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[Intervention Review]

Pharmacological treatment for pain in Guillain-Barré syndrome

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ABSTRACT

Background

Pain in Guillain-Barré syndrome (GBS) is common, yet it is often under recognised and poorly managed. In recent years, a variety of pharmacological treatment options have been investigated in clinical trials for people with GBS-associated pain. This is an updated version of the original Cochrane review published in Issue 10, 2013.

Objectives

To assess the efficacy and safety of pharmacological treatments for various pain symptoms associated with GBS, during both the acute and convalescent (three months or more after onset) phases of GBS.

Search methods

On 3 November 2014, we searched the Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL, MEDLINE and EMBASE. In addition, we searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs in participants with confirmed GBS, with pain assessment as either the primary or secondary outcome. For cross-over trials, an adequate washout period between phases was required for inclusion.

Data collection and analysis

Two review authors independently screened the titles and abstracts of identified records, selected studies for inclusion, extracted eligible data, cross-checked the data for accuracy and assessed the risk of bias of each study.

Main results

Three short-term RCTs, which enrolled 277 randomised participants with acute phase GBS, were included. Risk of bias in the included studies was generally unclear due to insufficient information. None of the included studies reported the primary outcome selected for this review, which was number of patients with self reported pain relief of 50% or greater. One small study investigated seven-day regimens of gabapentin versus placebo. Pain was rated on a scale from 0 (no pain) to 10 (maximum pain). Amongst the 18 participants, significantly lower mean pain scores were found at the endpoint (day 7) in the gabapentin phase compared to the endpoint of the placebo phase (mean difference -3.61, 95% CI -4.12 to -3.10) (very low quality evidence). For adverse events, no significant differences were found in the incidence of nausea (risk ratio (RR) 0.50, 95% CI 0.05 to 5.04) or constipation (RR 0.14, 95% CI 0.01 to 2.54). A second study enrolling 36 participants compared gabapentin, carbamazepine and placebo, all administered over seven days. Participants in the gabapentin group had significantly lower median pain scores on all treatment days in comparison to the placebo and carbamazepine groups ($P < 0.05$). There

Pharmacological treatment for pain in Guillain-Barré syndrome (Review)

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were no statistically significant differences in the median pain scores between the carbamazepine and placebo groups from day 1 to day 3, but from day 4 until the end of the study significantly lower median pain scores were noted in the carbamazepine group ($P < 0.05$) (very low quality evidence). There were no adverse effects of gabapentin or carbamazepine reported, other than sedation. One large RCT (223 participants, all also treated with intravenous immunoglobulin), compared a five-day course of methylprednisolone with placebo and found no statistically significant differences in number of participants developing pain (RR 0.89, 95% CI 0.68 to 1.16), number of participants with decreased pain (RR 0.95, 95% CI 0.63 to 1.42) or number of participants with increased pain (RR 0.85, 95% CI 0.52 to 1.41) (low quality evidence). The study did not report whether there were any adverse events.

Authors' conclusions

Since the last version of this review we found no new studies. While management of pain in GBS is essential and pharmacotherapy is widely accepted as being an important component of treatment, this review does not provide sufficient evidence to support the use of any pharmacological intervention in people with pain in GBS. Although reductions in pain severity were found when comparing gabapentin and carbamazepine with placebo, the evidence was limited and its quality very low. Larger, well-designed RCTs are required to further investigate the efficacy and safety of potential interventions for patients with pain in GBS. Additionally, interventions for pain in the convalescent phase of GBS should be investigated.

PLAIN LANGUAGE SUMMARY

Drug treatment for pain in Guillain-Barré syndrome

Review question

Our aim in this review was to find out whether medicines for pain in Guillain-Barré syndrome (GBS) are safe and effective.

Background

GBS is a rare disease that affects the nerves and nerve roots outside the brain and spinal cord. It occurs when the person's immune system attacks the nerves. The trigger is sometimes an infection. Pain in GBS is often under recognised and poorly managed.

Study characteristics

We first carried out a wide search of medical databases to find studies that met the requirements for this review. We identified three studies, which involved 277 participants who were randomly assigned to different treatments for pain in GBS. Two studies compared a pain medicine (gabapentin or carbamazepine) with placebo (inactive treatment). The other study compared a steroid medicine with placebo.

Key results and quality of the evidence

Two medicines, gabapentin and carbamazepine, reduced pain severity compared to placebo (inactive) treatment and they had few side effects. One study found that people taking gabapentin had less pain, sleepiness or need for additional pain killers than those given carbamazepine. However, these studies were small and the treatment period was short. One trial, with 223 participants, found that methylprednisolone, which is a steroid medicine, did not affect the numbers of people who developed pain or change the numbers with more pain or less pain compared with placebo. This study did not report whether there were any side effects.

This review does not provide enough evidence to say whether or not treatments for pain in people with GBS work. Although both gabapentin and carbamazepine reduced the severity of pain compared to placebo, and few side effects were reported, the studies were small and the quality of the evidence was very low. Much larger, well-designed studies are needed to confirm that drug treatments are safe and effective for people with pain in the period soon after onset of GBS. Long-term studies of pain treatments at the stage when people with GBS are recovering should also be conducted and these should include assessment of effects of pain treatments on quality of life.

This review was first published in 2013 and an updated search in 2014 revealed no additional studies. The evidence is current to November 2014.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Gabapentin compared with placebo for pain in Guillain-Barré syndrome

Gabapentin compared with placebo for pain in Guillain-Barré syndrome

Patient or population: patients with pain in Guillain-Barré syndrome

Settings: intensive care units in India

Intervention: gabapentin

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Gabapentin				
Number of patients with self reported pain relief of 50% or greater (not measured)	Not reported	Not reported				
Pain score (numerical rating scale of 0 to 10: 0 = no pain, 10 = worst pain)	In Pandey 2002 , mean pain scores decreased from 7.83 ± 0.78 (SD) at baseline (day 0) to 5.67 ± 0.91 on day 7. In Pandey 2005 , median pain scores decreased from 8.0 (1.0 (IQR)) at baseline (day 0) to 6.0 (1.8) on day 7.	In Pandey 2002 , mean pain scores decreased from 7.22 ± 0.83 at baseline to 2.06 ± 0.63 on day 7. In Pandey 2005 , median pain scores decreased from 8.0 (1.0) at baseline (day 0) to 2.0 (0.8) on day 7.	Pandey 2002 mean difference -3.61 (-4.12 to -3.1) on day 7 Pandey 2005 not reported	54 (2 studies)	⊕⊕⊕⊕ very low ^{1,2,3}	Gabapentin superior to placebo in reducing pain scores
Sedation score (numerical rating scale of 1 to 6: 0 = anxious, agitated, or restless, 6 = asleep, no response)	In Pandey 2002 , mean sedation scores changed from 1.44 ± 0.51 (SD) at baseline (day 0) to 3.63 ± 0.51 on day 7. In Pandey 2005 , median sedation scores changed from 1.0 (1.0 (IQR)) at baseline (day 0) to 4.0 (1.0) on day 7.	In Pandey 2002 , mean sedation scores changed from 1.38 ± 0.50 at baseline to 2.44 ± 0.50 on day 7. In Pandey 2005 , median sedation scores changed from 2.0 (1.0) at baseline to 2.0 (0.0) on day 7.	Pandey 2002 mean difference -1.19 (-1.52 to -0.86) on day 7 Pandey 2005 not reported	54 (2 studies)	⊕⊕⊕⊕ very low ^{1,2,3}	Gabapentin superior to placebo in reducing sedation scores

Rescue anal- gesic con- sumption	<p>In Pandey 2002, mean fentanyl consumption change from day 1 to day 7 was -3 µg.</p> <p>At day 7, mean fentanyl consumption was 317 ± 24 µg</p> <p>In Pandey 2005, mean fentanyl consumption change from day 1 to day 7 was -240 µg.</p> <p>At day 7, mean fentanyl consumption was 351 ± 34 µg.</p>	<p>In Pandey 2002, mean fentanyl consumption change from day 1 to day 7 was -146 µg.</p> <p>At day 7, mean fentanyl consumption was 66 ± 16 µg</p> <p>In Pandey 2005, mean fentanyl consumption change from day 1 to day 7 was -214 µg.</p> <p>At day 7, mean fentanyl consumption was 126 ± 26 µg.</p>	<p>Pandey 2002</p> <p>mean difference -251 mcg (-265 to -238 mcg) on day 7</p> <p>Pandey 2005</p> <p>-225 mcg (-249 to -200 mcg) on day 7</p>	<p>54 (2 studies)</p>	<p>⊕⊕⊕⊕ very low^{1,2,3}</p>	<p>Gabapentin superior to placebo in reducing fentanyl consumption</p>
Nausea	111 per 1000	56 per 1000 (6 to 560)	RR 0.50 (0.05 to 5.04)	18 (1 study)	⊕⊕⊕⊕ very low ^{1,2,4}	From Pandey 2002 , no significant difference
Constipation	167 per 1000	23 per 1000 (2 to 423)	RR 0.14 (0.01 to 2.54)	18 (1 study)	⊕⊕⊕⊕ very low ^{1,2,4}	From Pandey 2002 , no significant difference

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IQR:** interquartile range; **RR:** risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Insufficient information for random sequence generation and allocation concealment was provided.

² Insufficient information to assess adequacy of methods to ensure blinding.

³ Only 54 participants.

⁴ Only 18 participants.

Summary of findings 2. Carbamazepine compared with placebo for pain in Guillain-Barré syndrome

Carbamazepine compared with placebo for pain in Guillain-Barré syndrome

Patient or population: patients with pain in Guillain-Barré syndrome

Settings: intensive care units in India

Intervention: carbamazepine

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Carbamazepine				
Number of patients with self reported pain relief of 50% or greater (not measured)	Not reported	Not reported				
Pain score (numerical rating scale of 0 to 10: 0 = no pain, 10 = worst pain)	In Pandey 2005 , median pain scores decreased from 8.0 (1.0 IQR) at baseline (day 0) to 6.0 (1.8) on day 7. Median daily scores from day 1 to 7 were 4.0, 4.0, 4.0, 6.0, 6.0, 6.0, and 6.0, respectively).	In Pandey 2005 , median pain scores decreased from 8.0 (1.0) at baseline to 3.0 (1.0) on day 7. Daily scores from day 1 to 7 (3.0, 3.0, 3.0, 4.0, 4.0, 3.5, and 3.0, respectively) were significantly lower than placebo from day 4 onwards (P < 0.05).	Not reported	24 (1 study)	⊕⊕⊕⊕ very low ^{1,2,3}	
Sedation score (numerical rating scale of 1 to 6: 0 = anxious, agitated, or restless, 6 = asleep, no response)	In Pandey 2005 , median sedation scores changed from 1.0 (1.0 IQR) at baseline (day 0) to 4.0 (1.0) on day 7. Median daily scores from day 1 to 7 were 4.0, 4.0, 4.0, 4.0, 4.0, 4.0, and 4.0, respectively).	In Pandey 2005 , median sedation scores changed from 2.0 (1.0) at baseline to 3.0 (1.0) on day 7. Daily scores from day 1 to 7 (3.0, 3.0, 3.0, 3.5, 3.0, 3.0, and 3.0, respectively) were significantly lower than placebo on all days.	Not reported	24 (1 study)	⊕⊕⊕⊕ very low ^{1,2,3}	
Rescue analgesic consumption	In Pandey 2005 , mean fentanyl consumption change from day 1 to day 7 was -240 µg. At day 7, mean fentanyl consumption was 351 ± 34 µg.	In Pandey 2005 , mean fentanyl consumption change from day 1 to day 7 was - 173 µg. At day 7, mean fentanyl consumption was 174 ± 30 µg.	Mean difference -176 µg (-202 to -150 µg) on day 7	24 (1 study)	⊕⊕⊕⊕ very low ^{1,2,3}	Relative effect was calculated at the endpoint. Carbamazepine is superior to placebo in reducing fentanyl consumption

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IQR:** interquartile range; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Insufficient information for random sequence generation and allocation concealment was provided.

² Insufficient information to assess adequacy of methods to ensure blinding.

³ Only 24 participants.

Summary of findings 3. Methylprednisolone compared with placebo for pain in Guillain-Barré syndrome

Intravenous immunoglobulin (IVIg) and methylprednisolone compared with IVIg and placebo for pain in Guillain-Barré syndrome

Patient or population: patients with Guillain-Barré syndrome, with varying severities of pain

Settings: hospitals in the Netherlands

Intervention: IVIg and methylprednisolone

Comparison: IVIg and placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IVIg/placebo	IVIg/methylprednisolone				
Number of patients with self reported pain relief of 50% or greater (not measured)	Not reported	Not reported				
Number of participants with pain after 4 weeks	518 per 1000	459 per 1000 (352 to 601)	RR 0.89 (0.68 to 1.16)	223 (1 study)	⊕⊕⊕⊕ Low ¹	No significant difference
Number of participants with decreased pain after 4 weeks	304 per 1000	288 per 1000 (191 to 431)	RR 0.95 (0.63 to 1.42)	223 (1 study)	⊕⊕⊕⊕ Low ¹	No significant difference

Number of participants with increased pain after 4 weeks	232 per 1000	197 per 1000 (121 to 327)	RR 0.85 (0.52 to 1.41)	223 (1 study)	⊕⊕○○ Low ¹	No significant difference
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IQR:** interquartile range; **IVIg:** intravenous immunoglobulin; **RR:** risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Insufficient information to assess adequacy of methods to ensure blinding.

Summary of findings 4. Gabapentin compared with carbamazepine for pain in Guillain-Barré syndrome

Gabapentin compared with carbamazepine for pain in Guillain-Barré syndrome

Patient or population: intensive care unit in India

Settings: intensive care unit in India

Intervention: gabapentin

Comparison: carbamazepine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Carbamazepine	Gabapentin				
Number of patients with self reported pain relief of 50% or greater (not measured)	Not reported	Not reported				
Pain score (numerical rating scale of 0 to 10: 0 =	In Pandey 2005 , median pain scores from day 1 to day 7 were 6.0, 6.0, 5.0,	In Pandey 2005 , median pain scores from day 1 to day 7 (3.5, 2.5, 2.0, 2.0, 2.0, 2.0, and 2.0) were significantly lower	Not reported	24	⊕○○○ very low ^{1,2,3}	Gabapentin may be superior to carbamazepine

no pain, 10 = worst pain)	4.0, 4.0, 3.5, and 3.0, respectively.	versus carbamazepine on each day ($P < 0.05$). Baseline pain scores were similar between groups.				in reducing pain scores
Sedation score (numerical rating scale of 1 to 6: 0 = anxious, agitated, or restless, 6 = asleep, no response)	In Pandey 2005 , median sedation scores from day 1 to day 7 were 2.0, 3.0, 3.0, 3.0, 3.5, 3.0, 3.0, and 3.0, respectively.	In Pandey 2005 , median sedation scores from day 1 to day 7 (2.0, 2.0, 2.0, 2.0, 2.0, 2.0, and 2.0, respectively) were significantly lower versus carbamazepine on each day ($P < 0.05$). Baseline sedation scores were similar between groups.	Not reported	24	⊕⊕⊕⊕ very low ^{1,2,3}	Gabapentin may be superior to carbamazepine in reducing sedation scores
Rescue analgesic consumption	In Pandey 2005 , mean fentanyl consumption change from day 1 to day 7 was -173 µg. At endpoint (day 7), mean fentanyl consumption was 174±30 µg.	In Pandey 2005 , mean fentanyl consumption change from day 1 to 7 was -214 µg. At day 7, mean fentanyl consumption was 126 ± 26 µg.	Mean difference	24	⊕⊕⊕⊕ very low ^{1,2,3}	Relative effect was calculated at the endpoint. Gabapentin is superior to carbamazepine in reducing sedation scores

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Insufficient information for random sequence generation and allocation concealment was provided.

² Insufficient information to assess adequacy of methods to ensure blinding.

³ Only 24 participants.

BACKGROUND

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (Issue 10, 2013), "Pharmacological treatment for pain in Guillain-Barré syndrome".

Description of the condition

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with a worldwide annual incidence of around one case per 100,000, with approximately one-third of all cases triggered by *Campylobacter jejuni* infection (Israeli 2012; McGrogan 2009). Other causes may include vaccination or surgery (Israeli 2012). At least four subtypes of GBS exist, including acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN) and Miller Fisher syndrome (Hughes 2005a). Pain is a symptom common to all subtypes, occurring in up to 89% of patients during the course of the disease (Moulin 1997). Possible mechanisms of pain in GBS include inflammation and compression of nerve roots leading to radicular pain, and demyelination and degeneration of sensory nerves, which alter the balance of sensory input from myelinated and unmyelinated fibres to the dorsal horn of the spinal column (Pandey 2005). There are different kinds of pain involved in GBS, such as neuropathic pain, musculoskeletal pain and visceral pain (Pentland 1994). The intensity of pain may be severe in the acute phase (Ruts 2010). In a prospective study, the percentage of patients reporting pain decreased significantly between the two-week (71%) and two-month (50%) evaluations. However, up to one-third of patients still suffered from painful symptoms two years after onset of the syndrome (Forsberg 2004).

Description of the intervention

The most commonly prescribed analgesics are nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. Anticonvulsants and antidepressants are also very commonly used by specialists. However, NSAIDs and opioids are not uniformly effective for pain symptoms evoked by different mechanisms, and safety concerns such as gastrointestinal bleeding in those receiving NSAIDs or addiction in those receiving opioids may limit their usefulness. The NSAIDs, such as aspirin, appear to be effective only for muscle and joint pain in GBS (Pentland 1994). Epidural opioids have been shown to be effective in GBS, even against burning pain (Ennis 1991). Case studies have reported that capsaicin may also be effective (Morgenlander 1990), while corticosteroids have not been shown to reduce pain (Ruts 2007). Evidence suggests that anticonvulsants and antidepressants are more effective than the traditional analgesics for treating neuropathic pain; therefore they may be effective for neuropathic components of pain in GBS (Moore 2011; Moore 2012).

How the intervention might work

NSAIDs inhibit both cyclo-oxygenase-1 and cyclo-oxygenase-2, preventing the production of prostaglandins which cause pain and inflammation (Peterson 2010). Opioids act directly on the nervous system through binding to specific opioid receptors to reduce pain (Zöllner 2008). Capsaicin is believed to reduce pain sensitivity through depletion of substance P and defunctionalisation of nociceptor fibres (Anand 2011). Corticosteroids are thought to reduce inflammation of the perineurium and epineurium in GBS (Berciano 2000). For anticonvulsant drugs, the mechanisms of analgesic action remain poorly understood. Possible explanations

include that they enhance γ -aminobutyric acid (GABA) inhibition, have a stabilising effect on neuronal cell membranes, and block new synapse formation (Bennett 2004; Eroglu 2009; Woolf 1999). The anxiolytic effects of anticonvulsants may also contribute to pain relief (Sullivan 2006). The mechanisms of action of antidepressants include modulation of inhibitory neurotransmitter pathways via prevention of uptake of noradrenaline and 5-hydroxytryptamine, as well as up-regulation of opioid receptor densities and endogenous opioid levels (Sawynok 2001).

Why it is important to do this review

Pain in GBS is often under treated and poorly managed (Moulin 1997). In recent years, a variety of pharmacological treatment options have been investigated in clinical trials for patients with GBS-associated pain. While studies have shown the possible effectiveness of individual therapies (Pandey 2002; Tripathi 2000), in the peer reviewed literature there is no systematic review with meta-analysis that assesses the efficacy and safety of pharmacological treatment for pain in GBS.

OBJECTIVES

To assess the efficacy and safety of different pharmacological treatments for various pain symptoms associated with GBS, during both the acute and convalescent (three months or more after onset) phases of GBS.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs evaluating pharmacological treatment for pain in GBS. For cross-over trials, an adequate washout period between treatment phases was required for inclusion. At the same time, we attempted to assess whether the order of each treatment phase may affect outcomes where symptoms are expected to improve relatively quickly in acute GBS. Both phases of eligible cross-over trials were included. We intended to perform sensitivity analysis with exclusion of cross-over trials from the analysis.

Types of participants

Inclusion criteria:

- GBS confirmed according to diagnostic criteria (Asbury 1990);
- people who explicitly suffered from GBS-related pain;
- all ages and both sexes;
- both acute GBS and convalescent GBS; and
- all forms of pain associated with GBS, for example neuropathic pain, musculoskeletal pain and visceral pain.

Types of interventions

Experimental intervention: any pharmacological treatment, alone or combined with other treatment.

Control intervention: no treatment; placebo alone or combined with other treatment (concomitant interventions would have to be the same in each group); or other pharmacological or non-pharmacological intervention. We analysed different control groups separately.

For the acute phase of GBS, the minimum acceptable duration of treatment for inclusion was one week. For the convalescent phase of GBS, the minimum duration of treatment for inclusion was one month.

Types of outcome measures

We included studies that reported pain assessment. We also intended to include studies that did not report pain provided they otherwise satisfied the inclusion criteria and they reported secondary outcome data. If data were available, we collected and analysed the outcomes of all participants initially randomised. We intended to separately measure and analyse the data on the acute and convalescent (three months or more after onset) phases of GBS; however, no studies provided data on the convalescent phase.

Primary outcomes

We intended to calculate the number of participants with self reported pain relief of 50% or greater at the endpoint of treatment. The preferred method of pain assessment was pain intensity or change as measured by a visual analogue scale (VAS) or a similarly validated scale (numerical or categorical) that could be converted to a 0 to 100 scale. However, no studies provided such data.

Secondary outcomes

We intended to analyse secondary outcomes based on core outcome recommendations from best practice guidelines (Dworkin 2008; Moore 2010). We analysed efficacy outcomes using data reported at the end of treatment and safety outcomes from data reported at any time in a participant's treatment.

1. The number of participants reporting pain relief of 30% or greater (derived using the same pain assessments as the primary outcome).
2. The number of participants reporting global impression of clinical change (PGIC) much or very much improved.
3. The number of participants reporting PGIC very much improved.
4. Mean changes in the score of validated quality of life scales (QOLs).
5. The number of withdrawals due to lack of efficacy.
6. The number of participants experiencing any adverse event.
7. The number of participants experiencing any serious adverse event.
8. The number of withdrawals due to adverse events.

If a statistically significant absolute risk reduction (ARR) existed between interventions, we intended to derive the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) and make direct or indirect comparisons with other interventions when possible. As noted below, no data were reported in any of the included studies for the secondary outcomes 1 through 4.

We inserted 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4) for each comparison and reported primary and secondary outcomes where available.

Search methods for identification of studies

This search was run for the original review on the 27th August, 2012.

Electronic searches

For our updated review we searched the Cochrane Neuromuscular Disease Group Specialized Register (3 November 2014), the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 10 in *The Cochrane Library*), MEDLINE (January 1966 to October 2014) and EMBASE (January 1980 to October 2014).

The detailed search strategies are included in the appendices: Cochrane Neuromuscular Disease Group Specialized Register (Appendix 1), CENTRAL (Appendix 2), MEDLINE (Appendix 3) and EMBASE (Appendix 4).

In an effort to identify unpublished and ongoing trials, we searched the US National Institutes of Health clinical trial site (<http://www.clinicaltrials.gov/>) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictpr/en/>) (Appendix 5).

Searching other resources

We scanned conference abstracts from the last three years for relevant studies in the World Congress of Neurology (2011, 2013), International Congress on Neuropathic Pain (2010, 2013), Networking World Anesthesia Convention (2012, 2013, 2014) and GBS/Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) International Symposium (2010, 2012, 2014). We checked the reference section of included studies and contacted study authors to identify any additional published or unpublished data.

Data collection and analysis

Selection of studies

Two review authors (JL, LNW) independently evaluated titles and abstracts of identified trials to determine eligibility. We obtained the full text of all potentially relevant studies for further consideration. We resolved any disagreement by discussion, or the third author (EM) arbitrated if necessary.

Data extraction and management

Two review authors (JL, LNW) independently extracted eligible data from the published reports onto standardised forms and cross-checked data for accuracy. The third author (EM) resolved any disagreements regarding data extraction. One author (JL) entered data into the Cochrane statistical software Review Manager 5.1 (RevMan 2011) and the other authors (LNW, EM) checked the accuracy of the data entry.

We used checklists to independently record details of the following:

- study design;
- total study duration;
- methods of generating a randomisation schedule;
- method of concealment of allocation;
- blinding;
- use of an intention-to-treat analysis (ITT) (all participants initially randomised would be included in the analyses as allocated to groups);
- adverse events and dropouts for all reasons;
- participants (country, number of participants, age, sex, inclusion and exclusion criteria);

- comparison (details of the intervention in treatment and control groups, details of co-intervention(s) in both groups, duration of treatment);
- outcomes and timepoints of measures (number of participants in each group and outcome, regardless of compliance); and
- factors that influence heterogeneity (sample size, missing participants, confidence intervals and P values in measurement, and subgroup analyses).

Assessment of risk of bias in included studies

Two review authors (JL, LNW) independently assessed the risk of bias of all included studies using a domain-based evaluation (Higgins 2011). We made critical assessments for each of the following different domains: sequence generation (randomisation), allocation concealment, blinding (of participants and personnel, and of outcome assessors), incomplete outcome data, selective reporting and other bias. We entered our judgement for each domain into a 'Risk of bias' table using the categories 'low risk', 'high risk' or 'unclear risk' (unclear risk indicates either lack of information or uncertainty over the potential for bias). Where possible, we obtained the protocols of included trials or entries in clinical trial registries to assist in the assessment of risk of bias from selective outcome data reporting.

Measures of treatment effect

We attempted to measure the data from all participants initially randomised. We presented dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs) to express the effect size. When a statistically significant ARR existed between interventions, we derived the NNTB or NNTH. Where dichotomous data were not available, or could not be mathematically derived from continuous data, we expressed continuous outcomes such as VAS pain intensity difference as mean differences (MDs) with 95% CIs.

Unit of analysis issues

We dealt with any unit of analysis issues, such as cluster randomisation, more than one intervention performed in individuals, or multiple observations for the same outcome, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We used ITT analysis. The ITT population consisted of participants who were randomised and took the assigned study medication. We intended to assign zero improvement for dichotomous outcomes for participants who withdrew due to lack of efficacy or adverse events; however there were no withdrawals in any of the included studies.

Assessment of heterogeneity

We intended to visually inspect forest plots for evidence of heterogeneity and quantify heterogeneity using the I^2 statistic (Higgins 2011). If we found statistically significant heterogeneity ($I^2 > 50\%$), we intended to explore factors for the heterogeneity; however there were insufficient data to perform meta-analysis.

Assessment of reporting biases

If we identified sufficient RCTs (more than 10 studies), we intended to examine potential publication bias using a funnel plot (Egger 1997); however only three studies met the inclusion criteria.

Data synthesis

We would have analysed and reported data from acute (three months or less from onset) and convalescent (more than three months from onset) phases separately if data had been available. If significant heterogeneity was found ($I^2 > 50\%$), we intended to calculate overall effects using a random-effects model instead of a fixed-effect model. Since we were not able to combine outcome data from different studies, we provided a descriptive summary of the results. We analysed different control groups separately.

Subgroup analysis and investigation of heterogeneity

We planned to analyse subgroups of studies categorised according to baseline differences, such as different kinds of pain (for example neuropathic pain, musculoskeletal pain and visceral pain); different interventions; different control groups; and different dosage and duration of interventions. However, we were not able to perform any of these analyses due to lack of data.

Sensitivity analysis

We planned to perform sensitivity analysis where studies of greater than one month duration but less than 12 weeks were removed, and where cross-over trials were removed from the analysis. We also intended to examine the robustness of results to fixed-effect versus random-effects model assumptions, and the inclusion or exclusion of studies with high risk of bias for a particular domain. However, we were not able to perform any sensitivity analysis due to lack of data.

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

From our original review, searches of the electronic databases identified 164 papers in MEDLINE, 182 papers in EMBASE, 7 papers in the Cochrane Neuromuscular Disease Group Specialized Register and 10 papers in CENTRAL. After screening the titles and abstracts, we obtained and assessed full papers of nine articles. Finally, three studies were eligible and were included. On re-running the searches in 2014, we identified 64 papers after deduplicating the results. We acquired and screened the full text of only one article; this study did not meet inclusion criteria. Agreement between the review authors on exclusion was 100%. We found no relevant ongoing or unpublished trials from our searches of the trials registers (Figure 1).

Figure 1. Study flow diagram.

Included studies

The three included RCTs (Pandey 2002; Pandey 2005; Ruts 2007) were performed in the acute phase of GBS and enrolled 277 randomised participants. One RCT (Pandey 2002), enrolling 18

participants, was a cross-over trial with seven days of therapy and a two-day washout between phases. The other two studies were parallel trials (Pandey 2005; Ruts 2007). Two trials (Pandey 2002; Pandey 2005) enrolled patients from intensive care units in India and administered gabapentin (combined n = 30) for seven days.

Pandey 2005 also enrolled an arm receiving carbamazepine (n = 12) for seven days. One study (Ruts 2007) with 223 participants administered methylprednisolone (n = 111) for five days. While the duration of treatment in this study did not meet our pre-specified inclusion criteria, we made a post hoc decision to include it given that methylprednisolone can be considered a prophylactic treatment and, therefore, was likely to have a duration of action beyond the five days on which it was administered.

We provided details of the included trials in the [Characteristics of included studies](#) tables. No studies reported data from the convalescent phase of GBS.

Excluded studies

We excluded seven studies (Brisby 2002; Forsberg 2004; Korinthenberg 2005; Morgenlander 1990; Odaka 2005; Sendhilkumar 2013; Tripathi 2000) after full-text evaluation. We provided the reasons for exclusion in [Characteristics of excluded studies](#).

Risk of bias in included studies

The details of the risk of bias are provided in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.
Yellow = unclear risk of bias; green = low risk of bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Pandey 2002	?	?	?	?	+	+	+
Pandey 2005	?	?	?	?	+	+	+
Ruts 2007	+	+	?	+	+	+	+

Allocation

Only one RCT (Ruts 2007) provided details of random sequence generation or allocation concealment. We therefore assigned an unclear risk of bias to the other two RCTs.

Blinding

No RCT adequately described methods to ensure double-blinding. Again, we assigned each study an unclear risk of bias.

Incomplete outcome data

No withdrawals or deaths were found in any of the included RCTs. We assigned each study a low risk of bias.

Selective reporting

All the pre-specified outcomes were reported in the results sections of the included studies. We therefore assessed each study as having a low risk of bias.

Other potential sources of bias

We did not find any potential publication bias. There were too few trials available for a funnel plot analysis.

Effects of interventions

See: [Summary of findings for the main comparison Gabapentin compared with placebo for pain in Guillain-Barré syndrome](#); [Summary of findings 2 Carbamazepine compared with placebo for pain in Guillain-Barré syndrome](#); [Summary of findings 3 Methylprednisolone compared with placebo for pain in Guillain-Barré syndrome](#); [Summary of findings 4 Gabapentin compared with carbamazepine for pain in Guillain-Barré syndrome](#)

Primary outcome measure

None of the included studies reported results as the number of patients with self reported pain relief of 50% or greater.

Secondary outcome measures

1. The number of participants reporting pain relief of 30% or greater (derived using the same pain assessments as the primary outcome).
2. The number of participants reporting global impression of clinical change (PGIC) much or very much improved.
3. The number of participants reporting PGIC very much improved.
4. Mean changes in the score of validated quality of life scales (QOLs).

None of the included studies measured or reported outcomes recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), that is, secondary outcomes 1 through 4 above ([Dworkin 2008](#)). Therefore, we compared mean or median pain scores as measured by numerical pain rating scales (0 to 10: 0 = no pain, 10 = worst pain) and additional pain outcomes including number of participants developing pain, and analgesic consumption.

Pain scores

In [Pandey 2002](#), participants had significantly lower mean pain scores at the endpoint of the gabapentin phase (day 7) compared to the endpoint of the placebo phase (MD -3.61, 95% CI -4.12 to -3.10, $n = 18$ in both phases). Of note, while within-group comparisons were not part of our analysis, pain was lower each day from day 1 to 7 versus baseline (day 0) during the gabapentin phase, decreasing from 7.22 ± 0.83 (mean $\pm$ standard deviation) at baseline to 2.06 ± 0.63 on day 7 ($P < 0.001$ for all comparisons). The decrease in pain scores during the placebo phase was not significant on any day versus baseline (day 0: 7.83 ± 0.78 , day 7: 5.67 ± 0.91).

In [Pandey 2005](#), participants in the gabapentin group ($n = 12$) had significantly lower median pain scores (3.5, 2.5, 2.0, 2.0, 2.0, 2.0, and 2.0; from day 1 to 7, respectively) on all treatment days in comparison to the placebo (6.0, 6.0, 6.0, 6.0, 6.0, 6.0, and 6.0) ($n = 12$) and carbamazepine (6.0, 6.0, 5.0, 4.0, 4.0, 3.5, and 3.0) ($n = 12$) groups ($P < 0.05$). There were no statistically significant differences in the median pain scores between the carbamazepine and placebo groups from day 1 to day 3 (3.0, 3.0, and 3.0 versus 4.0, 4.0, and 4.0), but from day 4 until the end of the study significantly lower median pain scores were noted in the carbamazepine group (4.0, 4.0, 3.5, and 3.0) compared with placebo (6.0, 6.0, 6.0, and 6.0) ($P < 0.05$).

Number of participants with pain

When intravenous immunoglobulin (IVIg) plus methylprednisolone ($n = 111$) was compared with IVIg plus placebo ($n = 112$), after four weeks no significant differences were found in the number of participants with pain (RR 0.89, 95% CI 0.68 to 1.16, $P = 0.38$), number of participants with decreased pain severity (RR 0.95, 95% CI 0.63 to 1.42, $P = 0.80$) and number of participants with increased pain severity (RR 0.85, 95% CI 0.52 to 1.41, $P = 0.54$) ([Ruts 2007](#)).

Analgesic consumption

In [Pandey 2002](#), significant reductions in fentanyl consumption were reported when comparing the gabapentin phase to the placebo phase ($n = 18$ in both phases) for each day from day 1 to day 7 ($P < 0.001$ for each day). At day 7 (endpoint) the mean difference in fentanyl consumption was -251 μ g (95% CI -265 to -238 μ g).

In [Pandey 2005](#) on day one, mean fentanyl consumption was lower in both the gabapentin and carbamazepine groups compared to placebo but no difference was found between the gabapentin and carbamazepine groups ($n = 12$ in all groups). From day two, there were significant differences in fentanyl consumption amongst the three groups, with the lowest consumption in the gabapentin group and the highest in the placebo group ($n = 12$ in all groups). At the endpoint, a reduction in fentanyl consumption of 225 μ g (95% CI -249 to -200 μ g) was found when comparing gabapentin versus placebo; 176 μ g (95% CI -202 to -150 μ g) when comparing carbamazepine and placebo; and 48 μ g (95% CI -71 to -26 μ g) when comparing gabapentin with carbamazepine ($n = 12$ in all groups).

5. The number of withdrawals due to lack of efficacy

No participants withdrew due to lack of efficacy (or for any other reason) in any of the included studies.

6. The number of participants experiencing any adverse event

Two trials ([Pandey 2002](#); [Pandey 2005](#)) reported adverse events (or lack of). In [Pandey 2002](#), no significant differences were found in the incidence of nausea (RR 0.50, 95% CI 0.05 to 5.04, $P = 0.56$) or constipation (RR 0.14, 95% CI 0.01 to 2.54, $P = 0.19$) between gabapentin and placebo. In [Pandey 2005](#), other than sedation, no adverse events were reported. [Ruts 2007](#) did not describe reporting of adverse events.

In [Pandey 2002](#), there was a significant reduction in mean sedation scores (numerical rating scale of 1 to 6: 0 = anxious, agitated, or restless; 6 = asleep, no response) at the endpoint of the gabapentin phase versus the placebo phase (MD -1.19, 95% CI -1.52 to -0.86), which the authors attributed to reduced requirements for fentanyl in the gabapentin phase. Similarly, in [Pandey 2005](#) a significant difference in median sedation scores was recorded during the study

period in the gabapentin (2.0 on all days 1 to 7), carbamazepine (3.0, 3.0, 3.0, 3.5, 3.0, 3.0, and 3.0; days 1 to 7, respectively) and placebo (4.0, 4.0, 4.0, 4.0, 4.0, 4.0, and 4.0) groups, again attributed to differences in fentanyl consumption. Participants in the gabapentin and carbamazepine groups had significantly lower sedation scores compared with placebo ($P < 0.05$). When comparing active interventions, sedation scores were significantly lower in those receiving gabapentin versus those receiving carbamazepine for each day from days 1 to 7 ($P < 0.05$).

7. The number of participants experiencing any serious adverse event

In [Pandey 2002](#) and [Pandey 2005](#) no participant experienced a serious adverse event. As noted above, [Ruts 2007](#) did not describe reporting of adverse events. There were no deaths reported in any of the studies.

8. The number of withdrawals due to adverse events

There were no withdrawals due to adverse events (or for any other reason) in any of the included studies.

DISCUSSION

Summary of main results

Three RCTs enrolling 277 randomised participants were included. Two studies ([Pandey 2002](#); [Pandey 2005](#)) compared gabapentin with placebo ([Summary of findings for the main comparison](#)). [Pandey 2002](#) was a cross-over trial with a two-day washout, which we deemed to be adequate for gabapentin considering its half-life of five to seven hours. While the study authors primarily reported within-group changes, between-group comparisons demonstrated significant reductions in pain and sedation scores at the study endpoint, as well as in fentanyl consumption throughout the study. [Pandey 2005](#) reported between-group comparisons and demonstrated results similar to [Pandey 2002](#) in pain scores, sedation scores and analgesic consumption. We were not able to statistically combine the data from these studies due to their nature (cross-over versus parallel group) and method of data reporting (means versus medians). [Pandey 2005](#) also compared carbamazepine with placebo ([Summary of findings 2](#)) and demonstrated statistically significant reductions in pain (although only after day 3) and fentanyl consumption. One study that we excluded ([Tripathi 2000](#)) (duration of therapy was only three days) also compared carbamazepine with placebo in a similar population and reported similar reductions in pain and analgesic consumption in the carbamazepine phase. One RCT ([Ruts 2007](#)) compared a five-day course of methylprednisolone with placebo (with both groups also receiving IVIg) ([Summary of findings 3](#)). At the four-week endpoint there were no significant differences in number of participants with pain, number of participants with decreased pain severity, and number of participants with increased pain severity between groups.

One RCT ([Pandey 2005](#)) compared the active interventions gabapentin and carbamazepine ([Summary of findings 4](#)) and found that participants receiving gabapentin had significantly reduced pain scores and fentanyl consumption.

No significant differences were found in adverse event rates in the gabapentin or carbamazepine groups versus placebo groups. Reductions in sedation scores were thought to be secondary to

reductions in opioid consumption, rather than a direct effect of the interventions.

Overall completeness and applicability of evidence

Although significant reductions in pain and sedation scores were observed in those receiving gabapentin and carbamazepine versus placebo, the number of RCTs and participants enrolled were limited. Equally, although the pharmacological interventions studied appeared to be safe, the low number of participants enrolled and the short duration of studies means that safety in larger populations over longer periods of treatment cannot be estimated. Although not explicitly stated, given the participants' symptoms, it appears that no studies reported data from people in the convalescent phase of GBS; therefore no conclusions can be made regarding the efficacy of treatments in this population.

Quality of the evidence

For all the included RCTs, we evaluated the quality of evidence as very low, except for [Ruts 2007](#) where the evidence quality was low. Only one RCT described details of random sequence generation and allocation concealment ([Ruts 2007](#); [van Koningsveld 2004](#)). The numbers of participants enrolled in each trial, with the exception of [Ruts 2007](#), were very small and the duration of the trials was short (five to seven days of treatment). Moreover, we were unable to perform meta-analysis because of the nature of the reported data and the heterogeneity of the study designs. [Pandey 2002](#) reported pain and sedation scores for each treatment on different days. It did not report any measure of uncertainty for the treatment difference, such as standard error or confidence intervals. Given the crossover nature of the design, neither can be easily estimated; therefore there is insufficient information to include data from this study in a meta-analysis. The paper does appear to make comparisons between groups at each follow-up time. However, this is not clearly explained in the paper, and the methods of analysis are not those traditionally employed with crossover trials, casting doubt upon their validity. [Pandey 2005](#) is a parallel group study, potentially providing data appropriate for meta-analysis. However, data are reported as medians and inter-quartile ranges rather than means and standard deviations (SDs), which are required for meta-analysis. Although means and SDs can be derived from these values, the reporting of medians and inter-quartiles suggests that the data are not normally distributed; therefore such derivations may not be appropriate. [Ruts 2007](#) measures pain as a binary outcome (yes/no) rather than on a scale. While the comparisons in this study may be appropriate for inclusion in a meta-analysis, no other study reported similar data. Last, none of the studies described how GBS was diagnosed.

Potential biases in the review process

Although our search strategy was rigorous, it is possible that certain studies were not identified, for example publications that were not in English and not included in any database we searched. Furthermore, the methodology of the included trials was not clearly described in certain categories, which affected our judgement of the quality of the evidence.

Agreements and disagreements with other studies or reviews

A single consensus review assessed supportive treatments for GBS, which included pain management ([Hughes 2005b](#)). In that

review, the authors believed carbamazepine or gabapentin may be beneficial for pain in GBS, but the use of opioid analgesics may also be necessary. Therefore, our conclusions with regard to carbamazepine and gabapentin are consistent with the previous consensus review and we have found no data for this systematic review providing evidence for other interventions.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review we found no new studies. While management of pain in GBS is essential, and pharmacotherapy is widely accepted as being an important component of treatment, this review did not find sufficient high quality evidence investigating the use of any pharmacological intervention in people with pain in GBS. Although reductions in pain severity were found when comparing gabapentin and carbamazepine with placebo, the evidence was limited and its quality was generally very low.

Implications for research

Large, well-designed RCTs are required to further investigate the efficacy and safety of potential interventions, such as gabapentin

and carbamazepine, for patients with pain in GBS. Additionally, interventions for pain in the convalescent phase of GBS should be investigated.

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References to other published versions of this review

Liu 2013

Liu J, Wang LN, McNicol ED. Pharmacological treatment for pain in Guillain-Barré syndrome. *Cochrane Database of Systematic Reviews* 2013, Issue 10. [DOI: [10.1002/14651858.CD009950](https://doi.org/10.1002/14651858.CD009950)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Pandey 2002

Methods	Double-blinded, placebo-controlled, cross-over study
Participants	18 (13 male) participants (mean age 31.05 years), with acute phase GBS admitted to ICU for ventilatory support
Interventions	Gabapentin phase (n = 18): 15 mg/kg/day in 3 divided doses. Powder dissolved in 5 ml of water and administered through feeding tube

Pharmacological treatment for pain in Guillain-Barré syndrome (Review)

Pandey 2002 (Continued)

Placebo phase (n = 18): inert powder on same schedule as gabapentin phase

Each administered for 7 days with 2-day washout between phases

Outcomes	Reductions in the scores of Numeric Pain Rating Scale and Ramsay Sedation Scale, rescue analgesic consumption and adverse events were investigated each day from day 0 to day 7 of treatment
Notes	Fentanyl 2 µg/kg was administered as a rescue analgesic on patient demand or when the pain score was > 5 on a numeric rating scale of 0 to 10 Single centre, ICU in India No funding information or declarations of interest provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or deaths
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	None detected

Pandey 2005

Methods	Double-blinded, placebo-controlled, parallel study
Participants	36 (22 male) participants with acute phase GBS admitted to ICU for ventilatory support. The mean age was 31.0 in the gabapentin group (n = 12), 34.7 in the carbamazepine group (n = 12) and 30.9 in the placebo group (n = 12)
Interventions	Participants were randomly assigned to 3 equal groups (n = 12) to receive gabapentin powder (300 mg 3 times a day), carbamazepine powder (100 mg 3 times a day), or matching placebo powder (3 times a day) - all dissolved in 10 ml of water and administered through feeding tube Each group received therapy for 7 days

Pandey 2005 (Continued)

Outcomes	Reductions in the scores of Numeric Pain Rating Scale and Ramsay Sedation Scale, rescue analgesic consumption and adverse events were investigated each day from day 0 to day 7 of treatment
Notes	Analgesia was provided with intravenous fentanyl 2 µg/kg on patient demand, given over 2 min Single centre, ICU in India No funding information or declarations of interest provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or deaths
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	None detected

Ruts 2007

Methods	Double-blinded, placebo-controlled, parallel study
Participants	223 (129 male) participants with acute phase GBS were randomised. The median age was 51 in the IVIg/methylprednisolone group, and 50 in the IVIg/placebo group
Interventions	IVIg/methylprednisolone (500 mg for 5 days, n = 111) versus IVIg/placebo (n = 112)
Outcomes	Pain severity at baseline: none, mild (pain but no real complaints), moderate (complaints but no analgesics necessary) or severe (analgesics necessary) Number of participants with pain, number of participants with decreased pain severity, and number of participants with increased pain severity after 4 weeks
Notes	The study also included a 52-week retrospective study in a subset of participants (results not included in this review) Multicentre study (setting unclear) in the Netherlands

Ruts 2007 (Continued)

No funding information or declarations of interest provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with random block sizes of 4, 6, or 8 generated by computer
Allocation concealment (selection bias)	Low risk	When a neurologist identified a participant, they phoned a 24-h hotline and were given a number according to the randomisation list
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In most cases, neurologists who knew the medication allocation were not involved in assessment of treatment effect
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or deaths
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	None detected

GBS: Guillain-Barré syndrome

ICU: intensive care unit

IVIg: intravenous immunoglobulin

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brisby 2002	Not an RCT
Forsberg 2004	Not an RCT
Korinthenberg 2005	No pain outcomes
Morgenlander 1990	Not an RCT
Odaka 2005	Not an RCT
Sendhilkumar 2013	Not pharmacological intervention
Tripathi 2000	Duration of treatment was less than one week (only 3 days for each phase)

APPENDICES

Appendix 1. Cochrane Neuromuscular Disease Group Specialized Register (CRS) search strategy

#1 MeSH DESCRIPTOR Guillain-Barre Syndrome [REFERENCE] [STANDARD]
 #2 "Guillain Barre" [REFERENCE] [STANDARD]
 #3 "acute polyradiculoneuritis" or "acute polyneuritis" [REFERENCE] [STANDARD]
 #4 MeSH DESCRIPTOR Polyneuropathies [REFERENCE] [STANDARD]
 #5 MeSH DESCRIPTOR Polyradiculoneuropathy [REFERENCE] [STANDARD]
 #6 inflammatory NEAR neuropathy or inflammatory NEAR neuropathies [REFERENCE] [STANDARD]
 #7 #1 or #2 or #3 or #4 or #5 or #6 [REFERENCE] [STANDARD]
 #8 "ascending paralysis" [REFERENCE] [STANDARD]
 #9 landry* near2 guillain [REFERENCE] [STANDARD]
 #10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 [REFERENCE] [STANDARD]
 #11 MeSH DESCRIPTOR Pain Explode All [REFERENCE] [STANDARD]
 #12 "neuropathic pain" or "musculoskeletal pain" or "radicular pain" or "acute pain" or "chronic pain" or neuralgia [REFERENCE] [STANDARD]
 #13 #11 or #12 [REFERENCE] [STANDARD]
 #14 #10 and #13 [REFERENCE] [STANDARD]
 #15 (#10 and #13) AND (INREGISTER) [REFERENCE] [STANDARD]

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor Guillain-Barre Syndrome explode all trees
 #2 "guillain barre"
 #3 MeSH descriptor Polyradiculoneuropathy explode all trees
 #4 "acute polyradiculoneuritis" or "acute polyneuritis"
 #5 landry* NEXT "ascending paralysis"
 #6 (#1 OR #2 OR #3 OR #4 OR #5)
 #7 MeSH descriptor Pain explode all trees
 #8 "neuropathic pain" or "musculoskeletal pain" or "radicular pain" or "acute pain" or "chronic pain" or neuralgia
 #9 (#7 OR #8)
 #10 (#6 AND #9)

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to October Week 4 2014>
 Search Strategy:

1 randomized controlled trial.pt. (397786)
 2 controlled clinical trial.pt. (90503)
 3 randomized.ab. (293092)
 4 placebo.ab. (154196)
 5 drug therapy.fs. (1777958)
 6 randomly.ab. (205733)
 7 trial.ab. (305213)
 8 groups.ab. (1307610)
 9 or/1-8 (3350308)
 10 exp animals/ not humans.sh. (4082107)
 11 9 not 10 (2854354)
 12 guillain barre.tw. or exp Guillain-Barre Syndrome/ (7229)
 13 (acute polyradiculoneuritis or acute polyneuritis).tw. (174)
 14 Polyneuropathies/ or Polyradiculoneuropathy/ (7928)
 15 landry* ascending paralysis.mp. (9)
 16 (landry adj1 guillain).mp. (181)
 17 or/12-16 (12850)
 18 exp pain/ (319553)
 19 neuropathic pain.tw. (10709)
 20 musculoskeletal pain.tw. (2977)
 21 radicular pain.tw. (1504)
 22 acute pain.tw. (4663)
 23 chronic pain.tw. (20009)
 24 neuralgia.mp. (17855)

25 or/18-24 (335590)
26 11 and 17 and 25 (189)
27 remove duplicates from 26 (177)

Appendix 4. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2014 Week 44>

Search Strategy:

1 crossover-procedure.sh. (40446)
2 double-blind procedure.sh. (115879)
3 single-blind procedure.sh. (18953)
4 randomized controlled trial.sh. (352001)
5 (random\$ or crossover\$ or cross over\$ or placebo\$ or (doubl\$ adj blind\$) or allocat\$).tw,ot. (1069468)
6 trial.ti. (163914)
7 clinical trial/ (834742)
8 or/1-7 (1660365)
9 (animal/ or nonhuman/ or animal experiment/) and human/ (1296091)
10 animal/ or nonanimal/ or animal experiment/ (3265163)
11 10 not 9 (2734068)
12 8 not 11 (1559236)
13 limit 12 to embase (1288131)
14 Guillain Barre syndrome/ (10068)
15 guillain barre.mp. (12303)
16 polyradiculoneuropathy/ (2238)
17 polyneuropathy/ (11851)
18 (acute polyradiculoneuritis or acute polyneuritis).mp. (185)
19 landry* ascending paralysis.mp. (9)
20 (landry adj1 guillain).mp. (157)
21 or/14-20 (24351)
22 pain/dt (32524)
23 neuropathic pain.mp. (24621)
24 musculoskeletal pain.mp. (7598)
25 radicular pain.mp. (3342)
26 acute pain.mp. (7290)
27 chronic pain.mp. (46558)
28 neuralgia/ or neuralgia.tw. (15042)
29 or/22-28 (118316)
30 13 and 21 and 29 (212)
31 remove duplicates from 30 (210)

Appendix 5. ICTRP search strategy

Guillain-Barre Syndrome or acute polyradiculoneuritis or acute polyneuritis

WHAT'S NEW

Date	Event	Description
4 February 2019	Amended	See Published notes .

HISTORY

Protocol first published: Issue 7, 2012

Review first published: Issue 10, 2013

Date	Event	Description
14 January 2015	New citation required but conclusions have not changed	No new eligible RCTs for inclusion
3 November 2014	New search has been performed	New search

CONTRIBUTIONS OF AUTHORS

JL and LNW identified and assessed studies, and extracted and analysed data.

JL wrote up the manuscript, which was reviewed by LNW and EM.

EM commented on and revised the review and re-analysed the data.

DECLARATIONS OF INTEREST

EM has consulted for Javelin Pharmaceuticals, Wyeth and Ortho-McNeil-Janssen Pharmaceuticals.

JL and LNW: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- EM is supported by the Richard Saltonstall Charitable Foundation, USA.

Financial

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

[Ruts 2007](#) was included despite not meeting all inclusion criteria (see [Included studies](#)).

For completeness, and where other data were not available, we reported the results from pain outcomes such as analgesic consumption that were not specified as secondary outcomes in our protocol.

We searched an additional trials registry that was not specified in our protocol, WHO ICTRP.

Both phases of the eligible cross-over trial, [Pandey 2002](#), were included. We intended to perform sensitivity analysis with exclusion of cross-over trials from the analysis, but there were insufficient data.

JL and LNW selected studies and EM arbitrated if there was disagreement. In the protocol we stated that JL and EM would select studies and LNW arbitrate.

We included 'Summary of findings' tables for each comparison.

NOTES

A full search on 1 February 2019 did not identify any potentially relevant studies and we did not update the text of the review. The review will be re-assessed for updating in two years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published.

INDEX TERMS

Medical Subject Headings (MeSH)

Amines [adverse effects] [therapeutic use]; Analgesics [adverse effects] [*therapeutic use]; Carbamazepine [adverse effects] [therapeutic use]; Constipation [chemically induced]; Cyclohexanecarboxylic Acids [adverse effects] [therapeutic use]; Gabapentin; Guillain-Barre Syndrome [*complications]; Immunoglobulins, Intravenous [therapeutic use]; Methylprednisolone [therapeutic use];

Nausea [chemically induced]; Pain [complications] [*drug therapy]; Pain Measurement; Randomized Controlled Trials as Topic; gamma-Aminobutyric Acid [adverse effects] [therapeutic use]

MeSH check words

Humans