The evidence for cannabis in Tourette syndrome: where are we?

Presented By:

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• Paul Sandor, MD FRCPC
1. To describe the current evidence for cannabinoids in the management of tics

2. To know when to consider cannabis in the management of tics for adults with Tourette syndrome (TS)

3. To advise patients with TS on the potential benefits and harms of cannabinoids, and on practicalities around administration
MEDICATIONS FOR TICS

• $\alpha_2$-Agonists - Level B, low-moderate confidence
• Antipsychotics - Level C, moderate confidence
• Adverse effects - Level A
• Other
  • THC, adults - Level C, low confidence

Pringsheim et al, 2019
Reason for Referral

Cannabis for tics
BRIEF HISTORY OF CANNABIS IN CANADA

• 1923: Cannabis criminalized
• 2001: Medical Marihuana Access Regulations – medical cannabis
• 2013: Marihuana for Medical Purposes Regulations – plethora of options
• 2015: Definition of medical cannabis expanded – cannabis oil, fresh buds
• 2018: Cannabis Act - recreational
• 2019: Cannabis edibles, topicals, concentrates*
<table>
<thead>
<tr>
<th>Commonly Treated Conditions*:</th>
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</thead>
<tbody>
<tr>
<td><strong>Conditions we see:</strong></td>
</tr>
<tr>
<td>• Anxiety</td>
</tr>
<tr>
<td>• PTSD</td>
</tr>
<tr>
<td>• ADD/ADHD</td>
</tr>
<tr>
<td>• Depression</td>
</tr>
<tr>
<td>• Insomnia</td>
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<tr>
<td>• Stress</td>
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<tr>
<td>• Panic Disorder</td>
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<tr>
<td>• Bipolar Disorder (Type 2)</td>
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<tr>
<td>• Borderline Personality Disorder</td>
</tr>
</tbody>
</table>

(PTSD)

(isorder (ADHD))
OPINION

Why We Need to Press Pause on Any Kind of Cannabis Promotion

Many companies are selling marijuana as if the drug is totally harmless. It’s not

November 25, 2018 | By Ruth Ross

If you talk to your friends or peruse the Internet, you will hear a lot about the wonders of cannabis. It makes you high, it makes you happy. It relieves pain, it curbs nausea, it reduces anxiety, it helps with depression and it aids sleep.

https://magazine.utoronto.ca/opinion/why-we-need-to-press-pause-on-cannabis-promotion/
• THC – partial agonist CB$_1$R & CB$_2$R
• CBD – negative allosteric modulator CB$_1$R & CB$_2$R
• Hundreds of compounds
• Terpenes
CANNABINOID PRODUCTS

• Pharmaceutical
  - Nabilone
  - Dronabinol
  - Nabiximols
  - Cannabidiol

• Inhaled cannabis
  - Smoking
  - Vaporizing
  - Vaping

• Oral cannabis
  - Oil
  - Capsules
  - Edibles
### Benefits
- Antiemetic
- Appetite stimulation
- Decr pain
- Anti-spastic
- Anti-seizure

### Harms
- Dizziness
- Sedation
- Fatigue
- Psychomotor slowing
- “high”
- Amotivation
- Depression
- Irritability
- Anxiety
- Derealization/depersonalization
- Altered perception
- Psychosis
- Dry mouth
- Red eyes
• 14 of 17 patients decreased tics & related symptoms (Müller-Vahl et al, 1998)

• 17 of 18 patients very much or much improved (Abi-Jaoude et al, 2017)

• 38 of 42 patients of any kind of benefit (Thaler et al, 2018)
  - Hallucinations (4), irritability and confusion (6), cognitive decline (7), acute psychotic episode (1)

• 10 of the 42 patients stopped after one year

• 98 patients: preference for THC-rich medical cannabis (Milosev et al, 2019)

• Pediatric age: 7 cases (reviewed by Szejko et al, 2022)
• 12 adults, single dose cross-over RCT: oral THC > placebo (TSSL -14 vs -5, p=0.015) (Müller-Vahl et al, 2002)

• 24 adults, 6-wk RCT oral THC vs placebo: TSSL overall significant (p=0.037), but inconsistent (Müller-Vahl et al, 2003)

• 16 adults, 12-wk open-label THC/palmitoylethanolamide: YGTSS-TTS 20% improvement (Bloch et al, 2021)

• 49 adults, 12-wk RCT monoacylglycerol lipase inhibitor: YGTSS-TTS p=0.04 in favor of placebo (Müller-Vahl et al, 2021)

• 18 adults, 12-wk open-label cannabis: YGTSS 38% improvement (Anis et al, 2022)
Efficacy and tolerability of three vaporized medical cannabis products and placebo for tics

- **Primary efficacy** endpoint: MRVTRS
- **Secondary efficacy** endpoints: PUTS, SUDS, CGI-I
- Correlation with cannabinoid plasma levels
- Tolerability
RCT OF CANNABIS FOR ADULTS WITH TS

vaporized cannabis, 0.25 g

• THC 10%

• THC/CBD 9%/9%

• CBD 13%

• placebo THC <0.3%, CBD <0.3%
Single dose $\rightarrow$ 2-week washout $\rightarrow$ Single dose $\rightarrow$ 2-week washout $\rightarrow$ Single dose $\rightarrow$ 2-week washout $\rightarrow$ Single dose

0, 0.5, 1, 2, 3, 5 hours

- MRVTRS, PUTS, SUDS, CGI-I
- Blood sampling: THC, OH-THC, COOH-THC, CBD
ANALYSIS

- Nonlinear mixed effects modelling
- Repeated measures
- Adjusted for baseline score
- Treatment order effects
- Correlation with cannabinoid plasma levels
- Adjusted for multiple comparisons
PARTICIPANTS

68 screened

17 met inclusion criteria

12 randomized

5 w/d prior to randomization
- Schedule (1)
- Using cannabis (1)
- Needle phobia (1)
- Product supply (2)
DEMOGRAPHICS & CLINICAL HX

- 11 males, 1 female; 38 yo (22-54)
- OCD (7), ADHD (6), anxiety (4), depression (3), ASD (1)
- YGTSS-TTS 28.7 (15-44)
- Concurrent meds - 7 participants
  - Antipsychotic (3) - Benztropine (2)
  - SSRI (3) - Bupropion (1)
  - Stimulant (2) - Anticonvulsant (1)
  - Benzodiazepine (3) - Other (4)
- Past cannabis use (3)
3 dropouts

• Adverse event - syncope/seizure (1)
• Unable to draw blood (1)
• Schedule (1)
Efficacy...

MRVTRS

PUTS

SUDS

p = 0.98

p = 0.019

p = 0.001
---EFFICACY---

**CGI-I**

**CBD**
- **very much improved**
- **much improved**

<table>
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<th>Time (hours)</th>
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<th>2</th>
<th>3</th>
<th>5</th>
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<td>3</td>
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**Placebo**

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**THC**

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<td>2</td>
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**THC/CBD**

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PLASMA LEVELS

THC levels

OH-THC levels

COOH-THC levels

CBD levels

Product

- Placebo
- CBD
- THC
- THC_CBD
Correlations with cannabinoid plasma levels across all time points

CBD 13%

THC 10%

THC/CBD 9%/9%
• Sample size
• Single dose
• Fixed dose
• Delivery
• Blinding
• Adult population
• Chronic treatment cross-over RCT
• THC-based oil
• Flexible dosing
In Practice
AAN GUIDELINES ON CANNABINOIDS

- THC, *adults* - Level C, low confidence
  - Treatment resistant
  - Already using efficiently
- Medical supervision - Level A
- Lowest dose - Level A
- Periodically re-evaluate need - Level A
- Driving - Level A

*Pringsheim et al, 2019*
 POTENTIAL OPTIONS

• Pharmaceutical
  - Nabilone
  - Dronabinol
  - Nabiximols
  - Cannabidiol

• Inhaled cannabis
  - Smoking
  - Vaporizing
  - Vaping

• Oral cannabis
  - Oil
  - Capsules
  - Edibles
• Harms / functional impact
• Psychosis, mania
• PK/PD interactions - CYP450 2C9, 3A4
• Smoking
• Driving
• Legal
CONCLUSIONS

• THC - benefit, harms
• CBD - no clear anti-tic effect
• Caution
• Evidence still emerging
• Collaborative relationship
• Adults