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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.

Keywords: adjuvants pharmaceutical, analgesics, chronic, pain

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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.

Number needed to treat = $1/(P_c - P_i)$

Eq. (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.
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 α2δ 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 α2δ 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

\[\text{GABA, N-}\text{methyl-D-aspartate; TCAs, tricyclic antidepressants; VGCCs, voltage-gated Ca}^{2+}\text{ channels.}\]
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

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**Table 3 Gabapentin for chronic neuropathic pain**

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<tr>
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<th>NNT for moderate or better improvement (compared with placebo)</th>
<th>Pooled sample size</th>
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<tr>
<td>Diabetic neuropathy</td>
<td>2.9 (95% CI 2.2–4.3) RR 2.2 (95% CI 1.7–3) 281 patients (four studies)</td>
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<tr>
<td>PHN</td>
<td>3.9 (95% CI 3.5–5.7) RR 2.5 (95% CI 1.8–3.3) 428 patients (two studies)</td>
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<tr>
<td>All neuropathic pain</td>
<td>4.3 (95% CI 3.5–5.7) RR 2.2 (95% CI 1.8–2.7) 941 patients (six studies)</td>
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**Table 4 Antidepressants for all types of chronic neuropathic pain**

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<th>NNT for moderate pain relief or better (compared with placebo)</th>
<th>Pooled sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic neuropathy</td>
<td>1.3 (95% CI 1.2–1.5) RR 12.4 (95% CI 5.2–29.2) 177 patients (five studies)</td>
<td></td>
</tr>
<tr>
<td>PHN</td>
<td>2.7 (95% CI 2–4.1) RR 2.2 (95% CI 1.6–3.1) 219 patients (four studies)</td>
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CI, confidence interval; NNT, number needed to treat; PHN, postherpetic neuralgia; RR, relative risk. Adapted from [8].
suggest that cannabinoids have analgesic properties. Evidence from animal studies and preclinical data

Cannabinoids and up to three plasters (420 cm²) may be applied once reactions were common. Dosage titration is not necessary [22]. It was generally well tolerated but application site

4.4 (95% CI 2.5–17.5) for a 50% ongoing pain reduction the basis of data from 58 patients with peripheral neuro-

pathic pain syndromes, lidocaine plaster 5% had a NNT

the presumed mechanism of action is

mainly via peripheral sodium-channel blockade [21]. On

ment of PHN. The presumed mechanism of action is

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, cannabinoinds, 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**