PREVENTION. CARE. RECOVERY.

Te Kaporeihana Āwhina Hunga Whara

Considered Judgement Form

This form is a checklist of issues that may be considered by the Purchasing Guidance Advisory Group when making purchasing recommendations.

Meeting date: 14 August 2007

Topic: Anticonvulsants for neuropathic pain

Background

Anticonvulsant drugs have been used to manage neuropathic pain since the 1960s. Their use carries some risks and dose-limiting adverse effects are common, including some serious or fatal effects. Anticonvulsant drugs that have been used for neuropathic pain include carboxamides (carbamazepine, oxcarbazepine), the hydantoins (phenytoin also known as diphenylhydantoin), the valproates (sodium valproate, divalproex sodium), benzodiazepines (clonazepam, lorazepam), lamotrigine, fructose derivatives (topiramate), levetiracetam and the GABA analogues (tiagabine, vigabatrin, gabapentin and pregabalin). Some of these drugs are not available in New Zealand.

Neuropathic pain encompasses a heterogeneous group of painful disorders that may be classified either as peripheral (post-herpetic neuralgia, painful diabetic neuropathy, HIV-induced sensory neuropathy, tumour infiltration neuropathy, phantom limb pain, postoperative pain, complex regional pain syndromes and trigeminal neuralgia) or central (central post-stroke pain syndrome, spinal cord injury, pain from multiple sclerosis) in origin. Symptoms of neuropathic pain are often chronic and under-treated.

A number of agents have been used to treat neuropathic pain including antidepressants (e.g. amitriptyline), non-steroidal anti-inflammatory drugs (NSAIDs), opioids and anticonvulsants.

1. Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency

Comment here on the extent to which the service/product/ procedure achieves the desired outcomes. Specific reference needs to be made to safety. Report number needed to treat and harm where possible, any issues concerning the quantity of evidence and its methodological quality and the extent to which the evidence is directly applicable or generalisable to the New Zealand Population, and the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence

Carbamazepine

Two RCTs with important limitations (Rull 1969, Wilton 1974) demonstrated that carbamazepine was efficacious for the treatment of painful diabetic neuropathy. NNT calculated from Rull's study was 2.3 (1.6-3.9). One RCT with important limitations suggested that carbamazepine may be efficacious for pain relief in patients with Guillain-Barre syndrome (Pandey 2005).

Four studies (Campbell 1966, Rockliff 1966, Killian 1968 and Nicol 1969) demonstrated that carbamazepine was superior to placebo for trigeminal neuralgia. NNT was 1.4 (1.1-1.9) based on the study by Killian, and 2.1 (1.4-3.9) based on the study by Nicol.

One study (Leijon 1989) investigated the use of carbamazepine for post stroke pain, and found that 800mg daily produced a small but not statistically significant effect [NNT of 3.4 (1.7-105)]. In this study, amitriptyline 75mg/day was found to be significantly superior to placebo with a NNT of 1.7 (1.2 -3.1).

The combined NNH of major harm (drop outs due to side effects) for carbamazepine in neuropathic pain

(Finnerup 2005) was 21.7 (12.6-78.5).

Clonazepam
Clonazepam was superior to placebo in a single study for stomatodynia (Gremeai-Richard 2004) and in another single study of temporomandibular joint dysfunction and associated myofascial pain (Harkins 1991). Both studies have significant limitations. Adverse effects: mild sedation on early morning rising was reported in 3 of 10 treated patients for the first 3-7 days (Harkins 1991).

Lamotrigine
Four RCTs reported in three papers were found (Eisenberg 2001, Vinik 2007 and Jose 2007) on the use of lamotrigine for painful diabetic neuropathy. Lamotrigine was only superior to placebo in one of four measurements in the study reported by Eisenberg. Lamotrigine at doses between 50 to 200mg daily did not differ from amitriptyline at doses between 10 to 50mg (Jose 2007). Two other two RCTs (Vinik 2007) did not find consistent evidence to support that lamotrigine is superior to placebo.

Meta analysis: the pooled result based on three studies (Eisenbery 2001 and Vinik 2007) indicates that there is no statistically significant difference between lamotrigine and placebo [risk difference, 3% (95%CI -13% to 19%)] for painful diabetic neuropathy.

A small crossover study (Zakrzewska 1997, n=14) reported that lamotrigine was superior to placebo in treating trigeminal neuralgia. NNT calculated from this study was 2.1 (1.3-6.1). Lamotrigine was used as an "add on therapy" to carbamazepine or phenytoin in this study.

Lamotrigine was reported to be superior to placebo for HIV-neuropathy in one study (Simpson 2000) with significant adverse events. NNH calculated from this study was 3.3 (2.0-10.1). In another study (Simpson 2003), lamotrigine was found to be superior to placebo with respect to efficacy of pain relief in patients who were receiving neurotoxic antiretroviral toxic neuropathy (ATN), but did not differ from placebo with respect to pain relief in patients who were not receiving ATN. NNT calculated from this study was 5.4(3.1-20.4).

Lamotrigine was superior to placebo in treating central post-stroke pain (Vestergaard 2001). However, lamotrigine did not differ from placebo in treating spinal cord injury (Finnerup 2002).

Lamotrigine was similar to placebo in treating intractable neuropathic pain (McCleane 1999).

Lorazepam
A high quality study (Max 1988) found that lorazepam was similar to placebo in treating post herpetic neuralgia. In the same study, amitriptyline was found to be superior to lorazepam.

Oxcarbazepine
Three studies (Beydoun 2006, Grosskopf 2006 and Dorgra 2005) used oxcarbazepine for painful diabetic neuropathy. Oxcarbazepine was not superior to placebo in two studies (Beydoun 2006 and Grosskopf 2006). However, the study by Dorgra found that oxcarbazepine was superior to placebo. NNT calculated from this study was 7 (3.3-41.0) and NNH was 6 (3.1-13.1).

Meta analysis: the pooled result based on three studies (Dogra 2005, Beydoun 2006 and Grosskopf 2006) indicates that oxcarbazepine is associated with statistically significant side effects when compared with placebo [risk difference, 2***5%*** (95%CI 18% to 32%)]. NNH calculated from the result was 4 (3.1-5.6).

Phenytoin
Two randomised crossover studies (Chadda 1978, Saudek 1977) on the use of phenytoin for diabetic neuropathy were found. The study by Saudek found that phenytoin did not differ from placebo in pain reduction. However, the study by Chadda found that phenytoin was superior to placebo in improvement of pain symptom. NNT calculated from this study was 2.1 (1.5-3.6).

One study (McCleane 1999) reported that intravenous phenytoin (15mg/kg) was superior to placebo for patients with mixed neuropathic pain.

Sodium valproate
Two studies (Kochar 2002 and Kochar 2004) found that sodium valproate was superior to placebo in treating painful diabetic neuropathy. NNT calculated from the first study (Kochar 2002) was 2.1 (1.2-2.2), and 2 (1-3) from the second study (Kochar 2004).

A randomised crossover study (Otto 2004) found that sodium valproate did not differ from placebo for polyneuropathy.

Sodium valproate was found to be superior to placebo in treating postherpetic neuralgia (Kochar 2005). However, sodium valproate was not superior to placebo in treating spinal cord injury pain (Drewes 1994).

Topiramate
Two studies (Raskin 2004 and Thienel 2004) were found to use topiramate for diabetic neuropathy. Topiramate was not superior to placebo in the study reported by Thienel. However, it was found to be superior to placebo in the study reported by Raksin with a NNT of 8 (4.3-28.5).

Meta analysis: the pooled result based on these two studies (Raskin 2004 and Thienel 2004) indicates that topiramate is associated with increased events of side effects that cause drop outs from study [risk difference, 16**%** (95%CI 12% to 19%)]. NNH calculated from the result was 6.3 (5.3-8.3).

A single crossover study (Khoromi 2005) found that topiramate was superior to diphenhydramine for chronic lumbar radicular pain. NNH calculated from this study was 4.4 (2.7-12.1).

A very small sample size (n=3) crossover study (Gilron 2001) found that topiramate was not superior to placebo for trigeminal neuralgia.

Vigabatrin
No randomised studies were found that investigated the use of vigabatrin for treatment of neuropathic pain.

Gabapentin
Painful diabetic neuropathy: five studies (Backonja 1998, Dallocchio 2000, Gorson 1999, Morello 1999 and Simpson 2001) were found that examined the use gabapentin in painful diabetic neuropathy.

Two studies (Backonja 1998 and Simpson 2001) found that gabapentin was superior to placebo. Gabapentin was only superior to placebo for 1 of 4 measures of pain relief in the study reported by Gorson in 1999. Meta analysis based on three studies (Backonja 1998, Gorson 1999 and Simposon 2001) indicates that about 24% (risk difference, 95%CI 14%-35%) of patients are likely to benefit from gabapentin treatment. NNT estimated from the result is 4.2 (95%CI 2.9-7.2).

In two studies (Dallocchio 2000 and Morello 1999) which compared gabapentin with amitriptyline for diabetic neuropathy, gabapentin was not superior to amitriptyline. Meta analysis based on these two studies indicates that there is no statistically significant difference in pain relief between gabapentin and amitriptyline RR=1.08 (95%CI 0.76- 1.55); risk difference=5% (-17% to 28%).

Post-herpetic neuralgia: gabapentin was found to be superior to placebo in treating post-herpetic neuralgia in two studies (Rice 2001, Rowbotham 1998). Meta analysis based on these two studies indicates that about 24% (risk difference, 95%CI 17%-31%) of patients with post-herpetic neuralgia are likely to benefit from gabapentin treatment. NNT estimated from the result is 4.2 (95%CI 3.2-5.9).

Gabapentin was found to be superior to placebo in treating phantom limb pain (Bone 2002) and Complex Regional Pain Syndrome I (Van de Vusse 2004).

One study (Hahn 2004) investigated the use of gabapentin for HIV neuropathy. The study reported that the changes between gabapentin and placebo over 5 weeks did not show a significant difference for the pain score or for the sleep interference score.

Two studies (Serpell 2002 and Gilron 2005) investigated the use of gabapentin in patients with mixed neuropathic pain conditions. Serpell reported that gabapentin was superior to placebo. However, patients failing to respond to gabapentin previously were excluded from the study, which may overestimate the effect. In the study reported by Gilron, combination of gabapentin and morphine was superior to placebo (lorazepam: up to 1.6 mg/day) for patients with diabetic neuropathy or post herpetic neuralgia.

Two studies found that gabapentin was superior to placebo in spinal cord injury pain (Levendoglu 2004 and Tai 2002). However, the data from the studies are not available to calculate NNTs.

There is an absence of studies that investigate the long term effects of gabapentin on neuropathic pain, and the use of gabapentin in children.

Side effects: meta analysis based on eleven studies which compared with placebo (Rowbotham 1998, Rice 2001, Backonja 1998, Gorson 1999, Simposon 2001, Levendoglu 2004, Hahn 2004, Van de Vusse 2004, Bone 2002, Serpell 2002 and Gilron 2005) indicates that about 4% (risk difference, 95%CI 1%-7%) of patients are likely to be discontinued from gabapentin treatment due to side effects. NNH estimated from the

result is 25 (95%CI 14.2-100).

Pregabalin

Painful diabetic neuropathy: three studies (Rosenstock 2004, Lesser 2004 and Richter 2005) investigated the use of pregabalin for diabetic neuropathic pain. All three studies found that pregabalin was superior to placebo. Patients who did not respond to gabapentin previously were excluded from two studies (Rosenstock 2004 and Richter 2005). The exclusion may lead to an overestimate of the effect of pregabalin since only certain types of patients in the studies were included. Pregabalin is considered to be similar to gabapentin in terms of their mechanisms of action. Meta analysis based on these three studies indicates that about 26% (risk difference, 95%CI 19%-34%) of patients are likely to benefit from pregabalin treatment. NNT estimated from the result is 3.9 (95%CI 2.9-5.3).

Post-herpetic neuralgia: pregabalin was found to be superior to placebo for post-herpetic neuralgia in three studies (Dworkin 2003, Sabatowski 2004 and Van Seventer 2006). Meta analysis based on these two studies indicates that about 25% (risk difference, 95%CI 18%-31%) of patients are likely to benefit from pregabalin treatment. NNT estimated from the result is 4.0 (3.2-5.6).

Pregabalin was found to be superior to placebo in treating patients with mixed conditions (diabetic neuropathy or post-herpetic neuralgia) in one study (Freynhagen 2005).

Siddall reported that pregabalin was superior to placebo for spinal cord injury pain (Siddall 2005). All patients in this study were allowed to remain on existing pain therapies including opioids, tricyclic antidepressants, NSAIDS/COX2 and anticonvulsants except gabapentin which had to be discontinued at least a week before the study protocol began. NNT calculated from this study was 7.1(3.9-37.2).

Side effects: meta analysis based on seven studies which compared with placebo (Rosenstock 2004, Lesser 2004, Richter 2005, Dworkin 2003, Sabatowski 2004, Siddall 2006 and Van Seventer 2006) indicates that about 9% (risk difference, 95%CI 4%-15%) of patients are likely to be discontinued from pregabalin treatment due to side effects. NNH estimated from the result is 11.1(6.7-25).

2. Cost

Comment on any economic costs associated with this service, product or procedure

An NHS economic evaluation report (Cepeda 2006) estimated the following; probability of having 50% or more pain relief, direct cost per patient per month, and probability of having major adverse effects (AE).

	Probability of pain relief	Cost (US$, year 2004)	Probability of major AE
Amitriptyline (75mg/d)	0.68	29	0.07
Carbamazepine (800mg/d)	0.63	50	0.05
Gabapentin (2400mg/d)	0.40	270	0.10
Tramadol (200mg/d)	0.59	98	0.12

An assessment summary from PHARMAC in 2003 concluded “a rapid economic analysis was conducted to assess the cost effectiveness of gabapentin as a last-line agent, compared with placebo. This resulted in a cost per quality-adjusted life (QALY) year of $3000 to $5000. However, gabapentin is not cost-effective to use as first-line therapy.

Scottish Medicines Consortium (SMC, 7 July 2006) states “pregabalin (Lyrica) is not recommended for use within NHS Scotland for the treatment of peripheral neuropathic pain in adults. Comparative clinical and cost effectiveness have not been demonstrated.”

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA 2005) stated “The costs associated with pregabalin treatment may not compare favourably with that of generic gabapentin. However, gabapentin is not approved for the treatment of peripheral neuropathic pain (NeP) by Health Canada. While pregabalin appears to be an effective treatment for NeP, there is no evidence that it offers advantages compared with other treatments being used in Canada. The long-term effects of treating NeP with pregabalin are largely unknown, because long-term RCTs are unavailable. Comparative cost and consequence data from head-to-head trials with recommended therapies are needed to define pregabalin's place in NeP therapy”.

Direct cost of amitriptyline, carbamazepine, gabapentin and pregabalin per patient per month in New Zealand is as following at this stage:

	Cost (NZ$, year 2007)
Amitriptyline (75mg/d)	4
Carbamazepine (800mg/d)	33
Gabapentin (2400mg/d, Nupentin)	134
Gabapentin (2400mg/d, Neurontin)	297
Pregabalin (600mg/d)	250

3. Clinical impact

Comment on the clinical impact e.g. size of population, magnitude of effect, relative benefit over other management options, resource implications, balance of risk and benefit.

Diabetes mellitus appears to be particularly relevant because of the high incidence of diabetes mellitus in NZ, particularly in Maori/Pacific people. It is estimated that 11-24% of people with diabetes have diabetic peripheral neuropathy (DPN).

About 50% patients with spinal cord injury suffer from central neuropathic pain.

4. Equity, Maori Health, Pacific Health, Acceptability

Comment on the extent to which the service, product or procedure reduces disparities in health status (equity of access, resources, health outcome), is consistent with the treaty of Waitangi and encourages Maori/ Pacific participation in providing and using service, product and procedures, and is consistent with values and expectations of New Zealanders.

As above.

5. Evidence Statement

Summarise the advisory group's synthesis of evidence relating to this service, product or procedure, taking the above factors into account, and indicate the evidence level that applies.

Peripheral neuropathic pain

Carbamazepine
There is strong evidence to support that carbamazepine is effective for the treatment of trigeminal neuralgia. There is some evidence to support that carbamazepine is effective for the treatment of diabetic neuropathy. Evidence from a single randomised study indicates that carbamazepine may be effective for pain related to Guillain-Barre syndrome, however, more studies are needed to determine the effectiveness of the treatment.

Clonazepam
There is limited evidence that clonazepam is effective for pain reduction in patients with temporomandibular joint dysfunction and in patients with stomatodynia.

Lamotrigine
There is limited evidence that lamotrigine is superior to placebo with respect to pain relief in patients with trigeminal neuralgia and HIV neuropathy. There is strong evidence from four RCTs and a meta analysis to support almost no effectiveness of lamotrigine for pain reduction in patients with painful diabetic neuropathy.

Lorazepam
A single randomised controlled study indicates that lorazepam is no more efficacious than placebo for reduction of pain in patients with post herpetic neuralgia.

Oxcarbazepine
Only one in three randomised studies supported the use of oxcarbazepine for painful diabetic neuropathy. Oxcarbazepine is associated with significantly increased side effects that lead to drop outs from the treatment.

Phenytoin
One of two studies of using oral phenytoin for patients with diabetic neuropathy showed benefit in terms of pain reduction. There is limited evidence that intravenous phenytoin can reduce pain in acute flare-ups of neuropathic pain.

Sodium valproate
There is some evidence to support that sodium valproate is effective to treat diabetic neuropathy and postherpetic neuralgia.

Topiramate
The effectiveness of using topiramate for diabetic neuropathy remains inconclusive. A small study does not support the use of topiramate for trigeminal neuralgia. Topiramate is, however, associated with a significant increase in side effects that lead to treatment drop outs. One single study found that topiramate might reduce chronic lumbar nerve root pain.

Vigabatrin
The effectiveness of vigabatrin for neuropathic pain cannot be evaluated due to the absence of randomised controlled studies.

Gabapentin
There is strong evidence to support that gabapentin is effective for diabetic neuropathy and post-herpetic neuropathy when compared with placebo.

At this stage there are no published studies that directly provide evidence to support that gabapentin is superior to other anticonvulsants and antidepressants (amitriptyline) in treating peripheral neuropathic pain. The cost effectiveness of using gabapentin for neuropathic pain has not been demonstrated.

Gabapentin is associated with fewer major side effects (led to drop outs from the treatment) than other anticonvulsants e.g. oxcarbazepine and topiramate

Pregabalin
There is relatively strong evidence to support that pregabalin is effective for diabetic neuropathy and post-herpetic neuropathy when compared with placebo.

At this stage there are no published studies that directly provide evidence to support that pregabalin is superior to other anticonvulsants and other agents (e.g. antidepressants) in treating peripheral neuropathic pain. The cost effectiveness of using pregabalin for neuropathic pain has not been demonstrated.

In terms of effectiveness (NNTs estimated from meta analysis), pregabalin appears to be very similar to gabapentin.

Pregabalin is associated with fewer major side effects (led to drop outs from the treatment) than other anticonvulsants e.g. oxcarbazepine and topiramate.

Central neuropathic pain

Only a few randomised controlled studies have investigated the use of anticonvulsants for post-stroke pain and spinal cord injury pain. More well-designed studies are needed for further evidence assessment and decision making.

Carbamazepine
The evidence to support the use of carbamazepine for post-stroke pain is weak.

Lamotrigine
The evidence to support the use of lamotrigine for post-stroke pain is insufficient. Available study does not support that lamotrigine is effective to treat spinal cord injury pain.

Sodium valproate
A single available study does not support that sodium valproate is effective to treat spinal cord injury pain.

Gabapentin
There is some but not strong evidence to support the use of gabapentin for spinal cord injury pain.

Pregabalin
There is insufficient evidence to support that pregabalin is effective for spinal cord injury pain. Only one randomised controlled trial was identified that supports its effectiveness, however the study could be criticised.

6. Possible Purchasing Options

List the possible purchasing options.

Peripheral neuropathic pain

A. Consider the purchase of carbamazepine or sodium valproate as first line medicines for peripheral neuropathic pain. Clonazepam, lamotrigine and phenytoin can also be considered in some conditions for which there is limited evidence supporting their use. Lorazepam, oxcarbazepine and topiramate may not be considered due to the lack of evidence or significantly increased risk of major side effects.

B. Consider the purchase of the generic form of gabapentin as second line medicine for peripheral neuropathic pain

C. Pregabalin should not be considered for peripheral neuropathic pain at this stage unless other second-line treatments have been trialled and proven ineffective.

Central neuropathic pain

D. Consider the purchase of carbamazepine as first line treatment and lamotrigine as second line treatment for post-stroke pain.

E. Consider the purchase of the generic form of gabapentin for spinal cord injury pain, with regular review on evidence.

F. Consider the purchase of pregabalin for spinal cord injury pain on a case by case basis at this stage.

7. Purchasing Recommendations

What recommendation(s) does the advisory group draw from this evidence?

Peripheral Neuropathic Pain

A. Recommend to purchase carbamazepine or sodium valproate as first line medicines for peripheral neuropathic pain. Clonazepam, lamotrigine and phenytoin can also be considered in some conditions for which there is limited evidence supporting their use. Lorazepam, oxcarbazepine and topiramate are not recommended due to the lack of evidence or significantly increased risk of major side effects.

B. Recommend to purchase the generic form of gabapentin as second line medicine for peripheral neuropathic pain

C. Pregabalin should not be considered for peripheral neuropathic pain at this stage unless other second line treatments have been trialled and proven ineffective.

Central neuropathic pain

D. Recommend to purchase carbamazepine and lamotrigine for post-stroke pain.

E. Recommend to purchase the generic form of gabapentin for spinal cord injury pain, with regular review on evidence regarding the effectiveness.

F. It is not currently cost-effective for ACC to purchase pregabalin or neurontin for central neuropathic pain based on current New Zealand prices except in exceptional circumstances. Other options must have also been exhausted.

Additional Information: See related form ACC 2531 Anti-convulsants (non subsidised) for Neuropathic Pain Management – Prescriber Checklist: Guidelines for ACC Contribution to Cost

References

Backonja, M., A. Beydoun, et al. (1998). "Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial." JAMA 280(21): 1831-6.

Beydoun, A., A. Shaibani, et al. (2006). "Oxcarbazepine in painful diabetic neuropathy: results of a dose-ranging study." Acta Neurologica Scandinavica 113(6): 395-404.

Bone, M., P. Critchley, et al. (2002). "Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study." Regional Anesthesia & Pain Medicine 27(5): 481-6.

Campbell, F. G., J. G. Graham, et al. (1966). "Clinical trial of carbazepine (tegretol) in trigeminal neuralgia." Journal of Neurology, Neurosurgery & Psychiatry 29(3): 265-7.

Cepeda, M. S. and J. T. Farrar (2006). "Economic evaluation of oral treatments for neuropathic pain." Journal of Pain 7(2): 119-28.

Chadda, V. S. and M. S. Mathur (1978). "Double blind study of the effects of diphenylhydantoin sodium on diabetic neuropathy." Journal of the Association of Physicians of India 26(5): 403-6.

Dallocchio, C., C. Buffa, et al. (2000). "Gabapentin vs. amitriptyline in painful diabetic neuropathy: an open-label pilot study." Journal of Pain and Symptom Management 20(4): 280-5.

Dogra, S., S. Beydoun, et al. (2005). "Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study." European Journal of Pain: Ejp 9(5): 543-54.

Drewes, A. M., A. Andreasen, et al. (1994). "Valproate for treatment of chronic central pain after spinal cord injury. A double-blind cross-over study." Paraplegia 32(8): 565-9.

Dworkin, R. H., A. E. Corbin, et al. (2003). "Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial." Neurology 60(8): 1274-83.

Eisenberg, E., Y. Lurie, et al. (2001). "Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study." Neurology 57(3): 505-9.

Finnerup, N. B., M. Otto, et al. (2005). "Algorithm for neuropathic pain treatment: an evidence based proposal." Pain 118(3): 289-305.

Finnerup, N. B., S. H. Sindrup, et al. (2002). "Lamotrigine in spinal cord injury pain: a randomized controlled trial." Pain 96(3): 375-83.

Freynhagen, R., K. Strojek, et al. (2005). "Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens." Pain 115(3): 254-63.

Gilron, I., J. M. Bailey, et al. (2005). "Morphine, gabapentin, or their combination for neuropathic pain." New England Journal of Medicine 352(13): 1324-1334.

Gilron, I., S. L. Booher, et al. (2001). "Topiramate in trigeminal neuralgia: a randomized, placebo-controlled multiple crossover pilot study." Clinical Neuropharmacology 24(2): 109-12.

Gorson, K. C., C. Schott, et al. (1999). "Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial." Journal of Neurology, Neurosurgery & Psychiatry 66(2): 251-2.

Gremeau-Richard, C., A. Woda, et al. (2004). "Topical clonazepam in stomatodynia: a randomised placebo-controlled study." Pain 108(1-2): 51-7.

Grosskopf, J., J. Mazzola, et al. (2006). "A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy." Acta Neurologica Scandinavica 114(3): 177-80.

Hadj, A. (2005). "Pregabalin for perpheral neuropathic pain." Canadian Coordinating Office for Health Technology Assessment (Issue 67).

Hahn, K., G. Arendt, et al. (2004). "A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies." Journal of Neurology 251(10): 1260-6.

Harkins, S., J. Linford, et al. (1991). "Administration of clonazepam in the treatment of TMD and associated myofascial pain: a double-blind pilot study." Journal of Craniomandibular Disorders 5(3): 179-86.

Jose, V., A. Bhansali, et al. (2007). "Randomized double-blind study comparing the efficacy and safety of lamotrigine and amitriptyline in painful diabetic neuropathy." Diabetic Medicine 24(Feb): 376-383.

Khoromi S, Patsalides A, et al. (2005). Topiramate in chronic lumbar radicular pain. Journal of Pain 2005;6(12):829-36.

Killian, J. M. and G. H. Fromm (1968). "Carbamazepine in the treatment of neuralgia. Use of side effects." Archives of Neurology 19(2): 129-36.

Kochar, D. K., P. Garg, et al. (2005). "Divalproex sodium in the management of post-herpetic neuralgia: a randomized double-blind placebo-controlled study." Qjm: Monthly Journal of the Association of Physicians 98(1): 29-34.
Kochar, D. K., N. Jain, et al. (2002). "Sodium valproate in the management of painful neuropathy in type 2 diabetes - a randomized placebo controlled study." Acta Neurologica Scandinavica 106(5): 248-52.
Kochar, D. K., N. Rawat, et al. (2004). "Sodium valproate for painful diabetic neuropathy: A randomized double-blind placebo-controlled study." Qjm: Monthly Journal of the Association of Physicians 97(1): 33-38.
Leijon, G. and J. Boivie (1989). "Central post-stroke pain--a controlled trial of amitriptyline and carbamazepine." Pain 36(1): 27-36.
Lesser, H., U. Sharma, et al. (2004). "Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial." Neurology 63(11): 2104-10.
Levendoglu, F., C. O. Ogun, et al. (2004). "Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury." Spine 29(7): 743-51.
Max, M. B., S. C. Schafer, et al. (1988). "Amitriptyline, but not lorazepam, relieves postherpetic neuralgia." Neurology 38: 1427-1432.
McCleane, G. (1999). "200 mg daily of lamotrigine has no analgesic effect in neuropathic pain: a randomised, double-blind, placebo controlled trial." Pain 83(1): 105-7.
McCleane, G. J. (1999). "Intravenous infusion of phenytoin relieves neuropathic pain: a randomized, double-blinded, placebo-controlled, crossover study." Anesthesia & Analgesia 89(4): 985-8.
Morello, C. M., S. G. Leckband, et al. (1999). "Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain." Archives of Internal Medicine 159(16): 1931-7.
Nicol, C. F. (1969). "A four year double-blind study of tegretol in facial pain." Headache 9(1): 54-7.
Pandey, C. K., M. Raza, et al. (2005). "The comparative evaluation of gabapentin and carbamazepine for pain management in Guillain-Barre syndrome patients in the intensive care unit." Anesthesia & Analgesia 101(1): 220-5.
Raskin, P., P. D. Donofrio, et al. (2004). "Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects." Neurology 63(5): 865-73.
Rice, A. S. C., S. Maton, et al. (2001). "Gabapentin in postherpetic neuralgia: A randomised, double blind, placebo controlled study." Pain 94(2): 215-224.
Richter, R. W., R. Portenoy, et al. (2005). "Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial." Journal of Pain 6(4): 253-60.
Rockliff, B. W. and E. H. Davis (1966). "Controlled sequential trials of carbamazepine in trigeminal neuralgia." Archives of Neurology 15(2): 129-36.
Rosenstock, J., M. Tuchman, et al. (2004). "Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial." Pain 110(3): 628-38.
Rowbotham, M., N. Harden, et al. (1998). "Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial." JAMA 280(21): 1837-42.
Rull, J. Q., R; Gonzalez-Millan, H; Lozano Castenada, O (1969). "Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine: double-blind crossover study." Diabetologia 5: 215-220.
Sabatowski, R., R. Galvez, et al. (2004). "Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial." Pain 109(1-2): 26-35.
Saudek, C. D., S. Werns, et al. (1977). "Phenytoin in the treatment of diabetic symmetrical polyneuropathy." Clinical Pharmacology & Therapeutics 22(2): 196-9.
Scottish Medicines Consortium "Adivice following an independent review panel---Pregabalin (No.157/05, 7 July 2006)." On www.scottishmedicines.org.uk/smc/, accessed on 18 May 2007.
Serpell, M. G. and Neuropathic pain study group (2002). "Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial." Pain 99(3): 557-66.
Siddall, P. J., M. J. Cousins, et al. (2006). "Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial." Neurology 67(10): 1792-800.
Simpson, D. A. (2001). "Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy." Journal of Clinical Neuromuscular Disease 3(2): 53-62.
Simpson, D. M., J. C. McArthur, et al. (2003). "Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial." Neurology 60(9): 1508-14.
Simpson, D. M., R. Olney, et al. (2000). "A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy." Neurology 54(11): 2115-9.

Tai, Q., S. Kirshblum, et al. (2002). "Gabapentin in the treatment of neuropathic pain after spinal cord injury: a prospective, randomized, double-blind, crossover trial." Journal of Spinal Cord Medicine 25(2): 100-5.

Thienel, U., W. Neto, et al. (2004). "Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials." Acta Neurologica Scandinavica 110(4): 221-31.

Van de Vusse, A. C., S. G. Stomp-van den Berg, et al. (2004). "Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1 [ISRCTN84121379]." BMC Neurology 4: 13.

Van Seventer R, Feister HA, Young JP, Jr., Stoker M, Versavel M, Rigaudy L(2006). Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. Current Medical Research & Opinion 2006;22(2):375-84.

Vestergaard, K., G. Andersen, et al. (2001). "Lamotrigine for central poststroke pain: A randomized controlled trial." Neurology 56(2): 184-190.

Vinik, A. I., M. Tuchman, et al. (2007). "Lamotrigine for treatment of pain associated with diabetic neuropathy: Results of two randomized, double-blind, placebo-controlled studies." Pain 128: 169-79.

Wilton, T. D. (1974). "Tegretol in the treatment of diabetic neuropathy." South African Medical Journal Suid-Afrikaanse Tydskrif Vir Geneeskunde. 48(20): 869-72.

Zakrzewska, J. M., Z. Chaudhry, et al. (1997). "Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial." Pain 73(2): 223-30.