Rationalizing the use of antidepressants in painful rheumatic conditions

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'Pain and depression are often linked, and several studies have indicated that pain and depression share common neurochemical mechanisms'

Pain is the main symptom of most of rheumatic conditions. In many cases, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids control pain effectively. However, in some cases, additional treatments such as antidepressants and anticonvulsants are required [1]. Although antidepressants have been used as analgesics drugs for more than 40 years, they have only recently been approved for analgesic use, and only in neuropathic pain [2]. In the meantime, although they have become common drugs for the management of chronic pain, many issues still remain to be elucidated, especially in rheumatology. To explore the relevant use of antidepressants in rheumatic conditions, a task force from the French Society of Rheumatology Comprehensive Epidemiologic Data Resource (CEDR) was established. The literature review was based on 137 relevant papers, 99 selected for detailed analysis, 77 randomized controlled studies and 12 meta-analyses or literature review.

Antidepressants in rheumatology: analgesics of the future?

In rheumatology, the prescription of antidepressants is increasing for many conditions [3,4], including fibromyalgia [5,6], rheumatoid arthritis [7], spondylarthropathies [8], low back pain [9,10] and osteoarthritis [4]. Antidepressants have mostly central analgesic action (supraspinal or spinal). However, a peripheral analgesic mechanism of action has also been demonstrated, based on animal models with an inflammatory component, which suggests their potential effect in inflammatory joint diseases [11]. Related to these ubiquitous effects, antidepressants may be considered as a promising therapeutic analgesic class in rheumatology. However, many questions remain unanswered, 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?
- What are the optimum rheumatological conditions where antidepressants are adequate?

Based on a literature analysis focussed on rheumatic conditions, we will try to answer those questions.

Is there a real analgesic effect of antidepressants?

For a long time, antidepressants were not considered to be analgesic agents. However, although they can act as antidepressants in certain patients with chronic pain, they have a genuine analgesic action that has been demonstrated in both experimental and clinical conditions [1,11–17]. In global assessments of the effects of antidepressants in chronic pain states, there is a consensus that the tricyclic group of antidepressants have the best validated analgesic effect [18], and that data regarding selective serotonin reuptake inhibitors (SSRIs) are conflicting [14–17].

Tricyclic antidepressants (TCAs) and new dual antidepressants (serotonin and noradrenalin reuptake inhibitors [SNRIs]), which comprise venlafaxine, milnacipran and duloxetin, are both effective in neuropathic pain management. Venlafaxine was demonstrated to reduce neuropathic pain following chemotherapy for breast cancer [19] and may also improve fibromyalgic patients [20]. Duloxetin was the first antidepressant to be approved by the US FDA for treating neuropathic pain in diabetic patients [21], and milnacipran has demonstrated good results in fibromyalgia [22]. However, except in neuropathic conditions and in fibromyalgia, there is no convincing study that really aimed to compare TCAs with SSRIs or SNRIs in specific chronic pain states, particularly in rheumatology.

Is the analgesic effect of antidepressants linked to mood disturbances?

Pain and depression are often linked, and several studies have indicated that pain and depression share common neurochemical mechanisms [23].

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Based on the studies conducted to date, it cannot be affirmed that antidepressants are analgesics, because they improve the emotional response to pain. However, some areas of the CNS that integrate the emotional and affective components of pain, such as the anterior cingulated cortex and amygdala, are susceptible to regulation by antidepressants in both pain conditions and depression. In fact, it has been demonstrated by several clinical studies that the analgesic effect of antidepressants is independent of their antidepressant action, without any effect on mood in depressed chronic-pain patients [24,25].

Is there a dose–response effect in chronic rheumatological pain?

There are conflicting data for a dose-dependent response to antidepressant treatment in terms of pain relief [26,27]. For the newer antidepressants, mainly in neuropathic pain, some studies suggested that plasma concentration and effect are correlated (e.g., between sertraline and paroxetine for neuropathic pain), while others reported no such correlation (e.g., between fluoxetine and citalopram for neuropathic pain) [12]. However, we identified no studies that dealt specifically with rheumatological painful conditions.

When does the analgesic action of antidepressants in chronic pain begin?

The analgesic response appears to start before the antidepressant response. An analgesic response is usually observed within 1 week of starting treatment, whereas the antidepressant response has usually been demonstrated to usually occur after the first 2 weeks [3,28].

What are the best routes & patterns of administration?

The advantages of the various routes of administration are unclear in humans. Owing to a marked first-pass effect, oral bioavailability ranges from 20–80% [29], 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 [30]. However, apart from a possible indication in patients unable to swallow, the parenteral route appears to have no other real advantage, despite reports that it may accelerate the onset of the therapeutic effect [31].

What are the predominant antidepressants side effects in pain management?

Imipraminic drugs, and TCAs in particular, cause side effects in 30–100% of patients treated for painful conditions [14]. Side effects appear to occur more frequently in fibromyalgia (occurring in 70–95% of cases) [32]. With TCAs, side effects parallel analgesic effects and, in most cases, depend on dose [33]. Rapid wash-out may lead to severe symptoms, such as nausea, vomiting and trembling [34]. Before beginning TCA treatments, the physician should check for orthostatic hypotension and perform an electrocardiogram (ECG). To date, no recommendations have been published with a view to preventing the side effects of TCAs. The effects of combined treatment with tramadol should also be monitored, due to frequent co-utilization in rheumatic conditions [35].

SSRIs and SNRIs 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 [36,37], but are clinically relevant in a lower proportion (0–41%) [38]. This may account for the lower rate of treatment dropouts with SSRIs and SNRIs than with TCAs in pain studies [4,34,36].

Should antidepressants always be used in fibromyalgia syndrome?

Despite their widespread use in fibromyalgia, tricyclic drugs have only a moderate effect, and only a minority of patients display sustained, marked improvement (without a lasting effect) [3,5,6,39,40]. Amitriptyline and cyclobenzaprine have a greater effect on sleep disorders and fatigue than on pain [41]. Most of the studies reported the use of tricyclic drugs at doses lower than those used to treat depression. Recent studies have assessed the effects of newer antidepressants, such as citalopram [37,42], fluoxetine [43] or SNRIs [20,22,44,45], with doses that are higher than or similar to those used in depression. However, it appears that these drugs, and particularly SNRIs, are better tolerated than tricyclic drugs at high doses and that they exhibit significant and lasting effect.

Should antidepressants be used in chronic low back pain?

Few randomized, controlled trials have been published on this topic, but some reviews have precisely examined the analgesic and functional

effects of antidepressants in low back pain [9,46,47,48]. Analysis of these studies has suggested that antidepressants are slightly more effective than placebo for the relief of low back pain. Antidepressant treatment also tends to improve function and everyday activities, although this trend is not statistically significant [49,50]. Tricyclic and tetracyclic antidepressants appear to produce moderate symptom reductions for patients with chronic low back pain, independently of a patient's depression status. The effect of antidepressants on health-related quality of life, mood and functional status is still unclear [9,10]. SSRIs do not appear to be beneficial and there have been no studies with SNRIs in chronic low back pain.

Is it helpful to use antidepressants in osteoarthritis & inflammatory rheumatic diseases?

There have been more than 15 randomized controlled trials published on the use of antidepressants in osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS) [8,36,51–56]. In almost all these trials, efficacy in the control of pain and symptoms appears to be independent of the antidepressant effect (with the exception of [56,57], which included depressed patients). Thus, amitryptyline, 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 antidepressants are usually detected after 1 week of treatment.

None of the studies specifically considered OA. Therefore, it is difficult to determine whether antidepressants are beneficial for this condition. Some studies have grouped together patients with OA, RA and AS, and have reported a small, but significant, analgesic effect with TCAs and SSRIs [4]. In the study perfomed by Lin, in a large and diverse population of older adults with arthritis (mostly osteoarthritis) and comorbid depression, benefits of improved depression care have extended beyond reduced depressive symptoms and included decreased pain as well as improved functional status and quality of life [58].

General guidelines for the use of antidepressants in rheumatology

Since antidepressant use is growing in rheumatology, and due to the paucity of relevant data, a task force from the French Society of Rheumatology was established to develop general guidelines on the use of antidepressants in rheumatic conditions. After the literature review, in the same way that was established with previously published guidelines on the treatment of chronic pain [59], we have proposed ten guidelines concerning the use of antidepressants in painful rheumatic conditions [60].

Conclusions

The published studies provide little information useful to determine the rheumatological conditions in which antidepressants exhibit greater analgesic effects. More studies have focussed on fibromyalgia than on other conditions, but, although there is a trend towards the use antidepressants in fibromyalgia, only weak analgesic effects have been demonstrated. The results of studies on osteoarthritis, low back pain and RA are less convincing. It is also not currently possible to determine which individual 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. Until more convincing data are available, we have established clinical guidelines to help clinicians to manage their chronic pain patients with antidepressants [60]. We hope to revise these recommendations in the near future, in order to keep it relevant, according to most recent experimental and clinical findings, but mostly to both the patient's and physician's experience.

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