NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

UNIVERSITY OF
OXFORD

Neuropathic pain: it's high time we sorted this out

Student EBM presentations

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October 2015

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The Question

The Scenario:

Mr W is a visiting 65 y/o Canadian man with debilitating idiopathic peripheral neuropathic pain. He is currently on conventional therapy, including NSAIDS and a weak opioid. Unfortunately he suffers intolerable adverse effects with stronger opioids and is investigating alternative treatments

P	Adults with peripheral neuropathic pain (PNP)
I	THC-based therapies
C	Placebo or standard care
O	Patient reported pain and adverse effects

We ask:

"Can THC-based therapies provide effective analgesia for adults with peripheral neuropathic pain?"

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Search Terms

(((cannab* OR Marijuana OR THC)) AND neuropathic pain) AND (systematic review[Publication Type] OR Clinical trial[Publication Type])

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AND	All Fields	neuropathic pain	Show index list
AND	Publication Type	systematic review OR Clinical trial	Show index list

Search History (5 searches) *(close)* View Saved

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☐	2	neuropathic pain.mp. or neuropathic pain/	27436	Advanced	Display More »
☐	3	1 and 2	1160	Advanced	Display More »
☐	4	(systematic review or clinical trial).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1169604	Advanced	Display More »
☐	**5**	**3 and 4**	**358**	**Advanced**	Display More »

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CONTRACT

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Search Results

- MEDLINE – 52 results
- EMBASE – 358 results

We chose the following paper to analyse →

ORIGINAL ARTICLE

A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment

M. Serpell[1], S. Ratcliffe[2], J. Hovorka[3], M. Schofield[4], L. Taylor[5], H. Lauder[5], E. Ehler[6]

1 Pain Clinic Office, Gartnavel General Hospital, University of Glasgow, UK
2 MAC Clinical Research, Trafford Park, Manchester, UK
3 Neurology Department, Na Fratisku Hospital, Prague, Czech Republic
4 West Suffolk Hospital, Bury St Edmunds, UK
5 GW Pharma Ltd, Porton Down Science Park, Salisbury, UK
6 Neurologické odd, Krajská nemocnice Pardubice, Pardubice, Czech Republic

- RCT published within the last year
- Focused on peripheral neuropathic pain and use of THC
- Full text was accessible

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The Study Appraisal

✓ Inclusion Criteria

- ≥18 y.o.
- Mechanical allodynia
- Sum score of at least 24 on a pain 0-10 NRS for >6 days during baseline period
- >6 month history of PNP
- Receiving standard treatment for PNP
- Analgesic regimen stable for at least 2 weeks preceding study entry
- PNP caused by at least one of:
  - Post-herpetic neuralgia
  - Peripheral neuropathy
  - Focal nerve lesion
  - Radiculotherapy
  - Complex Regional Pain Syndrome (CRPS) Type II
- Pain not wholly relieved by current therapy

x Exclusion Criteria

- Severe pain from other concomitant conditions
- History of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders
- Known hypersensitivity to test drugs
- CRPS type I, diabetes mellitus
- Known history of alcohol or substance abuse
- Pregnant/lactating women and women planning a pregnancy
- Intending to travel/donate blood during the study

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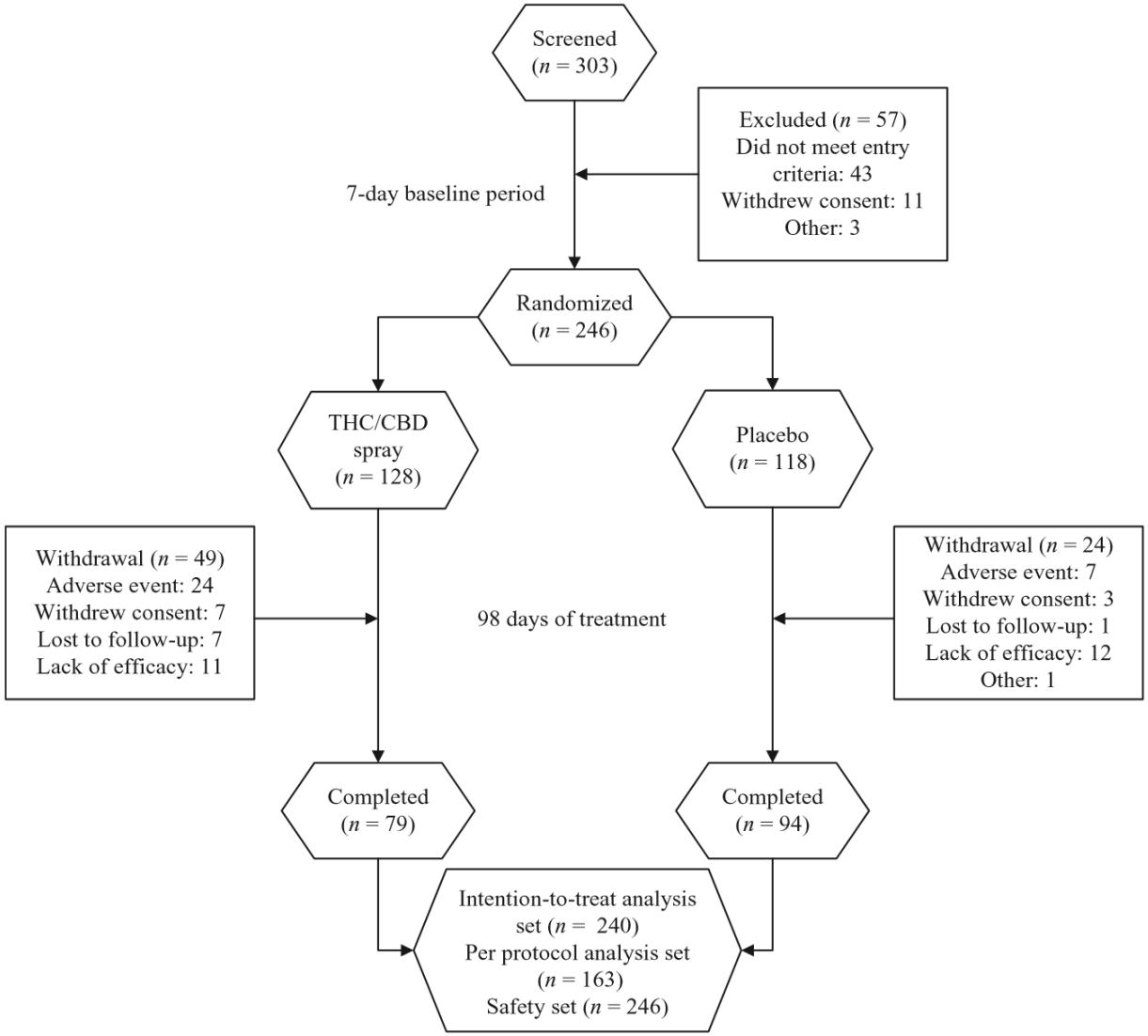
The Study Appraisal

- Randomisation
  - Used a pre-determined computer-generated randomisation code in blocks of four
- Double-blinding
  - Study medication pre-packed by GW Clinical Trials Supplies and labelled with patient numbers
  - Both THC/CBD and placebo contained peppermint oil and colourants to mask smell, taste and colour
- Statistical Test
  - Two sided ANCOVA at 5% significance level
- Primary Outcome
  - Daily log of Numerical Rating Scale (NRS) measuring on a 0-10 scale the average level of nerve pain over last 24hrs
- Secondary Outcomes
  - Weekly neuropathic pain scale (NPS) collected from patient diaries
  - Sleep quality NRS 0-10 on days 15, 43, 71, 99, 127
  - At baseline and 127 days:
    - Subject Global Impression of Change (SGIC, subjective)
    - Brief Pain Inventory – Short Form
    - Dynamic Allodynia Test
    - Punctate Allodynia Test
    - EQ-5D (self rated health status questionnaire)

The Study Appraisal



A total of **173 out of the 246** randomised patients completed the study = **29.7%** drop-out rate.

>20% lost to follow up, possibly poses a serious threat to the validity of data?

Furthermore for a significance level of 5% and an 80% power, a total of **87 evaluable patients** are needed in each group: this was not achieved in the intervention group (n=79)

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The Results

Table 2 Summary of the analysis of all primary and secondary efficacy endpoints (ITT and PP analysis sets). Treatment differences between THC/CBD spray and placebo are presented using change from baseline to the end of treatment data for each endpoint, unless otherwise stated.

Endpoint	ITT analysis set			PP analysis set		
Primary endpoints						
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
30% responder analysis (PNP 0–10 NRS)	1.970	1.049 to 3.702	0.034	2.266	1.124 to 4.568	0.021
	Treatment difference (SE)	95% CI	*p*-value	Treatment difference (SE)	95% CI	*p*-value
PNP 0–10 NRS	–0.34 (0.230)	–0.79 to 0.11	0.139	–0.48 (0.303)	–1.08 to 0.12	0.116
Secondary endpoints						
	Treatment difference (SE)	95% CI	*p*-value	Treatment difference (SE)	95% CI	*p*-value
NPS	–2.86 (2.211)	–7.22 to 1.50	0.198	–5.26 (2.873)	–10.94 to 0.41	0.069
Sleep quality 0–10 NRS	–0.83 (0.306)	–1.43 to –0.23	0.007	–0.91 (0.369)	–1.63 to –0.18	0.015
BPI-SF (pain severity composite score)	–0.25 (0.236)	–0.72 to 0.21	0.288	–0.27 (0.291)	–0.85 to 0.30	0.349
BPI-SF (average pain)	–0.34 (0.237)	–0.81 to 0.12	0.148	–0.47 (0.299)	–1.06 to 0.13	0.122
BPI-SF (worst pain)	–0.30 (0.265)	–0.82 to 0.22	0.255	–0.39 (0.322)	–1.02 to 0.25	0.234
BPI-SF (pain interference composite score)	–0.32 (0.241)	–0.80 to 0.15	0.183	–0.39 (0.304)	–0.99 to 0.21	0.204
Dynamic allodynia test	0.08 (0.305)	–0.52 to 0.68	0.795	–0.27 (0.359)	–0.98 to 0.44	0.460
Punctate allodynia test	–0.14 (0.118)	–0.37 to 0.09	0.233	–0.06 (0.150)	–0.35 to 0.24	0.701
EQ-5D (weighted health status index VAS)	–0.01 (0.024)	–0.06 to 0.04	0.617	–	–	–
EQ-5D (self-rated health status VAS)	–0.75 (2.459)	–5.60 to 4.09	0.760	–	–	–
Use of rescue analgesia	–0.38 (0.237)	–0.85 to 0.09	0.112	0.40 (0.316)	–1.02 to 0.23	0.211
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
50% responder analysis (PNP 0–10 NRS)	1.699	0.645 to 4.476	0.280	2.045	0.750 to 5.576	0.157
SGIC (end of treatment only)	1.762	1.080 to 2.876	0.023	2.988	1.661 to 5.378	0.0003

BPI-SF, Brief Pain Inventory (short form); CBD, cannabidiol; CI, confidence interval; ITT, intention-to-treat; NRS, numerical rating scale; PNP, peripheral neuropathic pain; PP, per protocol; SGIC, Subject Global Impression of Change; THC, Δ^9-tetrahydrocannabinol; VAS, visual analogue scale.

Statistically significant

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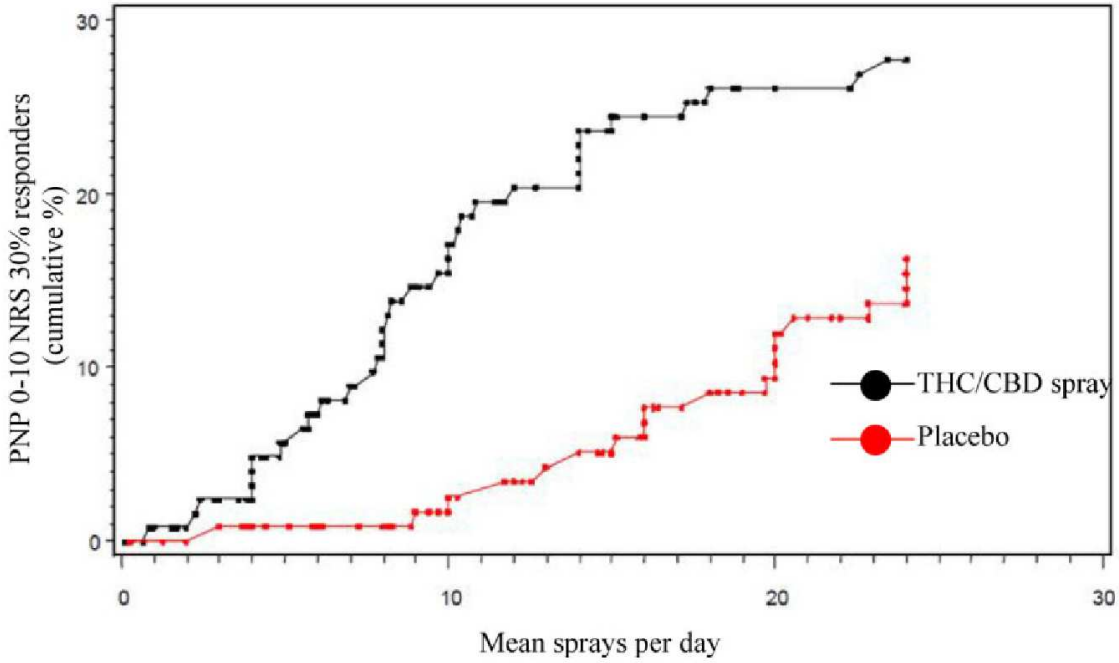
30% Responder Analysis



30% Responder Analysis = the proportion of patients showing ≥30% improvement from baseline to end of treatment in PNP 0-10 NRS (i.e. a clinically relevant improvement)

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Safety and Tolerability

Table 4 Number of patients with at least one all-causality or treatment-related AE with an incidence of 3% or greater by primary system organ class and preferred term (as medically encoded using the Medical Dictionary for Regulatory Activities [MedDRA] version 8.1).

	All-causality		Treatment-related	
	THC/CBD spray (*n* = 128)	Placebo (*n* = 118)	THC/CBD spray (*n* = 128)	Placebo (*n* = 118)
System organ class Preferred term	No. of patients (%)		No. of patients (%)	
Total subjects with at least one AE	109 (85)	83 (70)	97 (76)	56 (47)
Nervous system disorders	79 (62)	34 (29)	73 (57)	20 (17)
Gastrointestinal disorders	60 (47)	43 (36)	48 (38)	30 (25)
General disorders and administration site conditions	45 (35)	30 (25)	38 (30)	23 (19)

- A number of treatment-related adverse effects were recorded, primarily affecting the nervous and gastrointestinal systems
- Overall AEs were noticeably more common in the THC/CBD spray patients
- E.g. psychiatric disorders were experienced by 28% of THC/CBD spray patients versus only 9% receiving placebo.
- However the majority of THC/CBD patient AEs were mild to moderate, and all serious AEs from both groups were considered unrelated to treatment

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The Implications

1. The validity of the trial is questionable due to the 29.7% drop out rate and consequently reduced sample size
2. The only statistically significant results obtained were changes in 30% responders and sleep patterns in favour of THC/CBD
3. There was a high incidence of mild to moderate adverse effects in THC/CBD patients

- Overall, based off the data available from this RCT we would not feel confident advising Mr W to take THC for his PNP

- However, we found a systematic review that provides more statistically powerful data in favour of THC as an analgesic in PNP (Andreae et al. 2015, at the time of writing not accessible)

- For Mr W we would advise he keep to his current analgesia whilst trying different strong opioids. If none are tolerable, we would advise he consult his GP to ask for alternate analgesics and pain management therapy

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