Efficacy of Nabiximols in Reducing Frequency of Cannabis Use 3 months After Treatment Cessation: Results from a Randomised Controlled Trial.

Presented by
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• Iain McGregor has a patents to WO2018107216A1, WO2017004674A1, and WO2011038451A1 issued and licensed, and patents to AU2017904438, AU2017904072, and AU2018901971 pending.
• One of the most effective ways to treat dependence on an addictive agent is to replace that agent with an agonist that actually contains the addictive agent or which mimics the pharmacological profile of that agent but is…
  • Cheaper
  • Safer
  • Allows patient to:
    o establish new routines,
    o remove themselves from using milieu
    o extinguish conditioned cues associated with the original addictive agent

  … all in the absence of intense withdrawal
• Methadone/buprenorphine (SOP for heroin addiction)
• Nicotine Patches/Gum/Spray (for Tobacco)
Increasing evidence shows use of cannabis agonist medications may be effective at treating cannabis use disorder.

- Dronabinol: THC
- Nabilone: Synthetic THC
- Nabiximols: THC and CBD

End of medication

Short 9-day inpatient withdrawal  
N.S. difference in relapse one month after medication phase

\[ F_{8325.1} = 2.83, P \leq .01 \]
Background

- Short-term withdrawal management limited in efficacy
  - Longer-term cannabis agonist treatment more effective?
  - 12-week outpatient randomised, placebo-controlled trial
  - Less use days during trial period but n.s. difference in abstinence
- Do reduced rates of cannabis use persist after treatment ends?
Do reduced rates of cannabis use persist after treatment ends?

Why is this question important?
What model of care do we use for cannabis agonist treatment?

**Short-to-Medium Term**
- Nicotine Replacement Therapy
  - Several weeks treatment
  - Then stop

**Maintenance Model**
- Methadone/Buprenorphine
  - Indefinite

If Nabiximols conferred no post-treatment advantage over placebo in either days used or abstinence rates it would suggest the maintenance model is more appropriate.
Research Question

• During 12-week Trial
  • Days Used of Illicit Cannabis in previous 28 days measured at 28-day intervals for 12 weeks during trial period
  • But also at a post-treatment interview, 3 months after treatment ended
  • Was the incremental improvement in frequency of cannabis use due to nabiximols over and above standard treatment (case management + voluntary counselling) plus placebo preserved 3 months after agonist treatment ended?
    • Tested group differences in frequency of days used at each point during the trial and at 3-month post-treatment follow-up (MMRM), then simple effects of group at each time point
    • Group difference in odds of abstinence at 3-month follow-up
• Difference between groups in days used at each time point compared to difference at baseline

Results

- Difference between groups in days used at each time point compared to difference at baseline

Adjusted for multiple comparisons using the Benjamini-Hochberg method, error bars = standard error

Important to note the dropout rate
• Abstinence at week 24

\[ p = 0.014 \]

<table>
<thead>
<tr>
<th>% abstinent at week 24</th>
<th>Placebo</th>
<th>Nabiximols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinent:</td>
<td>6/29 (21%)</td>
<td>14/26 (54%)</td>
</tr>
</tbody>
</table>
• Urinalysis validating self-reported abstinence at week 24
  • Self Reported abstinence in previous 28 days
  • Compared to abstinence criteria of < 50 ng/ml THCCOOH
  • 10/33 (30%) reported abstinence, 23/33 (70%) non-abstinence
  • 91% agreement, 9% disagreement were low SR use/UR abs
  • To a great extent people told the truth about their abstinence

<table>
<thead>
<tr>
<th>Confusion Matrix</th>
<th>Receiver Operating Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC-COOH&lt;sup&gt;b&lt;/sup&gt;</td>
<td>TPR&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Self-Reported Cannabis Use&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>a</sup>: 0 = Zero self-reported cannabis use days in previous 28 days; 1 = one day or more of self-reported illicit cannabis use in previous 28 days.  
<sup>b</sup>: 0 = THC-COOH levels < 50 ng/ml; 1 = THC-COOH levels ≥25% of levels at previous measurement and ≥200 ng/ml.  
<sup>c</sup>: TPR = True Positive Rate = Sensitivity.  
<sup>d</sup>: TNR = True Negative Rate = Specificity.  
<sup>e</sup>: PLR = Positive Likelihood Ratio = True Positive Rate/False Positive Rate.  
<sup>f</sup>: NLR = Negative Likelihood Ratio = False Negative Rate/True Negative Rate.  
<sup>g</sup>: AUC = Area Under the Curve.
• Benefits of nabiximols maintained 3 months after treatment cessation

• Compared with Allsop et al (2014) where nabiximols was associated with no post-treatment benefit over placebo
  • Longer period of treatment more successful in achieving sustained reductions in cannabis use
  • Which persist beyond the cessation of treatment

• Suggests that model of care of cannabis agonist treatment may resemble nicotine replacement therapy (time-limited model) rather than opioid replacement therapy (maintenance model).

• Medication used to manage withdrawal, reduce cravings and change behavioural patterns in short-term which then may translate to benefits that persist after stopping medication
Limitations

• 43% follow-up rates
  • Exactly the same rates in both groups but
  • Might be an unobserved interaction effect whereby more lost to follow-up due to relapse (i.e. rather than simply being uninterested in participating) in the Nabiximols group
• 3-month follow-up, longer duration needed
• These limitations, and the fact that 60% were not abstinent indicate merits of stepped care approach
Stepped Care Approach for Cannabis Treatment

Client presents for Treatment → Counselling + Supportive Case Management → Client reduces Cannabis use → Client continues to use Cannabis → 8 to 12 weeks of nabiximols + counselling → Client reduces Cannabis use → Client continues to use Cannabis → Long Term nabiximols + counselling
The Team

The ARC-D Study Group
• Backwards Difference Coding: Testing group difference at each timepoint relative to previous timepoint

Results

- Adjusted for multiple comparisons using the Benjamini-Hochberg method, error bars = standard error