The road to consensus: considerations for the safe use and prescribing of COX-2-specific inhibitors

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TO THE EDITOR: Regarding the position statement about COX-2 inhibitors, we agree that openness about all potential conflicts of interest is the least we should expect from guideline developers, but this is not enough.[1] Fifteen (65%) of the 23 members of the Australian COX-2 Specific Inhibitor Prescribing Group (including all eight of the rheumatologists involved) declared current financial links with Pfizer and Merck, Sharp and Dohme, the two drug companies marketing COX-2 inhibitors in Australia.[2] The Prescribing Group can be viewed at best as a tight collaboration between some healthcare professionals and drug companies. At worst the statement published in the Journal can be seen as the "happy end" of a successful marketing campaign, which began some years ago with the enrolment of the most influential Australian rheumatologists to the advisory boards of the drug companies.[3]

Members of the group disregarded the "industry" bias on the basis that "some form of bias is the inevitable consequence of knowledge and involvement". However, numerous studies have shown that industry-sponsored drug information is characterised by an overemphasis on the benefits of drugs and a minimisation of the risks.[4]

Full trial results with celecoxib are available on the United States Food and Drug Administration website and had been consulted by the Prescribing Group.[5] These data show that celecoxib is not better than diclofenac ($P = 0.414$) or ibuprofen ($P = 0.64$) in terms of ulcer complications, the prespecified primary outcome of the trials. There was also no significant difference between celecoxib and diclofenac for the combined outcome of complicated and benign ulcers ($P = 0.296$).

It has been shown that the results previously presented in *JAMA* for celecoxib were flawed and had been manipulated.[6,7] The wide distribution of the *JAMA* article by the drug company as part of intensive marketing campaigns contributed to huge sales for celecoxib. Sales of celecoxib between August 2000 and June 2002 cost Australian taxpayers more than $288m through the Pharmaceutical Benefits Scheme (PBS), more than five times the cost for all other NSAIDs during the same time frame.[8] There is some evidence to show that the PBS blow-out observed after the launch of COX-2 inhibitors is at least partly due to their use outside their approved indications (osteoarthritis and rheumatoid arthritis).[9] The Prescribing Group did not give any indication for the use of COX-2 inhibitors and did not consider the cost issue, arguing that "there is little pertinent cost-effectiveness literature in the public domain".

The position statement appeared to be an evidence-based review of the safety of COX-2 inhibitors involving eminent rheumatologists, active members of the PHARM committee and National Prescribing Service staff. We believe, however, that the statement promotes misinformation from the pharmaceutical industry. We invite readers to look at sources of drug information that are truly independent of drug companies, such as the *Australian Medicines Handbook* (www.amh.net.au), *Australian Prescriber* (www.australianprescriber.com) and *Therapeutic Guidelines* (www.tg.com.au).

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TO THE EDITOR: We agree that the "what", "how" and "who" of guideline development all deserve equal, explicit and systematic attention.[1]

A fundamental task for architects of consensus guidelines is to get the "what" right first. Agreement about the importance of the topic and the objective of the exercise is crucial to its ultimate success. Edmonds and colleagues state that "formulation of precise indications for the use of NSAIDs [non-steroidal anti-inflammatory drugs] rather than CSIs [COX-2-specific inhibitors] (or vice versa) would generate interminable controversy".[2] The foundation for this assertion is not clear and the authors do not present data about the level of agreement on this by the experts initially assembled.

The NSW Therapeutic Assessment Group (NSW TAG) believes that providing timely, independent and evidence-based guidance to clinicians about the place in therapy for such new drugs is extremely important. The membership of NSW TAG identified this as a priority soon after the marketing of celecoxib in Australia, and agreed unanimously to develop evidence-based recommendations on indications for the use of this drug. Our consensus development process involved a wide variety of experts in therapeutics and was successfully completed without generating "interminable controversy".[3] We wonder whether our different experiences may be partly related to a difference in the initial level of consensus on the importance of the chosen topic.

The "how" of the process followed by Edmonds et al is not described in sufficient detail to enable systematic evaluation of its validity. How systematic was the search for

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There should be no more than 5 references. The reference list should not include anything that has not been published or accepted for publication. Reference details must be complete, including: names and initials for up to 4 authors, or 3 authors et al if there are more than 4 (see mja.com.au/public/information/uniform.html#refs for how to cite references other than journal articles).

evidence or the process for inclusion or exclusion of studies? What was the level of evidence on which final recommendations were based?

Importantly, high quality guideline development processes require a "balance of healthcare disciplines in the guideline development group".[4] Getting the right "who" is a prerequisite for getting the "how" right. Edmonds et al state that membership was arbitrary, with predominant representation from rheumatologists and relevant pharmaceutical companies. Given the problems associated with physician–industry interactions,[5] it has been suggested that authors with significant conflicts of interest should be excluded from participating in guideline development.[6] The rationale for arbitrary selection of members and inclusion of members from the pharmaceutical industry is not explicitly stated.

These issues may have contributed to the difficulties the group experienced, and may detract from the validity of their recommendations. Future trips down the "road to consensus" should run more smoothly after careful consideration of the "what", "how" and "who" at the outset — no "ifs and buts" about it.

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IN REPLY: Both Vitry and Hurley and Gazarian and Kaye would have had our consensus group address different or broader issues than safe prescribing and use of COX-2-specific inhibitors (CSIs). Indications for use, leakage and cost effectiveness are important issues, but our goal, clearly stated in our article,[1] was different and, we believe, important: if a clinician has decided to use a CSI, what considerations are needed to prescribe the drug safely? Disagreements in reaching consensus were not, as suggested by Gazarian and Kaye, due to confusion about the aim of the exercise, but to differences in interpreting evidence and expressing conclusions in simple and direct terms. It would have been easy to avoid these problems by limiting participants to a small group of like-minded colleagues, but we chose to involve a broad range of people who may represent a more realistic spectrum of attitudes and approaches.

We find Vitry and Hurley gratuitously pejorative in their description of the participants in this exercise. With the exception of two rheumatologists with epidemiological expertise (who did not sign off on the position statement[2]), all the rheumatologists involved were members of one or both advisory boards. They were a relevant group precisely because this role should involve a responsibility to provide sound advice to the industry paying for it, and equally to the profession, both in the interests of good patient care. "Current financial links" is not the way such a consultancy is usually described. They call the exercise "at best a tight collaboration between some healthcare professionals and drug companies" and "at worst … as the 'happy end' of a successful marketing campaign". Given that one of the two pharmaceutical companies involved declined to sign off on the statement, as did two rheumatologists who were advisory board members for the other company, this is a curious outcome of "tight collaboration".

With respect to the relative safety of selective versus non-selective COX inhibitors, our considerations were based on data available from peer-reviewed studies published to the end of May 2001 and available on the United States Food and Drug Administration website, as indicated in the position statement[2] and the accompanying article.[1] A number of the references quoted by Vitry and Hurley became available after May 2001. Renewed scrutiny and analysis of existing datasets is interesting, but the results are best used to decide whether unresolved issues are of sufficient importance to justify further studies, and how these could be designed to deliver evidence that will convince us all, one way or the other. We made the point at the conclusion of the position statement that this is an evolving field and that conclusions may well change with emerging data.[3]

We consider the statements made in the considerations article[1] represent a fair expression of our assessment of the data available to us. Not everyone in the group agreed. In publishing the position statement with the list of participants who endorsed it and those who did not, and by adding an article on the process we adopted, we hoped to highlight the fact that there are controversies and uncertainties about aspects of CSIs which require careful consideration in clinical use and further high quality data to resolve currently unresolvable issues.

1. Edmonds JP, Day RO, Bertouch JW. The road to consensus: considerations for the safe use and prescribing of COX-2-specific inhibitors. *Med J Aust* 2002; 176: 332-334. http://www.mja.com.au/public/issues/176_07_010402/edm10003_fm.html
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Guideline-discordant care in acute myocardial infarction: predictors and outcomes

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TO THE EDITOR: Advocating implementation of evidence-based clinical practice guidelines is one aspect of the current drive to provide quality healthcare across different centres.

Quality theory demands that outcomes are continuously sought and that practices are modified accordingly — the "quality loop".

Therefore, Scott and Harper are to be applauded for their pursuit of improved outcomes, not just improved processes, in studying guideline-discordant care in acute myocardial infarction.[1] I believe that this type of study, which objectively demonstrates the role of practice guidelines in "real world" practice, is very important.

However, as a geriatrician, my patient population is unlikely to intersect with populations enrolled in large cardiology trials (eg, those for thrombolysis in myocardial infarction).[2,3] Comorbidities, such as renal impairment, cognitive impairment and poor functional status at baseline, were not explicit exclusion criteria, but, when present, would have reduced an individual's chance of being enrolled.

These types of comorbidities are likely to be associated with a reluctance on the part of patients and physicians to pursue life-prolonging interventions. They are also likely to be associated with poorer outcomes, whatever the intervention. Therefore, I believe that these non-cardiac comorbidities are potential confounders for study designs, such as that of Scott and Harper.[1]