A systematic review of NSAIDs withdrawn from the market due to hepatotoxicity: lessons learned from the bromfenac experience
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CRD summary
The authors concluded that there were limited safety data from controlled clinical trials about the withdrawn non-steroidal anti-inflammatory drugs bromfenac, benoxaprofen and ibufenac. The authors' conclusions about such limited data appear to be supported by the evidence presented, but poor reporting means it is not possible to assess the reliability of these conclusions.

Authors' objectives
To evaluate clinical trial data on the hepatotoxicity of three non-steroidal anti-inflammatory drugs (NSAIDs) that have been withdrawn from the market due to hepatotoxicity: bromfenac, benoxaprofen and ibufenac.

Searching
MEDLINE and the Cochrane CENTRAL Register were searched, without any language restrictions, from inception using the reported keywords. In addition, the U.S. Food and Drug Administration (FDA) web-based archive was searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 40 patients per treatment arm and a study period of at least 4 weeks were eligible for inclusion in the review.

Specific interventions included in the review
Studies that evaluated exposure to bromfenac, benoxaprofen or ibufenac over at least 4 weeks were eligible for inclusion. The included studies evaluated benoxaprofen (600 mg/day) for 4 weeks or 4 months and bromfenac (50 to 200 mg/day) for between 4 and 36 weeks. The control interventions, where reported, included ibuprofen (1,200 to 1,800 mg/day), naproxen (1,000 mg/day), diclofenac (150 mg/day) and placebo.

Participants included in the review
Studies of patients with osteoarthritis or rheumatoid arthritis were eligible for inclusion. The review did not present further information about the participants in the included studies.

Outcomes assessed in the review
Studies that assessed the following measures were eligible for inclusion: alanine aminotransferase (ALT) elevations greater than three times the upper limit of normal (ULN); bilirubin elevations at least 1.5 times greater than the ULN; discontinuation of study because of elevation of transaminase; liver-related clinical events; hospitalisation for liver diagnoses; and death due to liver disease. The included studies reported the number of patients with ALT elevations between 1.2 and 3 times the ULN, between 3 and 8 times the ULN, and over 8 times the ULN, as well as liver-related hospitalisations and deaths and withdrawal due to elevated liver tests.

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

Assessment of study quality
Two reviewers independently assessed the validity of published studies using the Jadad criteria (reporting of randomisation, blinding and description of withdrawals). Any disagreements were resolved by consensus.
**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

**Methods of synthesis**
How were the studies combined?
The studies were described in the text of the review and some aspects were documented in tables.

How were differences between studies investigated?
Some differences between the studies were apparent from the text and tables.

**Results of the review**
Five trials (number of participants unclear) were included in the review. Two RCTs of benoxaprofen were identified from bibliographic databases (123 individuals assigned to benoxaprofen). Three RCTs of bromfenac were identified through the FDA website (648 individuals assigned to bromfenac, 189 to placebo and 273 to an alternative NSAID).

**Benoxaprofen.**
One double-blind RCT (60 assigned to benoxaprofen) reported no liver-related deaths over 4 months. One double-blind RCT (63 assigned to benoxaprofen) reported no ALT/AST elevations over 4 weeks; this study did not adequately account for all randomised patients.

**Bromfenac.**
The three double-blind RCTs accounted fully for all randomised patients. The studies did not assess the causality of ALT elevations. Two RCTs (234 and 108 assigned to bromfenac, respectively) reported 1% of patients with ALT elevations greater than 8 times the ULN and withdrawal due to elevated liver tests in 5% and 6% of patients. One of the RCTs reported ALT elevations between 3 and 8 times the ULN in 10% of patients taking bromfenac. The third RCT (306 assigned to bromfenac) reported that 3% of patients were withdrawn due to elevated liver tests. A pooled analysis of the three RCTs showed that 2.8% (n=23) of patients had ALT elevations of more than 3 times the ULN. Safety updates submitted 18 months after the original data showed that 2.8% of patients (34 out of 1,195) who had been exposed to bromfenac for 1 month had ALT elevations more than 3 times the ULN, while 0.5% (6 out of 1,190) had ALT elevations more than 8 times the ULN. The original clinical trials reported no hospitalisations for hepatitis or jaundice.

**Authors’ conclusions**
There were limited safety data from controlled clinical trials about the withdrawn NSAIDs bromfenac, benoxaprofen and ibufenac.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. It was not clear why only RCTs were included in this review of safety data, and the eligible outcomes appeared very specific; more information on safety might have been available if these restrictions had been lifted. The search was very limited and consisted of two databases and the FDA website, so it is possible that relevant studies were missed. Attempts were made to minimise language and publication bias. Study validity was assessed using specified criteria, but the results were not reported in full. Methods were used to minimise reviewer errors and bias in the assessment of validity, but were not reported for the study selection and data extraction processes.

The characteristics of the included studies were not reported in full: for example, the medical condition of the participants and the number of patients allocated to control treatments in some RCTs were not reported. The authors’ conclusions about the limited controlled clinical trial data appear to be supported by the evidence presented, but
shortcomings in the reporting and review methods mean it is not possible to assess the reliability of these conclusions.

**Implications of the review for practice and research**

Practice: The authors stated that clinicians should report cases of serious hepatotoxicity to the FDA through the MEDWATCH system.

Research: The authors stated the need for active post-marketing surveillance studies to identify potential rare causes of hepatotoxicity. In future studies of drugs, elevated transaminases in combination with symptoms suggestive of hepatitis or hepatocellular jaundice should be systematically assessed to determine their use as surrogate markers for serious hepatotoxicity.

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