Gastrointestinal safety profile of nabumetone: a meta-analysis
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Authors' objectives
To compare the incidence of severe gastrointestinal (GI) adverse events (especially the rate of perforations, ulcers, and bleeds (PUBs) in patients taking nabumetone in comparison with conventional nonsteroidal anti-inflammatory drugs (NSAIDs).

Searching
The authors searched MEDLINE (January 1980 to November 1998) using the MeSH terms and/or textwords 'NSAID', 'ulcer', 'bleeds', 'nabumetone or relafen or relifex or relifen'. The authors also searched PubMed on the Internet, the nabumetone database provided by SmithKline Beecham Pharmaceuticals, and the reference lists of retrieved studies for additional trials. The authors also manually searched all abstracts published between 1995 and 1998 from six additional journals relevant to this topic. The search was limited to English language publications.

Study selection
Study designs of evaluations included in the review
Comparative, randomised controlled trials (RCTs), and long-term studies (postmarketing, open-label, or extended studies) with more than ten patients in each treatment arm. Cross-over studies were excluded to avoid any possible carry-over GI toxicity from the previous treatment.

Specific interventions included in the review
Nabumetone (0.5-2, 1, 1.5, 1-2, 1.5-2, g twice a day (bid) or four times a day (qd) or one dose taken every night (nocte)) in comparison with conventional NSAIDs including: naproxen (250 or 500 mg bid or qd, or 1 g nocte), diclofenac SR (100-150 mg qd or 100 mg nocte), piroxicam (20-30 mg qd), aspirin (3.6 g qd), indomethacin (75-150 mg qd), and ibuprofen (600 mg qid).

Participants included in the review
Patients aged over 18 years with rheumatoid arthritis (RA) or osteoarthritis (AO) or other musculoskeletal disorders.

Outcomes assessed in the review
The incidence of severe gastrointestinal (GI) adverse events (especially the rate of perforations, ulcers, and bleeds (PUBs)).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed quality.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The reviewers extracted data for the following categories: study identification and year of publication, country, illness, number of patients, mean age, drug intervention and dosage, treatment duration and estimated exposure. The authors also extracted data on all GI adverse events, PUBs, GI adverse event-induced drop-outs and treatment-related hospitalisations.
Studies were grouped into endoscopic or nonendoscopic comparative studies, and postmarketing or open-label studies.

**Methods of synthesis**

How were the studies combined?
First, pooled crude incidence rates for GI-related adverse events and PUBs were calculated.

Second, the estimated rate of PUBs per 100 patient-exposure years was calculated using the reported average treatment duration.

Third, pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method.

How were differences between studies investigated?
The authors used the Breslow-Day test for heterogeneity.

**Results of the review**

Thirteen studies were included in the review with 29 treatment arms and 49,501 participants (eight non-endoscopic studies had 16 treatment arms and 7,468 participants, four endoscopic studies had 244 participants, and 3 postmarketing or open-label studies had 37,712 participants).

Nonendoscopic comparative studies (n = 8): In patients treated with nabumetone, 25.3% experienced a variety of GI adverse events, irrespective of treatment duration. This was significantly lower than in patients treated with a comparator NSAID (28.2%, P = 0.007, chi-square test 7.278, df = 1). The test for heterogeneity did not show any statistically significant difference between individual studies (P= 0.7761, df = 7).

When studies were stratified by treatment duration, a significant difference was seen only at 6 months (P < 0.0001). Dyspeptic symptoms, flatulence, constipation and diarrhea were the most commonly reported adverse events, accounting for 98.6% of the total GI adverse events.

An overall incidence of PUBs (6 studies) was reported in 0.062% of patients treated with nabumetone, regardless of treatment duration. This was significantly lower than in patients treated with comparator NSAIDs (0.916%, P < 0.0001, chi-square test = 32.12, df =1). This difference was consistently seen over time.

The estimated rate of PUBs per 100 patient-exposure years in patients treated with nabumetone was 0.087% of patients compared with 2.882% of patients treated with comparator NSAIDs (OR 35.5, 95% CI: 5.3, 757.5).

Endoscopic comparative studies (n = 4): Test for heterogeneity did not show any statistically significant difference between individual studies (P= 0.8537, df = 3).

An overall incidence of PUBs was reported in 2.6% of patients treated with nabumetone, compared with 21% of patients treated with a comparator NSAID.

The estimated rate of PUBs per 100 patient-exposure years in patients treated with nabumetone was 2.5% of patients compared with 20.9% of patients treated with comparator NSAIDs (OR 10.1, 95% CI: 2.8, 43.5).

Postmarketing or open-label studies (n = 3): In two of the studies, 36 PUBs were recorded during the exposure period and after adjustment for patient-exposure years, the rate of PUBs was 0.21 per 100 patient-exposure years.

Drop-outs and hospitalisations (n = 4): The drop-out rate for nabumetone was 8.64% compared to 11.26% in patients treated with a comparator NSAID (OR 1.3, 95% CI: 1.1, 1.6). Treatment related hospitalisations were reported in 0.18% of patients treated with nabumetone compared to 2.03% for patients treated with a comparator NSAID (OR 3.7, 95% CI: 1.3, 10.7).

**Authors' conclusions**
The authors state that this meta-analysis shows that significantly fewer treatment-related GI adverse events are seen in patients treated with nabumetone than with a comparator NSAID. After adjustment for patient-exposure years, the development of PUBs is ten to 36 times less likely in patients treated with nabumetone than with a comparator NSAID. Significantly more patients dropped out or were hospitalised when treated with a comparator NSAID than with nabumetone. Nabumetone is very safe for the GI tract.

CRD commentary
The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search appears to be thorough. While they searched for unpublished and grey literature, the authors may have missed additional studies by restricting the searches to the English language.

The quality of the included studies was not assessed or discussed in the review. The authors have also not reported how the articles were selected, or who performed the selection and data extraction.

The data extraction is reported in tables and discussed in the text of the review. The studies were combined in a statistical meta-analysis where possible and heterogeneity was assessed.

A possible conflict of interest may be the assistance and analysis provided by researchers at the pharmacological company who market nabumetone.

The authors' conclusions appear to follow from the results.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors state that further research should pay attention to the adverse event of undiagnosed silent ulcer causing chronic microbleeding when evaluating GI bleeding related to NSAID treatment.

Bibliographic details

PubMedID
10628594

Other publications of related interest
This additional published commentary may also be of interest. Nabumetone and meloxicam gastrointestinal safety. Bandolier 2000;76:7.

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Inflammatory Agents, Non-Steroidal /adverse effects; Butanones /adverse effects; Digestive System /drug effects; Dyspepsia /chemically induced; Endoscopy, Gastrointestinal; Humans; Product Surveillance, Postmarketing; Treatment Outcome

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.