotonin binding to receptors
- Stimulation of serotonin receptors by nicotine causes abnormal neurologic, circulatory and psychologic functioning

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Autoresuscitation

- Hypoxia and/or hypercarbia stimulates a central response in respiratory drive, increasing respiratory rate and depth
- Control centers for autoresuscitation reside in nucleus tractus solitarius
- NTS receives input from chemoreceptors and baroreceptors as well as cranial nerves regulating blood pressure, respiratory drive, heart rate amongst other critical bodily functions

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Autoresuscitation Animal Model

- Animal models have demonstrated nicotine dysregulates nAChR in the NTS causing diminished response to hypoxia, hypercarbia and additionally causing bradycardia and hypotension
- In these animal models hypoxic insults in addition to nicotine resulted in death whereas non-nicotine exposed animals were able to recover

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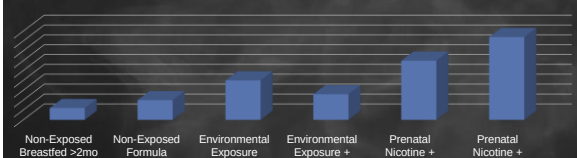
SIDS Risk Stratification



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Importance of breastfeeding

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Maternal Impact

Breastfeeding >13 months confers:

Decreased risk of breast and ovarian cancer

Decreased risk of ischemic stroke

Decreased risk of myocardial infarction

Decreased risk of Type 2 Diabetes and Metabolic Syndrome

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Infant Impact

Prolonged breastmilk feedings confer:
Decreased risk of sudden infant death syndrome

Decrease risk of immune mediated chronic diseases

Decreased risk of hospitalization related to respiratory and gastrointestinal illnesses

Decreased risk of childhood leukemia and lymphoma

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Societal Impact

Improves maternal infant bonding and decreases risk of abuse and neglect

Improved maternal and infant health keeps children in school and employees in the work force

Fewer healthcare dollars spent on preventable illnesses

Decreased preventable maternal and child death

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Summary

- Any source of nicotine or THC exposure places fetal and infant development at increased risk
- Nicotine causes adverse change to milk production, milk composition and immunoactive and protective qualities
- Permanent lung and brain alterations and immune dysfunction in exposed neonates
- Early life THC exposure likely has lifelong neurologic and behavioral impact

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What next?

- Is it safe to breastfeed while smoking?
  - *No, but is it better to not breastfeed? We need more studies and information*
- How many cigarettes are too many?
  - *One is too many...*
- Can smoking (*anything*) while pregnant or breastfeeding cause harm?
  - *Yes*
- Are there still benefits from breastfeeding if mom smokes?
  - *Both mom and baby potentially still benefit in some respects but perhaps not others*

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So What Now?

- What should our advice be?
  - **Quit** smoking, or **cut down** as much as possible
  - Smoke AFTER breastfeeding and give as much time between a cigarette and breastfeeding as possible
  - Knowledge is power – use of THC is harmful, nicotine products are harmful
  - Limit exposures:
    - Don't smoke around baby
    - Decrease 2nd and 3rd hand smoking

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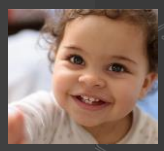
Community Resources



Https://www.Bewellarkansas.Org/be-well-baby/

Participants must be:
Pregnant at 36 weeks gestation or less
Current smoker or smoked within 3 months of pregnancy
A smoker who lives with someone enrolled in be well

Participation is free to all
There are NO age, income or insurance requirements for any participants

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Resources for Healthcare Providers and Parents

- https://www.acog.org/womens-health/infographics/marijuana-and-pregnancy
- https://cdphe.colorado.gov/marijuana-health-care-provider-resources
- https://www.cdc.gov/marijuana/factsheets/pregnancy.htm

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