Guidelines for the use of antidepressants in painful rheumatic conditions

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Abstract

Objectives: Antidepressants are widely used to treat painful chronic rheumatic conditions but, contrary to neuropathic conditions, little is known about their true analgesic properties and value in these situations. Our group, which focuses on pain in rheumatology, aimed to develop recommendations for the use of antidepressants in rheumatology, based on evidence-based review of published data and expert opinion.

Method: We identified relevant drugs and conditions and searched Medline, Embase and Pascal (1966–2003) for relevant publications in a number of European languages. We scored each study for quality, and used an expert consensus approach to formulate recommendations.

Results: We identified 77 studies and 12 meta-analyses and literature review on the use of antidepressant to treat painful rheumatological conditions. Forty-nine of these clinical studies were considered valid and were used to develop the recommendations. When evidence was lacking we based recommendations on our clinical experience.

Conclusions: These recommendations for the treatment of painful rheumatological conditions with antidepressants were developed using evidence-based and expert consensus approaches and are the first of their kind in this field. Our review of the literature highlights the need for further, well-designed clinical studies of the use of antidepressants to treat painful rheumatological conditions.

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1. Introduction

Pain is the main symptom of many rheumatic conditions, inflammatory conditions and degenerative diseases. In many cases, analgesics, non steroidal anti-inflammatory drugs (NSAIDs) or opioids control pain effectively. However, in some cases, additional treatments, such as antidepressants and anticonvulsants, are required (Curatolo and Bogduk, 2001; Sawynok et al., 2001; Watson and Peter, 1994). The prescription of antidepressants (Blier and Abbott, 2001; Bryson and Wilde, 1996; Eschalier et al., 1998) is increasing for many conditions, including fibromyalgia, rheumatoid arthritis, spondylarthropathies, low back pain and osteoarthritis. Although antidepressants have often been shown to reduce pain, the results obtained are variable (Barkin and Fawcett, 2000; Lynch, 2001; Onghena and...
Van Houdenhove, 1992; Zitman et al., 1992) and many questions remain unanswered (Egbunike and Chaffe, 1990; Phillip and Fickinger, 1993; Sindrup et al., 1992). For example: Does the analgesic effect depend on the antidepressant effect? What is the optimal dose? When is such treatment appropriate? How long should treatment be continued?

Guidelines are therefore required concerning the use of these drugs. This document reviews the available evidence and then proposes a framework for the development of guidelines, without providing detailed advice about doses or formulations. It is designed to be a starting point for discussion and to be sufficiently flexible to gain practical acceptance in different countries. It aims to help prescribers (in primary care or specialist settings) to use antidepressants appropriately for the management of pain in rheumatic conditions.

2. Methods

2.1. The expert panel

This study was carried out by a working group of nine experts for the CEDR (Cercle d’Etude de la Douleur en Rhumatologie) a specific interest group of the French Society of Rheumatology that focuses on rheumatic pain. Seven of the experts involved in this study were rheumatologists, one of whom was also a pharmacologist. The other members were a psychiatrist and a neurologist/pharmacologist.

2.2. Search strategy

Relevant treatments and conditions were identified by the panel. We then searched the Medline, Embase and Pascal databases for publications in several European languages. Search terms used were: antidepressant, pain, rheumatoid arthritis, osteoarthritis, low back pain, fibromyalgia, fibrositis, rheumatic diseases, spondylarthropathy, ankylosing spondylarthrosis, and sympathetic dystrophy. The search period covered 1966 to August 2002. Studies were scored using the EULAR guidelines, from 0 to 28 (Pendleton et al., 2000), based on a checklist. This checklist consists of 27 items distributed between five sub-scales and was developed on the basis of epidemiological principles, reviews of study designs, and existing checklists for the assessment of randomised 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 one question, giving a maximum score of 28. Power calculations are scored as 1 if present and 0 if absent.

2.3. Guideline development

All potentially relevant papers were retrieved and their findings were analyzed by all members. The list of clinical questions used to define the scope of the literature search was also used to structure the recommendations together with another set of guidelines (on the use of opioids for the treatment of chronic pain) which had been developed by a similar expert group, including one of the CEDR panel members (Kalso et al., 2003). Separate sections were drafted by various participants using the evidence from the literature review wherever possible.

The draft recommendations were circulated among the authors for further review and critical evaluation. A Delphi approach was then employed to reach consensus and all the recommendations were collated and sent back to the experts, who were asked to rank the 10 most important proposals. A final draft of the recommendations was generated, taking into account the comments and criticisms of the nine panel members. 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 post or 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 like is not identified. These elements are presented to the group in such a way as to suppress any identification. Here are the ten steps for the Delphi method:

1. Formation of a team to undertake and to monitor a Delphi on a given subject.
2. Selection of one or more panels to participate in the exercise. Panel members are usually experts in the area to be investigated.
4. Testing the questionnaire for proper wording (e.g., ambiguities, vagueness).
5. Transmission of the first questionnaires to the panelists.
7. Preparation of the second-round questionnaires (and possible testing).
8. Transmission of the second-round questionnaires to the panelists.
9. Analysis of the second-round responses (steps 7–9 are reiterated as long as many times as required to achieve stable results).
10. Preparation of a report by the analysis team to present the conclusions of the exercise.

The recommendations were then tested according the AGREE method (AGREE Collaboration, 1999) by two independent reviewers and the strength of the evidence supporting each recommendation was indicated, from A to D (Shekelle et al., 1999). The purpose of the Appraisal of Guidelines Research & Evaluation (AGREE) Instrument is to provide a framework for assessing the quality of clinical practice guidelines. The AGREE Instrument is designed to assess guidelines developed by local, regional, national or international groups. The AGREE Instrument is generic and can be applied to guidelines in any disease area. The AGREE Instrument assesses both the quality of the reporting, and the quality of some aspects of recommendations. It provides an assessment of the predicted validity of a guideline, the likelihood that it will achieve its intended outcome. It does not assess the impact of a guideline on patients’ outcomes.

3. Results

We identified 137 relevant papers and, of these, selected 99 for detailed analysis: 77 were randomised controlled studies and 12 were meta-analyses or literature review. The results are summarised below.

3.1. Global review of analgesic effects of antidepressants

3.1.1. Analgesic effect of antidepressants

Analysis of 39 studies in various chronic non-malignant painful conditions (Onghena and Van Houdenhove, 1992) found that antidepressants had an analgesic effect, confirmed by Lynch in a meta-analysis of 59 studies (Lynch, 2001). In neuropathic pain, the results are convincing and have demonstrated differential analgesic effects regarding the group of the drug: McQuay et al. (1996) and Sindrup and Jensen (1999) found that TCAs were more effective than serotonin-specific reuptake inhibitors (SSRIs) in relieving neuropathic pain. In global assessment of effects of antidepressants in chronic pain states, most of the authors have concluded that the tricyclic group of antidepressants is analgesic and that data regarding selective serotonin reuptake inhibitors are conflicting (Lynch, 2001). A review of the use of antidepressants in pain management, including rheumatic conditions (Smith, 1998) found little reason to replace TCAs by SSRIs in pain management. In a other review comparing some of the newer antidepressants with TCAs (Ansari, 2000), only paroxetine and citalopram were found to have a positive effect on neuropathic pain. Venlafaxine was recently shown to reduce neuropathic pain following chemotherapy for breast cancer (Tasmuth et al., 2002), and may also improve fibromyalgic patients (Sayar et al., 2003). But, except in neuropathic conditions and in fibromyalgia, there is no convincing study that really aimed to compare TCAs with SSRIs or other new antidepressants in specific chronic pain states and specifically rheumatological. For most of the authors antidepressant analgesic effects are independent of their effects on mood (Magni, 1991).

3.2. Evaluation of the dose–response effect in chronic pain

There is no clear evidence for a dose-dependent response to antidepressant treatment in terms of pain relief (McQuay et al., 1993). However, we identified no studies that dealt specifically with rheumatic pain. Conflicting data have been obtained concerning the possible relationship between concentration and analgesic effect, but current therapeutic plasma concentration ranges seem to give an acceptable response for TCAs. Several studies in which TCAs were administered for various types of neuropathic pain reported a relationship between serum drug concentration and analgesic effect (Furlanut et al., 1993; Sindrup et al., 1991). For the newer antidepressants, also in neuropathic pain, some studies suggested that plasma concentration and effect are correlated (e.g. for sertraline and paroxetine for neuropathic pain) and others reported no such correlation (e.g. for fluoxetine and citalopram for neuropathic pain) (see references in Ansari (2000)).

3.3. Onset of action in chronic pain

The analgesic response seems to start before the antidepressant response. An analgesic response is usually observed within one week of starting treatment, whereas the antidepressant response usually occurs after the first two weeks (see references in Onghena and Van Houdenhove (1992)).

3.4. Evaluation of different routes and patterns of administration

The advantages of the various routes of administration are unclear in humans. Due to a marked first-pass effect, oral bioavailability ranges from 20 to 80% (see references in Furlanut et al. (1993)) and genetic polymorphism may also play a role in the pronounced pharmacokinetic variability observed with these drugs. Parenteral administration overcomes the problem of first-pass metabolism, and results in high plasma concentrations. However, apart from a possible indication in patients unable to swallow, the parenteral route seems to have no other real advantage, despite reports that this
route may accelerate the onset of the therapeutic effect (Pollock et al., 1986).

3.5. Antidepressants side effects

Imipraminic drugs, and TCAs in particular, cause side effect in 30–100% of patients treated for painful conditions (Eschalier et al., 1998; McQuay et al., 1993). Side effects are more frequent in fibromyalgia, occurring in 70–95% of cases (Carette et al., 1986; Carette et al., 1994). Side effects parallel TCAs analgesic effects and, in most cases, depend on dose (McQuay et al., 1996). Rapid wash-out may lead to severe symptoms, such as nausea, vomiting, and trembling (Sindrup et al., 1992). Before starting TCA treatments, the physician should check for orthostatic hypotension and perform an ECG. No recommendations have yet been published with a view to preventing the side effects of TCAs. The effects of combined treatment with tramadol should also be monitored (Reus and Rawitscher, 2000), due to frequent co-utilization in rheumatological conditions.

SSRIs have been demonstrated to be well tolerated and safe. The only reported side effects are abdominal symptoms at the start of the treatment, and serotoninergic syndrome. Side effects are reported in up to 80% of patients treated for painful conditions (Bird and Brogini, 2000; Norregard et al., 1995; Wolfe et al., 1994) but are clinically relevant in a lower proportion (0–41%) (Jung et al., 1997). This may account for the lower rate of treatment drop-outs with SSRIs than with TCAs (Bird and Brogini, 2000; Sindrup et al., 1992; Usha Rani et al., 1996) in pain studies. In fibromyalgia, SSRIs are well tolerated, about as well as placebo (Cantini et al., 1994; Norregard et al., 1995; Wolfe et al., 1994), and are therefore more readily prescribed. Furthermore, no tests are required before starting SSRI treatment. Combination with tramadol is also not recommended.

3.6. Use of antidepressants in patients with specific rheumatological conditions

3.6.1. Fibromyalgia syndrome

We identified 47 studies on the use of antidepressants in fibromyalgia, including 25 controlled trials, most of which involved tricyclic agents; and there were three meta-analyses on this topic (Arnold et al., 2000; O’Malley et al., 2000; White and Harth, 1996). The median quality score of these papers was 14.5 (range: 8–24).

Despite their widespread use, tricyclic drugs have only a moderate effect and only a minority of patients display sustained, marked improvement (Bennett et al., 1988; Bibolotti et al., 1986; Cantini et al., 1994; Caruso et al., 1987; Fossaluzza and De Vita, 1992; Goldenberg et al., 1986, 1996; Hamaty et al., 1989; Hannonen et al., 1998; Heymann et al., 2001; Jaeschke et al., 1991; Quiambry et al., 1989; Reynolds et al., 1991; Scudds et al., 1989; Simms et al., 1991). A major placebo effect was identified in fibromyalgia studies, and antidepressants have not been shown to have a lasting effect.

Amitriptyline is the most widely used drug for which an effect on pain, fatigue, sleep and general conditions has been demonstrated (Carette et al., 1986; Goldenberg et al., 1986, 1996). Amitriptyline and cyclobenzaprine have a greater effect on sleep disorders and fatigue than on pain (Carette et al., 1994). Most of the studies reported the use of tricyclic drugs at doses lower than those used to treat depression, probably due to the side effects of these drugs.

Recent studies have assessed the effects of newer antidepressants, such as citalopram (Andenberg et al., 2000; Norregard et al., 1995) and fluoxetine (Arnold et al., 2002; Cortet et al., 1992; Geller, 1989; Wolfe et al., 1994) or others (Dwight et al., 1998; Olin et al., 1998; Sayar et al., 2003), in patients with fibromyalgia. In these cases, the doses used were higher than or similar to those used in depression (Simms et al., 1991). Few studies have been carried out on the newer antidepressants and the available studies had low quality scores in many cases. However it seems that although these drugs are better tolerated than tricyclic drugs at high doses, their efficacy is limited (Arnold et al., 2002).

Overall, TCAs appear to be the most effective antidepressants for the management of pain and other symptoms in fibromyalgia, even if a large placebo effect was observed in many of these studies (Heymann et al., 2001; Lawson, 2002). A symptomatic effect on fibromyalgia is observed even at low doses (Ataoglu et al., 1997). SSRIs are better tolerated but less effective, making it necessary to increase the dose to obtain significant pain relief.

3.6.2. Low back pain

Seven randomised, controlled trials of good quality have been published on this topic. Four reviews have precisely examined the analgesic and functional effects of antidepressants in low back pain (Salerno et al., 2002; Staiger et al., 2003; Turner and Denny, 1993; van Tulder et al., 1997). The median quality score of clinical papers was 11 (range: 6–15). Analysis of these studies suggested that antidepressants were slightly more effective than placebo for the relief of low back pain. Antidepressant treatment also tended to improve function and everyday activities, although this trend was not statistically significant (Jenkins et al., 1976; Trèves et al., 1991). One study indicated that imipramine was more effective than placebo, but only in terms of the “numbers of days had to lie down” and “number of days with at least some restriction of normal activity” (Alcoff et al., 1982). Another study (Pheasant et al., 1983) showed that amitriptyline was better than placebo, comparing the use of rescue analgesics in both treatment groups. Nortriptyline and maprotiline were
significantly more effective than placebo, but nonetheless had only moderate analgesic effects (Atkinson et al., 1998; Atkinson et al., 1999; Dickens et al., 2000). In conclusion, tricyclic and tetracyclic antidepressants appear to produce moderate symptom reductions for patients with chronic low back pain, independently of a patient’s depression status. Selective serotonin reuptake inhibitors (SSRIs) do not appear to be beneficial. The effect of antidepressants on health-related quality of life, mood and functional status is unclear (Staiger et al., 2003; Ward, 1986).

### 3.6.3. Osteoarthritis and inflammatory rheumatic diseases

We identified 15 randomised controlled trials on osteoarthritis (OA), rheumatoid arthritis (RA), and ankylosing spondylitis (AS). Fourteen of these studies were placebo-controlled and one compared amitryptiline with paroxetine. Only eight of these 15 trials were considered to meet the minimum standards in terms of methodological quality to demonstrate efficacy (Ash et al., 1999; Bird and Broggini, 2000; Frank et al., 1988; Ganvir et al., 1980; Grace et al., 1985; Koh et al., 1997; Macfarlane et al., 1986; Parker et al., 2003). These studies scored from 13 to 22 on a scale with a maximum of 28 (median quality score: 16.4). In almost all these trials, efficacy in the control of pain and symptoms was independent of the antidepressant effect (with the exception of Parker et al. (2003) and Sarzi Puttini et al. (1988)), which included depressed patients). Thus, amitryptiline, trimipramine, dothiepine and paroxetine may have analgesic effects in patients with RA, and amitryptiline may be effective in reducing symptoms in AS. Analgesic effects of antidepressant were usually detected after one week of treatment. Low doses of amitryptiline (10–30 mg daily) may be sufficient to provide an analgesic effect (Fowler et al., 1977; Hood et al., 2001; MacNeill and Dick, 1976; McQuay et al., 1992).

None of the studies specifically dealt with OA; it is therefore difficult to determine whether antidepressants are beneficial for this condition. Some studies grouped together patients with OA, RA and AS, and reported a small, but significant analgesic effect with TCAs and SSRIs (Gringras, 1976; McDonald Scott, 1969; Thorpe and Marchant-Williams, 1974; Usha Rani et al., 1996). In the study performed by Lin et al. (2003) in a large and diverse population of older adults with arthritis (mostly osteoarthritis) and comorbid depression, benefits of improved depression care extended beyond reduced depressive symptoms and included decreased pain as well as improved functional status and quality of life.

### 3.7. General guidelines for the use of antidepressants

Based on the findings of the 75 studies analyzed, the clinical experience of the expert panel, and previously published guidelines on the treatment of chronic pain (Kalso et al., 2003) we propose the following guidelines concerning the use of antidepressants in painful rheumatic conditions. The strength of the evidence supporting each recommendation is indicated, from A to D (Shekelle et al., 1999).

1. Due to their analgesic and antidepressant properties, antidepressants can improve the symptoms and quality of life of patients suffering from painful chronic degenerative and inflammatory osteoarticular and spinal diseases. Their use should be included in a global management programme together with non-pharmacological approaches. 

2. Antidepressants, especially tricyclic drugs, are recommended as analgesics for fibromyalgia. They should not be first choice analgesic treatment in low back pain, osteoarthritis and inflammatory rheumatic painful diseases.

3. To increase compliance, patients prescribed antidepressants for analgesic use should be informed of the type of drug, its side effects, the aim of the treatment and the expected delay until the analgesic effects begin.

4. Antidepressants may be prescribed as analgesics in non-depressed patients. The first-choice treatment should be a TCA, initiated at a low dose, which is then increased to the maximal tolerated dose or to the minimal effective dose.

5. Newer antidepressants with mixed action or specific serotonin reuptake inhibitors should be tried only if TCAs prove to be ineffective, poorly tolerated or if they are contraindicated. Another antidepressant (from the same class or another class) can be tried after failure of the initial antidepressant treatment, regardless of whether this failure is related to a lack of efficacy or unbearable side effects.

6. The side effects of antidepressants used as analgesics are similar to those observed in the treatment of depression. They may be treated from treatment initiation and throughout the treatment period.

7. If TCAs are prescribed to elderly patients, the physician should monitor blood pressure, cognition and intestinal transit.

8. The assessment of treatment efficacy should not be limited to pain evaluation. It should include functional evaluation, analgesic consumption, sleep quality and duration evaluation, and psychosociological assessment, and should be started after one week of treatment.

9. There is no optimal duration of antidepressant treatment. Antidepressant treatment should be maintained for at least 4 weeks before being stopped due to lack of efficacy. Total duration should be determined with respect to the initial
objectives, accepted by both the patients and the physician, and after careful risk-benefit evaluation.

10. After 3 to 6 months of remission, the dose may be gradually decreased, with regular pain assessments. Stopping the treatment too abruptly may lead to nausea, vomiting and trembling.

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; D: based on category 4 evidence or extrapolated from category 2 or 3 evidence (Shekelle et al., 1999).

4. Conclusions

Guidelines should be based on available evidence and this was the goal of this expert group. However, we soon realised that little or no evidence was available for many of the key issues, because of the paucity of appropriate clinical studies and as clinical studies does not reflect the real clinical situations, e.g. and long-term utilization in painful chronic situations. The published studies provide little information useful to determine which individuals respond to antidepressants with analgesic effects. More studies have focused on fibromyalgia than on other conditions, but although there is a trend towards the use antidepressants in fibromyalgia, no clear analgesic effects have been demonstrated in this situation. The results of studies on osteoarthritis, low back pain and rheumatoid arthritis are not very convincing. There has also been no comparative study of patients with different, specific rheumatological conditions. It is also not yet possible to determine which type of pain will respond most strongly to treatment with antidepressants. Furthermore, it is not possible to define predictive factors for analgesic effects: psychological status does not predict analgesic effect and antidepressants do not exhibit more powerful analgesic effects in depressed patients.

These recommendations have been tested by two independent reviewers, according the AGREE method (AGREE Collaboration, 1999), specifically dedicated for the assessment of clinical guidelines. Global assessment was good, and specific assessments of each the 6 domains were rated with scores ranging from 53% to 100%, thus allowing the spreading of these recommendations.

These recommendations also gave us the opportunity to define research guidelines. The responsiveness of many chronic pain conditions, especially rheumatological, to antidepressants has not been assessed in controlled settings and we know very little about the long-term (months to years) efficacy and adverse effects of antidepressants. Some clinicians have reported successful treatment with SSRIs following the failure of tricycles drugs, however no clinical studies have been performed in this area. Further studies are needed to investigate the role of plasma concentration, the influence of concomitant psychiatric disturbances, and the type of organic lesions on the analgesic response to antidepressant effects. Another field for future research is the possibility of co-administering drugs to increase the efficacy of antidepressants or to reduce their adverse effects. Following the development of clinical guidelines (AGREE Collaboration, 1999), we have planned to revise these recommendations in a next future, to keep it relevant, according to most recent clinical findings, and mostly to both the patient’s and physician’s experience.

References


