Editorial

Pragmatic Decisions Over Nonsteroidal Antiinflammatory Drug Treatment in Osteoarthritis — Continuous Versus Intermittent

The business of evidence has always been in a state of tension between a statistical perspective examining clinical trial efficacy and a clinical perspective predicated in maximizing benefits to the individual patient. A particular criticism of evidence-based medicine has been that while "Managers and trialists may be happy for treatments to work on average, patients expect their doctors to do better than that."[1] That clinical perspective has never been better stated in rheumatology — that while it is good to feel better, it is better to feel good[2].

Feeling good is strongly associated with chronic painful conditions only in a negative sense: the more pain, the worse the quality of life[3]. Because chronic pain is longstanding[4] and interferes with a whole range of activities of daily living[5], it is unsurprising that chronic musculoskeletal pain has a large negative influence on quality of life, as large as or larger than any other chronic disease for people living in the community[6].

Quantity of life is also negatively affected by chronic pain. Severe chronic pain is associated with increased mortality[7]. Increased disease activity is associated with increased mortality in ankylosing spondylitis[8]. Walking disability in patients with osteoarthritis (OA) is associated with a substantial increase in all-cause mortality[9]. Circulatory problems appear to underlie increased mortality, with lack of activity probably a major facilitator[10].

Although clinical trials designed to assess efficacy have overwhelmingly reported population average results, we now have an increasing number of individual patient data analyses that give more useful information. They tell us 2 things. First, they tell us that there is an unequal distribution of benefit, with some patients having good pain relief, while many have none. Second, that pain benefits can be staggeringly good for some patients, with a substantial minority achieving pain intensity reduction of 50%, 70%, or above[11]. This is the outcome that patients say they want from treatment[12], and achieving these outcomes makes patients feel good. In OA, major improvement in health status is directly related to large reductions in pain[13]. Benefits of good pain relief extend to sleep, fatigue, depression, and work, all of which contribute to very significant gains in quality of life[14].

All of which, interesting though it is, begs the main question of how to achieve the best results in the individual patient. With OA, in particular, patients may experience asymptomatic periods alternating with flares, or have more continuous symptoms. Flares tend to be unpredictable, depending perhaps on activity level or disease progression. The question most often asked is whether treatment with oral drugs should be continuous, or intermittent and taken on an as-needed basis, when flares occur. The general advice to use nonsteroidal antiinflammatory drugs (NSAID) at the lowest dose and for the shortest possible time implies the latter.

A new pragmatic trial reported in this issue of *The Journal*[15] adds much-needed evidence and contradicts the common view. It tested both continuous and intermittent celecoxib in patients with knee or hip OA. The trial had all the criteria of a high quality study: central randomization and a double-dummy design to ensure blinding; it was large, involving 858 patients, and it was of long duration, lasting 22 weeks. Most known sources of bias were therefore excluded, and the trial met criteria for good evidence in chronic pain trials[16].

The selection of patients is crucial in pragmatic trials; this study selected only responders to celecoxib. Enrolled patients demonstrated a flare on withdrawal of NSAID [pain ≥ 4 but < 9 on a numeric rating scale (NRS)], and both patient and physician assessments of arthritis that were "fair, poor, or very poor," inter alia. They also demonstrated resolution of flare during an open-label run-in with celecoxib 200 mg, where resolution involved pain reduced to $<$ 4 on NRS and patient and physician scores of "good or very good." The study was therefore fully enriched. This is

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entirely appropriate for a pragmatic study, as we know that only about 40% of patients with OA have good pain relief (defined as at least 50% pain intensity reduction over baseline at 12 weeks) from any one NSAID[11].

All the outcomes favored continuous NSAID use. The average number of flares per month was lower by almost half (0.5 per patient per month) compared with intermittent use (0.9 per patient per month). Continuous use resulted in significantly more flare-free days, less pain, less use of rescue medication, lower WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scores, less stiffness, and better physical function, with no increase in serious adverse events, discontinuations, or particular adverse events. There was no difference in new onset or worsened hypertension.

The authors also provide the number of flares experienced by individual patients in both treatment groups in addition to statistical analysis. Even a cursory examination shows how the pattern of flares differed, and Figure 1 shows the different distributions of flare frequency for the 2 treatment groups. For continuous NSAID use, the majority of patients (80%) experienced 3 or fewer flares over the 22 weeks; for intermittent use this was much less frequent (62%). For continuous NSAID use, only 20% of patients had 4 flares or more and 2% had 10 flares or more; for intermittent NSAID use, 38% of patients had 4 flares or more; and 9% had 10 or more.

Difference in flare frequency is not inconsequential. Those patients with 2 or more flares had significant worsening in physical function and pain compared with those with fewer than 2 flares. There were also differences, some statistically significant, in quality of life indicators, but all were in the same direction, of poorer quality of life associated with more flare episodes.

This is further confirmation that effective treatment of chronic pain conditions comes with substantial benefits in function and quality of life: more are likely to feel good and fewer to feel worse. This insight is important also for the benefit-risk calculation, for effective treatment means significant and tangible benefit now to set aside potential risk at some time in the future. When the effect of not treating or treating ineffectively has its own risks in poor quality and possibly quantity of life, the benefit-risk equation is not as one-sided as it was once portrayed. For many patients with OA, the balance has been tipped towards continuous NSAID treatment.

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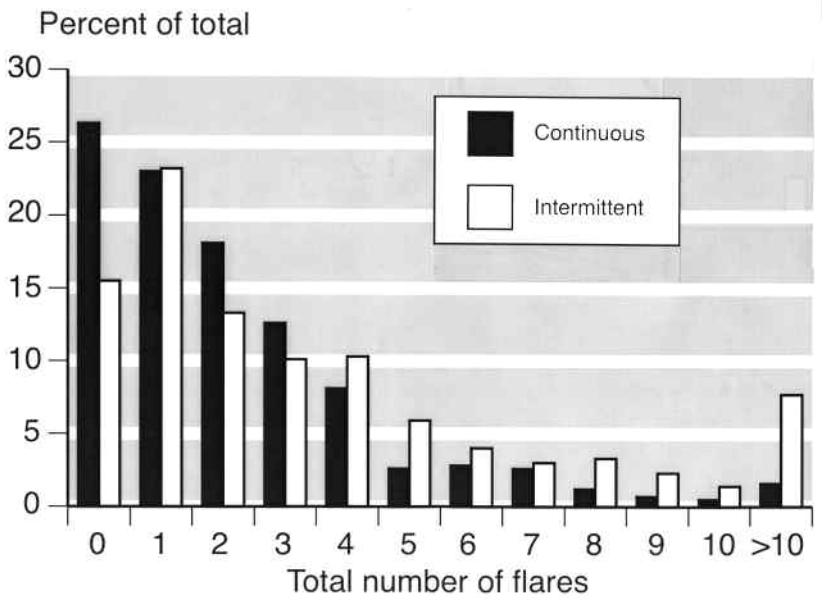

Figure 1. Distribution of flare frequency over 22 weeks in continuous and intermittent NSAID treatment groups[15].

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