Title	Adjuvant analgesics in neuropathic pain
Author(s)	Kong, VKF; Irwin, MG
Citation	European Journal Of Anaesthesiology, 2009, v. 26 n. 2, p. 96-100
Issued Date	2009
URL	http://hdl.handle.net/10722/58176
Rights	Creative Commons: Attribution 3.0 Hong Kong License

Adjuvant analgesics in neuropathic pain

Vincent K.F. Kong and Michael G. Irwin

Conventional analgesics have limited efficacy in the management of neuropathic pain. An adjuvant analgesic is a drug that has a primary nonpain indication but which may be analgesic in certain circumstances, and many of these have established a role in the pharmacological treatment of neuropathic pain. The number needed to treat is an indirect statistical measure that can be used to compare relative efficacy of different adjuvant analgesics and, from this, there is currently insufficient evidence to suggest that any one adjuvant analgesic has absolute advantages over another. Analgesic efficacy, tolerability, safety/toxicity, drug interactions, ease of use, and cost-effectiveness are essential factors that guide the selection of an adjuvant analgesic. Cost-effectiveness data are absent for the vast majority of these drugs. Pharmacological treatments should be used as part of a multimodal therapeutic programme for the management of neuropathic pain. *Eur J Anaesthesiol* 26:96–100 © 2009 European Society of Anaesthesiology.

European Journal of Anaesthesiology 2009, **26**:96–100

Keywords: adjuvants pharmaceutical, analgesics, chronic, pain

Department of Anaesthesiology, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Correspondence to Michael G. Irwin, Associate Professor and Head, Department of Anaesthesiology, The University of Hong Kong, Queen Mary Hospital, Hong Kong
Tel: +852 28555791; fax: +852 28553384; e-mail: mgirwin@hkucc.hku.hk

Received 11 March 2008 **Revised** 28 April 2008
Accepted 10 June 2008

Introduction

Neuropathic pain is the result of an injury or malfunction in the peripheral or central nervous system. It may affect up to 8% of adults in the UK and is one of the most difficult types of chronic pain to treat as well as having a devastating impact on psychological health, social functioning, and other aspects of health-related quality of life (QoL) [1]. Nearly 50% of patients with neuropathic pain have inadequate pain relief, and conventional analgesics are generally not effective [2]. Adjuvant analgesics are drugs (with different mechanisms of action, Table 1) that may primarily have nonpain indications but which may be analgesic in certain circumstances. Although adjuvant analgesics have long been the mainstay of pharmacological treatment of neuropathic pain, only a few are specifically licensed for this indication (Table 2). The clinical decision to prescribe drugs for 'off-label' indications should be ideally based on professional judgement in terms of safety quality, and efficacy. Currently available pharmacologic agents with proven efficacy are: anticonvulsants, antidepressants, topical preparations, and some novel agents. Those that have been approved for neuropathic pain management include carbamazepine, phenytoin, gabapentin, pregabalin, duloxetine, lidocaine plaster, capsaicin and sativex (GW Pharmaceuticals, Salisbury, Wiltshire, UK). These will be discussed in this review after a brief introduction of number needed to treat (NNT) and number needed to harm (NNH).

Numbers needed to treat and numbers needed to harm

The NNT is a clinically useful measure for assessing, comparing, pooling and reporting relative effectiveness of interventions in the absence of head-to-head or direct comparisons. It is the number of people who must be treated for one person to benefit over a defined period of time and is calculated as the reciprocal value of an absolute risk reduction, that is, the difference between the proportion of events in the control group (P_c) and the proportion of events in the intervention group (P_i) [Eq. (1)] [3]. NNTs are treatment specific, outcome specific, and are relative to the comparator within a defined period of time. NNT also depends on the baseline risk of events. Practically speaking, a NNT of two or three would normally indicate an effective therapy. The NNT can be applied to an adverse event, when it becomes the NNH. Unlike the NNT, the NNH should preferably be as large as possible, indicating a low probability of such an event. The discrepancy between NNH and NNT reflects the therapeutic index of a treatment.

$$\text{Number needed to treat} = 1/(P_c - P_i) \quad (1)$$

Pooled NNT values from multiple trials are commonly presented in meta-analyses to summarize treatment effects in a clinically relevant way. Making clinical decisions based on pooled NNT values may be misleading due to variation in the baseline risks between the trials such as differences in patient characteristics, clinical settings, treatment durations, outcome measures, and disease incidences [4]. Moreover, pooled NNT values are not adjusted for study quality or sample size. As a single measure of health benefit, NNT conveys some but not all the necessary information for making clinical decisions.

0265-0215 © 2009 Copyright European Society of Anaesthesiology DOI:10.1097/EJA.0b013e328318c706

Table 1 Mechanisms of action of adjuvant analgesics for neuropathic pain

Drug classes	Adjuvant analgesics	Proposed mechanism(s) of action
Anticonvulsants	Carbamazepine	Sodium-channel blocker; serotonergic receptor agonist; serotonin reuptake inhibitor
	Phenytoin	Sodium-channel blocker
	Gabapentin/pregabalin	Modulation of cellular calcium influx into nociceptive neurons: binding to the $\alpha_2\delta$ subunit of VGCCs; reduction in neurotransmitter release; decrease in neuronal hyperexcitability
Antidepressants	TCAs	Serotonin, noradrenaline, and dopamine reuptake inhibitor; sodium, potassium, and calcium-channel blocker; α-adrenergic, cholinergic, and histaminic blockade; effects on GABA and adenosine; NMDA-receptor antagonist; modulation of descending inhibitory pathways
	Venlafaxine	Dual serotonin and noradrenaline reuptake inhibitor (weak noradrenaline reuptake inhibitor at low dose); sodium-channel blocker
	Duloxetine	Potent balanced serotonin and noradrenaline reuptake inhibitor
Topical agents	Lidocaine patch	Sodium-channel blocker; physical barrier against mechanical stimulation
	Capsaicin cream	Activation of vanilloid neuronal membrane receptors on subpopulations of sensory nociceptive C or Aδ fibres; prolonged desensitization of capsaicin-sensitive nociceptors; depletion of substance P
Others	Cannabinoids	Peripheral and central cannabinoid receptors (CB1 and CB2) agonists
	Ziconotide	Neuron-specific N-type voltage-sensitive calcium-channel blocker; inhibition of neurotransmitter release

GABA, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; TCAs, tricyclic antidepressants; VGCCs, voltage-gated Ca^{2+} channels.

Anticonvulsants

The basis for the use of anticonvulsants for the treatment of neuropathic pain stems from some similarities in the pathophysiology with epilepsy. They have been used for this purpose for over 40 years. In the UK, carbamazepine and phenytoin are licensed for the treatment of neuropathic pain associated with trigeminal neuralgia. Carbamazepine is a traditional treatment for trigeminal neuralgia. It blocks voltage-dependent sodium channels, reduces ectopic nerve discharges and stabilizes neural membranes [5]. Carbamazepine had a NNT of 1.9 [95% confidence interval (CI) 1.4–2.8] for any pain relief in trigeminal neuralgia (two studies in the 1960s, 47 participants receiving carbamazepine), a NNT of 2.5 (95% CI 1.8–3.8) for at least moderate pain relief in any neuropathic pain (four studies, 91 participants), and a NNH of 3.7 (95% CI 2.4–7.8) for minor adverse effects [6]. Phenytoin is one of the oldest adjuvant analgesics. It has an inhibitory effect on presynaptic glutamate release in addition to sodium-channel blockade [7]. The NNT of phenytoin for effectiveness in diabetic neuropathy (one study, 38 participants receiving phenytoin) was 2.1 (95% CI 1.5–3.6) [8]. Use of these older anticonvulsants is often restricted by the need for pharmacokinetic monitoring, unfavourable tolerability, side-effect profiles, and significant drug interactions.

Gabapentin, a structural analogue of the neurotransmitter γ-aminobutyric acid (GABA), was initially introduced as an anticonvulsant but subsequently shown to have analgesic properties. After binding to the $\alpha_2\delta$ subunit of voltage-dependent Ca^{2+} channels (VGCCs), there is a reduction in neurotransmitter release and hence a decrease in neuronal hyperexcitability [9]. It was shown to be effective for the treatment of a variety of neuropathic pain conditions in doses up to 3600 mg daily [10] (Table 3). There were significantly greater improvements in QoL parameters in gabapentin-treated patients compared with patients who received placebo. Gabapentin has a favourable safety and tolerability profile. Common side effects were dizziness, somnolence, headache, diarrhoea, confusion and nausea, but, interestingly, there was no significant difference between gabapentin and placebo for withdrawal due to adverse effects. Gabapentin is an attractive agent for patients receiving multiple medications due to the lack of major drug interactions and it is now available in generic formulations.

Pregabalin, an $\alpha_2\delta$ ligand with anticonvulsant, analgesic and anxiolytic properties, was designed as a more potent successor to gabapentin. It probably has a similar mechanism of action, but, when compared with gabapentin, pregabalin has the advantages of six times higher affinity

Table 2 Adjuvant analgesics licensed for neuropathic pain

		Approved neuropathic pain conditions	
Drug classes	Generic name	In the UK	In the USA
Anticonvulsants	Carbamazepine	Trigeminal neuralgia	
	Phenytoin	Trigeminal neuralgia	
	Gabapentin	Neuropathic pain	PHN
	Pregabalin	Peripheral and central neuropathic pain	PHN and painful diabetic peripheral neuropathy
Antidepressants	Duloxetine	Painful diabetic peripheral neuropathy	
Topical agents	Lidocaine 5% patch	PHN	
	Capsaicin 0.075% cream	PHN and painful diabetic peripheral neuropathy	

PHN, postherpetic neuralgia.

Table 3 Gabapentin for chronic neuropathic pain

Neuropathic pain conditions	NNT for moderate or better improvement (compared with placebo)	Pooled sample size
Diabetic neuropathy	2.9 (95% CI 2.2–4.3) RR 2.2 (95% CI 1.7–3)	281 patients (four studies)
PHN	3.9 (95% CI 3–5.7) RR 2.5 (95% CI 1.8–3.3)	428 patients (two studies)
All neuropathic pain	4.3 (95% CI 3.5–5.7) RR 2.2 (95% CI 1.8–2.7)	941 patients (six studies)
Adverse effects	NNH (compared with placebo)	
Minor harm (tolerable adverse effects)	3.7 (95% CI 2.4–5.4)	269 patients (two studies)
Major harm (any effect leading to withdrawal from the studies)		
No statistically significant difference between gabapentin and placebo groups		
Data from 1075 patients (five studies)		

CI, confidence interval; NNH, number needed to harm; NNT, number needed to treat; PHN, postherpetic neuralgia; RR, relative risk. Adapted from [7].

for the presynaptic calcium channel, more rapid onset of action, high oral bioavailability and linear pharmacokinetics [11]. Pregabalin was licensed in the UK for peripheral neuropathic pain syndromes in 2004 and central neuropathic pain in 2006. More recently, it has acquired an indication for the treatment of generalized anxiety disorder.

Pregabalin has been assessed in nearly 2000 patients from eight clinical trials for the treatment of neuropathic pain in patients with postherpetic neuralgia (PHN), painful diabetic peripheral neuropathy (DPN) and spinal cord injury [12]. It was associated with rapid and sustainable reduction in neuropathic pain and its associated sleep interference at dosage ranging from 150 to 600 mg day^{-1}. Common adverse effects were dizziness, somnolence, peripheral oedema, weight gain, dry mouth, asthenia and blurred vision. For PHN and DPN, pregabalin had a combined NNT of 4.2 (95% CI 3.4–5.4) and NNH for withdrawal of 11.7 (95% CI 8.3–19.9) [13].

Pregabalin has potential for abuse and dependence [14]. In the United States, it has been designated as a Schedule V controlled substance by the Drug Enforcement Administration (DEA), as it has psychological effects that are similar to those of diazepam and alprazolam. A history of drug abuse should be evaluated before starting treatment and signs of pregabalin abuse (including dose escalation, tolerance and drug-seeking behaviour) should be monitored during its administration.

Antidepressants

Antidepressants have analgesic effects that are independent of their antidepressant activities [15]. Tricyclic antidepressants (TCAs) relieve various peripheral neuropathic pain conditions except HIV-related neuropathies (Table 4). Until recently, the efficacy of these drugs has been ascribed to inhibition of serotonin and noradrenaline reuptake. TCAs overall (Table 5 for individual agents) had a NNT of 3.6 (95% CI 3–4.5) [relative risk (RR) 2.1 (95% CI 1.8–2.5)] for the achievement of at least moderate pain relief in neuropathic pain, a NNH for adverse effects of 6 (95% CI 4.2–10.7), and a NNH for withdrawal of 28 (95% CI 17–68) [16]. The use of TCAs is usually limited by significant anticholinergic, antihistaminergic, or α-adrenergic side effects particularly in the elderly. There are some new data on better-tolerated antidepressants, such as venlafaxine and duloxetine, in the treatment of neuropathic pain.

Venlafaxine, which also exerts the same dual inhibitory action on serotonin and noradrenaline reuptake [17], had a NNT of 3.1 (95% CI 2.2–5.1) [RR 2.2 (95% CI 1.5–3.1)] for the achievement of moderate pain relief or better in neuropathic pain, a NNH for adverse effects of 9 (95% CI 3.5–13) and a NNH for withdrawal of 16 (95% CI 8–436) [16]. The efficacy of duloxetine has been established in three clinical trials involving 1139 patients with painful DPN [18]. Duloxetine, a balanced serotonin–noradrenaline reuptake inhibitor (SNRI), is the first and currently the only antidepressant to be licensed for the treatment of painful DPN. At doses of 60 mg once or twice daily, it had a rapid and sustained analgesic effect [19]. There were significantly greater improvements in functional outcomes and QoL parameters in duloxetine-treated patients compared with patients who received placebo [20]. None of these clinical trials included data that could be used in NNT calculations.

Topical agents

There is a growing body of evidence on the efficacy of topical agents in a variety of neuropathic pain conditions. Topical analgesics have favourable safety profiles and

Table 4 Antidepressants for all types of chronic neuropathic pain

Neuropathic pain conditions	NNT for moderate pain relief or better (compared with placebo)	Pooled sample size
Diabetic neuropathy	1.3 (95% CI 1.2–1.5) RR 12.4 (95% CI 5.2–29.2)	177 patients (five studies)
PHN	2.7 (95% CI 2–4.1) RR 2.2 (95% CI 1.6–3.1)	219 patients (four studies)

CI, confidence interval; NNT, number needed to treat; PHN, postherpetic neuralgia; RR, relative risk. Adapted from [8].

Table 5 Tricyclic antidepressants for chronic neuropathic pain

TCAs	NNT for moderate pain relief or better (compared with placebo)	Pooled sample size
Amitriptyline (up to 150 mg daily)	3.1 (95% CI 2.5–4.2)	588 patients (10 studies)
Desipramine	2.6 (95% CI 1.9–4.5)	100 patients (two studies)
Imipramine	2.2 (95% CI 1.7–3.22)	114 patients (three studies)

CI, confidence interval; NNT, number needed to treat; TCAs, tricyclic antidepressants. Adapted from [8].

minimal risk of drug–drug interactions because of their localized activities and low systemic absorption.

Transdermal lidocaine plaster is licensed for the treatment of PHN. The presumed mechanism of action is mainly via peripheral sodium-channel blockade [21]. On the basis of data from 58 patients with peripheral neuropathic pain syndromes, lidocaine plaster 5% had a NNT of 3.6 (95% CI 2.2–11.7) for a 30% reduction in pain and 4.4 (95% CI 2.5–17.5) for a 50% ongoing pain reduction [22]. It was generally well tolerated but application site reactions were common. Dosage titration is not necessary and up to three plasters ($420\,cm^2$) may be applied once daily for a maximum of $12\,h\,day^{-1}$. For the treatment of PHN, lidocaine plaster is more expensive than other adjuvant analgesics and should be reserved as an option for treatment-resistant patients only.

Capsaicin and several related compounds called capsaicinoids are produced as a secondary metabolite by chili peppers, probably as deterrents against herbivores. Pure capsaicin is a hydrophobic, colourless, odourless, crystalline to waxy compound and is a chemical irritant. It selectively binds to transient receptor potential vanilloid type 1 (TRPV1) receptors on the membranes of pain and heat-sensing neurons. TRPV1 is a heat-activated channel that is nonselective for cations and modestly permeable to calcium, with permeability ratios of calcium to sodium between four (heat-activated current) and 10 (capsaicin-activated current) [23]. When capsaicin binds to TRPV1, it causes the channel to lower its opening threshold, thereby opening it at temperatures less than the body's temperature, which is why capsaicin is linked to the sensation of heat. Prolonged activation of these neurons by capsaicin depletes presynaptic substance P, one of the body's neurotransmitters for pain and heat. Neurons that do not contain TRPV1 are unaffected [24]. Topical capsaicin 0.075% was evaluated in a meta-analysis with data from 665 patients (six clinical studies) for neuropathic conditions [25]. The NNTs for a 50% reduction in pain from 4 and 8-week treatment compared with placebo were 6.4 (95% CI 3.8–21) and 5.7 (95% CI 4–10), respectively. Treatment had to be applied three or four times daily. The NNH for adverse event-related withdrawals was 7.5 (95% CI 5.5–12). Common local adverse effects were redness, stinging, and burning sensation.

Cannabinoids

Evidence from animal studies and preclinical data suggest that cannabinoids have analgesic properties. Sativex (GW Pharmaceuticals, Salisbury, Wiltshire, UK), a cannabis plant-based prescription pharmaceutical product administered as an oromucosal spray delivering a fixed dose of 2.7 mg tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD), was approved in Canada for multiple sclerosis-related central neuropathic pain in 2005 and is available in the UK as an unlicensed medicine. It is also available in Catalonia, Spain, for 600 patients with multiple sclerosis and a number of other conditions under a compassionate access programme. Cannabinoids target two specific receptors: CB1 and CB2 [26]. On the basis of clinical data from 298 patients (seven studies, mostly crossover design) with multiple sclerosis-related neuropathic pain, cannabinoid-based treatments produced endpoint-baseline score reductions of 1.6 ± 0.4 points on the 11-point pain rating scale ($P < 0.001$) [27]. A reduction of approximately 2 points from baseline on an 11-point pain rating scale or a 30% reduction on pain severity from baseline represents clinically meaningful improvement [28]; however, crossover trials tend to overestimate efficacy because intention to treat analysis cannot be used. Dizziness is commonly associated with cannabinoid-based treatments.

Ziconotide

Ziconotide is a synthetic equivalent of a naturally occurring conopeptide (ω-conotoxin M-VII-A), an N-type calcium-channel blocker found in the piscivorous marine snail, *Conus magus* [29]. Ziconotide, as an intrathecal infusion, is approved by the Food and Drug Administration (FDA) of the United States for the management of severe chronic pain in patients who are intolerant of or refractory to other treatments. The emerging evidence of using ziconotide for severe refractory neuropathic pain is promising but limited to very little clinical data (mainly from case reports). Common adverse effects are dizziness, nausea, confusion and nystagmus. Ziconotide is contraindicated for patients with certain preexisting mental disorders (e.g. psychosis) due to evidence that they are more susceptible to certain severe side effects.

Future developments

There are at least 50 new agents undergoing clinical development for neuropathic pain and eight drugs are in phase III clinical trials at present, including glutamate antagonists, cytokine inhibitors, vanilloid-receptor agonists, catecholamine modulators, ion-channel blockers, anticonvulsants, opioids, cannabinoids, cyclo-oxygenase (COX) inhibitors, acteylcholine modulators, adenosine receptor agonists and several miscellaneous drugs [30].

Other drugs to be considered include: oxcarbazepine, topiramate, lamotrigine, sodium valproate, clonazepam, mexiletine, and amantadine. Preclinical studies suggest that gene therapy, stem cell therapy and viral vectors for delivery of biologic antinociceptive molecules are emerging options.

Conclusion

There is good evidence supporting the use of adjuvant analgesics in neuropathic pain, especially for those common neuropathic pain conditions such as trigeminal neuralgia, painful DPN and PHN; however, the data on adjuvant analgesics in central neuropathic pain are limited. The selection of an adjuvant analgesic for neuropathic pain should be based on proven efficacy, tolerability, safety, toxicity, drug interactions, ease of use and cost-effectiveness. The evidence to support switching of drugs within the same class or between different classes is weak. Combination therapy, in most cases, is also not evidence based. Even the most appropriate treatment strategy may only be able, at best, to reduce neuropathic pain to a more tolerable level.

At the moment, most clinical trials of neuropathic pain conditions have focused mainly on disease-based but rarely symptom-based treatment, based on the premise that neuropathic pain medications should be selected by the aetiology of the patient's disease and not by the patient's symptoms. Future studies should be focused on mechanisms responsible for the initiation or maintenance of neuropathic pain.

References

1 Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain* 2006; **7**:281–289.
2 Foley KM. Opioids and chronic neuropathic pain. *N Engl J Med* 2003; **348**:1279.
3 Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988; **318**:1728–1733.
4 Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses: sometimes informative, usually misleading. *Br Med J* 1999; **318**:1548–1551.
5 Burchiel KJ. Carbamazepine inhibits spontaneous activity in experimental neuromas. *Exp Neurol* 1988; **102**:249–253.
6 Wiffen PJ, McQuay HJ, Moore RA. Carbamazepine for acute and chronic pain. *Cochrane Database Syst Rev* 2005:CD005451.
7 Yaari Y, Devor M. Phenytoin suppresses spontaneous ectopic discharge in rat sciatic nerve neuromas. *Neurosci Lett* 1985; **58**:117–122.
8 Wiffen P, Collins S, McQuay H, *et al.* Anticonvulsants drugs for acute and chronic pain. *Cochrane Database Syst Rev* 2005:CD001133.
9 Maneuf YP, Gonzalez MI, Sutton KS, *et al.* Cellular and molecular action of the putative GABA-mimetic, gabapentin. *Cell Mol Life Sci* 2003; **60**:742–750.
10 Wiffen PJ, McQuay HJ, Edwards JE, Moore RA. Gabapentin for acute and chronic pain. *Cochrane Database Syst Rev* 2005:CD005452.
11 Gilron I, Flatters SJ. Gabapentin and pregabalin for the treatment of neuropathic pain: a review of laboratory and clinical evidence. *Pain Res Manage* 2006; **11**:16A–29A.
12 Dworkin RH, Thakur R, Griesing T, *et al.* Randomized clinical trials of pregabalin for neuropathic pain: methods, results, and implications. *Prog Neurother Neuropsychopharmacol* 2008; **3**:167–187.
13 Finnerup NB, Otto M, McQuay HJ, *et al.* Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005; **118**: 289–305.
14 Blommel ML, Blommel AL. Pregabalin: an antiepileptic agent useful for neuropathic pain. *Am J Health Syst Pharm* 2007; **64**:1475–1482.
15 Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. *Basic Clin Pharmacol Toxicol* 2005; **96**:399–409.
16 Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev* 2007:CD005454.
17 Siepmann T, Mueck-Weymann M, Oertel R, *et al.* The effects of venlafaxine on cognitive functions and quantitative EEG in healthy volunteers. *Pharmacopsychiatry* 2008; **41**:146–150.
18 Kajdasz DK, Iyengar S, Desaiah D, *et al.* Duloxetine for the management of diabetic peripheral neuropathic pain: evidence-based findings from post hoc analysis of three multicenter, randomized, double-blind, placebo-controlled, parallel-group studies. *Clin Ther* 2007; **29 (Suppl)**:2536–2546.
19 Pritchett YL, McCarberg BH, Watkin JG, Robinson MJ. Duloxetine for the management of diabetic peripheral neuropathic pain: response profile. *Pain Med* 2007; **8**:397–409.
20 Armstrong DG, Chappell AS, Le TK, *et al.* Duloxetine for the management of diabetic peripheral neuropathic pain: evaluation of functional outcomes. *Pain Med* 2007; **8**:410–418.
21 Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996; **65**:39–44.
22 Meier T, Wasner G, Faust M, *et al.* Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. *Pain* 2003; **106**:151–158.
23 Nilius B, Owsianik G, Voets T, Peters JA. Transient receptor potential cation channels in disease. *Physiol Rev* 2007; **87**:165–217.
24 Veronesi B, Oortgiesen M. The TRPV1 receptor: target of toxicants and therapeutics. *Toxicol Sci* 2006; **89**:1–3.
25 Mason L, Moore RA, Derry S, *et al.* Systematic review of topical capsaicin for the treatment of chronic pain. *Br Med J* 2004; **328**:991–994.
26 Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacol Ther* 1997; **74**:129–180.
27 Iskedjian M, Bereza B, Gordon A, *et al.* Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin* 2007; **23**:17–24.
28 Skov MJ, Beck JC, de Kater AW, Shopp GM. Nonclinical safety of ziconotide: an intrathecal analgesic of a new pharmaceutical class. *Int J Toxicol* 2007; **26**:411–421.
29 Farrar JT, Portenoy RK, Berlin JA, *et al.* Defining the clinically important difference in pain outcome measures. *Pain* 2000; **88**:287–294.
30 Gilron I, Coderre TJ. Emerging drugs in neuropathic pain. *Expert Opin Emerg Drugs* 2007; **12**:113–126.