Clinical use of pregabalin in the management of central neuropathic pain

Nanna B Finnerup
Troels S Jensen

Danish Pain Research Center, Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

Abstract: Central neuropathic pain (central pain) is treated with antidepressants, various anticonvulsants, opioids, and cannabinoids, but in many cases treatment is insufficient and associated with a range of side-effects. This review addresses a new treatment for neuropathic pain, the anticonvulsant pregabalin. We review the pharmacology, mode of action, pharmacokinetics, and safety of pregabalin as well as two randomized efficacy studies in central pain and a brief overview of efficacy in peripheral neuropathic pain. Pregabalin appears to have efficacy in treating central pain comparable to that in peripheral neuropathic pain as well as efficacy of other recommended drugs for central pain. Pregabalin also improves disturbed sleep and anxiety. Pregabalin is well tolerated; the most common side-effects are somnolence, dizziness, ataxia, and weight gain. Pregabalin is suitable for patients on multiple drugs although there may be additive CNS-related side-effects. Thus, pregabalin has a primary role in central pain patients.

Keywords: central pain, neuropathic pain, pregabalin, pharmacology

Introduction

Central neuropathic pain (central pain) is pain caused by a disease or lesion in the central nervous system. Central pain develops in about 8% of stroke patients (Andersen et al 1995), 25% of patients with multiple sclerosis (Osterberg et al 2005), and 40%–50% of patients with spinal cord injury (Budh et al 2003; Siddall et al 2003; Werhagen et al 2004) and may develop secondary to brain and spinal cord tumors and other diseases affecting the central nervous system. Central pain thus affects a large number of patients worldwide and often it has a substantial impact on the quality of life, mood, sleep, cognition, social relations, etc. Central pain is characterized by ongoing pain, which may be burning, squeezing, pricking, and shooting and/or evoked types of pain, eg, pain evoked by light touch. The pain is located within an area of sensory disturbance covering various proportions of the deafferented body regions. Treatment of central pain is often difficult and requires a different approach than nociceptive pain. Central pain is usually treated with antidepressants, anticonvulsants, and opioids; treatments which provide partial pain relief at best and which are often associated with side-effects.

Pregabalin is a novel, centrally acting neuromodulating agent that was approved by the US Food and Drug Administration (FDA) in 2004 for the treatment of painful diabetic peripheral neuropathy and post-herpetic neuralgia. In 2005 it was approved as adjunctive therapy in adults with partial seizures and recently it has been approved for the treatment of fibromyalgia. Pregabalin is approved by the European Medicines Agency (EMEA) for the treatment of peripheral and central neuropathic pain in adults, as adjunctive therapy in adults with partial seizures, and for the treatment of

Correspondence: Nanna B Finnerup
Danish Pain Research Center, Aarhus University Hospital, Norrebrogade 44, Bldg. 1A, 8000 Aarhus, Denmark
Tel +45 89 49 34 55
Fax +45 89 49 32 69
Email finnerup@ki.au.dk

generalized anxiety disorder (GAD) in adults (EMEA 2006; Pfizer 2007). The trade name of pregabalin is Lyrica®, marketed by Pfizer.

Pregabalin pharmacology, mode of action and pharmacokinetics

Pregabalin ((S)-3-(aminomethyl)-5-methylhexanoic acid) is a structural derivative of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Pregabalin is structurally related to gabapentin and has a similar pharmacological profile and anticonvulsant and analgesic activity (Ben-Menachem 2004). The predominant mechanism of action is thought to be through its presynaptic binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels which in turns leads to reduced release of neurotransmitters, eg, glutamate, substance P, and calcitonin gene-related peptide (Fehrenbacher et al 2003; Sills 2006; Li et al 2006; Dooley et al 2007; Taylor et al 2007). Such decrease in neurotransmitter release from synapses in several neuronal tissues in the spinal cord and brain is likely to attenuate neuronal hyperexcitability and abnormal synchronization and may thus explain its anticonvulsant, analgesic, and anxiolytic activity (Taylor et al 2007). Pregabalin does not appear to act through the GABAergic neurotransmitter system (reviewed in, eg, (Sills 2006) and (Taylor et al 2007)) and although it has been shown to act on voltage-gated potassium channels (McClelland et al 2004), this mechanism of action is not thought to contribute significantly to the pharmacological profile (Sills 2006).

Pregabalin has linear pharmacokinetics and a predictable dose-response relationship. The pharmacokinetic and safety properties of pregabalin have been studied in healthy subjects and patients with renal impairment (Randinitis et al 2003). The oral bioavailability is 90% and dose-independent, and pregabalin is rapidly absorbed in the fasting state with a T_{max} of 1 hour which is reduced by food consumption by 35%. Food does not alter the area under the curve and has no clinically significant effect. Steady-state plasma concentration is obtained after 24–48 hours.

Pregabalin does not bind to plasma proteins and thus readily penetrates the blood-brain barrier. Over 98% of pregabalin is excreted unchanged in urine. The elimination half-time is 4.8–6.3 hours but is increased in patients with renal impairment and dependent on the creatinine clearance. Therefore, dose reduction is needed in patients with impaired renal function (ie creatinine clearance <60 mL/min) (Randinitis et al 2003) (Table 1). Data are lacking for elderly patients.

Pregabalin is not metabolized in the liver and has no effect on the cytochrome P450 system or other liver enzymes and has no plasma protein binding consistent with the lack of interactions with other anticonvulsants, certain antidiabetics, and oral contraceptives (Ben-Menachem 2004; Tassone et al 2007). Additive adverse effects on cognitive and gross motor functioning have been seen with pregabalin co-administered with oxycodone, lorazepam, and ethanol, and concomitant treatment with pregabalin and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain (EMEA 2004; Pfizer 2007).

Table 1 Pregabalin dosage adjustment based on renal function (Pfizer 2007)

Creatinine clearance (mL/min)	Total pregabalin daily dose (mg)			Dose regiment
≥60	150	300	600	bid or tid
30–60	75	150	300	bid or tid
15–30	25–50	75	150	qd or bid
<15	25	25–50	75	qd

Abbreviations: tid, three divided doses; bid, two divided doses; qd, single daily dose.

Efficacy studies

Peripheral neuropathic pain

Pregabalin has in large published parallel-group design studies consistently been shown to relieve post-herpetic neuralgia (Dworkin et al 2003; Sabatowski et al 2004; Freynhagen et al 2005; van Seventer et al 2006) and painful diabetic neuropathy (Lesser et al 2004; Rosenstock et al 2004; Freynhagen et al 2005; Richter et al 2005) with a combined number needed to treat (NNT) for doses ranging from 300 mg to 600 mg of 3.9 (3.3–4.7). For comparison, the NNT values in peripheral neuropathic pain are 2.3 (2.1–2.7) for tricyclic antidepressants, 2.7 (2.1–3.6) for opioids, 3.9 (2.7–6.7) for tramadol, 4.4 (2.5–17) for topical lidocaine, and 5.5 (3.4–14) for serotonin noradrenaline reuptake inhibitors, but differences in design and study population may make direct comparison of NNT values difficult (Finnerup et al 2005). The total number of patients included 1028 exposed to pregabalin and 575 to placebo in the 300–600 mg dose range. Two studies in painful diabetic neuropathy reported by the European Medicines Agency in 2004 (EMEA 2004) are still unpublished; one study including 396 patients showed efficacy of pregabalin 300/600 mg daily, while a 3-armed study with pregabalin 600 mg (n = 87), amitriptyline 75 mg (n = 88) and placebo (n = 81) failed to show a significant pain-relieving effect with pregabalin (p = 0.08). The difference in mean endpoint score between pregabalin and placebo for all peripheral neuropathic pain studies ranged

from –0.18 to –1.57 points for the 300 mg daily score and from –0.64 to –2.02 points for the 600 mg daily score (EMEA 2004). There was no effect of pregabalin 75 mg daily and inconsistent efficacy for 150 mg daily. Efficacy was observed from week 1 and maintained throughout the study periods. The first studies on pregabalin (Dworkin et al 2003; Lesser et al 2004; Rosenstock et al 2004; Sabatowski et al 2004) excluded patients who failed to respond to previous treatment with gabapentin, which may bias the efficacy outcome measures in favor of pregabalin (Finnerup et al 2005), but more recent trials without this exclusion criterion have comparable NNT values (Freynhagen et al 2005; Richter et al 2005; van Seventer et al 2006). Somnolence is a frequent adverse event present in 20%–30% and subanalyses have shown that the pain relieving effect was larger in patients experiencing somnolence as an adverse effect (EMEA 2004). However, pregabalin still had a pain relieving effect in those patients not experiencing somnolence as an adverse effect (EMEA 2004). The published clinical trials found dose-dependent efficacy in pain relief as well as improvements in sleep and global impressions of changes (integrating the effect of treatment and side-effects), and some studies also in quality of life measures (Lesser et al 2004; Sabatowski et al 2004) and mood (Rosenstock et al 2004).

Central pain

Two randomized placebo-controlled trials have been conducted in central pain (Table 2). The first study published is a parallel group design study in central neuropathic pain due to spinal cord injury (Siddall et al 2006). A baseline week was followed by a 3-week titration period where pregabalin was increased up to 300 mg bid and a 9-week fixed dose period. Seventy patients were allocated to the pregabalin arm and 76 to the placebo arm. Concurrent pain medication was kept constant during the trial and included tricyclic antidepressants in 33% in the pregabalin group and 18% in the placebo group, opioids in 30% and 48%, and antiepileptic drugs except gabapentin in 11% and 9 % respectively. Muscle relaxants (including baclofen) were used by 54% in the pregabalin group and 37% in the placebo group while benzodiazepines were used by 40% and 39% respectively. The mean pregabalin dose during the fixed dose period was 460 mg/day. Pain was evaluated daily on a numeric rating scale (NRS, 0–10) and the primary efficacy measure was the weekly mean pain score at endpoint (last week on study drug). The improvement in pain score from baseline (pregabalin – placebo) was –1.53 (–0.92 to –2.15), similar to values observed in studies in peripheral neuropathic pain. The effect was significant from week 1 and remained so for the duration of the study. Pregabalin also improved pain-related sleep interference and anxiety. The NNT for 50% pain relief (7.1 (3.9–37)) was higher than in most peripheral neuropathic pain studies; however, the NNT for 30% pain relief (3.9 (2.5–9.1)) and pain improvement on the patient global impression of change (2.9 (20–5.1)) was similar to what is observed in post-herpetic neuralgia and painful diabetic neuropathy (Lesser et al 2004; Rosenstock et al 2004; Sabatowski et al 2004; Freynhagen et al 2005; van Seventer et al 2006).

Recently, pregabalin was studied in a parallel group design study in patients with central pain following stroke or spinal cord injury (Vranken et al 2007). The etiology was stroke in 19 patients (of these thalamic lesion in 4 and brainstem infarction in 3) and spinal cord injury in 21 patients (of these 11 had a complete injury). The diagnoses were evenly distributed among patients allocated to pregabalin (n = 20) and to placebo (n = 20). For the diagnosis of central pain, the pain should be described as burning, paroxysmal episodes of shooting pain, or pain on light touch, and patients had to score above 12 on the Leeds Assessment of Neuropathic Symptoms and Signs questionnaire (LANSS) (Bennett 2001). A baseline pain score above 6 (visual analog scale, VAS) was required. In a flexible-dose regime and with no base-line period, patients received escalating doses of either pregabalin tablets 150 mg or matching placebo capsules bid titrated at 3-day intervals until a pain reduction of 1.8 on a VAS was obtained, they reached the maximum daily dose of 600 mg, or had intolerable side-effects. The patients then remained on the final dose during the remainder of the study period, which

Table 2 Randomized placebo-controlled trials of pregabalin in central pain

Study	Population	Design	Daily dose	NNT	
				50% pain relief	30% pain relief
Siddall et al 2006	Spinal cord injury pain (n = 70)	Parallel	Up to 600 mg, average 460 mg	7.1 (3.9–37)	3.9 (2.5–9.1)
Vranken et al 2007	Spinal cord injury pain and central post-stroke pain (n = 40)	Parallel	Up to 600 mg, average 460 mg	3.3 (1.9–14.3)	4.0 (2.0–328)

Abbreviation: NNT, number needed to treat.

was 4 weeks. Patients treated with gabapentin discontinued this treatment at least 3 days before receiving study medication. Pain medication that was continued during the trial was opioids in 53%, antidepressants in 30%, and carbamazepine in 10%. Baclofen was used by 10%. Seventeen patients in the pregabalin group completed the study: nine received 600 mg and eight received 300 mg daily. The primary efficacy parameter was the pain intensity based on the average of 3 VAS pain scores measured during the 24 hours prior to baseline and at the end of the 4-week treatment period. The improvement in pain score from baseline (pregabalin – placebo) was −2.18 (−0.57 to −3.80) with no difference in efficacy between the groups with spinal and brain injury. The NNT for 50% pain relief was low, 3.3 (1.9–14.3), and for 30% pain relief it was 4.0 (2.0–328).

In both studies, pregabalin was an add-on analgesic, which suggests that responses may be due to synergistic interactions. In painful diabetic neuropathy pregabalin was effective as monotherapy (Lesser et al 2004; Rosenstock et al 2004; Richer et al 2005), and in both studies in central pain, effect sizes were similar regardless of whether patients used any concomitant analgesics (Siddall et al 2004; Vranken et al 2007). This would suggest that pregabalin is effective as monotherapy also in central pain, but potential synergistic effects need to be studied in appropriately designed studies.

Safety and tolerability

Pregabalin is generally well tolerated with no contraindications except for known hypersensitivity to pregabalin or its components. The most common adverse reactions in the peripheral neuropathic pain studies were dose-related dizziness (22%–38%) and somnolence (11%–25%), which does not resolve in about one third of patients. These side-effects pose a risk for accidental injury in the elderly. Other adverse reactions were dry mouth, asthenia, blurred vision, ataxia, peripheral edema, and weight gain not limited to patients with edema. Adverse events were usually mild or moderate. There are little data on withdrawal phenomena. In short term trials pregabalin treatment is not associated with clinical significant withdrawal syndromes (Frampton and Foster 2006), but abrupt discontinuation may cause insomnia, nausea, headache, or diarrhea and it is recommended to taper off during at least one week (Pfizer 2007). In case of persistent blurred vision, a visual field testing and funduscopic examination may be considered, and patients are advised to report unexplained muscle pain particularly if accompanied with malaise and fever (Pfizer 2007) due to unsettled relation of pregabalin to rhabdomyolysis and creatine kinase elevations. Pregabalin is recommended to be used with caution in patients with congestive heart failure (NYHA, (New York Heart Association) class III and IV) because of limited data in this population (Pfizer 2007).

In the two studies in central pain, patients with a creatinine clearance below 60 mL/min were excluded. The frequency of somnolence in the trial by Siddall et al (2006) (41% in the pregabalin group and 9% in the placebo group) was more common than in studies in peripheral neuropathic pain, which may be attributed to additive effects of concomitant medications such as baclofen and benzodiazepines in this patient population. In the study by Vranken et al (2007), somnolence occurred in 45% but was equally common in the placebo group. Other more frequent adverse reactions in the pregabalin group in the Siddall study included: dizziness observed in 24%, edema in 20%, asthenia and dry mouth each in 16%, constipation in 13%, amnesia in 10%, and blurred vision in 9%. The frequency of peripheral edema (10%) was not higher than that observed in peripheral neuropathic pain. Two patients in the placebo group and eight in the pregabalin group had a weight gain ≥7%. The median time to onset of somnolence and dizziness was within 8 and 6 days and lasted 53 days and 33 days respectively. Adverse reactions were generally mild to moderate. Withdrawal due to side-effects occurred in 15 pregabalin- and 9 placebo-treated patients. Two adverse reactions were considered related to treatment: one had a withdrawal reaction 1 day following pregabalin discontinuation with increased spasticity and impaired coordination, and one had edema, hypervolemia and reduced platelet count caused by an infection. In the study by Vranken et al (2007), side-effects were mild to moderate with no difference in frequency of adverse reactions in the two study groups. Withdrawal due to adverse reactions occurred in 3 patients in each group.

Discussion

Few other randomized trials have been performed in central pain (Finnerup and Sindrup 2007). The related drug gabapentin has been studied in spinal cord injury pain (Levendoglu et al 2004). Gabapentin up to 3600 mg relieved intensity and frequency of pain and several pain descriptors in 20 paraplegics with complete spinal cord injury. The tricyclic antidepressant (TCA) amitriptyline has been studied in a three-way crossover study in post-stroke pain (Leijon and Boivie 1989). Amitriptyline in doses up to 75 mg daily had a significant pain-relieving effect, which correlated with total plasma concentration. Amitriptyline did not relieve

nociceptive and neuropathic pain in spinal cord injury, but neuropathic pain was not evaluated separately (Cardenas et al 2002). The anticonvulsant and sodium blocker lamotrigine reduced central post-stroke pain in doses of 200 mg/day as well as cold allodynia (Vestergaard et al 2001), but in spinal cord injury pain, lamotrigine 200–400 mg daily was not more effective than placebo in reducing pain, although a post-hoc analysis suggested that it may be effective in a subgroup of patients with incomplete injury and evoked pain (Finnerup et al 2002). In multiple sclerosis, cannabinoids have been shown to relieve central pain (Svendsen et al 2004; Rog et al 2005). Opioids also relieve central pain (Rowbotham et al 2003). Carbamazepine did not relieve post-stroke pain (Leijon and Boivie 1989) and mexiletine (Chiou-Tan et al 1996) and valproate (Drewes et al 1994) had no significant effect in spinal cord injury pain, but these studies all include a low number of patients with a risk of a type II error.

Treatment of central and peripheral neuropathic pain is limited by side-effects and high potential for drug interaction. Side-effects to TCAs attributed to anticholinergic actions are common, eg, dry mouth, constipation, and urinary retention, and there is a risk of somnolence and confusion, orthostatic hypotension, and gait disturbances. The most serious side effect is cardiotoxicity (Ray et al 2004), and TCAs are contraindicated in patients with heart failure and cardiac conduction blocks, and ECG is therefore needed before initiating treatment. Lamotrigine treatment is associated with dizziness, ataxia, diplopia, somnolence, nausea, and allergic exanthema and Stevens-Johnson syndrome, and very slow-dose escalation is recommended. Side-effects to cannabinoids include dizziness, drowsiness, impaired psychomotor function, and other psychoactive effects like dysphoria, and there is an unsettled issue with respect to risk of precipitating psychosis or schizophrenia (Semple et al 2005). The most common adverse effects of opioids are sedation, constipation, and nausea. Other side-effects include confusion, especially in elderly patients, urinary retention, dizziness, and dysphoria as well as risk of abuse and addiction. It is therefore recommended to consider long-term opioids for non-cancer pain only when other reasonable therapies fail to provide adequate pain relief (Kalso et al 2003).

In summary, amitriptyline (central post-stroke pain), lamotrigine (central post-stroke pain but a negative trial in spinal cord injury pain), gabapentin (spinal cord injury pain), and pregabalin (spinal cord injury and central post-stroke pain), and cannabinoids (central pain in multiple sclerosis) have proven to be effective, but large-scale randomized controlled studies are lacking, and a treatment algorithm for central pain still needs to be based partly on established treatments for peripheral neuropathic pain for which TCAs, serotonin-noradrenaline reuptake inhibitors, gabapentin/pregabalin, and opioids/tramadol have consistently shown efficacy (Finnerup et al 2005). There is no evidence to suggest that pregabalin and gabapentin have different efficacy or side effects determined by NNT or NNH values (Finnerup et al 2005). Differences between the two drugs relates to slightly higher expenses for pregabalin at the moment but more favorable dosing (twice daily dose possible) and linear kinetics with pregabalin. Thus, based on evidence for efficacy, gabapentin, pregabalin, and TCAs consistently relieve peripheral neuropathic pain as well as central pain (except for the lack of efficacy of amitriptyline in spinal cord injury mixed pain). Of these, gabapentin and pregabalin may be considered the first-line drugs for the treatment of central pain due to their consistent efficacy, safety, and minimal potential for drug-drug interactions, and TCAs a second line-treatment if no contraindications exist. Possible third-line treatments for central pain include opioids and tramadol, cannabinoids in multiple sclerosis, lamotrigine, and serotonin-noradrenaline reuptake inhibitors, which have not yet been tested in central pain but have a better side-effect profile than TCAs. In many cases, treatment provides no or only partial pain relief, and often combination therapy is used. There is a strong rational for combining drugs with different mode of actions (Backonja et al 2006), but little clinical evidence. In one randomized trial, gabapentin and morphine combined achieved better analgesia at lower doses than with either drug alone (Gilron et al 2005).

The recommended dose of pregabalin is 75–150 mg twice daily or 50–100 mg 3 times a day in patients with a creatinine clearance of at least 60 mL/min. Dosing is usually started at 75 mg once or twice daily and may be increased to 300 mg/ day within 1 week based on efficacy and tolerability. Dose may be increased up to 600 mg daily after yet another 2–4 weeks. Patients with post-stroke pain may be more susceptible to medication than other patient populations. For that reason it is advisable in some patients to start with a low pregabalin dose of 25 mg and increase slowly. The dose should be adjusted for patients with renal impairment (Table 1). There are limited data on long-term efficacy and adherence.

Conclusion

Based on efficacy and safety, pregabalin is considered a first-line drug together with gabapentin in the treatment of central pain. Pregabalin and gabapentin may especially have

a primary role in patients with anxiety and sleep disturbances and in patients who are taking multiple drugs. Somnolence, dizziness, and accidental falls may be a concern, especially in the elderly and in those treated with other drugs with CNS-related side-effects.

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References

Andersen G, Vestergaard K, Ingeman NM, et al. 1995. Incidence of central post-stroke pain. *Pain*, 61:187–93.

Backonja MM, Irving G, Argoff C. 2006. Rational multidrug therapy in the treatment of neuropathic pain. *Curr Pain Headache Rep*, 10:34–8.

Ben-Menachem E. 2004. Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia*, 45 Suppl 6:13–8.

Bennett M. 2001. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain*, 92:147–57.

Budh CN, Lund I, Ertzgaard P, et al. 2003. Pain in a Swedish spinal cord injury population. *Clin Rehabil*, 17:685–90.

Cardenas DD, Warms CA, Turner JA, et al. 2002. Efficacy of amitriptyline for relief of pain in spinal cord injury: results of a randomized controlled trial. *Pain*, 96:365–73.

Chiou-Tan FY, Tuel SM, Johnson JC, et al. 1996. Effect of mexiletine on spinal cord injury dysesthetic pain. *Am J Phys Med Rehabil*, 75:84–7.

Dooley DJ, Taylor CP, Donevan S, et al. 2007. Ca2+ channel alpha2delta ligands: novel modulators of neurotransmission. *Trends Pharmacol Sci*, 28:75–82.

Drewes AM, Andreasen A, Poulsen LH. 1994. Valproate for treatment of chronic central pain after spinal cord injury. A double-blind cross-over study. *Paraplegia*, 32:565–9.

Dworkin RH, Corbin AE, Young JP, Jr., et al. 2003. Pregabalin for the treatment of postherpetic neuralgia: A randomized, placebo-controlled trial. *Neurology*, 60:1274–83.

EMEA. European Medicines Agency. 2004. Lyrica – scientific discussion. Accessed 25 June 2007. URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/lyrica/084504en6.pdf

EMEA. European Medicines Agency. 2006 Lyrica – scientific discussion. Accessed 25 June 2007. URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/lyrica/Lyrica%20H-546-II-07-AR.pdf

Fehrenbacher JC, Taylor CP, Vasko MR. 2003. Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. *Pain*, 105:133–41.

Finnerup NB, Otto M, McQuay HJ, et al. 2005. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain*, 118:289–305.

Finnerup NB, Sindrup SH. 2007. Central pain – pharmacological treatments. In Schmidt RF, Willis WW, eds. Encyclopedic reference of pain. Heidelberg: Springer-Verlag.

Finnerup NB, Sindrup SH, Bach FW, et al. 2002. Lamotrigine in spinal cord injury pain: a randomized controlled trial. *Pain*, 96:375–83.

Frampton JE, Foster RH. 2006. Pregabalin: in the treatment of generalised anxiety disorder. *CNS drugs*, 20:685–93.

Freynhagen R, Strojek K, Griesing T, 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*, 115:254–63.

Gilron I, Bailey JM, Tu D, et al. 2005. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*, 352:1324–34.

Kalso E, Allan L, Dellemijn PL, et al. 2003. Recommendations for using opioids in chronic non-cancer pain. *Eur J Pain*, 7:381–6.

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

Lesser H, Sharma U, LaMoreaux L, et al. 2004. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. *Neurology*, 63:2104–10.

Levendoglu F, Ogun CO, Ozerbil O, et al. 2004. Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine*, 29:743–51.

Li CY, Zhang XL, Matthews EA, et al. 2006. Calcium channel alpha(2)delta(1) subunit mediates spinal hyperexcitability in pain modulation. *Pain*, 125:20–34.

McClelland D, Evans RM, Barkworth L, et al. 2004. A study comparing the actions of gabapentin and pregabalin on the electrophysiological properties of cultured DRG neurones from neonatal rats. *BMC Pharmacol*, 4:14–40.

Osterberg A, Boivie J, Thuomas KA. 2005. Central pain in multiple sclerosis--prevalence and clinical characteristics. *Eur J Pain*, 9:531–42.

Pfizer. 2007. Lyrica product resumé. 2007. Accessed 25 June 2007. URL: http://www.pfizer.com/pfizer/download/uspi_lyrica.pdf

Randinitis EJ, Posvar EL, Alvey CW, et al. 2003. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol*, 43:277–83.

Ray WA, Meredith S, Thapa PB, et al. 2004. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther*, 75:234–41.

Richter RW, Portenoy R, Sharma U, et al. 2005. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. *J Pain*, 6:253–60.

Rog DJ, Nurmikko TJ, Friede T, et al. 2005. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*, 65:812–9.

Rosenstock J, Tuchmann M, LaMoreaux L, et al. 2004. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain*, 110:628–38.

Rowbotham MC, Twilling L, Davies PS, et al. 2003. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med*, 348:1223–32.

Sabatowski R, Galvez R, Cherry DA, 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*, 109:26–35.

Semple DM, McIntosh AM, Lawrie SM. 2005. Cannabis as a risk factor for psychosis: systematic review. *J Psychopharmacol*, 19:187–94.

Siddall PJ, Cousins MJ, Otte A, et al 2006. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology*, 67:1792–800.

Siddall PJ, McClelland JM, Rutkowski SB, et al. 2003. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain*, 103:249–57.

Sills GJ. 2006. The mechanisms of action of gabapentin and pregabalin. *Curr Opin Pharmacol*, 6:108–13.

Svendsen KB, Jensen TS, Bach FW. 2004. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ*, 329:253–61.

Tassone DM, Boyce E, Guyer J, et al. 2007. Pregabalin: A novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther*, 29:26–48.

Taylor CP, Angelotti T, Fauman E. 2007. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. *Epilepsy Res*, 73:137–50.

van Seventer R., Feister HA, Young JP, Jr., et al. 2006. Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. *Curr Med Res Opin*, 22:375–84.

Vestergaard K, Andersen G, Gottrup H, et al. 2001. Lamotrigine for central poststroke pain: A randomized controlled trial. *Neurology*, 56:184–90.

Vranken JH, Dijkgraaf MG, Kruis RM et al. 2007. Pregabalin in patients with central neuropathic pain: A randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. Pain, in press.

Werhagen L, Budh CN, Hultling C, et al. 2004. Neuropathic pain after traumatic spinal cord injury - relations to gender, spinal level, completeness, and age at the time of injury. *Spinal Cord*, 42:665–73.