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Pharmacologic treatment of neuropathic pain

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Abstract

There is currently no consensus concerning the optimal therapeutic stragegy for neuropathic pain, despite an increasing number of clinical trials demonstrating successful pain relief with several drugs. Treatments have generally been selected on the basis of evidence for efficacy in randomized placebo-controlled trials conducted in disease-based groups of patients, notably in postherpetic neuralgia and diabetic polyneuropathy. These studies plead in favour of the overall efficacy of tricyclic antidepressants, standard and newer antiepileptics, opioids, tramadol, systemic and topical local anaesthetics, and some NMDA receptor antagonists ; whereas evidence for efficacy is less for selective serotonin reuptake inhibitors, antiarrhythmics (mexiletine), and capsaicin. Pharmacological tests, notably therapeutic infusions, have been proposed for predicting the effectiveness of long-term treatments, but are not routinely performed. An analysis of the various neuropathic symptoms, aimed at selecting treatments targeted at mechanisms, may ultimately help the choice of different pharmacologic agents.

Key words : Neuropathic pain ; pharmacologic treatment ; evidence-based medicine ; symptom-based treatment ; mechanism-based treatment.

Introduction

Neuropathic pain (i.e., pain associated with injury of the peripheral or central nervous system) generally presents with a combination of painful and nonpainful symptoms, including : spontaneous ongoing (notably burning) pain, paroxysmal pain, allodynia, hyperalgesia, aftersensation, summation of pain, paresthesias, dysesthesias, and sensory deficit in the painful area. Despite an increasing number of clinical trials demonstrating successful pain relief with several agents, the pharmacologic treatment of neuropathic pain still represents a challenge for the clinician, since response to therapy is generally incomplete and many drugs used for this condition induce significant side effects. However, therapeutic advances have recently been obtained following the introduction of better tolerated treatments, which include newer antiepileptics and topical anaesthetics. Furthermore, owing to a better understanding of neuropathic pain, there is a trend towards the development of more specific therapeutic strategies, based on precise identification of the various neuropathic pain symptoms and where the aim is to select treatments targeting mechanisms.

This paper provides a review of the current pharmacologic treatments of neuropathic pain. We provide some recommendations as regards the initiation of pharmacotherapy and then present treatments with established efficacy on the basis of randomized controlled trials. Finally, we consider the various therapeutic strategies for neuropathic pain.

Initiation of therapy

Several issues should be considered when initiating pharmacologic treatment for neuropathic pain.

– Whenever possible, *preemptive or early management* should be envisaged. This especially concerns postherpetic neuralgia. Thus antiviral therapy has been shown to reduce the duration of zoster associated pain (see Alper and Lewis, 2000) and initial treatment with amitriptyline during the acute zoster phase may reduce the intensity of persistent postherpetic pain at 3 months (Bowsher, 1997).
– In order to improve compliance, *realistic expectations* should be set with the patients regarding the efficacy of treatments (which is often incomplete) and they should be informed about potential side effects. The physician should also keep in mind that most currently prescribed analgesics have not received official authorization for neuropathic pain in Europe, with the exception of gabapentin (in some European countries). The importance of these issues has been confirmed in a recent systematic survey of pain patients receiving antidepressants, showing that the reading of information leaflets may decrease adherence because of the fear of side-effects, addiction, and of the type of drugs prescribed (Cedrachi *et al.*, 1999). Conversely, it has been shown that counselling about antidepressant

treatment significantly improved adherence in depressive patients (Peveler *et al.*, 1999), and this probably also applies to pain patients.
- Systemic treatments should be initiated using *individual titration* taking into account efficacy or intolerable side effects.
- Finally, pharmacotherapy should always be viewed in the context of *global management* of patients with neuropathic pain, which includes treatment of the affective disorders associated with pain (depression, anxiety) and management of disability. Noninvasive treatments such as transcutaneous electrical nerve stimulation may also be prescribed as first choice, especially if the painful area is limited.

Treatments with established efficacy for neuropathic pain

Neuropathic pain is generally refractory to conventional analgesics, such as acetaminophen, aspirin, and nonsteroidal anti-inflammatory agents. Other pharmacologic classes have been shown to be effective in the treatment of such pain on the basis of randomized controlled trials (see Attal, 1999 ; Sindrup and Jensen, 1999, 2000 ; Kingery, 1997). They include systemic treatments (notably antidepressants, older and newer antiepileptics, opioids, local anaesthetics and derivatives, NMDA receptor antagonists) and topical agents (notably capsaicin and local anaesthetics). Furthermore, intrathecal therapy may be proposed in refractory cases.

Systemic treatments

Antidepressants

It is now largely established that antidepressants induce specific analgesic activity, which is generally considered to relate mainly to a central blockade of monoamine reuptake (serotonin and/or noradrenalin), resulting in enhancement of the descending monoaminergic inhibitory pathways (Max, 1994). However, other mechanisms have been proposed, such as blockade of adrenergic receptors on regenerating sprouts, NMDA antagonistic effects, action on endogenous opioid systems, and sodium channel blockade.

The efficacy of various tricyclic antidepressants (TCAs) (imipramine, clomipramine, amitriptyline, desipramine, nortriptyline, maprotiline) versus placebo has been confirmed in several neuropathic pain conditions, such as diabetic neuropathy, postherpetic neuralgia and central poststroke pain (McQuay *et al.*, 1996 ; Collins *et al.*, 2000). These drugs are considered to be more effective for continuous pain, but effects on paroxysmal pain and on self-assessment of allodynia have also been reported. TCAs generally display similar overall efficacy, whereas selective serotonin reuptake inhibitors (SSRIs) are generally less effective (Ansari, 2000). In diabetic neuropathy, citalopram and paroxetine were shown to be significantly effective versus placebo, whereas fluoxetine is ineffective. A mixed inhibitor of noradrenaline and serotonin reuptake, venlafaxine, has been shown to alleviate thermal allodynia in mononeuropathic rats and may be effective in painful neuropathies on the basis of small open trials (Kaminski-Price *et al.*, 2000 ; Pernia *et al.*, 2000).

There is considerable interindividual variability in the optimal dosage of antidepressants for pain relief and contradictory results have been reported concerning correlation with plasma levels. However, a dose-response relationship has been reported for amitriptyline in chronic pain. The average dosage of TCAs used in trials is 75 mg/day, whereas that of the SSRIs is 40 mg/day. Treatment guidelines recommend initiating TCAs at low dosages (10-20 mg/day) and increasing titration weekly to intolerable side-effects or efficacy (Watson, 1995 ; Bowsher, 1995). The onset of efficacy is usually 4-5 days to 1 week after reaching optimal dosages. Currently there are no data on the optimal duration of treatment. It is recommended to keep dosages stable for at least several months if pain has abated and then attempt a reduction.

The main limitations concerning the use of TCAs relate to their unfavorable side-effect profile. Most patients do not reach the optimal dosage that would be effective for their pain (McQuay *et al.*, 1996). More selective drugs generally have a better side-effect profile. Nortriptyline, a noradrenergic metabolite of amitriptyline, has shown similar efficacy but less sedation and orthostatic hypotension than amitriptyline, and has therefore been recommended for first-line therapy (Watson *et al.*, 1998). SSRIs may be beneficial as first-line therapy in elderly patients, because of a lower incidence of anticholinergic side-effects (McQuay *et al.*, 1996).

Antiepileptics

Standard antiepileptics

The antiepileptics carbamazepine and phenytoin are generally considered to act as sodium channel blockers (Tanelian and Brose, 1991) and may therefore reduce ectopic activity in the peripheral nerves or dorsal root ganglion, one of the major peripheral mechanisms of neuropathic pain. Despite their broad utilization in various neuropathic pain syndromes, standard antiepileptics have only been extensively studied in trigeminal neuralgia, where they are considered a choice treatment (McQuay *et al.*, 1995 ; Tremond-Lucas *et al.*, 2000). In diabetic neuropathy, carbamazepine proved effective in two small placebo-controlled trials, whereas the results obtained with phenytoin are less consistent (the drug was effective in one

small trial, but ineffective in the longest trial, lasting for 23 weeks). The efficacy of these antiepileptics is generally disappointing in central pain, with negative results for carbamazepine and valproate. No placebo-controlled study has been conducted with clonazepam, although this drug is extensively used in France, mostly because of its sedative and anxiolytic properties.

In most studies, standard antiepileptics appear to be effective not only on pain but also on paresthesias and dysesthesias. Although they have been reported to specifically relieve lancinating pain of various etiologies, a recent placebo-controlled study of patients with peripheral neuropathy showed that phenytoin infusion was equally effective on several symptoms, including burning sensation, numbness, and shooting pain (McCleane, 1999).

The incidence of side-effects with standard antiepileptics is usually high (25-50% in clinical trials) (McQuay *et al.*, 1995). These effects usually consist of drowsiness, dizziness, and somnolence. In addition, carbamazepine induces significant enzymatic induction with a risk of significant drug interaction (Virani *et al.*, 1997). Titration should begin with a low initial dosage (100 mg/day for carbamazepine, 150 mg/day for phenytoin) and be increased to efficacy or intolerable side-effects. The average analgesic dosages are 600 mg/day for carbamazepine and 300 mg/day for phenytoin. However, higher dosages have been used (up to 1600 mg/day for carbamazepine and 600 mg/day for phenytoin).

Oxcarbazepine

Oxcarbazepine is a keto-analogue of carbamazepine with a distinct pharmacokinetic profile, that induces less enzyme induction. This drug has been shown to be effective in trigeminal neuralgia and may also be beneficial for other neuropathic pains (Beydoun, 2000). Oxcarbazepine may be better tolerated than carbamazepine and appears to be an effective substitute in patients intolerant for carbamazepine or with significant drug-drug interaction.

Lamotrigine and topiramate

Lamotrigine and topiramate possess additional mechanisms of action as compared to standard antiepileptics, which may account for a broader spectrum of efficacy. Lamotrigine acts by blocking sodium channels and reducing the release of glutamate. Topiramate also blocks sodium channels and may act on AMPA (amino-3-hydroxy-5-methyl-4-isoxalon)/kainate receptors (Meldrum, 1996).

Recent double-blind studies have reported a significant efficacy for lamotrigine in refractory trigeminal neuralgia - in combination with carbamazepine (Zakrzewska *et al.*, 1998)- painful diabetic neuropathy, HIV-related neuropathy, and central poststroke pain (McCleane, 2000 ; Simpson *et al.*, 2000 ; Vestergaard *et al.*, 2001). However, negative results have been reported in one study, possibly due to insufficient dosages (McCleane, 1999b). In fact, it seems that the drug must be titrated up to 200 to 500 mg/day to reach clinically significant efficacy (McCleane, 2000). The initial titration must be very slow in order to minimize the risk of serious complications, such as skin rashes.

Open-label pilot studies have also suggested efficacy of topiramate in painful neuropathies. Specific side-effects include cognitive impairment, renal lithiasis, and weight loss.

Gabapentin

Gabapentin, a cyclic GABA analogue, has multiple sites of action in the central nervous system, that may account for its analgesic properties : notably it potentiates GABAergic transmission and binds to a subunit of calcium channels, the alpha2delta subunit, common to all calcium channels types. Two large-scale placebo-controlled studies have demonstrated the significant overall efficacy of this drug (titrated to 3600 mg/day) in patients with postherpetic neuralgia and diabetic neuropathy (Rowbotham *et al.*, 1998 ; Backonja *et al.*, 1998). Quality of life and sleep also improved significantly under active treatment. Most side-effects occurred during titration and were usually mild to moderate, consisting of dizziness and somnolence (about one fourth of patients). In a double-blind trial for pain due to diabetic neuropathy, gabapentin (900-1800 mg/d) was found to be as effective as amitriptyline (25-75 mg/day) (Morello *et al.*, 1999). Gabapentin is now largely used in clinical practice in various pain conditions because of its favorable side-effect profile and absence of drug interaction (Magnus, 1999 ; Treimond-Lucas *et al.*, 2000). It may be effective for several components of neuropathic pain, including paroxysmal pain, and brush-induced allodynia, and may have a broad-spectrum analgesic activity in various neuropathic pain conditions, including central pain (Attal *et al.*, 1998). Gabapentin has recently been approved in several European countries for the treatment of neuropathic pain. Dosages used vary from 1200 mg/day to 3600 mg/day, and the optimal dosage appears to be 1800 mg/day.

Opioids and tramadol

Although there is a large consensus concerning the effectiveness of *opioids* in nociceptive pain, their efficacy in neuropathic pain was debatable until recent years (Portenoy, 1996 ; Dellemijn, 1999). However, on the basis of several controlled studies, it is now generally admitted that these drugs may relieve neuropathic pain, provided that sufficient doses are administered, using individual

titration (refs. in Dellemijn, 1999 ; Flor *et al.*, 2001). In fact, the doses necessary to obtain an analgesic effect in neuropathic pain have been reported to be twice as high as those usually required to relieve nociceptive pain (Benedetti *et al.*, 1998). The effects of opioids are usually considered weaker in central pain (Eide *et al.*, 1995 ; Attal *et al.*, 2000b), but a subgroup of such patients may benefit from this treatment (Attal *et al.*, 2000b).

Few studies have used long-term administration of strong opioids in neuropathic pain. Dellemijn *et al.* (1998) reported a 2 year follow-up study of patients treated with transdermal fentanyl after an initial trial of intravenous fentanyl. In their study, 35% of patients stopped treatment prematurely because of side-effects and only 17% reported significant improvement at 2 years. We recently observed similar results in an 18 month follow-up study of patients with central pain receiving sustained release morphine (Attal *et al.*, 2000b).

Tramadol is a centrally acting analgesic drug which probably acts through both monoaminergic and opioid mechanisms and with a low risk for tolerance. In two recent placebo-controlled studies, tramadol (200-400 mg/day) was significantly effective in diabetic neuropathic pain and painful polyneuropathy (Sindrup *et al.*, 1999 ; Harati *et al.*, 1999) with persisting effect over a 6 month follow-up period (Harati *et al.*, 2001). In these studies, the drug significantly relieved ongoing pain and paresthesias and improved self-assessment of touch-evoked allodynia. Most patients presented with side-effects, including tiredness, dizziness, dry mouth, sweating, constipation, micturition difficulties, and nausea.

Local anesthetics and derivatives

Local anaesthetics and derivatives (antiarrhythmics) are considered to act mainly as sodium channel blockers (Tanelian and Brose, 1991 ; Brau *et al.*, 2001), although they may also display central action notably at the spinal level.

Intravenous lidocaine (1-5 mg/kg over 30 min to 2 h) has been shown to relieve spontaneous pain and brush-induced allodynia in patients with various peripheral nerve lesions (Kalso *et al.*, 1998 ; Wallace *et al.*, 2000b ; Baranowski *et al.*, 1999 ; Rowbotham *et al.*, 1991), and presents moderate analgesic effects in central pain (Attal *et al.*, 2000a). Duration of lidocaine action is variable, with only a few patients benefiting from long-term efficacy, lasting for up to 3 weeks in one study (Kalso *et al.*, 1998). Side-effects of lidocaine infusion consist of lightheadedness, somnolence, nausea, and perioral numbness, but severe cardiovascular side-effects such as bradycardia and convulsions are potential complications.

The antiarrhythmic *mexiletine*, a structural analogue of lidocaine, has been shown to be effective in treatment of pain due to various peripheral nerve injuries but negative results have also been reported, possibly because of the drug's poor therapeutic ratio (Kalso *et al.*, 1998 ; Wallace *et al.*, 2000a). Dosages administered range from 450 mg/day to 900 mg/day, but individual titration should be performed. Side-effects generally consist of nausea, dizziness, headache, sleep disturbances and fatigue. Although no serious cardiac effects have been reported in patients with neuropathic pain, transient tachycardia and palpitations have occurred and the potential cardiotoxic effects warrant caution when this drug is used in elderly patients.

NMDA receptor antagonists

Because of their major role in the development of central sensitization after nerve injury, NMDA receptor antagonists have been studied for the treatment of various neuropathic pains (Fisher *et al.*, 2000). One of the most commonly used NMDA antagonists is ketamine, a traditionally used anesthetic that binds noncompetitively to the phencyclidine site of the NMDA receptor. Results of several double-blind placebo-controlled trials have shown intravenous or subcutaneous ketamine (0.15 - 0.2 mg/kg bolus, 0.3 mg/kg/h infusion) to be significantly effective in postherpetic neuralgia, peripheral nerve injuries, phantom limb pain, and central pain. However, use of this treatment is limited by intolerable side-effects, notably psychomimetic effects. Clinical experience with oral ketamine in the treatment of neuropathic pain is limited and interesting results have been reported in only a very small proportion of patients due to side-effects (Haines and Gaines, 1999).

Dextromethorphan, amantadine, memantine, and riluzole produce weaker NMDA blockade than ketamine and results have been disappointing (Nicolajsen *et al.*, 2000 ; Nelson *et al.*, 1998 ; Galer *et al.*, 2000 ; Gilron *et al.*, 2000). In fact, positive results were only obtained for high-dose dextrometorphan in diabetic polyneuropathy and for intravenous infusion of amantadine in cancer polyneuropathy (Nelson *et al.*, 1998 ; Pud *et al.*, 1999). Newer promising compounds now undergoing phase II/III trials include more selective NMDA antagonists, which act on the strychnine-insensitive glycine site of the NMDA receptor, and other glutamate receptor antagonists.

Other systemic treatments

Other pharmacologic treatments have been studied for neuropathic pain, although less commonly used (Attal, 1999).

– Significant results have been reported with systemic *clonidine* in postherpetic neuralgia.

However, the drug induces numerous side-effects (somnolence, dizziness).
- Oral *nonsteroidal anti-inflammatory* drugs proved effective in diabetic neuropathy but ineffective in postherpetic neuralgia and radiculopathy.
- The efficacy of *baclofen* has been clearly established in trigeminal neuralgia but was not confirmed in other peripheral neuropathies.
- *Levodopa* recently proved superior to placebo in painful diabetic neuropathy, which may be due to an action at the spinal level or at the supraspinal level on the descending noradrenergic pathways.
- *Sympatholytics* have essentially been used in Complex Regional Pain Syndromes, but evidence for their efficacy in neuropathic pain is lacking (Kingery, 1997).

Topical agents

Several topical agents have been studied in pain due to peripheral nerve injury, notably diabetic neuropathy and postherpetic neuralgia. These drugs offer significant advantages over systemic therapy for elderly patients because of their generally better safety profile, especially when the area of pain is limited.

Local anaesthetics

Several double-blind placebo-controlled trials have demonstrated the effectiveness of *topical patches and lidocaine gel* applied to painful skin in postherpetic neuralgia, even in refractory patients (Galer *et al.*, 1999 ; Rowbotham *et al.*, 1996). These treatments may also be beneficial for other types of neuropathic pain (Devers and Galer, 2000). Lidocaine patches (Lidoderm®) have recently been approved by the FDA for the treatment of postherpetic neuralgia. The advantages of these treatments are the lack of systemic side-effects and ease of application (once daily) without dose titration. An eutectic mixture of lidocaine and prilocaine (EMLA®) cream also seems to be effective in these patients, particularly those with paroxysmal pain and mechanical allodynia, on the basis of open studies (Attal, 1999). Because of their excellent safety profile, topical anesthetics have therefore been recommended as first-line therapy in patients with postherpetic neuralgia (Galer *et al.*, 1999 ; Rowbotham *et al.*, 1996).

Capsaicin

Capsaicin, the pungent component of chili peppers, is a neurotoxin that presents analgesic properties. The mechanisms of its analgesic action probably relate to its effect on C nociceptive fibers : more specifically, capsaicin binds to a specific vanilloid receptor, the recently cloned VR-1 receptor (Caterina *et al.*, 1997), which induces initial activation (responsible for the burning sensation) and subsequent desensitization of nociceptors. Several double-blind placebo-controlled studies have demonstrated the effectiveness of capsaicin cream (0.025 - 0.075%) in peripheral neuropathies, notably diabetic neuropathy and postherpetic neuralgia, and this treatment is currently approved in the USA for the treatment of postherpetic neuralgia (Zostrix®). However, negative results have also been reported. In addition, since most patients present with burning sensation and erythema, the blinding is probably unmasked in studies using a neutral placebo. In fact, in the only study using an "active" placebo that caused erythema, capsaicin was not found to be superior to placebo, because of a high placebo effect (64%) (Low *et al.*, 1995).

Use of capsaicin is limited by the practical difficulties of treatment (i.e., need for multiple daily applications) and the burning sensation, which may lead to premature arrest of the drug in up to one third of patients. Coadministration of lidocaine ointment has been advocated for severe capsaicin-related pain. Applications have to be repeated four times a day and efficacy is generally obtained within 2 to 4 weeks.

Because of its major limitations and inconsistent efficacy, capsaicin has only limited use in the treatment of neuropathic pain and should only be prescribed as an adjuvant therapy when other treatments have failed. The best theoretical indications for capsaicin seem to be the pain and hyperalgesia (thermal and mechanical) elicited by C nociceptor sensitization.

Other topical agents

Aspirin/diethyl ether mixture proved effective in postherpetic neuralgia but is difficult to use in clinical practice, whereas aspirin in chloroform lotion is not more effective than placebo in chlorophorm (Attal, 1999).

Transdermal clonidine has been studied in diabetic neuropathic pain and appears to be significantly more effective than placebo in a subgroup of patients, notably those with shooting pains (Attal, 1999).

Intrathecal administration

Drugs may also be administered intrathecally in patients with refractory neuropathic pain. However, few systematic controlled studies have evaluated the benefit of such treatments.

Intrathecal baclofen may be effective in refractory neuropathic pain, notably due to spinal cord injury, but only case reports have been published so far.

Epidural clonidine was reported to be significantly effective in refractory neuropathic cancer pain and may be combined with opioids.

Intrathecal methylprednisolone delivered weekly for up to four weeks has recently been found effective on spontaneous pain and allodynia, versus lidocaine and no treatment, in a large randomized double-blind study including 277 patients with refractory postherpetic neuralgia (Kotani *et al.*, 2000). There were no complications related to this treatment, in particular no arachnoiditis. According to the authors, the effects of methylprednisolone in this study are mainly mediated by the anti-inflammatory action of the drug at the spinal cord level.

Spinally administered ziconotide, a neuron-specific N-type calcium channel blocker, has been found effective in refractory chronic pain on the basis of several double-blind randomized trials including patients with neuropathic pain, and has recently received FDA approval for chronic pain. This drug is not associated with development of tolerance after prolonged use and may be advantageous as compared with currently available intrathecal therapies for intractable neuropathic pain (Jain, 2000).

Combination of analgesics

Multiple analgesic combinations are largely used in clinical practice in neuropathic pain, based on past experimentation and case reports, although there are currently no randomized double-blind studies comparing such combinations with monotherapy. Therefore, there is no need to systematically prescribe multiple analgesics as first-line therapy, because of the risk of cumulative side effects, and of drug-drug interactions (Virani *et al.*, 1997). However, there are at least two conditions where such combinations may be appropriate.

First, a combination of analgesics may be required to improve the balance between analgesia and adverse effects, notably in the case of *additive or synergistic* effects. Thus, NMDA receptor antagonists potentiate the effects of opioids in animals and may reduce tolerance to morphine (Dickenson, 1997). In the USA, a combination of dextromethorphan and morphine (MorphiDex®), proved effective for the treatment of moderate to severe chronic pain, including neuropathic pain, and may help significantly reduce morphine daily doses (Katz, 2000). Opioids may also be combined with other drugs. Thus, the anticonvulsant gabapentin has recently been shown to enhance the analgesic effect of morphine in acute experimental pain in healthy volunteers (Eckard *et al.*, 2000), and this deserves specific studies in neuropathic pain.

Second, a combination of analgesics may also be advocated because of c*omplementary effects on multiple pain symptoms or complementary action mechanisms*. Thus, it seems rational to prescribe topical agents in combination with centrally acting drugs. Antidepressants and antiepileptics are often used in combination and may have a broader spectrum of efficacy than each drug administered alone. However, this has not been confirmed in systematic studies.

Therapeutic strategy

There is currently no consensus concerning the optimal therapeutic strategy for neuropathic pain. Treatments are generally selected on the basis of evidence for efficacy and safety in randomized placebo-controlled studies conducted in disease-based groups of patients ("evidence-based medicine"). Pharmacological tests, notably therapeutic infusions, have been proposed to predict the effectiveness of long-term treatments. There is now a trend torwards developing more specific therapeutic strategies, based on an analysis of the various neuropathic symptoms and aimed at selecting treatments targeted at mechanisms (Woolf and Mannion, 1999 ; Woolf and Decosterd, 1999).

Evidence-based evaluation

The choice of treatments for neuropathic pain has traditionally been based on the evidence for efficacy in double-blind randomized trials, performed in patients classified according to their disease. These trials have essentially been conducted for postherpetic neuralgia and diabetic neuropathic pain and have attempted to evaluate in a simple fashion the effects of treatments on measures such as pain intensity, pain relief, patient satisfaction, drug preference, etc. Systematic reviews of such trials have evaluated the "Number Needed to Treat" to obtain one patient with at least 50% pain relief (McQuay *et al.*, 1995, 1996 ; Collins *et al.*, 2000 ; Sindrup and Jensen, 1999, 2000) (Table 1), and the "Number Needed to Harm" for adverse effects and drug related study withdrawal (McQuay *et al.*, 1995, 1996 ; Collins *et al.*, 2000). The NNT method allows sampling of large patient populations and accordingly permits a more precise evaluation of the efficacy of treatments. Because it is treatment-specific, it overcomes problems associated with highly variable placebo rates in pain trials. It may also reveal differences according to the aetiology of pain. As shown in Table 1, three major pharmacological classes present with favorable NNT in neuropathic pain : antidepressants, antiepileptics, and opioids/tramadol. However, only antidepressants and gabapentin have been studied in several types of neuropathic pain (postherpetic neuralgia, polyneuropathy). Other pharmacological classes such as mexiletine and capsaicin have much higher NNT and may only be considered as last choice, also because of their less

Table 1

Number Needed to Treat for different drug classes or drugs in the treatment of neuropathic pain
(oral or percutaneous administration only)
Adapted from : Sindrup and Jensen, 1999, 2000

NNT	Polyneuropathy	n-active n-placebo	Postherpetic neuralgia	n-active n-placebo	Central pain	n-active n-placebo
TCAs	2.6	266/277	2.3	77/68	1.7 (1 study)	14/15
SSRIs	6.7*	81/81				
Phenytoin, CBZ	2.5**	68/68			3.4 (CBZ) (1 study)	14/15
Gabapentin	4.1	119/116	3.2	109/116		
Mexiletine	38***	79/81			no dichotomous data	
Opioids		–	2.5 (oxycodone)	38/38		
Tramadol	3.4	97/97				
Capsaicin	5.9	183/204	5.3	16/16		
L-Dopa	3.4	14/11				
Dextrometorphan	1.9	13/13	NA	13/13	NA	

n-active, n-placebo : total number of patients on active and placebo treatment for which the NNT was calculated.
NA : non active
TCA : tricyclic antidepressants
SSRI : Selective serotonin reuptake inhibitors
CBZ : carbamazepine
* The NNT for paroxetine was 2.9 versus 7.7 for citalopram
** These data were derived from one study in each group and one negative study (concerning phenytoin) was not included in the analysis in the absence of dichotomous data.
*** This value may be biased due to the lack of dichotomous data in most trials.

favorable side-effect profile or practical difficulties in clinical use (Table 1).

The NNT method has several major limitations and biases. First, it should always be calculated for a sufficiently large number of patients evaluated in several double-blind trials, since a favorable NNT score may simply result from one positive trial including a small number of patients. For instance, levodopa has an NNT of 3.4 in diabetic neuropathy, which is similar to that of antiepileptics and tramadol. However, this drug has only been evaluated in a small placebo-controlled study in 14 patients, whereas the number of patients receiving antiepileptics or tramadol in double blind trials is consistently higher (Table 1). Second, the calculation of NNT is performed with dichotomous data in which only the number of patients with at least 50% pain relief is evaluated. However, several well conducted studies do not provide any dichotomous data and thus cannot be considered in the calculation of the NNT, which may lead to important bias. In particular, the NNT for mexiletine is very high since several positive trials could not be included in the analysis. Furthermore, other assessments, such as the proportion of patients with 30% benefit may be clinically relevant, notably in the case of refractory pain and are not taken into account in the NNT method. Third, the NNT by itself is not sufficient to provide recommendations for therapeutic choice in neuropathic pain, since it does not consider the side- effect profile of the drug which is evaluated by the NNH. Finally, and most importantly, the NNT only evaluates one dimension of neuropathic pain, i.e., the spontaneous ongoing pain, and does not take into account the efficacy of treatments on other components of pain, such as allodynia and paroxysmal pain. Therefore, other measures of NNT including other components of pain should be used in the future to allow more satisfactory inter-drug efficacy comparisons.

The NNH could only be calculated for antidepressants and antiepileptics in a subset of publications providing dichotomous data. The NNT for minor adverse effects is about 3 for antiepileptics and antidepressants, whereas the NNH for severe side-effects (drug-related withdrawals) is 17 for tricyclics, but not different from placebo for antiepileptics (Collins *et al.*, 2000).

Pharmacologic tests

Infusion tests

Several pharmacologic infusion tests have been advocated as predictive of the efficacy of chronic analgesic treatment but few appear to be really helpful in clinical practice (Galer *et al.*, 1996 ; Dellemijn, 1999 ; Canavero and Bonicalzi, 1999 ; Raja *et al.*, 1991). Use of lidocaine infusions may predict the efficacy of oral mexiletine according to some authors (Galer *et al.*, 1996), but this has not been confirmed by others, at least in central pain (Attal *et al.*, 2000). Intravenous opioid infusions (fentanyl, morphine) may be predictive of responsiveness to long-term opioids, since most patients who fail to respond to acute opioids do not subsequently respond to transdermal or oral opioids. However, a majority of those who initially respond to the infusion test discontinue the use of opioids after several months, mainly because of side-

effects (Dellemijn *et al.*, 1998 ; Attal *et al.*, 2000). Use of phentolamine infusion tests to predict responsiveness to sympathetic nerve blocks has been recommended (Arner, 1991 ; Raja *et al.*, 1991), but negative results have been reported (Verdugo *et al.*, 1994). Finally, some authors have recommended the use of acute administration of NMDA antagonists, such as ketamine, for predicting responsiveness to oral NMDA antagonists (ketamine, amantadine) or analogues such as lamotrigine (which blocks glutamatergic release) (Canavero and Bonicalzi, 1998). However, this has not been confirmed by specific studies.

Local anaesthetic blockade

In some patients with peripheral nerve injury pain, placebo-controlled local anaesthetic blockade may probably be helpful to detect those who will further respond to topical anaesthetics, although this has not been confirmed by systematic prospective studies. Relief of pain and allodynia by such blocks suggests that these symptoms are primarily mediated by peripheral mechanisms (Fields *et al.*, 1998). Further systematic studies should be performed in order to confirm the validity of this approach in patients with pain due to peripheral nerve injuries, notably in painful mononeuropathies with limited painful area.

Symptom-based and mechanism-based treatment

Although traditional double-blind trials have been of major importance for confirming the overall efficacy of treatments used for neuropathic pain, they have generally been based on a simple and global measure of pain and therefore have generally not provided sufficient information concerning the effects of drugs on the various neuropathic pain symptoms. Therefore, a symptomatic approach, based on a detailed analysis of the components of pain and deficits, appears to be important for assessing treatment outcome (Table 2). This analysis is currently best performed by using quantitative sensory tests but may probably be simplified in the future owing to the development of specific self-questionnaires. It appears to be particularly helpful for revealing specific anti-allodynic or anti-hyperalgesic effects of treatments (Table 2) and also has pathophysiological implications. Thus, double-blind trials in patients with neuropathic pain have demonstrated similar efficacy of the NMDA antagonist ketamine on spontaneous pain, mechanical allodynia, and temporal summation of pain (evoked by repetitive mechanical stimuli), suggesting that these symptoms could be maintained by common NMDA-mediated central sensitization mechanisms (Felsby *et al.*, 1996 ; Eide *et al.*, 1994, 1995). We have reported that systemic lidocaine reduced spontaneous pain and mechanical static/dynamic allodynia/hyperalgesia in neuropathic pain patients, but failed to modify thermally evoked pains, suggesting that these painful symptoms could be related to distinct mechanisms and pointing to modality-specific effects of the drug (Attal *et al.*, 2000 ; Attal *et al.*, manuscript in preparation).

However, symptoms alone are not sufficient tools for defining treatment strategies, since they are not equivalent to mechanisms (Woolf and Mannion, 1999 ; Woolf and Decosterd, 1999). The best therapeutic approach would therefore rely on identification of the mechanisms presumably responsible for the pain. An example of this approach is provided by postherpetic neuralgia patients, in whom distinct mechanisms have been proposed to account for their pain on the basis of their clinical symptomatology and response to simple pharmacologic tests (Fields *et al.*, 1998). Thus, a subset of patients present with prominent brush-induced allodynia, little or no heat deficit (suggesting the relative preservation of C nociceptors), and significant response to local anaesthetic blockade. It has been proposed that pain and allodynia in these patients was primarily mediated by abnormally sensitized remaining nociceptors. In this group, topical agents may therefore be proposed as first choice. In contrast, other patients present with spontaneous pain and little or no allodynia coexisting with massive heat deficit (suggesting a massive loss of nociceptors), which suggests that their pain is primarily due to central mechanisms. In these patients, more centrally acting drugs, such as antidepressants or gabapentin, may be indicated (Fields *et al.*, 1998). This approach could probably be relevant for other types of neuropathic pain.
However, the limitations of this approach in clinical practice have recently been underlined : patients often have a combination of several mechanisms, drugs may affect multiple types of pain and the pain's origin may influence the analgesic response (Max, 2000). Furthermore, it does not seem possible to generalize this approach to all painful conditions, since it implies a complete understanding of the action mechanisms of all the drugs used and also of the pathophysiology of the pains, which is unrealistic. It is especially difficult to use in central pain, where mechanisms are far less understood than those of peripheral neuropathic pain. For these reasons, this strategy is now essentially limited to clinical research or may only be applied to well studied pain conditions, such as postherpetic neuralgia.

Recommendations for drug choice in neuropathic pain

Based on the *NNT method*, tricyclics and antiepileptics, notably gabapentin, are considered the mainstay in various types of neuropathic pain

Table 2

Effects of systemic drugs or drug classes evaluated on painful neuropathic symptoms in double-blind placebo-controlled trials using quantitative sensory tests (references in italics) or systematic self-evaluation

Drugs or drug classes	References	Central/ peripheral neuropathic pain	Continuous pain	Paroxysms of pain*	Brush-induced allodynia	Static mechanical allodynia/ hyperalgesia	Heat allodynia/ hyperalgesia	Cold allodynia/ hyperalgesia
TCA (oral)	refs in Sindrup and Jensen, 99	p	+	+	+ self-report	ND	ND	ND
carbamazepine (oral)	refs in McQuay *et al.*, 95	p	+	+	ND	ND	ND	ND
phenytoin (iv)	McCleane, 99a	p	+	+	+ self-report	ND	ND	ND
gabapentin (oral)	Rowbotham *et al.*, 98 ; Backonja *et al.*, 98	p	+	+	ND	ND	ND	ND
lamotrigine (oral)	McCleane, 99b ; Simpson *et al.*, 2001	p	±	– (1 study)	– (1 study)	ND	ND	ND
	Vestergaard, 2001	c	+	ND	–	–	ND	+
lidocaine (iv)	Baranowski, 99 ; *Wallace, 2000*	p	+	NA	+	– (1 study)	– (1 study)	+ (1 study)
	Attal, 2000a	c	+	NA	+	+	–	–
mexiletine (oral)	*Wallace et al., 2000*	p	–	ND	+	ND	ND	ND
opioids (iv)**	*Eide et al., 94* ; Rowbotham *et al.*, 91	p	±	NA	+	ND	– (1 study)	ND
	Eide et al., 95 ; Attal et al., 2000b	c	±	NA	+	–	–	–
oxycodone (oral)	Watson and Babul, 98	p	+	+	+ self-report	ND	ND	ND
tramadol (oral)	Sindrup *et al.*, 98 ; Harati *et al.*, 98	p	+	+	+ self-report	ND	ND	ND
ketamine (iv)	*Felsby et al., 96 ; Eide et al., 94*	p	+	NA	+	ND	+ (1 study)	ND
	Eide et al., 95	c	+	NA	+	ND	ND	ND

TCA : tricyclic antidepressants
CRPS : Complex Regional Pain Syndrome type II (causalgia)
NA : not applicable (i.e., the number of paroxysms was not evaluated due to the short-term administration)
ND : not done
p : peripheral
c : central
*The intensity but not the number of paroxysms was evaluated (using Visual Analog Scale). In the two studies performed with gabapentin, the effects on paroxysms were determined by the McGill Pain Questionnaire.
** Opioids (iv) : alfentanil, morphine

(Collins *et al.*, 2000 ; McQuay *et al.*, 1995), and tricyclic agents, followed by gabapentin and tramadol, have been recommended as first choice in painful polyneuropathy (Sindrup and Jensen, 2000). However, recommendations for initial drug choice in neuropathic pain should not only be based on the NNT method. For instance, the prescription of a tricyclic antidepressant as first choice in a patient with postherpetic neuralgia exhibiting intense brush-induced allodynia in a relatively small painful area may be less beneficial than the use of an anaesthetic agent first. Thus, other important clinical aspects, such as *the pain symptomatology, the area of pain and the side-effect profile,* should be considered when initiating drug therapy for neuropathic pain and should be incorporated in a therapeutic algorithm. In some cases, such as postherpetic neuralgia, a mechanism-based approach appears to be possible and may be of assistance in an ultimate choice between two drugs. This rational approach also appears to be more relevant for evaluating newer pharmacological agents, the mechanisms of which of action are better understood and may help to better define the choice of analgesic combinations.

Conclusion

The pharmacologic treatment of neuropathic pain is still considered to be a challenge for the clinician, although several drugs have now proved effective. The choice of pharmacologic treatments should combine, whenever possible, the classical "evidence-based" evaluation of treatments with a more symptom-oriented and mechanism-based approach. This approach appears to be more relevant for evaluating newer pharmacological agents and may help to better define the choice of analgesic combinations.

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