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A Randomised Placebo Controlled Double Blind Clinical Trial of Cannabis Based Medicinal Product (Sativex) in Painful Diabetic Neuropathy: Depression is a Major Confounding Factor.

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Running title: Randomised Controlled Trial of Sativex in Painful Diabetic Painful Neuropathy.

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Objective- To assess the efficacy of Sativex, a cannabis based medicinal extract, as adjuvant treatment in painful-DPN.

Research design and methods- In this randomized controlled trial, 30 subjects with painful-DPN received daily Sativex or placebo. Primary outcome measure was change in mean daily pain scores and secondary outcome measures included quality of life assessments.

Results- There was significant improvement in pain scores in both groups but mean change between groups was not significant. There were no significant differences in secondary outcome measures. Patients with depression had significantly greater baseline pain scores that improved regardless of intervention.

Conclusion- This first ever, trial assessing the efficacy of cannabis has shown it to be no more efficacious than placebo in painful-DPN. Depression was a major confounder and may have important implications for future painful-DPN trials.

Painful diabetic peripheral neuropathy (DPN) is a common and distressing complication of diabetes (1). Unfortunately drug treatments are often ineffective and complicated by unwanted side-effects. Thus, there is need for better treatments. We report the first randomised placebo controlled trial assessing the efficacy and safety of a cannabis based medicinal extract (Sativex) in intractable painful-DPN.

RESEARCH DESIGN AND METHODS

Thirty-eight patients with chronic painful-DPN (NTSS 6 Score (2) >4 and <16) for at least six months with stable glycaemic control (Hba1c<11%) were assessed. Those with persistent pain, despite an adequate trial of tricyclic antidepressants were recruited. All patients gave written informed consent. The study had Sheffield Ethics Committee approval.

A prospective, randomised, double blind, placebo controlled trial design was employed. Baseline pain scores were obtained pre-randomisation. Three modalities of pain (superficial, deep and muscular pain) were assessed daily using a 100mm visual analogue scale (VAS). The dose of study medication was titrated over 2 weeks, followed by a 10 week maintenance phase. At baseline, depression was assessed using the 7-item depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) (3). Patients continued pre-existing neuropathic pain treatments during the study.

Improvements in pain as assessed by the pain diary and Neuropathic Pain Scale (NPS, 4) questionnaire, was used as the primary outcome measure. Study endpoint was the final week mean pain and NPS score, whilst taking maximum tolerated dose of study medication. A total pain score (TPS, average score of all three pain modalities) was also calculated. Secondary outcome measure was quality of life (QOL), assessed by McGill Pain and QOL (5), SF-36 Health Survey (6) and EuroQOL (7) questionnaires. Tolerability and side effects were evaluated using standardised forms.

Sativex [tetrahydrocannabinol (27mg/ml) and cannabidiol (25mg/ml)] and its matching placebo were presented as a pump action spray. Doses were administered sublingually in divided doses up to four times a day.

Statistical Analysis. An intent-to-treat analysis was undertaken. Differences in subgroup baseline characteristics were correlated to the outcome and adjustments performed at a coefficient >0.50. The distributions of outcome measures with each of the covariates were analysed. Multiple linear regression was used for a normal distribution, whilst skewed distribution was initially transformed. Data on proportions was analysed using Fisher's exact test.

In a post-hoc analysis patients were divided into those with depression (HADS-D score $\geq$10) and no depression (HADS-D score <10). Using ANCOVA we compared mean change in TPS from baseline between these groups. The interaction between depression and treatment was assessed using two-factor analysis of variance. Each treatment arm was divided into patients with and without depression and outcomes compared using independent sample t-test.

RESULTS

Of 30 patients randomised, six withdrew because of adverse events. We excluded one placebo treated patient from the intent-to-treat analysis (n=29) because of a protocol violation.

Primary outcome measure. Covariates used in the analysis were duration of diabetes, baseline scores, age and sex. There was no significant difference in mean change TPS between Sativex and placebo [p=0.40 (SEM=9.5; 95%CI -11.3:27.8)] at endpoint. Similarly there was no difference in mean change in superficial [p=0.72 (9.1;-15.3:21.93)], deep [p=0.38 (10.5;-12.2:30.8)] and muscular [p=0.26 (10.3;-9.15:33.0)] pain VAS. Differences in NPS did not reach statistical significance [p=0.62 (7.8; -20.1:12.1)].

Eight (53%) Sativex treated patients responded (defined as $\geq$ 30% total pain VAS improvement) versus nine (64%) placebo patients (p=0.55, odds ratio 0.63, 95%CI 0.14:2.82).

Secondary outcome measures. McGill pain questionnaire showed no difference in sensory scale (p=0.65, 3.3;-5.39:-8.44), affective scale (p=0.81, 1.3;-3.0:2.4), VAS (p=0.24, 1.0;-0.91:3.4) and present pain intensity (p=0.57, 0.53;-0.79:1.4) between study cohorts. EuroQOL and SF-36 questionnaires showed improvement in both groups but differences between groups were not statistically significant.

Post-hoc analysis. We excluded one patient (Sativex) because baseline HADS-D was incomplete. Mean HADS-D for patients with depression (n=10) and no depression (n=18) were 13.4(SD 3.5) and 5.94(2.2) respectively. Patients with depression had significantly higher baseline TPS [62.3(22.1) vs. 43.4(24.3); p=0.05] and greater TPS improvement [-31.6(24.2) vs. -10.7(25.0); p=0.04, SEM 9.8, 95%CI 0.54:41.1] compared to those without depression. There was no significant interaction between treatment group and depression. However, there was a significant main effect of depression on TPS [p=0.05], suggesting that in both treatment arms, patients who were depressed were more likely to respond to intervention [Sativex arm, depressed (-36.7(28.6) vs non depressed (-4.9(14.4); p=0.02; -56.5:-7.2, placebo arm, -26.5(20.7) vs –17.3(33.1); p=0.60; -45.9:27.6].

CONCLUSIONS

Despite being common, there are few effective treatments that provide symptomatic relief for painful-DPN (8). For centuries, cannabinoids have been consumed for their analgesic properties and more recently studied in other neuropathic conditions (9). In this study, when compared to placebo, Sativex failed to show statistically significant improvements in primary and secondary outcome measures. Depression was identified as a major confounder of study outcome. Patients with depression had higher baseline pain scores and were also more likely to respond favourably to intervention, regardless if Sativex or placebo.

Most painful-DPN trials to date either have not screened for depression or exclude those that have it (10, 11). This study demonstrates that depression is potentially a major confounder in chronic pain trials. Future trials should consider screening for depression before recruiting patients.

As in a number of recent studies, there was a large placebo effect that may have led to a failure to show differences in outcome measures (12). This may provide an insight into the nature of pain in DPN and the placebo effect. There is a need for more robust and objective

endpoints for use in clinical trials of painful-DPN.

Use of concomitant medications may be a confounding factor. They were continued because Sativex was proposed for adjunctive use in painful-DPN. Also, it was felt ethically inappropriate to discontinue treatments that patients may be benefiting from. This may have attenuated the analgesic response to Sativex. The use of specific painful DPN QOL questionnaires (13) may have captured subtle changes missed by the generic ones used in this study.

Finally, whilst the search for therapeutic agents to halt or reverse the neuropathic process continues, more effective treatments are required which provide better symptom control with fewer side effects. The assessment of depression may be important when designing future clinical trials into painful-DPN.

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Table 1: Demographics, primary and secondary outcome measures.

	BASELINE		ENDPOINT		
	Sativex	**Placebo**	**Sativex**	**Placebo**	**p**
Age (Years)	58.2 (8.8)	54.4 (11.6)			0.24
Sex (Female)	4	7			0.38
BMI (Kg/M^2)	31.9 (6.3)	31.6 (8.2)			0.92
Cannabis (previous use)	2	0			0.60
HbA1c (%)	8.64 (1.7)	8.39 (1.6)			0.72
Diabetes Duration (Years)	11.2 (8.4)	13.7 (6.0)			0.37
Type of Diabetes (Type 2)	13	11			0.23
Study Medication Amount (ml)			0.70 (0.38)	0.73 (0.38)	0.84
Pain Diary Scores					
Superficial Pain	52.3 (33.0)	45.9 (24.6)	37.9 (32.1)	30.2 (30.1)	0.72
Deep Pain	63.1 (29.4)	47.4 (21.4)	44.5 (32.7)	24.9 (29.5)	0.38
Muscular Pain	52.0 (34.2)	41.4 (28.3)	37.9 (32.9)	20.4 (29.9)	0.26
TPS	55.8 (26.7)	44.9 (21.5)	40.1 (28.5)	25.2 (28.8)	0.40
Neuropathic Pain Scale					
Total Score	67.1 (19.4)	63.6 (14.0)	51.6 (21.9)	51.9 (24.1)	0.62
McGill Pain Questionnaire					
Sensory Scale	19.2 (6.9)	16.3 (6.3)	14.7 (7.2)	12.5 (8.7)	0.65
Affective Scale	4.6 (4.3)	5.0 (3.8)	3.1 (2.3)	3.6 (3.8)	0.81
VAS	7.6 (1.8)	6.9 (1.7)	5.1 (2.2)	3.8 (2.6)	0.24
Present Pain Intensity	2.5 (1.1)	2.0 (1.0)	2.1 (1.1)	1.4 (1.7)	0.57
EQ-5D Questionnaire					
Health Status Index	0.40 (0.21)	0.43 (0.21)	0.54 (0.22)	0.6 (0.2)	0.87
Health Status VAS	46.0 (20.4)	44.6 (21.8)	58.1 (20.5)	56.4 (11.7)	0.92
SF 36 Questionnaire					
Physical Functioning	26.9 (15.1)	30.8 (22.7)	30.5 (16.6)	36.5 (27.9)	0.63
Role Physical	8.9 (27.1)	12.5 (23.5)	12.5 (32.1)	39.3 (47.7)	0.12
Bodily Pain	22.4 (15.5)	25.7 (11.3)	35.6 (16.6)	41.2 (24.6)	0.64
General Health	33.5 (18.7)	28.4 (20.8)	34.1 (18.2)	29.6 (19.5)	0.78
Vitality	28.3 (23.2)	30.8 (19.2)	33.9 (22.4)	39.6 (19.4)	0.45
Social Functioning	50.8 (32.5)	48.2 (24.9)	55.4 (25.3)	67.0 (27.6)	0.08
Role Emotional	38.1 (41.1)	33.3 (40.8)	54.8 (46.4)	47.6 (48.4)	0.76
Mental Health	57.9 (22.6)	57.1 (19.9)	64.4 (20.3)	59.4 (20.6)	0.76

Pain diary scores derived from 100mm visual analogue scale (VAS) completed daily. Total pain score (TPS) derived from average of superficial, deep and muscular pain scores. Results expressed as Mean (SD).