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RESEARCH

Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study

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ABSTRACT

Objective To compare the analgesic efficacy and side effects of the synthetic cannabinoid nabilone with those of the weak opioid dihydrocodeine for chronic neuropathic pain.

Design Randomised, double blind, crossover trial of 14 weeks' duration comparing dihydrocodeine and nabilone.

Setting Outpatient units of three hospitals in the United Kingdom.

Participants 96 patients with chronic neuropathic pain, aged 23-84 years.

Main outcome measures The primary outcome was difference between nabilone and dihydrocodeine in pain, as measured by the mean visual analogue score computed over the last 2 weeks of each treatment period. Secondary outcomes were changes in mood, quality of life, sleep, and psychometric function. Side effects were measured by a questionnaire.

Intervention Patients received a maximum daily dose of 240 mg dihydrocodeine or 2 mg nabilone at the end of each escalating treatment period of 6 weeks. Treatment periods were separated by a 2 week washout period.

Results Mean baseline visual analogue score was 69.6 mm (range 29.4-95.2) on a 0-100 mm scale. 73 patients were included in the available case analysis and 64 patients in the per protocol analysis. The mean score was 6.0 mm longer for nabilone than for dihydrocodeine (95% confidence interval 1.4 to 10.5) in the available case analysis and 5.6 mm (10.3 to 0.8) in the per protocol analysis. Side effects were more frequent with nabilone.

Conclusion Dihydrocodeine provided better pain relief than the synthetic cannabinoid nabilone and had slightly fewer side effects, although no major adverse events occurred for either drug.

Trial registration Current Controlled Trials ISRCTN15330757.

INTRODUCTION

The potential role of cannabinoid agents in the management of neurological disease has attracted considerable interest. Much of the evidence is anecdotal and little sound clinical research is available. A meta-analysis examining cannabinoids failed to find convincing evidence of analgesic activity beyond that of weak opioids, although animal work continues to suggest that cannabinoids may be useful for neuropathic pain.[1] A paper published after completion of this trial showed some benefit in alleviating central pain in patients with multiple sclerosis.[2]

Nabilone is a synthetic cannabinoid that is licensed in the United Kingdom for the treatment of chemotherapy induced nausea and vomiting. It is active against cannabinoid receptors 1 and 2, and it is significantly more potent than delta-9-tetrahydrocannabinol (THC).[3] Nabilone has a high bioavailability and disappears from plasma in a biphasic manner. Its rapid redistribution means it has a plasma half life of two hours, and its total half life of only 20 hours implies rapid metabolism and excretion. Clinical observation indicates that its action is more prolonged, however, possibly because of the presence of active metabolites.[4]

Dihydrocodeine is a weak step II (World Health Organization analgesic ladder) opioid, which is often prescribed in primary care to treat chronic pain.[5] Its psychotropic and sedative side effects make it a good comparative agent for a study with nabilone.[6]

Neuropathic pain is a common condition associated with various injuries to the central and peripheral nervous systems. It is often refractory to treatment with currently available drugs, and other classes of "adjuvant" drugs may be needed.[7]

Animal work has indicated a potential therapeutic role for cannabinoids in neuropathic pain, and a study of patients with refractory chronic pain conditions showed benefit from treatment with nabilone.[8] The pain clinic in Newcastle started using nabilone on an empirical basis in several chronic pain conditions in 1999 and found some evidence of efficacy.[9] We therefore performed a randomised crossover trial to compare the analgesic efficacy of nabilone with that of dihydrocodeine for neuropathic pain. We also compared the side effects of both drugs.

METHODS

Participants and setting

Our study took place between July 2001 and November 2002 in outpatient facilities of three hospitals in the United Kingdom—the Royal Victoria Infirmary, Newcastle upon Tyne; the Gartnavel General Hospital, Glasgow; and the James Cook University Hospital, Middlesbrough.

The trial protocol was shown to all clinicians who worked in the chronic pain units of the participating hospitals and clinicians who refer patients to the trial centres were told about the trial. All suitable patients (box) with neuropathic pain (such as burning, stabbing, or paraesthesia within the distribution of a peripheral nerve) and a clear clinical history of its cause were referred by the participating pain consultants for screening. One clinician (BF) screened, followed up, and monitored all participants during the trial.

We screened 100 patients aged 24-84 years with chronic neuropathic pain (see box for predefined diagnostic criteria) for one to two weeks. To justify treatment and enable improvements to be seen, the patient's mean pain score had to be greater than 40 mm on a 0-100 mm visual analogue scale. Ninety six patients were randomised to one of the two treatment sequences. We allowed participants to keep taking stable analgesics, except for dihydrocodeine, which was stopped two weeks before the start of the study drugs. All other analgesics were continued. We excluded patients taking antipsychotics, benzodiazepines (except for night sedation), and monoamine oxidase inhibitors. Patients taking any cannabinoid preparation at the time of screening were also excluded, as were those with ongoing legal action associated with their clinical condition. Patients with severe hepatic or renal disease, epilepsy, bipolar disorder, psychosis, or a history of substance misuse were not included in the trial.

Procedures

After initial recruitment, patients supplied a daily pain score for one week. During this week, a urine sample was tested for cannabis and patients with a positive sample were excluded. We took blood samples to measure full blood count, electrolytes, urea, liver function, and serum glucose. Urine was tested for protein, blood, pH, and ketones using a dipstick. Patients with abnormal values were not included in the trial, except for those who had abnormal plasma glucose and known insulin dependent diabetes.

Patients underwent an abbreviated neurological examination, which included examining muscle strength in both ankles and testing for ankle reflexes (when appropriate), clinical allodynia, and hyperalgesia. Patients also had a general medical examination, which concentrated on the skin, the respiratory system, the cardiovascular system, and the gastrointestinal system.

During the screening visit, patients filled in a hospital anxiety and depression score (HAD score) and a short form 36 quality of life questionnaire (SF-36—commonly used to measure health related quality of life).[10 11] All patients watched a demonstration of six psychometric tests and practised the tests on the computer until they were confident in the use of the hardware.

Our study was a randomised, double blind, controlled, crossover trial of three months' duration. The

Table 1 | Timetable of visits and procedures

	Study phase								
Timetable of observations	Screening		Drug A			Washout		Drug B	
Study week	-1	0	2	4	6	8	10	12	14
Visit	Screening	1	2	3	4	5	6	7	8
Patient baseline data	X								
Inclusion and exclusion criteria	X								
Demographics	X								
Medical history	X								
Previously or currently taking drugs	X								
Physical examination	X		X	X	X	X	X	X	X
Abbreviated neurological examination	X								
HAD score		X							X
SF-36 score		X							X
Psychometric testing	X	X							X
Blood sampling	X								X
Urine sampling	X								
Side effect and adverse effect assessment			X	X	X	X	X	X	X
Pain score recording		X	X	X	X		X	X	X
Drug dispensing		X	X	X	X		X	X	X

HAD=hospital anxiety and depression; SF-36=short form-36.

three trial periods were—treatment period 1 (six weeks), washout period (two weeks), and treatment period 2 (six weeks). Participants made eight specified visits at weeks 0, 2, 4, 6, 8, 10, 12, and 14 (table 1).

All patients were asked to fill in a diary recording the average daily pain score, the number of hours slept, details of interruptions to sleep (using a tick box), and the amount of study drug taken. During the washout phase the patients recorded the number of rescue tablets (paracetamol 500 mg and codeine 30 mg per tablet) taken each day.

At each visit the patients filled in a side effects assessment form. During the fourth and eighth visits they also filled in a HAD score and SF-36 form and worked through the six psychometric tests.

Outcome measurements

The pain score was the primary outcome variable. Pain scores are just one way to measure the benefit of treatment in patients with chronic pain. Improvements in mood, sleep, and quality of life are equally important for most patients. Secondary outcomes were anxiety and depression as measured by the HAD score, each of the eight domains and the "change in health" measured by the SF-36,[12] and the weekly average number of hours slept each night calculated from the diaries. We calculated the scores for the psychometric tests from the absolute results of each test divided by the time taken to perform the test.

We used an eight item questionnaire that asked about the most common side effects of dihydrocodeine and nabilone. Each question could be answered by circling one of five discretional answers ranging from "Yes, very much" to "Definitely not." Other side effects could also be recorded. Only the answers "Yes, very much" and "Yes, quite a lot" were counted as side effects for the analysis.

Study drugs

The trial drugs were given in an escalating manner (fig 1). If the patient developed side effects, the dosage was reduced to the previous value for the remainder of the trial period after discussion with the investigator. Patients were weaned off the drugs by halving the dose every three days, and patients did not take any trial drug for the last six days of the washout period but were allowed up to eight tablets of rescue drugs a day.

The pharmacy at St Mary's Hospital supplied identical white capsules containing 250 µg nabilone or 30 mg dihydrocodeine. The pharmacies at the treatment centres, the patients, and all clinical personnel involved in the trial were unaware of treatment allocation at all times.

Code breaking envelopes were kept in each hospital pharmacy and each was used for only one patient. The code was disclosed only to the requesting doctor who was not involved in the study.

Statistical considerations

We randomised patients to receive nabilone first then dihydrocodeine or vice versa. Treatment was allocated by random permuted blocks of 10, stratified by centre. We used a model with fixed patient effect, period effect, and treatment effect but no term for the carryover effect of treatment to analyse the data.[13] Normal errors were assumed and this was checked using normal probability plots. Calculations of sample size were complicated by the lack of information on within patient variation for the visual analogue score. A study that randomised 30 patients to each treatment sequence would have 90% power to detect a difference in mean visual analogue score between the treatments equal to 60% of the within patient standard deviation, at 5% significance. This is broadly in line with previous

Inclusion and exclusion criteria

Diagnostic criteria
- Sensory abnormality
- Allodynia
- Burning pain
- Lancinating pain
- Sympathetic dysfunction

Inclusion criteria
- Presence of neuropathic pain according to the diagnostic criteria
- Patient taking a stable dose of analgesic
- Age 18-90

Exclusion criteria
- Epilepsy
- Liver disease
- Psychosis
- Bipolar disorder
- Substance misuse
- Renal failure
- Adverse events to dihydrocodeine or nabilone

Excluded drugs
- Dihydrocodeine
- Antipsychotics
- Monoamine oxidase inhibitors

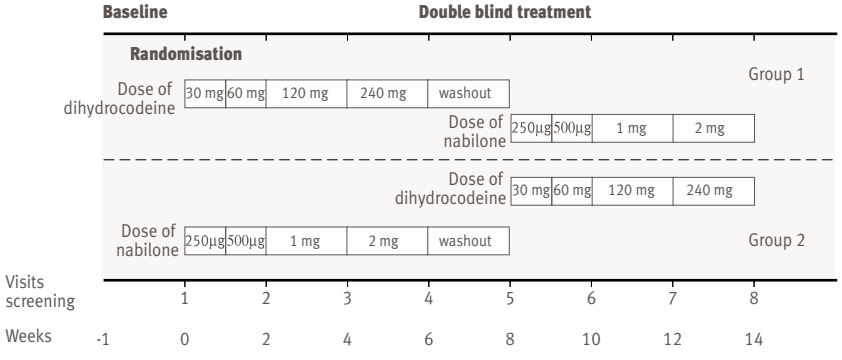

Fig 1 Study design

studies.[14 15] We anticipated that as many as 30% of patients would drop out, so we aimed to recruit 100 patients.

Each treatment period lasted six weeks and we collected data at the end of each period for all variables except the pain score; this score was recorded daily and weekly means were analysed. The treatment periods were separated by a washout period of two weeks. We excluded carryover by basing the analysis on data from the last two weeks of each treatment period—weeks 5-6 and weeks 13-14. If data from one of the last two weeks were missing, we substituted data from the preceding week (week 4 or week 12). Because the use of data from earlier weeks could produce bias from carryover effects, if no data were available on a patient in the last three weeks of the period, the treatment period was excluded. The use of a fixed patient effect in the analysis meant that the patient was then excluded from the analysis.

Two analyses are presented. The available case analysis used the fullest dataset—all patients randomised who provided data in each treatment period (week 4 or beyond and week 12 or beyond). The per protocol analysis excluded patients who did not comply with the trial drugs, as assessed by their pain diary.

Data were prepared used Minitab version 13 and analyses were carried out with Stata version 7. We recoded and tabulated the side effects using SPSS version 11.

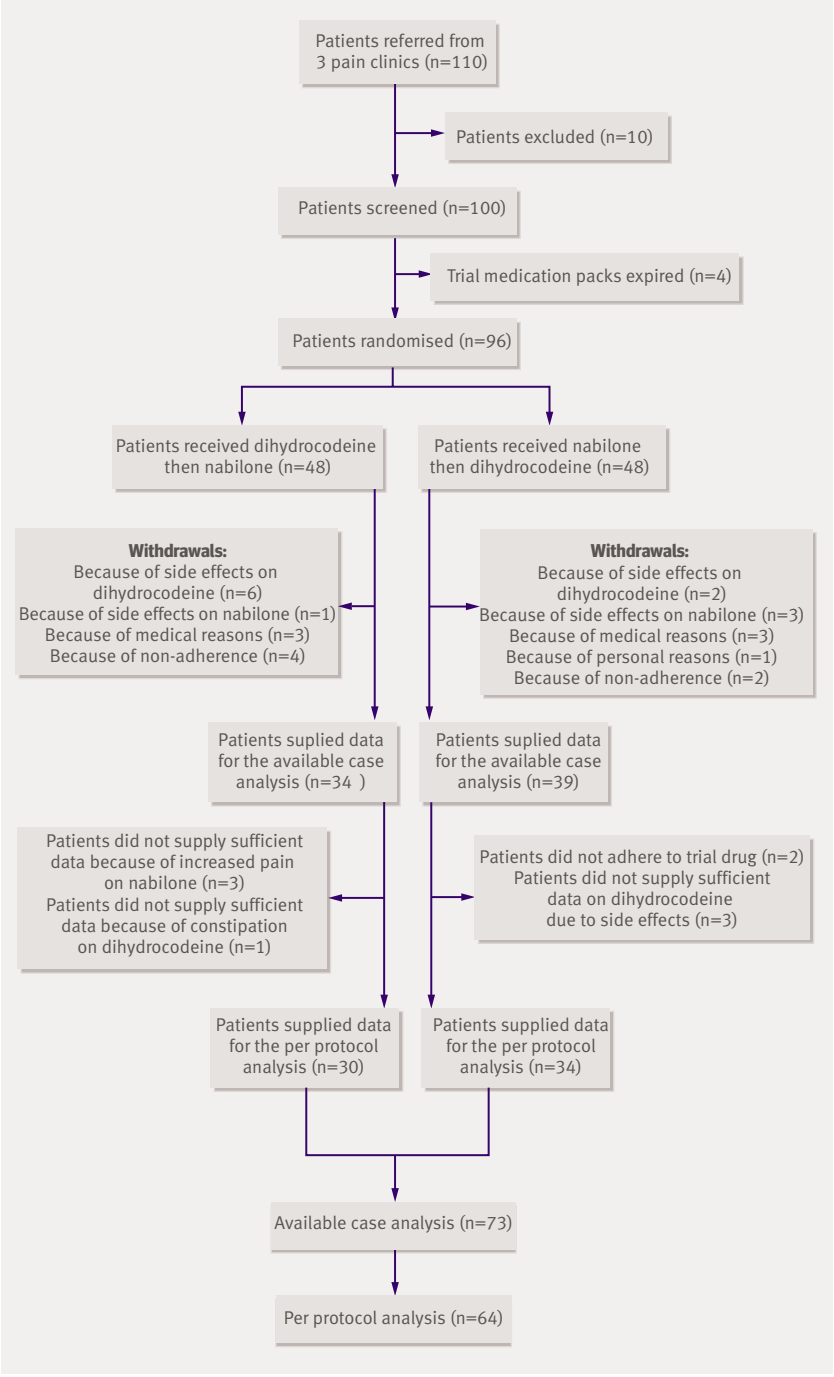

Fig 2 Study flow chart

RESULTS

We screened 110 patients (fig 2). Ten were excluded because of comorbidity or non-compliance with the trial requirements. We screened 100 patients but randomised only 96. Table 2 shows their demographic profile and their clinical history with regard to neuropathic pain and its treatment.

We allocated 48 patients to receive dihydrocodeine and 48 to receive nabilone as first treatment. The available case analysis included 73 patients, and 64 were retained for the per protocol analysis (fig 2). The six non-compliant patients did not attend follow-up appointments so only partial data from one study period were available. We performed a detailed breakdown of the data by each centre and by the sequence of the treatment received. We found no differences between centres or treatment sequences.

The mean baseline visual analogue score was 69.6 mm (range 29.4-95.2) on a 0-100 mm scale. The mean (SD) visual analogue score was 59.93 (24.42) for patients taking nabilone and 58.58 (24.08) for those taking dihydrocodeine. The mean (SD) for nabilone minus dihydrocodeine was 1.59 (9.19) for patients who took nabilone first then dihydrocodeine and −4.39 (10.32) for patients who took dihydrocodeine first then nabilone.

Dihydrocodeine was a significantly better analgesic than nabilone. The available case analysis produced a treatment effect (in the direction nabilone minus dihydrocodeine) of 6.0 mm (95% confidence interval 1.4 to 10.5, P=0.01). The equivalent figures for the per protocol analysis were 5.6 mm (0.8 to 10.3, P=0.023).

If we assume that a drop in the visual analogue score of more than 10 mm is a clinically relevant treatment effect, three of the 64 patients in the per protocol dataset had a clinically relevant response on nabilone compared with 12 patients on dihydrocodeine. No patient responded to both of the investigated drugs. Forty nine patients had no clinically relevant drop in their pain score on either treatment.

Table 3 gives details of the secondary outcomes. In the available case analysis, the treatment effect for the

Table 2 | Study population

	Treatment group			
	Dihydrocodeine then nabilone		Nabilone then dihydrocodeine	
	Patients (n)	Mean (SD)	Patients (n)	Mean (SD)
Demographic details				
Female	25		21	
Male	23		27	
Age (years)	48	50.6 (15.2)	48	49.7 (12.0)
Height (cm)	48	168.6 (9.6)	48	169.0 (11.5)
Weight (kg)	48	73.9 (15.4)	48	77.7 (18.3)
Duration of pain (months)	48	79.8 (67.9)	48	73.0 (70.3)
Baseline visual analogue score	47	68.0 (12.4)	48	66.4 (14.9)
Neuropathic pain syndrome				
Cervical radiculopathy	0		1	
Complex regional pain syndrome	5		4	
Demyelination	4		7	
Diabetic neuropathy	4		3	
Guillain-Barré syndrome	0		1	
Mononeuritis multiplex	1		0	
Myelopathy	2		4	
Neuropathy	1		0	
Post-herpetic neuralgia	4		3	
After injury or surgery	22		20	
Spinal artery thrombosis	2		0	
Spinal cord injury	1		0	
Transverse myelitis	1		4	
Trigeminal neuralgia	1		1	
Previous treatment with non-steroidal anti-inflammatory drugs				
No	16		9	
Yes	32		39	
Previous treatment with weak opioid				
No	10		6	
Yes	38		42	
Previous treatment with antidepressant				
No	5		7	
Yes	43		41	
Previous treatment with anticonvulsant				
No	7		9	
Yes	41		39	
Previous treatment strong opioid				
No	37		29	
Yes	11		19	
Signs of sensory abnormality				
No	3		3	
Yes	45		45	
Signs of allodynia				
No	22		15	
Yes	26		33	
Symptoms of burning pain				
No	16		14	
Yes	32		34	
Symptoms of lancinating pain				
No	5		7	
Yes	43		41	
Symptoms of sympathetic dysfunction				
No	35		38	
Yes	13		10	
Origin of pain				
Central	10		20	
Peripheral	38		28	

Table 3 | Secondary outcomes for patients with neuropathic pain treated with nabilone or dihydrocodeine

Outcome measured	Number of patients analysed	Treatment effect (95% confidence interval)	P value
Available case analysis			
Sleep	71	0.2 (−0.1 to 0.5)	0.20
Anxiety	70	−0.6 (−1.4 to 0.3)	0.19
Depression	70	−0.2 (−1.2 to 0.9)	0.72
Change in health	70	0.0 (−0.2 to 0.2)	0.88
Physical functioning	71	−1.2 (−4.5 to 2.1)	0.48
Social functioning	71	3.4 (−4.1 to 10.8)	0.37
Role, physical	69	8.9 (1.1 to 16.7)	0.03
Role, emotional	69	−1.2 (−11.8 to 9.5)	0.83
Mental health	71	2.5 (−2.7 to 7.6)	0.35
Vitality	71	−2.0 (−7.2 to 3.3)	0.46
Bodily pain	71	−5.2 (−10.1 to −0.4)	0.03
General health	70	0.8 (−3.1 to 4.6)	0.70
Per protocol analysis			
Sleep	63	0.2 (−0.1 to 0.5)	0.28
Anxiety	62	−0.6 (−1.6 to 0.3)	0.18
Depression	62	−0.2 (−1.2 to 0.9)	0.78
Change in health	62	0.0 (−0.3 to 0.2)	0.76
Physical functioning	63	−1.4 (−5.1 to 2.4)	0.47
Social functioning	63	2.3 (−5.3 to 9.9)	0.54
Role, physical	62	10.8 (2.3 to 19.2)	0.01
Role, emotional	62	−0.6 (−11.4 to 10.2)	0.92
Mental health	63	2.0 (−3.2 to 7.1)	0.45
Vitality	63	−2.3 (−7.6 to 3.0)	0.39
Bodily pain	63	−5.7 (−10.9 to −0.5)	0.03
General health	63	0.5 (−3.7 to 4.7)	0.81

Positive values indicate higher scores with nabilone. Negative values indicate higher scores with dihydrocodeine.

SF-36 domain "role physical" was 8.9 (1.1 to 16.9, P=0.03); these figures were 10.8 (2.3 to 19.2, P=0.01) for the per protocol analysis. In this domain, higher scores indicate a better outcome, so these results show that nabilone was significantly superior to dihydrocodeine on this measure. In the available case analysis, the treatment effect for the SF-36 domain bodily pain was −5.2 (−10.1 to −0.4, P=0.03); these figures were −5.7 (−10.9 to −0.5, P=0.03) for the per protocol analysis. Higher scores in the bodily pain domain indicate a better outcome, so these results show that dihydrocodeine was statistically superior to nabilone. These results agree with those of the primary outcome analysis.

Analysis of the psychometric testing found no significant differences between the two drugs.

Table 4 provides details of the side effects. Nabilone was associated with more sickness than dihydrocodeine. Dihydrocodeine was associated with more tiredness and nightmares than nabilone. No major adverse events occurred when patients were taking either drug and both drugs were equally well tolerated.

DISCUSSION

The weak opioid, dihydrocodeine, was a statistically better treatment for chronic neuropathic pain than nabilone. More patients had clinically significant pain relief from dihydrocodeine, although a small number of patients responded well to nabilone. The side effects of both treatments were generally mild and in the expected range.

Strengths and weaknesses

Our study had intrinsic sensitivity as it showed a difference between the two treatments.

Weaker points of the study were that 33 patients failed to complete the trial and the population studied had a variety of neuropathic pain syndromes. The high dropout rate can be explained partially by the cross-over design—unlike a parallel group design this type of trial exposes patients to two rather than one treatment.

In addition, the cannabinoid that we used was synthetic and not plant based, so that the results are not necessarily relevant to people who smoke marijuana preparations. However, the active constituents of such preparations have been well characterised and no compounds have been found to offer novel or unpredicted actions at cannabinoid receptors.

Implications

The analgesic effects of opioids and cannabinoids are mediated by separate mechanisms—the analgesic effects of nabilone are not mediated by opioid receptors.[16] A recent study found that THC was not

Table 4 | Side effects of nabilone or dihydrocodeine in patients with neuropathic pain

Side effect	Nabilone	Dihydrocodeine
Tiredness	79	102
Sleeplessness	46	38
Sickness	46	10
Tingling	25	24
Strangeness	27	33
Nightmares	7	18
Shortness of breath	18	20
Headaches	20	19
Other	66	41
Total	334	305

an effective analgesic when used alone but had a pronounced synergistic effect when used with an opioid.[17] We found that the weak opioid, dihydrocodeine, provided better pain relief than the cannabinoid, nabilone, in the treatment of chronic neuropathic pain. However, the clinical significance of this difference is small, and neither drug was particularly effective. Nabilone significantly improved patients' scores on the "role physical" domain of the SF-36. Once again, the clinical relevance of this improvement is relatively small.

More patients taking dihydrocodeine had constipation, and surprisingly nabilone was more likely to cause nausea even though it is used as an antiemetic.

Dihydrocodeine is a weak opioid with 10% of the potency of oral morphine, so our maximum dose of 240 mg was equivalent to around 24 mg of oral morphine.[18] No data are available for the therapeutic dosing of nabilone, and the dose of 2 mg was arrived at as a compromise between safety and the effective dose seen in our clinical practice.[9] The observed side effect profile argues against giving higher doses of nabilone.

Dihydrocodeine is a slightly more effective analgesic than codeine but less effective than tramadol and morphine.[19,20] This low potency opioid was more effective than the potent cannabinoid, nabilone, which argues against using this cannabinoid in clinical practice and supports previous findings.[21]

Marijuana preparations act mainly through THC—the most abundant and potent naturally occurring cannabinoid. There has been some interest in combining cannabidiol with THC as a way to reduce some of the side effects of the active cannabinoid. Although these actions may be related to the antagonist activity of cannabidiol, it has been suggested that cannabidiol has intrinsic antipsychotic activity unrelated to its cannabinoid receptor effect. However, a recent study found that including cannabidiol in THC preparations had no advantages.[22] Animal models provide no evidence that cannabidiol has any form of central analgesic activity and our findings—that the intrinsic analgesic activity of nabilone in neuropathic pain is at best modest—are relevant to the cannabinoid debate.

Much has been made of the poor availability of oral cannabinoids compared with inhaled agents. Recent studies investigated an oromucosal spray of THC as a way to deliver it to the central nervous system rapidly.[2,22] However, the rapid administration of psychotropics has different effects from those seen after slower administration. Cannabis—like many other recreational drugs such as alcohol, amphetamines, and opioids—acts on areas of the brain related to the "reward" pathways. Cannabinoid 1 receptors are colocalised with opioid receptors on dopaminergic cells of the nucleus accumbens, probably the most important structure in the human reward system.[23] The reward system is triggered by rapidly rising drug concentrations, so smoking, "snorting," or injecting certain drugs has a greater effect on the system than oral ingestion. For this reason, the results of studies using rapid administration must be interpreted with caution. Oral ingestion avoids high peak concentrations, and considerations relating to bioavailability are less relevant when drugs are used to treat chronic pain, where fixed regular dosing is the norm.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Cannabinoids have been used as analgesics for centuries but the evidence base for their use is poor

Psychotropic side effects limit therapeutic dosing in patients with chronic pain

Neuropathic pain is a common and difficult to treat condition that has limited treatment options

WHAT THIS STUDY ADDS

Nabilone, a synthetic oral cannabinoid, is not more effective for treating neuropathic pain than the oral opioid dihydrocodeine

Contributors: BF helped design the trial, analyse the data, write the initial draft of the article, and conduct the trial. MGS referred the Glasgow patients and helped design the trial and write the article. JH referred the Middlesbrough patients and helped design the trial and write the article. JNSM wrote the statistical part of the article and helped design the trial and analyse the data. DK designed the trial, was the principal investigator, and referred the Newcastle patients. BF is guarantor.

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Competing interests: BF's salary was provided as part of the above research grant although he was employed by the Newcastle upon Tyne

University Hospitals Trust. None of the other authors have any competing interests.

Ethical approval: The joint ethics committee for the Newcastle and North Tyneside Health Authority, the west ethics committee for the Northern Glasgow University Hospitals NHS Trust, and the South Tees local research committee in Middlesbrough.

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