

2012

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Kruckow, K. (2012) 'Pregabalin for treating Painful Diabetic Neuropathy in Type 1 and Type 2 Diabetic Patients', *The Plymouth Student Scientist*, 5(1), p. 61-78.

<http://hdl.handle.net/10026.1/13966>

The Plymouth Student Scientist
University of Plymouth

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Pregabalin for treating Painful Diabetic Neuropathy in Type 1 and Type 2 Diabetic Patients

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Abstract

Background: It has been estimated that chronic painful diabetic neuropathy (PDN) affects 1 in 6 (16.2%) of all diabetic patients (Diabetes UK, 2010) yet the symptoms of PDN continue to present a huge challenge in its management both for physicians and patients.

Objectives: To ascertain whether pregabalin is effective as a treatment for relieving pain in PDN and to identify which dose: 150/300/600 mg/d is most effective.

Search methods: "Pregabalin" and "Painful Diabetic Neuropathy" were entered into Pubmed and Scirus. "Humans" and "randomised controlled trial" were entered as limiters. The search was completed using the Athens log in through the University of Plymouth on 28th February 2011.

Selection criteria: Randomised double-blind controlled trials, with patients diagnosed with Type 1 or Type 2 diabetes mellitus and a diagnosis of PDN for a duration of ≥ 1 year were selected. Studies which reported the effectiveness of taking dosages of pregabalin of 150 mg per day (mg/d), 300 mg/d or 600 mg/d and a placebo for pain relief were used in this meta-analysis. Only completed studies were included.

Data collection and analysis: The author used strict inclusion criteria to extract the data. Revman 5 was used to analyse the mean difference with 95% confidence intervals and fixed effects for pain relief when taking either pregabalin or placebo.

Main results: The search yielded fourteen studies. Thirteen were available via the University of Plymouth subscription and one was requested via the inter-library loans service. Six studies including 1,628 participants were eligible as having the correct inclusion criteria and measuring the correct endpoints. Overall, pregabalin was more effective at reducing mean pain scores in comparison to the placebo with a total mean difference of -0.90 in favour of pregabalin. The dose 600 mg/d had a significant effect on pain relief in comparison to the placebo with a mean difference of -1.19 in favour of pregabalin. The dose 300 mg/d also had a significant effect on pain relief in comparison to the placebo with a mean difference of -0.86 in favour of pregabalin. The dose 150 mg/d had a significant effect on pain relief in comparison to the placebo with a mean difference of -0.38 in favour of pregabalin. There was a significant difference in efficacy between 150 mg/d and 600 mg/d of pregabalin. There was no significant difference between 300 mg/d and 600 mg/d doses. There was also no significant difference between 150 mg/d and 300 mg/d doses of pregabalin.

Conclusions: Pregabalin 150 mg/d, 300 mg/d and 600 mg/d effectively reduced pain in patients with PDN. 600 mg/d dose relieved pain most effectively and 150 mg/d was the least effective.

Background

Description of painful diabetic neuropathy

Currently, the prevalence of diabetes globally is 285 million and by 2030 this is estimated to rise to 438 million people (Diabetes UK, 2010). PDN can affect all people with diabetes irrelevant of the type of diabetes they are diagnosed with and is estimated to affect 1 in 6 (16.2%) of people with diabetes (Diabetes UK, 2010). It is most likely to develop in those people whose blood glucose is poorly controlled and those who have had a longer duration of diabetes (Pirat, 1977). Haemoglobin A_{1C} (HbA_{1C}) is a test that measures the amount of glucose bound to the haemoglobin in blood. This test is carried out approximately twice a year in diabetic patients (Walker and Rodgers, 2004). A good HbA_{1C} result is 7% or below (Walker and Rodgers, 2004). However, even with very good long-term glycaemic control (HbA_{1C} < 7%) the incidence of PDN during a lifetime of a diabetic is 20% (Martin *et al.* 2006). This suggests that no matter how well blood glucose is managed, there will always be patients presenting with PDN.

PDN can interfere with many aspects of life and it can severely negatively affect patients' daily functions. The symptoms of PDN are typically burning, aching and tingling pains (Huizinga and Peltier, 2007) which are sometimes described by patients as 'electric-shock' and 'stabbing' sensations. The pain is usually worst at night time (Boulton *et al.* 2005) and is usually excruciating (Aring *et al.* 2005). In an estimated 5-10% of diabetic patients, the symptoms of PDN significantly decrease quality of life (Rogers *et al.* 2004). There have been many advances in the understanding of the pathophysiology of PDN. However, there have been very few treatments that are aimed at interrupting these processes. Treatment has therefore focused on controlling blood glucose and painful symptoms.

Aetiology of Painful Diabetic Neuropathy

The mechanism by which PDN develops is not fully understood and research is still ongoing. PDN is thought to be the result of a number of different processes (Quan, 2010). Unlike most cells in the body, neurons are insulin-independent. Glucose can pass from the outside of the cell to the inside without requiring insulin (Ryle and Donaghy, 1995). The glucose is used for energy as normal but excess glucose during hyperglycaemia will enter the polyol pathway and be converted by aldose reductase and sorbitol dehydrogenase enzymes into sorbitol (Quan, 2010). In people with hyperglycaemia, the excess levels of glucose in the blood rises and the affinity of the aldose reductase enzyme increases leading to higher levels of sorbitol to be produced. The sorbitol cannot cross the cell membranes and so accumulates within the cell. The result of this is that osmotic stresses on the cells occur by excess water being drawn into the cell. This can damage the cells and even cause cell lysis. In addition, decreased membrane Na⁺/K⁺-ATPase activity, damage to axons and structural damage to neurons can lead to the abnormal generation of action potentials (Quan, 2010). This means that the neurons are being inappropriately stimulated, leading to the chronic pain seen in PDN. The repair mechanisms of neurons are also affected in PDN. Excess glucose reacts with nucleotides, proteins and lipids resulting in 'advance glycation end products' (AGE). AGE is believed to interfere with the metabolism in cells and axonal transport (Ryle and Donaghy, 1995). Oxidative stress is also thought to contribute to PDN. In a hyperglycaemic state, the number of free radicals increases. These are believed to seriously affect several

mechanisms. These mechanisms include direct damage to blood vessels which leads to ischaemic nerves and AGE reaction facilitation (Quan, 2010). Tavakoli *et al.* (2008) emphasised that hyperglycaemia in the short-term may induce oxidative stress, which can consequently result in neuropathy, hence why HbA_{1c} level may be more important than duration of diabetes as a risk factor for developing PDN.

Description of pregabalin and how it may reduce pain

Pregabalin belongs to the anticonvulsant class of drugs (British National Formulary, 2011). It works by mimicking the gamma-aminobutyric acid (GABA) neurotransmitter in the central nervous system (Gajraj, 2007). It has been found to be inactive at GABA_A and GABA_B receptors and “is not converted metabolically to GABA” (Rosenstock *et al.* 2004). Also, it does not interfere with the uptake or degradation of GABA (Rosenstock *et al.* 2004). Pregabalin binds with high affinity to the alpha₂-delta subunit protein of voltage-gated calcium channels (Gee *et al.* 1996). By binding to the calcium channels, pregabalin reduces the inflow of calcium, which subsequently results in a decrease in the release of a number of different neurotransmitters (Fink *et al.* 2002) which include glutamate, substance P and noradrenaline (Dooley *et al.* 2000). When the neurotransmitters are not released, they cannot diffuse into the synaptic cleft and bind to the receptors on the postsynaptic cell. Therefore a nerve impulse is not generated (Rang *et al.* 2007). Hence the relief in pain.

Why is this meta-analysis important?

The management of PDN continues to be a huge challenge for doctors and their patients. An estimated 16.2% of people with diabetes will develop PDN (Diabetes UK, 2010) making it a relatively common complication of diabetes. Furthermore, it is estimated that in 5-10% of diabetic patients, the painful symptoms of PDN significantly decrease their quality of life (Rogers *et al.* 2004). Treatment of PDN can often be challenging because it is difficult to select a pharmacological agent that is suitable from the many that are available. A ‘trial and error’ method is often used until a suitable drug is found for the patient.

In 2010, the National Institute for Clinical Excellence (NICE) published guidelines for the treatment of PDN which have suggested that pregabalin should be used as second-line treatment after amitriptyline or duloxetine has been tried. Rogers *et al.* (2004) supported this by stating that “pregabalin is more potent” meaning the therapeutic effect can be seen with low doses, which subsequently will result in fewer side effects.

It is important that results from previous meta-analyses can be repeated with the addition of recent randomised controlled trials. This can then take into account new studies and determine whether results are consistent. This meta-analysis is therefore important to show whether pregabalin is effective as an analgesic in patients with PDN, particularly at the lower doses.

Objectives

1. To ascertain whether pregabalin is effective as a treatment for relieving pain in patients with PDN.

2. To identify which dose: 150/300/600 mg/d is most effective at relieving pain in patients with PDN.

Methods

Criteria for considering studies for this meta-analysis

Identification of studies by electronic searches

The studies were identified by searching Pubmed and Scirus using the key words "Pregabalin" and "Painful Diabetic Neuropathy".

The limits "humans" and "randomised controlled trial" were applied to the search. Required journals which were not subscribed to by the University of Plymouth were ordered through the inter-library loans service.

Selection of studies

The studies all had to satisfy strict inclusion criteria and if the study did not fulfil all of the criteria, it was excluded.

Types of study

This meta-analysis only used randomised double-blind controlled trials and the studies were only included if they used human subjects.

Types of participants

Males and females ≥ 18 years of age who had been diagnosed with diabetes mellitus and subsequently PDN. All participants had a HbA_{1c} of $\geq 11\%$.

Types of intervention

Studies were included if they assessed the efficacy of pregabalin for doses of 150, 300 or 600 mg/d in randomised controlled trials. The efficacy of pregabalin as an analgesic in PDN was compared against a placebo in each study.

Outcomes measured

The primary outcome measured was the analgesic effect from taking pregabalin.

Data collection and analysis

Data extraction and management

The studies that matched the inclusion criteria were put into an inclusion table stating their main characteristics. Some of the studies investigated the effect of more than one dose of pregabalin. If the doses investigated were 150, 300 or 600 mg/d, they were used in the analysis.

Measures of treatment effect

The mean difference and standard error (SE) for mean pain scores of all doses of pregabalin in all six of the studies were entered into RevMan5. The standard error was calculated using the following equation (Gardner and Altman, 1986) for studies that did not state it in their results.

$$SE = \frac{\text{Difference between mean and CI}}{1.96}$$

Once all of the data was entered, RevMan calculated a weighted mean average so that it could show the effects of individual studies as a contribution to the total. Fixed effects models using inverse variance and 95% confidence intervals were used to calculate the mean difference between pregabalin and placebo trials for pain relief. The results of the comparisons were presented in forest plots. On a forest plot, there are blocks presented for each study. This shows the weight assigned to the study. The larger the area of the block, the greater weight the study has in the meta-analysis. This would mean that the larger the block, the more the study would dominate the calculation of the pooled result. Either side of the block, there is a horizontal line. This represents the 95% confidence interval. Cochrane (2009) stated that “the confidence interval indicates where 95% of the results from the study would be expected to lie”. Heterogeneity was measured by RevMan by measuring I^2 . This enables the author to see if there is any variation between studies within the comparisons.

Three more analyses were carried out using the same process outlined above. The first used a dose of 600 mg/d, the second used a dose of 300 mg/d and the third used a dose of 150 mg/d. An interval plot was then constructed using Excel to display the total mean difference and confidence intervals for each dose of pregabalin.

To assess publication bias, a funnel plot was produced using RevMan for the overall effect of all pregabalin doses in relieving pain. A funnel plot was only produced for comparison one. The reason for this is that it is recommended by Cochrane (2009) that tests for funnel plot asymmetry are only to be used when there are at least 10 studies included in the meta-analysis. When there are less than ten studies, “the powers of the tests are too low to determine chance from real asymmetry”.

Results

Description of studies

Results of the search

The search yielded 15 studies. Two of the studies were the same study but published in two different journals. So in total there were 14 studies. The characteristics of the studies were looked at in order to identify whether the study was to be included or excluded. Table 2 shows the characteristics of included studies and Table 3 shows the characteristics of excluded studies. Journals not subscribed to by the University of Plymouth were requested through the inter-library loans service.

Included Studies

Six studies which matched all the inclusion criteria were included in the meta-analysis. All of the studies tested the efficacy of pregabalin to relieve pain in PDN and the main aims of each study can be seen in Table 1. The main characteristics of the included studies are outlined in Table 2. There were 11 individual trials for different doses of pregabalin within the six studies. A total of 1,628 participants, both male and female aged ≥ 18 years were used in the analysis. Five trials with 392 participants contributed to the high dose comparison (600 mg/d), four trials with 490

participants contributed to the 300 mg/d dose and two trials with 178 participants contributed to the low dose (150 mg/d) comparison.

Table 1: The main aims of the six studies used in this meta-analysis.

Authors	Year	Title	Aim
Arezzo <i>et al.</i>	2008	Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial.	The main aim of this study was to evaluate the efficacy and safety of pregabalin 600 mg/d for PDN and to examine the impact of pregabalin on sensory and motor nerve conduction.
Lesser <i>et al.</i>	2004	Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial.	The main aim of this study was to assess the efficacy of pregabalin 75/300/600 mg/d for the symptomatic relief of PDN.
Richter <i>et al.</i>	2005	Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial.	The main aim was to evaluate the efficacy of pregabalin 150 or 600 mg/d for the treatment of PDN.
Rosenstock <i>et al.</i>	2004	Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial.	The main aim was to evaluate the effectiveness of pregabalin for the systematic treatment of PDN, in particular the relief of pain.
Satoh <i>et al.</i>	2011	Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial.	The main aims of this study were to evaluate the efficacy, safety and pharmacokinetics of pregabalin as a treatment for PDN in Japanese patients.
Tölle <i>et al.</i>	2008	Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study.	The main aim of this study was to assess the efficacy and safety of pregabalin 150/300/600 mg/d to reduce pain in people with PDN.

Table 2: Characteristics of included studies. Note: RCT = Randomised Controlled Trial. M = Male, F = Female. SD = Standard Deviation.

Study	Double-Blind RCT	M/F	Mean Age (yrs)	Mean duration of diabetes	Type of diabetes	Mean duration of PDN	Placebo	Method and timing of pregabalin intake
Efficacy and safety of pregabalin 600 mg/d	Double-blind RCT	M and F include	All subjects ≥18. Mean age	10 yrs	Type 1 and Type 2 diabetes mellitus	~5 yrs	Placebo not stated	Pregabalin 600 mg/d or placebo was administered as two divided

for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. Arezzo et al. 2008		d in study. 167 subjects in total.	not stated.		with HbA _{1c} ≤ 11%			doses. Daily dosage was escalated over a 1 week period beginning with a single dose of 150 mg pregabalin on day 1 followed by two doses of 150 mg pregabalin on days 2-6 and two doses of 300 mg pregabalin on day 7 which were continued for 12 weeks.
Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Lesser et al. 2004	Double-blind RCT	202 M 135 F	59.9 (10.5 SD)	Not stated.	Type 1 and Type 2 diabetes mellitus with HbA _{1c} ≤ 11% (91% of subjects Type 2).	1 to 5 yrs. Mean duration of PDN for subjects not stated.	Placebo not stated.	Pregabalin or matching placebo capsules were administered orally, three times a day for a period of 5 weeks.
Relief of Painful Diabetic Peripheral Neuropathy with Pregabalin: A Randomized, Placebo-Controlled Trial. Richter et al. 2005	Double-blind RCT	149 M 97 F	57.1 ± 10.3 for placebo. 56.3 ± 9.4 for 150 mg/d patients. 57.8 ± 9.5 for 600 mg/d patients.	10.6 ± 8.3 yrs for placebo. 8.2 ± 9.1 yrs for 150 mg/d patients. 9.3 ± 8.8 yrs for 600 mg/d patients.	Type 1 and Type 2 diabetes mellitus with HbA _{1c} ≤ 11%	1 to 5 yrs. Mean duration of PDN for subjects not stated.	Placebo not stated.	Pregabalin was provided as two differently sized capsules. One with small-sized capsules containing 25mg pregabalin or placebo and the other with large-sized capsules containing 100 mg pregabalin or placebo. Patients took 2 capsules from each bottle 3 times daily. The treatment was given for 6 weeks duration.

Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Rosenstock et al. 2004	Double-blind RCT	164 M 128 F	59.7 (11.4 SD).	9.3 yrs (10.3 SD)	Type 1 and Type 2 diabetes mellitus with HbA _{1c} ≤ 11% (87% of patients had Type 2).	1 to 5 yrs. Mean duration of PDN for subjects not stated.	Lactose USP	All medications were packaged in blinded fashion and administered orally. Capsules were supplied in bottles, and patients were instructed to take one capsule three times a day for 8 weeks.
Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. Satoh et al. 2011	Double-blind RCT	240 M 77 F	61.3 (9.6 SD) for placebo. 61.3 (10.3 SD) for 300 mg/d subjects. 62.2 (10.3 SD) for 600 mg/d subjects.	Not stated.	Type 1 and Type 2 diabetes mellitus.	Not stated.	Placebo not stated.	Patients took pregabalin 150 or 300 mg or placebo twice daily during the 12-week fixed-dose treatment phase. A 1 week titration phase was conducted previously to this whereby patients took pregabalin 75 mg twice daily and was slowly increased until the target dose was reached.
Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: A randomized, double-blind study. Tölle et al. 2008	Double-blind RCT	219 M 176 F	58.61 yrs (11.5 SD)	Not stated.	Type 1 and Type 2 diabetes mellitus with HbA _{1c} ≤ 11%	≥ 1 year. Mean duration of PDN for subjects not stated.	Placebo not stated.	Placebo/150/300/600 mg/day pregabalin were all administered by twice daily dosing for 11 weeks.

Excluded Studies

Eight studies were excluded because they did not match the inclusion criteria. The reasons for exclusion from the analysis are shown in Table 3.

Table 3: Characteristics of excluded studies

Excluded study	Reason for exclusion
Bansal <i>et al.</i> 2009	This study did not state the HbA _{1c} level for the patients.
Baron <i>et al.</i> 2009	The study was not limited to pregabalin. It assessed a combination therapy. Also, it included postherpetic neuralgia patients.
Baron <i>et al.</i> 2008	This was an open-label, flexible-dose study. Patients were not limited to PDN.
Freyenhagen <i>et al.</i> 2006	Assessed pregabalin for neuropathic pain in general and was not specific to PDN patients.
Freyenhagen <i>et al.</i> 2005	Assessed pregabalin for neuropathic pain in general and was not specific to PDN patients.
Hoffman <i>et al.</i> 2010	This study didn't assess pregabalin. It assessed health status.
Rodriguez <i>et al.</i> 2007	This study was a cost-effective analysis looking at both PDN and postherpetic neuralgia patients.
Zin <i>et al.</i> 2010	This study included both PDN and postherpetic neuralgia patients.

Effects of interventions

Comparison 1: Overall effect of all doses of pregabalin as an analgesic.

The forest plot for comparison 1 did show some variation in the results. The overall standardised mean difference in mean pain score calculated using the fixed effects model was -0.90 in favour of pregabalin ($P < 0.00001$) (Figure 1). There was moderate heterogeneity ($I^2 = 66%$) ($P = 0.0009$).

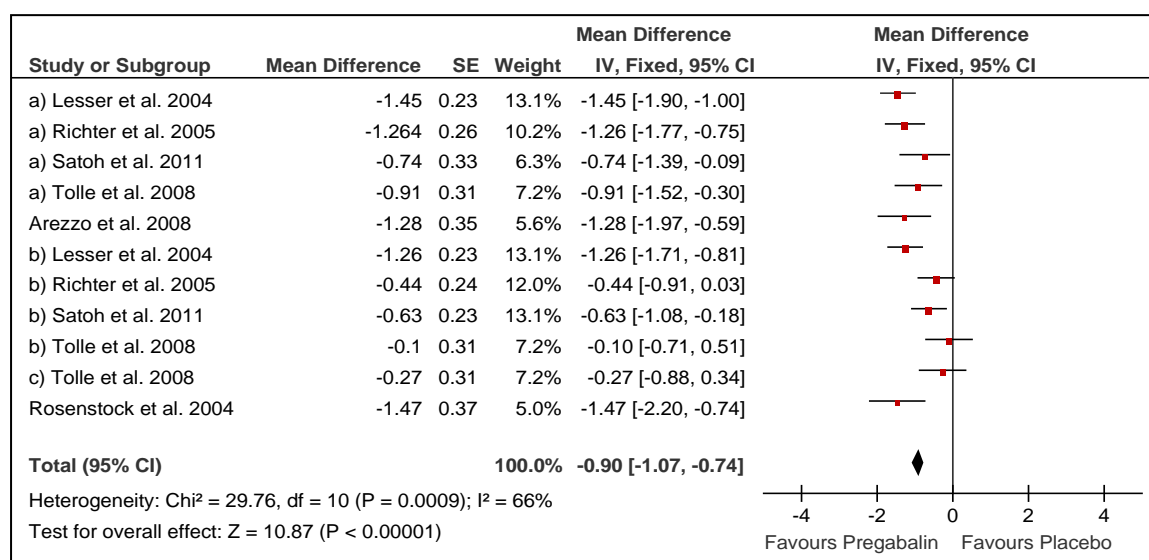


Figure 1: Forest plot of comparison one: All doses of Pregabalin versus Placebo, outcome: analgesic effect. All pregabalin doses showed a more significant analgesic effect compared to placebo.

Comparison 2: Efficacy of 600 mg/d of pregabalin as an analgesic for PDN.

The forest plot showed the results of studies for mean difference and 95% confidence intervals were not significantly different. This shows that all of the studies showed a positive effect for pregabalin as an analgesic.

The overall standardised mean difference in mean pain score calculated using the fixed effects model was -1.19 in favour of pregabalin ($P < 0.00001$) (Figure 2). There was very low heterogeneity ($I^2 = 2\%$) ($P = 0.39$).

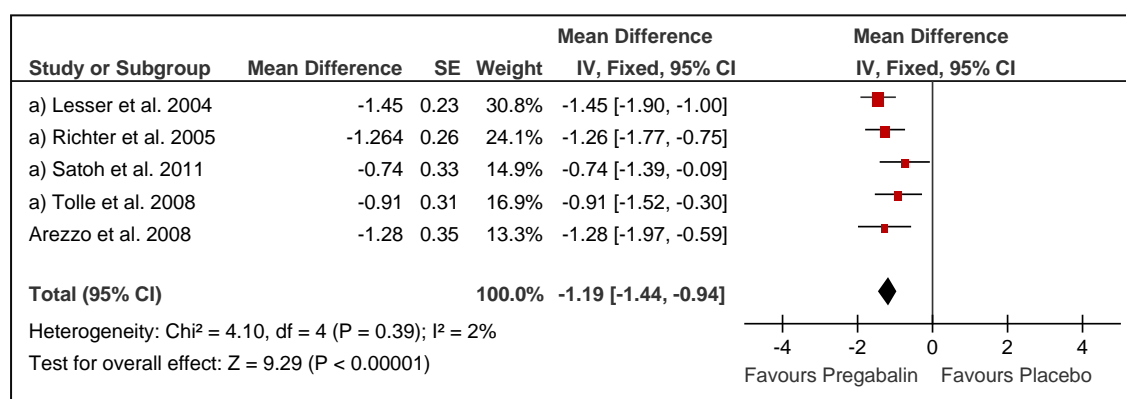


Figure 2: Forest plot of comparison two: 600 mg/day of Pregabalin versus Placebo, outcome: analgesic effect. 600 mg/day pregabalin showed a more significant analgesic effect compared to placebo.

Comparison 3: Efficacy of 300 mg/d of pregabalin as an analgesic for PDN.

The forest plot showed that the 300 mg/d trials differed in their efficacy.

The overall standardised mean difference in mean pain score calculated using the fixed effects model was -0.86 in favour of pregabalin ($P < 0.00001$) (Figure 3). There was high heterogeneity ($I^2 = 76\%$) ($P = 0.005$).

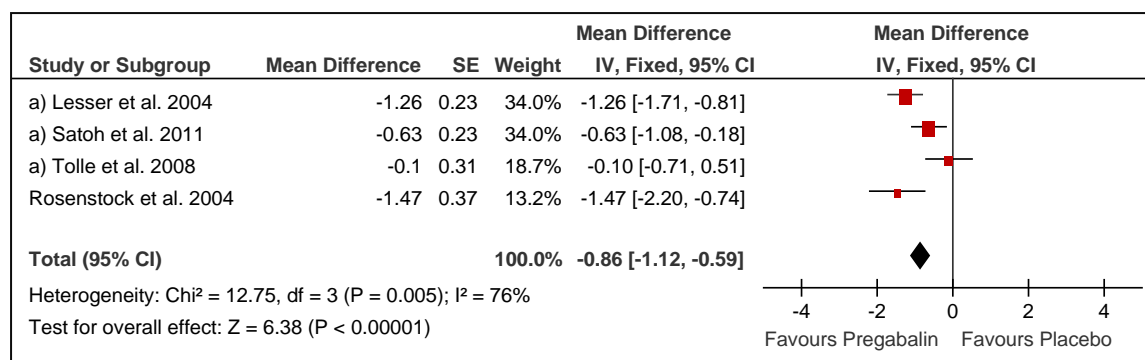


Figure 3: Forest plot of comparison three: 300 mg/day of Pregabalin versus Placebo, outcome: analgesic effect. 300 mg/day pregabalin showed a more significant analgesic effect compared to placebo

Comparison 4: Efficacy of 150 mg/d of pregabalin as an analgesic for PDN.

The forest plot showed the results of studies for mean difference and 95% confidence intervals were not significantly different. This shows that all of the studies showed a positive effect for pregabalin as an analgesic.

The overall standardised mean difference in mean pain score calculated using the fixed effects model was -0.38 in favour of pregabalin ($P = 0.05$) (Figure 4). There was no heterogeneity ($I^2 = 0\%$) ($P = 0.66$).

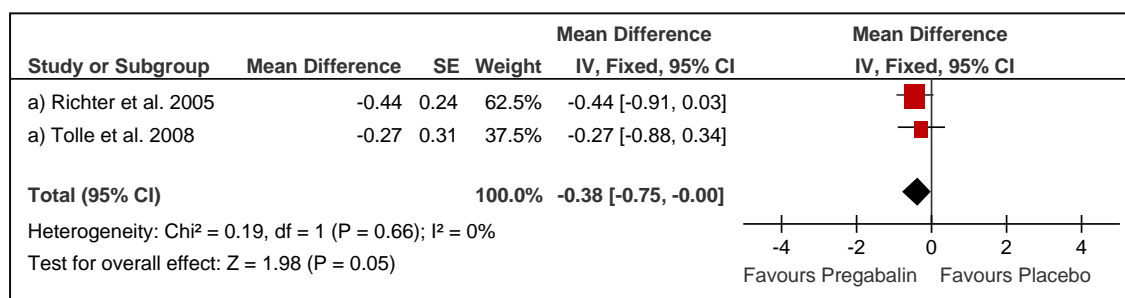


Figure 4: Forest plot of comparison four: 150 mg/day of Pregabalin versus Placebo, outcome: analgesic effect. 150 mg/day pregabalin showed a more significant analgesic effect compared to placebo.

Comparison 5: Comparing the mean differences for the three pregabalin doses 600 mg/d, 300 mg/d and 150 mg/d.

The interval plot showed that the 150 mg/d and 600 mg/d doses of pregabalin were significantly different as the 95% confidence intervals do not overlap. 300 mg/d and 600 mg/d pregabalin doses show that they are not significantly different because the confidence intervals overlap. The 150 mg/d and 300 mg/d doses also show that they are not significantly different because the confidence intervals overlap (Figure 5).

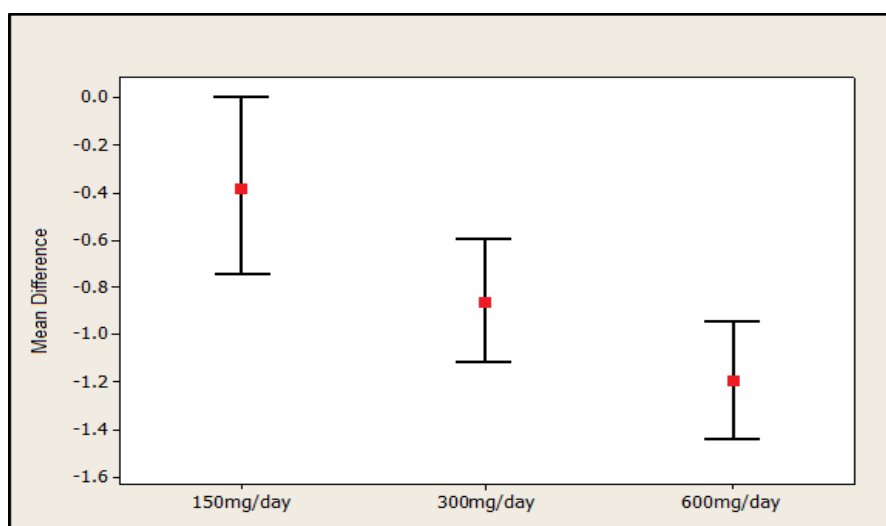


Figure 5: An interval plot for doses 600 mg/d, 300 mg/d and 150 mg/d. The 150 mg/d and 600 mg/d doses show they are significantly different because the confidence intervals do not overlap. There are no significant differences between 150 mg/d and 300 mg/d. There are also no significant differences between 300 mg/d and 600 mg/d.

The data for comparison one was plotted using a funnel plot (Figure 6). This was symmetrical and so did not show publication bias.

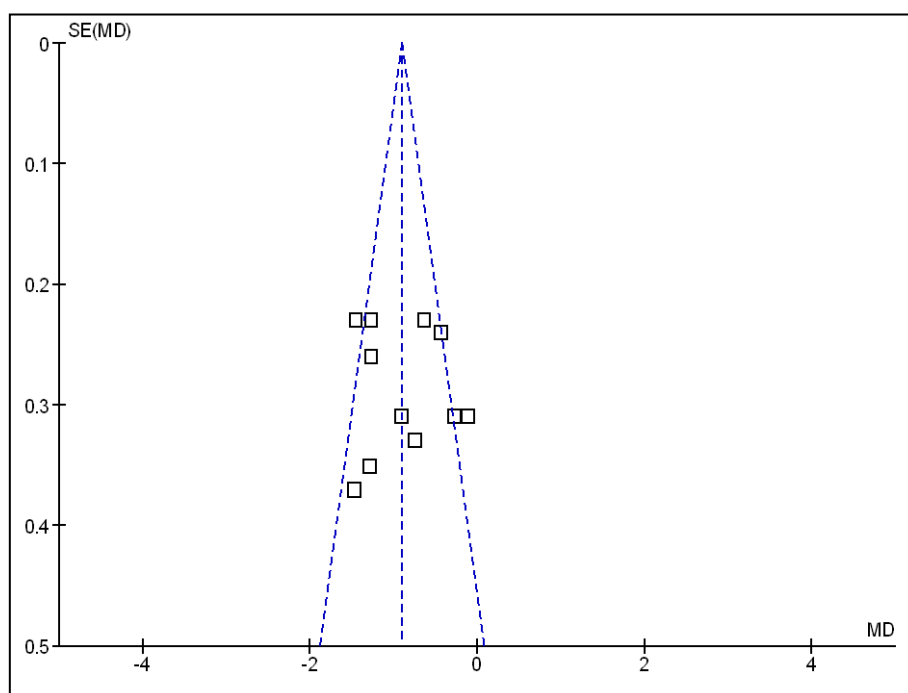


Figure 6: Funnel plot of comparison one: All doses of Pregabalin versus Placebo, outcome: analgesic effect.

Discussion

Overall completeness and applicability of evidence

After looking at the results, a conclusion can be made that all pregabalin doses significantly relieve pain in patients with PDN. These results are supported by Hurley *et al.* (2008) who conducted a meta-analysis of randomised controlled trials involving 728 participants and doses of pregabalin between 75-600 mg/d. A weighted mean difference of 1.15 was seen between pregabalin and placebo for all dosages and it was shown that pregabalin significantly reduces pain scores. Additional supportive research comes from Sharma *et al.* (2000) who found that pregabalin at a dose of 300 mg/d or above showed significant reduction in pain from PDN which is in line with the results found in this meta-analysis. Furthermore, a meta-analysis conducted by Semel *et al.* (2010) involving 2516 patients, studied 150-600 mg/d pregabalin for neuropathic pain and found results in line with this analysis. However, unlike this study, Semel *et al.* (2010) found no significant difference between baseline and endpoint mean pain score for the 150 mg/d dose. Only two studies were included in this meta-analysis for the 150 mg/d dose. When looking at comparison 4 for 150 mg/d, the lower value for the 95% confidence interval was -0.00 (Figure 4). If more studies had have been included, this value may have been lower and results similar to Semel *et al.* (2010) may have been found. However, Semel *et al.* (2010) included both post-herpetic neuralgia and PDN patients in their meta-analysis. It therefore is not specific to PDN. A strength of this study is that it is specific to PDN patients only therefore the results from this study may be more applicable.

In this meta-analysis, a dose-response relationship of pregabalin was seen for all three doses. However, there was only a significant difference in mean difference of mean pain scores (with 95% confidence intervals) between 150 mg/d and 600 mg/d doses. There was not a significant difference between 300 mg/d and 600 mg/d and there was also no significant difference between 150 mg/d and 300 mg/d pregabalin in reducing the mean pain scores. The results of this meta-analysis therefore support the use of 150 mg/d pregabalin initially for the treatment of patients with PDN with the aim of achieving pain relief at the lowest dose possible. However, if the patient does not feel that this dose gives sufficient pain relief, titrating the dose upwards would be recommended to either 300 mg/d or 600 mg/d to whichever suits the patient best. This is supported by the national institute for clinical excellence (NICE) who state that 150 mg/d should be the starting dose and that it should be titrated upwards to achieve the “person’s maximum tolerated dose up to a maximum dose of 600 mg/d” (NICE, 2010). By taking the approach of starting at the lower dose, it will prove to be more cost effective. 150 mg/d and 300 mg/d capsules of pregabalin cost £64.40 for a packet of 56-capsules, whereas 600 mg/d capsules cost £128.80 (British National Formulary, 2011).

The original objectives were met in this meta-analysis as conclusions were able to be drawn and show that pregabalin is effective as an analgesic in patients with PDN. The second objective was also met, as all three doses: 150mg/d, 300 mg/d and 600 mg/d were identified as being suitable for use in treating PDN.

Quality of the evidence variation

Cochrane (2009) stated that a systematic review is likely to contain heterogeneity due to the diversity in scientific method (as well as other factors) as different studies are being combined in one analysis. Therefore, to a certain extent, heterogeneity is to be expected. In this meta-analysis, the I^2 test was used to test for heterogeneity. The I^2 expresses the amount of heterogeneity as a percentage. Low heterogeneity is 25%, moderate describes a heterogeneity of 50% and 75% is described as high (Higgins *et al.* 2003).

The heterogeneity in this meta-analysis varied greatly between comparisons, ranging from zero to high heterogeneity (comparison 1 = 66%, comparison 2 = 2%, comparison 3 = 76% and comparison 4 = 0%). A reason for the 0% heterogeneity in comparison 4 could be that only two studies were included in this comparison. If more studies for 150 mg/d pregabalin would have been included, a larger variation in the data may have been seen.

One reason heterogeneity could have been increased in comparisons 1 and 3 is due to patients in the studies included not acting as their own controls. A separate group of patients were selected to take the placebo. This may have implications on the validity of this meta-analysis. There are a number of varying factors associated with individuals which can influence the drug responses in patients. These include genetic variation, other drugs a person may be taking, remembering to take the pregabalin, along with others. A more scientifically valid study would have been to only include randomised controlled, double-blind crossover studies in this meta-analysis. This would have ensured that the patients would have acted as their own controls. However, cross-over studies are not without disadvantages. Also, unless the patients are made to take the drug in front of the experimenter (which is

unrealistic and not practical), it is never going to be possible to be one hundred percent sure that patients have remembered to take the drug.

The heterogeneity seen in comparison 1 may be due to all of the doses being included in this comparison. There was a significant difference in the mean differences between 150 mg/d and 600 mg/d (Figure 5) which is displayed by the moderate variance seen. Glasziou and Sanders (2002) suggested that heterogeneity may be due to two main reasons. The first reason is that 'study design features' can vary e.g., duration of follow-up. Secondly, the heterogeneity may be due to 'real variation'. This includes factors that may affect the treatment effect e.g. age, gender and intervention factors such as dose, timing and duration of treatment (Glasziou and Sanders, 2002). The studies included in this meta-analysis differed in the 'duration of treatment'. Duration of treatment ranged between 5 and 12 weeks. This factor could have caused heterogeneity.

A limitation of this analysis is that the studies that were included only tested pregabalin treatment for 12 weeks or less. Therefore it is beyond the scope of this analysis to predict the long-term effectiveness or safety of pregabalin as a treatment for PDN for more than 12 weeks duration. Long-term use of the drug may cause patients to become resistant to the drug or develop side-effects. Furthermore, the tolerability of pregabalin over a long term needs to be tested. Long-term trials on the use of pregabalin for diabetic neuropathy are lacking and future studies should focus on assessing the long-term use of pregabalin in PDN patients. However, despite this, pregabalin has been shown to be tolerable and safe in a long-term 18 month study by Uthman *et al.* (2010) who studied the use of pregabalin in epileptic patients and confirmed it to be safe, effective and generally well tolerated in long-term use. Furthermore, pregabalin has been identified as being a drug "free from drug-drug interactions". It therefore provides a suitable treatment option for elderly patients in particular who may be more at risk of possible drug-drug interactions due to their polypharmacy.

Each of the six studies included in this meta-analysis required patients to record their pain scores using the Likert pain scale of 1-10 in a diary. This method of measuring treatment effect is subjective. However, although this is a subjective and non-scientific method, it should be emphasised that pain is a subjective experience which differs from patient to patient. Therefore, there is no objective way of measuring pain.

Publication bias

It is important to take into account publication bias. The results of the studies included in this meta-analysis showed only positive results. Because of this, there was a risk that there may have been publication bias in the studies of pregabalin treatment for PDN. When publication bias is present in a meta-analysis, it suggests that the published studies may not be a true representation of all the valid studies that have been carried out. The publication bias can have a knock-on effect for meta-analyses and systematic reviews, leading to incorrect conclusions to be made. This can ultimately result in healthcare professionals making inaccurate choices about patient treatment (Chalmers, 1990). A funnel plot was constructed for comparison one. The funnel plot was symmetrical (Figure 6) demonstrating that publication bias was not present in this meta-analysis and showing that the positive results reported in the studies were due to pregabalin being an effective analgesic for PDN.

Conclusions

In conclusion, the analgesic effect of pregabalin in patients with PDN was reported for all three 150mg/d, 300 mg/d and 600 mg/d doses. A dose-response relationship was seen for all three dosages. However, there is a significant difference between 150 mg/d and 600 mg/d pregabalin. This study supports the use of 150 mg/d pregabalin for treating PDN. If 150 mg/d is unsuccessful, the dose should be titrated upwards to 300 mg/d or 600 mg/d to achieve analgesia.

Acknowledgements

Special thanks to Dr Stephen Thompson at the School of Biomedical & Biological Sciences at the University of Plymouth for providing guidance on this report.

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