How Do Gastrointestinal or Liver Comorbidities Influence the Choice of Pain Treatment in Inflammatory Arthritis? A Cochrane Systematic Review

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ABSTRACT. ***Objective.*** To assess efficacy and safety of pharmacological pain treatment in patients with inflammatory arthritis (IA) and gastrointestinal (GI) or liver comorbidities.

Methods. A systematic literature search was performed using Medline, Embase, and Cochrane Controlled Trial Register up to June 2010, as well as American College of Rheumatology and European League Against Rheumatism meeting abstracts (2007-2010). The population investigated was defined as patients with IA and existing or prior reported GI or liver disease treated with nonsteroidal antiinflammatory drugs (NSAID), opioids or opioid-like drugs, paracetamol, antidepressants, neuromodulators, or muscle relaxants. Outcomes of interest were defined as efficacy evaluated by common pain measures and safety evaluated by withdrawals due to adverse events, worsening of comorbidity, and mortality.

Results. Out of 2869 identified studies only a single open-arm trial fulfilled inclusion criteria assessing the safety and efficacy of naproxen in 58 patients with active rheumatoid arthritis and GI comorbidities. The presence of fecal occult blood was reported in 1/58 participants tested between Weeks 1 to 26 and 2/32 participants tested between Weeks 27 to 52. Over the course of the study, 7 participants (12.1%) withdrew due to adverse events; no serious adverse events were reported. Among the 14 studies excluded due to inclusion of a mixed population (osteoarthritis or other rheumatic conditions) or an intervention that was already withdrawn, 5 trials reported a higher risk of developing GI events in patients with prior GI events when treated with NSAID.

Conclusion. Very little evidence regarding safety and efficacy of pain treatment in patients with IA and GI or hepatic comorbidities was found. In patients with a history of GI events, extrapolating from other studies, NSAID should be used cautiously since there is evidence that these patients are at a higher risk of developing adverse events. (J Rheumatol Suppl. 2012 Sept;90:74–80; doi:10.3899/jrheum.120346)

Key Indexing Terms:
INFLAMMATORY ARTHRITIS   PAIN   COMORBIDITIES   GASTROENTEROLOGY
LIVER   NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Chronic inflammatory diseases of the musculoskeletal system including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and other forms of seronegative spondyloarthritides (SpA) are common disorders affecting about 1% of the population[1]. Over time, a persistent inflammatory process leads to joint destruction, causing chronic pain, which may persist despite optimal disease-modifying treatment.

Chronic pain is also a large contributor to physical disability and loss of quality of life in these patients, and treating

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pain is thus a crucial step to maintain both functional integrity and a high quality of life[2].

Nonsteroidal antiinflammatory drugs (NSAID) are the most commonly used medications for the treatment of pain, especially in inflammatory diseases, as the mechanism of action is the inhibition of the enzyme cyclooxygenase. Pharmacological pain treatment with other substances such as paracetamol, opioids, muscle relaxants, neuromodulators, and antidepressants are also in widespread use for pain management in inflammatory arthritis (IA), reflecting the multimodal process that is thought to underlie pain in most cases.

Patients with chronic inflammatory diseases are also known to develop extensive comorbid conditions over time[3,4,5], which in many cases may limit the use of pain medication. The objective of our report, which is part of the 3e (Evidence, Expertise, Exchange) Initiative[6], is to systematically review the existing literature to address the following question: "How do comorbidities influence the choice of pain treatment in patients with inflammatory arthritis?". Given the broad scope of this review, the question was divided by major organs that may represent comorbid conditions reflecting (a) gastrointestinal (GI) and hepatic disease and (b) cardiovascular and kidney diseases. This review will focus on the pre- and co-existing GI or hepatic conditions, while a second review elsewhere in this series will address the cardiovascular and renal comorbidities[7]. This article is a shortened version of a Cochrane review[8].

MATERIALS AND METHODS
The research question of this review was "How do gastrointestinal or hepatic comorbidities influence the choice of pain treatment in patients with inflammatory arthritis?". It was performed according to the updated guidelines for Cochrane systematic reviews[9].

Rephrasing the research question. The initial question formulated by the experts was translated into an epidemiological research question according to the PICO method (Population, Intervention, Control, and Outcome)[10]. The population was defined as adults (age > 18 yrs) with inflammatory arthritis including diseases such as RA, PsA, AS, and other forms of seronegative SpA, consistent with all other questions addressed in the context of this 3e Initiative. For our question, the population was specifically limited to patients with existing or prior reported GI or hepatic comorbid conditions. The intervention was specified as pharmacological pain treatment including NSAID, opioids or opioid-like drugs, paracetamol, antidepressants, neuromodulators, or muscle relaxants, regardless of dose, route, frequency, and duration of treatment. Interventions that had been withdrawn from use were excluded. Patients with IA but without any known GI or hepatic comorbidity, but who were treated with the same intervention, or patients as defined above but treated with placebo, were defined as controls. The outcome was split into efficacy and safety: efficacy of pain treatment was evaluated by common pain measures, such as visual analog scale; safety was the major outcome, and was evaluated by withdrawals due to adverse events and serious adverse events, worsening of the comorbid condition, and mortality, as measured in the respective studies.

Types of studies included. All published randomized controlled trials (RCT) or controlled clinical trials with pseudorandomized methods of allocating treatment were considered to assess efficacy. For safety assessment, we also considered uncontrolled (single-arm) trials, controlled before-after studies, interrupted time series, cohort studies, case-control studies, and case series with at least 10 cases followed consecutively. We included only studies that were published as full articles or that were available as a full trial report. There were no language restrictions.

Systematic literature search. To identify all relevant studies we searched the following electronic databases: Medline (from 1950 to present), Embase (from 1980 to present), and the Cochrane Central Register of Controlled Trials. A comprehensive search strategy was developed in close cooperation with an experienced librarian from the Cochrane Collaboration Group (see online Appendix I, available from www.3epain.com). In order to retrieve additional references, an additional search for systematic reviews was carried out in the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects (Cochrane Library, Issue 6, 2010). References from studies were screened in order to identify all possible studies for this systematic review. Further, the conference proceedings for the American College of Rheumatology (ACR) and the European League Against Rheumatism for 2007 to 2010 were hand-searched to identify unpublished studies. The literature search was last updated on June 18, 2010.

Selection of articles. Two reviewers (HR, SR) independently screened each title and abstract retrieved by the searches and selected studies for full-text review. Articles that did not fulfill inclusion criteria or had insufficient data for analysis were excluded; all reasons for exclusion were documented.

Data extraction and assessment of quality and evidence level. For all included studies, the following data were extracted onto standardized forms: study design, characteristics of study population and comorbid conditions, treatment regime and duration, and outcome including adverse events. The raw data (means and standard deviations for continuous outcomes and number of events for dichotomous outcomes) were extracted for the outcomes of interest. If necessary, authors were contacted to provide additional information.

To assess risk of bias for trials identified for our analyis, we used the Cochrane risk of bias assessment tool, which includes sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias[11]. Other tools identified for use were the Newcastle-Ottawa Scale to assess the quality of cohort and case-control studies[12] and recommendations of the Centre for Review and Dissemination[13] to assess the quality of case series.

Data analysis. If data were missing, we assumed the data to have a poor outcome; for dichotomous outcomes (e.g., number of withdrawals due to adverse events), the withdrawal rate was calculated using number of patients randomized in the group as denominator (worst-case scenario).

The results of each study were to be plotted as point estimates with 95% confidence intervals. Point estimates were to be measured as relative risk for dichotomous outcomes, and mean difference and standard deviation for continuous outcomes. Summarizing the data in a metaanalysis was planned only if the data from the different studies were sufficiently clinically and statistically homogeneous.

If sufficient data were available, subgroup analyses were planned, e.g., differences between type of IA (RA vs AS, PsA, SpA).

RESULTS
A total of 2869 articles and 11 additional meeting abstracts from conference proceedings were identified by the search strategy, and 73 articles and one conference abstract were retrieved for detailed review (Figure 1). Of these, of only 1 single-arm trial[14] fulfilled inclusion criteria.

Excluded studies. The main reason for exclusion of studies after detailed review was that they did not include patients with GI or hepatic comorbidities. Six articles were excluded as they concerned drugs withdrawn from use[15,16,17,18,19,20], one conference abstract was excluded as no full report or publication was available[21], and 8 studies were excluded because they included a mixed population of osteoarthritis (OA), IA, and other rheumatic conditions such as low back pain, and did
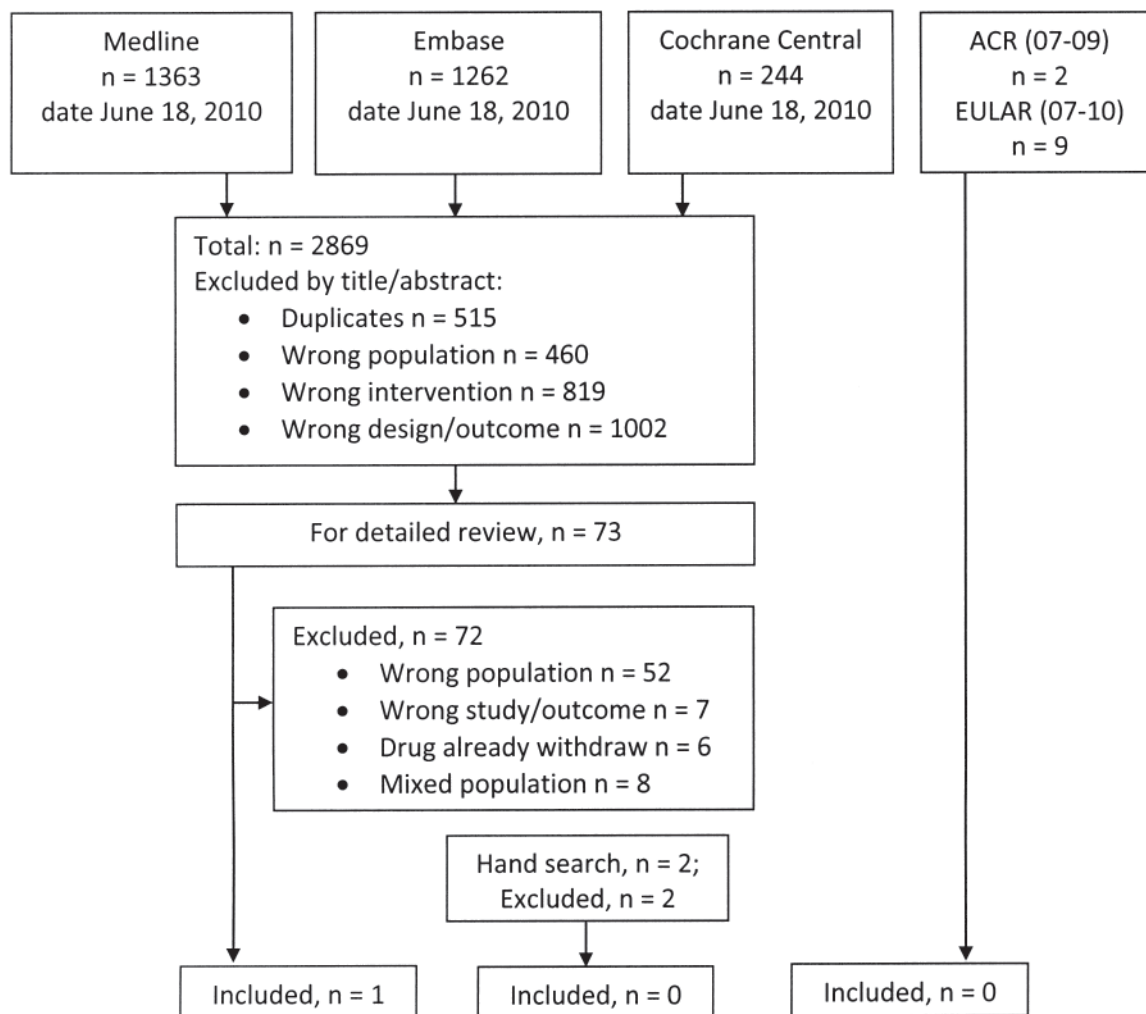
Figure 1. Literature search from which 73 articles and 1 review were selected for detailed review. One article met the inclusion criteria.

not present separate results for patients with IA[22,23,24,25,26,27,28,29]. A summary of search results is depicted in Figure 1 (for detailed information on exclusion of articles see online Appendix II, available from www.3epain.com).

Included study. In a small single open-arm trial, Roth and Boost[14] investigated the safety of naproxen (dosage not specified) in 58 patients with RA, and with GI dysfunction of varying degrees of severity (reflux disease, peptic ulcer, gastritis, pylorospasm, gastric hypersecretion) and reported intolerance to antiinflammatory medication in a 52-week study. Participants were allowed to continue stable maintenance doses of corticosteroids, gold, or antimalarials. All other NSAID were discontinued, but salicylates, while discouraged, were permitted, provided their use was reported. In addition, patients continued on antacids and a bland diet. Study characteristics are depicted in Table 1.

The main outcomes of the study, as identified in the results, were GI side effects assessed by fecal occult blood testing, adverse effects, and other adverse effects leading to discontinuation of treatment. Response to treatment was also evaluated according to the number of painful or tender joints, number of swollen joints, number of hot or red joints, and number of clinically active joints. Therapeutic response to naproxen on a scale of poor, fair, good, or excellent was also reported, as well as number of withdrawals due to inefficacy. There was no indication of who performed the outcome assessments; further, the exact timing was not specified, but was reported as occurring at baseline and in Weeks 1 to 26 and Weeks 27 to 52.

Because the trial was a single-arm open trial it was deemed to be at high risk of bias with low quality (Table 2).

Efficacy. Over time, significant reductions in the mean number of painful or tender joints were reported (baseline: 21.6; Weeks 1 to 26: 13.5; Weeks 26 to 52: 7.6), swollen joints (16.5; 11.4; 6.9), hot or red joints (8.7; 3.0; 0.3) and clinically

Table 1. Description of the included study.

Methods

Single arm open trial. Study duration: 52 weeks.

Participants

Participants were 58 patients with active rheumatoid arthritis (RA). Inclusion criteria: RA and concomitant upper gastrointestinal dysfunction of varying degrees and severity and history of intolerance to antiinflammatory medication. Exclusion criteria: not reported. Mean age, years: females 50.8, males 52.0 (SD not reported). Female: 62%; Mean disease duration: ≥ 170 months (SD not reported).

Stable maintenance doses of disease modifying antirheumatic drugs and corticosteroids were allowed: 13 patients (22.%) gold; 4 patients (10%) hydroxychloroquine; 27 patients (47%) corticosteroids. 12 patients (21%) took salicylates during the study. All participants continued antacids and a bland diet.

The types of GI dysfunction in the cohort included hiatus hernia (as determined by upper gastrointestinal radiographic examination at baseline) (n = 40), gastric ulcer (n = 12), duodenal ulcer (n = 23), gastric hypersecretion (n = 25), pylorospasm (n = 12), gastritis (n = 8) and/or gastric resection (n = 6). Twenty-six participants had both a hiatus hernia and either a gastric or duodenal ulcer while 10 participants had all 3. A "number of participants" were reported to have had upper GI bleeding problems prior to entering the study.

Interventions

Naproxen dosage not specified, taken for up to 52 weeks. [It was reported that the 35 participants (60.3%) who had remained in the study and had taken naproxen for longer than 6 months had taken dosages ranging from 500 to 750 mg daily.]

Outcomes

There was no indication of who performed the outcome assessment. Timing of outcome assessment was not specified but reported as occurring at baseline and in weeks 1-26 and weeks 27-52. According to the results, the following outcomes were assessed: Safety: 1. Number of patients with positive occult fecal blood. 2. Adverse effects. 3. Adverse effects leading to discontinuation of treatment. Efficacy: 1. .Mean number of painful or tender joints. 2. Mean number of swollen joints. 3. Mean number of hot and/or red joints. 4. Mean number of clinically active joints. 5. Therapeutic response (indicated on a categorical scale of either excellent, good, fair or poor response)

Notes

Safety: There was no control group. 1. Fecal occult blood was found in 0/54 participants tested at baseline, 1/58 participants tested between weeks 1-26 and 2/32 participants tested between weeks 27-52. 2. Over the duration of followup a variety of side effects were reported including nausea (n = 4), diarrhea (n = 3), constipation (n = 1), abdominal pain (n = 6), dyspepsia (n = 5), melena (n = 1), skin eruption (n = 2), itching (n = 2), insomnia (n = 2), blurred vision (n = 2) and proteinuria (n = 1). For weeks 1-26 nine participants reported side effects of mild to moderate severity, and for weeks 27-52 three participants reported mild to moderate severity side effects. 3. Seven participants withdrew due to adverse events: lightheadedness and weakness: n = 1, nausea: n = 1, proteinuria: n = 1, sweating and flushes: n = 1, inability to concentrate: n = 1, skin eruption and pruritus: n = 1, abdominal pain: n = 1.

Efficacy: There was no control group, no measures of variance were reported for continuous outcomes, for both continuous and categorical outcomes results were only reported as weeks 1-26 and weeks 27-52, and results were presented only descriptively. As presented in the article, results at baseline (n = 57), 1-26 weeks (n = 58) and 27-52 weeks (n = 35) were as follows: 1. Mean number of tender or swollen joints: 21.6: 13.5; 7.6. 2. Mean number of swollen joints: 16.5; 11.4; 6.9. 3. Mean number of hot and/or red joints: 8.7; 3.0; 0.3. 4. Mean number of clinically active joints: 21.9; 14.8; 9.8. Therapeutic response at weeks 1-26 (n = 58): excellent : n = 12; good: n = 17; fair: n = 12; poor: n = 17. Therapeutic response at weeks 27-52 (n = 35): excellent: n = 13; good: n = 17; fair: n = 3; poor: n = 2 (n = 35). Fourteen participants (24.1%) were reported to have withdrew from the study due to lack of efficacy although the time point was not specified.

Table 2. Quality assessment of the included study according to the guidance recommended by the Centre for Reviews and Dissemination.

Quality Assessment	Authors' Judgment	Explanation
Is the study based on a representative sample selected from a relevant population?	No	Only 58 patients with active rheumatoid arthritis (RA) and upper gastrointestinal (GI) dysfunction; according to age (mean age 50.8 years), gender (62% female) and disease duration (≥ 170 months) the cohort is a representative sample of RA population
Are the criteria for inclusion explicit?	No	Only described: patient with active RA but not according to which disease activity score or who decided whether active or not; GI dysfunction of varying degree and severity assessed by whom?
Did all individuals enter the survey at a similar point in their disease progression?	No	Only quoted 58 patients with active RA and upper GI dysfunction; GI comorbidities of varying degree and severity; disease activity of RA unclear
Was followup long enough for important events to occur?	Yes	52 weeks
Were outcomes assessed using objective criteria or was blinding used?	No	Outcome was assessed "between weeks 1-26" or "between weeks 27-52"
If comparisons of subseries are being made, was there sufficient description of the series and the distribution of prognostic factors?		No subseries were made

active joints (21.9; 14.8; 9.8). At Weeks 1 to 26, 12 participants were reported to have an excellent therapeutic response, 17 a good response, 12 a fair response, and 17 a poor response. At Weeks 27 to 52, the number of participants with excellent, good, fair, and poor response were 13, 17, 3, and 2, respectively. Fourteen participants (24.1%) were reported to have withdrawn from the study due to lack of efficacy, although the timepoint was not specified.

Safety. The authors reported the presence of fecal occult blood in 0/54 participants tested at baseline, 1/58 tested between Weeks 1 to 26, and 2/32 tested between Weeks 27 to 52. Over the course of the study, 7 participants (12.1%) withdrew due to adverse events, but of these only 2 participants withdrew due to GI side effects (abdominal pain: n = 1; nausea: n = 1). No serious adverse events occurred, but a variety of side effects were reported including nausea (n = 4), diarrhea (n = 3), constipation (n = 1), abdominal pain (n = 6), dyspepsia (n = 5), melena (n = 1), skin eruption (n = 2), itching (n = 2), insomnia (n = 2), blurred vision (n = 2), and proteinuria (n = 1). For Weeks 1 to 26 only 9 participants reported side effects of mild to moderate severity, and for Weeks 27 to 52 only 3 participants reported mild to moderate side effects.

DISCUSSION

Our objective for this systematic review was to summarize the evidence of pharmacological pain management in patients with inflammatory arthritis and GI or liver comorbidities. Although a considerable percentage of patients seen in daily practice present with such comorbid conditions[3,4,5], evidence on their effect is difficult to find in clinical trials, since they would represent typical exclusion criteria.

Only 1 single-arm open trial at high risk of bias assessing efficacy and safety of naproxen in 58 RA patients with concomitant GI comorbidity fulfilled our inclusion criteria. In terms of safety, fecal occult blood was found in 3/58 participants, 7 participants (12.1%) withdrew due to adverse effects, including only 2 who withdrew due to GI adverse effects, and no serious adverse events were reported.

No evidence regarding the efficacy or safety of other pharmacological pain therapies in RA, or for any pain treatments in other inflammatory diseases, was identified. Further, we found no evidence regarding the efficacy and safety of any pharmacological therapies in people with RA, PsA, AS, or SpA and concomitant hepatic comorbidities.

Several studies that appeared to address our research ques-

tion were excluded as they included a mixed population of participants and did not report results for the IA participants separately. In a post-hoc multivariable analysis of a large RCT of patients with RA or OA receiving etoricoxib or diclofenac, Laine, *et al*[26] found that a prior lower GI clinical event was the most important predictor of future events, with about a 4-fold increase in risk. Similar results were found in a cohort study assessing the efficacy and tolerability of meloxicam compared with comparator NSAID in 4526 patients with a mixed diagnosis (RA, OA, and other rheumatic conditions including low back pain and AS). Patients with a history of perforation, ulceration, or GI bleeding who had received one of the comparator NSAID appeared to be at increased risk of GI toxicity compared with those who did not have a history of GI events. Interestingly, in those who had received meloxicam, there did not appear to be a significant difference in development of GI toxicity or GI bleeding in those with and those without a history of GI events.

In 2 studies, Chan, *et al*[22,24] assessed the incidence of recurrent ulcer bleeding in participants with RA, OA, and other types of arthritis; subjects who had a healed bleeding ulcer were randomized to receive either diclofenac plus a proton-pump inhibitor or celecoxib. They found that among patients with previous ulcer bleeding, neither celecoxib nor diclofenac plus omeprazole adequately prevented recurrence of ulcer. In contrast, the authors did show, in a recent larger third trial including the same study population and intervention[23], that fewer participants in the celecoxib group developed a clinically significant upper or lower GI event compared with those in the diclofenac plus omeprazole group.

In a small RCT[27] 67 patients with mixed diagnoses (RA, OA, back pain, PsA, and AS) who had been treated with NSAID and developed a gastric or duodenal ulcer were randomized to 1 of 4 treatment groups receiving ranitidine or sucralfate with or without withdrawal of NSAID. Although the proportion with healed ulcers favored the NSAID withdrawal group, this did not reach statistical significance.

In another RCT, including 224 patients with and without a history of peptic ulcer treated with either naproxen or diclofenac, there were no significant differences between groups in endoscopic grades of ulcers. As well, the proportion of patients with worsening of endoscopic grading was almost equal for those patients with and those without a history of peptic ulcer[28].

Several studies that were excluded due to inclusion of a withdrawn drug also appeared to be relevant to our research question as they showed an increased risk of GI events in patients who had a prior GI event[15,16,17,18].

Almost no evidence could be found regarding IA patients with concomitant hepatic disorders. One small case series including 11 patients with rheumatic conditions (RA, vertebral syndrome) and hepatic comorbidities treated with acemetacin (NSAID) for 10 days reported an improvement of pain and no withdrawals due to adverse events[29].

In conclusion, there is scant evidence, based upon our review, to guide clinicians about how GI or liver comorbidities should influence the choice of pain treatment in patients with IA. However, based upon additional studies that included a mixed population of participants with a range of rheumatic conditions, NSAID should be used cautiously in patients with IA and a history of GI comorbidity since there is consistent evidence that these patients may be at increased risk.

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Radner, et al: Pain, inflammatory arthritis, comorbidities

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