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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