Antiepileptic drugs to treat pain in rheumatic conditions. Recommendations based on evidence-based review of the literature and expert opinion

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Accepted 23 April 2008

Abstract

Objectives: Neuropathic pain is commonly encountered in rheumatology practice, often associated with nociceptive mechanisms. It is caused by nervous system lesions, and the usual treatments with analgesics and anti-inflammatory drugs are mostly ineffective. Antiepileptic drugs (AED) have proved effective in relieving neuropathic pain. AED are recently used by rheumatologists since the role of neuropathic pain in rheumatological conditions has only recently been documented. Nevertheless, the tendency seems to be reversed when these drugs are used inappropriately. The CEDR (Cercle d’Etude de la Douleur en Rhumatologie), a specific interest group of the French Society of Rheumatology that focuses on pain in rheumatology, undertook to develop recommendations for the use of AED in Rheumatology.

Methods: A list of questions concerning the prescription of AED in painful rheumatic conditions was validated by a working group of 7 experts from the CEDR. The list of questions was used to draw up the recommendations. A literature review was performed using electronic databases (Medline, Embase and Cochrane library between 1980 and 2007) without limitations on the type of publication: case reports, clinical trials, literature review and guidelines about therapeutic management of neuropathic pain. Selected studies were scored for quality. Based on the literature and clinical experience, recommendations were developed using the Delphi method.

Results: We identified 29 studies concerning the use of AED in painful rheumatic conditions and 16 studies were considered valid and scored for quality. These few studies, the guidelines published for neuropathic pain treatment and the clinical experience of each expert, were used to develop 11 recommendations for the use of AED in painful rheumatic conditions.

Conclusion: These recommendations can be used as guidelines to help prescribers to use AED for the management of pain in rheumatic conditions until further scientific evidence becomes available.

Keywords: Antiepileptic drugs; Pain; Rheumatic diseases; Recommendations; Review

1. Introduction

The management of purely neuropathic pain or neuropathic pain associated with nociceptive mechanisms is a common issue in rheumatology. This is the case in polyneuropathy, mononeuropathy, autoimmune inflammatory diseases, tunnel syndromes, radiculopathies and failed back surgery syndrome, complex regional pain syndromes, or even fibromyalgia [1]. The
management of pain in such diseases or syndromes is not always successful, particularly with analgesics and anti-inflammatory drugs. Antiepileptic drugs (AED) have proved to be effective in the treatment of diabetic neuropathy, post-herpetic pain, phantom limb pain, etc. Finnerup et al. proposed an evidence-based algorithm for neuropathic pain treatment [2]. They recommend initiating oral therapy with AED or a tricyclic antidepressant (TCA) or a mixed serotonin-norepinephrine re-uptake inhibitor (SNRI). TCA appear to be more effective and much less expensive than AED, but have a higher risk of adverse effects. Newer SNRI may not be as effective as TCA, but appear to be better tolerated.

AED have been recently used in rheumatological practice. Published therapeutic trials on AED in painful rheumatic conditions are generally not controlled, with small sample sizes, and many different types of neuropathic conditions are often found in a same trial. Randomized, placebo-controlled studies are rare. Many questions remain unanswered, for example: what are the indications for an AED? Which AED should be prescribed?

Although the literature is scarce, guidelines concerning the use of these drugs in painful rheumatic conditions are, therefore, required because AED are frequently used inappropriately. The CEDR (Cercle d’Etude de la Douleur en Rhumatologie) undertook to develop recommendations based on evidence and expert opinion. A list of questions concerning the prescription of AED in rheumatology was developed by a group of experts from the CEDR. These questions were used to guide the literature review and to draw up the recommendations using the Delphi method. Since little information is available, these recommendations aim to help prescribers to use AED appropriately for pain management in rheumatic conditions. They are a starting point for discussion and promotion of further clinical studies.

2. Method

2.1. List of questions

A list of clinical questions (n = 16) was established by the experts to structure the recommendations in the same way as a similar expert group from the CEDR for the published guidelines concerning antidepressants in painful rheumatic conditions [3]. This list of questions was evaluated for its comprehension and relevance and finally, 11 questions were retained:

1. What are the indications for an AED?
2. What is the position of AED in the pharmacological management of these painful rheumatic conditions?
3. Which AED should be prescribed?
4. What initial dosage and titration must be used?
5. What patient information should be taken into account?
6. What prophylactic measures against side effects can be planned?
7. What are the principal safety recommendations?
8. Is combination therapy useful?
9. How should the treatment efficacy be assessed?
10. In cases of insufficient efficacy with an AED, could the prescriber change for another AED?
11. How and when should AED be withdrawn?

2.2. Review of the literature and scoring

The literature was reviewed by a working group of 7 experts from the CEDR (Cercle d’Etude de la Douleur en Rhumatologie), a specific interest group of the French Society of Rheumatology that focuses on painful rheumatic diseases. The search was conducted using electronic databases (Medline, Embase and Cochrane library), with no limitations on the type of publication. The review was restricted to articles in English and French published between 1980 and July 2007.

For questions 1, 2 and 3, the search terms used were: painful rheumatic conditions, rheumatic diseases, rheumatoid arthritis, spondylarthropathy, osteoarthritis, low back pain, sciatica, radiculopathy, failed back surgery syndrome, fibromyalgia, complex regional pain syndrome, reflex sympathetic dystrophy, antiepileptic drugs, anticonvulsants. All published papers were analyzed by all members of the group. Studies were scored using the EULAR guidelines [4], from 0 to 28, based on Down’s checklist [5]. This checklist consists of 27 items distributed between 5 sub-scales and was developed on the basis of epidemiological principles, reviews of study designs, and existing checklists for the assessment of randomized, controlled trials. This methodological checklist provides a quality assessment of the reporting, external and internal validity and statistical power of each study. All studies are scored 0–1 for 26 questions and 0–2 for 1 question, giving a maximum score of 28. Power calculations are scored as 1 if present and 0 if absent.

For questions 4–11, the search was wider including randomized controlled and double-blind therapeutic trials with AED in neuropathic pain, systematic literature review on this subject and existing guidelines.

2.3. Delphi method and development of recommendations

Based on clinical experience and on the evidence from the literature review wherever possible, each question was completed by all members of the expert panel. The recommendations were obtained by a Delphi approach to reach consensus. The Delphi method is an exercise in group communication among a panel of geographically dispersed experts. It enables experts to deal systematically with a complex problem or task. The essence of the technique is fairly straightforward. It comprises a series of questionnaires sent by e-mail to a pre-selected group of experts. These questionnaires are designed to elicit and to develop individual responses to the problems posed and to enable the experts to refine their views as the group’s work progresses in accordance with the assigned task. The Delphi method makes it possible to overcome the
disadvantages of conventional committee action. The group interaction in Delphi is anonymous, in that the originator of comments, forecasts, and the likes are not identified. These elements are presented to the group in such a way as to suppress any identification.

Several responses (≤5) were authorized for each question. The different responses to the 11 selected questions were collected (75 responses corresponding to the 11 questions). Substantially overlapping propositions were combined. The edited list was then returned to the experts, who were then asked to score the proposals. Propositions were accepted if over half of the participants accepted them in any round, whereas propositions receiving only 1 vote was removed. Propositions receiving less than 50% of the votes but more than one vote entered the next Delphi round. After 3 Delphi rounds, a final draft of the recommendations was generated, taking into account the comments and criticisms of the 7 panel members (finally 21 responses selected).

The recommendations were then tested according to the Appraisal of Guidelines Research & Evaluation method [6] by 2 independent reviewers and the level of evidence supporting each recommendation was indicated, from A to D [7].

The strength of recommendations (SOR) was graded using the EULAR visual analog scale (VAS) [8,9]. Participants were asked to score their SOR for each proposition using both 0–100 mm VAS (0 mm = not recommended at all, 100 mm = fully recommended). Participants were asked to determine their scores by taking into account both the research evidence and their clinical expertise. The mean VAS and 95% CI were calculated.

3. Results

3.1. Antiepileptic drugs for treatment of painful rheumatic conditions

AED can relieve neuropathic pain, and several medical teams recommend their use in the treatment of certain types of painful rheumatic conditions [10–12]. From the literature review we identified 29 relevant studies, and 16 of these were selected for detailed analysis and attribution of a quality score.

The selection criteria were: (1) randomized and controlled trial, (2) prospective open and observational studies, (3) minimum sample of 10 patients, and (4) pain relief considered as a primary outcome and measured with validated scales. The efficacy of oxcarbazepine (OXC) (150–900 mg/day) was assessed in an open study with a subgroup analysis of 18 patients with radiculopathy refractory to GBP. At final outcome, the treatment duration varied from 1 to 10 months. Among the 11 patients with lower limb radiculopathy, OXC had a positive effect on pain intensity (visual analog score of pain and SF-McGill Pain Questionnaire) in 9 patients [17].
### Table 1
Published open or observational studies on the use of antiepileptic drugs in the treatment of painful rheumatic conditions

<table>
<thead>
<tr>
<th>Author (year) [reference]</th>
<th>Study type</th>
<th>Product/ compared with</th>
<th>Indication</th>
<th>Duration of treatment</th>
<th>Number of patients</th>
<th>Outcome evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naidu et al. (1991) [27] (16/28)</td>
<td>Prospective</td>
<td>Phenytoin</td>
<td>Rheumatoid arthritis</td>
<td>24 weeks</td>
<td>35</td>
<td>Pain index</td>
<td>Reduced morning stiffness at W8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Articular index</td>
<td>Improved pain, articular index, and strength at W24</td>
</tr>
<tr>
<td>Rovetta et al. (1999) [22] (11/28)</td>
<td>Prospective</td>
<td>Gabapentin 100 mg/day vs paracetamol 3 g/day</td>
<td>Shoulder–hand syndrome</td>
<td>3 months</td>
<td>14 (aged 54–65 years)</td>
<td>VAS for pain</td>
<td>VAS reduction from 75 to 38 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Degree of mobility</td>
<td>Increased mobility</td>
</tr>
<tr>
<td>Devulder and De Laat (2000) [16] (6/28)</td>
<td>Prospective</td>
<td>Lamotrigine from 125 to 700 mg/day</td>
<td>Refractory chronic neuropathic pain</td>
<td>NP</td>
<td>20 including 7 with postoperative lumbar sciatica</td>
<td>Numeric pain scale</td>
<td>Among the patients with postoperative lumbar sciatica: 2 failures, 2 patients with temporary improvement and 2 with prolonged improvement</td>
</tr>
<tr>
<td>Ward et al. (2002) [17] (9/28)</td>
<td>Open</td>
<td>Oxcarbazepine from 150 to 900 mg/day</td>
<td>Neuropathic pain refractory to gabapentin</td>
<td>1–10 months</td>
<td>18 including 12 with radiculopathy</td>
<td>VAS for pain</td>
<td>VAS reduction from 77 to 34 mm, and SF MGPQ score reduction from 24.5 to 8.7</td>
</tr>
<tr>
<td>Royal et al. (2002) [23] (8/28)</td>
<td>Open</td>
<td>Oxcarbazepine from 150 to 1200 mg/day</td>
<td>Complex regional pain syndrome refractory to gabapentin</td>
<td>1–10 months</td>
<td>18</td>
<td>VAS for pain</td>
<td>VAS reduction from 74 to 33 mm, and SF MGPQ score reduction from 28.1 to 9.3</td>
</tr>
<tr>
<td>Eisenberg et al. (2003) [15] (12/28)</td>
<td>Open</td>
<td>Lamotrigine from 25 to 400 mg/day, dose maintained for 4 weeks</td>
<td>Refractory sciatica</td>
<td>10 weeks</td>
<td>14</td>
<td>VAS and numeric scale for pain</td>
<td>Improvement at 400 mg/day: VAS reduction from 80 to 40 mm. Dose-dependent effect ++</td>
</tr>
</tbody>
</table>

VAS: visual analog scale; and SF MGPQ: short-form McGill Pain Questionnaire.
The score of quality is based on a checklist from 0 to 28 [5].
<table>
<thead>
<tr>
<th>Author (year) [reference]</th>
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<th>Product/compared with</th>
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<th>Number of patients</th>
<th>Outcome evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richards et al. (1987) [26] (15/28)</td>
<td>RCT, SB</td>
<td>Phenytoin 100 mg/day vs IM gold salts 50 mg/week</td>
<td>Rheumatoid arthritis</td>
<td>24 weeks</td>
<td>60</td>
<td>Pain Morning stiffness</td>
<td>40% pain improvement in gold salts group vs 12% in phenytoin group</td>
</tr>
<tr>
<td>Rao et al. (1995) [28] (19/28)</td>
<td>RCT, DB</td>
<td>Phenytoin 200 mg vs auranofin 6 mg vs chloroquine 150 mg/day</td>
<td>Rheumatoid arthritis</td>
<td>6 months</td>
<td>100</td>
<td>VAS for pain Index of synovitis Morning stiffness ESR and CRP</td>
<td>Chloroquine &gt; 2 other groups VAS reduction from 40.6 to 18.2 mm in phenytoin group</td>
</tr>
<tr>
<td>Serpell (2002) [13] (23/28)</td>
<td>RCT, DB</td>
<td>Gabapentin from 900 to 2400 mg/day vs placebo</td>
<td>Neuropathic pain</td>
<td>8 weeks</td>
<td>305 including 28% of CRPS, 9% of radiculopathies</td>
<td>Daily pain (11-point Likert scale)</td>
<td>21% of responders (pain score reduction &gt; 50%) to gabapentin vs 14% in placebo group</td>
</tr>
<tr>
<td>Van de Vusse et al. (2004) [21] (20/28)</td>
<td>RCT, DB, CO</td>
<td>Gabapentin up to 1800 mg/day vs placebo</td>
<td>CRPS</td>
<td>2 × 3 weeks separated by a 2-week break</td>
<td>58</td>
<td>VAS for pain Patient’s opinion</td>
<td>No significant improvement in VAS Patient’s opinion: 43% improvement with gabapentin vs 17% with placebo</td>
</tr>
<tr>
<td>Todorov et al. (2005) [19] (13/28)</td>
<td>Open comparative randomized</td>
<td>Gabapentin up to 2400 mg/day vs tiagabine up to 24 mg/day</td>
<td>Chronic pain</td>
<td>3 months</td>
<td>91 including 23 cases of neck pain, 8 cases of low back pain, 6 cases of fibromyalgia</td>
<td>Pain scale (11-point Likert scale) Sleep quality (11-point scale)</td>
<td>2.3-point reduction on pain scale with tiagabine, and 1.3 with gabapentin Improved sleep quality with tiagabine</td>
</tr>
<tr>
<td>Radahakrishnan et al. (2005) [20] (22/28)</td>
<td>RCT, DB</td>
<td>Gabapentin 800 mg vs placebo given preoperatively, then morphine in postoperative period</td>
<td>Pain following lumbar surgery (laminectomy, discectomy) for the first 8 h</td>
<td>24 h</td>
<td>60</td>
<td>Verbal pain scale (while resting and active) Postoperative morphine consumption</td>
<td>No differences between groups as regards to pain and morphine consumption</td>
</tr>
<tr>
<td>Khoromi et al. (2005) [14] (22/28)</td>
<td>RCT, DB, CO</td>
<td>Topiramate from 50 to 400 mg/day vs “active” placebo: diphenhydramine 6.25–50 mg/day</td>
<td>Chronic lumbar radicular pain</td>
<td>14 weeks (2 × 6 weeks separated by a 2-week break)</td>
<td>42</td>
<td>Numeric pain scale Patient’s opinion Oswestry LBPDQ SF36 BDI</td>
<td>No significant improvement in leg pain Significant overall pain improvement with topiramate No differences between groups as regards Oswestry LBPDQ, SF36, and BDI</td>
</tr>
<tr>
<td>Crofford et al. (2005) [24] (22/28)</td>
<td>RCT, DB</td>
<td>Pregabalin 150 mg/day vs 300 mg/day vs 450 mg/day vs placebo</td>
<td>Fibromyalgia</td>
<td>8 weeks</td>
<td>529</td>
<td>Numeric pain scale Fatigue Sleep quality SF36</td>
<td>Pregabalin 450 &gt; placebo 29% of responders (pain score reduction &gt; 50%) to pregabalin vs 13% in placebo group Improved fatigue, sleep quality, and several parts of SF36</td>
</tr>
</tbody>
</table>

(continued on next page)
and weight loss and change on all the SF36 scales. The NNT for pain rating index was 3.1.

In a 3-month open, randomized and comparative study with 91 patients, among whom only 8 suffered from chronic low back pain tiagabine (TG) (at a mean dosage of 15 mg/day) was as effective as GBP (at a mean dosage of 915 mg/day) [19].

In a randomized, double-blind, placebo-controlled study in 60 patients, GBP (administered at a dosage of 400 mg on the day before surgery and 2 h before surgery) failed to relieve the postoperative, acute low back pain immediately following laminectomy [20]. But the outcome measures were a verbal rating scale of pain every 2 h and the total morphine consumption for 8 h post-surgery.

### 3.1.3. Complex regional pain syndromes (CRPS)

GBP is the most reported AED in the treatment of CRPS— even though the pathophysiology of this syndrome remains unclear. In a randomized, double-blind, crossover, placebo-controlled study in 58 patients, GBP (administered at an initial dosage of 600 mg/day and increased up to 1800 mg/day) failed to relieve the pain associated with CRPS, except for patients in the particular subgroup that started out by receiving GBP [21]. The treatment decreased the sensory deficit but had no positive effect on allodynia, edema size, or joint mobility. However, in a randomized, placebo-controlled study in 305 patients suffering from neuropathic pain, including 85 cases of CRPS, GBP therapy had a positive effect on pain intensity and quality of life at a dose ranging from 900 to 2400 mg/day [13]. In a comparative study in 14 patients with suspected phenobarbital-induced shoulder-hand syndrome, GBP (100 mg/day) was as effective as acetaminophen (3 g/day) in relieving pain and improving joint mobility at 3 months — rehabilitation being maintained in both groups [22]. However, in this study, the very small daily dose of GBP is surprising. In an open study in 18 patients suffering from CRPS (with 5 withdrawals: 4 because of side effects and 1 because of ineffective treatment), the efficacy of OXC was assessed at a dose of 300—1200 mg/day after GBP therapy had failed to show efficacy. OXC had a positive effect on pain intensity and mobility [23].

### 3.1.4. Fibromyalgia

In a randomized double-blind placebo-controlled study in 529 patients with fibromyalgia — pregabalin (PGL) had a significant positive effect on pain intensity at a dose of 450 mg/day, and on sleep, fatigue and quality of life at small a dose as 300 mg/day [24]. The NNT for responders having ≥50% pain improvement from baseline and ≥30% are 6.3 and 4.6, respectively, in the 450 mg group. There was, however, a 22.5% withdrawal rate for this study, due to side effects or ineffective treatment. More recently, a 12-week randomized double-blind study compared GBP (1200—2400 mg/day) with placebo in 150 patients with fibromyalgia [25]. GBP-treated patients had a significantly greater improvement in the Brief Pain Inventory (BPI) average pain severity score. Among GBP-treated patients, 51% achieved response to treatment defined as a reduction of ≥30% in the BPI pain score compared to 31% in the placebo group. Several
secondary outcome criteria (e.g., fibromyalgia impact questionnaire, sleep quality, patient global impression of improvement, quality of life) improved significantly in the GBP group contrary to the mean tender point threshold and depressive symptoms. GBP was generally well tolerated with no difference between treatment groups for discontinuation due to adverse events.

3.1.5. Rheumatoid arthritis

In a randomized study in 60 patients with rheumatoid arthritis, phenytoin was compared with allochryne administered on a weekly basis over a period of 24 weeks. After 4 weeks of treatment, allochryne was significantly superior to phenytoin with respect to both morning stiffness and pain scores [26]. These negative results were not confirmed by the 2 successive studies conducted by Rao et al. The first one was an open study in 35 patients with active rheumatoid arthritis [27]. After 8 weeks treatment, morning stiffness was significantly reduced. After 24 weeks treatment, pain index, articular index, and grip strength were significantly improved. Having obtained such results, Rao et al. (1995) then conducted a randomized, double-blind study in 132 patients with rheumatoid arthritis, in which they compared phenytoin (200 mg/day) with 2 disease-modifying treatments (auranofin at a dosage of 6 mg/day, and chloroquine at 150 mg/day) over a period of 6 months [28]. In each of the 3 groups, pain, inflammatory syndrome, and morning stiffness were reduced, while grip strength was increased. Rather than suggesting — like Rao et al. — the use of phenytoin as a disease-modifying treatment for rheumatoid arthritis (considering the greater efficacy of the latest treatments available), we may still take into consideration the analgesic properties of phenytoin.

3.1.6. Neck pain

In an open, randomized study in 91 patients, among whom 23 suffered from neck pain, TG (at a mean dosage of 15 mg/day) and GBP (at a mean dosage of 915 mg/day) had a positive effect on pain intensity and sleep. However, the analysis of the study results was general and the study included many different subgroups such as cervical pain, lumbar pain, neuropathic pain, multiple pain syndrome and musculoskeletal headache [19].

3.2. Global review of analgesic effects of antiepileptic drugs and guidelines in neuropathic pain

The use of antiepileptic drugs in the treatment of neuropathic pain has been evaluated in various randomized, controlled clinical trials (RCT) with evidence of efficacy. Recent systematic reviews of these trials have summarized the results [2,29,30]. Finnerup et al. (2005) [2] have published a review of RCT in different neuropathic pain syndromes. The NNT and the NNH were used to compare the efficacy and safety of the various treatments. Using this approach, the authors proposed an evidence-based treatment algorithm in peripheral neuropathic pain. TCA have lower NNT values than GBP/PGL, but this difference may be due to differences in study design. As GBP/PGL have higher NNH values and lack serious adverse effects, the proposed algorithm classified these 2 drug families at the same level as first-line treatment of peripheral neuropathic pain. Moreover, the European Federation of Neurological Societies (EFNS) guidelines on pharmacological treatment of neuropathic pain recommended TCA or GBP/PGL as a first choice in painful polyneuropathies [29]. The neuropathic pain special interest group of the International Association for the Study of Pain (IASP) recently published evidence-based guidelines for the pharmacological management of neuropathic pain that take into account clinical efficacy, adverse effects, impact on health-related quality of life, convenience and costs [31]. Recommended first-line treatments include certain antidepressants, calcium channel \( \alpha 2-\delta \) ligands (i.e., gabapentin and pregabalin) and topical lidocaine.

The usefulness of a combination therapy has been assessed in 2 RCT: the combination GBP—venlafaxine yielded better results in pain, mood and quality of life than placebo—venlafaxine in diabetic neuropathic pain [32] and the combination GBP—morphine yielded better results than GBP alone, morphine alone, or placebo in diabetic neuropathic pain and post-herpetic neuralgia [33]. The EFNS guidelines proposed a combination therapy with drugs targeting separate mechanisms in cases of insufficient efficacy with monotherapy [29].

3.3. Dosage and titration

The therapeutic management of patients treated with AED must be customized. Treatment must be initiated at low doses with a gradual increase in order to achieve a therapeutic effect with acceptable adverse effects. Titration must thus be performed to obtain the best possible efficacy/safety ratio [34]. Only with PGL is it possible to prescribe an initial dose similar to the maintenance dose — with the possibility of increasing the dose in the case of insufficient efficacy.

Table 3 gives an overview of AED most used for treating neuropathic pain, their respective initial dose, dosage regimen, and effective and maximum doses.

3.4. Side effects and safety recommendations

On the whole, first-generation AED are associated with more side effects than second-generation ones [34—36]. The side effects considered as very frequent (>10%) mainly involve the central nervous system. These side effects are drowsiness, dizziness and ataxia. They are associated with almost all AED. Other very frequent side effects include headache, asthenia, diplopia, and peripheral edema. Hypotension is mainly associated with oxcarbazepine (OXC).

Some side effects considered as frequent (1—10%) are associated with OXC, TPM, and PGL: they include neuro-psychic disturbances, such as memory disorders, concentration problems, confusion, depression, and nervousness. PGL and TPM can cause paresthesia. Digestive side effects are also frequent: nausea, vomiting, diarrhea, and constipation — mainly with OXC and PGL. Valproic acid (VA), GBP, and PGL can cause weight gain, whereas TPM can cause weight loss. Hematological disorders are frequently associated with...
VA (coagulation disorders, anemia, and thrombocytopenia), carbamazepine (CBZ) (leukopenia, thrombocytopenia), and LTG (leukopenia), and very rarely associated with OXC and PGL. Cutaneous lesions such as rash or urticaria are frequently associated with most AED. Although very rare, some severe cutaneous lesions (Stevens–Johnson syndrome, Lyell syndrome) can be associated with LTG, VA, CBZ, and OXC.

Liver enzymes, blood cells and platelets must be monitored with CBZ and sodium levels with CBZ and OXC. There are many drug interactions involving CBZ, which is an enzyme inducer (metabolized by the liver, via the cytochrome P450 enzymatic system).

In patients with renal failure, practitioners need to adapt the dosage of GBP, PGL, OXC, and TPM. There are no available data on the bioavailability of LTG in patients with renal failure.

In patients with hepatic insufficiency, practitioners should pay special attention to the liver profile when using TPM, LTG, VA, or TG.

### 3.5. General guidelines for the use of antiepileptic drugs in painful rheumatic conditions

Based on the few studies, the clinical experience of the expert panel, and previously published guidelines on the treatment of neuropathic pain [2,29–31] we propose the following guidelines concerning the use of AED in painful rheumatic conditions. The level of evidence supporting each recommendation is indicated from A to D [7]. The strength of recommendation (SOR) is given as the mean VAS (95% CI).

1. AED can be proposed for chronic painful rheumatic conditions with a neuropathic element best identified by an interview (burning, painful cold, electric shocks, tingling, numbness), a clinical examination (hypesthesia, allodynia, hyperpathia) and the DN4 questionnaire. AED can be used for chronic lumbar and sciatic pain, complex regional pain syndromes and fibromyalgia.

   **Level of evidence:** B; **SOR:** 80.1 (66–90).

2. AED can be prescribed after failure of analgesics, including tramadol, either immediately before antidepressants or after failure of antidepressants.

   **Level of evidence:** D; **SOR:** 80.4 (60–93).

3. Second-generation AED (especially, gabapentin and pregabalin) are recommended since they induce fewer side effects and there is more information on these compounds in the literature.

   **Level of evidence:** A; **SOR:** 84.3 (70–99).

4. Treatment with an AED must be started at low doses and titration performed to obtain the best efficacy/safety ratio.
Level of evidence: A; SOR: 94 (82–100).

(5) To improve compliance, the patient should be informed of the following when first prescribed an AED for analgesic purposes:
- the analgesic efficacy of AED, besides their use in epilepsy,
- their mechanism of action,
- the titration procedure aiming to find the best efficacy/safety ratio, and also a longer delay of action,
- the unwanted side effects,
- treatment objectives.

Level of evidence: D; SOR: 87.6 (70–100).

(6) The unwanted side effects of AED used as analgesics are similar to AED used for epilepsy. No prophylaxis is planned, but gradual dose increase improves safety and reduces unwanted central neurological effects, particularly in elderly patients, patients with renal or hepatic failure, or in combination with other drugs affecting the central nervous system.

Level of evidence: A; SOR: 88.9 (79–98).

(7) The principal precautions for use are as follows:
- the prescription of AED for analgesic purposes is contra-indicated in the event of pregnancy,
- if cutaneous anomalies appear, treatment with AED must be withdrawn,
- side effects are particularly frequent in elderly subjects since the pharmacokinetics are modified and they often receive several treatments. The combination of AED with other sedative drugs decreases vigilance, increases behavior and balance disorders, thus increasing the risk of falls,
- AED should be used with precaution in the event of renal or hepatic failure.

Level of evidence: A; SOR: 86.1 (72–97).

(8) Drug combinations:
- AED can be combined with any analgesic,
- combination with antidepressants is poorly evaluated; precautions must be taken and close monitoring implemented because there is a risk of potentiation of side effects. Combination should only be considered if the treatments are not effective when taken as monotherapy,
- given the lack of information in the literature, the combination of 2 AED should be avoided for pain therapy.

Level of evidence: D; SOR: 80.3 (60–98).

(9) Treatment efficacy is to be assessed with patients, including pain evaluation, quality of life and sleep, and consumption of combined analgesics. The therapeutic effect may not be felt for a while, so AED, at the maximum stable dose tolerated, should be taken for at least 4 weeks before discontinuing due to treatment failure.

Level of evidence: D; SOR: 83.3 (70–94).

(10) If an AED is withdrawn because of unwanted effects, it is probably of interest to try another AED since it may be better tolerated.

Lack of efficacy of a given AED does not indicate that of other AED. Some studies demonstrated the efficacy of a compound in cases refractory to another AED. It is possible to rotate different AED.

Level of evidence: C; SOR: 74.3 (50–95).

(11) AED treatment should be discontinued in the event of failure, intolerance or remission. Except in the event of intolerance where withdrawal is usually sudden, AED should be withdrawn gradually over a few days to avoid withdrawal symptoms.

There is no optimal treatment duration, it depends on the initial objectives discussed with the patient and the benefit/risk ratio. After 3–6 months remission, the dose of AED can be gradually decreased, while pain should be re-evaluated regularly.

Level of evidence: D; SOR: 82.1 (68–100).

A = based on category 1 evidence; B = based on category 2 evidence or extrapolated recommendation from category 1 evidence; C = based on category 3 evidence or extrapolated recommendation from category 1 or 2 evidence; and D = based on category 4 evidence or extrapolated from category 2 or 3 evidence [7].

The new neuropathic pain diagnostic tool mentioned in the first recommendation is the DN4 questionnaire developed and validated by the French Neuropathic Pain Group [37]. This clinician-administered 10-item questionnaire consists of both sensory descriptors and signs related to bedside sensory examination. It is rapid and helpful in daily practice to detect neuropathic pain.

4. Conclusion

AED have proven effective for neuropathic pain syndromes in various randomized, controlled studies [38]. In their recently proposed algorithm for the therapeutic management of peripheral neuropathic pain, Finnerup et al. [2] consider AED as a first-line treatment, on the same level as tricyclic antidepressants. More recently, the EFNS and the IASP neuropathic pain special interest group guidelines propose the same first choice of treatment [29,31]. The use of AED is fairly common in rheumatology practice, and there are as yet few therapeutic trials investigating AED in the treatment of rheumatological pain.
Most studies on the subject are not controlled, with small sample sizes, and often include a wide variety of conditions within the same study. There are few randomized, controlled studies. Little or no evidence was available for many of the key issues because of the lack of clinical trials. Most studies have focused on low back pain, sciatica, complex regional pain syndromes and fibromyalgia and although there is a trend towards the use of AED in these painful rheumatic conditions, no clear evidence has been demonstrated. As there is a lack of guidelines regarding the use of AED in painful rheumatic diseases, we propose recommendations based on the results of the few trials available, on the published guidelines proposed for neuropathic pain management and on expert opinion. These recommendations aim to help clinicians to use AED in rheumatological conditions for the better management of its treatment. Further studies are needed to better define the indications of AED for painful rheumatic diseases, the position of AED in medical treatment strategy and the possibility of co-administering drugs to increase the efficacy of AED or to reduce their adverse effects.

Conflict of interest

For each author, there is no conflict of interest related to the involved drugs.

Acknowledgments

The authors would like to thank the members of the CEDR (Cercle d’Etude de la Douleur en Rhumatologie) for their expert suggestions.

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Please cite this article in press as: Vergne-Salle P et al., Antiepileptic drugs to treat pain in rheumatic conditions. Recommendations based on evidence-based review of the literature and expert opinion, Joint Bone Spine (2008), doi:10.1016/j.jbspin.2008.04.011


