Gender and cannabis interactions in psychosis

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Disclosures
Nothing to disclose.

Learning Objectives
- Differences in biology between males and females that may be relevant to the development of psychosis
- Cannabis 101
  - what the key constituents are
  - An overview of the pharmacokinetics of THC
- Differences between men and women with psychosis in metabolism and in clinical outcomes
- Understanding of the current clinical picture of women with psychosis who use cannabis.

Gender and Health
www.newsweek.com
Gender

- A source of ongoing debate: "How different are men and women?"
- Canadian Journal of Public Health

Inherent biological differences

- Focus on factors related to differences between men and women that may be relevant to differences in clinical outcomes in psychosis
  - Brain Size differences
  - Tract differences
  - Metabolic differences

Size differences

- We accept that women on average have smaller body sizes than men.
- Similarly, there is only 5% overlap in brain size between men and women.

Tract differences

- Evidence of sexual dimorphism in organization of white matter tracts in the brain
- Very recent work has shown widespread differences in the trajectory during development between males and females
- More advanced development in females (lower mean diffusivity, radial and axial diffusivity, and higher FA). Divergence much larger at lower ages (8–9 years) with diffusion measures tending to converge between 10 and 14 years of age. (Seunarine, K. K. et al. (2016))
Neurochemistry

- NAA is a measure of the energy expenditure of neurons in the brain when measured by 1H-MRS.
- NAA differences have been found between male and female subjects (Jung et al, 2005).
- Analysis of our 1-MRS data also suggests increased NAA in females compared to males.

Metabolic differences

- Females have greater sensitivity to insulin in skeletal muscle.
- Changes in lipid utilization with changes in menstrual cycle.
- Pharmacokinetics in women is affected by slower gastrointestinal motility, less intestinal enzymatic activity, and slower glomerular filtration rate.

Gender in Psychosis

- Studies complicated by the relative inequality of numbers of male to female patients.
- Clinically different presentation leading to a different diagnosis?

Metabolic differences

- Women with psychosis had significantly lower LDL-c from age 46 and significantly lower total cholesterol before age 33 and after age 45 than controls.
Clinical picture

- At entry to early intervention services, female patients had more suicide attempts (Tseliou 2015).
- Males have been found to have more severe negative symptoms in several studies but some studies show no gender effects.

Social functioning

- Better in women compared to men.
- In early psychosis, women more likely to be married, have children, better GAF scores, less unemployment.
- Results are less clear between the genders in studies with schizophrenia patients.

Cannabis

- Most common recreational drug
- Soon to be legalized

But how much do we know about its effects?
- Complete cure-all versus completely harmless
Complicated

Chemical constituents

- For simplicity often refer to 4 main cannabinoids in Cannabis
  - Delta-9 THC
  - Cannabidiol (CBD)
  - Cannabinol (CBN)
  - Delta-8 THC
- As for the rest...

Delta-9 THC

- is the psychotropic component of cannabis
- euphoria and in some cases anxiety and panic reactions.

This is not your grandpa’s marijuana

- THC potency has increased from 4.56% in 1996 to 11.75% in 2008 (Burdorf et al., 2011).
- In the 1960s estimated to be less than 1% and was 3% in the 1970s-1980s (methodological considerations)
Chemical constituents

- Cannabidiol (CBD)
  - Does not interact with cannabinoid receptors
  - Lacks psychotropic and most other effects of Δ9-THC, but has anticonvulsant activity in animals (the receptor problem here).
  - MJ Use in first seizure clinic would suggest that it is not protective from seizures (Crocker et al., 2016 submitted)
  - May attenuate some unwanted psychological effects of THC, hence the interest in CBD:THC ratios.

- Cannabinol (CBN)
  - Present in very low quantities in cannabis
  - May have immunosuppressive properties and binds to CB2 receptors. Very weak affinity for CB1 and does not have strong psychotropic effects (https://pubchem.ncbi.nlm.nih.gov/compound/cannabinol)
  - Some suggestion of sleep inducing properties in the cannabis blogs.

- Delta-8 THC
  - Psychoactive
  - Very low quantities
  - Some work being done on blocking polyglutamine huntingtin toxicity in PC12 cells (https://pubchem.ncbi.nlm.nih.gov/compound/2977#section=BioAssay-Results)
Trends of Drug use by Gender

- CADUMS 2012
  - 13.7% for males aged 15 years and over
  - 7% for females aged 15 years and over

Increased risk?

- Only use at half the rate of males (7% compared to 14%) of the users but half of cannabis related ER visits are females.
- the most commonly reported features in lone-cannabis cases are neuro-behavioural (agitation/aggression (22.9 %), psychosis (20.0 %), anxiety (20.0 %)) and vomiting (17.1 %).

Increased risk?

- Fatality can result but usually males amongst these fatal lone-cannabis cases:
- “an 18-year-old male collapsed with an asystolic cardiac arrest whilst smoking cannabis and suffered hypoxic brain injury related to prolonged cardiac arrest. THC was detected in a urine sample taken at ED arrival; no other drugs were detected.” (Dines et al., 2015)

Poorer Picture?

- Cannabis slows gastric emptying in women but not men (Esfandyari et al., 2006)
- Women reported more dizziness than men (Matthew et al., 2003)
- Women also report subjective feelings of being “high” at a lower dose than men (Fogel et al., 2016) but develop tolerance more rapidly than men.
- Women are also more likely to report withdrawal symptoms (Levin et al., 2010).
Cannabis and Psychosis

- Consistent demonstration of an association between adolescent cannabis use and development of psychosis
- Preventable risk factor for psychosis development
- Mechanistic link between cannabis use and SCZ. THC especially as is found in skunk CB can cause acute, transient, dose-dependent psychosis.

Correlations with co-morbid drug use

- Almost half of the patients treated for cannabis-induced psychosis developed a schizophrenia-spectrum disorder subsequently (Arendt et al., 2005).
- Men had higher levels of alcohol and cannabis use together compared to women and men who used and had psychosis were more likely to use other recreational drugs (Van Mastrixt et al., 2004).

Cannabis and FEP

- Much less is known about the combined picture.
- Once gender is added in the amount we know declines even further.
Age of onset

- Work in males with psychosis has consistently shown that age of onset of psychosis correlates with the age of onset of psychosis (Large et al., 2011; Di Forti et al., 2014).
- Only a couple of studies have been done in female subjects and recently we have begun examining this in our clinic. The same trend appears to hold for females.

Clinical Outcomes with co-morbid drug use

- Cessation of substance use improves outcome in patients with a psychotic illness.
- Female gender is one of the most powerful predictors of good outcome at 6 years, together with good insight and less substance use (McGorry et al., 2009).
- Substance abuse may have a more severe negative impact on the course of schizophrenia in women than men and may warrant closer attention (Lange et al., 2014).

Addiction issues

- Significantly more men with psychosis than women met criteria for SUD at baseline. One study showed cannabis use disorders at baseline: males = 27.5% of participants, females = 11% of participants.
- However, at follow-up, men with SUD significantly reduced but not for women. Cannabis use disorders at follow-up: males = 15.4%, females = 9.5% (Lange et al., 2014).

Modeling

- Modeling gender, FEP and cannabis use show better processing speed and social cognition, male gender, and fewer negative symptoms predicted how recently cannabis was used (Arnold et al., 2015).
Mechanisms?

- Animal model of female adolescent cannabinoid exposure shows decreased LTP and may represent an inability to adapt to external influences (Lovelace et al., 2015).
- Then there is cholesterol and NAA in differences in females combined with hormones.

Clinical Outcomes from our clinic

- Cessation of substance use improves outcome in patients with a psychotic illness.
- More relapses and hospitalizations seen over the first year at NSEPP in women with psychosis who used cannabis at clinic entry compared to women who did not.
- Overall prognosis for women with psychosis who use cannabis may be poor.

Summary

- While less common for women with psychosis to have cannabis use disorder (CUD), early indications are that poorer outcomes may be expected for these individuals even compared to males with psychosis and CUD.
- The reasons behind this are presently unknown.

Final thought

- While young males are usually the focus of addiction concern, young females may be more challenging if addicted.
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