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Fast Tracked Original Paper

Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial

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Abstract: The analgesic effectiveness and adverse effect incidence of a daily dose of 10 or 20 mg of oral methadone were evaluated in 18 patients with a diverse range of chronic neuropathic pain syndromes, who had all responded poorly to traditional analgesic regimens. Analgesia was seen after each dose of methadone. As compared with placebo, the 20 mg daily dose (given as 10 mg bd) resulted in statistically significant ($P = 0.013$–0.020) improvements in patient Visual Analogue Scale ratings of maximum pain intensity, average pain intensity and pain relief, recorded at the same time daily. The analgesic effects extended over 48 hours, as shown by statistically significant ($P = 0.013$–0.020) improvements in all three outcomes on the rest days instituted between each daily dose. Analgesic effects (lowered maximum pain intensity and increased pain relief, on the day of dosing only) were also seen when the lower daily dose of 10 mg methadone (given as 5 mg bd) was used, but these failed to reach statistical significance ($P = 0.064$ and 0.065, respectively). Interpatient analysis showed that the analgesic effects were not restricted to any particular type of neuropathic pain. Patient compliance was high throughout the trial. One patient withdrew during the 10 mg and six during the 20 mg methadone treatment periods. This is the first double-blind randomized controlled trial to demonstrate that methadone has an analgesic effect in neuropathic pain. *Palliative Medicine* 2003; **17:** 576–587

Key words: methadone; neuropathic pain; pain relief; randomized control trial

Introduction

Over the past decade there has been renewed interest in the analgesic properties of methadone. Anecdotal reports and a number of open case series have described the successful use of methadone, principally in cancer pain syndromes that have responded poorly to high doses of other strong opioids. The discovery that opioids like methadone have nonopioid properties of relevance to the aetiology of neuropathic pain provided a rationale that they may have advantages over morphine in the treatment of such pain syndromes.[1] Of particular interest are the N-methyl-D-aspartate (NMDA) receptor antagonistic properties and biogenic amine reuptake inhibitory properties that methadone shares with levorphanol and dextromethorphan, but that are not seen in opioids such as morphine, codeine, oxycodone and fentanyl.[2] In animal models of neuropathic pain, drugs possessing these nonopioid properties are antinociceptive, and, when coadministered with opioids, strongly potentiate the antinociception elicited by the opioids,[3–8] and also delay the development of analgesic tolerance and physical dependence.[9–12] Although several clinical studies have supported these conclusions,[13] no adequately blinded studies have examined whether methadone has a significant clinical effect in the management of neuropathic pain. We therefore sought to demonstrate through an experimental rather than a pragmatic study whether small doses of methadone had an analgesic effect when given to patients with chronic nonmalignant neuropathic pain. For this purpose, we designed a double-blind,

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randomized crossover trial to compare the effect of daily divided doses of 10 mg (Phase 1 of the trial) or 20 mg (Phase 2) of methadone versus placebo in patients suffering from various types of neuropathic pain. Most of these pains had been found resistant to normal doses of amitriptyline, gabapentin, carbamazepine or other treatment methods. The design of the trial allowed for intrapatient analysis (*n*-of-1) as well as the conventional interpatient analysis.

Methods

Ethical approval was obtained to recruit outpatients having a history of more than three months of non-malignant neuropathic pain, which had not been satisfactorily relieved by other interventions or by current or previous drug regimens, at the Pain Clinic, Walton Centre for Neurology and Neurosurgery, Liverpool. The diagnosis of neuropathic pain, defined as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system'[14] was made by the referring consultant and confirmed by a pain specialist. Eligible patients were 18–80-year old males and females, who were able to understand the trial assessments. Patients who were pregnant or lactating, or patients with a known hypersensitivity to opioids or a history of alcohol or drug abuse, were not considered. The patients' GPs were informed of their patients' involvement in the trial before they commenced any study medication. The study was in two phases, each of 20 days duration. Patients continued on all current medications during the study.

Materials

Duma pots, with child-resistant and tamper-evident seals, each containing two capsules of either methadone 10 mg or matching placebo, were manufactured by Penn Pharmaceuticals, Tredegar, Gwent, UK. Polywad was included to reduce free space. The Duma pots containing methadone 5 mg and matching placebo pots were then packaged in a random order and labelled Phase 1, with a patient number and an odd day number, from 1 to 19. The Duma pots containing methadone 10 mg and matching placebo pots were similarly randomized and labelled Phase 2, with a patient number and odd day number. The randomisation (eight replications of a Latin Square Design) was carried out by Penn Pharmaceuticals, and the treatment code was not broken until the study was complete. The treatments were therefore identified only by phase (1 or 2), patient number (1–19) and day (odd numbered days from 1 to 19), and they were not distinguishable by taste or by appearance. Neither the investigators nor the patients were aware of the identity of the medications.

Initial assessments

Patients who consented to participate in the trial had a 'cooling off' period of at least seven days to reconsider before returning to the Pain Clinic for an initial assessment. At this assessment a research nurse identified areas of altered sensation and recorded the characteristics and location of the pain. Baseline assessments of individual patient's pain characteristics were made using the Neuropathic Pain Scale (NPS) of Galer and Jensen,[15] and Visual Analogue Scale (VAS) recordings of their maximum and average pain intensity for the previous week. Horizontal scales (100 mm) were used with 0 'no pain' and 100 'worst pain possible'. On the evening of the baseline assessment, patients made VAS recordings of their maximum and average pain intensity for the day.

Patient assessments

Patients were seen as outpatients at the start of each phase, carefully instructed on the use of pain diaries and VAS, and issued with the study medications and a pain diary. For Phase 1, 10 Duma pots each containing two capsules of either 5 mg of methadone or placebo was issued. Patients were instructed that on waking on odd numbered days they should self-administer orally one capsule taken from the Duma pot labelled for that day, and the other capsule at least 10 hours later. They were told that even days (2–20) were rest days when no study capsules should be taken. Thus after 20 days each patient took 10 mg of methadone on five of the study days and doses of placebo for five of the study days, each daily dose of methadone or placebo being followed by a day when neither drug or placebo was taken. They were further instructed that every evening (at least three hours after taking their last dose of either methadone or placebo on odd numbered days, and at the same time on even numbered 'rest' days) they should assess and record pain relief and maximum and average pain intensity for the day in their pain diary. They were also asked to record a) any adverse effects, and classify each as mild, moderate or severe, and b) any 'as required' (PRN) analgesics they may have taken that day. If they experienced severe adverse effects, or wished for any other reason to withdraw from the study, they were instructed to contact the research nurse.

After the 20-day treatment they returned to the clinic where the NPS assessment was repeated, and the patient was asked to record in the evenings a VAS assessment of that day's maximum and average pain intensity. Provided that any adverse effects (volunteered or declared during questioning) during Phase 1 of the trial were considered tolerable, patients were invited to proceed to Phase 2 of the trial.

Phase 2 was conducted in the same way, but the Duma pots issued contained 10 mg of methadone or placebo, to provide twice the daily dosing (20 mg) of methadone.

NPS and maximum and average pain intensity assessments were again carried out and recorded at the end of the phase. The baseline characteristics of all the 11 patients who completed both phases of the trial, and those who were subsequently prescribed regular methadone, were reassessed after 28 days.

Statistical methods

In each phase of the trial, two-tailed paired *t*-tests were used to compare the patients' mean response in terms of VAS scores (maximum intensity and average intensity of pain, pain relief) on the five days in which they took methadone, and on the five days in which they took placebo. This approach was also used to compare pain levels on the rest days with those on placebo days. All patients (except one where there was incomplete data) were included in the analysis. Results are presented as the mean of the difference for each patient between their mean pain level on methadone and placebo, with the 95% confidence interval (CI) around the mean difference. The intrapatient analysis was carried out for each patient using a two-sample *t*-test, to compare his/her mean VAS scores on methadone and placebo. All analysis was carried out using SPSS for Windows v.10. Statistical significance was taken as $P < 0.05$. The use of an *n*-of-1 design allowed for intrapatient analysis, and the sample size of 18 patients and the crossover design gave 80% power with alpha = 0.05 and beta = 0.2 to detect a 20% difference between the mean effects of the five days on the two dosage levels.

Results

Thirty-three suitable patients were invited to enrol in the trial. Of these, 14 declined to participate; five patients gave no reason, three patients associated methadone with addiction, two patients did not want to take any further medication and four patients gave 'depression when new therapies fail', 'having to declare a methadone script would damage my employment prospects', 'not 100% sure I want to be on methadone' and inability to understand the trial assessments as respective reasons.

The remaining 19 patients, details of whom are given in Table 1, were recruited to the trial. All reported a continuous pattern of pain of central nervous system (CNS) or peripheral nervous system (PNS) origin. Eighteen patients completed Phase 1, patient 9 withdrawing on day 5 because of adverse effects. A further patient (patient 3) did not complete data on rest days, and so was removed from the rest day analysis of Phase 1. The same patient declined entry into Phase 2 of the trail due to an intercurrent illness. Six (patients 7, 10, 11, 15, 17 and 19) of the remaining 17 patients entering Phase 2 of the trial failed to complete, mainly because of severe nausea, leaving 11 patients in the final analysis.

Clinical assessment

Table 2 gives the results of the NPS assessments and the VAS score assessments before the start of the trial (visit one), and, where applicable, between Phases 1 and 2 of the trial (visit two). A summary of the pain characteristics of all patients at the start of the trial is given in Table 3.

Diary recordings

For each patient, VAS scores on the five days that methadone was taken, and on the five days that placebo was taken were averaged, and the mean methadone and placebo VAS scores are presented in Table 4 (Phase 1) and Table 5 (Phase 2). The mean differences in these VAS scores for Phases 1 and 2 of the trial, and the mean differences between the VAS scores following methadone or placebo treatment on the rest days were calculated and are given in Table 6.

As compared with placebo, there were statistically significant improvements in all three outcomes in Phase 2 of the trial on days when 20 mg of methadone was self-administered orally (Table 6, columns on the right); specifically, there was a VAS reduction in maximum pain intensity of 16.0 ($P = 0.013$), a VAS reduction of average pain intensity of 11.85 ($P = 0.020$) and an increase in VAS pain relief of 2.16 ($P = 0.015$). Analgesic effects (lowering of VAS by 9.74 for maximum pain intensity, and increased VAS score for pain relief) were also seen in Phase 1 of the trial on days in which 10 mg of methadone was self-administered orally (Table 6, columns on left), but these failed to reach statistical significance ($P = 0.065$ and 0.64, respectively).

In Phase 2 of the trial (but not in Phase 1) significant analgesic effects were also seen on rest days that corresponded with a 20 mg dose of methadone taken the preceding day (Table 6). Compared with placebo, there was a lowering of VAS score for maximum pain intensity by 12.02 ($P = 0.010$), a lowering of VAS score for average pain intensity by 10.46 ($P = 0.026$) and an increase in the VAS score for pain relief of 0.94 ($P = 0.025$).

For the days on which methadone was self-administered, these effects of methadone as a percentage of the mean placebo scores are shown in Table 7. For example, in Phase 2 of the trial (Table 7, columns on right), the mean VAS score for maximum pain intensity after taking placebo was 74.7, and this was reduced by 12.4% when methadone was taken ($P = 0.013$); the mean VAS score for average pain intensity after taking placebo was 67.3, and this was reduced by 9.7% when methadone was taken ($P = 0.020$); and the mean VAS score for pain relief after

Table 1 Patient details

Patient no.	Age (years)	Sex	Diagnosis	Site of pain	Duration of pain (months)	Current (co)analgesics	Previous (co)analgesics	Aggravating factors[a]	Relieving factors[a]
1	52	M	Genitofemoral neuralgia	Genital/inguinal	84	Nefopam 30–60 mg bd; paracetamol 1 g bd	Nortriptyline, gabapentin, carbamazepine	M	None
2	54	F	Central post-stroke pain	Haemibody	84	Nortriptyline 150 mg nocte; lamotrigine 200 mg bd	Gabapentin, mexiletine	F, M, E, C, T, H	R, E
3	71	F	Sciatica	Leg	17	Amitriptyline 25 mg nocte; gabapentin 1500 mg/day; paracetamol 1 g qds; tramadol 100 mg bd	Carbamazepine, capsaicin, cocodamol	M, F, T	R, T
4	70	M	PHN	Face and head	36	Paracetamol 1 g qds; codeine phosphate 30 mg qds	Gabapentin, tramadol, carbamazepine, amitriptyline, capsaicin, Emla cream, sodium valproate	F, M, T, W, H, P	R
5	53	M	Post-traumatic neuralgia	Arm	108	Diclofenac 50 mg tds; dothiepin 50 mg nocte; coproxamol 2 tabs qds	Amitriptyline, dihydrocodeine, baclofen, ketamine, tramadol	M	R, H, E
6	80	M	PHN	Face and head	24	Amitripyline 50 mg nocte; cocodamol 2 tabs od	Carbamazepine, capsaicin, clonazepam, gabapentin	F, C, T, W	R, C
7	59	M	Diabetic polyneuropathy	Left leg and arms/hands	30	Coproxamol 2 tabs qds	Tramadol, nortriptyline, gabapentin, carbamazepine	M, F, C, T	R
8	75	F	PHN	Face and head	42	None	Cocodamol, capsaicin, amitriptyline, carbamazepine, sodium valproate, clonazepam, lamotrigine	E, C, T	H, E, M
9	71	M	Idiopathic polyneuropathy	Legs and feet	180	None	Amitriptyline, carbamazepine, gabapentin	F, C, T	R, H, T
10	68	F	Sciatica	Leg	60	Coporoxamol 2 tabs qds; meloxicam 15 mg od; amitriptyline 10 mg nocte	Gabapentin, tramadol	M, C, T, S	R
11	59	M	Diabetic polyneuropathy	Legs and feet	60	None	Gabapentin, amitriptyline, sodium valproate, mexiletine, carbamazepine, capsaicin	M, S	None
12	57	M	Transverse myelitis	Back–left thoracic	120	Codydramol 2 tabs od; amitriptyline 50 mg nocte	Gabapentin, lamotrigine, prednisolone	C, R	M
13	27	F	Postsurgical neuralgia	Arm	48	None	Gabapentin, lamotrigine, amitriptyline, tramadol, coproxamol, cocodamol, diclofenac	M, T, H	None
14	56	M	Diabetic polyneuropathy	Legs/feet and hands	36	Tramadol 100 mg qds	Gabapentin, capsaicin, amitriptyline, coproxamol	M	None
15	41	M	CRPS II	Arm and hand	72	Amitriptyline 125 mg nocte; gabapentin 600 mg tds; capsaicin tds; codydramol 2 tabs tds	Ibuprofen, diclofenac, ketorolac, ketamine, fentanyl	F, M, E, T, H	None
16	48	M	Intercostal neuralgia	Chest	36	Gabapentin 600 mg tds; carbamazeine 200 mg tds; codydramol 2 tabs od	Tramadol, amitriptyline, MST, indomethacin, capsaicin	M	None
17	73	M	Diabetic polyneuropathy	Legs and feet, arm and hand	240	Nefopam 30 mg bd	Gabapentin, amitriptyline, carbamazepine, sodium valproate, tramadol, dothiepin, mexiletine	M	None
18	52	M	Central post-stroke pain	Shoulder and arm	60	Carbamazepine 400 mg bd; amitriptyline 10 mg nocte; coproxamol 2 tabs qds	Dihydrocodeine, nabumetone	M, C, T	None
19	66	F	Radiculopathy	Arms and hands	84	Prednisolone 4.5 mg od; amitripyline 10 mg nocte; MST 30 mg bd; nabumetone 200 mg bd	Coproxamol, paracetamol, ibuprofen, carbamazepine	F, M, E, C	R, H, E

[a]Aggravating/relieving factors: M, movement; F, friction; E, emotion; C, cold; T, touch; H, heat; W, wind; P, perspiration; and S, standing; R, rest.

Table 2 Clinical assessment of patients

Patient no.	Visit no.[a]	NPS											VAS scores (0–100)			
		Intense	Sharp	Hot	Dull	Cold	Sensitive	Itch	Time pain quality	Unpleasant	Intense deep	Intense surface	Max pain today	Ave pain today	Max pain past week	Ave pain past week
1	one	8	8	2	6	0	2	0	a) background pain all time+flare up	8	8	7	81	76	85	85
1	two	8	8	1	7	0	1	0	a) background pain all time+flare up	9	8	7	70	63		
2	one	9	1	7	8	8	9	1	a) background pain all time+flare up	9	8	7	73	43	75	39
2	two	9	1	6	8	8	8	0	a) background pain all time+flare up	9	8	8	71	67		
3	one	7	0	6	0	0	10	0	a) background pain all time+flare up	8	8	0	42	33	54	37
4	one	9	9	9	1	0	10	8	a) background pain all time+flare up	10	10	10	88	77	96	70
4	two	10	10	9	0	0	10	1	a) background pain all time+flare up	10	10	9	99	98		
5	one	8	0	0	9	0	0	0	a) background pain all time+flare up	8	7	0	66	57	69	71
5	two	7	0	0	0	0	0	0	a) background pain all time+flare up	8	8	0	78	60		
6	one	8	9	7	9	5	9	10	a) background pain all time+flare up	8	9	7	82	73	90	70
6	two	7	7	6	5	4	8	7	a) background pain all time+flare up	7	8	5	48	30		
7	one	8	9	9	10	7	9	8	a) background pain all time+flare up	9	9	7	87	86	93	68
7	two	8	9	7	7	5	7	6	a) background pain all time+flare up	9	8	7	84	80		
8	one	7	6	5	7	0	5	6	a) background pain all time+flare up	7	8	6	85	76	79	57
8	two	8	6	8	8	1	8	10	a) background pain all time+flare up	9	8	9	80	75		
9	one	8	9	7	3	1	6	9	a) background pain all time+flare up	4	8	3	56	32	87	47
10	one	8	9	0	9	10	8	0	a) background pain all time+flare up	9	9	0	63	60	76	76
10	two	6	0	0	9	8	0	0	a) background pain all time+flare up	9	9	7	47	55		
11	one	10	10	10	5	10	5	0	a) background pain all time+flare up	10	10	4	79	84	81	82
11	two	8	8	8	1	2	8	1	b) Single pain all the time	8	8	8	89	89		
12	one	6	7	0	8	0	3	0	a) background pain all time+flare up	7	7	2	75	60	84	57
12	two	6	3	0	8	0	0	1	a) background pain all time+flare up	7	7	0	65	44		
13	one	8	10	0	8	3	10	1	a) background pain all time+flare up	8	8	10	76	76	100	79
13	two	10	10	2	7	0	10	5	a) background pain all time+flare up	10	8	10	86	81		
14	one	9	10	10	3	4	10	0	b) Single pain all the time	10	10	8	100	100	100	98
14	two	10	10	10	9	10	10	3	b) Single pain all the time	10	10	10	100	100		
15	one	8	3	9	9	1	9	0	a) background pain all time+flare up	10	10	9	89	91	87	84
15	two	10	3	9	9	1	10	8	a) background pain all time+flare up	10	9	10	90	90		
16	one	6	0	6	6	0	0	0	b) Single pain all the time	9	7	6	68	67	76	69
16	two	6	0	6	7	0	5	0	b) Single pain all the time	8	5	5	52	32		
17	one	7	8	7	7	6	6	6	a) background pain all time+flare up	7	8	7	53	39	58	47
17	two	7	7	7	7	7	7	7	b) Single pain all the time	7	7	7	80	78		
18	one	4	8	8	3	4	2	1	a) background pain all time+flare up	7	8	8	19	16	72	37
18	two	4	1	2	5	0	7	0	a) background pain all time+flare up	5	7	0	42	31		
19	one	10	10	2	10	10	1	1	a) background pain all time+flare up	10	10	10	99	99	97	98
19	two	10	10	8	7	10	7	4	a) background pain all time+flare up	10	10	10	99	98		

Neuropathic pain scale (Galer and Jensen[15]) scores (0–10) at visit one (pretrial assessment), and, where applicable, visit two (between Phases 1 and 2 of the trial). Our VAS scores (0–100) of maximum and average pain intensity on the day of the visit, and over the seven days prior to the visit are also given (right hand columns).
[a] Visit no. one = day before Phase 1; Visit no. two = day before Phase 2.

Table 3 Summary of pain characteristics of patients at start of trial

Patient characteristic	Patient number																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Allodynia																			
Punctate		✓	✓	✓		✓	✓		✓				✓		✓			✓	
Static							✓								✓				
Dynamic				✓		✓	✓		✓			✓	✓		✓			✓	
Thermal		✓	✓	✓		✓	✓		✓						✓			✓	
Hyperpathia				✓			✓								✓				
Hyperalgesia															✓				
Hypoaesthesia	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Paraesthesia												✓							
Dysaesthesia		✓							✓		✓				✓			✓	✓

A tick indicates the characteristic was confirmed during the initial assessment, e.g., patient 2 had punctuate and thermal allodynia, and dysaesthesia.

Table 4 Patients' diary assessments – Phase 1 (10 mg methadone per day)

Patient no.	Max intensity drug	Max intensity placebo	Average intensity drug	Average intensity placebo	Relief drug	Relief placebo
1	67.8	63.6	57	52	37.8	41.6
2	70.8	69.2	59.6	65.8	2	0
3	74.6	73.2	54.6	56.2	46.8	46.2
4	97	97.6	96.2	96.6	2.6	2.4
5	65.8	69.2	58.8	60.8	31.6	26.8
6	63.6	73.6	49.8	55.8	12.4	5.6
7	80.4	80.4	71.0	79.4	18.8	10.8
8	43.4	66.8	32	49	58.2	24.2
9	51	53	36	35	32	0
10	47.4	72.8	47.4	69.2	41.4	13.4
11	75	81.8	75	79.8	6.4	6
12	60	63	47.8	42.8	39.8	36.8
13	86.2	85	81.4	80	0	0
14	99.2	98.4	96.2	94.6	0.4	1.6
15	87.2	87.2	82.8	86.4	4	4.2
16	60	56.4	45	41.8	31	28
17	73.8	64	63.8	65	1.2	0.6
18	42	69.8	33.4	46.4	44	28.6

VAS scores for each outcome (maximum pain intensity, average pain intensity, and pain relief) were taken at the end of days in which 5 mg of methadone or placebo was self-administered on awaking, and 10 hours later. The table gives the mean of these scores for the five days in which methadone or placebo was taken.

Table 5 Patients diary assessment – Phase 2 (20 mg methadone per day)

Patient no.	Max intensity drug	Max intensity placebo	Average intensity drug	Average intensity placebo	Relief drug	Relief placebo
1	29.8	57.2	31.4	46	62.2	41.2
2	73	69.8	66.8	66.6	0.8	0.4
4	98.6	98.2	97.4	97.6	2.8	2.4
5	58.8	62.4	54	55.2	38.6	37.4
6	60.6	67.2	43	48.4	17.2	13.4
8	57.2	70.6	44.8	58.6	46.8	36.4
11	57.2	67.8	41.8	36.6	49.2	47
13	89.2	95.6	88.4	93.6	4	0
15	97	98.4	93.8	97.4	3.6	0.4
16	49.8	63.2	40.4	53.4	47.6	18.4
18	37	63.6	26.6	47	74.6	52.2

Mean of VAS scores, calculated as described in Table 4, for the five days in which 10 mg bd of methadone or placebo was self-administered.

Table 6 Diary assessments – comparison of methadone versus placebo

	Comparison of methadone versus placebo					
	Phase 1 methadone 10 mg daily (n = 18)			Phase 2 methadone 20 mg daily (n = 11)		
Outcome	M (SD)	95% CI	P	M (SD)	95% CI	P
Maximum intensity	−4.71 (10.1)	−9.74, 0.32	0.065	−9.25 (10.14)	−16.07, −2.43	0.013
Average intensity	−3.20 (8.23)	−7.29, 0.89	0.117	−6.56 (7.86)	−11.85, −1.28	0.020
Relief	5.07 (10.83)	−0.32, 10.46	0.064	9.07 (10.28)	2.16, 15.98	0.015
	Comparison of rest day after methadone v rest day after placebo					
Maximum intensity	−1.67 (6.15)	−4.83, 0.32	0.279	−7.03 (7.42)	−12.02, −2.04	0.010
Average intensity	−2.66 (8.80)	−7.18, 0.89	0.231	−5.65 (7.16)	−10.46, −0.84	0.026
Relief	0.93 (10.71)	−4.58, 6.43	0.725	6.10 (7.67)	0.94, 11.25	0.025

The table shows the mean differences (M) and standard deviations (SD) between the mean VAS scores following methadone or placebo treatment in Phase 1 (data given in Table 4) and Phase 2 (Table 5). Also shown are: diary assessments – comparison of results on rest days after taking methadone versus results on rest days after taking placebo. The mean differences between the mean VAS scores on the rest days following methadone or placebo treatment are presented. The mean VAS scores (data not presented) were calculated similarly for mean VAS scores on the days of dosing (Tables 4 and 5).

Table 7 Diary assessments: effect of methadone as a % of mean placebo scores

Outcome	Phase 1 (n = 18)		Phase 2 (n = 11)	
	Mean VAS placebo	Mean as % of mean placebo	Mean VAS placebo	Mean as % of mean placebo
Maximum pain intensity	73.3	6.4	74.7	12.4
Average pain intensity	65.6	4.9	67.3	9.7
Pain relief	15.0	33.8	18.9	48.0

taking placebo was 18.9, and this was increased by 48% after taking methadone (P = 0.015).

Analgesic effects of methadone were pronounced in six of the 11 patients who completed Phase 2 of the trial. Statistically significant improvements in all three outcomes were seen in patient 8 (suffering from postherpetic neuralgia); the mean differences as compared with placebo in VAS scores for maximum pain intensity was −18.4 (P = 0.02), for average pain intensity −15.4 (P = 0.05) and for pain relief +22.2 (P = 0.01). Patient 18 (central poststroke pain) had significant reductions in the VAS scores for maximum pain intensity and average pain intensity and a significant increase in the VAS scores for pain relief. Patients 2 (central poststroke pain) and 16 (intercostal neuralgia) had significant improvements in pain relief. Patient 11 (diabetic polyneuropathy) had a significant reduction in maximum pain intensity. Patient 15 (complex regional pain syndrome type II) had a significant reduction in average pain intensity.

Adverse effects

The total incidence of adverse effects, during Phases 1 and 2 of the trial, on the days and following rest days in which methadone was taken, and on the days and following rest days in which placebo was taken, are given in Table 8.

During Phase 1, one patient (patient 9) withdrew from the trial, because of severe nausea, dizziness and sweating on the first occasion he took methadone. Of the six patients who withdrew during Phase 2 of the trial, three (patients 10, 11 and 17) withdrew on days when they were taking methadone, and three (patients 7, 15 and 19) on days when they were taking placebo. The reasons were severe nausea (patients 11, 15 and 17), severe nausea and dizziness (patient 7), severe nausea, vomiting, dizziness and sweating (patient 10) and disorientation with severe headaches (patient 19). Four patients (patients 8, 14, 16 and 18) reported no adverse effects during Phase 1, and four (patients 5, 8, 14 and 16) reported no adverse effects in Phase 2 of the trial. Adverse effects were reported as mild to moderate in other patients who completed the trial.

Discussion

The particular problems of studies in patients with neuropathic pain[16] were largely overcome by our design choice for this trial. An extra complication arose though, because of the very variable biological half-life of methadone, quoted as from 10 to over 75 hours.[17] For this reason we instituted a rest day between dosing of either methadone or placebo. For the same reason, we decided against a comparison of methadone versus morphine, an 'adjuvant' analgesic, e.g., amitriptyline, or an 'active' placebo, e.g., a benzodiazepine. The possibility of such drugs being administered on top of a carryover dose of methadone, even after a rest day, would have further complicated interpretation, and would have introduced the possibility of extra toxicological risks. We are aware, however, that not using an 'active' placebo may have risked an unintentional 'unblinding' due to side effects, affecting patients' retrospective pain assessments.

We stress that the object of our study was to demonstrate whether or not methadone demonstrated an analgesic effect in patients with a variety of neuropathic pain syndromes, previously resistant to treatment. In each phase of the trial, the randomization was such that dosing of the methadone could occur on any of five nonconsecutive days over a 20-day period, conditions that were designed to optimize the analysis of an effect, but which would not of course be applied in clinical practice (i.e. the trial design was experimental rather than pragmatic).

In our study, methadone given orally at a daily divided dose of 20 mg elicited well-defined analgesic effects. As compared with placebo, there were statistically significant (P = 0.013–0.020) improvements in all the three outcomes we chose (maximum intensity of pain, average intensity of pain and the relief of pain) over the days in which 10 mg of methadone was taken on wakening, and a further 10 mg taken 10 hours later. Analgesic effects (observed as lower pain maximum intensity and increased pain relief) were also seen in Phase 1 of the study when the lower total daily dose of 10 mg of methadone was used, but these failed to reach statistical significance (P = 0.064 and 0.065, respectively).

Table 8 Analysis of individual patients reporting adverse effects (specific patients and number of patients reporting adverse effects on methadone day/following rest day, or placebo day/following rest day)

	Phase 1				Phase 2			
Started	19				17			
Completed	18				11			
No of patients without AEs	4				4			
	Methadone day or rest day after methadone		Placebo day or rest day after placebo		Methadone day or rest day after methadone		Placebo day or rest day after placebo	
	No of patients	Patient number	No of patients	Patient number	No of patients	Patient number	No of patients	Patient number
Nausea	7	3, 4, 6, 7, 9, 11, 15	4	3, 6, 7, 15	8	2, 4, 6, 7, 10, 11, 13, 17	4	4, 6, 7, 15
Vomiting	4	7, 9, 11, 15	1	15	1	10	1	6
Somnolence	2	2, 13	2	2, 7	3	2, 13, 18	2	2, 18
Dizziness	6	1, 6, 9, 10, 13, 15	0		3	1, 10, 13	1	7
Constipation	2	6, 7	1	6	3	4, 6, 12	1	4
Pruritis	2	7, 12	0		2	12, 13	1	4
Diarrhoea	2	5, 17	0		2	2, 17	0	
Head ache	5	1, 3, 7, 10, 19	2	10, 19	0		2	2, 19
Loss of energy	0		2	2, 7	1	2	0	
Sweating	2	9, 11	0		3	1, 4, 10	1	4
Disorientation	1	9	0		0		1	19
Blurred vision	1	9	0		0		0	
Dry mouth	0		1	3	0		0	
Insomnia	1	7	0		1	7	2	7,13
Loss of appetite	1	7	1	7	1	7	1	7

Interestingly, the analgesic effect elicited by 20 mg methadone persisted for at least 27 hours. This was evident from analysis of VAS scores on the rest days following 20 mg methadone dosing, when statistically significant ($P = 0.010–0.026$) improvements in all the three outcomes were seen. This carryover effect presumably arises from the long half-life of methadone.

There are six recorded controlled studies on the effect of opioid mu agonists on neuropathic pain. In only one of these was the opioid given orally. Watson and Babul[18] compared the effect of controlled release oxycodone (20–60 mg day over four weeks, mean daily dose 45 mg) versus placebo in 50 patients with postherpetic neuralgia (PHN) in a random order crossover trial. Data analysis was confined to the 38 patients who completed the trial. There was no significant lowering of pain intensity scores during the first week, but a significant lowering of pain intensity by the second week, and lowering of pain intensity, steady pain, brief pain and skin pain during the last week.

Two of the other five controlled studies involved the use of bolus IV injections of the opioid. In Arner and Meyerson's pioneering study of complex randomized, double-blind, placebo-controlled design,[19] 15 mg morphine was given IV on at least four occasions to patients with various neuropathic pains, without eliciting pain-relieving effects. And in a crossover study, Kupers *et al.*[20] examined the effects of IV morphine (0.3 mg/kg) in 14 patients with neuropathic pain of central or peripheral origin; as compared with placebo, pain intensity was unchanged, but affective pain ratings were significantly decreased.

The remaining three studies used IV infusions of the opioids. Rowbotham *et al.*,[21] in a double blind, crossover trial compared the effects of one hour infusions of morphine (average total dose 19.2 mg) in 19 patients with PHN. As compared with a matching saline placebo infusion, the morphine infusion caused a significant reduction in pain intensity ($P = 0.04$) and an increase in pain relief ($P = 0.01$). Wiley *et al.*,[22] in a randomized, double blind study, infused fentanyl over 90 minutes (to a total of 5.4 μg/kg) in patients with PHN. As compared with placebo, pain intensity and allodynia severity were significantly reduced. And finally, Dellemijn and Vanneste,[23] in a crossover, randomized trial, infused IV fentanyl (5 μg/kg/hour), diazepam (0.2 mg/kg/hour) or saline for five hours into 50 patients with different types of neuropathic pain. The fentanyl infusions produced equal relief of pain unpleasantness and intensity, whereas these parameters were unaffected by the diazepam or saline infusions.

In summary, these studies show that analgesic effects were either not observed with morphine or opioid pure mu receptor agonists, or were observed after a time delay, or were observed only after IV infusion of the opioid, with relatively high doses of the opioid. Such responses correspond to current concepts,[24] that opioids (by implication, opioid mu receptor agonists) do have effects on neuropathic pain, but only at doses higher than those effective in nociceptive pain.

Over recent years there has been increasing anecdotal evidence of the value of methadone in the relief of neuropathic pain.[25,26] Interpretation of these anecdotal reports is difficult though, as successful switches from high-dose morphine to opioids lacking methadone's additional nonopioid properties, e.g., hydromorphone and oxycodone, have also been reported.[27] It may be argued that the beneficial effects may arise not only because of intrinsically higher activity of the substituting opioids against neuropathic pain, but also through the relief of dose-limiting side effects associated with the metabolites of morphine (e.g., hallucinations, myoclonus, delirium).

The results of our controlled trial are of interest in that they confirm that methadone does demonstrate an analgesic effect in neuropathic pain, giving some support to our rationale for using methadone as an alternative strong opioid in chronic cancer pain.[28] What this study does not answer is whether, in neuropathic pain, this analgesic effect can be explained solely because of its opioid mu agonist activity, or whether the putative nonopioid properties of methadone offer specific advantages. In our trial with methadone, our patients took relatively small doses of methadone on wakening (5 or 10 mg), and a further oral dose approximately 10 hours later (i.e., 10 or 20 mg of methadone was taken during the course of the day), pain indices were measured three hours later, significant reductions in pain intensity and average pain intensity, and increases in pain relief were then observed against a wide range of neuropathic pains. Thus, analgesic effects are observed within a few hours of oral administration, using doses of methadone that are considered low even in the treatment of nociceptive pain.

An extra dimension possessed by methadone in contrast to opioids used in previous trials is that it combines mu opioid receptor agonist activity with NMDA receptor antagonist activity, and an ability to inhibit the reuptake of biogenic amines. It seems very unlikely, however, that these nonopioid activities can solely account for methadone's activity in our trial. Substances possessing NMDA receptor antagonist properties may be antinociceptive in animal models of neuropathic pain,[4] but McQuay *et al.*[29] found that dextromethorphan, with an affinity for the NMDA receptor very similar to that of methadone, failed to elicit any analgesic effects in patients with neuropathic pains and under trial conditions very similar to those pertaining in our study. A main distinction between the two drugs is that methadone is a powerful opioid mu receptor agonist, whereas dextromethorphan has only very weak opioid mu agonist activity. One explanation

for the analgesic effect observed in our study is the combination of methadone's opioid mu agonist and one or other, or both, of its nonopioid activities on the receptor population concerned in the expression of neuropathic pain. Indeed, in the caudate-putamen nucleus, mu opioid and NMDA-type glutamate receptors are colocalized in spiny neurones,[30] anatomy that is favourable for synergistic interactions of ligands binding at the two receptor sites. Support for this view is forthcoming from work in laboratory animals, and from clinical work. In animal models of neuropathic pains (referred to in the Introduction), NMDA receptor antagonists strongly potentate the antinociception elicited by the opioids. And in a multicentre, randomized trial, Harati *et al.*[31] found that tramadol, a weak opioid mu agonist but with NMDA and amine reuptake activities, reduced the pain intensity associated with diabetic neuropathy at least as effectively as pure, powerful opioid mu agonists.

The analgesic effect observed in our study, on the days that methadone was taken and on subsequent rest days, should encourage larger pragmatic clinical trials comparing methadone with other mu opioid agonists lacking additional nonopioid properties. Although 33 patients were invited to participate in our trial, it is significant that a number declined because of an association of methadone with chemical dependency; and of the 19 patients who did take part, seven (37%) withdrew from the study because of adverse effects. An exploration is, therefore, warranted of the usefulness of other opioids, which possess a combination of opioid and nonopioid activities, which might prove equally effective with a reduced incidence of side effects, while lacking the negative associations of methadone. We are particularly interested in the potential of d1-morphine,[2] and we have initiated pharmacological and toxicity studies as a prelude to clinical investigations.

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