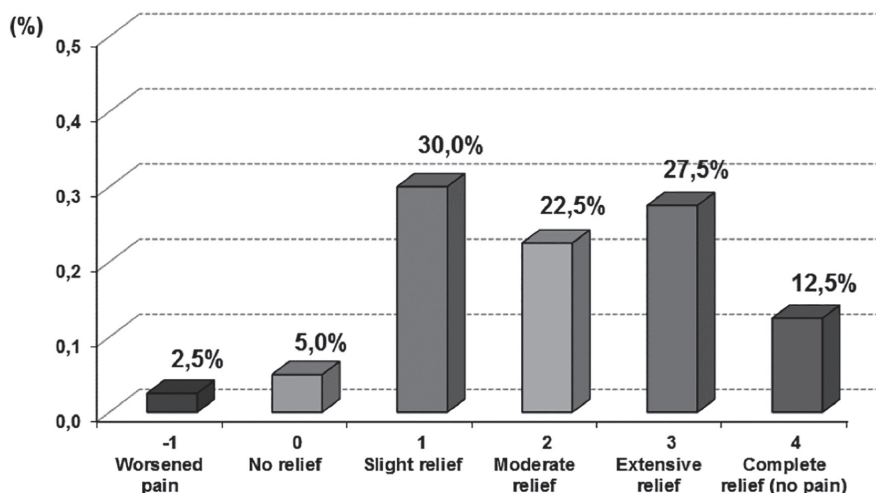


## Effects of a paracetamol and tramadol fixed-dose combination on pain, asthenia, cognitive disorders and sleep quality in fibromyalgia

Sirs,

Fibromyalgia (FM) is a complex syndrome associated with a wide range of symptoms such as asthenia, sleep disturbance and cognitive disorders, that frequently lead to wrong diagnoses and pointless tests or examinations (1-3). FM is characterised by abnormal levels of serotonin and norepinephrine, which are involved in FM-related symptoms (4). The modulatory effects of tramadol on serotonergic and noradrenergic transmission may play an important role in controlling these symptoms. We focused our attention on a fixed combination of tramadol 37.5 mg + paracetamol 325 mg, which could represent a useful approach to the management of FM because of the combined, synergic analgesic effects of paracetamol on musculoskeletal pain and the noradrenergic and serotonergic activity of tramadol on FM-related symptoms (5). The fixed tramadol + paracetamol combination was successfully used in the treatment of FM in a randomised, double-blind, placebo-controlled clinical trial, where statistically significant differences were observed in the Fibromyalgia Impact Questionnaire in favour of the active treatment (6). In order to evaluate the effects of this fixed combination on FM-related symptoms, a retrospective observational study was performed. Sixty-nine consecutive outpatients, seen for the first time and diagnosed with FM, were identified in our registry between April 2011 and May 2012. All patients were prescribed a fixed combination of tramadol 37.5 mg + paracetamol 325 mg (3 tablets daily). About 45% patients were naïve to any treatment for FM. Therefore, in 31 patients (44.9%), the tramadol-paracetamol combination was the only therapy they received, in 27 patients (39.1%), the treatment was associated with cyclobenzaprine, and 7 patients (9.8%) received additional treatments for concomitant conditions.

The characteristics of pain were assessed at baseline considering the number of painful or tender points and the intensity of pain assessed using a 10 cm visual analogue scale (VAS). We also registered a more objective evaluation of pain, assigning a score, that we call "Evoked Pain Score" (EPS) to the intensity of patient's reaction to the touch of tender points; this score ranges from 0 (no reaction) to 4 (very strong reaction). In longitudinal studies on FM, improvements in pain scores are not necessary parallel to changes in evoked pain (7, 8). We decided to add the evaluation of EPS in order to have a more objective assessment of the patient.



**Fig. 1.** Analgesic effects of the treatment given at our sites and patients' judgment on pain relief. Data are reported as percentage of patients.

These measures were repeated at the second visit about 3 months later.

The results of the observational study were reported primarily using descriptive analysis. The changes between the first and second visits in the intensity of pain were analysed using a Wilcoxon test;  $p$ -values  $<0.05$  were considered statistically significant.

Asthenia was the most commonly reported symptom (98%), followed by sleep disorders (78%), cognitive disorders (75%) and headache (71%). An improvement in pain was observed in almost all patients (Fig. 1), with a statistically significant reduction in VAS (8.1 vs. 5.5;  $p < 0.001$ ), EPS (2.7 vs. 2.0;  $p < 0.001$ ) and FM-related symptoms. 58% of patients reported an improvement in sleep disturbance, followed by about 41 to 45% of patients who reported an improvement in asthenia, paraesthesia, headache and restless legs, while only 17% of patients reported an improvement in cognitive disorders. These symptoms are thought to be related to altered noradrenergic neurotransmission within the central nervous system and, therefore, they are targeted by noradrenergic compounds, such as tramadol, that is recommended by the EU and American guidelines for the treatment of FM (9, 10).

The combined mechanisms of action of paracetamol and tramadol are not merely analgesic; they may also provide a "ground-based" approach to FM and can be a valid analgesic treatment as they act on pain and on the associated symptoms.

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