Psychiatric comorbidity and cannabis use

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## Cannabis use

### Table 1.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Best estimate</th>
<th>Low</th>
<th>High</th>
<th>Best estimate</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis</td>
<td>177.63</td>
<td>125.30</td>
<td>227.27</td>
<td>3.8</td>
<td>2.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Opioids</td>
<td>33.04</td>
<td>28.63</td>
<td>38.16</td>
<td>0.7</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Opiates</td>
<td>16.37</td>
<td>12.80</td>
<td>20.23</td>
<td>0.35</td>
<td>0.28</td>
<td>0.43</td>
</tr>
<tr>
<td>Cocaine</td>
<td>17.24</td>
<td>13.99</td>
<td>20.92</td>
<td>0.37</td>
<td>0.30</td>
<td>0.45</td>
</tr>
<tr>
<td>ATS</td>
<td>34.40</td>
<td>13.94</td>
<td>54.81</td>
<td>0.7</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>“Ecstasy”</td>
<td>18.75</td>
<td>9.4</td>
<td>28.24</td>
<td>0.4</td>
<td>0.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Source: Estimates based on the UNODC annual report questionnaire.
Cannabis use
Cannabis use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>81.9%</td>
</tr>
<tr>
<td>Tobacco</td>
<td>35.3%</td>
</tr>
<tr>
<td>Cannabis</td>
<td>26.6%</td>
</tr>
<tr>
<td>Hypnotics</td>
<td>11.6%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>2.5%</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>2.2%</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>2.0%</td>
</tr>
<tr>
<td>Inhalants / Speed</td>
<td>1.7%</td>
</tr>
<tr>
<td>Volatiles</td>
<td>1.2%</td>
</tr>
<tr>
<td>Heroin</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Las drogas consumidas por un mayor porcentaje de estudiantes de 14 a 18 años siguen siendo el alcohol, el tabaco y el cannabis.

Les siguen los hipnosedantes, cocaína y extasis.
Cannabis administration

• **Smoked:**
  – Cigarettes, cigars, pipes, water pipes, *blunts/joints*

• **Ingested orally**
  – Cakes, infusions...
Cannabis products

- *Cannabis Sativa*
- Active component: delta-9-THC
- Derivates:
  - Marijuana: dried flowering tops and leaves (0.5-12% THC)
  - Hashish: resin of marijuana flowers (2-20% THC)
  - Hash oil (15-50% THC)
Cannabis products

- Cannabidiol (CBD)
  - Not impairs cognition
  - Anxiolytic and antipsychotic effects

Martín-Santos et al., 2012
Cannabis pharmacology

• The smoked cannabis is the most efficacy way to achieve the desired effects
• The THC delivered ranges from 20-70%
• Brain availability: 5-24%
Synthetic cannabinoids
Synthetic cannabinoids

• Known as *Spice*:
  – *K2, Moon Rocks, Yucatan Fire*
  – JWH-018 → JWH-073

• More potent than natural THC

• Elevate the mood, aid relaxation and alter perceptions

• Psychological disorders
Adverse Health Effects of Marijuana Use

Nora D. Volkow, M.D., Ruben D. Baler, Ph.D., Wilson M. Compton, M.D., and Susan R.B. Weiss, Ph.D.
# Cannabis adverse effects

Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

<table>
<thead>
<tr>
<th>Effects of short-term use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired short-term memory, making it difficult to learn and</td>
</tr>
<tr>
<td>to retain information</td>
</tr>
<tr>
<td>Impaired motor coordination, interfering with driving skills</td>
</tr>
<tr>
<td>and increasing the risk of injuries</td>
</tr>
<tr>
<td>Altered judgment, increasing the risk of sexual behaviors</td>
</tr>
<tr>
<td>that facilitate the transmission of sexually transmitted</td>
</tr>
<tr>
<td>diseases</td>
</tr>
<tr>
<td>In high doses, paranoia and psychosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effects of long-term or heavy use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction (in about 9% of users overall, 17% of those who</td>
</tr>
<tr>
<td>begin use in adolescence, and 25 to 50% of those who are</td>
</tr>
<tr>
<td>daily users)</td>
</tr>
<tr>
<td>Altered brain development</td>
</tr>
<tr>
<td>Poor educational outcome, with increased likelihood of</td>
</tr>
<tr>
<td>dropping out of school</td>
</tr>
<tr>
<td>Cognitive impairment, with lower IQ among those who were</td>
</tr>
<tr>
<td>frequent users during adolescence*</td>
</tr>
<tr>
<td>Diminished life satisfaction and achievement (determined on</td>
</tr>
<tr>
<td>the basis of subjective and objective measures as compared</td>
</tr>
<tr>
<td>with such ratings in the general population) *</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
</tr>
<tr>
<td>Increased risk of chronic psychosis disorders (including</td>
</tr>
<tr>
<td>schizophrenia) in persons with a predisposition to such</td>
</tr>
<tr>
<td>disorders</td>
</tr>
</tbody>
</table>

* The effect is strongly associated with initial marijuana use early in adolescence.

Volkow et al., 2014
• Is cannabis...
  – An addictive drug?
  – A gateway drug to the use of harder drugs?
  – A risk factor for impaired brain development?
  – A risk factor for affective, anxiety disorders and suicide?
  – A risk factor for psychosis?
Risk of addiction

• The 9% of those who experiment with cannabis will become addicted

• The risk increases if:
  – Adolescent use: 1 out of 6
  – Daily use: 25-50%
Risk of addiction

• Cannabis withdrawal syndrome:
  – Irritability
  – Sleeping difficulties
  – Dysphoria
  – Craving
  – Anxiety

Gorelick et al., 2012
Gateway drug

• Regular cannabis users were most likely to later use other illicit drugs

• The earlier the age of onset of cannabis use, the more likely to use other drugs

Hall & Degenhardt, 2007
Gateway drug

**FIGURE 3** | Cannabis use is associated with progression to use other illicit substances in humans. Twin-studies illustrate that cannabis users have an increased risk of developing substance abuse disorder compared to their discordant twin. Graph based on data adapted from Lynskey et al. (22) (A). Cross-sectional studies reveal that earlier and more frequent cannabis use further increases this risk. Graph based on data adapted from Fergusson et al. (21) (B).
Gateway drug

• Can cannabis *prime* the brain by decreasing the reactivity of the mesolimbic dopamine neurons?

• Or,

• People with high risk to drug use, will start first with marijuana because of its accessibility?
Brain development

- Endogenous cannabinoid system involved in brain development
- Decrease in IQ in regular use of cannabis during adolescence
  - Verbal learning
  - Memory
  - Attention

Meier et al., 2012
Brain development

Meier et al., 2012
Memory

• Impairments in memory function depending on the type of cannabis:
  – THC > CBD

• Some impairments are recovered after abstinence, but some could persist

Schoeler & Bhattacharyya, 2013
Cannabis, depression and suicide
Cannabis, depression and suicide

• Likelihood of depression in heavy cannabis users:
  – OR: 1.62 (95% CI: 1.21-2.16)
Cannabis, depression and suicide

- Risk factor for suicide
  - It is not possible to prove causality
- Familial co-aggregation
- Related to the endocannabinoid system: CNR1
  - Modulates mood

*Serafini et al., 2012*
Cannabis and anxiety

A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population - a meta-analysis of 31 studies

Karina Karolina Kedzior and Lisa Tabata Laeber

Kedzior & Laeber, 2014
Cannabis and anxiety

- Anxiety and cannabis use:
  - OR=1.24 (95% CI: 1.06-1.45)

- Anxiety and cannabis use disorders:
  - OR=1.68 (95% CI: 1.23-2.31)

- Anxiety + depression and cannabis use:
  - OR=1.68 (95% CI: 1.17-2.40)
Cannabis and anxiety

- Anxiety and cannabis use:
  - OR=1.24 (95% CI: 1.06-1.45)

- Anxiety and cannabis use disorders:
  - OR=1.68 (95% CI: 1.23-2.31)

  But the association disappears after controlling for other confounding factors

- Anxiety + depression and cannabis use:
  - OR=1.68 (95% CI: 1.17-2.40)
Cannabis and psychosis

- Worsen the course of psychotic disorders (including schizophrenia)
- Induce immediate-onset psychomimetic symptoms (during intoxication)
- Acute episodes of psychosis:
  - Manifest immediately following exposure
  - Last beyond the intoxication
  - Require clinical intervention
Cannabis and psychosis

**FIGURE 1** | Effects of THC on the seven-item positive symptom and negative symptoms subscales of the Positive and Negative Syndrome Scale (PANSS). THC at both a low dose (2.5 mg) (green) and moderate dose (5 mg) (100) induce an increase in positive and negative symptoms, compared to placebo (yellow). Adapted from Ref. [69].

**FIGURE 2** | Effects of THC on the clinician- and subject-rated subscales of the Clinician Administered Dissociative Symptoms Scale (CADSS), a measure of perceptual alterations. THC at both a low dose (2.5 mg) (green) and moderate dose (5 mg) (100) induce an increase in perceptual alterations as rated by the clinician and the subject, compared to placebo (yellow). Adapted from Ref. [69].
Cannabis and psychosis

- Worsen the course of psychotic disorders (including schizophrenia)
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- Acute episodes of psychosis:
  - Manifest immediately following exposure
  - Last beyond the intoxication
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Cannabis and psychosis

• Mediators:
  – Age of exposure
  – Degree of schizotypy
  – Familial risk
  – Childhood trauma
  – Genetic factors
Cannabis and psychosis

• Age of exposure:
  – The earlier the age of exposure to cannabis, the greater the risk of psychosis outcome
  – Age of onset of psychosis in cannabis users was 2.7 years earlier than in non-users

Radhakrishnana et al., 2014
Cannabis and psychosis

Leeson et al., 2011
Cannabis and psychosis

• **Age of exposure:**
  – Window of vulnerability hypothesis
    • Cannabis affects the brain during a critical period of development
  – Earlier age of onset $\rightarrow$ increased cannabis exposure
  – Subjects prone to psychoses would self-medicate with cannabis to relieve symptoms

Radhakrishnana et al., 2014
Cannabis and psychosis

• Schizotypy:

  – High scoring schizotype subjects that use cannabis are more likely to experience psychotic-dysphoric phenomena and intoxicating effects during and after use

Stirling et al., 2008
Cannabis and psychosis

- **Family history:**
  - A familial predisposition to persistent psychotic disorders precipitated by cannabis use
  - 2.5 fold increased risk of cannabis induced psychosis in offspring of schizophrenic mothers

*Radharkrishnan et al., 2014*
Cannabis and psychosis

<table>
<thead>
<tr>
<th>Diagnosis in Family Member</th>
<th>Schizophrenia Spectrum Disorder (n=6476)</th>
<th>Cannabis-Induced Psychosis (n=609)</th>
<th>P Value</th>
<th>Schizophrenia Spectrum Disorder (n=6476)</th>
<th>Cannabis-Induced Psychosis (n=609)</th>
<th>P Value</th>
<th>Schizophrenia Spectrum Disorder (n=6476)</th>
<th>Cannabis-Induced Psychosis (n=609)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia spectrum disorder</td>
<td>3.58 (2.89-4.44)</td>
<td>4.51 (2.40-8.47)</td>
<td>.51</td>
<td>5.12 (4.40-5.94)</td>
<td>2.57 (1.32-5.00)</td>
<td>.03</td>
<td>4.16 (3.65-4.75)</td>
<td>2.72 (1.56-4.73)</td>
<td>.12</td>
</tr>
<tr>
<td>Schizophrenialike disorder</td>
<td>2.53 (2.02-3.17)</td>
<td>1.78 (0.74-4.30)</td>
<td>.42</td>
<td>2.76 (2.32-3.28)</td>
<td>3.45 (2.06-5.79)</td>
<td>.43</td>
<td>2.68 (2.13-3.36)</td>
<td>2.48 (1.10-5.55)</td>
<td>.85</td>
</tr>
<tr>
<td>Other psychosis</td>
<td>1.67 (1.40-1.99)</td>
<td>1.57 (0.84-2.93)</td>
<td>.84</td>
<td>1.92 (1.67-2.22)</td>
<td>2.62 (1.70-4.03)</td>
<td>.20</td>
<td>2.03 (1.53-2.70)</td>
<td>2.52 (1.04-6.10)</td>
<td>.66</td>
</tr>
<tr>
<td>Other diagnosis</td>
<td>1.71 (1.58-1.85)</td>
<td>2.28 (1.81-2.86)</td>
<td>.02</td>
<td>1.96 (1.83-2.11)</td>
<td>2.38 (1.92-2.96)</td>
<td>.10</td>
<td>1.79 (1.64-1.94)</td>
<td>2.09 (1.61-2.71)</td>
<td>.27</td>
</tr>
</tbody>
</table>

Data for 2.2 million persons born in Denmark between January 1, 1955, and July 1, 1990, and followed up between January 1, 1994, and July 1, 2005. All estimates were adjusted for age, sex, calendar period, place of birth, and the difference in age at onset between schizophrenia and cannabis-induced psychosis for each sex. Estimates were mutually adjusted for the different types of family history.

P values are for rowwise comparisons for the different types of first-degree relatives (eg, rate ratio of receiving treatment for a schizophrenia spectrum disorder compared with a cannabis-induced psychosis if there is a treatment history for schizophrenia spectrum disorder in the father).

Arendt et al., 2008
Cannabis and psychosis

- Childhood abuse:
  - Association of psychosis among children with a history of abuse who used cannabis prior to age 16 (OR: 11.96; 95% CI 2.10-68.22)
  - Not replicated in all studies

Radharkrishnan et al., 2014
Cannabis and psychosis

• Genetic factors:
  – COMT
  – AKT1
  – DAT1
  – NRG1
  – BDNF
  – CNR1

Pelayo-Terán et al., 2012; Radharkrishnan et al., 2014
Cannabis and psychosis

- COMT:
  - Higher psychosis risk in Val/Val and Val/Met individuals
  - Carriers of Val are more sensitive to THC, conditional on prior psychosis liability
  - Earlier age of onset of psychosis
  - Longer duration of untreated psychosis
  - Interaction with cannabis, childhood abuse and Val allele, and increased risk for psychosis

Pelayo-terán et al., 2012; Caspi et al., 2005
Cannabis and psychosis

Caspi et al., 2005

40% enzyme activity
Cannabis and psychosis

• AKT1:
  – Involved in cell proliferation, apoptosis and transcription
  
  – Increased risk of psychosis in the C/C carriers, when having used cannabis (rs2494732)
  
  – Impairment of the Continuous Performance Test reaction time and accuracy

*Van Winkel et al., 2011*
# Cannabis and psychosis

## Table 2 Continuous Performance Test Performance as a Function of Cannabis Use and AKT1 rs2494732 Genotype

### Cannabis use preceding onset of psychosis (n = 601)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>T/T</th>
<th>C/T</th>
<th>C/C</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never use</td>
<td>Use</td>
<td>Never use</td>
<td>Use</td>
</tr>
<tr>
<td>CPT, accuracy (%) (SD)</td>
<td>92.6 (11.0)</td>
<td>94.4 (8.7)</td>
<td>95.3 (8.5)</td>
<td>95.4 (6.7)</td>
</tr>
<tr>
<td>CPT, reaction time (ms) (SD)</td>
<td>434.9 (76.9)</td>
<td>412.3 (79.5)</td>
<td>437.5 (87.5)</td>
<td>434.1 (82.5)</td>
</tr>
<tr>
<td>CPT, false alarms (n) (SD)</td>
<td>1.16 (4.2)</td>
<td>0.81 (3.4)</td>
<td>0.44 (0.8)</td>
<td>1.01 (4.9)</td>
</tr>
</tbody>
</table>

### Cannabis use preceding onset of psychosis and absence of recent use (N = 408)\(^b\)

<table>
<thead>
<tr>
<th></th>
<th>T/T</th>
<th>C/T</th>
<th>C/C</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never use</td>
<td>Former use</td>
<td>Never use</td>
<td>Former use</td>
</tr>
<tr>
<td>CPT, accuracy (%) (SD)</td>
<td>92.6 (11.0)</td>
<td>94.0 (8.3)</td>
<td>95.3 (8.5)</td>
<td>96.4 (6.3)</td>
</tr>
<tr>
<td>CPT, mean reaction time (ms) (SD)</td>
<td>434.9 (76.9)</td>
<td>423.5 (88.9)</td>
<td>437.5 (87.5)</td>
<td>429.8 (88.9)</td>
</tr>
</tbody>
</table>

\(^a\)Genotyping failed in 10 patients.

\(^b\)Patients without current use: reported no use of cannabis in the last year and urinalysis confirmed the absence of current cannabis use.

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*Van Winkel et al., 2011*
Cannabis and psychosis

- DAT1:
  - VNTR: 9 repeat allele → lower enzymatic activity, higher dopamine levels
  - Associated with schizophrenia independent of cannabis use
  - The nine-repeat allele showed increased sensitivity to THC induced psychotomimetic effects

Bhattacharyya et al., 2012
Cannabis and psychosis

Bhattacharyya et al., 2012
Cannabis and psychosis

• NRG1:
  – Candidate gene for schizophrenia → neurodevelopmental processes
  – Mutant mice more sensitive to the behavioral effects of THC after stress interaction

Spencer et al., 2013
Cannabis and psychosis

- BDNF:
  - Neurtrophin, encourages growth and differentiation of neurons
  - Met66 allele:
    - Associated with the age of onset of psychosis
    - In females, cannabis was associated with earlier age of onset of psychosis

Decoster et al., 2011
Cannabis and psychosis

• CNR1:
  – Negative association with risk of psychosis
  – Schizophrenic G allele carriers were more sensitive to the effect of cannabis

Zammit et al., 2007; Ho et al., 2011
Cannabis and psychosis

Parakh & Basu, 2013
Conclusions

• Cannabis is associated with adverse effects with variable degree of confidence:
  – Addiction to cannabis → High
  – Progression to other drugs → Medium
  – Diminished lifetime achievement → High
  – Anxiety / Depression → Medium
  – Psychosis → Medium/High
Conclusions

• The effects are clearly worse if the age of onset is earlier and the use is regular
Brain development

Caspi et al., 2006