Cannabinoids Exacerbate Alcohol-induced Birth Defects in Rodents and Zebrafish

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Conflict of Interest:

No Disclosures
Synthetic Cannabinoids

Potent analogues of THC
Up to 100 x higher affinity for the cannabinoid receptors

Abuse has resulted in a significant increase in emergency room visits

Second only to natural cannabis as the most widely abused illicit substances in the United States and around the world.
Early mouse development

Equivalent to day 22 of gestation in humans
Synthetic cannabinoid-induced craniofacial malformations

Control  Midfacial Hypoplasia  Micrognathia

Gilbert et al., 2016
Dose-dependent synthetic cannabinoid-induced eye defects

Gilbert et al., 2016
Figure 2. Adjusted Prevalence of Marijuana Use Among 279,457 Pregnant Females in KPNC by Age, 2009-2016

Adjusted Prevalence of Marijuana Use, %

Year


Age <18 y
Age 18-24 y
Age 25-34 y
Age >34 y

Young-Wolff et al., 2017
These teratogenic effects are consistent across numerous different cannabinoids.

Fish et al., under review
Co-administration of alcohol and cannabinoids

<table>
<thead>
<tr>
<th>CB Dose (mg/kg)</th>
<th>Veh</th>
<th>1.4</th>
<th>2.8</th>
<th>Veh</th>
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Fish et al., under review
Replication of alcohol and cannabinoid effects in zebrafish

Fish et al., under review
These drugs mimic genetic mutations in the Sonic hedgehog (Shh) pathway.
Role of the Shh pathway gene in cannabinoid teratogenicity

Fish et al., under review
Rescue of CB and ethanol effects with Shh mRNA in fish

Fish et al., under review
Rescue of CB effects with CB1 receptor antagonist in mice

Fish et al., under review
What are the long-term effects of these cannabinoids?
Acute prenatal exposure impacts adult behavior in mice
Early mouse development

Day 7
Day 8
Day 9
Day 10
Day 11
Repeated Cannabinoid Exposure during early pregnancy

Live Fetuses/Litter (Mean + SEM)

CP 55,940 (mg/kg)

- Veh
- 0.1
- 0.03
Repeated Cannabinoid Exposure during early pregnancy

![Graph showing the number of live fetuses per litter (Mean ± SEM) for different CP 55,940 (mg/kg) doses: Veh, 0.1, and 0.03 mg/kg. The graph indicates a significant decrease in the number of live fetuses as the cannabinoid exposure increases.](image-url)
Early rat development

Day 8

Day 9

Day 10

Day 11

Day 12
Effect of repeated cannabinoid exposure on embryonic survival

Number of Live Fetuses

CP 55,940 (mg/kg) + Alcohol (2.0 g/kg)
Effect of repeated cannabinoid exposure on adolescent drinking behaviors

Alcohol Self-Administration (20% EtOH)

- Male, Veh
- Male, EtOH
- Male, CP + EtOH

Laura Ornellas
Besheer Lab
Conclusions

• THC and synthetic cannabinoids are potently teratogenic.

• Cannabinoids modify the teratogenicity of alcohol in a synergistic manner through a novel interaction between Smo and CB1.

• Repeated exposures are consistently embryolethal.

• Prenatal exposure increases adolescent drinking.

• The teratogenic effects of both natural and synthetic cannabinoids may be too often attributed to alcohol.
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NIAAA
National Institute on Alcohol Abuse and Alcoholism

CIFASD
Collaborative Initiative on Fetal Alcohol Spectrum Disorders