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REVIEW

Pregabalin in the Management of Painful Diabetic Neuropathy: A Narrative Review

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ABSTRACT

Pregabalin is a first-line treatment in all major international guidelines on the management of painful diabetic neuropathy (pDPN). Treatment with pregabalin leads to a clinically meaningful improvement in pain scores, offers consistent relief of pain and has an acceptable tolerance level. Despite its efficacy in relieving neuropathic pain, more robust methods and comprehensive studies are required to evaluate its effects in relation to co-morbid anxiety and sleep interference in pDPN. The sustained benefits of modulating pain have prompted further exploration of other potential target sites and the development of alternative GABAergic agents such as mirogabalin. This review evaluates the role of pregabalin in the management of pDPN as well as its potential adverse effects, such as somnolence and dizziness, which can lead to withdrawal in ~ 30% of long-term use. Recent concern about misuse and an increase in deaths linked to its use has led to demands for reclassification of pregabalin as a class C controlled substance in the UK. We believe these demands need to be tempered in relation to the difficulties it would create for repeat prescriptions for the many millions of patients with pDPN for whom pregabalin provides benefit.

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PLAIN LANGUAGE SUMMARY

Diabetic peripheral neuropathy (DPN) is a disease of the nerves in the hands and feet and is a common complication of both type 1 and type 2 diabetes. The symptoms of DPN include loss of sensation, weakness and pain. Around 30–40% of people with diabetes have DPN, and its burden will rise with the exponential increase of diabetes worldwide. pDPN is a debilitating complication not only affecting the patient's quality of life, but also has a major impact on the healthcare services. Pregabalin is a first-line therapy in pDPN that offers adequate pain relief and is well tolerated. Moreover, it is also effective in treating the co-morbidities of pDPN, which include anxiety and sleep interference. Nonetheless, further studies are required to investigate the effectiveness and underlying mechanisms of the benefits of pregabalin on anxiety and sleep disorders and to determine the type of patient that benefits most from this therapy. We also provide an overview of the mechanisms by which GABAergic drugs work in pDPN and consider new emerging therapies in this area.

INTRODUCTION

Pregabalin was approved for the management of neuropathic pain in 2004 in Europe and the US. First synthesised in 1990 [1], pregabalin (3-isobutyl gamma amino butyric acid gamma-analogue) [2] is a GABAergic drug primarily used in the treatment of neuropathic pain and is approved for use in over 120 countries. Its use as an adjuvant anti-epileptic is generally limited [3], although it is approved for use in partial seizures [4]. In clinical practice it can be used to treat generalised anxiety disorder because of its anxiolytic properties [4], but is primarily prescribed for painful diabetic neuropathy (pDPN), post-herpetic neuralgia and radicular pain as well as fibromyalgia [5, 6]. Pregabalin and gabapentin are considered first-line treatment in the majority of international clinical guidelines for pDPN and form a key part of its management. Five professional bodies have produced expert guidance on the management of pDPN [7–11] and pregabalin is recommended as first-line therapy in all five guidelines, whilst duloxetine is recommended as first line in four of the guidelines (except the American Academy of Neurology) [7–11]. The latter is driven by only one duloxetine trial, being graded as class 1 evidence, because completion rates of other trials are $< 80\%$ [10].

Pregabalin is structurally related to the inhibitory neurotransmitter GABA; however, its mechanism of action is distinct from GABAergic modulation and is yet to be fully elucidated. Pain relief usually occurs within 1 week of initiating therapy and is thought to be mediated via high-affinity binding to the alpha2-delta subunit ($\alpha 2\delta$) of voltage-gated calcium channels at the presynaptic terminals [12]. This results in modulation of the release of excitatory neurotransmitters such as glutamate [12] through the glutamate synthesising enzyme, branched-chain amino acid transaminase [13, 14].

Pregabalin's mechanism of action is similar to that of gabapentin; however, it has 2–4 times more potency and thus a lower dosing strategy is required [15]. Typically starting doses range from 75 to 150 mg per day for neuropathic pain, with relatively quick up-titration over several weeks to maximal tolerated doses (600 mg/day) due to the more linear pharmacokinetics compared with gabapentin [15]. It has high bioavailability ($\geq 90\%$ rapidly absorbed) [16, 17] with a half-life of approximately 9 h [18]. Very common adverse effects ($> 10\%$ of patients) include dizziness, somnolence and headache [17]. Pregabalin demonstrates quick absorption, reducing the probability of drug-drug interactions as it is not bound to plasma proteins and does not undergo first-pass metabolism in the liver [4, 19]. Although pregabalin poses low risk for addiction and drug dependence at therapeutic doses [20], recent statistics

in England and Wales showed a > 20-fold increase in the number of deaths linked to pregabalin—4 to 111 deaths from 2012 to 2016, whilst for gabapentin—8 to 59 deaths during the same period [21]. Rapid rise in mortality is associated with individuals with previous history of recreational polydrug misuse, or misuse in combination with opioids, as some report self-administration of dosages in excess (e.g., up to 10–20 times) of clinically advisable dosages [22]. Consequently, this led to guidance from Public Health England and the NHS on safe prescribing of both pregabalin and gabapentin [23]. However, in December 2017 NHS England launched a consultation to seek views on whether to schedule pregabalin and gabapentin as Controlled drugs in the UK. A similar consultation is underway with the WHO and a decision is expected in early 2019. Due to their "risk of addiction, potential illegal diversion and medicinal misuse" by a minority, the reclassification of these drugs will have major repercussions on the many millions of people suffering from neuropathic pain, as it will restrict prescribing and also prevent them from acquiring the drug on a repeat prescription.

METHODS

A comprehensive literature review was undertaken, incorporating article searches in electronic databases (EMBASE, PubMed, OVID) and reference lists of relevant articles with the authors' expertise in pDPN. The key following keywords were utilised; 'painful diabetic neuropathy', 'diabetic neuropathy', 'sleep interference', 'anxiety' and 'depression' in combination with 'pregabalin'. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

pDPN Prevalence and the Need for Therapy

Diabetes has reached epidemic proportions worldwide, with current International Diabetes Federation (IDF) estimates suggesting a prevalence of 425 million people worldwide in 2017, rising to 628 million by 2045 [24]. Epidemiological studies show DPN has a prevalence of 30–40% in patients with diabetes [25–27], which increases with the duration of disease, rising to approximately 50% in those patients who have had the disease for > 20 years [26]. The symptoms can be varied with patients presenting with paraesthesia, weakness and pain, which may by burning, tingling or shooting in nature. Pain can have a negative impact on patient's quality of life and sleep. There are currently no FDA approved therapies to prevent, slow or arrest DPN, and management involves achieving good glycaemic control and targeting modifiable vascular risk factors to halt the progression alongside symptomatic treatment. The management of pDPN is key to improving quality of life and general well-being; however, therapeutic options in pDPN are often limited by side effects. Pregabalin has a higher potency than gabapentin thus requiring lower doses, recommended dose of up to 600 mg/day in management of pDPN and a superior adverse effect profile [28]. It is the only agent in the gabapentanoid class with a current label for the treatment of pDPN [29]. Indeed, pregabalin is the only agent other than duloxetine and tapentadol to have FDA approval for the treatment of neuropathic pain [29].

Pharmacodynamics

GABA is a major inhibitory neurotransmitter in the central nervous system exerting inhibitory control on the spinal dorsal horn [30]. It is released by inhibitory descending fibres and interneurons and binds to both the $GABA_A$ (via ionotropic) and $GABA_B$ (via metabotropic) receptors depressing neuronal excitation and reducing glutamate release from primary afferent fibres onto dorsal horn neurones [31]. Modulation of excitatory neurotransmitters such as glutamate [12] through the glutamate synthesising enzyme, branched-chain amino acid transaminase, is thought to play a possible role in pain in pDPN [13, 14]. Loss of the GABAergic inhibitory process has been identified as an underlying mechanism of inflammatory and neuropathic pain [32]; however, the

exact mechanism remains unclear. A reduction in the expression of the potassium chloride transporter (KCC2) with primary sensory neurones exhibiting a higher intracellular chloride level has also been proposed as a possible contributory mechanism [33].

Despite being developed as a mimetic of GABA, pregabalin is not believed to produce any of its therapeutic effects directly via the GABA receptor. A high affinity to the α_2-δ subunit found in a number of voltage-gated calcium channels (VGCC) is considered its primary mechanism of action [34]. Indeed, genetic knock-out of α_2-δ in animal models entirely negates the analgesic effects of pregabalin [35, 36].

Absorption Distribution, Metabolism, Excretion and Interactions

Pregabalin's bioavailability is over 90% and is dose independent [37]. Food does not affect pregabalin's overall exposure; however, it can reduce the rate of absorption with the content of the food having little effect on this [38, 39]. Maximal serum concentrations appear 0.7–1.3 h post-dose [39] with the serum half-life ranging from 4.6 to 6.8 h [39]. Over 90% of its excretion is via the kidney [40]. There are very few drug-drug interactions reported with pregabalin [37], which may be in part because it has no significant effects on the CYP450 family [19]. As such, the only major clinical factor relevant to dosing is renal function. The maximum dose of 600 mg/day should only be used in patients with a creatinine clearance (CrCl) > 60 ml/min. In patients whose CrCL is 15–30 ml/min, the maximum dose should be reduced 150 mg in 1–2 divided doses and when CrCL is < 15 ml/min this needs to be reduced further to a maximum of 75 mg once daily. The indications, dosing, renal dosing, and minor and major side effects for pregabalin, gabapentin and the emerging GABAergic therapy, mirogabalin, are presented in Tables 1 and 2.

Adverse Effects

The frequently reported side effects of pregabalin include somnolence, dizziness, peripheral oedema and weight gain, which are usually mild to moderate [39, 41, 42]. These effects are thought to be related to the drug's effects on neurotransmitter release and calcium currents. Pregabalin may cause adverse events on cognition and coordination [43]. In addition, treatment is associated with weight gain, which is in part dependent on the total drug dose, thus raising an issue that needs to be considered in treating patients with type 2 diabetes. There is a theoretical risk of worsening metabolic control with the associated weight gain from gabapentanoids; a pooled analysis of data from 11 double-blind randomised controlled trials (RCT) of pregabalin (150–600 mg/day) vs. placebo showed no clinically meaningful effects of pregabalin on glycaemic or lipid profiles in patients with pDPN, whilst data on weight were not presented [44]. The effects on weight should be considered when starting pregabalin as part of a personalised treatment approach.

Efficacy of Pregabalin in pDPN: Evidence from RCTs

RCTs of pregabalin in pDPN, including NCT number, primary outcome measures and study population details, are summarised in Table 3.

The efficacy of pregabalin in pDPN is proven through numerous RCTs (Table 3) and systematic reviews. Pregabalin is the first drug to receive an approved labelling from the Food and Drug Association (FDA) for the treatment of pDPN and post-herpetic neuralgia [45]. It is the recommended first-line treatment in all five major international clinical guidelines for pDPN [7–11]. In an early RCT of pregabalin in pDPN in 2004, Rosenstock et al. showed significant improvement in the mean pain scores, sleep interference, mood disturbance and tension anxiety over 8 weeks on pregabalin 300 mg/day (n = 146) [46]. Pregabalin was well tolerated despite the mild-to-moderate adverse events of increased dizziness and somnolence [46]. A shorter 5-week double blind multi-centre RCT (n = 338) randomised patients to receive 150 mg/day, 300 mg/day or 600 mg/day of pregabalin or placebo [47]. Participants in the 300 mg/day and 600 mg/day subgroups showed

Table 1 Pregabalin, gabapentin doses, titration, side effects and major side effects

	Indications of use other than pDPN	Dose in pDPN	Renal impairment	Commonly reported side effects	Major side effects
Pregabalin (Lyrica)	General neuropathic pain, fibromyalgia, epilepsy, post-operative pain, generalised anxiety disorder, post-herpetic neuralgia	Initial: 75 mg BID Titration: 150 mg BID within 1 week based on efficacy and tolerability Maximum dose: 600 mg a day in patients with CrCl of $\geq$ 60 ml/min	CrCl < 15 ml/min: Initial dose: 25 mg OD Maintenance: 25–75 mg OD CrCl 15–30 ml/min: initial dose: 25–50 mg in 1–2 divided doses Maintenance: 25–150 mg/day in 1–2 divided doses CrCl 30–60 ml/min: initial dose: 75 mg/day in 2 or 3 divided doses Maintenance: 75–300 mg/day in 2–3 divided doses	Drowsiness, dizziness, fatigue, ataxia, headache, blurred vision, peripheral oedema, tremor, weight gain	Confusion, visual disturbance, abnormal gait, abnormality in thinking, amnesia, vertigo
Gabapentin (off-label) (Neurontin, Horizant, Gralise)	General neuropathic pain, fibromyalgia, epilepsy, restless legs syndrome, pain associated with Guillain-Barré syndrome, phantom limb pain	Neuropathic pain: initial dose: 300 mg day 1, 300 mg BD day 2, 300 mg TDS day 3 Therapeutic dose: 1800–3600 mg/day in 3 divided doses in patients with CrCl $\geq$ 60 ml/min Maximum dose: 3600 mg/day in 3 divided doses		Mood or behaviour changes, anxiety, panic attacks, trouble sleeping, impulsive, irritable, agitated, oedema	Increased seizures, severe weakness or tiredness, ataxia, upper GI pain, severe tingling or numbness, rapid eye movement, little or no urination, oedema, depression or suicidal thoughts

OD once daily, *BID* two times daily, *TDS* three times daily

Table 2 Emerging GABAergic therapies

	Indication	Dose	Renal impairment	Commonly reported side effects	Major side effects
Mirogabalin	Peripheral neuropathy fibromyalgia, post-herpetic neuralgia (marketing application submitted Feb. 2018; approval/launch planned for 2019) [117]	Initial dose: 15 mg OD Maintenance dose: 15 mg OD or BD Maximum dose: 30 mg/day	CrCl 15–29 ml/min: 7.5 mg OD CrCl 30–59 ml/min: 7.5 mg BD [118]	Somnolence, dizziness, headache, balance disorder, vomiting, peripheral oedema, fatigue, constipation, decreased appetite	Headache, cardiac conduction abnormality, arrhythmia

OD once daily, *BID* two times daily

an improvement in mean pain score, sleep interference score, patient global impression of change, short-form (SF) McGill Questionnaire and multiple domains for the SF-36 Health Survey [47]. There was a > 50% reduction in pain compared with baseline in 45% on 300 mg/day and 48% on 600 mg/day of pregabalin compared with 18% on placebo [47]. In both studies, improvement in pain and sleep began at 1 week and continued throughout the titration and maintenance phase.

In a 6-week RCT (n = 246) of patients randomised to 150 mg/day or 600 mg/day or placebo [48], 600 mg/day of pregabalin led to a reduction in the mean pain score to 4.3 (vs. 5.6 for placebo, P = 0.002) [49]. There was an increase in the proportion of participants who had a ≥ 50% reduction of the mean pain score from baseline (39% vs. 15% for placebo, P = 0.002). This trial did not show efficacy of 150 mg/day of pregabalin compared with placebo. Furthermore, a multi-centre trial (n = 338) reported significant reduction in the mean pain score in two different titration regimes of pregabalin with both final doses being 600 mg [49]. More recently, Toole et al. evaluated 395 patients over 12 weeks randomised to pregabalin 150 mg, 300 mg or 600 mg or placebo [28]. Forty-six per cent of patients on 600 mg/day report a > 50% improvement in mean pain score from baseline (vs. 30% in placebo, P = 0.036) [28]. Pregabalin 600 mg/day had superior efficacy; however, there was no significant benefit with 150 mg/day or 300 mg/day subgroups compared with placebo [28]. The authors suggest this finding may be a result of the larger placebo response in one of the countries that participated who represented 42% of the patients [28]. The number needed to treat (NNT) was 6.3, whilst the number needed to harm (NNH) (discontinuation because of adverse events) was 10.3 for pregabalin 600 mg/day [28]. Pooled data from a recent meta-analysis supported previous data showing that pregabalin was superior to placebo for improving mean pain scores [50]. A 50% pain reduction was greater with pregabalin than placebo. Three studies compared pregabalin at lower doses versus higher doses (600 mg/day) and the withdrawal rate was higher with pregabalin 600 mg/day [51]. Overall, pregabalin was well tolerated despite an increased risk of adverse events which limit dose titration.

Gilron et al. evaluated pregabalin across a range of neuropathic pain conditions, not limited to pDPN [52]. This RCT (n = 256) allowed for the assessment of concomitant, potentially confounding analgesics with stable dosing, thus reducing bias [52]. Flexible-dose pregabalin was prescribed for 4 weeks and some participants continued treatment for a further 5 weeks [52]. Modest levels of analgesia were observed at all

Table 3 Randomised controlled trials of pregabalin in patients with pDPN

Publication(s)	Study title	NCT ID	No. patients randomised	Primary outcome measures/results	Country (no. of study centres)
Mu et al. [119]	An 11-week randomised, double-blind, multi-centre, placebo-controlled study to evaluate the efficacy, safety and tolerability of pregabalin (300 mg/day) using a fixed dosing schedule in treatment of subjects with pain associated with diabetic peripheral neuropathy	NCT01332149	620 participants; pregabalin, n = 313 placebo, n = 307	Baseline MPS, change from baseline in MPS at end point (day 63/week 9) Improvement in MPS with pregabalin vs. placebo was not significant (P = 0.0559). Pregabalin significantly improved weekly MPS (P = 0.0164) and ≥ 50% responders at end point (P = 0.0384)	Multi-centre: Chinese population 30 study centres in China
Huffman et al. [120]	A phase 3B multi-centre, double-blind, randomised, placebo-controlled cross-over efficacy and safety study of pregabalin in the treatment of patients with painful diabetic peripheral neuropathy and pain on walking	NCT01474772	203 patients in 2-period crossover study (pregabalin, n = 198; placebo, n = 186)	No statistically significant treatment difference for pregabalin vs. placebo, mean DPN pain (P = 0.0656) and mean DPN pain on walking (P = 0.412)	Multi-centre, 30 study centres in US, Czech Republic, South Africa and Sweden
Raskin et al. [121]	A study of pregabalin in the treatment of subjects with painful diabetic peripheral neuropathy with background treatment of NSAID for other pain conditions	NCT01455415	154 patients pregabalin to placebo; 147 patients placebo to pregabalin	Weekly MPS at end point (14 weeks) showed no significant difference between pregabalin and placebo. Secondary end point: mean treatment difference in DPN-related sleep interference, favoured pregabalin over placebo (P = 0.0009)	Multi-centre 47 study centres in US [43], Czech Republic [3], Italy [1]

Table 3 continued

Publication(s)	Study title	NCT ID	No. patients randomised	Primary outcome measures/results	Country (no. of study centres)
Raskin et al. [122]	A phase 3B multi-centre, double-blind, randomised withdrawal efficacy and safety study of pregabalin in the treatment of patients with inadequately treated painful diabetic peripheral neuropathy	NCT01057693	665 patients in 6-week single-blind run-in period (pregabalin 300 mg/day); 294 patients with > 30% pain response were randomised to receive pregabalin (300 mg/day) or placebo for a further 12 weeks	In single-blind treatment phase, MPS decreased numerically. In double-blind treatment phase, MPS pregabalin group decreased from 6.8 at single-blind baseline to 2.9 (1.7) at double-blind end point, a change from single-blind baseline of − 3.9 (1.9). MPS placebo group decreased from 6.7 at single-blind baseline to 3.2 (1.9), a change from single-blind phase of − 3.5 (2.1); least squares mean difference, − 0.32), no significant difference	Multi-centre 129 study centres in the US [113], South Africa [11], Canada [5]
Satoh et al. [123]	Randomised, double-blind, multi-centre, placebo-controlled study to evaluate efficacy and safety of pregabalin (CI-1008) in the treatment for pain associated with diabetic peripheral neuropathy	NCT00553475	317 patients (placebo or pregabalin at 300 or 600 mg/day)	Significant reductions in pain with pregabalin at 300 and 600 mg/day vs. placebo, observed as early as week 1 and sustained throughout study period (− 0.63 and − 0.74, respectively)	Multi-centre Japanese population
Gilron et al. [52]	A randomised, placebo-controlled trial of the efficacy and safety of pregabalin in the treatment of subjects with peripheral neuropathic pain	NCT00219544	256 patients in run-in period; 165 (65%) had > 30% pain improvement, 157 were randomised to either pregabalin (n = 80) or to receive placebo (n = 77)	At the double-blind end point, MPS was 2.9 (1.9) in pregabalin group and 3.5 (1.7) in placebo group (P = 0.002)	Multi-centre Canadian population [25]

Table 3 continued

Publication(s)	Study title	NCT ID	No. patients randomised	Primary outcome measures/results	Country (no. of study centres)
Guan et al. [124]	An 8-week multi-centre, randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of pregabalin (150–600 mg/day) using a flexible dosing schedule in the treatment of subjects with symptoms of neuropathic pain	NCT00301223	Flexible-dose pregabalin 150–600 mg/day. Randomised in 2:1 ratio. Treatment pregabalin (n = 206), placebo (n = 102)	MPS with pregabalin resulted in significant improvement compared with placebo, a least squares mean difference score of − 0.6 (P = 0.005); 64% and 52% patients treated with pregabalin and placebo, respectively, reported ≥ 30% improvement in MPS (P = 0.04)	Multi-centre Chinese population
Parsons and Li [125]	A randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial of pregabalin versus placebo in the treatment of neuropathic pain associated with diabetic peripheral neuropathy	NCT00143156	Data pooled from 11 placebo-controlled trials to evaluate efficacy pregabalin flexible or fixed dose (150, 300 or 600 mg/day)	At baseline, 1816 patients had moderate pain (pregabalin, n = 1189) and 1119 patients had severe pain (pregabalin, n = 720). Pregabalin (300, 600 mg/day) significantly reduced MPS at end point compared with placebo ($p < 0.01$). Pregabalin improved PRSI and PGIC in moderate and severe cohorts compared with placebo	Multi-centre pooled data analysis
Freeman et al. [126]	A 14-week, double-blind, randomised, placebo-controlled, multi-centre study to evaluate the safety and efficacy of pregabalin (150–600 mg/day) using a flexible optimal dose schedule in patients with painful diabetic peripheral neuropathy (DPN)	NCT00156078	Data pooled from 16 randomised, placebo-controlled, parallel-group, double-blind trials of pregabalin for treatment of 3053 patients with DPN	At baseline, MPS of ≥ 4, for 4 or more days prior to randomisation. Flexible dose pregabalin (150–600 mg/day); no significant difference in MPS compared with placebo (A0081030). No significant difference in MPS with pregabalin (300 or 600 mg/day) compared with placebo (A0081071). No significant difference in MPS with pregabalin 600 mg/day (1008–040)	Multi-centre pooled data analysis (19 countries across Asia, Europe, Latin America and Middle East, US)

Table 3 continued

Publication(s)	Study title	NCT ID	No. patients randomised	Primary outcome measures/results	Country (no. of study centres)
Freeman et al. [127]	Meta-analysis: seven RCTs across a range of pregabalin doses	n/a	1510 patients in seven double-blind RCTs: pregabalin, $n = 953$; placebo, $n = 557$. MPS baseline was 6.5	MPS and PRSI score improved associated with pregabalin 150, 300 and 600 mg/day administered TID vs. placebo, $P < 0.007$	Multi-centre pooled data analysis (90% patients white, 58% male)
Freynhagen et al. [128]	Comprehensive drug safety evaluation of pregabalin in pDPN**	n/a	7510 patients included: 4884 on pregabalin and 2626 on placebo 31 RCTs of pregabalin in pDPN	Incidence of adverse events: dizziness (risk difference [95% CI]: 17.0 [15.4 to 18.6]), somnolence (10.8 [9.5 to 12.1]), peripheral oedema (5.4[4.3 to 6.4]), weight increase (4.7 [3.9 to 5.5]), dry mouth (2.9 [2.1 to 3.8]), constipation (2.3[1.5 to 3.2]), blurred vision (2.2 [1.6 to 2.9]), balance disorder (2.0 [1.5 to 2.5] and euphoric mood (1.6 [1.2 to 2.0])	Multi-centre pooled analysis RCT in Asia, Australia, Canada, Europe, Latin America, the Middle East, South Africa and the US
Semel et al. [129]	Evaluation of safety and efficacy of pregabalin in older patients with neuropathic pain: results from a pooled analysis of 11 clinical studies	n/a	2516 patients (white, $n = 2344$; male, $n = 1347$): pregabalin, $n = 1595$	MPS end point improvement observed for all pregabalin dosages (150–600 mg/day) in older patients (age $\geq$ 65 years old) ($p \leq 0.0009$)	Multi-centre (white predominant)
Moon et al. [130]	A 10-week, randomised, double-blind, placebo-controlled, multi-centre study to evaluate the efficacy and safety of pregabalin (150–600 mg/day) using a flexible, optimised dose schedule in subjects with peripheral neuropathic pain	NCT0014 1219	240 patients. Phase III trial. 2:1 ratio to pregabalin (150–600 mg/day) or placebo. Pregabalin, $n = 162$, placebo, $n = 78$	MPS significantly lower in pregabalin group than in placebo; least square mean difference, -0.50; -1.00 to 0.00; $P = 0.049$)	Korean population

Table 3 continued

Publication(s)	Study title	NCT ID	No. patients randomised	Primary outcome measures/results	Country (no. of study centres)
Arezzo et al. [131]	A 13-week, double-blind, placebo-controlled phase 4 trial of pregabalin (CI-1008, 600 mg/day) for relief of pain in subjects with painful diabetic peripheral neuropathy	NCT00159679	167 patients (pregabalin, $n = 82$, placebo, $n = 85$)	MPS lower than placebo (mean difference − 1.28; $P < 0.001$)	US 23 study centres
Freynhagen et al. [49]	Efficacy and safety of pregabalin using an individual optimal twice a day (BID) dose schedule in patients with chronic neuropathic pain	n/a	338 patients randomised in 1:2:2 ratio to placebo, flexible-dose pregabalin (150–600 mg/day) or fixed dose pregabalin (600 mg/day). PGB flexible dose, $n = 141$; PGB fixed dose, $n = 132$; placebo, $n = 65$	MPS significantly reduced for both flexible- and fixed-dose pregabalin versus placebo ($P = 0.002$) and PRSI significantly improved	European 60 study centres across 9 EU countries
Tolle et al. 2012 [132]	A 12-week, randomised, double-blind, multi-centre, placebo-controlled study of pregabalin twice a day (BID) for relief of pain associated with diabetic peripheral neuropathy	n/a	395 participants	MPS improved in participants receiving pregabalin 600 mg/day; 46% reported > 50% improvement MPS from baseline vs. placebo patients ($P = 0.036$). NNT was 6.3. Improvement in EQ-5D utility scores (all pregabalin doses vs. placebo. Number needed to harm (discontinuation because of adverse events) was 10.3 for pregabalin 600 mg/day	European 58 study centres in Europe (Germany, Hungary, Poland and the UK), Australia and South Africa

NCT ID clinicaltrials.gov registry number, *LOCF* last observation carried forward, *MPS* mean pain score; DPRS = daily pain rating scale, *PRSI* pain-related sleep interference, *PGIC* patient global impression of change, *NNT* number needed to treat

stages and at the final end point [52]. This was found to be greater in the pregabalin cohort compared with placebo in both pDPN and postherpetic neuralgia [52].

In clinical practice, lack of dose titration is common in primary care resulting in inadequate pain relief. Physicians treating patients with pDPN should escalate pregabalin to the dose that delivers optimal analgesia and tolerable side effects [53].

Head-to-Head Trials of Comparators, Combination Therapy and Meta-Analyses

In head-to-head studies of active comparators in pDPN, Bansal et al. [54] found no difference in the outcomes between amitriptyline and pregabalin. However, there was a greater proportion of adverse events in the amitriptyline group, 65% compared with 25% for pregabalin, and the preferred dose of pregabalin was 150 mg BID. A further RCT comparing pregabalin, amitriptyline and duloxetine found no single treatment was superior [55]. Pregabalin was found to improve sleep continuity, whereas duloxetine increased wake and reduced total sleep time [55]. There were significantly more adverse events in the pregabalin group. A meta-analysis by Quilici et al. [56] (funded by Eli Lilly) determining the comparative efficacy of duloxetine vs. pregabalin and gabapentin through an indirect analysis found that all were superior to placebo for all efficacy parameters, with some tolerability trade-offs. Indirect comparison of duloxetine with pregabalin found no differences in 24-h average pain score but significant differences in patient global impression outcomes, favouring pregabalin, and in dizziness, favouring duloxetine [56]. The estimated NNT for duloxetine was 5 (95% CI: 3–7) [56], which was comparable to NNTs reported elsewhere of 5.2 (95% CI: 3.7–8.5) and 4.1 (95% CI: 2.9–7.2) [8, 57] and to the NNT for pregabalin of 5 (95% CI: 4–8). The NNH for pregabalin was 19 (95% CI: 10–48) compared with duloxetine with an NNH of 11 (95% CI: 7–23) [56]. In a study conducted in Spain (and funded by Pfizer) of pregabalin versus usual care (antidepressants, opioids, anticonvulsants different from pregabalin) in the management of community-treated patients with refractory pDPN, pregabalin was associated with a non-significant higher quality-adjusted life-year (QALY) gain in a 12-week period [58]. In a further study by the same group, compared with gabapentin, pregabalin yielded an estimated mean of 8 [standard error (SE): 0.4] additional days with no or mild pain, 6 (SE: 0.4) days with $\geq$ 30% reduction in pain intensity, 9 (0.5) days with $\geq$ 50% reduction in pain intensity and a gain of 0.1186 (0.0002) QALYs for 12 weeks [59]. Although the average study drug cost was higher for pregabalin than gabapentin (€214.6 vs. €157.4: $P < 0.001$), there was a lower cost of concomitant analgesic medication (€176.5 vs. €306.7; $P < 0.001$) [59].

The complex nature of pDPN may require more than one therapy for adequate pain relief, but there are limited studies of combination therapies [60]. The COMBO-DN study is the largest trial to date comparing monotherapy with a combination duloxetine and pregabalin in 339 participants [61]. There was no difference between combination standard-dose and high-dose monotherapy of either treatment [61]. In a secondary analysis, duloxetine 60 mg was found to be superior to pregabalin 300 mg/day in the initial 8-week run-in phase. A further exploratory post hoc analysis of COMBO-DN showed that high-dose monotherapy was more favourable in patients with severe pain, whereas combination therapy was more beneficial in patients with moderate and mild pain [62]. Also, patients who received duloxetine (60 mg/day) as initial therapy had a better response to combined duloxetine and pregabalin for evoked or severe tightness and a greater benefit with high-dose duloxetine (120 mg/day) for paraesthesia-dysaesthesia [62, 63]. In another double-blind RCT with a parallel-group design comparing amitriptyline, duloxetine and pregabalin there was no significant difference in analgesic efficacy [64]. However, when determining polysomnographic parameters, pregabalin improved sleep continuity, whereas duloxetine increased wake and reduced total sleep time [64]. Despite the putative negative effects on sleep, duloxetine enhanced central nervous system arousal and

performance on sensory motor tasks; however, there were significantly more adverse events in the pregabalin group [64].

A study of pregabalin and 5% lidocaine medicated plaster ($n = 229$) in post-herpetic neuralgia or painful DPN [65] showed that patients who failed to respond to monotherapy of pregabalin gained additional benefit from the 5% lidocaine patch. This was in contrast to an RCT of the addition of low-dose 10 mg oxycodone or placebo in patients treated with pregabalin where there was no enhancement of the pain-relieving effects of pregabalin [66].

Anxiety, pDPN and Pregabalin

There is a well-recognised triad of chronic pain, anxiety/depression and sleep interference, which impairs the activities of daily living in pDPN [67]. pDPN has a substantial impact on quality of life [68, 69], with 50–70% of patients attending chronic pain clinics reporting sleep impairment [70–72], > 20% having major depression [73–76] and epidemiological data demonstrating excess anxiety levels compared with pain-free populations [77].

Pregabalin is approved in the European Union for use as an anxiolytic agent in the management of generalised anxiety disorder (GAD) and is commonly used-off label in the US [78]. With a mechanism of action distinct from other anxiolytic agents, it also offers broad-spectrum treatment for the characteristic psychosomatic symptoms of GAD including excessive generalised worry, hypervigilance and persistent nonspecific anxiety [5]. Therefore, pregabalin is beneficial as a therapy in both pDPN and anxiety disorders, as a therapy in itself or as an adjunct.

Numerous studies have demonstrated pregabalin maintains improvements in anxiety symptoms in the long term and increases the time to GAD compared with placebo [5]. A retrospective cohort study [79] of three comparable 13–16-week RCTs [42, 80, 81] with their corresponding 52-week extensions in a Japanese population evaluated the use of various pregabalin regimens in pDPN, spinal cord injury (SCI) and post-herpetic neuralgia. Significant improvements in pain and sleep interference were seen after 1 week and subsequently maintained across all conditions including pDPN compared with placebo. At the end of the study, the least-squares (LS) mean pain scores (LOCF) were significantly reduced with pregabalin in all three trials. In the SCI trial, a non-significant difference in comparison with placebo was observed for the HADS anxiety and depression subscale scores in the pregabalin-treated group [79]. On completion of the studies significantly more patients treated with pregabalin, experienced a pain reduction $\geq$ 30% across all RCTs [42, 80, 81]. An extension of all three trials additionally demonstrated that reductions in pain intensity were maintained over a 12-month period [42, 80, 81]. There were also notable improvements in 6 of the 16 SF-36 subscale scores in the DPN trial; the analgesic efficacy of pregabalin are similar across multiple neuropathic pain conditions and also improves quality-of-life measures and anxiety [79].

Pregabalin in the dose range 200–600 mg/day (in two or three daily divided doses) significantly reduces mean pain scores on the Hamilton Anxiety Scale for GAD and social anxiety disorder (SAD) [5, 51]. However, treatment-related adverse effects occurred in up to 50% of cases, of which somnolence precipitated study withdrawal for ~ 32% patients [51]. An open-label, non-comparative, flexible-dose study ($n = 217$) in pDPN or post-herpetic neuralgia similarly investigated the correlation of patient and physician general global impression of change (patient global impression of change (PGIC) and clinician global impression of change (CGI)) with changes in pain, sleep and anxiety score as primary outcomes assessed on visual or numeric scales [82]. This multi-centre study identified significant improvements in pain, anxiety and sleep (− 40%, − 42%, − 43%, respectively) when treated with pregabalin over 4 weeks from baseline to the end of the study [82]. The mean dose was ~ 300 mg/day but a limitation of these findings is the variable dosing regimen used [82]. Nonetheless, both pain and anxiety correlated with PGIC and CIGC and all correlations except paired CGIC/anxiety were statistically significant [82].

Sleep Interference and Chronic Pain

pDPN is associated with considerable sleep impairment, which has been highlighted as an important outcome measure [83, 84]. Sleep disturbance is associated with lower pain thresholds [85]. Pain sensitivity follows a diurnal pattern in keeping with a circadian variability with the variability of pain sensitivity increasing in response to the build-up of sleep pressure following sleep deprivation or disruption [86]. This variability has been further demonstrated in untreated pDPN and postherpetic neuralgia in two separate double-blind randomised controlled crossover trials where a relative pain intensity increase of 33% between 8 a.m. and 8 p.m. was reported [87–89].

The Locus Coeruleus: A Centre for Pain and Sleep Mediation

The locus coeruleus (LC) is a cluster of noradrenergic neurones in the dorsal pons with widespread projections throughout the brain [90]. The activity of the locus coeruleus peaks in wakefulness, declines during NREM sleep and is at its lowest during rapid eye movement (REM) sleep [90]. The LC has a complex role in neuropathic pain modulation as it may facilitate as well as inhibit pain development and maintenance of allodynia and hyperalgesia after nerve injury [91]. Studies limited to animal models have shown increased activity of the LC via surrogate markers of gene expression, which was directly proportional to the degree of allodynia [92]. Furthermore, an agonistic and analgesic effect was demonstrated when substance P was injected directly into the LC [93]. However, this effect was negated by prior injection of a neurokinin-1 receptor antagonist (the functional binding site of substance-P) and another agent, yohimbine, an alpha-2 adrenergic receptor antagonist [94]. Gabapentin demonstrates an 'anti-hypersensitivity' effect thought to be a direct effect on the LC in male rats in a peripheral nerve injury model, which shows increased LC activity [95].

Pregabalin, pDPN and Sleep

Pregabalin has shown considerable efficacy for improved sleep interference as demonstrated by an improvement in sleep quality in 77% of patients [96]. Pregabalin and gabapentin are effective in treating neuropathic pain and have a positive effect on co-morbid sleep disturbance compared with opiates and antidepressants [97]. Sleep disturbance as well as its severity correlates with the severity of neuropathic pain and is a predictor of response to pregabalin in a post hoc analysis of placebo-controlled trials [98]. Pregabalin significantly reduced pain scores and the greatest reduction was seen in those with the severest indices of sleep disturbance at baseline [98].

In a systematic review of nine clinical trials, pregabalin was found to be an effective and well-tolerated therapy to reduce pain and pain-related sleep disturbance in pDPN and postherpetic neuralgia [99]. It is important to note, however, that none of these studies reported objective sleep measures [99].

Phantom Limb and Pregabalin

Diabetes is the most common cause of non-traumatic lower limb amputation, with diabetic foot ulcers preceding > 80% of amputations in people with diabetes [100]. Phantom limb pain (PLP) can affect up to 80% of amputees [101] and is associated with considerable distress to patients and their carers. Pain often commences shortly after surgery once the initial surgical insult to the residual stump has passed. The phantom pain is described as shooting, stabbing, throbbing and/or burning, which often disturbs sleep [102]. It is associated with increased stress, anxiety, depression and reduced quality of life [103]. Mobilisation can be delayed whilst pain control is established, thus reducing the post-operative rehabilitation phase [104].

There remains a paucity of data in the use of pregabalin in PLP [105]. Currently, pre-emptive use of pregabalin for PLP is sporadic within the UK. Additional evidence is required in the form of well-designed and adequately powered RCTs

to ascertain the role of pregabalin in standard of care of amputees and PLP. Indeed, a systematic review of original research studies specifically investigating the pharmacological treatment of PLP suggested that gabapentin had a higher level of evidence than pregabalin [105].

Novel Therapies for pDPN

Voltage-sensitive calcium channels contain subunits alpha-2-delta 1 ($\alpha_2\delta$-1) and alpha-2-delta 2 ($\alpha_2\delta$-2) subunits. $\alpha_2\delta$-1 interacts with NMDA receptors and promotes synaptic expression of $\alpha_2\delta$-1-NMDA receptor complexes in neuropathic pain [106]. Gabapentin and pregabalin reduce neuropathic pain by non-selectively targeting the $\alpha_2\delta$-1 subunit bound to NMDA receptors [107], inhibiting release of neurotransmitters such as glutamate and reducing hyperexcitability at the spinal cord. Mirogabalin (DS-5565) (Daiichi-Sankyo, Japan) has demonstrated higher affinity for the $\alpha_2\delta$-1 [108]. Vinik et al. (2014) conducted a large multi-centre, phase 2 RCT incorporating an active comparator group with dose-ranging mirogabalin therapy (5, 10, 15, 20, 30 mg/day) compared with pregabalin and placebo [109]. An early reduction of average daily pain scores, sustained after 5 weeks of therapy, was reported with mirogabalin 15, 20 and 30 mg/day relative to placebo. In comparison, participants on pregabalin 300 mg/day reported no significant difference in pain reduction compared with placebo at the end of a 5-week treatment period. The most common adverse effects were dizziness (9.4%), somnolence (6.1%) and headache (6.1%) [109].

Voltage-gated sodium (Na) channels have emerged as promising therapeutic targets selectively targeting Na_v channels. In particular, $Na_v1.7$ has attracted the most attention as humans with $Na_v1.7$ gain-of-function mutations suffer severe chronic pain syndromes [110]. Numerous trials are ongoing for Na_v channel antagonists. There are ongoing studies by Pfizer (PF-05089771) [111], entering phase II trials in DPN), Biogen (BIIB074, previously known as CNV-1014802) [112], Xenon and Teva (XEN-402 or TV-45070; phase II in DPN) [113], Sumitomo Dainippon Pharma (DSP-2230; phase I trial) [114] and AstraZeneca (AZD-3161; phase II trial, GlaxoSmithKline (GSK-2339345) phase II trial) [115] and Gilead (GS-6615) [116].

CONCLUSION

pDPN significantly impacts the individual's quality of life, posing threats of chronic pain, sleep and mood disturbance. Management of the debilitating burden of pDPN thus requires symptomatic relief via well-researched pharmacotherapy such as pregabalin. Recommended as first line in the majority of guidelines, pregabalin is established as an effective and relatively well-tolerated agent, most useful in alleviating subjective sleep and mood disturbance. Pregabalin has good efficacy for treating pDPN and an adequate safety profile. Typically reported adverse effects of dizziness and somnolence prevent up-titration to the maximum of 600 mg/day. However, several randomised-controlled trials have demonstrated symptomatic improvement in pain and sleep disturbance being achieved at lower doses (300 mg/day). Despite numerous large multi-centre RCTs comparing pregabalin with placebo, the average follow-up duration is relatively short, averaging at 6 weeks up to the longest trial duration of 14 weeks. Longer follow-up duration would be necessary to further evaluate and recognise the potential for sustained benefits and tolerability, although this should not negatively impact its use as this is on par with other trials for treatments of pDPN.

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