Cannabis, the evidence

MCID minimally clinically important difference
VAS 1.5-2/10 or 30% reduction
Randomised control trials

Sample population

Group 1

New treatment

Outcome

Group 2

Control treatment

Outcome
Randomised Control Trials

- Often comparing two groups
- Placebo
- Randomised to reduce bias from chance
Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

Turo J. Nurmikko a,*, Mick G. Serpell b, Barbara Hoggart c, Peter J. Toomey d, Bart J. Morlion c, Derek Haines f
Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

Turo J. Nurmiakko a,*, Mick G. Serpell b, Barbara Hoggart c, Peter J. Toomey d, Bart J. Morlion e, Derek Haines f

Table 2
Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sativex (N = 63)</th>
<th>Placebo (N = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr mean (SD)</td>
<td>52.4 (15.8)</td>
<td>54.3 (15.2)</td>
</tr>
<tr>
<td>Women, N (%)</td>
<td>35 (55.6)</td>
<td>39 (62.9)</td>
</tr>
<tr>
<td>White, N (%)</td>
<td>61 (97)</td>
<td>60 (97)</td>
</tr>
<tr>
<td>Weight, kg mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>79.9 (16.7)</td>
<td>86.8 (16.7)</td>
</tr>
<tr>
<td>Women</td>
<td>72.0 (18.2)</td>
<td>72.7 (17.3)</td>
</tr>
<tr>
<td>Duration of pain, yr mean (SD)</td>
<td>6.4 (5.7)</td>
<td>6.2 (6.4)</td>
</tr>
</tbody>
</table>
Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

Turo J. Nurmikko a,*, Mick G. Serpell b, Barbara Hoggart c, Peter J. Toomey d, Bart J. Morlion c, Derek Haines f

N = 125
6.3 years duration of pain
Sativex -1.48
Placebo -0.52
Randomised control trial pitfalls

- Legislation
- Homogeneity of diagnosis
  - E.g. different pain diagnoses
- Numbers - neuropathic pain
- Industry sponsorship-vested interest
- Systematic reviews
A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis

R. M. Langford · J. Mares · A. Novotna · M. Vachova · I. Novakova · W. Notcutt · S. Ratcliffe

- MS with Central pain
- How do you diagnose? No gold standard or test to diagnose.
- Leads to variable sample
• 30% reduction in pain
• THC/CBD 50%
• Placebo spray 45%
• THC/CBD 1.93/10 Placebo 1.76/10
Neuropathic pain

- Changes in
  - sensory nerves,
  - spinal cord
  - brain
- Stimulus independent pain
- Hypersensitivity (alldynia)
Neuropathic pain

- post-herpetic neuralgia
- peripheral neuropathy
- focal nerve lesion
- radiculopathy
- Complex Regional Pain Syndrome (CRPS) type 2
Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Clinical Trial

Ronald J Ellis, Will Toperoff, Florin Vaida, Geoffrey van den Brande, James Gonzales, Ben Gouaux, Heather Bentley, and J Hampton Atkinson

Pain score 11.1/20
Cannabis Reduction 4.1/20 37%
Placebo Reduction 0.96/20 8.6%

Cannabis 46% achieved 30% reduction pain
Placebo 18% achieved 30% reduction in pain

N = 28 - 64% took opioids, 36% NSAIDS, 29% TCAs, 64% anticonvulsants
Neuropathic pain in HIV
Smoked cannabis for chronic neuropathic pain: a randomized controlled trial

Mark A. Ware MBBS, Tongtong Wang PhD, Stan Shapiro PhD, Ann Robinson RN, Thierry Ducruet MSc, Thao Huynh MD, Ann Gamsa PhD, Gary J. Bennett PhD, Jean-Paul Collet MD PhD

Average daily pain at baseline

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>6.89 (1.37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>4.0–9.2</td>
</tr>
</tbody>
</table>

Table 3: Effects of smoked cannabis and secondary outcomes, by potency of tetrahydrocannabinol (THC) received

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0</th>
<th>2.5</th>
<th>6.0</th>
<th>9.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average daily pain</td>
<td>6.1 (1.6)</td>
<td>5.9 (1.9)</td>
<td>6.0 (1.8)</td>
<td>5.4 (1.7)†</td>
</tr>
</tbody>
</table>

Post traumatic and post surgical neuropathic pain
N= 23 cross over trial 22% reduction pain intensity 1.49/10
A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment


- N = 303
- Neuropathic pain with allodynia - 6 years
- THC/CBD Spray in addition to usual analgesia
30% reduction pain
28% vs 16%
Analysis

- 35/128 35/79 responders
Cannabis-based medicines for chronic neuropathic pain in adults (Review)

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W
Cochrane review
Neuropathic pain

- THC/CBD oromucosal spray (nine studies with 1433 participants) was superior to placebo. SMD was -0.40 (95% CI -0.75 to -0.05) (P value 0.03).
30% reduction pain

- 10 studies with 1586 participants.
- 323 of 819 (39.4%) CBD/THC
- 251 of 767 (32.7%) placebo group
- (RD 0.09, 95% CI 0.03 to 0.15; P value 0.004; I² = 34%). NNTB was 11 (7 to 33).
Cancer pain

• Mass effects
  – Tissue compression bones, muscles, organs
  – Neuropathic

• Complications of treatment
  – Radiotherapy
  – Chemotherapy
Original Article

Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain

- 2.7THC & 2.5 CBD (Sativex)
- Incurable malignancy using strong opioids
- 2 week trial
- NPRS>4/10
Screened (n = 192)

2-day baseline period

Randomized (n = 177)

2-week treatment period

THC:CBD (n = 60)
- Withdrawn (n = 12):
  - Adverse event = 10
  - Consent withdrawal = 1
  - Other = 1
- Completed (n = 48)

THC extract (n = 58)
- Withdrawn (n = 13):
  - Adverse event = 7
  - Consent withdrawal = 2
  - Sponsor decision = 1
  - Protocol violation = 1
  - Other = 2
- Completed (n = 45)

Placebo (n = 59)
- Withdrawn (n = 8):
  - Adverse event = 3
  - Consent withdrawal = 2
  - Other = 3
- Completed (n = 51)

ITT population (n = 177)
Safety population (n = 177)
Fig. 3. Pain 0–10 Numerical Rating Scale scores: responder analysis (ITT analysis). aOdds ratio (95% CI) THC:CBD vs. placebo; bFisher’s exact test.
**NPRS (Pain score)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment Group</th>
<th>Baseline</th>
<th>Change From Baseline</th>
<th>Treatment Difference</th>
<th>Statistical Significance, P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pain severity NRS score</td>
<td>THC:CBD</td>
<td>5.68</td>
<td>-1.37</td>
<td>-0.67&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.014</td>
</tr>
<tr>
<td>(coprimary)</td>
<td>THC</td>
<td>5.77</td>
<td>-1.01</td>
<td>-0.32&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.245</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6.05</td>
<td>-0.67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Side Effects (60%)

- Somnolence
- Nausea
- Dizziness

*Table 4*

<table>
<thead>
<tr>
<th>Description of Event</th>
<th>THC:CBD n (%)</th>
<th>THC extract n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>8 (13)</td>
<td>8 (14)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (12)</td>
<td>7 (12)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Confusion</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (10)</td>
<td>4 (7)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (5)</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Raised gamma GT</td>
<td>2 (3)</td>
<td>5 (9)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>0</td>
<td>0</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3 (5)</td>
<td>0</td>
<td>0</td>
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</table>

Gamma GT = gamma glutamyl transferase.
Original Article

An Open-Label Extension Study to Investigate the Long-Term Safety and Tolerability of THC/CBD Oromucosal Spray and Oromucosal THC Spray in Patients With Terminal Cancer-Related Pain Refractory to Strong Opioid Analgesics

- Followed 43 patients from previous trial
- 22 centres 21 UK, 1 Belgium
- 37 THC/CBD 2 THC
- Monthly visits
- Median 25 days with maximum 579 days
Side effects

• Dizziness, nausea, vomiting, dry mouth, Somnolence, confusion
• 59% withdrew
Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial
Figure 3. Continuous responder analysis.
Figure 4. Analysis of change from baseline in NRS average pain score.
N = 76 randomised
N = 44 completers
19 dropped out in opioid group
Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis

D. R. Blake, P. Robson¹, M. Ho², R. W. Jubb³ and C. S. McCabe

N= 58
No dropouts in CBM group
CBM 2.2/7 = 31%

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>Baseline (mean/median)⁵</th>
<th>Endpoint (mean/median)⁵</th>
<th>Difference (mean/median)⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning pain on movement</td>
<td>CBM 7.0, Placebo 6.7</td>
<td>CBM 4.8, Placebo 5.3</td>
<td>−0.95</td>
</tr>
<tr>
<td>Morning pain at rest</td>
<td>CBM 5.3, Placebo 5.3</td>
<td>CBM 3.1, Placebo 4.1</td>
<td>−1.04</td>
</tr>
</tbody>
</table>
Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison

Paul Emery, Henning Zeidler, Tore K Kvien, Mario Guslandi, Raphael Naudin, Helen Stead, Kenneth M Verburg, Peter C Isakson, Richard C Hubbard, G Steven Geis

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th></th>
<th>Diclofenac</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 24</td>
<td>Baseline</td>
<td>Week 24</td>
</tr>
<tr>
<td>Pain VAS (mm)</td>
<td>47.4 (21.5)</td>
<td>40.8 (25.5)</td>
<td>51.7 (21.6)</td>
<td>43.1 (25.2)</td>
</tr>
</tbody>
</table>

N = 655
RA for over six months
Celecoxib 6.6/27.4 = 14%
Diclofenac 8.6/51.7 = 17%
Cannabis is another tool in the toolbox of analgesics. It is as effective as other analgesics in RCTs for chronic pain including cancer pain.

Cost is a significant barrier.

MCID (minimally clinically important difference)

VAS 1.5-2/10 or 30% reduction.

People are different and respond to different medications/ varying side effects due to genetic makeup/socio-cultural differences.