



## REVIEW ARTICLE

# Pain management in Guillain–Barre syndrome: A systematic review<sup>☆</sup>



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Methylprednisolone

### Abstract

**Introduction:** Pain is a common symptom in patients with Guillain–Barre syndrome. Intensity is moderate to severe in most cases and pain may persist after resolution of the disease.

**Objective:** Identify the most appropriate analgesic therapy for pain management in patients with Guillain–Barre syndrome.

**Material and methods:** Systematic review and selection of scientific articles on treatment of pain in Guillain–Barre syndrome patients, published between January 1985 and December 2012. We included only randomised, double-blind, controlled trials assessing the effectiveness of drugs for pain management in these patients.

**Results:** Four articles met the inclusion criteria. One evaluated the use of gabapentin, another evaluated carbamazepine, a third compared gabapentin to carbamazepine, and the last evaluated use of methylprednisolone. Both carbamazepine and gabapentin were useful for pain management. Patients experienced lower-intensity pain with gabapentin treatment in the study comparing that drug to carbamazepine. Methylprednisolone was not shown to be effective for reducing pain. The published data did not permit completion of a meta-analysis.

**Conclusions:** There is no robust evidence at present that would point to a single treatment option for this disorder. Further clinical studies of larger patient samples and with a longer duration are needed to characterise types of pain for each patient and measure pain intensity in an objective way.

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**PALABRAS CLAVE**

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 Carbamazepina;  
 Metilprednisolona

**Manejo del dolor en el síndrome de Guillain-Barré. Revisión sistemática****Resumen**

**Introducción:** El dolor es un síntoma muy frecuente en los pacientes con síndrome de Guillain-Barré, con una intensidad de moderada a severa en la mayoría de los casos; puede persistir luego de la resolución de la enfermedad.

**Objetivo:** Identificar la terapia analgésica más apropiada para el manejo del dolor en los pacientes con síndrome de Guillain-Barré.

**Material y métodos:** Se realizó una búsqueda y selección sistemática de los artículos científicos sobre el tratamiento del dolor en pacientes con síndrome de Guillain-Barré publicados entre enero de 1985 y diciembre de 2012. Se incluyeron solo ensayos clínicos aleatorizados, doble ciego, que evaluaron el efecto de los medicamentos en el tratamiento del dolor en estos pacientes.

**Resultados:** Cuatro artículos cumplieron los criterios de inclusión. Uno evaluó el uso de gabapentina, otro, el de carbamazepina, otro comparó el uso de gabapentina y carbamazepina, y el último evaluó el uso de metilprednisolona. Tanto carbamazepina como gabapentina fueron útiles en el manejo del dolor. En el estudio que comparó carbamazepina y gabapentina, los pacientes presentaron menor intensidad del dolor con el uso de este último. La metilprednisolona no mostró un efecto positivo en la reducción del dolor. Los datos publicados no permitieron la realización de un metaanálisis.

**Conclusiones:** No hay evidencia sólida en el momento actual para recomendar una opción terapéutica específica ante este problema. Es necesaria la realización de futuros estudios clínicos que incluyan un mayor número de pacientes, por un tiempo más prolongado, que individualicen los tipos de dolor por pacientes y midan objetivamente la intensidad de este.

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**Introduction**

Guillain–Barre syndrome (GBS) is a cellular and humoral autoimmune disorder in which the body generates autoantibodies that attack peripheral nerve components. It is characterised by symmetrical progressive weakness typically beginning in the lower limbs and accompanied by hyporeflexia or areflexia.<sup>1</sup> The estimated incidence rate is 1.1 to 1.8 new cases per 100 000 population per year. This rate increases with age: 1.7 to 3.3 new cases per 100 000 population over 50 per year.<sup>2</sup> Men are 1.5 times more likely to develop the syndrome than women.<sup>3</sup> Approximately two-thirds of all cases have a history of upper respiratory tract infection or diarrhoea before weakness presents. The most frequently implicated microbes are *Campylobacter jejuni* (30% of all cases), cytomegalovirus (up to 10% of cases), Epstein–Barr virus, varicella-zoster virus, and *Mycoplasma pneumoniae*.<sup>1</sup>

Cerebrospinal fluid from patients usually displays albuminocytological dissociation (increased protein level with normal cell count); this is more frequent after 2 weeks.<sup>1</sup> Electrophysiological studies are useful not only for confirming the diagnosis but also for identifying the disease subtype as acute inflammatory demyelinating polyradiculoneuropathy, acute sensorimotor axonal neuropathy, acute motor axonal neuropathy, or acute sensory axonal neuropathy.<sup>4</sup> There also exist such localised variants as facial diplegia with paraesthesia, pharyngeal-cervical-brachial weakness, and Miller Fisher syndrome, which combines ophthalmoplegia, ataxia, and areflexia.<sup>1</sup>

Disease management includes implementing support measures and immunotherapy with IVIg or

plasmapheresis.<sup>1,3</sup> GBS usually has a good prognosis and relapses are rare. However, approximately 2% of patients die and 20% are left with severe disabilities.<sup>1</sup>

Pain is the most common symptom of GBS; it presents in up to 72% of cases,<sup>5</sup> including the pure motor variants.<sup>6</sup> It is usually of moderate to severe intensity and can arise at any stage in the disease. In a longitudinal study including 156 patients with GBS, 36% of the total experienced the highest pain levels during the 2 weeks preceding onset of weakness, 66% during the acute phase, and 38% after 1 year.<sup>7</sup>

Pain is often underdiagnosed for two main reasons: lack of knowledge about the disease, and the fact that some of these patients are admitted to the intensive care unit (ICU) for ventilatory support, which makes it impossible for them to explain their physical state.<sup>8</sup>

This study presents a systematic review of the literature addressing pain management in GBS.

**Methods**

We identified and systematically selected scientific articles addressing pain management in patients with GBS which had been published between January 1985 and December 2012. The search was conducted in PubMed, Cochrane, Embase, and LILACS databases using the following combinations of terms: 'Guillain–Barre syndrome', 'Miller Fisher syndrome', 'pain', 'acute polyneuropathy', and 'polyradiculoneuropathy'. In addition, we manually reviewed the following journals in order to identify other articles potentially relevant to our study: *Archives of Neurology*; *Journal of Neurology*; *Annals of Neurology*; *Anesthesiology*;

*Neurology; Anaesthesia; Pain; Critical Care Medicine; Muscle & Nerve; Anaesthesia & Analgesia; Journal of Neurology, Neurosurgery & Psychiatry; Neurología; and Revista de Neurología.* Inclusion criteria were clinical trials published in either English or Spanish; we excluded summaries and articles not using scales to measure pain intensity, those not specifying drug dosage and administration frequency and times, and those not describing pain type. The search was completed electronically. We examined titles and abstracts of all selected articles, and those considered relevant for the purpose of our study were obtained in full-text format. Each of the authors read and analysed all articles. We gathered the following information from each article: criteria for GBS diagnosis, patient's age, type of pain, medication used for pain management (name, dosage, schedule, administration time), pain intensity (before and after medication), rescue treatment used, and whether the latter was administered at the ICU. An Excel spreadsheet was completed for each of the studies: each author extracted the data mentioned above and any discrepancies were discussed until consensus was reached. No researchers involved in other studies were contacted. In order to determine the validity of the studies included, we analysed whether patients were randomised; whether trials were simple-, double-, or triple-blind; and the number of withdrawals and drop-outs from each study.

## Results

We included 14 articles in our study.<sup>8–21</sup> Ten were case reports, and the remaining 4 were randomised double-blind placebo-controlled trials,<sup>8,17,19,20</sup> including 3 conducted in ICUs. The 4 clinical trials evaluated carbamazepine; gabapentin; carbamazepine vs gabapentin; and methylprednisolone. Interestingly, 3 of the 4 clinical trials assessed the pain-relieving effects of an antiepileptic drug, while the fourth evaluated methylprednisolone. Rescue medications were pethidine and fentanyl. It was not possible to conduct a meta-analysis of data reported by these studies due to the wide range of patient profiles, types of intervention, results obtained, and ways in which the outcomes were assessed. We have therefore conducted a qualitative review with particular emphasis on the results, their applicability, and the limitations of each study according to PRISMA recommendations<sup>21</sup> for this type of study.

The total number of GBS patients included was 289. They were all adults (aged 16–54 years) and 189 of them experienced pain.

Tripathi and Kaushik<sup>17</sup> conducted a randomised double-blind placebo-controlled study with 12 patients admitted to the ICU due to severe back pain and/or leg cramps and muscle pain to evaluate the analgesic effects of carbamazepine. The first group, which included 6 patients, was administered a placebo for 3 days, followed by carbamazepine for another 3 days. The second group (the remaining 6 patients) underwent treatment with carbamazepine for 3 days and subsequently administered a placebo for an additional 3 days. Carbamazepine was administered at a dose of 100 mg/8 hours via a feeding tube. Pain intensity was ranked on a 5-point scale (1, no pain; 2, no pain at rest but pain

when moving; 3, constant moderate pain; 4, severe pain; 5, unbearable pain).

Patients reporting pain intensities >2 were administered IV pethidine at a dose of 0.5 to 1 mg/kg. Patients experienced a significant decrease in pain intensity ( $1.7 \pm 0.8$ ) and pethidine requirement ( $1.1 \pm 1.0$  mg/kg/day) on the days carbamazepine was administered ( $P = .001$ ). Pain intensities for each group were as follows: group 1, at treatment onset:  $4.5 \pm 0.6$ ; day 5:  $2.2 \pm 0.5$ ; day 6:  $1.5 \pm 0.6$ ; day 7:  $1.5 \pm 0.6$ ; and group 2, at treatment onset:  $4.7 \pm 0.5$ ; day 1:  $2.7 \pm 0.9$ ; day 2:  $1.2 \pm 0.5$ ; day 3:  $1.2 \pm 0.5$ .

Pandey et al.<sup>8</sup> conducted another randomised double-blind placebo-controlled study including 18 patients admitted to the ICU for ventilatory support. Patients were divided into 2 groups. In the initial stage, one group was treated with gabapentin dosed at 15 mg/kg/day, given in 3 doses per day for 7 days, while the other group was administered a placebo for 7 days. After that stage and a 2-day washout period, patients who had previously received gabapentin were administered a placebo; those who had been administered a placebo were treated with gabapentin as in the initial stage. A Ryle tube was used to administer the compounds. When pain intensity was higher than 5 on a pain rating scale of 10, fentanyl dosed at 2 g/kg was administered as a rescue analgesic. Pain intensity was measured using the visual analogue scale. Patients who received gabapentin before placebo showed a significant decrease in pain intensity, reduced use of rescue analgesics, and fewer adverse effects. Pain intensity was  $7.22 \pm 0.83$  on day 0 (before treatment onset),  $2.33 \pm 1.67$  on day 2, and  $2.06 \pm 0.63$  on day 7 ( $P < .001$ ; statistical power > 99%). Use of rescue analgesics was  $211.11 \pm 21.38$   $\mu$ g on day 1 and  $65.55 \pm 16.17$   $\mu$ g on day 7 ( $P < .001$ ; statistical power > 99%). Adverse effects were reported by one patient in the group first treated with gabapentin (nausea) vs 5 patients in the group starting with placebo (nausea, 2; constipation, 3). According to the authors of the study, this may be due to greater consumption of rescue analgesics during the period in which patients took the placebo. The study by Pandey et al. does not specify the type of pain patients experienced.

These researchers conducted another randomised double-blind placebo-controlled study<sup>19</sup> including 36 patients with GBS admitted to the ICU. Patients were randomly assigned to receive either gabapentin (300 mg/day), carbamazepine (100 mg), or a placebo in 3 doses per day for 7 days. Medications were administered using a Ryle tube and pain intensity was measured on the visual analogue scale. In this study, the authors report greater decreases in pain intensity in the gabapentin group (mean scores: 3.5, 2.5, 2.0, 2.0, 2.0, 2.0, and 2.0) than in the groups receiving carbamazepine (6.0, 6.0, 5.0, 4.0, 4.0, 3.5, and 3.0) or placebo (6.0, 6.0, 6.0, 6.0, 6.0, 6.0, and 6.0) ( $P < .05$ ). The type of pain patients experienced is not specified.

Ruts et al.<sup>20</sup> conducted a randomised double-blind placebo-controlled study of 223 patients with GBS (55% of whom reported pain) to evaluate the effect of methylprednisolone on pain. One group (112 patients) received IVIg + methylprednisolone (500 mg for 5 days) while the second group (111 patients) was administered IVIg + placebo. The authors also conducted a retrospective study of 39 patients. In the 4-week period before the study began, at randomisation (week 0), this subgroup experienced the

following pain types: back pain (33%), interscapular pain (28%), muscle pain or cramps (24%), paraesthesia/dysaesthesia (18%), radicular pain (18%), joint pain (5%), visceral pain (5%), and other types (15%). The effectiveness of methylprednisolone was assessed based on the percentage of patients experiencing pain throughout the study period. Ruts et al. did not use a scale to measure pain intensity. According to their study, no significant decreases in the percentage of patients with pain were observed in the group receiving methylprednisolone (50% at randomisation, 49% at 4 weeks after randomisation) compared to changes in the placebo group (60% at randomisation, 57% at 4 weeks after randomisation).

Specified times of intervention for these 4 randomised double-blind placebo-controlled trials ranged from 3 days<sup>17</sup> to 4 weeks,<sup>20</sup> and all articles were published in English. Two of them included rescue analgesics and the variable 'pain intensity' was measured on the visual analogue scale.<sup>8,19</sup> Three studies included patients admitted to ICUs,<sup>8,17,19</sup> although they failed to specify disease severity, a factor affecting doctors' ability to communicate with patients. As can be seen, studies evaluating pain management in patients with GBS are scarce, the patients' profiles are heterogeneous, and many studies do not provide a description of the type of pain and the progress of different variables having to do with pain.

## Discussion

Pain is a common symptom among patients with GBS. Although it usually precedes weakness, it may also present during the acute stage of the disease and may even be reported a year after GBS onset.<sup>7</sup> Intensity is moderate to severe in most cases. Pain is frequently underdiagnosed due to lack of awareness by healthcare professionals and the difficulties in communicating with patients on mechanical ventilation. Although these patients are a small minority, they may need ventilatory support during the first weeks of the disease.<sup>8</sup>

Pain management in patients with GBS is complex due to the different types of pain they may experience; furthermore, several types of pain co-exist in most cases.

Little is known about the pathophysiology of pain in these patients; however, presence of multiple types of pain (back and sciatic pain, meningeal signs, dysaesthesia and paraesthesia, muscle pain, arthralgia, visceral pain, etc.)<sup>5</sup> suggests that its origin is both nociceptive and neuropathic. Experimental autoimmune neuritis in animal models is a T-cell-mediated acute demyelinating inflammatory disease induced by immunisation with peripheral nerve myelin proteins or by transfer of T-cells sensitised to those proteins.<sup>22</sup> This disease has shed light on the mechanisms of central and peripheral sensitisation, which have been extrapolated to neuropathic pain in GBS since inflammatory demyelinating polyneuropathy is its most frequent variant.<sup>22</sup> As a result, 3 causes for neuropathic pain have been established in these models: (1) demyelination and degeneration of sensory nerves; (2) autoimmune inflammation of the peripheral nervous system due to activation of T-cells, antigen-presenting cells, and macrophages that release such proinflammatory

cytokines as IL-18 and TNF- $\alpha$ ; and (3) increased levels and activation of microglia in the central nervous system.<sup>22</sup> One proposed explanation for back pain and sciatica is entrapment neuropathy,<sup>5</sup> and nociceptive pain may be linked to inflammation of nerve roots and peripheral nerves in the acute phase of the disease.<sup>20</sup>

A meta-analysis could not be conducted due to the characteristics of the articles obtained. These articles reported favourable results for carbamazepine<sup>17</sup> and gabapentin<sup>8</sup> as pain management in patients with GBS. In the study comparing the effects of gabapentin and carbamazepine,<sup>19</sup> patients taking gabapentin were shown to score significantly lower on the visual analogue scale. However, neither of the studies published by Pandey et al.<sup>8,19</sup> specifies the type of pain patients experienced, and this information is of vital importance because a wide range of pathophysiological mechanisms may underlie GBS. In consequence, results for the pharmacological treatment cannot be generalised.

According to the study by Ruts et al.,<sup>20</sup> methylprednisolone did not have a positive effect on pain reduction. Furthermore, the study does not use a scale to measure pain intensity, and results are therefore less precise.

Different drugs have been used over time to manage pain in GBS. Some case reports of patients treated with morphine, dexamethasone, and remifentanyl describe satisfactory results.<sup>9,10,12,18,23</sup> In a case report of a patient with Miller Fisher syndrome, NSAIDs were shown to be ineffective for pain management.<sup>16</sup> In recent decades, doctors have shown a growing interest in such drugs as carbamazepine and gabapentin since they are easy to administer, provoke fewer adverse effects, and have been approved to treat several neuropathic pain syndromes.<sup>24–27</sup>

Gabapentin acts on the central and peripheral nervous systems, at both the spinal and supraspinal levels.<sup>28</sup> It binds to the  $\alpha 2\delta$ -1 subunit of the voltage-gated calcium channels, especially the N-type, and this is thought to be the main mechanism behind its analgesic effect.<sup>28</sup> Its effects on the spinal region are as follows: (1) inhibiting the transport of the  $\alpha 2\delta$ -1 subunit from the dorsal root ganglion to the posterior horn of the spinal cord; (2) contributing to the activity of protein kinase C and the release of proinflammatory cytokines; (3) reducing pre-synaptic glutamate release in the dorsal root ganglion; and (4) blocking NMDA receptors.<sup>28</sup> At the supraspinal level, it acts by activating the descending pain inhibitory pathways, specifically in the locus coeruleus, where it increases noradrenalin release. Noradrenaline then binds to  $\alpha 2$  receptors in the spinal cord, where it inhibits neurotransmission of pain.<sup>28</sup>

The analgesic effect of carbamazepine is attributed to blockage of the voltage-gated sodium channels that are essential for pain transmission.<sup>29</sup> In a study with rats with saphenous neuromas secondary to saphenous nerve dissection, spontaneous activity was seen to be inhibited in both A- $\alpha\beta$  and A- $\delta$  fibres after administration of IV carbamazepine.<sup>30</sup>

Methylprednisolone is a glucocorticoid. Glucocorticoids are steroids; their anti-inflammatory and anti-suppressant properties are due to direct or indirect genomic effects and activation of second messenger cascades after activation of glucocorticoid receptors.<sup>31</sup> Johansson et al.<sup>32</sup> studied a rat model of mononeuropathy induced by a chronic constriction injury to the left sciatic nerve. After local administration of

methylprednisolone, the authors observed decreased heat hyperalgesia and mechanical allodynia, but no changes in mechanical hyperalgesia. Reduced neurogenic extravasation has been observed in rats undergoing saphenous and sciatic nerve dissection after systemic administration of methylprednisolone.<sup>33</sup>

Our study has several limitations. One of them is the publication bias: we found no articles in the literature evaluating drugs other than antiepileptics and methylprednisolone, which may result in overestimates of the benefits of these drugs compared to placebo. Since few published studies have addressed this topic, we should be mindful that studies with negative findings are often not published. The publication bias may affect these results as well. Furthermore, the reported follow-up times are excessively short for a disease that will become chronic in most cases and which requires increasing doses of analgesics which usually have a noticeable effect in the long term. This has been shown by other studies on neuropathic pain.

Although the literature does report use of opioids to manage pain in GBS, none of those studies met our inclusion criteria. Some case reports are available, but recommendations on opioid use cannot be made due to the limitations inherent to the study design. We located 10 case reports, 6 of which described opioid use as an analgesic: morphine in 4, remifentanyl in another, and a non-specified opioid in the remaining case report. We should highlight the case reports by Genis et al.<sup>10</sup> and Busquets et al.<sup>34</sup> These authors administered epidural morphine to patients with GBS who had not responded to oral or parenteral treatment. Pain was relieved satisfactorily with low doses of morphine; adverse effects were rare and morphine did not alter either reflexes or sensorimotor functions.

Some of the advantages of opioids are the wide range of available drugs and presentation forms, their effectiveness in the middle and long term, and their benefits in somatic, visceral, and neuropathic pain management.<sup>35</sup>

Opioids and antiepileptics have been used in combination therapy to treat different types of pain in some studies, yielding satisfactory results. This is the case of pregabalin and oxycodone, which have been proved effective against neuropathic pain in both cancer and non-cancer patients, as shown by a randomised prospective study by Garassino et al.,<sup>36</sup> a case report of a patient with lung cancer and exacerbation of symptomatic sciatica by Baba and Gomwo,<sup>37</sup> and the prospective study conducted by Gatti et al.<sup>38</sup> In a case report by Siniscalchi et al.,<sup>39</sup> the combination of carbamazepine and oxycodone achieved complete pain remission in a patient with trigeminal neuralgia. Carbamazepine may increase the analgesic effects of morphine in rats with postoperative pain, as suggested by Naseri et al.<sup>40</sup>

## Conclusions

Pain is highly prevalent and intense in patients with GBS; an adequate analgesic treatment is therefore of the utmost importance. However, there are very few randomised double-blind placebo-controlled clinical trials evaluating pharmaceutical pain management in the literature.

Evidence is not consistent enough to determine which options are the most appropriate for patients with GBS. Literature on this topic is scarce and conclusions cannot therefore be extrapolated to this patient population as a whole. There is little evidence on the benefits of pain management with such antiepileptics as gabapentin and carbamazepine, and with opioids in general. However, these treatment options have proved to be effective for other types of neuropathic pain and therefore constitute a valid treatment alternative. We need further studies including more patients and longer follow-up periods, which specify the type of pain, assess changes as the disease progresses, and measure pain intensity objectively with a pain rating scale. Meanwhile, other studies must assess the analgesic effects of other drugs used for neuropathic pain, including tricyclic antidepressants, selective norepinephrine and serotonin reuptake inhibitors, lidocaine, and topical capsaicin. In July 2012, the Cochrane Collaboration suggested conducting a review study to be led by Liu et al.<sup>41</sup> However, we feel that their findings will be no different from our own due to the scarcity of studies addressing this topic.

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## Conflicts of interest

The authors have no conflicts of interest to declare.

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