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Evidence-based pharmacological treatment of neuropathic pain syndromes

Review

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Summary. Neuropathic pain, caused or initiated by a primary lesion in the peripheral or central nervous system, can result in a dramatic reduction in the patient's quality of life. The expression neuropathic pain covers a heterogeneous group of conditions, including peripheral neuropathy, complex regional pain syndrome, trigeminal neuralgia and central pain. Neuropathic pain poorly responds to conventional analgesics. However, with appropriate therapy, a significant proportion of patients experience a substantial pain reduction. We present here an evidence-based review of the options for the treatment of neuropathic pain syndromes. Consideration is given to the mechanisms of action, numbers needed to treat (NNT), the recommended doses and the most frequent side-effects of the drugs for which consistent support has been found for treatment of these pain conditions.

Keywords: Neuropathic pain, therapy, randomized controlled trials, meta-analysis.

Introduction

Neuropathic pain is defined as pain caused by a lesion in the nervous system (Cruccu et al., 2004). It causes considerable suffering and a substantial reduction in the patients' health-related quality of life (Meyer-Rosberg et al., 2001a, b). The true prevalence of neuropathic pain is not known, as comprehensive epidemiological studies have not been performed. It has been estimated that 1–1.5% of the general population is affected, but even this might be an underestimate (Bowsher, 1991; Carter and Galer, 2001). Approximately 5% of patients with traumatic nerve injury suffer from neuropathic pain (Sunderland, 1993). Central neuropathic pain (CNP) has been reported in 28% of multiple

sclerosis patients, 75% of patients with syringomyelia (Boivie, 1999), 60–70% of patients with spinal cord injury (Bonica, 1991) and 8% of stroke patients (Andersen et al., 1995).

Neuropathic pain is a challenging condition to treat, in part because of the heterogeneity of the aetiologies, symptoms and underlying mechanisms. The awareness among clinicians of the evidence-based therapeutic options is less than optimum, probably because the complexity of the phenomenon makes the available data difficult to interpret. Recent studies have shown that most of the patients treated for neuropathic pain were receiving medication of unproven efficacy or suboptimum doses of the appropriate medication (Finnerup et al., 2001; Richeimer et al., 1997).

Most authors agree that a major break-through in the pharmacological treatment of neuropathic pain can be achieved only with therapy tailored to the individual patient on the basis of the mechanisms underlying the pain in that particular patient (Woolf and Mannion, 1999). However at present this is not achievable. Specific and sensitive diagnostic tools providing clear-cut evidence of the nature of the particular pathophysiological process involved are lacking.

In order to help clinicians in their choice of appropriate treatment decisions, we have reviewed all of the published randomised, controlled, double-blind trials for the pharmacological treatment of neuropathic pain. We have searched electronic databases (Medline, Web of Science, Cochrane Library) and also references from previously published reviews and clinical trials. A drug was considered to display consistently supported efficacy only if there were two or more large-scale, randomized, controlled, double-blind trials demonstrating its efficacy. If there was only one large or several small-scale, randomized, controlled, double-blind trials, the drug was considered to have limited support for its efficacy. For each drug with consistent support for its efficacy, we briefly present the most probable mechanism of action and indicate the number needed to treat for more than 50% pain relief (NNT), a clinically relevant parameter, whose use is widely accepted (McQuay and Moore, 1998). The NNT is the number of patients needed to be treated in order for one patient to achieve a pain reduction of more than 50% (an ''excellent/good'' response to treatment or the attainment of ''no pain/slight pain''). It is calculated as $\mathrm{NNT} = 1/((\text{goal achieved}_{\text{active}}/\text{total}_{\text{active}}) - (\text{goal achieved}_{\text{placebo}}/\text{total}_{\text{placebo}}))$ (Cook and Sacket, 1995). 95% confidence intervals can be calculated for the NNT (Altman, 1995; Thomas and Gart, 1977).

The drugs used to treat neuropathic pain are commonly classified according to their original therapeutic class (i.e. antidepressants, anticonvulsants, etc). Unfortunately, this may be misleading, since it might suggest that other drugs belonging to the same class as one with proven efficacy are also effective (a mistake frequently made by clinicians who are not familiar with neuropathic pain treatment).

Another reason why the treatment of neuropathic pain often fails is that it tends to be used in a uniform fashion across the patient population. In other words, a drug shown to be useful in one group of patients is actually used to

treat patients whose neuropathic pain is caused by a completely different pathology. The current data indicate that from a therapeutic point of view, at least four distinct aetiologic groups should be considered when a treatment decision is made: peripheral neuropathic pain (PNP), complex regional pain syndrome (CRPS), trigeminal neuralgia (TN) and central neuropathic pain (CNP).

Peripheral neuropathic pain

Most of the clinical trials in this category were conducted on patients with painful diabetic neuropathy (PDN) or postherpetic neuralgia (PHN); a few trials involved nerve injuries and mixed peripheral aetiologies. There is consistent support for the use of tricyclic antidepressants (TCAs), gabapentin, pregabalin, tramadol, oral opioids and topical lidocaine (Table 1). Agents that have to be administered intravenously (such as ketamine, IV-lidocaine or IV-alpha-lipoic acid) are rarely (if ever) of clinical importance for the treatment of these chronic conditions.

Tricyclic antidepressants inhibit the re-uptake of biogenic amines and are also strong sodium-channel modulators (Beydoun and Backonja, 2003; Sanchez and Hyttel, 1999). Thus TCAs may act both by enhancing dorsal horn inhibition and by diminishing peripheral sensitisation. The evidence for the efficiency of TCAs in treating neuropathic pain of peripheral origin (PNP) comes from the meta-analysis of many old and relatively small-scale trials (McQuay et al., 1996; Sindrup and Jensen, 1999). The findings of 17 active treatment arms involving more than 300 patients with PNP (Gomez-Perez et al., 1985; Kishore-Kumar et al., 1990; Kvinesdal et al., 1984; Langohr et al., 1982; Max et al., 1987, 1988, 1991; Sindrup et al., 1989, 1990a, c, 1992b; Turkington, 1980; Watson et al., 1982, 1992) demonstrated that approximately 30% of patients were responders (>50% relief), 30% exhibited minor side-effects and 4% suffered from major side-effects that led to discontinuation of the

Table 1. Drugs with consistent support for their efficacy in clinical management of neuropathic pain syndromes

Neuropathic pain syndrome	Drug	NNT (95% CI)	Recommended daily dose
Peripheral neuropathic pain*	TCAs	2.2 (1.9–2.6)	Up to 150 mg (titrate over 6 weeks)
	Gabapentin	4.4 (3.4–6.2)	1800–3600 mg (titrate over 2–4 weeks)
	Pregabalin	5.0 (3.5–8.6)	600 mg (titrate over 1 week)
	Tramadol	3.9 (2.7–6.7)	200–400 mg (titrate from 100 mg)
	CR-oxycodone	2.6 (1.9–4.1)	60–120 mg (titrate from 20 mg)
	Topical lidocaine	4.4 (2.5–17.5)	5% patch or gel (12 h on, 12 h off)
Trigeminal neuralgia	Carbamazepine	1.8 (1.4–2.7)	Up to 1000 mg (titrate from 200 mg)

NNT: the number of patients needed to be treated for one patient to achieve a pain reduction of more than 50%. *Except for HIV-associated polyneuropathy

therapy. For the treatment of PNP, the NNT value for 5 TCA drugs (amitriptyline, clomipramine, desipramine, imipramine, maprotiline) was calculated to be 2.2 (95% CI: 1.9–2.6) from 13 active treatment arms of placebo-controlled trials with a cross-over design involving 294 active patient episodes (Kalso et al., 1995; Kishore-Kumar et al., 1990; Kvinesdal et al., 1984; Max et al., 1987, 1988, 1991; Sindrup et al., 1990b, c, 1992b; Vrethem et al., 1997; Watson et al., 1982). However, when the dose of imipramine was adjusted so that the optimum plasma concentration was attained, an NNT of 1.4 resulted (Sindrup et al., 1990b). Titration up to the target plasma concentration could be achieved in 16 out of the 19 patients with PDN.

TCAs are initiated in a low bedtime dose (10–25 mg) which is gradually increased on a weekly basis (by 10–25 mg/day), usually up to 150 mg or until the side-effects interfere with a further increase of the dose.

The most frequent side-effects are sedation, anticholinergic effects (dry mouth, constipation and postural hypotension). In one large-scale study, the long-term use of TCAs was found to be associated with a 2.2-fold greater relative risk of myocardial infarction and a 1.7-fold increase in overall mortality as compared with placebo (Cohen et al., 2000). Thus, caution is demanded when TCAs are prescribed for older patients, especially those with cardiovascular risk factors, and a screening electrocardiogram is recommended before the therapy is started. TCAs are contraindicated in patients with a history of glaucoma, urinary retention or autonomic neuropathy.

Gabapentin is an anticonvulsant that acts on neuropathic pain, probably by reducing central sensitisation. It binds to the alpha2-delta sub-unit of a voltage-dependent calcium channel in laminae I and II, the termination sites of the nociceptors (Beydoun and Backonja, 2003; Gee and Brown, 2003). Gabapentin is the anticonvulsant for which the most convincing evidence has been obtained concerning its efficacy in the treatment of PNP (Table 1). Its efficiency for the symptomatic treatment of PDN has been revealed in two large trials: one published (Backonja et al., 1998) and one unpublished but described in a review (Backonja and Glanzman, 2002). As for PHN, gabapentin proved to be superior to placebo in two large trials (Rice et al., 2001; Rowbotham et al., 1998). In a recently published trial with parallel design involving 121 patients with neuropathic cancer-pain, gabapentin, as an add-on therapy to opioids has been shown to be superior to placebo (Caraceni et al., 2004). Gabapentin was likewise better than placebo in relieving post-amputation phantom limb pain in a small ($n = 14$) cross-over trial (Bone et al., 2002). Dichotomous data for calculating NNT could not be extracted from this paper. The findings of three published large trials involving a total of 728 patients demonstrated that gabapentin has an NNT of 4.4 (95% CI: 3.4–6.2) for the treatment of PNP (Backonja et al., 1998; Rice et al., 2001; Rowbotham et al., 1998). The efficacy of gabapentin was similarly observed in a large trial that enrolled patients with a wide range of neuropathic pain syndromes (not only PNP) (Serpell et al., 2002). That study furnished a much higher NNT (14.2) but it should be taken into account that 46% of the patients had CRPS or TN. The patients with CRPS (who appeared to display a poor response) accounted for 28% of the randomised patients. When the results of this trial are included for the meta-analysis, a NNT of

5.3 is obtained for gabapentin in the treatment of neuropathic pain (1033 patients). In Guillain-Barré syndrome, the pain is dual in nature, involving both nociceptive and neuropathic components. In a small study with cross-over design that enrolled 18 patients, gabapentin proved superior to placebo in the treatment of pain in Guillain-Barré syndrome (Pandey et al., 2002). A head-to-head comparison of gabapentin and amitriptyline for the treatment of PDN (n = 25) showed that the two drugs were equally effective (Morello et al., 1999).

The reduction of pain starts relatively soon after the initiation of therapy (during the first or second week of full-therapy). The side-effects (most frequently dizziness and somnolence; less commonly gastrointestinal symptoms and peripheral oedema) are mild to moderate and usually subside within 10 days after the initiation of treatment (Backonja and Glanzman, 2002).

It is recommended to start therapy at 900 mg/day (day 1: 300 mg/d at bedtime; day 2: 600 mg/d in two divided doses; day 3: 900 mg/d in three divided doses). Titrate by 100–300 mg to 1800 mg/day (divided in three doses/day) in the first 2 weeks, and then (if necessary and possible) increase the dose up to 3600 mg/day (divided in three doses/day) in an additional 2 weeks (Backonja and Glanzman, 2002). A lower dose of gabapentin (900 mg/day) failed to prove significantly superior to placebo in one trial on PDN patients (n = 40), though even this trial yielded a NNT of 5.0 (Gorson et al., 1999).

Pregabalin (Table 1) is a novel alpha2-delta ligand that was shown to be effective in the treatment of PHN in two large trials (n = 411) (Dworkin et al., 2003; Sabatowski et al., 2004). The NNT emerging from these trials was 5.0 (95% CI: 3.5–8.6), the effect starting as early as the first full day of treatment (1 week after the initiation of treatment).

The side-effects are mild to moderate (dizziness, somnolence, headache, dry mouth and peripheral oedema). During the first 3 days, 150 mg/day is administered (50 mg three times daily), followed by 300 mg/day for the next 4 days. From the beginning of the second week, 600 mg/day is administered to those patients whose creatinine clearance is more than 60 ml/min.

Tramadol (Table 1) is a centrally-acting analgesic, which has both direct opioid action and indirect monoaminergic action (like the TCAs). Two large studies proved its efficacy in the treatment of neuropathic pain in PHN and PDN (Boureau et al., 2003; Harati et al., 1998). One smaller study with a cross-over design revealed that tramadol was efficient in treating painful polyneuropathy of different origins (Sindrup et al., 1999). These studies, involving a total of 292 patients, gave an NNT of 3.9 (95% CI: 2.7–6.7). Tramadol is usually started at 100 mg/day and titrated up to 200–400 mg/day (in divided doses, four times daily). It has a low abuse liability, and the development of tolerance and dependence during long-term treatment is uncommon. The most frequent side-effects are somnolence, dizziness, headache, dry mouth, nausea, constipation and sweating. A meta-analysis by the Cochrane group of two of these studies led to the conclusion that tramadol is effective for the treatment of neuropathic pain (Duhmke et al., 2004). A 6-month open extension of the study on patients with PDN demonstrated that tramadol also provides long-term relief from the pain (Harati et al., 2000).

Opioids act through the descending inhibitory pathways modulating nociceptive impulses in the dorsal horn. There is increasing evidence of the efficacy of oral opioids in the treatment of neuropathic pain.

Oxycodone, a pure μ-opioid receptor agonist, was proved to be efficient in the treatment of neuropathic pain in two studies on patients with PDN (Gimbel et al., 2003; Watson et al., 2003) and in one study on PHN (Watson and Babul, 1998). Dichotomous data for the calculation of NNT could be extracted from two trials (Watson and Babul, 1998; Watson et al., 2003). These indicated that CR-oxycodone has an NNT of 2.6 (95% CI: 1.9–4.1) for relief from PNP (Table 1). It is started at 10 mg q12 h and gradually increased to 30–60 mg q12 h. The side-effects are those typical of opiates: somnolence, dizziness, nausea and constipation.

Morphine sulphate was shown in a small (n = 12) cross-over trial to be superior to placebo in the treatment of phantom limb pain (NNT = 3) (Huse et al., 2001). In a cross-over trial (n = 76), opioids (morphine, methadone) provided significant benefits for the treatment of PHN (Raja et al., 2002). This study yielded a NNT of 2.9 for 33% pain relief. The efficacy of methadone and levorphanol (μ-receptor agonists) in the treatment of neuropathic pain were demonstrated in trials on patients with mixed peripheral and central aetiologies (n = 18, cross-over design, and n = 81, parallel design) (Morley et al., 2003; Rowbotham et al., 2003).

Topical lidocaine reduces pain by blocking the sodium channels at the periphery. The efficacy of topical lidocaine for the treatment of pain in PHN was demonstrated by four trials with a total recruitment of more than 200 patients (Galer et al., 1999, 2002; Rowbotham et al., 1995, 1996). From one of these studies, a NNT as low as 2 was calculated; however, this study recruited only patients who had previously been successfully treated with topical lidocaine. One recent cross-over trial (n = 58) revealed that topical lidocaine was superior to placebo for the treatment of focal peripheral neuropathic pain syndromes (Meier et al., 2003). More than half of the patients had PHN. In this study, an NNT of 4.4 (95% CI: 2.5–17.5) was determined for ongoing pain, and an NNT of 8.4 for allodynia. Recently, an open-label, 3-week study with a 5-week extension, demonstrated the efficacy of 5% lidocaine patch for the symptomatic treatment of PDN (Barbano et al., 2004).

Lidocaine is applied as a 5% patch (1–4 patches, covering a maximum of 560 cm^2) on the painful area, 12 hours on, 12 hours off. Topical lidocaine has several advantages. Its side-effects are few and mild (skin irritation). It is easy to handle and it has no systemic activity. It does not interfere with systemic treatment and thus it is an excellent add-on therapy.

Limited support

In small-size, cross-over trials (n: 19 and 15, respectively), the selective serotonin re-uptake inhibitors *paroxetine* and *citalopram* were found to be effective in the treatment of PDN (NNT: 2.9 and 7.7, respectively) (Sindrup et al., 1990, 1992a). In a cross-over trail in which 40 patients with painful polyneuropathies of different aetiologies were randomised, *venlafaxine* (a serotonin and weak

norepinephrine re-uptake inhibitor) proved to be effective (NNT = 5.2) (Sindrup et al., 2003). A cross-over trial (n = 41) involving patients with neuropathic pain of different origins (mostly PNP) resulted in the finding that *sustained-release bupropion* (a norepinephrine and weak dopamine re-uptake inhibitor) was effective in the symptomatic treatment. The NNT for a result of ''improved or much improved'' was 1.6 (Semenchuk et al., 2001). Two relatively small studies with a parallel design showed that *sodium valproate* relieved pain in patients with PDN (Kochar et al., 2002, 2004). The efficiency for the symptomatic treatment of PDN, has been reported in one study each for *lamotrigine* (n = 59, parallel design), *acetyl-L-carnitine* (n = 333, parallel design), *topical isosorbide dinitrate spray* (n = 22, cross-over design) and *levodopa* (n = 25, parallel design, NNT = 3.4) (Eisenberg et al., 2001; DeGrandis et al., 2002; Yuen et al., 2002; Ertas et al., 1998).

There have been controversial findings concerning topical capsaicin, carbamazepine, oral phenytoin, dextromethorphan, mexiletine, non-steroid anti-inflammatory drugs and cannabinoids.

Although it has been argued that, for PNP, the aetiology does not affect the treatment outcome (Kingery, 1997), there is at least one exception. The only drug for which there is evidence as to its efficiency in the treatment of HIV-associated distal sensory polyneuropathy is lamotrigine. This was superior to placebo in a small trial (Simpson et al., 2000). However, in the subsequent large trial, lamotrigine was observed to relieve pain only in the subgroup of patients who were treated with neurotoxic antiretroviral therapy (n = 92, parallel design; NNT = 4.3) (Simpson et al., 2003).

Complex regional pain syndrome

A search of the literature did not indicate consistent support for the efficiency of any pharmacological therapy. However, there is limited support for a number of therapeutic options (Table 2).

Intravenous **bisphosphonate** therapy was found to relieve pain in two trials. One of them employed a daily infusion of 7.5 mg alendronate (n = 20, parallel design) and the other one used 300 mg/day clodronate (n = 32, cross-over design) (Adami et al., 1997; Varenna et al., 2000).

Table 2. Drugs with limited support for the treatment of complex regional pain syndrome and central neuropathic pain

Complex regional pain syndrome	Central neuropathic pain	
Intravenous: bisphosphonate; lidocaine	CPSP	Amitriptyline
Intranasal calcitonin		Lamotrigine
IVRB: bretylium; ketanserine		
Topical DMSO	SCI	Gabapentin
Epidural clonidine		Lamotrigine
Oral corticosteroid		

CPSP central post-stroke pain, *SCI* spinal cord injury

Intranasal **calcitonin** proved superior to placebo in one trial (n = 66, parallel design), while there was no demonstrable effect in another (n = 40, parallel design) (Bickerstaff and Kanis, 1991; Gobelet et al., 1992). A meta-analysis that included three open-label trials besides the two double-blind trials concluded that intranasal calcitonin provided effective pain relief (Perez et al., 2001).

Intravenous regional blockade with **bretylium** (n = 12, cross-over) or with **ketanserine** (n = 9, cross-over) was reported to be effective in one small trial each (Hord et al., 1992; Hanna and Peat, 1989).

In a small (n = 16) trial with a cross-over design, intravenous **lidocaine** reduced allodynia significantly more than did placebo (Wallace et al., 2000).

The effectiveness of topical **dimethylsulfoxide** 50% (DMSO), a free radical scavenger, has been demonstrated by the results of several open-label trials and one relatively small (n = 32) double-blind trial with a parallel design (Zuurmond et al., 1996).

Epidural **clonidine** proved effective in the symptomatic treatment of CRPS in a relatively small (n = 26, cross-over) trial (Rauck et al., 1993). However, this route of administration and the serious side-effects (sedation and hypotension) that can arise limit its clinical relevance.

Although the **corticosteroids** (10 mg prednisone three times daily) are generally thought of as a therapeutic option with clearly demonstrated efficacy, it should be borne in mind that both trials supporting it were non-blinded and relatively small in size (n = 23 and 36, parallel design) (Braus et al., 1994; Christen et al., 1982).

Trigeminal neuralgia

The only pharmacological treatment for TN that has been found consistent support for its efficacy is **carbamazepine**. It reduces high-frequency repetitive firing by inactivating voltage-gated sodium channels, especially after depolarisation. Thus, carbamazepine might target the ectopic discharges in the neuroma, as was shown in experimental models (Burchiel, 1988). Carbamazepine also reduces the release of excitatory neurotransmitters and enhances the release of serotonin (Beydoun and Backonja, 2003).

Four placebo-controlled studies, involving a total of 150 patients, proved the efficacy of carbamazepine in the symptomatic treatment of TN (Campbell et al., 1966; Killian et al., 1968; Nicol et al., 1969; Rockliff and Davis, 1966). Dichotomous data for calculation of the NNT could be extracted from two of these trials (Killian et al., 1968; Nicol et al., 1969), which gave an NNT for carbamazepine of 1.8 (95% CI: 1.4–2.7). Though an estimated 70–90% of patients with newly-diagnosed TN exhibit a good short-term response to carbamazepine, approximately 40% of the patients drop out after 1 year of treatment, mainly due to side-effects and the development of tolerance (Beydoun, 2002).

Carbamazepine is usually initiated at 200 mg, twice daily. Improvement starts after only a few days of treatment. However, in consequence of autoinduction, the dose has to be titrated up to 1000 mg/day or even higher. The most frequent side-effects are sedation, blurred vision, diplopia, dizziness, ataxia,

gait disturbance, nausea and vomiting. Because of the idiosyncratic haematological and hepatic effects, the routine monitoring of haematological and hepatic profiles must be performed. In addition, drug–drug interactions complicate its use in a combination therapy.

Oxcarbazepine has a much better side-effect profile than that of carbamazepine. Its efficacy for the treatment of TN was demonstrated in several open-label and four double-blind trials (Beydoun, 2002; Beydoun et al., 2002; Lindstrom, 1987). A meta-analyis of the data on 48 newly diagnosed TN patients and 84 patients with refractory TN failed to reveal any difference between oxcarbazepine and carbamazepine (Beydoun et al., 2002). The median dose for the new TN patients was 750 mg, and that for the refractory TN patients was 1200 mg. However, it should be taken into account that these trials have not been published as full-length, peer-reviewed publications (they are abstracts of congress-presentations).

Though phenytoin was the first drug to be used for the treatment of TN (Bergouignan, 1942), to date no randomised-controlled trial on its oral use has been reported. Intravenous phenytoin has been shown to reduce acute attacks of neuropathic pain, including TN (McClean, 1999).

One small-size ($n = 14$) trial with a cross-over design demonstrated that lamotrigine (400 mg/d) was efficient (NNT = 2.1) for the treatment of refractory TN (Zakrzewska et al., 1997). The major disadvantage of using lamotrigine for TN is that it requires a long titration period (6–8 weeks).

In a small ($n = 10$) cross-over trial, baclofen (60–80 mg/day) was found to be superior to placebo (NNT = 1.4) in the treatment of TN (Fromm et al., 1984).

Central neuropathic pain

Only limited support could be found for the pharmacological treatment of two CNP conditions: post-stroke pain and spinal cord injury (Table 2).

Amytriptyline (75 mg/day) proved to be superior to placebo in the treatment of central post-stroke pain in a small ($n = 15$) cross-over study (Leijon and Boivie, 1989). The NNT (for clinical responders, according to a global rating) was 1.7. **Lamotrigine** (200 mg/day) effectively relieves central post-stroke pain, as shown in a cross-over ($n = 30$) study (Vestergaard et al., 2001). The NNT (for clinical responders) was 2.9.

Gabapentine (titrated over 4 weeks to the maximum tolerated dose) was demonstrated to be effective in the treatment of pain after spinal cord injury, in two small cross-over trials involving a total of 27 patients (Levendoglu et al., 2004; Tai et al., 2002). In a small ($n = 22$) cross-over trial on patients with spinal cord injury pain, **lamotrigine** (400 mg/day) was effective only in the subgroup of patients with incomplete lesions (Finnerup et al., 2002).

In spite of the increasing availability of efficient therapeutic possibilities, the treatment of neuropathic pain often remains frustrating both for the patient and for the physician. Active involvement of the patient in the therapeutic decisions and the setting of realistic goals are extremely important. Although the existing evidence should guide the therapy, the physician should be flexible

in the choice of treatment, especially with patients who have already failed to respond to a number of therapies.

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References

Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V (1997) Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. Ann Rheumatol Dis 56: 201–204

Altman DG (1995) Practical statistics for medical research. Chapman & Hall, London, p 233

Andersen G, Vestergaard K, Ingeman-Nielsen M, Jensen TS (1995) Incidence of central post-stroke pain. Pain 61: 187–193

Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonsecca V, Hes M, LaMoreaux L, Garafalo E (1998) Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 280: 1831–1836

Backonja M, Glanzman RL (2002) Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther 25: 81–104

Barbano RL, Herrman DN, Hart-Gouleau S, Pennella-Vaughan J, Lodewick PA, Dworkin RH (2004) Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy. Arch Neurol 61: 914–918

Bergouignan M (1942) Cures heureuses de nevralgies faciales essentiales par le diphenylhydantoinate de soude. Rev Laryngol Otol Rhinol 63: 34–41

Beydoun A (2002) Clinical use of tricyclic anticonvulsants in painful neuropathies and bipolar disorders. Epilepsy Behav 3: S18–S22

Beydoun A, Schmidt D, D'Souza J (2002) Meta-analysis of comparative trials of oxcarbamazepine versus carbamazepine in trigeminal neuralgia. J Pain 3 [Suppl 1]: 38

Beydoun A, Backonja MM (2003) Mechanistic stratification of antineuralgic agents. J Pain Symptom Manage 25: S18–S30

Bickerstaff DR, Kanis JA (1991) The use of nasal calcitonin in the treatment of post-traumatic algodystrophy. Br J Rheum 30: 291–294

Boivie J (1999) Central pain. In: Wall PD, Melzak R (eds) Textbook of pain. Churchill Livingstone, Edinburgh, pp 879–914

Bone M, Critchley P, Buggy DJ (2002) Gabapentin in postamputation Phantom Limb Pain: a randomized, double-blind, placebo-controlled cross-over study. Reg Anesth Pain Med 27: 481–486

Bonica JJ (1991) Introduction: semantic, epidemiologic, and educational issues. In: Casey KL (ed) Pain and central nervous system disease: the central pain syndromes. Raven Press, New York, pp 13–29

Boureau F, Legallicier P, Kabir-Ahmadi M (2003) Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. Pain 104: 323–331

Bowsher D (1991) Neurogenic pain syndromes and their management. Br Med Bull 47: 644–666

Braus DF, Krauss JK, Strobel J (1994) The shoulder-hand syndrome after stroke: a prospective clinical trial. Ann Neurol 36: 728–733

Burchiel KJ (1988) Carbamazepine inhibits spontaneous activity in experimental neuromas. Exp Neurol 102: 249–253

Campbell FG, Graham JG, Zilkha KJ (1966) Clinical trial of carbamazepine (Tegretol) in trigeminal neuralgia. J Neurol Neurosurg Psychiatry 29: 265–267

Caraceni A, Zecca E, Bonezzi C, Arcuri E, Tur RY, Maltoni M, Visentin M, Gorni G, Martini C, Tirelli W, Barbieri M, De Conno F (2004) Gabapentin for neuropathic cancer pain: a randomized controlled trial from the gabapentin cancer pain study group. J Clin Oncol 22: 2909–2917

Carter GT, Galer BS (2001) Advances in the management of neuropathic pain. Phys Med Rehabil Clin North Am 12: 447–459

Christensen K, Jensen EM, Noer I (1982) The reflex sympathetic dystrophy syndrome response to treatment with systemic corticosteroids. Acta Chir Scand 148: 1442–1444

Cohen HW, Gibson G, Alderman MH (2000) Excess risk of myocardial infarcion in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med 108: 2–8

Cook RJ, Sackett DL (1995) The number needed to treat: a clinically useful measure of treatment effect. Br Med J 310: 452–454

Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpä M, Jørum E, Serra J, Jensen TS (2004) EFNS guidelines on neuropathic pain assessment. Eur J Neurol 11: 153–162

DeGrandis D, Minardi C (2002) Acetyl-L-carnitine (levacecarnine) in the treatment of diabetic neuropathy. A long-term, randomised, double-blind, placebo-controlled study. Drugs RD 3: 223–231

Duhmke RM, Cornblath DD, Hollingshead JRF (2004) Tramadol for neuropathic pain (Cochrane review). John Wiley & Sons, Chichester (The Cochrane Library, Issue 2)

Dworkin RH, Corbin AE, Young JP, Sharma U, LaMoreaux L, Bockbrader H, Garofalo EA, Poole RM (2003) Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 60: 1274–1283

Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A (2001) Lamotrigine reduces painful diabetic neuropathy. A randomized, controlled study. Neurology 57: 505–509

Ertas M, Sagduyu A, Arac N, Uludag B, Ertekin C (1998) Use of levodopa to relieve pain from painful symmetrical diabetic polyneuropathy. Pain 75: 257–259

Finnerup NB, Johannesen IL, Sindrup SH, Bach FW, Jensen TS (2001) Pain and dysaesthesia in patients with spinal cord injury: a postal survey. Spinal Cord 39: 256–262

Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS (2002) Lamotrigine in spinal cord injury pain: a randomized controlled trial. Pain 96: 375–383

Fromm GH, Terrence CF, Chattha AS (1984) Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. Ann Neurol 15: 240–244

Galer BS, Rowbotham MC, Perander J, Friedman E (1999) Topical lidocaine relieves post-herpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain 80: 533–538

Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC (2002) The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. Clin J Pain 18: 297–301

Gee NS, Brown JP (1996) The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2-delta subunit of a calcium channel. J Biol Chem 271: 5768–5776

Gimbel JS, Richards P, Portenoy RK (2003) Controlled-release oxycodone for pain in diabetic neuropathy. A randomized controlled trial. Neurology 60: 927–934

Gobelet C, Waldburger M, Meier JL (1992) The effect of adding calcitonin to physical treatment of reflex sympathetic dystrophy. Pain 48: 171–175

Gomez-Perez FJ, Rull JA, Dies H, Rodriquez-Rivera JG, Gonzalez-Baranco J, Lozano-Castaneda O (1985) Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy: a double blind cross over study. Pain 23: 395–400

Gorson KC, Schott C, Herman R, Ropper AH, Rand WM (1999) Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry 66: 251–252

Hanna MH, Peat SJ (1989) Ketanserin in reflex sympathetic dystrophy. A double-blind placebo controlled cross-over trial. Pain 38: 145–150

Harati Y, Gooch C, Swenson M, Edelman S, Greene D, Raskin P, Donofrio P, Cornblath D, Sachero R, Kamin M (1998) Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 50: 1842–1846

Harati Y, Gooch C, Swenson M, Edelman SV, Greene D, Raskin P, Donofrio P, Cornblath D, Olson WH, Kamin M (2000) Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy. J Diabetes Complications 14: 65–70

Hord AH, Rooks MD, Stephens BO, Rogers HG, Fleming LL (1992) Intravenous regional bretylium and lidocaine for the treatment of reflex sympathetic dystrophy; a randomized double-blind study. Anesth Analg 74: 808–821

Huse E, Larbig W, Flor H, Birbaumer N (2001) The effect of opioids on phantom limb pain and cortical reorganization. Pain 90: 47–55

Kalso E, Tasmuth T, Neuvonen PJ (1995) Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain 64: 293–302

Killian JM, Fromm GH (1968) Carbamazepine in the treatment of neuralgia: use of side-effects. Arch Neurol 19: 129–136

Kingery WS (1997) A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. Pain 73: 123–139

Kishore-Kumar R, Max MB, Schafer SC, Gaughan AM, Smoller B, Gracely RH, Dubner R (1990) Desipramine relieves postherpetic neuralgia. Clin Pharmacol Ther 47: 305–312

Kochar DK, Jain N, Agarwal RP, Srivastava T, Agarwal P, Gupta S (2002) Sodium valproate in the management of painful neuropathy in type 2 diabetes – a randomized placebo controlled study. Acta Neurol Scand 106: 248–252

Kochar DK, Rawat N, Agrawal RP, Vyas A, Beniwal R, Kochar SK, Garg P (2004) Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. QJM 97: 33–38

Kvinesdal B, Molin J, Frøland A, Gram LF (1984) Imipramine treatment of painful diabetic neuropathy. J Am Med Assoc 251: 1727–1730

Langohr HD, Stöhr M, Petruch F (1992) An open and double blind cross over study on the efficacy of clomipramine (Anafranil) in patients with painful mono- and polyneuropathies. Eur Neurol 21: 309–317

Leijon G, Boivie G (1989) Central post-stroke pain – a controlled trial of amitriptyline and carbamazepine. Pain 36: 27–36

Levendoglu F, Ogun CO, Ozerbil O, Ogun TC, Ugurlu H (2004) Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. Spine 29: 743–751

Lindstrom P (1987) The analgesic effect of carbamazepine in trigeminal neuralgia. Pain 28 [Suppl 4]: S85

Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, Dubner R (1987) Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology 37: 589–596

Max MB, Schafer SC, Culnane M, Smoller B, Dubner R, Gracely RH (1988) Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. Neurology 38: 1427–1432

Max MB, Kishore-Kimar R, Schafer SC, Meister B, Gracely R, Smoller B, Dubner R (1991) Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. Pain 45: 3–9

McClean GJ (1999) Intravenous infusion of phenytoin relieves neuropathic pain: a randomized, double-blinded, placebo controlled, crossover study. Anesth Analg 89: 985–988

McQuay HJ, Tramèr M, Nye BA, Caroll D, Wiffen PJ, Moore RA (1996) A systematic review of antidepressants in neuropathic pain. Pain 68: 217–227

McQuay HJ, Moore RA (1998) An evidence based resource for pain relief. Oxford University Press, Oxford, 252 pp

Meier T, Wasner G, Faust M, Kuntzer T, Ochsner F, Hueppe M, Bogousslavsky J, Baron R (2003) Efficacy of lidocaine patch 5% in the treatment of focal neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. Pain 106: 151–158

Meyer-Rosberg K, Burckhardt CS, Huizar K, Kvarnstrom A, Nordfors LO, Kristofferson A (2001a) A comparison of the SF-36 and Nothingam Health Profile in patients with chronic neuropathic pain. Eur J Pain 5: 391–403

Meyer-Rosberg K, Kvarnstrom A, Kinnman E et al. (2001b) Peripheral neuropathic pain-a multidimensional burden for patients. Eur J Pain 5: 379–389

Morello CM, Leckband DG, Stoner CP, Moorhouse DF, Sahagian GA (1999) Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy. Arch Intern Med 159: 1931–1937

Morley JS, Bridson J, Nash TP, Miles JP, White S, Makin MK (2003) Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. Palliative Med 17: 576–587

Nicol CF (1969) A four-year double blind study of Tegretol in facial pain. Headache 1: 54–57

Pandey CK, Bose N, Garg C, Singh N, Baronia A, Agarwal A, Singh PK, Singh U (2002) Gabapentin for the treatment of pain in Guillain-Barré syndrome: a double-blinded, placebo-controlled, cross-over study. Anesth Analg 95: 1719–1723

Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ (2001) Treatment of reflex sympathetic dystrophy (CRPS Type 1): a research synthesis of 21 randomized clinical trials. J Pain Symptom Manage 21: 511–526

Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, Royal RM, Max MB (2002) Opioids versus antidepressants in postherpetic neuralgia. Neurology 59: 1015–1021

Rauck RL, Eisenach JC, Jackson K, Young LD, Souther J (1993) Epidural clonidine treatment for refractory reflex sympathetic dystrophy. Anesthesiology 81: 1163–1169

Rice AS, Maton S (2001) Gabapentin in postherpetic neuralgia. A randomized, double-blind, placebo controlled study. Pain 94: 215–224

Richeimer SH, Bajwa ZH, Kachramann SS, Ransil BJ, Warfield CA (1997) Utilization patterns of tricyclic antidepressants in a multidisciplinary pain clinic: a survey. Clin J Pain 13: 324–329

Rockliff BW, Davis EH (1966) Controlled sequential trials of carbamazepine in trigeminal neuralgia. Arch Neurol 15: 129–136

Rowbotham MC, Davies PS, Fields HL (1995) Topical lidocaine gel relieves postherpetic neuralgia. Ann Neurol 37: 246–253

Rowbotham MC, Davies PS, Verkempinck C, Galer BS (1996) Lidocaine patch: a double-blind controlled study of a new treatment method for post-herpetic neuralgia. Pain 65: 39–44

Rowbotham MC, Harden N, Stacey B, Bernstein P, Magnus-Miller L (1998) Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 280: 1837–1842

Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D (2003) Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med 348: 1223–1232

Sabatowski R, Galvez R, Cherry DA, Jackuot F, Vincent E, Maisonobe P, Versavel M, 1008-045 Study Group (2004) Pregabalin reduces pain and improves sleep and mood disturbances in patients with postherpetic neuralgia: results of a randomized, placebo-controlled clinical trial. Pain 109: 26–35

Sanchez C, Hyttel J (1999) Comparison of the effects of antidepressants and their metabolites on the re-uptake of biogenic amines and on receptor binding. Cell Mol Neurobiol 19: 467–489

Semenchuk MR, Sherman S, Davis B (2001) Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. Neurology 57: 1583–1588

Serpell M (2002) Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. Pain 99: 557–566

Siddal PJ, Molloy AR, Walker S, Mather LE, Rutkowski SB, Cousins MJ (2000) The efficacy of intrathecal morphine and clonidine in treatment of pain after spinal cord injury. Anest Analg 91: 1493–1498

Simpson DM, Olney R, McArthur JC, Khan A, Godbold J, Ebel-Frommer K (2000) A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. Neurology 54: 2115–2119

Simpson DM, McArthur JC, Olney R, Clifford D, So Y, Ross D, Baird BJ, Barrett P, Hammer AE; and the Lamotrigine HIV Neuropathy Study Team (2003) Lamotrigine for

HIV-associated painful sensory neuropathies. A placebo-controlled trial. Neurology 60: 1508–1514

Sindrup SH, Ejlertsen B, Frøland A, Sindrup EH, Brøsen K, Gram LF (1989) Imipramine treatment in diabetic neuropathy: relief of subjective symptoms without changes in peripheral and autonomic nerve function. Eur J Clin Pharmacol 37: 151–153

Sindrup SH, Gram LF, Brosen K, Eshoj O, Mogensen EF (1990a) The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 42: 135–144

Sindrup SH, Gram LF, Skjold T, Frøland A, Beck-Nielsen H (1990b) Concentration-response relationship in imipramine treatment of diabetic neuropathy symptoms. Clin Pharmacol Ther 47: 509–515

Sindrup SH, Gram LF, Skjold T, Grodum E, Brøsen K, Beck-Nielsen H (1990c) Clomipramine vs desipramine vs placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study. Br J Clin Pharmacol 30: 683–691

Sindrup SH, Bjerre U, Dejgaard A, Brosen K, Aaes-Jorgensen T, Gram LF (1992a) The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. Clin Pharm Ther 52: 547–552

Sindrup SH, Tuxen C, Gram LF, Grodum F, Skjold T, Brøsen K, Beck-Nielsen H (1992b) Lack of effect of mianserin on the symptoms of diabetic neuropathy. Eur J Clin Pharmacol 43: 251–255

Sindrup SH, Jensen TS (1999) Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 83: 389–400

Sindrup SH, Andersen G, Madsen C, Smith T, Brosen K, Jensen TS (1999) Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. Pain 83: 85–90

Sindrup SH, Jensen TS (2002) Pharmacologic treatment of pain in polyneuropathy. Neurology 55: 915–920

Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS (2003) Venlafaxine versus imipramine in painful polyneuropathy. A randomized, controlled trial. Neurology 60: 1284–1289

Sunderland S (1993) Brachial plexus injuries. Clin Neurol Neurosurg 95 [Suppl]: S1–S2

Tai Q, Kirshblum S, Chen B, Millis S, Johnston M, DeLissa JA (2002) Gabapentin in the treatment of neuropathic pain after spinal cord injury: a prospective, randomized, double-blind, crossover trial. J Spinal Cord Med 25: 100–105

Tasmuth T, Hartel B, Kalso E (2002) Venlafaxine in neuropathic pain following treatment of breast cancer. Eur J Pain 6: 17–24

Thomas DG, Gart J (1977) A table of exact confidence limits for differences and ratios of two proportions and their odds ratios. J Am Stat Assoc 72: 73–76

Turkington RW (1980) Depression masquerading as diabetic neuropathy. JAMA 243: 1147–1150

Varenna M, Zucchi F, Ghiringhelli D, Binelli L, Bevilacqua M, Bettica P, Sinigaglia L (2000) Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. J Rheumatol 27: 1477–1483

Vestergaard K, Andersen G, Gottrup H, Kristensen BT, Jensen JS (2001) Lamotrigine for central poststroke pain. A randomized controlled trial. Neurology 56: 184–190

Vrethem M, Boivie J, Arnquist H, Holmgren H, Lindstrom T, Thorell LH (1997) A comparison of amitriptyline and maprotiline in the treatment of painful polyneuropathy in diabetics and non-diabetics. Clin J Pain 13: 313–323

Wallace MS, Ridgeway BM, Leung AZ, Gerayli A, Yaksh TL (2000) Concentration-effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II. Anesthesiology 92: 75–83

Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J (1982) Amitriptyline versus placebo in postherpetic neuralgia. Neurology 32: 671–673

Watson CP, Chipman M, Reed K, Evans RJ, Birkett N (1992) Amitriptyline versus maprotyline in postherpetic neuralgia: a randomized, double-blind, crossover trial. Pain 48: 29–36

Watson CP, Babul N (1998) Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology 50: 1837–1841

Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J (2003) Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain 105: 71–78

Woolf CJ, Mannion RJ (1999) Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 353: 1959–1964

Yuen KC, Baker NR, Rayman G (2002) Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray. A double-blind placebo-controlled cross-over study. Diabetes Care 25: 1699–1703

Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL (1997) Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. Pain 73: 223–230

Zuurmond WW, Langendijk PN, Bezemer PD, Brink HE, de Lange JJ, van Loenen AC (1996) Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. Acta Anaesthesiol Scand 40: 364–367

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