Channelling of patients taking NSAIDs or cyclooxygenase-2-specific inhibitors and its effect on interpretation of outcomes

T. M. MacDonald¹, D. Pettitt², F. H. Lee² and J. S. Schwartz³

When new drugs with improved safety or efficacy are introduced, they may be preferentially prescribed to specific populations of patients. Safety and efficacy may be underestimated if such channelling effects are not recognized. Meloxicam and cyclooxygenase (COX)-2-specific inhibitors were developed as safer alternatives to non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of osteoarthritis and rheumatoid arthritis. Studies of the use of meloxicam and COX-2-specific inhibitors demonstrate that both of these drugs are being prescribed to patients at increased risk of gastrointestinal adverse drug events. In the case of COX-2-specific inhibitors, this channelling appears to represent a prescribing pattern consistent with current recommendations. Subsequent analysis of the data, after adjusting for channelling bias, showed that the risk of gastrointestinal toxicity for meloxicam was similar to that for other NSAIDs, while COX-2-specific inhibitors reduced the risk of developing gastrointestinal adverse drug events by approximately 60%. These studies serve as examples of observed channelling bias and highlight the need for adjusting for channelling in order to provide a valid assessment of relevant outcomes for drugs likely to be preferentially prescribed to specific populations.

KEY WORDS: Channelling bias, Outcomes, NSAIDs, COX-2-specific inhibitors, Meloxicam.

Randomized clinical trials allow experimental control by equalizing the opportunity for patient exposure to intervention and comparator strategies. Thus, by the play of chance selection bias is avoided, treatment groups with similar baseline characteristics are generated and meaningful comparisons of efficacy and safety can be made. For this reason, randomized clinical trials are the gold standard for evaluating causal relationships. However, the cost and complexity of randomized clinical trials and the desire to evaluate clinically relevant safety and efficacy under conditions of routine clinical practice has led to the use of quasi- and non-experimental research methods, including case series, observational cohort and case–control studies. Increasingly, drug safety and effectiveness are assessed using observational postmarketing surveillance designs, characterized by spontaneous adverse event reporting such as the ‘yellow card’ system [1] and prescription-event monitoring [2], currently used in the UK. While observational postmarketing surveillance studies can help provide clinical evidence of a drug’s value, the interpretation of these studies is often challenging as the allocation of patients to treatment is not random and is thus subject to potential bias.

Channelling is a form of allocation or selection bias that occurs when interventions having similar indications are differentially prescribed to groups of patients at varying levels of risk or with prognostic differences [3]. The effect of channelling often goes unrecognized in observational studies and is rarely considered in the spontaneous reporting of adverse events. Failure to adjust for channelling may lead to a biased estimate of an intervention’s safety and toxicity, effectiveness, costs and overall value.

Channelling occurs when physicians preferentially prescribe a new and putatively safer drug to patients at...
increased risk of adverse events, or when a putatively more effective drug is prescribed to patients with more severe disease, worse functional status or greater comorbidity, or who are intolerant of other drugs within the therapeutic class. To the degree that a new drug is indeed safer or more effective, channelling may be appropriate. However, if analyses are not appropriately adjusted for such confounding differences in baseline risk, channelling may result in overestimation of adverse events or underestimation of effectiveness. For example, such systematic bias in observational spontaneous adverse event reporting systems may result in an erroneously high association between a drug and adverse events. It has been suggested that channelling occurs erroneously high association between a drug and adverse event reporting systems may result in an such systematic bias in observational spontaneous adverse event reporting systems may result in an erroneously high association between a drug and adverse events. It has been suggested that channelling occurs with β-agonists [4], antidepressants [5], simple analgesics such as paracetamol (acetaminophen) [6], non-steroidal anti-inflammatory drugs (NSAIDs) [7, 8] and the gastroprotective agents that are often concomitantly prescribed [9], and the recently introduced cyclooxygenase (COX)-2-specific inhibitors [10].

NSAIDs provide important analgesic and anti-inflammatory benefits. However, their use is associated with gastrointestinal toxicity, including symptomatic side-effects such as dyspepsia and severe complications such as upper gastrointestinal ulceration and bleeding, with significant clinical and economic impact [11, 12].

Non-selective NSAIDs inhibit both the proinflammatory COX isoenzyme (COX-2) and the COX isoenzyme associated with gastroprotection (COX-1). Meloxicam and COX-2-specific inhibitors were developed in an effort to alleviate gastrointestinal toxicity through selective inhibition of the COX-2 enzyme [13].

Meloxicam is an NSAID that demonstrates preferential COX-2 inhibition while still inhibiting COX-1 [14, 15]. In clinical trials, meloxicam appeared to have less gastrointestinal toxicity than non-selective NSAIDs [16–18]. However, in a prescription-event monitoring pharmacovigilance system it was associated with a higher than expected rate of adverse gastrointestinal events, although it was suggested that channelling of high-risk patients could have partially accounted for the results [19].

In contrast to meloxicam, the COX-2-specific inhibitors (celecoxib, rofecoxib, valdecoxib) with their COX-1-sparing effect have been demonstrated to have similar efficacy and less gastrointestinal toxicity than non-selective NSAIDs [20–25]. However, if COX-2-specific inhibitors are preferentially prescribed to patients with a high baseline risk of gastrointestinal adverse events, as is currently recommended [26, 27], the observed incidence rate for adverse gastrointestinal events may overestimate their actual gastrointestinal toxicity.

This paper reviews the evidence for channelling among users of meloxicam and COX-2-specific inhibitors and discusses the impact that this channelling may have on evaluation of the safety of these drugs compared with the older, non-selective NSAIDs when using observational data that are not adequately adjusted for selection bias.

Evidence of channelling of meloxicam and COX-2 specific inhibitors

Channelling of meloxicam was first suggested in a pharmacovigilance survey that reported a more frequent occurrence of gastrointestinal events among the 25% of meloxicam users who had a history of gastrointestinal events and the 16% of patients who were using gastroprotective agents [19]. Although no comparisons were made with patients taking other NSAIDs, two follow-up studies evaluated the extent of meloxicam channelling relative to other non-selective NSAIDs [7, 8].

An observational cohort study reported a significantly higher proportion of patients with a history of perforation, ulcers or bleeding among those taking meloxicam (12%) compared with those taking non-selective NSAIDs (7%; P < 0.001) [7]. Additionally, the proportion of patients with a history of prior non-selective NSAID use and NSAID-associated side-effects was higher in the meloxicam group than in the comparator non-selective NSAID group (70 vs 53% and 19 vs 6% respectively; P = 0.001).

A subsequent study by Lanes et al. [8] used the General Practitioners Research Database (GPRD) to characterize the baseline gastrointestinal risk of patients being prescribed meloxicam compared with the older and more commonly used non-selective NSAIDs ibuprofen, diclofenac, naproxen and indomethacin. This study, which evaluated a total of 25 000 patients (5000 patients taking each drug), supported the previous observation that patients at greater risk of gastrointestinal events were being prescribed meloxicam in preference to non-selective NSAIDs. Patients with a gastrointestinal history, defined by dyspepsia, gastritis, duodenitis or peptic ulcer within the past year, and the use of acid-suppressing drugs (H2-receptor antagonists or proton pump inhibitors) within the preceding 6 months were more than twice as likely to be prescribed meloxicam compared with the other NSAIDs, as suggested by the odds ratios (Table 1). The proportion of patients who reported recent use of aspirin, non-selective NSAIDs and oral corticosteroids was also consistently higher among meloxicam users.

Similarly, studies of COX-2-specific inhibitors have demonstrated selective channelling to specific patient populations. A study by Wolfe et al. [10] characterized the association between specific demographic or disease variables and the switching of patients to COX-2-specific drugs after their introduction onto the market compared with patients who continued to take a non-selective NSAID. Using univariate logistic regression, these authors showed that the strongest predictor of a switch to a COX-2-specific inhibitor was the use of gastroprotective agents, patients who used such drugs being more than twice as likely to switch [odds ratio (OR) 2.09, 95% confidence interval (CI) 1.90–2.31]. A history of adverse drug reactions of any kind, but especially those related to the gastrointestinal system, was also significantly associated with being switched to a COX-2-specific inhibitor (OR 1.79 and 1.74, 95% CI 1.59–2.02 and 1.47–2.06 for
TABLE 1. Odds ratios (95% CI) for receiving meloxicam compared with other non-selective NSAIDs for the gastrointestinal risk factors of recent (6-month) acid-suppressing drug use or gastrointestinal history (dyspepsia, gastritis, duodenitis, or peptic ulcer)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ibuprofen</th>
<th>Diclofenac</th>
<th>Naproxen</th>
<th>Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal history or recent use of acid-suppressing drugs</td>
<td>2.8 (2.6–3.1)</td>
<td>2.6 (2.4–2.8)</td>
<td>2.6 (2.4–2.8)</td>
<td>2.2 (2.0–2.4)</td>
</tr>
<tr>
<td>Gastrointestinal history</td>
<td>2.4 (2.2–2.7)</td>
<td>2.2 (2.0–2.4)</td>
<td>2.2 (2.0–2.4)</td>
<td>1.9 (1.8–2.2)</td>
</tr>
</tbody>
</table>

*aAcid-suppressing drugs included H2-receptor antagonists and proton pump inhibitors.
Adapted with permission from Lanes et al. [8].

any drug reaction and gastrointestinal drug reactions respectively).

When univariate Poisson regression was used to determine the association between continuous variables (health resource utilization), it was observed that patients who were switched to COX-2-specific inhibitors consumed significantly more health-care resources prior to therapy than those who continued taking non-selective NSAIDs [10]. Among the continuous variables, the best predictor of a switch to a COX-2-specific inhibitor was gastrointestinal diagnostic tests, with a 6-month incidence rate ratio of 1.81 (95% CI 1.51–2.16), but increased hospitalizations, specialist visits and diagnostic procedures were also associated with the likelihood of a switch. Although a limitation of this study was its reliance on patient self-reporting and the use of questionnaires rather than medical records, it clearly highlights the potential for introducing channelling bias when assessing treatment effects in observational studies of COX-2-specific inhibitors.

Another recently published study evaluated three patient cohorts—non-selective NSAID users, acetylsalicylic users and COX-2-specific inhibitor users—by searching a medical records database for 1 yr prior to the index prescription date to identify determinants of COX-2-specific inhibitor use as opposed to other NSAID agents [28]. As shown in Table 2, predictors of COX-2-specific inhibitor prescription relative to non-specific NSAIDs included variables associated with gastrointestinal risk (age and gastrointestinal history), as well as factors suggesting a more serious disease state (number of physician service claims and use of other medications). These same factors had a negative predictive association for COX-2-specific inhibitors relative to paracetamol, suggesting that patients at risk were also more likely to be prescribed paracetamol. Although this study did not compare paracetamol with non-selective NSAIDs to determine channelling, a study by the same authors reported that patients at high risk of gastrointestinal events were more likely to be prescribed paracetamol than non-selective NSAIDs [6].

Data from a more extensive (22 064 000 patient-years) GPRD-based study identifying patients exposed to older non-selective NSAIDs, meloxicam or COX-2-specific inhibitors show that the last two agents are being channelled to patient populations with similar risk characteristics (Figs 1 and 2) [29]. Multivariate analysis demonstrated that the population channelled to the newer agents was distinctly different from that using the older, non-selective NSAIDs. As shown in Figs 1 and 2, most of the risk factors for upper gastrointestinal haemorrhage were more prevalent among patients prescribed meloxicam and COX-2-specific inhibitors. Patients channelled to either meloxicam or COX-2-specific inhibitors were older, were more likely to have a history of upper gastrointestinal symptoms and a history of use of medications (ulcer healing drugs, corticosteroids and anticoagulants) associated with a risk of upper gastrointestinal complications such as haemorrhage. These patients also were more likely to have arthritis and higher comorbidity, as suggested by a greater number of physician contacts and a higher rate of prescriptions for nitrates and calcium channel blockers.

Using multivariate logistic regression analysis for COX-2-specific inhibitor and non-selective NSAID cohorts identified through managed care claims records, a series of categorical and continuous covariates strongly associated with more severe disease and potential risk of gastrointestinal toxicity were demonstrated to be predictive of physician prescription of COX-2-specific inhibitors (Pettitt D, Singh G, Schwartz JS and Goldstein JL, submitted for publication). These covariates included greater comorbidity and higher chronic disease score, greater gastrointestinal health resource...
utilization (hospitalizations, use of gastroprotective agents), higher medical charges in the preceding 6 months, and a history of multiple NSAID use or multiple switching of NSAIDs, with the likelihood of COX-2-specific inhibitor use increasing as the number of prior NSAID switches increased.

Evaluation and interpretation of outcomes

The above studies demonstrate that patients with greater disease severity, more comorbid conditions and a higher prevalence of gastrointestinal risk factors are preferentially prescribed meloxicam and COX-2-specific inhibitors. Indeed, such channelling is appropriate to the degree that COX-2-specific inhibitors are as effective as non-selective NSAIDs but safer, with fewer gastrointestinal side-effects and complications, and is consistent with current practice guidelines [26, 27].

Such channelling effects confound the ability to determine the safety and effectiveness of COX-2-specific inhibitors in a naturalistic setting. Thus, observational data, such as regulatory postmarketing surveillance registries and reporting systems and managed care databases, must be adjusted for selection bias resulting from differing risk profiles in order to obtain valid estimates of drug safety, effectiveness, resource use and costs, and cost-effectiveness.

Propensity scores represent the probability of being prescribed one therapy rather than another conditional upon all the identified covariates. Propensity scores are constructed by combining individual covariates and risk factors into a single risk variable and are useful when there is a need for adjustment for differences in multiple baseline characteristics [30]. The propensity score distributions obtained in the GPRD study for meloxicam and COX-2-specific inhibitors compared with non-selective NSAIDs confirmed that the multivariate risk profiles of the two groups were different [29]. Figure 3 shows the results of stratification using both propensity scores and individual risk factors, and demonstrates that there was little risk reduction with meloxicam relative to other NSAIDs (Fig. 3A). In contrast, the use of COX-2-specific inhibitors results in a 64% reduction in gastrointestinal adverse event risk ($P < 0.05$), in spite of the higher baseline risk resulting from channelling (Fig. 3B).

CCB = calcium channel blocker; UHD = ulcer healing drug; PPI = proton pump inhibitor; $H_2A$ = histamine receptor antagonist; Hx = history.

**Fig. 1.** Channelling bias for meloxicam and risk factors for upper gastrointestinal haemorrhage, adjusted using analysis of covariance. The length of the bars is proportional to the extent to which channelling occurred for each factor, and the width is proportional to the log of the relative risks for upper gastrointestinal haemorrhage for each factor.
Factors and stratified by both history of gastrointestinal ulcer and ulcer-healing drug exposure (Table 3). All these studies are subject to similar limitations of unrecorded risks, such as incomplete medical history information, which may also bias these results. However, the consistency of evidence suggests that channeling of meloxicam and COX-2-specific inhibitors is common and significant. When adjusted for such channeling, COX-2-specific inhibitors are associated with a significantly reduced risk of adverse gastrointestinal events. Failure to adjust for such channeling will underestimate the safety benefits of COX-2-specific inhibitors (and the resulting reductions in resource use and costs of care). In contrast, in the one study that reported this, meloxicam was not associated with a reduced risk of gastrointestinal events relative to non-selective NSAIDs. Thus, adjustment for channeling bias is required when interpreting observational drug databases, such as regulatory postmarketing surveillance registries and reporting systems, and managed care databases.

Conclusions
Channelling potentially represents a methodological impediment to the accurate characterization and comparison of toxicity, effectiveness, costs of care and cost-effectiveness among drugs in observational studies. The results reviewed here confirm the presence of channeling among users of meloxicam and COX-2-specific inhibitors, these drugs being preferentially prescribed for patients at increased baseline risk of gastrointestinal adverse events compared with patients being prescribed non-selective NSAIDs. In the studies reported here, adjusting for channeling suggests that meloxicam has a relative risk of upper gastrointestinal haemorrhage similar to that of non-selective NSAIDs. In contrast, the use of COX-2-specific inhibitors appears to result in a significant reduction in the risk of clinically important upper gastrointestinal events, even in patients at risk of these events. Adjusting for channeling, either by covariate analysis or propensity scoring, is required for the valid assessment of clinically relevant outcomes in these situations.

Note added after submission
A recently published study further supports the data and conclusions presented here. In a comparison between celecoxib and meloxicam of the incidence of gastrointestinal events using prescription-event monitoring,
a greater proportion of high-risk patients were channelled to celecoxib, especially those patients with a prior history of upper gastrointestinal events (54.7 vs 29.2%). Additionally, when the crude rate ratios, which did not show a difference in incidence rates between the drugs, were adjusted for risk factors, the rate ratios showed a relative reduction by celecoxib in symptomatic upper gastrointestinal events (0.77, 95% CI 0.69–0.85) and upper gastrointestinal complications (0.56, 95% CI 0.32–0.96) compared with meloxicam [31].

**Fig. 3.** Relative risk of upper gastrointestinal haemorrhage relative to non-selective NSAIDs after adjusting for channelling and stratified by propensity scores. (A) Meloxicam. (B) COX-2-specific inhibitors. Relative risk of non-selective NSAIDs was taken to be 1.0; adjustment for individual risk factors included all risk factors subject to channelling towards meloxicam and COX-2-specific inhibitors, as shown in Figs 1 and 2.

**Table 3.** Risk of upper gastrointestinal perforation, ulcers or bleeding stratified by ulcer history, NSAID use and ulcer-healing drug exposure, and adjusted for channelling on the variables of age, gender, history of gastrointestinal physician encounters, comorbidity, and corticosteroid and anticoagulant use

<table>
<thead>
<tr>
<th>History of gastrointestinal ulcer</th>
<th>Ulcer-healing drug exposure</th>
<th>Drug exposure</th>
<th>Incidence rate per 100 patient-years (95% CI)</th>
<th>Adjusted relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>NSAID</td>
<td>2.19 (1.88–2.54)</td>
<td>1.00 (0.99–1.01)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>COX-2</td>
<td>3.92 (3.31–4.62)</td>
<td>0.44 (0.33–0.60)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>NSAID</td>
<td>7.09 (4.92–12.45)</td>
<td>1.00 (0.99–1.01)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>COX-2</td>
<td>4.76 (2.56–8.48)</td>
<td>0.64 (0.27–1.47)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>NSAID</td>
<td>13.73 (9.33–20.17)</td>
<td>1.00 (0.99–1.01)</td>
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<tr>
<td></td>
<td>Yes</td>
<td>COX-2</td>
<td>5.67 (2.84–11.34)</td>
<td>0.42 (0.14–1.17)</td>
</tr>
</tbody>
</table>

Data are from a managed care population.
These studies serve as examples of observed channeling bias and highlight the need for adjusting for channeling in order to provide a valid assessment of relevant outcomes for drugs likely to be preferentially prescribed to specific populations.

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