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Review

Pregabalin and gabapentin for the treatment of sciatica

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ABSTRACT

Whilst pregabalin (PGB) and gabapentin (GBP) are both used to treat neuropathic pain, their relative role in sciatica is unclear. Our aim was to extensively review the roles of PGB and GBP in treating sciatica. The efficacy, side effects (SE) profile and cost of PGB and GBP in neuropathic pain states were reviewed with special reference to sciatica. Eleven articles matched the criteria: seven systematic reviews, one retrospective cross-sectional study, one placebo-controlled-crossover study, one randomized placebo-controlled double-blind study and one case report. GBP and PGB appeared to demonstrate comparable efficacy and SE. However, the amount and quality of evidence was low, and only indirect comparisons were available. Importantly, no direct "head-to-head" study existed. Globally, costs varied widely (by up to 31 times) and unpredictably (PGB cheaper than GBP, or vice versa). Formulary regulator rulings were globally disparate; however, many exclusively favoured the more expensive drug (whether GBP or PGB). No studies assessed PGB-GBP interchange. Weak evidence suggests that efficacy and SE with GBP and PGB are probably similar; however, firm conclusions are precluded. Despite weak data, and having cited minor titration, but definite cost, advantages, UK National Institute for Health and Clinical Excellence favoured PGB over GBP. Given that no evidence supports unhindered PGB-GBP interchange, neither drug should probably be favoured. Prospective "head-to-head" studies are urgently required to provide robust evidence-based knowledge for choice of GBP or PGB in sciatica.

1. Introduction

Both gabapentin (GBP) and pregabalin (PGB) have been widely used to treat neuropathic pain (NP) states, including sciatica. However, the efficacy and side effects (SE) of GBP and PGB for the treatment of patients with sciatica have not been firmly established. Only two limited specific reviews exist to our knowledge. The first emanates from the UK National Institute for Health and Clinical Excellence (NICE-UK) [1]. The second is a recent systematic review, and meta-analysis, for the pharmacological treatment of sciatica, by Pinto et al. [2]. Both could only make indirect comparisons between GBP and PGB, whilst the review of Pinto et al. was based on one study for each drug and both trials failed to satisfy accepted criteria for high-quality design [2,3]. No review appears to have sufficiently examined the SE and quality of life differences between the two drugs.

Sciatica or sciatic neuralgia, a common form of lumbosacral radiculopathy, is characterised by low back pain which radiates to the leg and which may be accompanied by sensory loss, motor weakness and/or reflex abnormalities. Sciatica is a symptom defined as well-localised leg pain, with a sharp, shooting or burning quality that approximates to the dermatomal distribution of the sciatic nerve down the posterior lateral aspect of the leg [2]. It is often associated with numbness or paraesthesia in the same distribution but typically extends beyond the limits of perceived pain in either a dermatomal or sclerotomal anatomical fashion [4,5]. The term "sciatica" is used by clinicians in different ways; some refer to any leg pain referred from the back as sciatica; others prefer to restrict the term to pain originating from the lumbar nerve roots. Others believe sciatica is a form of "neuropathic" pain caused by compression or irritation of the roots or nerves that comprise the sciatic nerve [2,6]. These definitional inconsistencies potentially confound analysis within and between studies.

A substantial proportion of patients with sciatica have persistent pain for 2 years or longer [2], which contributes to absence from employment and applications for worker's compensation.

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The annual prevalence of sciatica is estimated to be between 1.6% and 43% [6]. While guidelines provide clear and generally consistent recommendations for prescribing analgesics to treat non-specific low back pain, often the same guidelines are applied for the dissimilar diagnosis of sciatica, and more recently, non-evidenced based use of either PGB or GBP has become common practice.

Chronic low back pain per se can often be managed with a simple analgesic regimen that includes paracetamol, non-steroidal anti-inflammatory agents (such as ibuprofen), or opioid analgesics (such as codeine or tramadol). Sciatica, however, like most "neuropathic" pain states, is often resistant to simple analgesic regimens [2,6]. NP is typically managed by the addition anti-convulsant drugs to basic analgesic regimes; the drugs most commonly used are GBP or PGB. Sciatica is therefore increasingly being treated with the addition GBP or PGB [2,6]. Both are analgesics derived from gamma-aminobutyric acid (GABA) that modulate calcium-channel subunits, possibly decreasing neurotransmitter release that occurs in sciatica.

It is important to note that either PGB or GBP are likely to constitute second-line treatment, either as an alternative to surgery, or as a penultimate step before committing to surgery (with its greater risks). That is, patients may be offered either drug at a stage in their management where response to standard first-line analgesics has proven insufficient. However, the precise role of PGB or GBP in sciatica has been surprisingly under-explored [2,7]. In consequence, individual prescribers have defaulted to a position of equipoise pending the outcome of direct, high quality research to rationalise the use of PGB or GBP in the treatment of sciatica [7].

We aim to review the utility (efficacy, SE profile and cost) of PGB and GBP in NP states with special reference to sciatica.

2. Methods

Studies to be included in this review were identified using electronic searching of the Pubmed/Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Cochrane databases from the earliest records to 14 March 2015**.** Key search and medical subject heading terms used included "pregabalin", "gabapentin", and "sciatica". Terms were selected based on the keywords and the title in the review which included the synonyms "radiculopathy", "nerve root compromise or compression", "nerve root pain or entrapment", "lumbosacral radicular syndrome", or "pain defined as radiating below the knee". Terms were not used individually, but in combination in order to achieve focused results. Combinations included "pregabalin AND sciatica", "gabapentin AND sciatica" and "pregabalin AND gabapentin AND sciatica".

The identified citations were refined to publications in English and studies carried out in humans. Further refinement included studies limited to describing safety, efficacy and/or tolerability of PGB and/or GBP in sciatica. Studies that analysed other NP conditions in combination with sciatica were also included. Articles exploring GBP and PGB as combination treatments were excluded as well as trial protocols and post-surgical populations.

One reviewer screened all relevant titles and abstracts and excluded irrelevant papers. Two reviewers independently evaluated the full reports for eligibility. Discussion and consensus was used to resolve differences in assessment. To identify potential articles missed by the electronic search, the bibliographies of the identified articles were analysed and any appropriate article based on title and abstract was also retrieved.

Decisions to include papers in this review did not depend on their quality. The goal was to present all published studies that met our inclusion criteria regardless of the design type and quality.

Formal meta-analytic methods were precluded because of the broad scope of adverse events and painful symptoms, the variety of measures used to assess adverse effects, and the different study definitions of pain. This review is a quantitative and semi-qualitative synthesis of the relevant, representative, and evidence-based literature.

3. Results

Thirteen studies were identified in the initial search with two studies being excluded due to irrelevance [8,9]. Eleven studies were identified in the literature review that examined the safety, efficacy and/or tolerability of PGB and GBP for patients with sciatica. All 11 studies were included in this review. They included seven systematic reviews, one retrospective cross-sectional study, one placebo controlled crossover study, one randomised placebo-controlled double-blind study and one case report (Table 1).

3.1. Efficacy: GBP

3.1.1. Sciatica

The use of GBP to reduce pain has been extensively covered in systematic reviews. In a review and meta-analysis involving 23 studies for the drug treatment of sciatica, GBP showed greater efficacy in pain reduction compared to placebo in participants with chronic sciatica (mean difference −26.6; 95% confidence interval [CI], −38.3 to −14.9) [2].

3.1.2. Other conditions

Additionally, a systematic review of 29 studies involving 3,571 patients was performed in 2011 to analyse the effects of GBP in chronic NP and fibromyalgia. GBP was superior to placebo in 14 studies with 43% of patients improving with GBP and 26% with placebo; the number needed to treat (NNT) was 5.8 (95% CI, 4.8 to 7.2) Furthermore, using the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) definition of substantial benefit, GBP was superior to placebo in 13 studies with 31% of patients improving with GBP compared to 17% with placebo [10].

In another systematic review of GBP use in acute and chronic pain, the study showed no benefit for GBP compared to placebo for pain at rest [11]. In chronic pain, the NNT for improvement in all trials with evaluable data is 4.3 (95% CI, 3.5 to 5.7) with 42% of participants improving on GBP compared to 19% on placebo [11]. A larger systematic review examining 174 trials in NP showed that GBP had an overall number needed to harm (NNH) of 32.5 (95% CI, 18 to 222) when used as a treatment for a variety of NP disorders [12].

An earlier review for acute and chronic pain reported that a single-placebo controlled trial of GBP in post-herpetic neuralgia had an NNT of 3.2 (95% CI, 2.4 to 5.0). In the same review, for diabetic neuropathy, NNT for effectiveness was 3.8 (95% CI, 2.4 to 8.7) for the population treated with GBP [13].

In light of this evidence for GBP utility, a cross-sectional study into painful neuropathic disorders found that average daily doses for GBP were commonly suboptimal for pain management among these patients [14].

However, for most of these systematic reviews, even when restricting inclusion to randomised, double-blind studies, the review incorporated a majority of trials with either an unclear or

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Table 1
Studies included in the literature review

Study	Design	Objectives	Findings
Sumracki N. et al. (2012) [17]	Randomised, double-blind, placebo-controlled, three-way crossover study in unilateral sciatica	Tolerability and efficacy of minocycline and pregabalin	Although not significant once adjusting the p value, the 28% (95% CI 0% to 56%) reduction of hyperalgesia in the affected leg prior to intradermal capsaicin by single oral dose minocycline is a novel finding that glial attenuation may be anti-hyperalgesic in humans
Moore R.A. et al. (2011) [10]	Systematic review of randomised double-blind studies in chronic neuropathic pain and fibromyalgia	Tolerability and efficacy of gabapentin compared to placebo	Gabapentin was superior to placebo in 14 studies with 43% improving with gabapentin and 26% with placebo; the NNT was 5.8 (95% CI 4.8 to 7.2)
Wiffin P.J. et al. (2005) [11]	Systematic review of randomised trials for acute and chronic pain	Tolerability and efficacy of gabapentin compared to placebo	The study in acute post-operative pain showed no benefit for gabapentin compared to placebo for pain at rest. In chronic pain, the NNT for improvement in all trials with evaluable data is 4.3 (95% CI 3.5 to 5.7). Forty-two percent of participants improved on gabapentin compared to 19% on placebo
Finnerup N.B. et al. (2010) [12]	Systematic review of randomised, double-blind placebo controlled trials for neuropathic pain	Pharmacological management of neuropathic pain	Tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors, the anticonvulsants gabapentin and pregabalin, and opioids are the drug classes for which there is the best evidence for a clinical relevant effect
Straube S. et al. (2010) [15]	Systematic review of double-blind trials compared with placebo for established acute post-operative pain in adults	Efficacy and tolerability of single-dose oral gabapentin and placebo	At least 50% pain relief over 6 hours was achieved by 15% with gabapentin and 5% with placebo. Significantly fewer participants needed rescue medication within 6 hours with gabapentin than with placebo. About one-third of participants reported adverse events with both gabapentin and placebo. No serious adverse events occurred with gabapentin
Wiffen P.J. et al. (2005) [13]	Systematic review of randomised controlled trials for acute and chronic pain	Anticonvulsant drugs efficacy and tolerability	The only included placebo-controlled study in acute pain found no analgesic effect of sodium valproate. Three placebo-controlled studies of carbamazepine in trigeminal neuralgia had a combined NNT for effectiveness of 2.5 (95% CI 2.0 to 3.4). A single placebo-controlled trial of gabapentin in post-herpetic neuralgia had an NNT of 3.2 (95% CI 2.4 to 5.0)
Grice G.R. et al. (2008) [21]	Case report on sciatica	A report of gabapentin usage for two patients	The first patient was treated with many alternative drugs and he was then prescribed gabapentin. His pain substantially improved, even after the first dose. The second patient was a 68-year-old treated with gabapentin 100 mg at bedtime, whose pain improved rapidly
Gore M. et al. (2007) [14]	Retrospective cross-sectional study about painful peripheral neuropathic disorders	Usage patterns of common drugs for PND	Use of medications with clinically demonstrated efficacy in PND was high. Average daily doses of select neuropathic pain-related medications among PND patients were lower than those recommended for neuropathic pain. The use and doses of evidenced-based neuropathic pain-related medications was low, and lower than the use of NSAID (a medication class with no proven efficacy for PND) in each group, suggesting possible sub-optimal neuropathic pain management among these patients
Pinto et al. (2012) [2]	Systematic review and meta-analysis of drugs for treatment of sciatica	Efficacy and tolerability of drug treatments for sciatica	NSAID showed low evidence of efficacy ($p < 0.06$). No NSAID displayed better effects than the other. Corticosteriods showed significant effects on pain ($p < 0.01$) Gabapentin showed great efficacy compared to placebo ($p < 0.01$). Topirimate showed no better effects than placebo. Combination of antidepressant and opioid had no significant effect compared with placebo For all included studies, the median rate of adverse events was 17% for active drugs and 11% for placebo
Burke S.M. et al. (2010) [16]	Randomised double-blind placebo controlled study of lumbar discectomy	Tolerability and efficacy of pregabalin compared to placebo	The decrease in PPI-VAS score at 3 months was greater in patients who received pregabalin than those who received placebo. The Roland Morris disability score at 3 months was less in patients who received pregabalin. Pregabalin administration was associated with greater pain tolerance thresholds in both lower limbs compared with placebo at 24 hours post-operatively
Moore R.A. et al. (2009) [18]	Systematic review of randomised double-blind trials in acute and chronic pain	Efficacy and tolerability of pregabalin	There was no clear evidence of beneficial effects of pregabalin in established acute post-operative pain. No studies evaluated pregabalin in chronic nociceptive pain, like arthritis

CI = confidence interval, NNT = number needed to treat, NSAID = non-steroidal anti-inflammatory drugs, PND = painful neuropathic disorders, PPI-VAS = Present Pain Intensity-Visual Analog Scale.

high risk of bias due to design flaws, differing measured outcomes, dosage variation and inconsistent conditions being treated.

3.1.3. Single-dose GBP

Single-dose GBP was explored in a review consisting of four unpublished studies for acute postoperative pain in adults [15]. At least 50% pain relief over 6 hours was achieved by 15% of patients with GBP 250 mg and 5% with placebo, giving a risk: benefit of 2.5 (95% CI 1.2 to 5.0) and an NNT of 11 (6.4 to 35). Also noteworthy was that significantly fewer participants needed rescue medication within 6 hours with GBP 250 mg than with placebo [15].

The conclusions were that GBP appears to provide high level pain relief in about one-third of people who take it for NP. Conversely, over half of those treated with GBP do not report worthwhile pain relief. Overall, evidence for using this drug in some conditions is low, which leaves the question as to why GBP works under some circumstances but not others. This finding precludes us confidently concluding efficacy in sciatica [2,10].

3.2. Efficacy: PGB

The reduction of NP and sciatica has been less explored for PGB compared to GBP.

3.2.1. Sciatica

The use of PGB to reduce pain and time to loss of response was reviewed in a meta-analysis involving 23 studies for the drug treatment of sciatica. Most patients with chronic lumbosacral radiculopathy responded to PGB therapy; however, time to loss of response did not significantly differ between PGB and placebo [2].

A randomised, double-blind placebo controlled trial examined the effect of PGB on pain following lumbar discectomy in 40 participants. The decrease in pain score was greater at 3 months for patients treated with PGB compared to placebo ($p = 0.08$). PGB was associated with greater pain tolerance thresholds in both lower limbs compared with placebo at 24 hours postoperatively [16].

In a randomised, double-blind, placebo-controlled, three-way cross-over study of 18 patients with unilateral sciatica, PGB did not reduce capsaicin-induced spontaneous pain. Importantly however, the design of the study was primarily focused on the activity of an alternative drug, minocycline, in unilateral sciatica [17].

3.2.2. Other conditions

A systematic review involving 174 studies of various NP conditions suggested that PGB is a member of a class of drugs in which there is best evidence for clinical effect. When the data was pooled, PGB displayed a NNH of 10.6 (95% CI 8.7 to 14) which was approximately three times less than its comparator agent GBP. This tends to indicate that PGB has a higher adverse event rate [12].

A large systematic review which studied more than 70,000 participants concluded that there was no clear evidence of beneficial effects of PGB for acute pain. No studies included in the review explored chronic pain. The best (lowest) NNT for each condition for at least 50% pain relief over baseline (substantial benefit) for PGB compared with placebo was 3.9 (95% CI 3.1 to 5.1) for postherpetic neuralgia, 5.0 (95% CI 4.0 to 6.6) for painful diabetic neuropathy, 5.6 (95% CI 3.5 to 14) for central NP, and 11 (95% CI 7.1 to 21) for fibromyalgia [18].

Overall, the reviewed studies failed to satisfy accepted criteria defining a high-quality trial [3] and led to a generalised conclusion that individualisation of treatment with PGB is needed to maximise pain relief and minimise adverse effects. Patients with niche indications or where there is a contraindication to GBP due to SE are often prescribed PGB.

3.3. SE: GBP

Adverse events in populations administering GBP or PGB were frequent, but mostly tolerable.

3.3.1. Sciatica

A large review and meta-analysis reported two out of 25 patients treated with GBP experienced an adverse event including dizziness, somnolence, chest pain, fainting, dry mouth, constipation, weight increase, headache or peripheral oedema. However the numbers of adverse effects were fewer compared to PGB. In this study, patients allocated to the placebo control arm reported no adverse events [2].

3.3.2. Other conditions

A study on GBP for treating chronic NP and fibromyalgia reported that 12% of patients withdrew from the study because of adverse events when the dose was 1,200 mg or more. This compares with 8% for placebo, giving a risk ratio of 1.4 (95% CI 1.1 to 1.7). Somnolence, drowsiness, sedation, peripheral oedema and ataxia were the most common complaints from participants receiving GBP. All-cause withdrawals occurred in 20% of participants being treated with GBP compared to 19% receiving placebo (risk ratio 1.1, 95% CI 0.9 to 1.2), and 66% of GBP patients experienced at least one adverse event compared to only 51% on placebo (risk ratio 1.3, 95% CI 1.2 to 1.4) [10]. Of these mentioned adverse events, 4% in GBP patients and 3.2% in placebo patients were considered to be serious [10].

Another review examined the utility of GBP in acute and chronic pain, with the authors reporting the NNH for each episode of major harm from GBP usage. Major harm was considered to be any effects that lead to participants withdrawing from the study. The resultant NNH for major harm was not statistically significant, however for minor harm, the authors report a NNH of 3.7 (95% CI 2.4 to 5.4). The most common adverse events were dizziness (24%), somnolence (20%), headache (10%), diarrhoea (10%), confusion (7%) and nausea (8%) [11].

3.3.3. Single-dose GBP

Single-dose GBP was compared to placebo for established acute post-operative pain in adults. A low-quality review which included four unpublished studies showed 28% of patients taking GBP experienced at least one adverse event compared to 32% for placebo. The relative risk for treatment with GBP was 0.91 (95% CI 0.66 to 1.3). No serious adverse events were reported with GBP use; however there was a report of "heart arrest" occurring one day after study completion. Withdrawals from the study were limited, with only 3/370 participants receiving GBP leaving the study due to fever [15].

3.4. SE: PGB

3.4.1. Sciatica

The SE of PGB were reported in a randomised double-blind placebo controlled study when used to treat pain following lumbar discectomy. Visual disturbances occurred in 2/18 patients in the PGB group, however these were self-limiting and resolved within 4 hours in all cases. Somnolence and dizziness were also reported in patients receiving PGB [16].

In a small randomised double-blind cross-over study where PGB was used as a control, 14 of the 18 participants (78%) experienced adverse events following PGB treatment. These events included dizziness, nausea and tiredness. However, these events were reported retrospectively at the end of the study [17].

A large systematic review and meta-analysis which included studies using various treatments for sciatica reported that 31 of

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110 patients allocated to PGB treatment experienced at least one adverse event, including dizziness, somnolence, chest pain, fainting, dry mouth, constipation, weight increase, headache or peripheral oedema. A greater number of adverse events were reported with the usage of PGB [2]. Additionally, the systematic review found that patients allocated to the placebo control arm did not report a single adverse event [2].

3.4.2. Other conditions

Conclusions about the frequency of SE associated with PGB could not be reported in a study for acute and chronic pain, because these events were not recorded in all studies. Consequently, the authors had to perform dose-dependent adverse event analysis with the results showing no link between a higher dose and greater adverse outcome. The only reported adverse events were somnolence and dizziness [18].

The rate and type of reported adverse events varied substantially between drugs and between trials of the same medication.

3.5. Costing and national formulary listing: PGB and GBP

The cost of each drug varied widely between countries (Table 2); for example, costs for GBP varied by a factor of 31 (all costs reported in USD) between the UK and USA (from $8.43 to $263.32). The cost also varied unpredictably (Table 2); for example, in Australia, PGB ($51.71 for 56 150 mg capsules) was more expensive than GBP ($29.13 for 100 400 mg capsules), whilst in New Zealand GBP was more expensive than PGB. Moreover, costs for both drugs were markedly more expensive (by a factor of six for GBP) in New Zealand compared to Australia ($173.56 for GBP and $115.51 for PGB).

Paradoxically, most nations (4/7) for which data could be easily obtained solely favoured the more expensive drug, whether GBP or PGB (Table 2). For example, New Zealand and Singapore listed only GBP, whilst Australia and Europe listed only PGB for NP; in all cases, the listed drug was the more expensive (Table 2). By contrast, USA, UK and Canada listed both drugs. However, the criteria required to obtain GBP in the USA and Canada were more stringent than with PGB, thus, PGB was still favoured in these countries. Interestingly, in the USA where both drugs were listed, PGB and GBP were both comparable in cost (PGB: $221.86 for 56 150 mg capsules compared to GBP: $263.32 for 100 400 mg capsules); a similar situation prevailed in Canada. However whilst cost comparability between PGB and GBP also prevailed in Europe, only PGB was listed in Europe (22). Finally, whilst both PGB and GBP were listed in some UK hospitals, PGB was markedly more expensive (by a factor of 13) than GBP.

Table 2
National formulary regulator rulings and costs in USD across nations

	Gabapentin	Pregabalin
Australia [22]	NL ($29.13)	L ($51.71)
New Zealand [23,24]	L ($173.56)	NL ($115.51)
Canada [25,26]	L ($110.32)	L ($140.01)
Europe [19,27]	NL ($147.32)	L ($182.76)
USA [28,29]	L ($263.32)	L ($221.86)
Singapore [30,31]	L ($174.06)	NL (not available)
UK [32,33]	L ($8.43)	L ($113.31)

Price is reflective of pregabalin 150 mg capsules quantity 56 and gabapentin 400 mg capsules quantity 100.
Listing generally equates with favoured, that is, more difficult to obtain the "not listed" drug. In some countries (Australia), this means that the listed drug is subsidised and that not listed drugs will incur greater cost to the patient.
L = listed, NL = not listed.

4. Discussion

Only two limited specific reviews which assess for the role of PGB or GBP in sciatica exist to our knowledge. The first emanates from NICE-UK which recommended a variety of treatment modalities for the relief of pain associated with neuropathic conditions [1]. NICE-UK guidelines state that there is evidence for the efficacy of PGB and GBP for treating NP disorders, including sciatica; however, "adverse effects should be discussed with each patient, and weighed against potential benefits". Whilst both PGB and GBP were considered efficacious, NICE-UK nevertheless favoured PGB over GBP for three main reasons: (1) lower NNT values from meta-analysis comparisons, (2) simpler dosing and titration regime with PGB and (3) cost-effectiveness over GBP.

However, when considering NICE-UK guidelines, it is important firstly to note that they were derived only from indirect comparisons with weak power. Furthermore, NNT values were quoted which are open to bias, and for which CI cannot be reliably determined. Regarding dosing, the regime for PGB – whilst simpler (twice daily dosing) – is not majorly different from GBP (thrice daily dosing). Furthermore, whilst GBP should be titrated with delayed dosage increments (for example, 4 days), many now also consider that, in order to offset SE, PGB should similarly be introduced in a "low and slow" incremental fashion. Thus, the advantages of PGB titration seem exaggerated. Finally, it is important to note that costs for either PGB or GBP vary widely and unpredictably globally (Table 2). Thus, while NICE-UK considered PGB more cost effective, the converse is true in other countries, such as Australia where GBP is substantially cheaper in than PGB. Despite this, and somewhat surprisingly, only PGB is subsidised on the Australian Pharmaceutical Benefits Scheme, presumably reflecting the influence of NICE-UK guidelines.

The second and most recent systematic review and meta-analysis concerning drug treatment for sciatica is that of Pinto et al. [1]. However, only one study each for GBP and PGB was included. The appraisal and conclusions of the study highlighted the low quality of extant trials, and the fact that the best primary management for sciatica remained unclear. The review of Pinto et al. showed significant efficacy for GBP without any comment on PGB. Our review, by contrast, examines 11 studies in which PGB or GBP were used to treat NP, including sciatica.

Inconclusive evidence for either PGB or GBP in the treatment of sciatica and NP conditions is reflected worldwide by significant disparity in the rulings of individual formulary regulators. For example, GBP is currently available on the government-funded Pharmaceutical Benefits Scheme (PBS) in Australia, and some hospitals in the UK, but only for epilepsy; it is not listed for NP. PGB, by contrast, is subsidised on the Australian PBS for NP. The Food and Drug Administration in the USA, along with Health Canada, have adopted similar reimbursement criteria to that of the Australian PBS; notwithstanding, both GBP and PGB can be accessed in the USA and Canada via special access schemes if patients satisfy stringent criteria for NP. In marked contrast, GBP is listed for use in both partial seizures and NP throughout Europe. The rulings of formulary regulators have therefore been inconsistent, and dependent upon the individual body.

Our review has confirmed the absence of any adequately powered direct "head-to-head" trial comparing GBP and PGB. Formulary regulators have therefore globally used indirect

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comparisons to inform listing decisions. Such indirect comparisons possess numerous limitations, including differing patient demographics, primary outcomes and pain measurement scales. Based on NICE-UK guidelines, weak evidence suggests that efficacy and SE profiles of PGB and GBP in sciatica are probably similar; however, firm conclusions are necessarily precluded. NICE-UK noted one factor in favouring PGB over GBP, that PGB had distinct pharmacokinetic advantages, including higher bioavailability, more rapid absorption and increased binding affinity. However, such factors are secondary, and had only gained eminence owing to a lack of firm evidence for primary factors (that is, efficacy and SE profiles).

The lack of firm evidence for the use of either PGB or GBP in sciatica has, in consequence, permitted global inconsistency in the rulings of individual formulary regulators regarding drug preference. Given that NICE-UK guidelines were ultimately largely influenced by cost considerations, one might have expected that similar considerations would also account for the wide disparity found in formulary regulator rulings. However, paradoxically, most countries for which data could be easily obtained have solely favoured the more expensive drug (whether GBP or PGB; Table 2). Some nations (UK, USA and Canada) appear to have accepted a degree of equipoise, in agreement with current evidence, and have listed both drugs. Particularly in the UK, free interchange between PGB and GBP is therefore also possible. However, whilst USA and Canada listed both drugs, the criteria required to obtain GBP are more stringent than with PGB; thus, PGB is still favoured in these countries. In marked contrast, free interchange between PGB and GBP has been thwarted in Australia, New Zealand, Europe and Singapore. Whilst NICE-UK noted cost effectiveness to secondarily justify a bias toward PGB, cost cannot explain the formulary regulator rulings in these countries, where the more expensive drug was solely listed.

In Australia, the recent addition of PGB to the PBS for NP in 2013 has created a conflict in that some long-standing users of GBP, who were previously controlled on GBP, were subsequently forced to either incur greater costs, or to switch to PGB (with potentially less utility). The Australian Pharmaceutical Benefits Advisory Committee rejected applications to subsidise GBP for the treatment of NP on the grounds of lack of evidence in the proposed population (that is, clinical trial data did not reflect the population covered by the proposed PBS restriction) and uncertain cost-effectiveness in this patient group. However, prescribing authorities in Europe appear to have taken a different view (Table 2).

The Spine Patient Outcomes Research Trial (SPORT) study [20] showed that many patients with sciatica will spontaneously improve in the medium term with non-operative management; thus, every attempt should be made to avoid a potentially unnecessary operation. Given that some patients may benefit from either PGB or GBP but not both, free interchange between PGB and GBP should be facilitated and not obstructed as it is in many countries. However, given that no evidence supports unhindered PGB-GBP substitution, free interchange should not be forced as has occurred in countries like Australia, where many patients have been forced to interchange GBP with PGB. Based on current evidence, neither drug should probably be favoured.

5. Conclusion

Weak evidence suggests that efficacy and SE with GBP and PGB are probably similar; however, firm conclusions are precluded. Despite weak data, and having cited minor titration but definite cost advantages, NICE-UK favoured PGB over GBP. However, globally, costs vary widely and unpredictably; paradoxically, many formulary regulators exclusively favour the more expensive drug, whether GBP or PGB. Given that to our knowledge no evidence supports unhindered PGB-GBP interchange, neither drug should probably be favoured. Prospective "head-to-head" studies are urgently required to provide robust evidence-base for relative GBP/PGB use in sciatica.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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