

Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study

D.K. KOCHAR, N. RAWAT, R.P. AGRAWAL, A. VYAS¹, R. BENIWAL²,
S.K. KOCHAR and P. GARG

From the Departments of Medicine, ¹Neurology, and ²Preventive and Social Medicine, SP Medical College, Bikaner, India

Received 7 April 2003 and in revised form 8 October 2003

Summary

Background: Various drugs are effective in the management of painful diabetic neuropathy, but none is completely satisfactory. We previously found sodium valproate to be effective and safe in a short-term study.

Aim: To test the effectiveness and safety of sodium valproate in the management of painful diabetic neuropathy over 3 months.

Design: Randomized double-blind placebo-controlled study.

Methods: Consecutive attending patients with type 2 diabetes mellitus with painful neuropathy were asked to participate in the trial: 48 agreed. Five were excluded: three with HbA_{1c} > 11, one with too low a pain level and one who withdrew consent. The remaining 43 were given either drug (group A) or placebo (group B). Each patient was assessed clinically. Quantitative assessment of pain was done by McGill Pain Questionnaire,

Visual Analogue Score and Present Pain Intensity, at the beginning of the study, after 1 month and after 3 months. Motor and sensory nerve conduction velocities were measured initially and after 3 months. Liver function tests and other adverse drug-related effects were assessed periodically.

Results: Of the 43 patients, four dropped out: one in group A and three in group B. There was significant improvement in pain score in group A, compared to group B, at 3 months ($p < 0.001$). Changes in electrophysiological data were not significant. The drug was well-tolerated by all patients, except one, who had raised serum AST and ALT levels after 1 month of treatment, and whose treatment was discontinued.

Discussion: Sodium valproate is well-tolerated, and provides significant subjective improvement in painful diabetic neuropathy.

Introduction

Diabetic neuropathy is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in a patient with diabetes, after the exclusion of other causes.¹ In the course of diabetes, some 20%–90% of individuals eventually develop diabetic neuropathy.² The aetiological factors attributed to diabetic neuropathy can be grouped into those having a definite role (e.g. poor glycaemic control,

duration of disease) and those with a probable added influence (e.g. hypertension, age, smoking, hyperinsulinaemia, dyslipidaemia).^{3–7}

Painful diabetic neuropathy requires medical attention because of its adverse effect on quality of life. The important drug interventions in its management include non-steroidal anti-inflammatory drugs (NSAIDs), anti-depressants and anti-epileptic

Address correspondence to Professor D.K. Kochar, C-54, Sadul Ganj, Bikaner (Raj) 334 003, India.
e-mail: drdkkochar@indiatimes.com

QJM vol. 97 no. 1 © Association of Physicians 2004; all rights reserved.

drugs,^{8–10} but there are problems with side-effects and contraindications for all these drugs. Other drugs used for pain relief have include clonazepam, gabapentine, lamotrigine, baclofen, i.v. lidocaine or mexiletine, aldose reductase inhibitors, gamma-linolinic acid, nucleosides, nerve growth factor and capsaicin-containing ointments, but none is entirely satisfactory.

Sodium valproate, which has proved to be effective in trigeminal neuralgia and migraine prophylaxis,¹⁰ has also shown significant role in the subjective improvement of painful diabetic neuropathy, with a unique advantage of low toxicity and favourable side effect profile.¹¹ In an earlier study,¹¹ we observed a significant subjective improvement in painful diabetic neuropathy in patients receiving sodium valproate in comparison to placebo at the end of one month. Because that was a short-term study, we began a fresh one in January 2002 to study the usefulness and safety profile of this drug over a longer period in the management of painful diabetic neuropathy.

Methods

Patient and control selection

A consent form explaining the nature of the study in detail was given to consecutively attending patients of diabetes mellitus with painful neuropathy, and the first 48 patients were included in the trial and asked to attend on a specific date. Five patients were not included in the study: three had $HbA_{1c} > 11$, one had too low a pain score (Visual Analogue Scale < 4), and one patient withdrew consent; thus 43 patients were followed up for 3 months. The medications offered to the patients were given in packets containing sufficient drug to last for 3 months, bearing a distinctive code number. All patients were subjected to thorough interview, clinical examination and relevant laboratory investigations. All were asked to fill in (by themselves or with assistance) a short-form McGill pain questionnaire (SF-MPQ), visual analogue score (VAS) and present pain intensity (PPI), first initially, then after 1 month and then 3 months. Biochemical examinations, which included urinalysis, fasting blood sugar, HbA_{1c} , lipid profile and liver function tests (serum bilirubin, AST, ALT) were done at the beginning of the study. Liver function test and blood sugar were studied on every subsequent visit to check glycaemic control and to rule out any hepatotoxicity of sodium valproate.

Depending on the specific code number, the patients received either 500 mg (one tablet) of

sodium valproate once a day, or similar type of placebo one tablet once a day. At the end of one week, leading questions were asked for sodium valproate toxicity in the form of nausea and vomiting, and the patients were examined for detailed neurological examination, specially nystagmus and ataxia. Serum AST/ALT was done in all the patients, and patients having normal values were subsequently put on one tablet two times a day for remaining three months. Patients who showed signs of intolerance did not continue in the study.

A specific member of research project was responsible for the administration of drug or placebo. Clinical evaluation, nerve conduction study and pain scoring was done by another member of the team, who was completely blinded to the drug status. All the data, along with code numbers, were submitted to the statistician, and after decoding, the patients were divided into group A (receiving drug) and Group B (receiving placebo). All patients were kept euglycemic by diet alone, OHA, OHA + insulin or insulin alone. None of the patients were allowed to take analgesics for control of pain.

Selection criteria

(i) Diabetes for at least 6 months on stable dosage of insulin or oral hypoglycemic agent and having reasonable diabetic control ($HbA_{1c} < 11$). (ii) Daily neuropathic pain of at least moderate severity for > 3 months, which interfered with daily activity or sleep. (iii) Pain intensity of > 4 on a visual analogue pain scale. (iv) Written consent to participate in the study.

Exclusion criteria

Patients suffering from liver disease, pulmonary tuberculosis, thyroid disorders, uraemia, vitamin deficiency, hereditary and paraneoplastic neuropathy, alcoholism, or patients on steroid therapy, were not included after relevant clinical and biochemical examination.

Laboratory studies

Fasting blood sugar estimation was by the glucose oxidase method. Glycated haemoglobin (HbA_{1c}) of each patient was measured by high-performance liquid chromatography. Electrophysiological studies, in the form of motor (MNCV) and sensory (SNCV) nerve conduction studies, were performed at the beginning of the study and after 3 months in patients of both groups. All recording sessions for MNCV and SNCV were in a shielded, partially soundproof chamber. MNCV was done in the

Table 1 Baseline characteristics

	Group A (drug)	Group B (placebo)	<i>p</i>
<i>n</i>	21	18	
Age	54.38 ± 8.77	56.24 ± 8.75	0.496
Sex (M:F)	12:9	9:9	
Duration of type 2 diabetes (years)	8.85 ± 4.18	8.80 ± 3.84	0.969
BMI (kg/m ²)	24.43 ± 3.76	24.30 ± 3.07	0.901
Weight/height ratio	0.93 ± 0.08	0.91 ± 0.08	0.0641
A/B index	0.89 ± 0.10	0.91 ± 0.09	0.590
HbA _{1c} (%)	8.78 ± 1.26	8.58 ± 1.10	0.587
FBS (mg%)	148.19 ± 22.30	151.7 ± 1.10	0.620
Dyslipidaemia	34% (7/21)	50% (9/18)	0.455
Microalbuminuria	28.58% (6/21)	22.22% (4/18)	0.733
Retinopathy	34% (7/21)	27.78% (5/18)	0.754

median, ulnar, peroneal and posterior tibial nerves on both sides. Sensory nerve conduction velocity was done in the median nerve of both sides in upper limbs and in the sural nerve in the lower limb.

Statistical analysis

The demographic characteristics and data of the two groups were comparable (Table 1). All values (e.g. fasting blood glucose, HbA_{1c}, albuminuria) were expressed as means ± SEM. The responses to drugs were compared statistically in relation to painful diabetic neuropathy (0, 1 month, 3 months). Data comparisons between the groups were by ANOVA, and *post hoc* comparisons by Tukey's HSD for unequal *n*.

Results

Clinical data

Figure 1 shows the flow of patients through the study. Changes in pain score from baseline to end of treatment (assessed by SF-MPQ, VAS and PPI) are shown in Table 2. Differences between sodium valproate and placebo group were significant at the endpoint for all three scores, both at the end of one month and after three months.

In group A (the drug group), initial mean SF-MPQ was 19.47 ± 6.79, falling to 9.66 ± 5.96 (*p* < 0.001) after 3 months. Similarly, mean VAS fell from 6 ± 1.95 (baseline) to 3 ± 2.12 (3 months) (*p* < 0.001), and mean PPI from 2.71 ± 1.00 (baseline) to 1.33 ± 0.66 (3 months) (*p* < 0.001). These variables did not change significantly over the same period in the placebo group (Figures 2, 3 and 4, Table 2).

Electrophysiological data are shown in Table 3. There were no statistically significant differences between the groups, either initially or after 3 months, neither group showing any improvement over the study course.

Safety profile

Of the 22 patients who received the drug, two developed nausea, and one developed minor drowsiness, which had disappeared by the next visit. Only one patient showed a major side-effect, in the form of deranged liver function tests (serum bilirubin 3 mg%, AST 120 U/l, ALT 124 U/l) at one month, and was removed from the study. All other patients tolerated the drug well (Table 4). The 21 patients receiving placebo had no side-effects.

Discussion

Painful diabetic neuropathy significantly affects the quality of life, so far no ideal drug has been available for its management. In the absence of curative therapy, the main aim of management is to provide symptomatic pain control using pharmacological and non-pharmacological agents, and to preserve good glycaemic control. Pharmacological therapy includes tricyclic antidepressant, narcotic analgesics, anticonvulsants and anti-arrhythmic drugs, but adverse effects have limited the effectiveness of these agents.⁹

Double-blind trials of the tricyclic antidepressant amitriptyline have demonstrated significant benefits in reducing burning, aching, sharp, throbbing, and stinging pain.⁹ This dose-dependent effect is independent of mood elevation.¹⁰ However, the use of amitriptyline in patients with heart block, urinary tract obstruction, orthostatic hypotension, or

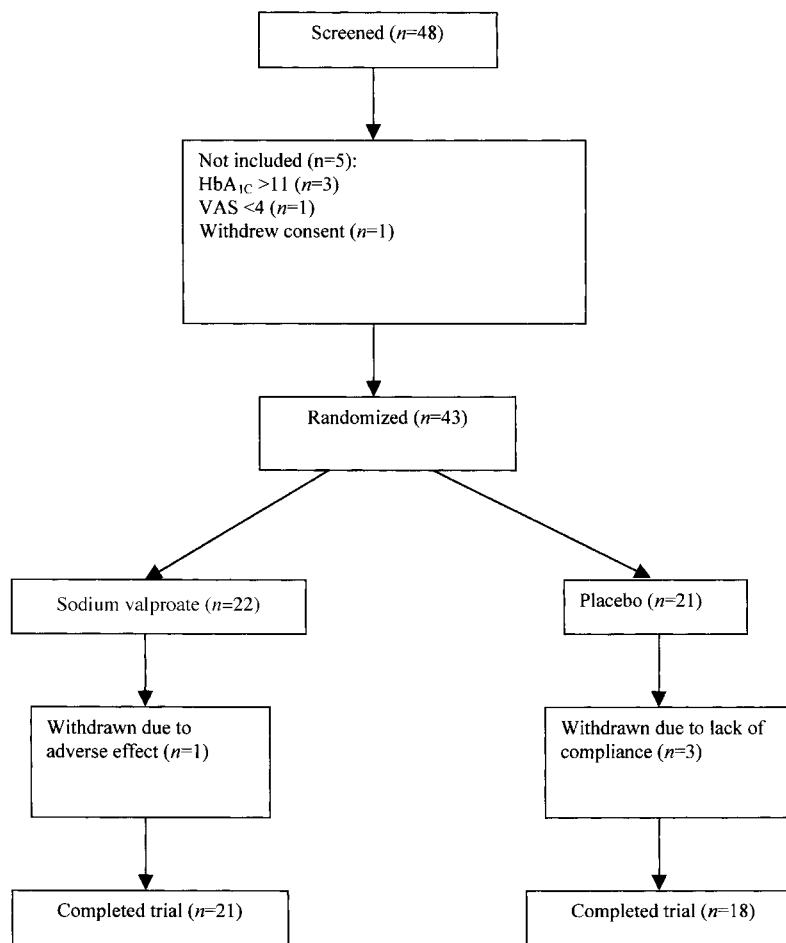


Figure 1. Flow chart: study completion status.

Table 2 Changes in pain scores

Parameter	Sodium valproate (n= 21)			Placebo (n= 18)			Drug vs. placebo	
	Baseline	1 month	3 months	Baseline	1 month	3 months	Difference at 3 months	p
SF-MPQ	19.47 ± 6.79	12.95 ± 5.41	9.66 ± 5.96	17.76 ± 5.23	18.86 ± 5.47	17.88 ± 5.42	-8.10	<0.001
VAS	6 ± 1.95	3.95 ± 1.74	3 ± 2.12	5.71 ± 1.70	6 ± 1.84	6 ± 1.84	-3.0	<0.001
PPI	2.71 ± 1.00	1.71 ± 0.84	1.33 ± 0.66	2.57 ± 0.92	2.67 ± 0.92	2.61 ± 0.92	-1.28	<0.001

Data are means ± SEM.

narrow-angle glaucoma, is contraindicated. Diphenyl hydantoin which is commonly used in the management of painful neuropathy,¹² was found to be of no significant value in a double-blind cross-over study.¹³ In three controlled, double blind studies, carbamazepine was shown to be of value in painful diabetic neuropathy, but because its potential toxicity, its use is limited.¹⁴⁻¹⁶ Other drugs in use for pain relief are clonazepam, baclofen, i.v. lidocaine or mexiletine, aldose reductase inhibitors, gamma linolenic acid,

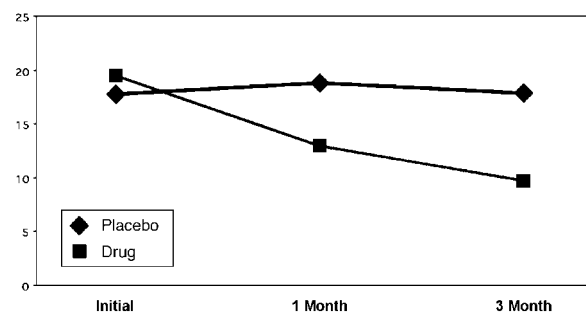


Figure 2. Changes in McGill pain questionnaire score.

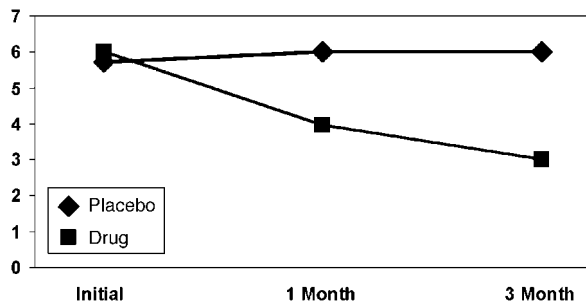


Figure 3. Changes in visual analogue score.

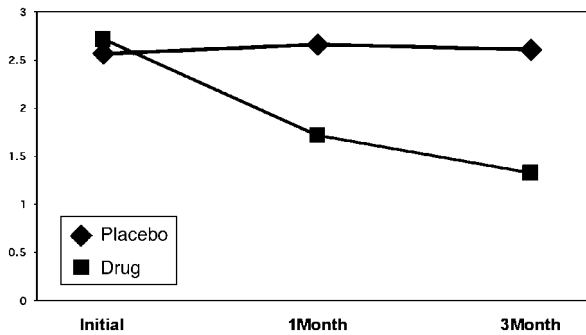


Figure 4. Changes in present pain intensity score.

nucleosides, nerve growth factors and capsaicin-containing ointment.^{17–21} The use of these drugs for long duration in painful diabetic neuropathy is limited because of their adverse side effects. Capsaicin-containing ointments produce initial irritation, which is too unpleasant for continuous use.²² Gabapentin has been shown to be more effective than placebo in doses ranging from 900 to 3600 mg/day.²³ The lower end of this dose range may be relatively ineffective. The main side-effects of gabapentin are dizziness, somnolence, headache, diarrhoea, confusion and nausea.²³ We previously observed a significant subjective improvement in painful diabetic neuropathy in patients receiving sodium valproate in comparison to placebo at the end of one month,¹¹ and unlike other anti-epileptic drugs, it has a favourable side effect profile.⁸ This study tested the efficacy and safety of sodium valproate over a period of 3 months.

At the end of the study, there was a statistically significant reduction in pain score values (SF-MPQ, VAS and PPI) in patients treated with sodium valproate, compared to placebo. Motor and sensory nerve conduction velocities, which were

Table 3 Nerve conduction studies

	Group A (drug)			Group B (placebo)		
	Baseline	3 months	<i>p</i>	Baseline	3 months	<i>p</i>
<i>Median motor</i>						
NCV	43.80 ± 10.17	43.54 ± 11.90	0.99	36.74 ± 14.73	37.32 ± 14.77	0.98
DL	4.20 ± 1.52	4.38 ± 1.47	0.88	4.46 ± 1.19	4.04 ± 1.30	0.22
Amp	4.20 ± 2.54	4.18 ± 2.35	1.00	3.97 ± 1.79	4.06 ± 1.71	0.99
<i>Ulnar motor</i>						
NCV	47.89 ± 8.23	47.12 ± 7.16	0.82	49.29 ± 9.04	47.33 ± 8.03	0.18
DL	3.52 ± 1.19	3.56 ± 1.52	0.99	3.54 ± 0.97	3.62 ± 1.14	0.98
Amp	2.54 ± 1.72	2.48 ± 1.68	0.91	2.34 ± 1.34	2.06 ± 1.12	0.44
<i>Peroneal motor</i>						
NCV	32.10 ± 15.35	31.08 ± 15.00	0.34	39.14 ± 6.91	38.18 ± 6.91	0.70
DL	4.47 ± 2.63	4.15 ± 2.29	0.71	5.13 ± 1.42	5.06 ± 1.29	0.99
Amp	1.87 ± 1.57	1.87 ± 1.65	1.00	1.90 ± 1.20	2 ± 1.38	0.51
<i>Tibial motor</i>						
NCV	34.07 ± 13.71	34.02 ± 12.96	1.00	34.63 ± 10.06	33.44 ± 10.64	0.79
DL	4.99 ± 2.53	5.09 ± 2.79	0.99	5.51 ± 1.96	4.96 ± 2.37	0.55
Amp	3.92 ± 2.49	3.85 ± 2.52	0.95	4.22 ± 2.81	3.97 ± 2.31	0.41
<i>Median sensory</i>						
NCV	39.44 ± 18.99	38.47 ± 18.80	0.88	36.74 ± 20.48	39.60 ± 19.47	0.55
Amp	8.57 ± 7.27	8.40 ± 6.60	1.00	11.74 ± 11.05	9.94 ± 6.26	0.45
<i>Sural sensory</i>						
NCV	14.21 ± 15.71	14.06 ± 15.63	0.98	13.96 ± 15.13	14.97 ± 15.48	0.54
Amp	3.74 ± 4.48	3.76 ± 4.53	0.83	4.58 ± 4.77	4.84 ± 4.77	0.79

NCV, nerve conduction velocity; DL, distal latency; Amp, amplitude. Data are means ± SEM.

Table 4 Side-effect profile of sodium valproate ($n=22$)

Side-effects	n
Nausea	2
Sedation	1
Liver changes	1
Pancreatitis	0
Weight gain	0
Tremor	0
Thrombocytopenia	0
Polycystic ovaries	0

deranged in the beginning of study in diabetic patients of both groups showed no improvement after 3 months. Similar findings were observed in the earlier study.¹¹

Sodium valproate probably acts by potentiating the inhibitory transmitter γ -aminobutyric acid (GABA), and has been shown to prevent its degradation and neuronal uptake, without altering the response to exogenously applied GABA.²⁴ Sodium valproate increases brain GABA levels, and in doing so, may suppress migraine-1-related events in the cortex.²⁴ There is experimental evidence that it suppresses neurogenic inflammation and directly attenuates nociceptive neurotransmission.²⁵ In addition, valproate reportedly alters levels of excitatory and inhibitory neurotransmitters, and exerts direct effect on neuronal membranes *in vitro*.²⁵ These observed effects may ultimately result from a combination of actions at different loci. Its mechanism of action in pain relief is not yet fully defined.

To conclude, our study shows a useful role of sodium valproate in the management of painful diabetic neuropathy, assessed by three different pain scores (SF-MPQ, VAS and PPI), and the drug was well-tolerated by our patients.

References

- Boulton AJM, Gries FA, Jervell J. Guidelines for the diagnosis and out patient management of diabetic peripheral neuropathy. *Diabet Med* 1998; **15**:917–31.
- Gallai V, Firenze C, Mazzotta G, Delegatto S. Neuropathy in children and adolescence with diabetes mellitus. *Acta Neurol Scand* 1988; **78**:136–40.
- Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4400 patient observed between 1947 and 1973. *Diabetes Care* 1978; **1**:168–88.
- Partanen J, Niskanen L, Lehtinen J, et al. Natural history of peripheral neuropathy in patient with non-insulin dependent diabetes mellitus. *N Engl J Med* 1995; **333**:89–94.
- Fedele D, Comi G, Coscelli C, et al. A multicentre study on the prevalence of diabetic neuropathy in Italy. *Diabetes Care* 1997; **20**:836–43.
- Benbow S, Mac Farlane IA, William G. Painful diabetic neuropathy and its relationships to other painful neurogenic conditions. *Pract Diabetes* 1992; **9**:62–5.
- Boulton AJM, Knight G, Drury J, et al. The prevalence of symptomatic, diabetic neuropathy in an insulin treated population. *Diabetes Care* 1985; **8**:125–8.
- Low PA, Dotso RR: Symptomatic treatment of painful neuropathy (editorial). *JAMA* 1998; **280**:1863.
- Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 1987; **37**:589.
- McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. *Br Med J* 1995; **311**:1047–52.
- Kochar DK, Jain N, Agarwal RP, Srivastava T, Agarwal P, Gupta S. Sodium valproate in the management of painful neuropathy in type-2 diabetes—a randomized placebo control study. *Acta Neurol Scand* 2002; **106**:248–52.
- Ellenberg M. Treatment of diabetic neuropathy with diphenylhydantoin. *NY State Med J* 1968; **68**:2653.
- Saudek CD, Werns S, Reidenbert MM. Phenytoin in the treatment of lancinating pain. A comparison. *Anaesthesia* 1981; **36**:1129.
- Rull JA, Quibrera R, Gonzalez Millan H, et al. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): Double blind crossover trial. *Daibetologia* 1969; **5**:215.
- Wilton TD. Tegretol in the treatment of diabetic neuropathy. *S Afr Med J* 1974; **48**:869.
- Chakarbarti AK, Samantary SK. Diabetic peripheral neuropathy. Nerve conduction studies before, during and after carbamazepine therapy. *Austral NZ Med* 1976; **6**:565.
- Capsaicin Study Group. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. *Diabetes Care* 1992; **15**:159.
- Boulton AJM, Levin S, Comstock J. A multicentre trial of the aldose reductase inhibitor tolterastat in patients with symptomatic neuropathy. *Diabetologia* 1990; **33**:431.
- Crepaldi G, Fedele D, Tiengo A, et al. Ganglioside treatment in diabetic peripheral neuropathy: a multicenter trial. *Acta Diabetol Lat* 1983; **10**:265.
- Dejgard A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. *Lancet* 1988; **1**:9.
- Dyck PJ. Nerve growth factor and diabetic neuropathy. *Lancet* 1996; **348**:1044–5.
- Tandan R, Lewis GA, Krusinski PB. Topical capsaicin in painful diabetic neuropathy. *Diabetes Care* 1992; **15**:8.
- Backonja M, Beydown A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetic mellitus. *JAMA* 1998; **280**:1831–6.
- Cutrer FM, Limmeroth V, Moskowitz MA. Possible mechanisms of valproate in migraine prophylaxis. *Cephalalgia* 1997; **17**:93–100.
- Chong MS, Smith TE, Hanna M. Anticonvulsants for the management of Pain. *Euro Pain J* 2002; **2**:5–18.