Are there enough scientific evidences to recommend psychotropic substances for medical use?

Implications of a critical umbrella review

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Some *biodata* on the speaker ...

- **NOT** an expert in cannabis and cannabinoids
- My major expertise in biostatistics, systematic reviews and meta-analyses (*research methodology*)
- I have published so far up to 20 systematic reviews and meta-analyses (some of them in high/very high impact-journals, including Frontiers in physiology, Seizure, Epilepsy and behavior, Drugs, Human vaccines and immunotherapeutics, Cochrane database of systematic reviews, PLOS ONE, etc.)
- I have collaborated and actually collaborate with the Cochrane Association
Systematic reviews and meta-analyses: primary and secondary literature (meta-literature)

**PRIMARY LITERATURE**
- Original research and/or new scientific discoveries
- Immediate results of research activities
- Often includes analysis of data collected in the field or laboratory

**SECONDARY LITERATURE**
- Summarizes and synthesizes primary literature
- Usually broader and less current than primary literature
- Good place to look up facts or get a general overview of a subject

**TERTIARY LITERATURE**
- Summaries or condensed versions of materials
- Usually with references to primary or secondary sources

**EXAMPLES:**
- Literature review articles
- Books
- Textbooks, Dictionaries, Encyclopedias, Handbooks

Since most information sources in the secondary literature contain extensive bibliographies, they can be useful for finding more information on a topic.
A Borgesian scientific library
Fourteen types of reviews according to the SALSA committee.
Why a meta-analysis?

• Meta-analysis is a quantitative approach in which individual, primary study findings are statistically pooled and analyzed together.

• This approach is the best way to overcome the very common issue of small sample sizes and low statistical power.

• Meta-analysis can be defined as the statistical analysis of a large collection of analysis results from individual studies – including, for example, Randomized Controlled Trials (RCTs) - for the purpose of integrating the findings and providing an updated synthesis of the current state of art in that research field (Glass 1976).
What is a meta-analysis?

• Gene Glass was a scientist under psychotherapy. His rival, Eysenck, claimed that psychotherapy was uneffective and did not work. Glass invented meta-analysis to prove Eysenck was wrong.

• When Glass published in the American Psychologist an article on the effectiveness of psychotherapy together with Mary Lee Smith in 1977, Eysenck responded to the article by calling it “mega-silliness”
What is a meta-analysis?

- Smith et al. 1991: OR = 1.3 (0.5, 2.6)
- Jones et al. 1993: OR = 2.1 (1.0, 3.4)
- Smith et al. 1999: OR = 1.8 (0.9, 3.2)
- Ng et al. 2004: OR = 2.3 (1.9, 2.7)
- Chu et al. 2009: OR = 2.1 (1.8, 2.5)

Summary measure: OR = 2.2 (1.9, 2.4)
An umbrella review of the published systematic reviews/meta-analyses

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<th>Search strategy item</th>
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An umbrella review of the published systematic reviews/meta-analyses

• The current umbrella review has been performed according to the «Preferred Reporting Items for Systematic Reviews and Meta-analyses» (PRISMA) guidelines

• 4,923 articles have been screened

• The full text of 192 articles has been analyzed in-depth

• 173 articles have been excluded with reasons

• 19 systematic reviews/meta-analyses have been included in the current umbrella review
Psychotropics and efficacy/effectiveness

- Psychotropics and chronic pain
  - Psychotropics and neuropathic pain
  - Psychotropics and chronic cancer-pain
  - Psychotropics and chronic non-cancer pain
- Psychotropics and acute post-operative pain
- Psychotropics and pain (overall)
- Psychotropics and neuro-psychiatric disorders
  - Psychotropics and multiple sclerosis
  - Psychotropics and Tourette’s syndrome
- Psychotropics and rheumatic disorders
Psycotropics and chronic pain

24 crossover and parallel design RCTs were included. Pooled effect sizes were found favorable towards CBMs over placebo. Not all of the studies yielded results in the same direction, and a statistical heterogeneity was in evidence ($I^2=77.83\%$, $P<0.0001$).
Psychotropics and chronic pain 2

Effect sizes remained **significant** after excluding active-controlled studies.
Psychotropics and neuropathic pain

11 RCTs were included. Pooled effect sizes were found favorable towards CBMs over placebo. However, in this analysis, all of the studies yielded results in the same direction, but there was a statistical heterogeneity in evidence ($I^2=75.70\%, P<0.0001$).
Low-strength evidence was found that cannabis preparations have the potential to improve neuropathic pain but insufficient evidence in other patient populations. Most studies are small, many have methodologic flaws, and the long-term effects are unclear given the brief follow-up duration of most studies. The applicability of these findings to current practice may be low in part because the formulations studied may not be reflective of what most patients are using, and because the consistency and accuracy of labeled content in dispensaries are uncertain.
Evaluation of these studies suggested that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments. Cannabis-based medicinal extracts used in different populations of chronic nonmalignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments.
Psychotropics and cancer-pain

3 RCTs were included. Pooled effect sizes were found favorable towards CBMs over placebo. In this analysis, all of the studies yielded results in the same direction, but a statistical heterogeneity was in evidence (I²=59.0%, P <0.01).
Psychotropics and chronic non cancer-pain

14 RCTs were included. Pooled effect sizes were found favorable towards CBMs over placebo. However, in this analysis, all of the studies yielded results in the same direction, but there was a statistical heterogeneity in evidence (I²=72.56%, P <0.0001).
An updated systematic review of randomized controlled trials examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to PRISMA guidelines for systematic reviews reporting on health care outcomes. Eleven trials published since our last review met inclusion criteria. The quality of the trials was excellent. Seven of the trials demonstrated a significant analgesic effect. Several trials also demonstrated improvement in secondary outcomes (e.g., sleep, muscle stiffness and spasticity). Adverse effects most frequently reported such as fatigue and dizziness were mild to moderate in severity and generally well tolerated.

This review adds further support that currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.
Psychotropics and chronic pain

• The results of 43 RCTs (a total of 2,437 patients) were included in this review, of which 24 RCTs (a total of 1,334 patients) were eligible for meta-analysis.

• This analysis showed limited evidence showing more pain reduction in chronic pain -0.61 (-0.78 to -0.43, P <0.0001), especially by inhalation -0.93 (-1.51 to -0.35, P=0.001) compared to placebo.

• Moreover, even though this review consisted of some RCTs that showed a clinically significant improvement with a decrease of pain scores of 2 points or more, 30% or 50% or more, the majority of the studies did not show an effect.

• Consequently, although the primary analysis showed that the results were favorable to CBMs over placebo, the clinical significance of these findings is uncertain.

• The most prominent AEs were related to the central nervous and the gastrointestinal systems.
3 RCTs were included. Pooled effect sizes were found favorable towards CBMs over placebo. In this analysis, all of the studies yielded results in the same direction, but there was a statistical homogeneity in evidence (I²=72.99%, P <0.05).
Psychotropics and pain (overall)

- Of the 9 included trials (222 patients), 5 trials related to cancer pain, 2 to chronic non-malignant pain, and 2 to acute postoperative pain. No randomised controlled trials evaluated cannabis; all tested active substances were cannabinoids. Oral delta-9-tetrahydrocannabinol (THC) 5-20 mg, an oral synthetic nitrogen analogue of THC 1 mg, and intramuscular levonantradol 1.5-3 mg were about as effective as codeine 50-120 mg, and oral benzopyranoperidine 2-4 mg was less effective than codeine 60-120 mg and no better than placebo. Adverse effects, most often psychotropic, were common.

- Cannabinoids are **no more effective** than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used. Before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid randomised controlled studies are needed.
Psychotropics and neuro-psychiatric disorders

- **No** RCTs have thus far examined the efficacy of marijuana for Tourette's disorder, post-traumatic stress disorder (PTSD), or Alzheimer's disease.

- **Lower-quality** studies examined the efficacy of marijuana, Δ⁹-tetrahydrocannabinol, and nabilone.

- The strength of evidence for the use of cannabinoids for these conditions is **very low** at the present time.
Sativex appears effective in counteracting spasticity in multiple sclerosis patients.
Six studies were systematically reviewed for treatment dosage and duration, objective and subjective measures of spasticity, and reports of adverse events. Although there was variation in the outcome measures reported in these studies, a trend of reduced spasticity in treated patients was noted. Adverse events were reported in each study, however combined TCH and CBD extracts were generally considered to be well-tolerated.

We found evidence that combined THC and CBD extracts may provide therapeutic benefit for MS spasticity symptoms. Although some objective measures of spasticity noted improvement trends, there were no changes found to be significant in post-treatment assessments. However, subjective assessment of symptom relief did often show significant improvement posttreatment. Differences in assessment measures, reports of adverse events, and dosage levels were found.
16 trials including 2597 patients were eligible. Moderate-certainty evidence suggested a non-statistically significant decrease in spasticity (standardized mean difference (SMD) 0.36 [confidence interval (CI) 95% -0.17 to 0.88; p=0.18; I²=88%]), and spasm frequency (SMD 0.04 [CI 95% -0.15 to 0.22]). There was an increase in adverse events such as dizziness (risk ratio (RR) 3.45 [CI 95% 2.71-4.4; p=0.20; I²=23%]), somnolence (RR 2.9 [CI 95% 1.98-4.23; p=0.77; I²=0%]), and nausea (RR 2.25 [CI 95% 1.62-3.13; p=0.83; I²=0%]).
6 studies and one RCT-report involved 298 patients (222 treated, 76 placebo); four examined Sativex (a cannabidiol/delta-9-tetrahydrocannabinol (THC) buccal spray) (observations = 196), five cannabidiol (n = 41), and three dronabinol (n = 91). Homogeneity chi(2) values were non-significant, allowing data combination. Analyses focused on baseline-endpoint score differences. Dizziness was the most commonly observed adverse event in the cannabidiol/THC buccal spray arms (39 +/- 16%), across all cannabinoid treatments (32.5 +/- 16%) as well as in the placebo arms (10 +/- 4%).
Cannabinoids relevantly decreased the number of incontinence episodes in all three studies. Pooling data showed the mean difference in incontinence episodes per 24 h to be -0.35 (95% confidence interval -0.46 to -0.24). Mild adverse events were frequent (38-100%), but only two patients (0.7%) reported a serious adverse event. Preliminary data imply that cannabinoids might be an effective and safe treatment option for NLUTD in patients with MS; however, the evidence base is poor and more high-quality, well-designed and adequately powered and sampled studies are urgently needed to reach definitive conclusions.
Psychotropics and Tourette’s syndrome

Only two trials were found that met the inclusion criteria. Both compared a cannabinoid, delta-9-Tetrahydrocannabinol (Delta(9)THC), either as monotherapy or as adjuvant therapy, with placebo. Not enough evidence to support the use of cannabinoids in treating tics and obsessive compulsive behaviour in people with Tourette's syndrome.
Pyschotropics and rheumatic disorders

• There is **preliminary** evidence of efficacy in fibromyalgia and rheumatoid arthritis

• Efficacy/effectiveness seems to be **moderate**, in part counteracted by potential adverse effects
2 studies were included. We found no convincing, unbiased, high quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone was low in people with fibromyalgia.
Psychotropics and rheumatic disorders 3

Two RCTs of 2 and 4 weeks duration respectively with nabilone, including 71 FMS patients, one 4-week trial with nabilone, including 30 spinal pain patients, and one 5-week study with tetrahydrocannabinol/cannabidiol, including 58 RA patients were included.

No RCT with OA patients was found. The risk of bias was high for three studies.

The findings of a superiority of cannabinoids over controls (placebo, amitriptyline) were not consistent. Cannabinoids were generally well tolerated despite some troublesome side effects and safe during the study duration.

Currently, there is insufficient evidence for recommendation for any cannabinoid preparations for symptom management in patients with chronic pain associated with rheumatic diseases.
Summarizing ...
Summarizing ...

Figure 2: Improvement in Pain

| Cannabinoid Events | Tolerance | Placebo | Cannabinoid vs Placebo | Weight,
No. | Total No. | No. | Total No. | No. | Total No. | No. | Total No. | % |
<table>
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<tr>
<th></th>
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<td>Alcohol</td>
<td>13</td>
<td>25</td>
<td>6</td>
<td>75</td>
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<tr>
<td>Ketamine</td>
<td>64</td>
<td>149</td>
<td>59</td>
<td>148</td>
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<tr>
<td>Johnson et al.</td>
<td>94</td>
<td>136</td>
<td>52</td>
<td>124</td>
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<tr>
<td>Langeland et al.</td>
<td>88</td>
<td>118</td>
<td>77</td>
<td>171</td>
</tr>
<tr>
<td>Pernier et al.</td>
<td>18</td>
<td>30</td>
<td>9</td>
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<td>Sethuraman et al.</td>
<td>8</td>
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<td>9</td>
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<tr>
<td>Goyak et al.</td>
<td>34</td>
<td>122</td>
<td>10</td>
<td>117</td>
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<tr>
<td>Subtotal / / 1-3 /</td>
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<td>660</td>
<td>209</td>
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<td>Overall / / 1-3 /</td>
<td>251</td>
<td>685</td>
<td>215</td>
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Odds ratios indicate 30% or greater improvement in pain with cannabis compared with placebo, stratified according to cannabis. The square data markers represent mean difference from primary studies, with sites reflecting the statistical weight of the study using random effects meta-analysis. The horizontal line indicates 95% CI. The blue diamond data markers represent mean difference from primary studies, with sites reflecting the statistical weight of the study using random effects meta-analysis. The horizontal line indicates 95% CI. The vertical dashed line shows the summary effect estimate, the solid vertical line shows the line of no effect (OR = 1).

Figure 3: Change in Atehrone Score for Cannabis Compared With Placebo, Stratified According to Cannabis

| Cannabinoid | No. of Patients | Mean Score Change | Mean Difference (95% CI) | Odds 
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<td>Cannabis</td>
<td>151</td>
<td>-1.0 (0.25)</td>
<td>-1.0 (0.25)</td>
<td>0.63</td>
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<tr>
<td>Control</td>
<td>151</td>
<td>-0.9 (0.25)</td>
<td>-0.9 (0.25)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Figure 4: Odds of Having Any Adverse Event With Cannabis Compared With Placebo, Stratified According to Cannabis

| Cannabinoid | No. of Patients | Placebo | Cannabinoid vs Placebo | Weight,
No. | Total No. | No. | Total No. | No. | Total No. | No. | Total No. | % |
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<td>151</td>
<td>127</td>
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<td>127</td>
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<tr>
<td>Control</td>
<td>151</td>
<td>151</td>
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The square data markers indicate odds ratios (OR) from primary studies, with sites reflecting the statistical weight of the study using random effects meta-analysis. The horizontal line indicates 95% CI. The vertical dashed line shows the summary effect estimate, the solid vertical line shows the line of no effect (OR = 1).
A total of 79 trials (6462 participants) were included; 4 were judged at low risk of bias. Most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. Compared with placebo, cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response (47% vs 20%; odds ratio [OR], 3.82 [95% CI, 1.55-9.42]; 3 trials), reduction in pain (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10-point scale; weighted mean difference [WMD], -0.46 [95% CI, -0.80 to -0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, -0.36 [95% CI, -0.69 to -0.05]; 7 trials). There was an increased risk of short-term AEs with cannabinoids, including serious AEs. Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.
Psychotropics and health-related quality of life
Psychotropics and health-related quality of life

• Results: Twenty studies met our pre-defined selection criteria. Eleven studies were randomized controlled trials (RCTs; 2322 participants); the remaining studies were of cohort and cross-sectional design. Studies of cannabinoids were mostly RCTs of higher design quality than studies of cannabis, which utilized smaller self-selected samples in observational studies. Although we did not uncover a significant association between cannabis and cannabinoids for medical conditions and HRQoL, some patients who used them to treat pain, multiple sclerosis, and inflammatory bowel disorders have reported small improvements in HRQoL, whereas some HIV patients have reported reduced HRQoL.

• Conclusion: The relationship between HRQoL and the use of cannabis or cannabinoids for medical conditions is inconclusive. Some patient populations report improvements whereas others report reductions in HRQoL. In order to inform users, practitioners, and policymakers more clearly, future studies should adhere to stricter research quality guidelines and more clearly report patient outcomes.
Psychotropics and harms/adverse effects
Psychotropics and harms/adverse effects

• According to 11 systematic reviews and 32 primary studies, harms in general population studies include increased risk for motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment. Although adverse pulmonary effects were not seen in younger populations, evidence on most other long-term physical harms, in heavy or long-term cannabis users, or in older populations is insufficient.

• Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects.
Psychotropics and harms/adverse effects 2

• The following were studied in patients with MS: (1) Spasticity: oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannabinol (THC) are probably effective, for reducing patient-centered measures; it is possible both OCE and THC are effective for reducing both patient-centered and objective measures at 1 year. (2) Central pain or painful spasms (including spasticity-related pain, excluding neuropathic pain): OCE is effective; THC and nabiximols are probably effective. (3) Urinary dysfunction: nabiximols is probably effective for reducing bladder voids/day; THC and OCE are probably ineffective for reducing bladder complaints. (4) Tremor: THC and OCE are probably ineffective; nabiximols is possibly ineffective. (5) Other neurologic conditions: OCE is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease. Oral cannabinoids are of unknown efficacy in non-chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy.

• Risk of serious adverse psychopathologic effects was nearly 1%.
In the 23 randomized controlled trials, the median duration of cannabinoid exposure was 2 weeks (range 8 hours to 12 months).
A total of 4779 adverse events were reported among participants assigned to the intervention. Most (4615 [96.6%]) were not serious.
Of the 164 serious adverse events, the most common was relapse of multiple sclerosis (21 events [12.8%]), vomiting (16 events [9.8%]) and urinary tract infection (15 events [9.1%]). The rate of nonserious adverse events was higher among participants assigned to medical cannabinoids than among controls (rate ratio [RR] 1.86, 95% confidence interval [CI] 1.57-2.21); the rates of serious adverse events did not differ significantly between these 2 groups (RR 1.04, 95% CI 0.78-1.39). Dizziness was the most commonly reported nonserious adverse event (714 events [15.5%]) among people exposed to cannabinoids.
Short-term use of existing medical cannabinoids appeared to increase the risk of nonserious adverse events. The risks associated with long-term use were poorly characterized in published clinical trials and observational studies. High-quality trials of long-term exposure are required to further characterize safety issues related to the use of medical cannabinoids.
Conclusions and take-home-message

• Concerning the studied outcomes (efficacy/effectiveness, impact on health-related quality of life and harms/adverse events), extant evidence is scarce/insufficient and of low quality

• Further high-quality studies (investigating in particular long-term effects) in the field are warranted

THANK YOU FOR YOUR ATTENTION