



# Cannabis and Psychosis

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Augusta University



Johnny's Ambassadors  
Webinar Series  
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## Learning Objectives

The presentation is designed to help you:

1. Assess the evidence for an association between cannabis and psychosis.
2. Discuss the epidemiology and phenomenology of psychosis and comorbid cannabis use
3. Discuss associations between cannabis use, and clinical course and outcomes in psychosis.



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## “Bonus” Learning Objective

4. Discuss pupillometry as a novel marker of suicide risk in patients with psychiatric disorders.



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## Disclosures

Past 12 months

- **Augusta University**
  - Salary, Grant support, Meeting expenses
- **National Institute of Mental Health**
  - Grant support, Consultant
- **Stanley Medical Research Institute**
  - Grant support
- **Psychiatric Times**
  - Honoraria, Editorial Board Member
- **Boehringer Ingelheim**
  - Advisory Board



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## Outline

- What is psychosis?
- Cannabis and psychosis risk
- Psychosis and comorbid cannabis use
- Cannabis use, clinical correlates, and outcomes in psychosis
- Pupillometry and suicide risk



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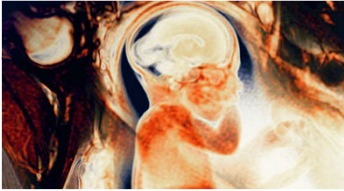
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## What is Psychosis?



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### What is Psychosis?

- Significant impairment in reality testing, as evidenced by:
  - Hallucinations
  - Delusions
  - Thought disorganization
  - Grossly disorganized behavior
- Psychosis is a symptom present in many conditions: schizophrenia, mood disorders, "organic" medical conditions

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### Standard Model of Schizophrenia

Schizophrenia  
=  
Disease with onset in late teens/early 20's  
=  
Psychosis (Hallucinations & Delusions)  
=  
Dopamine dysfunction  
=  
Brain disease

Kirkpatrick et al. (2013) Clinical Schizophrenia & Related Psychoses

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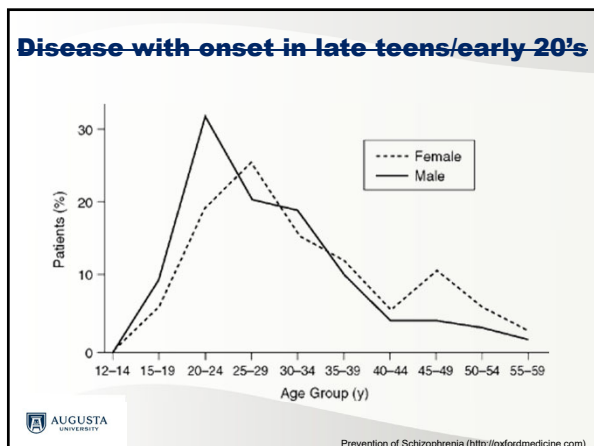
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## Brain Disease

- Replicated associations of anatomical and physiological abnormalities outside the brain in patients with schizophrenia AND 1<sup>st</sup> degree relatives:
  - Minor physical anomalies
  - Diabetes and abnormal glucose metabolism (prior to treatment)
  - Autoimmune disorders and inflammation



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Kirkpatrick et al. (2013) *Clinical Schizophrenia & Related Psychoses*

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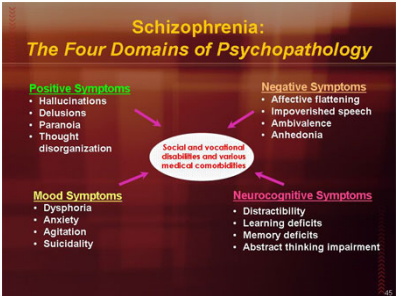
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## Psychosis (Hallucinations & Delusions)

### Schizophrenia: The Four Domains of Psychopathology



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Symptoms of Schizophrenia ([http://www.medscape.org/viewarticle/550755\\_13](http://www.medscape.org/viewarticle/550755_13))

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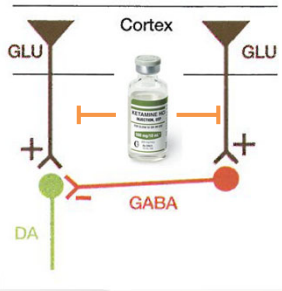
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## Dopamine dysfunction



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Krystal et al. (1994) *Arch Gen Psychiatry*

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### Schizophrenia Epidemiology

- Prevalence (# cases at any one time point)
  - 1% worldwide
- Incidence (# new cases annually)
  - 1.5 per 10,000 people
- Slightly more men are diagnosed (~ 3:2)
- Women tend to be diagnosed later in life

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Fisher et al. (2018) Up To Date

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### Schizophrenia Risk Factors

- Prenatal and early life infections
- Obstetric complications
- Season of birth
- Advanced paternal age
- Living in an urban area
- Immigration
- Childhood trauma
- Autoimmune disorders
- Genetics
- **Marijuana use**

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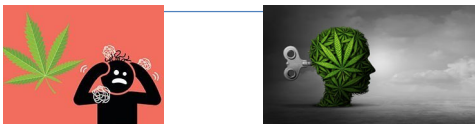
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### Cannabis and Psychosis Risk



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**Case Vignette**

- “Mr G” is a 39 year-old African-American male with a history of chronic schizophrenia, cannabis use disorder, and alcohol use disorder.
- He started smoking cannabis almost daily at age 20.
- When he was 22, he was in a motor vehicle accident while under the influence of substance and suffered a head injury.



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**Case Vignette (2)**

- Several months later, he was hospitalized for a first episode of psychosis.
- For more than a decade, he has been maintained on a long-acting injectable antipsychotic medication and is adherent with appointments.
- He tends go get paranoid under stress, but has not had any subsequent psychiatric hospitalizations.



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**Case Vignette (3)**

- He has continued to use cannabis regularly--daily to weekly--for almost 20 years.
- Although he worked prior to the onset of his illness, he has since been chronically unemployed.
- He lives at home with his parents, has never married, and does not have any children.
- He denies the need for treatment for alcohol and cannabis use disorder.



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### Case Vignette - Comments

- Mr G's case is all too familiar for psychiatrists.
- Substance use comorbidity in psychosis is the "rule", and it is often deleterious to the illness.
- Cannabis is one of the most commonly used substances by patients with psychosis.
- Modulation of the endocannabinoid system by the main psychoactive component in marijuana,  $\Delta^9$ -tetrahydrocannabinol, can induce psychosis and cognitive impairment.



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### Cannabis and Psychotic Experiences

- In an analysis of 61 cohorts (children and adults), those using cannabis were:
  - 2.5 times more likely to endorse current psychotic experiences
  - 1.8 times more likely to have new-onset psychotic experiences
- 7.4% of people with psychotic experiences go on to develop a psychotic disorder



Linscott and van Os. (2013) *Psychol Med*

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### Cannabis and Psychosis Risk

- In 30 studies, among 4205 individuals at "ultra high risk" for psychosis:
  - 27% were current cannabis users
  - 53% were lifetime cannabis users
  - 13% met criteria for active cannabis use disorder



Carney et al. (2017) *Acta Psych Scand*

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## Cannabis and Transition to Psychosis

- In 7 studies, including 1171 people at “ultra high risk” for psychosis:
  - Those with a current cannabis use disorder were **1.8 times** more likely to transition to (i.e., develop) a psychotic disorder



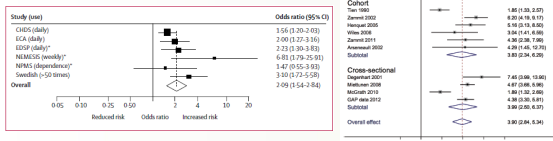
Kraan et al. (2016) *Psychol Med*

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## Cannabis and Psychosis Risk

- Frequent cannabis users are **2-4 times** more likely to develop a psychotic disorder, with evidence of a “dose-response” relationship.



Moore et al. (2007) *Lancet*  
Marconi et al. (2016) *Schiz Bull*

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## Shared Genetic Risk

- Genes that may predispose to cannabis use disorder are also associated with schizophrenia.

### A large-scale genome-wide association study meta-analysis of cannabis use disorder

Emma Johnson<sup>1</sup>, Datta Dhanraj<sup>2</sup>, Thangaraj Thangaraj<sup>3</sup>, Raymond Walters<sup>4</sup>, Remko Pollock<sup>5</sup>, Alexander S. Houts<sup>6</sup>, Sandra Sanchez-Berni<sup>7</sup>, Sarah E. Abel<sup>8</sup>, Frank P. White<sup>9</sup>, Tom F. Slater<sup>10</sup>, Dongqing Li<sup>11</sup>, Gwern W. Reynolds<sup>12</sup>, Hong Zhuo<sup>13</sup>, Junhua Zhou<sup>14</sup>, David A. Braggart<sup>15</sup>, Daniel F. Gudimov<sup>16</sup>, Andrew W. Ross<sup>17</sup>, David F. Adkins<sup>18</sup>, Jeffrey J. Goldstein<sup>19</sup>, Shihua Chen<sup>20</sup>, Shuang Chen<sup>21</sup>, Yan H. Jiang<sup>22</sup>, Joseph Breen<sup>23</sup>, Sandra A. Brown<sup>24</sup>, Kathleen B. Bucholz<sup>25</sup>, James Byrnes<sup>26</sup>, Christopher H. Rasmussen<sup>27</sup>, Cory A. J. Flint<sup>28</sup>, Joseph Degenhardt<sup>29</sup>, Donald M. Dick<sup>30</sup>, Benjamin D. O'Connell<sup>31</sup>, Paul A. Alpers<sup>32</sup>, Alan C. Cook<sup>33</sup>, Sarah E. Castel<sup>34</sup>, Sarah E. Castel<sup>35</sup>, David F. Adkins<sup>36</sup>, Ian Wright<sup>37</sup>, Donald Henderson<sup>38</sup>, Kenneth G. O'Keefe<sup>39</sup>, Penelope A. Lee<sup>40</sup>, Jennifer M. McClure<sup>41</sup>, Matthew B. McQueen<sup>42</sup>, Joseph D. Martin<sup>43</sup>, Gwern W. Reynolds<sup>44</sup>, Gwern W. Reynolds<sup>45</sup>, Michael R. Munafò<sup>46</sup>, John P. Rice<sup>47</sup>, Thomas W. Rice<sup>48</sup>, Thomas W. Rice<sup>49</sup>, Robert S. Stine<sup>50</sup>, Julie S. Sturgis<sup>51</sup>, Robert F. Tarter<sup>52</sup>, Thomas J. Crowley<sup>53</sup>, Thomas J. Crowley<sup>54</sup>, David M. Lyubovitsky<sup>55</sup>, Fariha F. Farooq<sup>56</sup>, Nicholas A. Gillespie<sup>57</sup>, Richard A. Grieco<sup>58</sup>, Kathleen M. Gilliland<sup>59</sup>, Andrea C. Heath<sup>60</sup>, Nicholas G. Martin<sup>61</sup>, John F. Honea<sup>62</sup>, Christian Hopfer<sup>63</sup>, John H.oyer<sup>64</sup>, William C. C. Duncan<sup>65</sup>, Kenneth S. Kendler<sup>66</sup>, Barbara A. Kennedy<sup>67</sup>, Henry P. Lester<sup>68</sup>, Pamela A. Madden<sup>69</sup>, Harriet M. Malt<sup>70</sup>, Brian S. Mathew<sup>71</sup>, Nicholas G. Martin<sup>72</sup>, Matthew McClure<sup>73</sup>, Andrew W. McQueen<sup>74</sup>, Sarah E. Castel<sup>75</sup>, David F. Adkins<sup>76</sup>, Benjamin D. O'Connell<sup>77</sup>, Michael C. O'Leary<sup>78</sup>, Michael W. Parnell<sup>79</sup>, Gwern W. Reynolds<sup>80</sup>, Gwern W. Reynolds<sup>81</sup>, Gwern W. Reynolds<sup>82</sup>, Gwern W. Reynolds<sup>83</sup>, Gwern W. Reynolds<sup>84</sup>, Gwern W. Reynolds<sup>85</sup>, Gwern W. Reynolds<sup>86</sup>, Gwern W. Reynolds<sup>87</sup>, Gwern W. Reynolds<sup>88</sup>, Gwern W. Reynolds<sup>89</sup>, Gwern W. Reynolds<sup>90</sup>, Gwern W. Reynolds<sup>91</sup>, Gwern W. Reynolds<sup>92</sup>, Gwern W. Reynolds<sup>93</sup>, Gwern W. Reynolds<sup>94</sup>, Gwern W. Reynolds<sup>95</sup>, Gwern W. Reynolds<sup>96</sup>, Gwern W. Reynolds<sup>97</sup>, Gwern W. Reynolds<sup>98</sup>, Gwern W. Reynolds<sup>99</sup>, Gwern W. Reynolds<sup>100</sup>





Johnson et al. (2020) *Lancet Psychiatry*

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## Schizophrenia and Comorbid Cannabis Use



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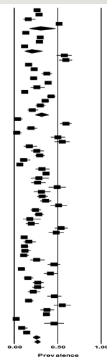
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### Epidemiology

- A review of 69 studies in community and clinical settings found that 26-36% of patients with schizophrenia have current or lifetime cannabis use
  - Higher rates in new-onset illness
  - More common in males
  - Some evidence that use declines over time (years)
- In 10 studies, the average time between the initiation of regular cannabis use and the onset of psychotic illness was ~ 6 years



Hunt et al. (2018) *Drug Alcohol Dep*  
Myles et al. (2016) *Aust N Z J Psychiatry*

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### Epidemiology (2)

- In 41 studies, the age of onset of psychosis was 32 months (2.7 years) EARLIER for cannabis users versus non-users.
  - Compared to 2 weeks later in tobacco smokers versus non-smokers

**META-ANALYSIS**

ONLINE FIRST  
**Cannabis Use and Earlier Onset of Psychosis**  
*A Systematic Meta-analysis*

Matthew Large, BS (Med), MBBS, FRANZCP; Swapnil Sharma, MBBS, FRANZCP;  
Michael T. Compton, MD, MPH; Tim Slade, PhD; Olav Nielssen, MBBS, MCrim, FRANZCP

AUGUSTA UNIVERSITY Large et al. (2011) *Arch Gen Psychiatry*

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### Symptoms

- In an analysis of 22 studies, no difference in psychopathology (positive, negative, and mood symptoms) in patients with psychosis and cannabis versus non-cannabis substance use
- BUT, interestingly...

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### Cognition (Thinking)

- In 10 studies (572 subjects), individuals with lifetime (but NOT current/recent) cannabis use had significantly BETTER:
  - Global cognition
  - Planning
  - Processing speed
  - Visual and working memory
- In 14 studies, those with CURRENT cannabis use had significantly LOWER/WORSE:
  - Premorbid & Current IQ
  - Verbal learning
  - Motor inhibition
  - Working memory

AUGUSTA UNIVERSITY Yucel et al. (2012) *Schiz Bull*  
Bogaty et al. (2018) *J Psych Res*

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### Illness Course

- In 15 studies (3678 subjects), cannabis users versus non-users were:
  - 2.5 times more likely to be non-adherent with antipsychotic medication at baseline
  - 5.8 times more likely to be non-adherent with antipsychotic medication at follow-up
- Continued cannabis use is also associated with:
  - Increased risk of illness relapse
  - Longer duration of hospitalization

AUGUSTA UNIVERSITY Foglia et al. (2017) *J Psychol Med*  
Schoeller et al. (2017) *Lancet Psychiatry*

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### IN SUMMARY

#### Cannabis Use Is Associated With:

- ↑ risk of psychotic experiences
- ↑ prevalence of use in people at ultra high-risk for psychosis
- ↑ risk of transition to psychotic disorder with current cannabis use disorder
- Dose-dependent association between use and risk of psychosis
- Genetic correlation between cannabis use and schizophrenia
- ↑ prevalence in first episode psychosis and chronic schizophrenia (especially males)
- Earlier age of onset of psychosis
- Variable effects on cognition in psychosis
- ↑ antipsychotic non-adherence in current users (at baseline and follow-up)
- ↑ risk of relapse of psychosis with continued use
- Longer duration of hospitalization for psychosis



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### Conclusions

- Targeting cannabis use during the high-risk period for psychosis may confer significant benefits on long-term outcomes.
- Continued cannabis use is also a potential target for intervention to improve antipsychotic adherence and other outcomes in patients with psychotic disorders.



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### BONUS! Pupillometry



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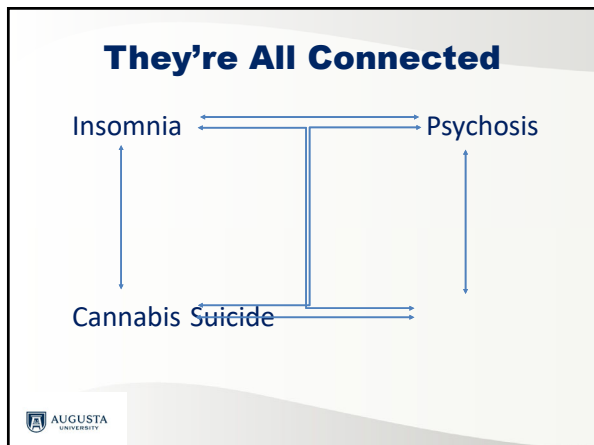
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### They're All Connected

- Limited by a lack of risk factors other than clinical/demographics (e.g., male, older age, mental illness, substance use, history of suicide attempt)
- There are no practical "point-of-care" biomarkers of suicide risk that can supplement clinical management



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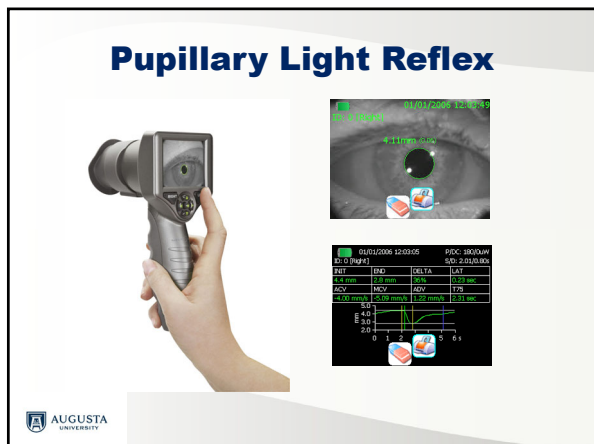
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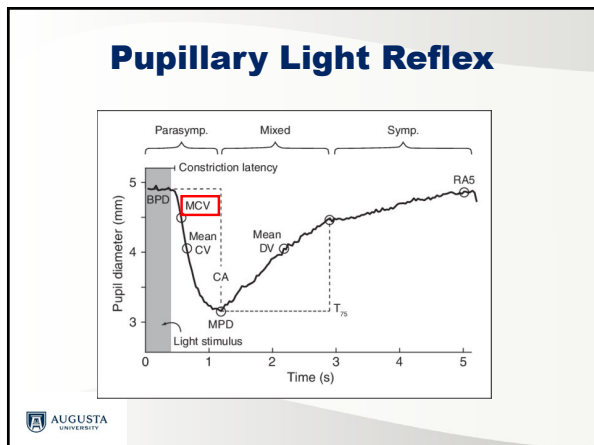
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### Preliminary Data

Patients with Schizophrenia or Major Depressive Disorder

Currently Suicidal	No	No	Yes	Yes
Ever Attempted Suicide	No	Yes	No	Yes
Subjects (n)	21	21	6	11
Age (years)	39	37	28	31
Gender (% male)	71	14	17	46
Race (% non-white)	48	52	33	51
MCV (mm/sec)	-3.7 ± 1.1	-4.4 ± 0.7	-4.7 ± 1.0	-4.5 ± 1.0

**American  
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### Acknowledgements



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### Thank you!

[brmiller@augusta.edu](mailto:brmiller@augusta.edu)



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