



Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial

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Abstract

A double-blind, randomised, placebo-controlled 8-week study was conducted to evaluate the efficacy and safety of gabapentin in the treatment of neuropathic pain, using doses up to 2400 mg/day. The study used a novel design that was symptom- rather than syndrome-based; an approach that aimed to reflect the realities of clinical practice. Participants had a wide range of neuropathic pain syndromes, with at least two of the following symptoms: allodynia, burning pain, shooting pain, or hyperalgesia. Patients were randomised to gabapentin ($n = 153$) or placebo ($n = 152$). Gabapentin was given in three divided doses, initially titrated to 900 mg/day over 3 days, followed by two further increases, to a maximum of 2400 mg/day if required by the end of week 5. The primary outcome measure was change in average daily pain diary score (baseline versus final week). Over the 8 week study, this score decreased (i.e. improved) by 1.5 (21%) in gabapentin treated patients and by 1.0 (14%) in placebo treated patients ($P = 0.048$, rank-based analysis of covariance). Significant differences were shown in favour of gabapentin ($P < 0.05$) for the Clinician and Patient Global Impression of Change, and some domains of the Short Form-McGill Pain Questionnaire. Improvements were also shown in patient-reported outcomes in quality of life, as seen by significant differences in favour of gabapentin in several domains of the Short-Form-36 Health Survey. Gabapentin was well tolerated and the majority of patients completed the study (79 versus 73% for placebo). The most common adverse events were mild to moderate dizziness and somnolence, most of which were transient and occurred during the titration phase. This study shows that gabapentin reduces pain and improves some quality-of-life measures in patients with a wide range of neuropathic pain syndromes. © 2002 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

Neuropathic pain affects approximately 1% of the population of the UK, and is one of the most difficult types of pain to treat (Karlsten and Gordh, 1997). It can arise from a wide variety of causes, such as trauma, disease, infection, or it may be idiopathic in origin. Common examples of neuropathic pain include diabetic neuropathy, postherpetic neuralgia (PHN), nerve root pain due to degenerative spine disease, phantom limb pain following amputation, and neuropathic pain subsequent to severe trauma or surgery. Neuropathic pain is typically severe, slow to resolve, and extremely distressing. Like other forms of chronic pain, it can have a devastating impact on patients' psychological

health, social functioning, and other aspects of health-related quality of life (Guerje et al., 1998).

Neuropathic pain usually responds poorly to the standard treatments described in the World Health Organization's analgesics ladder, such as non-steroidal antiinflammatory drugs (NSAIDs) and opioids (Karlsten and Gordh, 1997). Antidepressants have been shown to be of benefit in diabetic neuropathy, with the best effects achieved with tricyclic antidepressants (TCAs) (McQuay and Moore, 1998). However, the adverse events of TCAs are frequently severe enough to lead to drug withdrawal (Karlsten and Gordh, 1997), and no antidepressant is currently licensed for the treatment of neuropathic pain in the UK.

Antiepileptics have also demonstrated efficacy in some types of neuropathic pain. Systematic reviews have reported carbamazepine to be of significant benefit in trigeminal neuralgia, diabetic neuropathy, and central neuropathic pain (McQuay et al., 1995; Sindrup and Jensen, 1999). In March 2000, the antiepileptic gabapentin became the first

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agent to be licensed in the UK for the treatment of all neuropathic pain conditions, based on evidence from large randomised trials in two types of neuropathic pain: diabetic neuropathy (Backonja et al., 1998) and PHN (Rowbotham et al., 1998; Rice and Maton, 2001).

Case reports, pilot studies, and retrospective reviews also suggest efficacy for gabapentin in a variety of neuropathic pain syndromes (Wetzel and Connelly, 1997), including trigeminal neuralgia (Sist et al., 1997; Carrazana and Schachter, 1998; Valzania et al., 1998), complex regional pain syndromes (CRPS, Mellick et al., 1995; Mellick and Mellick, 1997), neuropathic pain associated with multiple sclerosis (Houtchens et al., 1997; Samkoff et al., 1997; Khan, 1998), neuropathic cancer pain (Caraceni et al., 1999), and other types of neuropathic pain (Rosenberg et al., 1997).

We conducted a randomised, double-blind, placebo-controlled study to examine the safety and efficacy of gabapentin at doses of up to 2400 mg/day in a wide range of neuropathic pain syndromes. This study used a novel approach in which the inclusion criteria were based on the presence of specific symptoms, allowing patients with diverse neuropathic pains to participate in the study. This approach reflects not only the realities of clinical practice, but also the recent trend towards defining neuropathic pain in terms of common symptoms and mechanisms rather than as a group of disparate syndromes (Woolf and Mannion, 1999).

2. Methods

2.1. Subjects

This randomised, double-blind, placebo-controlled, parallel group, multicentre study in 35 hospital outpatient pain clinics in the UK and Republic of Ireland was conducted between June 1999 and February 2000.

The aim of patient recruitment was to reflect common clinical conditions and practice in many chronic pain clinics. Patients were male or female, aged at least 18 years, and of any race. All were required to have a definite diagnosis of neuropathic pain, made and confirmed by an experienced, practicing chronic pain specialist and based on clinical grounds of history, examination, and appropriate investigation of symptoms and signs expressed by the patient. All investigators utilised the definitions of diagnostic criteria documented in the International Association for the Study of Pain (IASP) Classification of Chronic Pain to support their clinical judgement (Merskey and Bogduk, 1994). In addition to a definite diagnosis of neuropathic pain, all subjects were required to have at least two of the following non-specific symptoms, which are frequently seen but are not diagnostic of different underlying mechanisms of neuropathic pain: allodynia (pain from a non-noxious stimulus, e.g. touch), burning pain, shooting pain, or hyperalgesia

(increased sensitivity to a noxious stimulus). These symptoms could be associated with any neuropathic pain syndrome, and were selected because two common signs of nerve dysfunction are allodynia and hyperalgesia (Bourreau et al., 1990; Galer and Jensen, 1997; Bennett, 2001; Serra, 1999) and because patients commonly use 'burning' or 'shooting', or similar words, to describe their pain. Allodynia and hyperalgesia were demonstrated and explained to the patient by physical examination and reinforced by a written definition.

Patients had to complete at least 4 daily pain diaries during the 7 days prior to randomisation, yielding an average score ≥ 4 out of 11 over this period. Women were required to be non-pregnant (using barrier or hormonal contraception where appropriate), non-lactating, postmenopausal, or surgically sterilised.

Exclusion criteria included: failure to respond to previous treatment with gabapentin at ≥ 900 mg/day or failure to respond to gabapentin at any dose level due to side effects; known creatinine clearance ≤ 60 ml/min or known renal impairment; clinically significant hepatic, respiratory, haematological illnesses or unstable cardiovascular disease; significant neurological or psychiatric disorders unrelated to causes of neuropathic pain, which, in the opinion of the investigator, might impair the assessment of pain; other severe pain that might impair the assessment of neuropathic pain; any other serious or unstable conditions that might compromise participation in the study; illicit drug or alcohol abuse within the past year.

2.2. Study design

Using a centrally held, computer generated randomisation list, patients were randomised sequentially to gabapentin or placebo in a 1:1 ratio, in block sizes of four. Gabapentin and placebo were provided in the form of identical capsules.

The study included a 1-week baseline period, after which patients randomised to gabapentin entered a 5-week titration period, in which the initial dose for all patients was 900 mg/day (titrated up over 3 days). Patients who did not show at least 50% reduction in overall pain were increased to 1800 mg/day, and again, where necessary, to 2400 mg/day (dose level changes were made at two weekly intervals). Patients received therapy for a total of 8 weeks (Fig. 1).

Various specified drugs, physical therapies, and complementary remedies for the relief of neuropathic pain were prohibited prior to and during the study. Guanethidine or sympathetic blocks could not be used for the 3 months preceding the study or during the study; strong opioids, acupuncture, and homoeopathic remedies could not be used for 30 days prior to the study; a washout period of 14 days prior to screening was required for benzodiazepines, skeletal muscle relaxants, steroids, capsaicin, mexiletine, dextromethorphan, NSAIDs (used for the treatment of neuropathic pain), and antiepileptics; and the use of trans-

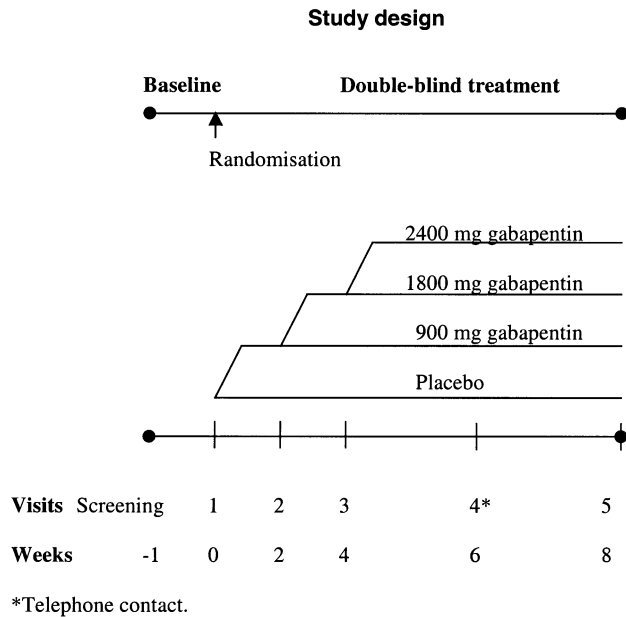


Fig. 1. Study design.

cutaneous electrical nerve stimulation (TENS) machines was prohibited throughout the study.

Patients were, however, allowed to continue on antidepressants (TCAs or selective serotonin reuptake inhibitors) if stable on treatment for 30 days preceding the study, but antidepressant treatment could not be started during the study. Existing treatment with aspirin (up to 300 mg/day) for cardiovascular prophylaxis and with NSAIDs for the treatment of conditions other than neuropathic pain was permitted, as were mild opioids (e.g. codeine phosphate, co-dydramol). Patients were permitted to take paracetamol (up to eight 500-mg tablets per day) or codeine/paracetamol (30 mg/500 mg) up to eight tablets per day as rescue medication.

2.3. Efficacy outcomes

The primary efficacy parameter was the change in mean weekly pain diary score from baseline to the final study week. On waking each morning, patients assessed the pain of the previous 24 h, using an 11-point Likert scale with 0 as 'no pain' and 10 as 'worst possible pain.' Baseline score was the mean of the last 4–7 pain diary entries preceding visit 1. The final weekly mean pain score (end point) was the mean pain score from the last 7 days preceding visit 5, or the final 7 days on study medication for patients who did not complete the study.

Secondary efficacy parameters were the diary assessment of individual pain symptoms (allodynia, burning pain, shooting pain, and hyperalgesia), the Short Form-McGill Pain Questionnaire (SF-MPQ); the Clinician Global Impression of Change (CGIC); and Patient Global Impression of Change (PGIC). Quality of life was assessed using the Short Form-36 (SF-36) Health Survey (Ware, 1993).

Allodynia and hyperalgesia were measured by asking the patient to self-evaluate according to the definition (written and explained to all patients) and then respond by visual analogue scale (VAS) of 0–10.

Patients were assessed every 2 weeks at scheduled visits or by telephone (Fig. 1) for reports of pain and adverse events (elicited by non-specific questioning). Data for the SF-MPQ, SF-36, CGIC, and PGIC were collected at week 7. The protocol was approved by the South and West Multi-centre Research Ethics Committee; each centre's Local Research Ethics Committee and patients provided written informed consent.

2.4. Data analysis

Patients were regarded as evaluable in the statistical analysis if, once randomised, they took at least one dose of study medication, and had both baseline and post-randomisation data available. Additionally, patients with baseline diary scores of <2 for any symptom were excluded from analysis of that symptom. All statistical tests were two-sided and performed at a 5% significance level.

The analysis of pain diary data, the primary efficacy variable, used analysis of covariance (ANCOVA), fitting treatment, geographic cluster (centre), and mean score from the final seven pre-treatment measurements as covariates. The primary analysis was based on a rank-based ANCOVA (Conover and Iman, 1982), since the planned analysis using raw data did not satisfy the required statistical assumptions and this situation could not be resolved by transformation.

Secondary analyses were of change in mean pain scores from each week of treatment, weekly and final diary scores for the four individual symptoms, each analysed using the same model as in the primary analysis. The CGIC and PGIC and percentage of patients with a $>50\%$ reduction in mean overall pain scores were analysed using a Mantel-Haenszel Chi-square test (an extension of the Chi-squared test for comparing proportions in the presence of confounding factors), adjusting for centre (Fleiss, 1981). Centres recruiting relatively lower numbers of participants were grouped together for the purposes of the analyses. Changes in each domain score of the SF-MPQ and SF-36 were analysed using ANCOVA.

In addition, an interaction test was performed to establish whether or not treatment effects differed among the various pain syndromes reported by this cohort. This required that data be grouped into five categories: back pain, CRPS, PHN, postsurgical pain, and other pain.

3. Results

3.1. Subjects

Of 351 patients screened, 307 were randomised. Twenty-four of the screened patients did not meet the entry criteria,

Profile of patients at each phase of the study

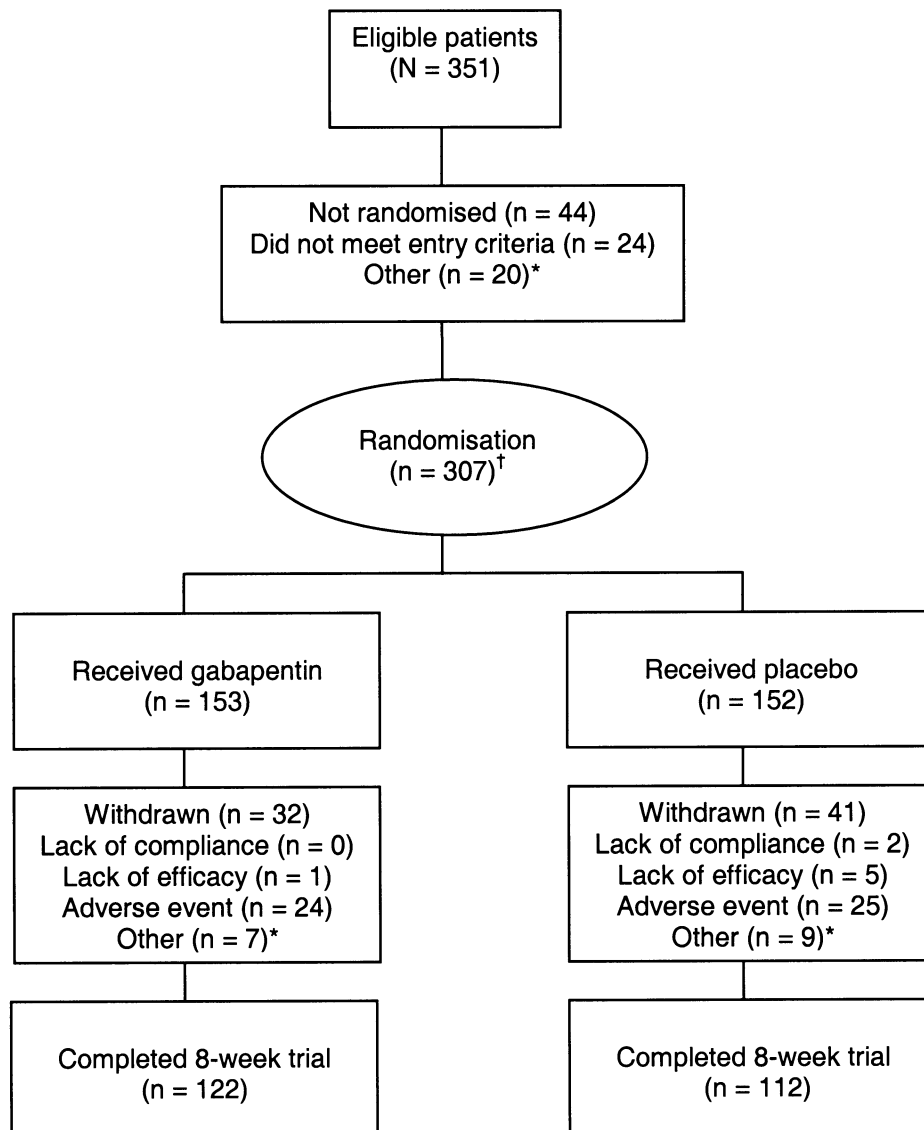


Fig. 2. Profile of patients at each phase of the study. * The majority of withdrawals due to “other” reasons involved withdrawal of consent or failure to return for a visit. † Two patients withdrew after randomisation, but prior to receiving treatment.

and 20 were withdrawn for other reasons. Two randomised patients withdrew before receiving any medication and 305 patients received active treatment (153 with gabapentin and 152 with placebo) (Fig. 2). Patient characteristics at baseline are summarised in Table 1. The treatment groups were well matched at baseline in terms of age, sex, duration of disease, and previous drug treatment (Table 1).

The numbers and percentages of patients suffering from different neuropathic syndromes are shown in Table 2. Of the four main symptoms of neuropathic pain, at baseline 211 (69%) reported allodynia, 245 (80%) burning pain, 262 (86%) shooting pain, and 217 (71%) hyperalgesia. The four main symptoms were reported by 111 (36%) patients; 103 (34%) and 91 (30%) reported three and two symptoms, respectively.

At week 5 (the end of the titration period), 101 patients were prescribed gabapentin 2400 mg/day; 19 were prescribed 1800 mg/day; and 27 were prescribed 900 mg/day (28 had been withdrawn by this point). In four gabapentin-treated patients the dosage was reduced during the study due to adverse events, and in one it was reduced due to adequate efficacy. The median duration of treatment was 57 days for both treatments (range 3–70 days for gabapentin and 5–71 days for placebo).

The most commonly reported concomitant medications during the study were paracetamol, 85 patients (28%); amitriptyline, 68 (22%); co-proxamol, 58 (19%); co-codamol, 51 (17%); co-dydramol, 30 (10%); dihydrocodeine, 20 (7%); and paracetamol plus codeine, 20 (7%). Forty-five

Table 1
Patient characteristics at baseline

	Placebo (<i>n</i> = 152)	Gabapentin (<i>n</i> = 153)
Men, <i>n</i> (%)	78 (51.3)	63 (41.2)
Women, <i>n</i> (%)	74 (48.7)	90 (58.8)
Median age, years (range)	56.1 (20.3, 86.2)	57.7 (25.9, 88.4)
Median duration of disease, years (range)	4.4 (0, 27.7)	5.2 (0, 30.8)
Pain <3 months, <i>n</i> (%)	19 (12)	18 (12)
Pain >5 years, <i>n</i> (%)	44 (29)	47 (31)
Previous drugs tried, <i>n</i> (%)		
Not known	3 (2)	1 (1)
0	1 (1)	3 (2)
1	32 (21)	33 (22)
2	59 (39)	43 (28)
3	33 (22)	42 (27)
4	12 (8)	15 (10)
5	4 (3)	9 (6)
6–10	7 (5)	7 (5)
> 10	1 (1)	0 (0)
Drug categories tried, <i>n</i> (%)		
Anticonvulsant	44 (29)	53 (35)
Amitriptyline	95 (65)	101 (66)
Mild analgesics	142 (93)	136 (89)

patients (15%) reported taking no additional medication for neuropathic pain. Six patients were reported as taking prohibited medications (carbamazepine, morphine, and sodium valproate) during the study. In two cases these continued at a steady dose throughout the study, but in four cases, they were started or stopped during the baseline or treatment evaluation periods and may have affected the estimates of efficacy.

Table 2
Patients suffering from different neuropathic syndromes at baseline^a

Syndrome	Number of patients (%)
Complex regional pain syndrome	85 (28)
Postherpetic neuralgia	43 (14)
Radiculopathy	27 (9)
Postlaminectomy	21 (7)
Posttraumatic	10 (3)
Poststroke	9 (3)
Postinguinal hernia repair	8 (3)
Thoracotomy	7 (2)
Phantom limb	7 (2)
Diabetic neuropathy	7 (2)
Postmastectomy	4 (1)
Trigeminal neuralgia	4 (1)
Atypical facial pain	4 (1)
Neuroma of peripheral nerve	3 (1)
Other postsurgical pain	28 (9)
Other neuropathic pain	38 (12)

^a Investigators used definitions of diagnostic criteria for neuropathic pain from the IASP classification of chronic pain (Merskey and Bogduk, 1994) to support their clinical judgement.

3.2. Efficacy outcomes

3.2.1. Pain diary scores

The primary efficacy variable, change in average daily pain score from baseline to the final week, showed significant differences between the gabapentin and placebo groups (Fig. 3). In gabapentin treated patients the mean pain diary score decreased by 1.5 (21%), from 7.1 to 5.6. In placebo-treated patients it decreased by 1.0 (14%), from 7.3 to 6.3. There was a significant difference between the treatments ($P = 0.048$, rank-based ANCOVA).

Analysis of the mean pain scores on a week-by-week basis showed that the difference between the treatment groups was statistically significant at weeks 1, 3, 4, 5, and 6 ($P < 0.05$ for weeks 1, 3, 5 and 6; $P = 0.01$ for week 4). At weeks 7 and 8 the gabapentin scores remained constant and there was an improvement in the mean placebo scores, resulting in a non-significant difference.

Tests for interaction of the treatment effect with baseline pain score and cluster were not significant, confirming the generalisability of the results across study centres and the range of baseline pain severity.

3.2.2. Response rate

Response to treatment was defined as a >50% reduction in mean pain score between baseline and the end of treatment. Patients withdrawing from the study due to lack of efficacy were classified as non-responders irrespective of the pain score. In the gabapentin-treated group, 21% of patients were classified as responders, compared with 14% of the placebo group ($P = 0.16$).

3.2.3. Individual pain symptoms

At each weekly assessment, all four symptoms (allodynia, burning pain, shooting pain, and hyperalgesia) improved more in gabapentin-treated patients than in those on placebo (Fig. 4). There were significant differences in burning pain (weeks 1 and 3) and hyperalgesia (weeks 3, 4, 5, and 6). However, there was no significant difference in the last-observation-carried-forward (LOCF) analysis. There were

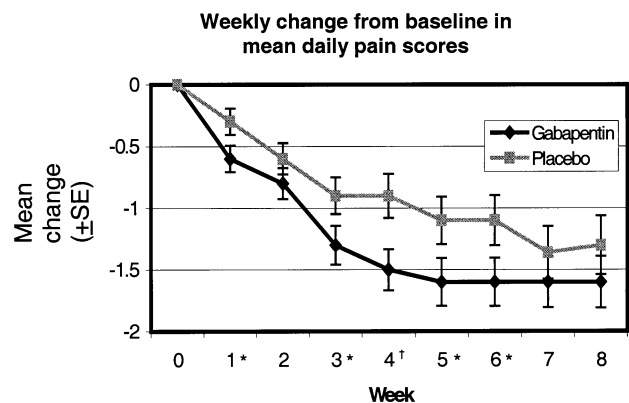


Fig. 3. Weekly change from baseline in mean daily pain scores. * $P \leq 0.05$ versus placebo, † $P \leq 0.01$ versus placebo Crank based ANCOVA.

no interactions of treatment with baseline or centre. Response rates for individual symptoms were consistently higher in the gabapentin group than in the placebo group: 23 versus 15% for allodynia; 32 versus 24% for shooting pain; 23 versus 15% for burning pain; 26 versus 17% for hyperalgesia.

3.2.4. Short Form-McGill Pain Questionnaire

All parameters of the SF-MPQ improved during treatment. Greater improvement was seen in gabapentin-treated patients. The difference between gabapentin and placebo was statistically significant ($P < 0.05$, ANCOVA) for the sensory score and total score.

3.2.5. Patient and CGIC

At the end of treatment, 34% (48/141) of gabapentin-treated patients categorised their pain as very much or much improved, compared with 16% (22/138) of placebo-treated patients ($P = 0.03$, Mantel-Haenszel). In the CGIC, investigators categorised 38% (53/142) of gabapentin-treated patients as very much or much improved, compared with 18% (25/142) of placebo-treated patients ($P = 0.01$, Mantel-Haenszel).

3.2.6. Health-related quality of life questionnaire (SF-36)

Two hundred ninety-seven patients completed the SF-36 questionnaire at baseline, and 270 had evaluable SF-36 results from the treatment period. Patients receiving gabapentin scored significantly higher for the bodily pain, social functioning, and role-emotional domains ($P < 0.05$, ANCOVA) than those receiving placebo (Fig. 5).

3.2.7. Interaction test

Data were grouped according to five major pain categories to allow an interaction test for assessment of differences in treatment effect according to type of pain. This test found no significant difference ($P = 0.29$) in treatment effect among the various pain syndromes analysed in this cohort.

3.3. Safety

The most commonly reported adverse events (reported by $>5\%$ of gabapentin-treated patients), are shown in Table 3. All reported occurrences of dizziness started during titration; 86% of occurrences were mild or moderate in intensity and 46% resolved prior to withdrawal. Ninety-one percent of cases of somnolence occurred during titration; 82% of reports were mild or moderate in intensity and 36% resolved prior to withdrawal.

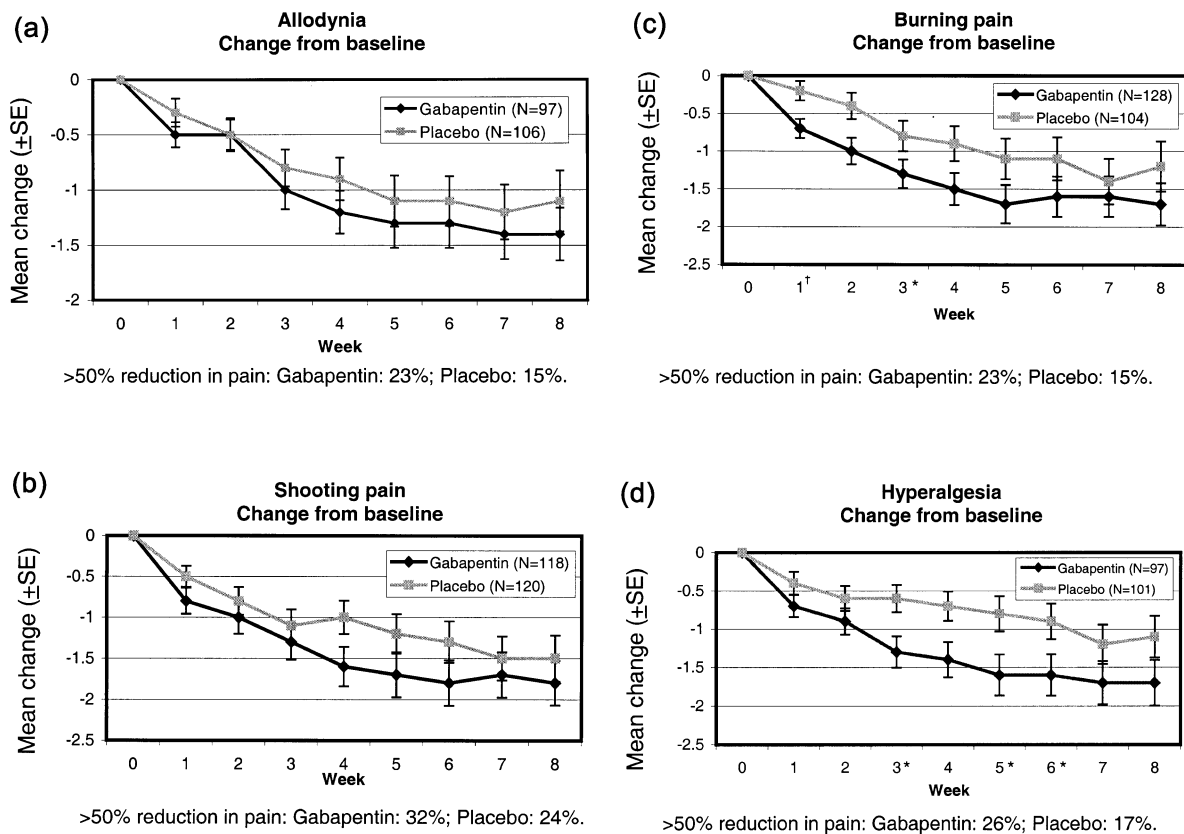
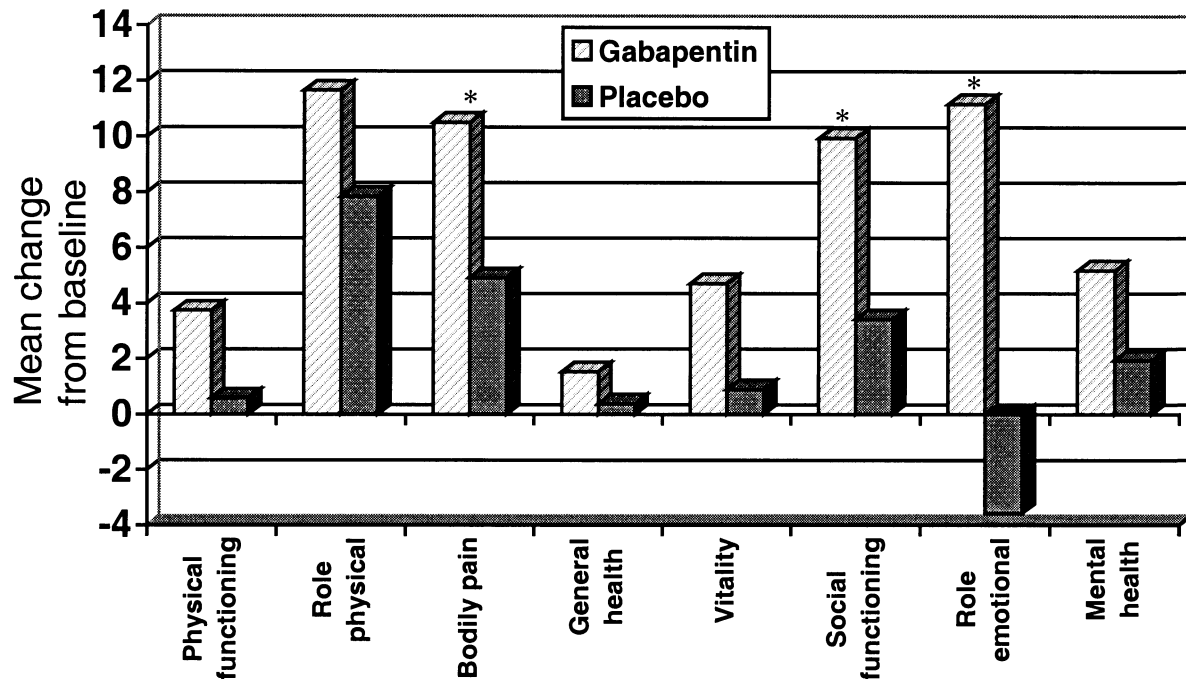


Fig. 4. (a) Allodynia: change from baseline. (b) Shooting pain: change from baseline. (c) Burning pain: change from baseline. * $P < 0.05$; † $P < 0.01$ (ANCOVA). (d) Hyperalgesia: change from baseline. * $P < 0.05$. † $P < 0.01$ (ANCOVA).

Summary of changes in domains of the Short Form-36 Health Survey



* $P < 0.05$ (ANCOVA).

Fig. 5. Summary of changes in domains of the Short Form-36 Health Survey. Scores represent mean change (SE) from baseline to final calculable score adjusted for specified covariates (baseline score and cluster/study centre). A positive change indicates improvement. * $P < 0.05$ versus placebo (Mantel-Haenszel).

Table 3
Summary of adverse events

Adverse events	Placebo ($n = 152$)	Gabapentin ($n = 153$)
All adverse events, n (%)	103 (67.8)	117 (76.5)
Possibly/probably treatment related, n (%)	56 (36.8)	88 (57.5)
Deaths, n (%)	2 (1.3) ^a	0 (0)
Serious, non-fatal adverse events, n (%)	2 (1.3)	4 (2.6)
Withdrawals		
Total due to adverse events, n (%)	25 (16.4)	24 (15.7)
Possibly/probably treatment related, n (%)	17 (11.2)	20 (13.1)
Adverse events occurring in >5% patients		
Dizziness, n (%)	12 (7.9)	37 (24.2)
Somnolence, n (%)	8 (5.3)	22 (14.4)
Infection, n (%)	19 (12.5)	14 (9.2)
Headache, n (%)	21 (13.8)	14 (9.2)
Nausea, n (%)	14 (9.2)	14 (9.2)
Flu syndrome, n (%)	7 (4.6)	11 (7.2)
Abdominal pain, n (%)	6 (3.9)	10 (6.5)
Accidental injury, n (%)	8 (5.3)	9 (5.9)
Diarrhoea, n (%)	6 (3.9)	8 (5.2)

^a Within 1 month after stopping study medication.

None of the serious, non-fatal adverse events that occurred were considered to be related to the study drug, except for one gabapentin-treated patient. This patient experienced a fainting episode, which resulted in a fractured wrist that was thought to be related to study medication.

Overall, the percentage of withdrawals due to adverse events was similar (at 16%) in the two treatment groups (Table 3). Seven patients withdrew from gabapentin treatment because of dizziness, compared with five from placebo. Four patients withdrew from gabapentin and two from placebo because of somnolence. Two additional patients withdrew from gabapentin, reporting both dizziness and somnolence.

4. Discussion

This double-blind, randomised, placebo-controlled, multicentre study indicates that gabapentin at doses up to 2400 mg/day reduces pain in patients with a wide range of neuropathic pain syndromes, selected on the basis of specific symptoms. There was no evidence that treatment effect differed according to pain syndrome. The primary outcome variable, mean pain diary score for the last 7 days of the

study, decreased by 1.5 (21%) in gabapentin-treated patients, compared with 1.0 (14%) in placebo-treated patients ($P = 0.048$, rank-based ANCOVA). There were also significant differences in the PGIC and CGIC, and in some domains of the SF-MPQ and SF-36.

This demonstration of the beneficial effect of gabapentin in a population selected on the basis of symptoms, rather than syndromes, comes in the wake of three recent, large, placebo-controlled studies in specific neuropathic pain syndromes: PHN and painful diabetic neuropathy (Backonja et al., 1998; Rowbotham et al., 1998; Rice and Maton, 2001). The first randomised, double-blind, placebo-controlled clinical trial in 165 patients in USA showed that gabapentin (up to 3600 mg/day) significantly reduced pain caused by diabetic neuropathy, as measured by daily pain diaries and a variety of other outcome measures (Backonja et al., 1998). Another double-blind, placebo-controlled trial in 229 patients also found that gabapentin (up to 3600 mg/day) significantly reduced pain caused by PHN (Rowbotham et al., 1998). Most recently, a double-blind, placebo-controlled study in 334 patients in the UK and the Republic of Ireland has demonstrated the efficacy and safety of gabapentin in PHN at doses of 1800 and 2400 mg/day (Rice and Maton, 2001).

To our knowledge, ours is the first large randomised, placebo-controlled trial in which the inclusion criteria were symptom-based. As a result, it included patients with a wide variety of neuropathic pain syndromes, representing the typical range of neuropathic pain disorders encountered in pain clinics. We also found, by interaction test analysis, that there were no differences in treatment effect among the various pain syndromes studied, with all types of pain showing responsiveness to gabapentin. Our study was also unusual in that it examined overall pain scores and scores for individual pain symptoms; a symptom-based analysis of neuropathic pain is increasingly regarded as important in the assessment of disease progression and treatment outcome (Woolf and Mannion, 1999). It has been demonstrated in humans that even a single disease entity such as PHN can produce at least two separate subsets of patients based on different symptoms and signs (Rowbotham and Fields, 1996). These symptoms and signs are presumably due to different neural abnormalities and hence will respond to different mechanistic approaches (Serra, 1999).

For ethical reasons, the study excluded patients who had previously failed to respond to gabapentin at ≥ 900 mg/day or to gabapentin at any dose due to side effects. Although no data are available for the number of gabapentin non-responders, it could not have been very large (only 24 of 351 patients screened did not meet the entry criteria), suggesting this was unlikely to affect the overall evaluation of the efficacy of gabapentin. In addition, excluding patients already known to be non-responders to a proposed treatment regimen reflects the reality of clinical practice.

All four symptoms (allodynia, burning pain, shooting pain, and hyperalgesia) showed a consistently greater

improvement in gabapentin-treated patients than in those on placebo (Fig. 4), although the difference was only statistically significant for burning pain (visits 1, 3, and 4) and hyperalgesia (visits 3, 4, 5, and 6). While, for each pain symptom, the percentage of responders was higher in the gabapentin group than in the placebo group, there is no evidence from this study to indicate that gabapentin is more beneficial in one pain symptom than another.

In an open-labelled series of 18 patients with mixed neuropathic pain, gabapentin demonstrated significantly better improvement in paroxysmal pain versus ongoing pain and in certain signs such as dynamic versus static mechanical allodynia (Attal et al., 1998). Thus, evidence that specific symptoms and signs should be evaluated is beginning to emerge, as these symptoms and signs may respond differently to treatment.

Due to the design of the study, it is not possible to draw any conclusions regarding a dose–response effect of gabapentin. In practice, the majority of patients (101 of 126) were titrated up to the maximum dose of 2400 mg/day after 4 weeks. Most patients tolerated gabapentin well enough to allow titration up to 2400 mg; only four gabapentin-treated patients required dose reduction during the study due to adverse events.

However, it is important to note that the clinical benefits of gabapentin were apparent early in treatment, before the dose had been titrated up to the maximal level. The effect on overall pain was significant during the first week, while all patients in the gabapentin-treatment group received only 900 mg/day. There was also a statistically significant effect on overall pain at weeks 3 and 4, before any of the patients had been titrated up to 2400 mg/day. This confirms the efficacy of gabapentin within the licensed dose range (up to 1800 mg/day in the UK). One reason pain scores did not further improve after week 6 may be that patients might have become more active toward the end of the study. This is supported by the improvements in SF-36 scores in the areas of social functioning and emotions, both at home and at work.

Although the reduction in mean pain scores and the response rates obtained with gabapentin in this study were modest, the refractory nature of the pain and its duration should be borne in mind. Previously, 66% of patients had tried amitriptyline and 32% had tried antiepileptics. A mean baseline pain score of 7.2 (indicating severe pain) suggests that these standard treatments for neuropathic pain were not particularly successful in this population. In addition, 22% of patients continued to take a stable dose of amitriptyline throughout the study. A recent editorial highlights the fact that some patients can rate the global impression of change in pain as ‘much improved’ with changes in pain VAS of as little as 0.5 because improvement is measured in other domains, e.g. sleep and function (Rowbotham, 2001).

The efficacy of treatments for neuropathic pain can be measured not only in terms of the amount of pain the patient experiences, but also in terms of their overall physical and

emotional well-being (quality of life). Neuropathic pain is known to reduce quality of life, including mood and physical and social functioning (Haythornthwaite and Benrud-Larson, 2000). This study used a validated instrument, the SF-36 Health Survey, to measure quality of life. Gabapentin-treated patients scored significantly better than placebo-treated patients for all eight domains. For three of the domains (bodily pain, social functioning, and role emotional), the difference was statistically significant. The beneficial effect of gabapentin on the social functioning and role emotional subscores is of particular interest, as the questions included in these domains focus on patients' ability to take part in everyday activities at work and at home.

Gabapentin was well tolerated in this study. The most common adverse events, which were more frequent in gabapentin-treated patients, were dizziness and somnolence. These events were usually mild to moderate in intensity, occurred early during treatment, and tended to resolve with continued treatment. The titration rate for this study was slower than in other trials, (Backonja et al., 1998; Rowbotham et al., 1998) which may partially explain the low rate of withdrawals due to adverse events. For some patients, gabapentin may offer advantages in terms of tolerability compared with TCAs or antiepileptics.

Gabapentin is currently the only agent licensed specifically for neuropathic pain in the UK, and offers clinicians a new useful option in the management of this group of disorders. This study supports the evidence from studies in PHN and painful diabetic neuropathy (Backonja et al., 1998; Rowbotham et al., 1998), and provides further evidence of the clinical utility of gabapentin, with significant beneficial effects on overall pain scores and quality of life. With slow titration to a dose of 2400 mg/day, the clinical benefits of gabapentin in this study were not compromised by side effects.

Perhaps as important as the efficacy outcome in this study, however, is its innovative design. It aimed to reflect the real-life management of neuropathic pain by including patients with a broad spectrum of both common and uncommon neuropathic pain syndromes, included on the basis of their symptomatology. Traditionally, neuropathic pain is classified on the basis of the aetiology of the insult to the nervous system or the anatomical distribution of the pain. This may be useful for differential diagnosis, epidemiological studies, or for treatment aimed at modifying the progression of the underlying diseases. However, it offers no framework for clinical management of the pain (Woolf and Mannion, 1999). Moreover, not all cases of neuropathic pain fall into precise diagnostic categories.

In the future, it may be possible to identify the mechanisms responsible for pain in a particular individual, and to tailor treatment to match the specific mechanisms. In the meantime, there is a clear clinical requirement for treatments that are effective not only in individual syndromes, but also across the broader range of neuropathic pain syndromes encountered in everyday clinical practice.

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