Cannabinoids and neuropathic pain

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Disclosures

• Consultant
  – Ironwood
  – Boehringer
• Grants
  – Valeant
  – Pfizer
  – Purdue
  – Janssen
• Speakers fees
  – Lilly
  – Purdue
  – Pfizer
Medical cannabis use

- Postal survey of 2969 subjects in UK (Ware 2005)
- CB use associated with younger age, male gender and previous nonmedical CB use
- Use in CNCP 10% with effects on pain, mood and sleep (Ware 2003)

Peripheral neuropathic pain models

- Nerve injury
  - Chronic constriction injury
  - Sciatic nerve ligation
  - Brachial plexus avulsion
  - Trigeminal neuralgia
- Diabetes
  - Streptozotocin
- Chemotherapy
  - Paclitaxel
  - Cisplatin
  - Vincristine
- HIV neuropathy
Central neuropathic pain models

• Spinal cord injury
• Multiple sclerosis
  – EAE

Cannabinoids in RCTs

• Herbal cannabis
• Nabilone
• Dronabinol
• Nabiximols
• CT-3 (Ajulemic acid)
MEDLINE search strategy

• MeSH headings
  – Cannabis OR Cannabinoids OR Cannabidiol OR Marijuana
    Smoking OR Tetrahydrocannabinol
• OR keyword
  – tetrahydrocannabinol-cannabidiol combination OR nabilone OR
dronabinol OR Cesamet OR Sativex OR Marinol OR nabiximols
• OR Keywords
  – cannabis OR cannabinoid* OR cannab* OR marijuana OR
  marihuana OR dronabinol OR tetrahydrocannabinol OR THC
• AND MeSH heading
  – Neuropathic pain
• AND MeSH heading
  – Clinical trial AND human

Results

• 17 studies found by search
  – 12 excluded (3 nonrandomised, 9 review)
• 7 added from one review (Lynch 2011) and authors knowledge
• 12 trials published from 2003-2011
  – 9 peripheral
    • 4 NeP (general)
    • 2 HIV
    • 1 brachial plexus avulsion, 1 PDN, 1 PTPS
  – 3 central
    • 3 MS
Results

• Total n=726
• Average duration 20 days (exposure to study drug);
  – range 0.6h - 10 weeks
• Mean effect size 0.9 (median 0.9);
  – range 0-1.25
• 8 studies reported a positive outcome on primary measure

Results

• By study drug:
  – 5 nabiximols
    • 2 MS
    • 1 brachial plexus avulsion*, 1 NeP*, 1 PDN*
  – 4 cannabis
    • 2 HIV neuropathy
    • 1 PTPS neuropathy, 1 NeP
  – 1 nabilone
    • 1 NeP*
  – 1 dronabinol (MS)
  – 1 CT-3 (NeP)*

*Negative study
Berman 2004

Fig. 4. Mean (±SE) BS-11 pain scores for last 7 days of each treatment period.

Svendsen 2004
Table 2  Adjusted mean differences in clinic visit scores over six weeks

<table>
<thead>
<tr>
<th>Measure</th>
<th>Active</th>
<th>Placebo</th>
<th>Diff.</th>
<th>95% CI for difference</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSS</td>
<td>-25.2 [n = 79]</td>
<td>-19.35 [n = 77]</td>
<td>-5.93</td>
<td>-13.52, 1.65</td>
<td>3.84</td>
<td>0.124</td>
</tr>
<tr>
<td>Primary symptom: VAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spasticity</td>
<td>-31.20 [n = 19]</td>
<td>-8.40 [n = 18]</td>
<td>-22.79</td>
<td>-35.52, -10.07</td>
<td>6.26</td>
<td>0.001</td>
</tr>
<tr>
<td>Spasms</td>
<td>-26.50 [n = 20]</td>
<td>-21.20 [n = 18]</td>
<td>-5.3</td>
<td>-19.81, 9.22</td>
<td>7.15</td>
<td>0.494</td>
</tr>
<tr>
<td>Bladder</td>
<td>-34.32 [n = 15]</td>
<td>-26.54 [n = 17]</td>
<td>-7.98</td>
<td>-27.44, 11.48</td>
<td>9.51</td>
<td>0.408</td>
</tr>
<tr>
<td>Pain</td>
<td>-11.44 [n = 18]</td>
<td>-20.17 [n = 18]</td>
<td>8.73</td>
<td>-10.39, 27.84</td>
<td>9.4</td>
<td>0.360</td>
</tr>
</tbody>
</table>

Reduction of pain by 30%:
- 52% of CB users
- 24% of placebo

NNT: 3.6
Nurmikko 2007

Adjusted Mean Pain NRS Scores (95% CI)

- * P<0.05
- ** P<0.01

Ellis 2009

DDS Pain

Study Phase
Efficacy of THC/CBD in Neuropathic Pain from Brachial Plexus Avulsion

- Baseline: 7.5
- Placebo: 6.9
- THC extract: 6.3*
- THC/CBD (1:1 ratio): 6.1**

*p=0.02; **p=0.005, compared to placebo

†Eleven-point Box Scale (BS-11)

Berman JS, et al., 2004.
Efficacy of THC:CBD in Patients With Intractable Cancer-Related Pain

Johnson JR, et al., 2010.

Phillips 2010 (HIV PSN)

Using the ITT analysis dichotomous VAS data from both trials, an NNT for smoked cannabis was calculated as 3.38 95% CI (2.19 to 7.50) (Table 3)

suggest that it is worth investigating [20]. In addition, the efficacy of cannabis in HIV-SN would suggest that cannabinoids with an appropriate therapeutic index when delivered by a mechanism other than smoking might be worthy of investigation [56].

smoked cannabis cannot be recommended as routine therapy,
Smoked cannabis for neuropathic pain

**Table 2: Pairwise comparisons of the effects of four potencies of smoked cannabis on average daily pain**

<table>
<thead>
<tr>
<th>Potency, % of THC</th>
<th>0</th>
<th>2.5</th>
<th>6.0</th>
<th>9.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2.5</td>
<td>–0.13</td>
<td>(−0.83 to 0.56)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6.0</td>
<td>–0.09</td>
<td>(−0.78 to 0.60)</td>
<td>0.04</td>
<td>(−0.64 to 0.73)</td>
</tr>
<tr>
<td>9.4</td>
<td>–0.71</td>
<td>(−1.40 to −0.02)</td>
<td>–0.58</td>
<td>(−1.27 to 0.11)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, THC = tetrahydrocannabinol.

Ware et al CMAJ 2010

Mixed Neuropathic Pain

- CT-3 (Ajulemic acid) 20mg
- No known action at CB1 or CB2
  - PPARγ?
- Reduction in VAS pain scores 2h after morning dose (11AM) but not evening (4PM)
Review of guidelines

• Moulin 2007
  – “Recommended fourth line agents include cannabinoids”
  – “The cannabinoids are analgesic agents with strong evidence of efficacy in animal models and increasing evidence of efficacy in NeP states. Dronabinol produced modest analgesia in an RCT of central pain in multiple sclerosis. A 50/50 mixture of THC/CBD in the form of an oromucosal spray provided significant benefit in a trial of central pain in MS”

Review of existing guidelines

• Attal 2010
  – “Cannabinoids (level A in MS and peripheral NP) are proposed for refractory cases”

• Dworkin 2007
  – “… the following specific medications should be considered for patients with central NP...cannabinoids for NP associated with multiple sclerosis (grade B recommendation). Lack of long-term follow-up data, limited availability, and concerns over precipitating psychosis or schizophrenia, especially in individuals with environmental or genetic risk factors [103], restrict the use of cannabinoids to second-line therapy for patients with multiple sclerosis NP at present, and additional trials are needed to further establish their efficacy and safety”
Review of guidelines

• Dworkin 2010
  – “Cannabinoids appear to be efficacious in multiple sclerosis-associated NP, but use of cannabinoids is limited by poor availability and concerns regarding risks of abuse and potential to precipitate psychosis, especially in high-risk individuals”

• Finnerup 2010
  – “Cannabinoids have a modest effect on central pain in multiple sclerosis. Cannabinoids, including Sativex spray, have also been shown to relieve peripheral neuropathic pain, but the effect size is small, and there was no effect in a small study in painful poly-neuropathy. Smoked cannabis has been shown to be superior to placebo in HIV neuropathy and mixed neuropathic pain”

Review of guidelines

• O’Connor 2012
  – Cites IASP, EFN, CPS guidelines
  – “Cannabinoids have demonstrated efficacy in pain associated with multiple sclerosis, but their use is limited by availability and concerns over long-term tolerability, risk of abuse, and potential to precipitate psychosis, especially in individuals at high risk”
Review of guidelines

• Bril 2012
  – Cannabinoids mentioned in abstract but not at all in text
• NICE guidelines (Date?)
  – Cannabinoids not mentioned at all

Issues in cannabinoid RCTs

• Blinding (not always considered)
• Functional assessments
• Small sample sizes
• Industry supported
• Publication bias
• Issues with smoking as delivery system
• QST as predictor of cannabinoid response?
New trials: ClinicalTrials.gov

• Nabiximols for chemotherapy-induced neuropathic pain (recruiting)
• Nabilone for the treatment of phantom limb pain (completed)
• Nabilone for PDN (Toth et al; in press)

Future

• FAAH inhibition?
• CB2 agonists
• Existing cannabinoids (nabiximols, dronabinol, nabilone)
• Herbal cannabis approaches...
  – Alternatives to smoked cannabis
  – HIV
  – Post-traumatic neuropathy