Author's response to reviews

Title: Cause for concern in the use of non-steroidal anti-inflammatory medications in the community - a population-based study.

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Author's response to reviews: see over
Response to Reviewers: Cause for concern in the use of non-steroidal anti-inflammatory medications in the community - a population-based study

Reviewer's report

Title: Cause for concern in the use of non-steroidal anti-inflammatory medications in the community - a population-based study.
Version: 1 Date: 25 February 2011
Reviewer: Gillian Caughey

Reviewer's report:
This is an interesting paper that describes the prevalence of NSAID use and their use in chronic conditions where their use is contraindicated or in groups of people at high-risk of adverse events, in a population based sample.

Abstract
Background: I would like to see a sentence of background into the context of the study and then the aims.

Added: Non-steroidal anti-inflammatory (NSAID) medications are a common cause of reported adverse drug side-effects.

Methods: First sentence of methods is not a sentence.

Changed to: Data was analysed from 3,175 adults attending first follow-up in 2004-06 of NWAHS, a longitudinal representative population study.

Data were weighted and then statistical analysis was performed? (as presented in methods sections), present in abstract in this order.

The sentence on data weighting has been moved to before the description of analysis, as suggested.

Simply say that multiple logistic regression was used to examine associations between socio-demographic characteristics and use of NSAIDs.

Change made as suggested.

Results: Report overall prevalence of NSAID use.

Has been added.

Is it 3206 participants or 3175 as reported in methods section (p4) ‘this analysis was conducted in 3175 subjects who provided medication data’

3,175 who provided medication data.

Introduction
A study was published last year (Drugs and Ageing, Pratt N etal) that reported increased risk of hospitalisation with NSAID use in ‘at-risk’ populations (incl diabetes) (P3, 2nd paragraph, 6th line)
The manuscript would be clearer if the authors described the at-risk groups,
chronic conditions or concomitant medicine use where NSAID use is contraindicated and why and referenced accordingly.

The following has been added to the last sentence of the Introduction so readers are clear which conditions are included: “(including co-existing contraindications to NSAID use and chronic conditions (including cardiac / cerebrovascular disease, hypertension, chronic kidney disease, diabetes, and high 10 year-risk for cardiovascular disease)”.

Results

Report the overall prevalence of NSAID use.

This has been added.

Is it possible to give an overall prevalence of those who have contraindications to NSAID use (either conditions, co-prescribed medicines) to give an overall quantification of potential treatment conflicts? ie. Xx% of those taking a NSAID had at-least one contraindication. This would provide an overview of the proportion of those who use a NSAID that are potentially at increased risk of adverse drug events. Obviously there would be some overlap with conditions and medicine use at the individual patient level that may need to be taken into account eg presence of CVD and use of ACE inhib

Of the overall sample, n=1697 (42%) had one or more of the identified chronic conditions where use of NSAIDs is contraindicated or were at high-risk of adverse events (i.e. cardiovascular disease, cerebrovascular disease, chronic kidney disease, hypertension, high-risk for cardiovascular disease). Among the 357 with NSAID use, 246 (69%) 274 (77%) had one or more contraindications, including 141 (75%) who use COX-2 inhibitors, and 109 (62%) of those taking ns-NSAIDs. If anti-reflux medications are included as a relative contra-indication, these numbers rise to 274 (77%) of all NSAID users, with 274 (84%) of COX-2 inhibitor users, and 121 (69%) of those using ns-NSAIDs, with 1819 (45%) of the population with a relative contra-indication.

We have added the following sentence to the 1st paragraph of the Discussion: “Around three-quarters of people using NSAIDs have one or more of cardiovascular disease, hypertension or chronic kidney disease”.

Discussion

Second paragraph, 1st sentence, I think you can be stronger in your language; the study (8) highlights the importance of examining patterns of NSAID use and also outcomes associated with use at a population level.

This sentence has been changed as suggested to read: “Recent evidence ... highlights the importance of examining patterns of NSAID use and also outcomes associated with use at a population level”.

The section from the sentence beginning “Unlike COX-2 inhibitors (2nd para 3rd sentence) up to the sentence “COX-2 inhibitor use was more common in people with
cardiac “is hard to follow. Either re-write or it may be more succinct to say there were clear differences in the trends of use of ns-NSAIDs and COX-2 inhibitors with the socio-demographic characteristics examined.

We agree with this point and have deleted the two sentences referred to and have now used the reviewers wording that “There were clear differences in the trends of use of ns-NSAIDs and COX-2 inhibitors with the socio-demographic characteristics examined.”

P7 1st para line 5 is it possible that clinicians were unaware in some instances of the contra-indications?

We have added the following sentence to the Discussion: “For a variety of reasons clinicians may not be aware of contraindications to NSAID use in individual patients, for example patients may see a number of general practitioners and specialists for their care”.

P8 1st para, the authors suggest potential strategies for patients, do they have any potential solutions to assist prescribers? Particularly with regard to balancing the risk / benefits in those at-risk patients?

This is a very complex subject, and a full discussion merits a paper on its own. At a simplistic level, prescribing software will alert to interactions but clearly this does not fully address the risk-benefit trade-off, particularly where patient utilities or preferences are concerned. To adequately cover this, we would contend requires sophisticated decision-support software which could present individually calculated risks against likely pain benefits.

We have made some additions to discussion to emphasize this point. This one reads:

"Given the scope of the problem identified in our study, efforts to improve the health literacy of the community have the potential to have a substantial impact on the burden-of-illness and costs of NSAIDs. The more widespread use of tools or decision-aids to assist patient decision-making may be a potential solution. However research to assess the impact of sophisticated decision-support software which could present individually calculated risks against likely pain benefits from NSAIDs to patients and doctors is needed."

Conclusion
The first line of the conclusion is somewhat disjointed from the key results of the paper. The conclusion in the abstract is nice

Conclusion from the abstract has been substituted here as the final conclusion.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Reviewer's report
Title: Cause for concern in the use of non-steroidal anti-inflammatory medications in the community - a population-based study.
Version: 1 Date: 22 February 2011
Reviewer: Treasure McGuire

Reviewer's report:
1. Discussion 1st paragraph & Table 2
Narrative states “Over half of people reporting NSAID use had hypertension, mostly uncontrolled” However Table 2 definition is “Hypertension: systolic #140 mm Hg and/or diastolic #90mm Hg or use of anti-hypertensive medication.” As the data in Table 1 does not differentiate between patients with hypertension that is well controlled on antihypertensives and those with hypertension not well controlled on antihypertensives, however can the authors claim “mostly uncontrolled”. Please clarify this point.

We have removed any reference to uncontrolled hypertension in the text and tables. The sentence in the results now reads:
“Among those people using NSAIDs, 61% had hypertension, with 41% reported concurrent use of anti-hypertensive medication (Table 2)”.

The sentence in the Discussion now reads:
“These include over half of people reporting NSAID use with hypertension and nearly one-third of reported users had Stage 3 or higher chronic kidney disease”.

2. Discussion (paragraphs 2 & 4) - Error/lacks clarity in interpretation
Some of the implications of results and concepts introduced to explain the results lack clarity. The authors need to decide whether the implications of key results relate to NSAID prescribers or NSAID users. A major flaw or study limitation was not acknowledged by the authors (and that could have been overcome in a study where patients actually brought in ALL their medication) was that the authors have not differentiated n-NSAID use that was clearly OTC (self directed) vs prescribed or prescriber recommended (even if purchased OTC).

As such, the study implications on the issue of whether clinician knowledge has minimal / no effect on NSAID prescribing can only be really be discussed in the context of COX-2 inhibitors (not n-NSAIDs). The issue of whether consumer knowledge of risk has minimal /no effects on NSAIDs has really not been clarified by these study results as we cannot differentiate the proportion of use that was truly patient initiated/controlled.

We appreciate the point that distinguishing whether NSAID use was prescriber or patient directed has some merit in thinking about this problem. However, we did not separate OTC from prescribed as we consider that determining “fault” by whether NSAID is prescribed or not is framing the issue too narrowly. The implications of the study relate to the therapeutic team, and solutions can only be effectively reached with a partnership approach between patient and clinician. As such, both clinicians and patients will need to become aware of the risks of NSAID use, the frequency of use in the face of relative contra-indications, and work towards concordance of both partners respective positions regarding NSAIDs. If a patient requires analgesia then
possible solutions and risks and benefits need to be communicated in such a way that understanding is achieved. Whist this may sound ideal, emphasising that it is the responsibility of clinicians to explore patient understanding and make people aware of the risks of NSAIDs, and that patient’s also need to take responsibility for understanding their medications. Clinical responsibility also may extend to pharmacists when NSAIDs are purchased OTC from pharmacies.

Nonetheless we recognise readers may wish to see the relevant data on OTC use. The following has been added to the Results:

“Among the 176 people using ns-NSAIDs, naproxen was used by 39.8%, diclofenac by 39.8%, and ibuprofen by 11.9%. Of these, there were 38 who exclusively purchased medication over-the-counter (ibuprofen 31 of 51 users; naproxen 7 of 21), i.e. 21.6% of ns-NSAID users purchased these only over-the-counter”.

The most important message for me from these data is that prescribers (specially wrt COX-2 inhibitors) are considering GIT but not considering or ignoring the cardiovascular & renal risks of these drugs before prescribing these medications. This issue could be further emphasised. However, when the issue is pursued in 4th paragraph of the discussion where increased clinician knowledge has minimal / no effect on NSAID prescribing, the narrative appears to suddenly jump from - the issue of prescriber perceptions of the importance of treatment risks in relation to prescribing to - perceptions of NSAID risks on NSAID use in NSAID users. Unless the authors have valid data to support on the latter issue, it may be better to not confuse these issues in the discussion.

The relevant sentence in the discussion has been added to and reads:

“COX-2 inhibitors can only be obtained by prescription, while some ns-NSAIDs can be purchased over-the-counter without a prescription (albeit at lower doses than possible via prescription), although this was a minority of users did this exclusively in our study”.

Further down in this paragraph, we have also added to the following sentence:

“As COX-2 inhibitors are a prescription only medication, and most ns-NSAID use was via prescription, our results suggest that the risks of COX-2 inhibitors for cardiac disease, hypertension or renal disease are regarded as acceptable or are ignored by many clinicians”.

In the 4th paragraph we have added the following sentence to signal patient knowledge and behaviour is relevant to NSAID use:

“Patient attitudes and knowledge as well as willingness to ask questions of clinicians will have impact on NSAID use”.

Minor Essential Revisions
The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

3. In Statistical analysis
The cohort attended follow-up in 2004-2006. However, data were weighted to the 1999 the 1999 Estimated Residential Population and 2001 Census for South Australia by region, age group, gender, and probability of selection in the household, to
provide population representative estimates. Has there been are more recent census ABS report for comparison than the 2001 report for Adelaide below? Australian Bureau of Statistics. 2001 Census Basic Community Profile and Snapshot: 405 Adelaide (Statistical Division), Australia, South Australia. Australian Bureau of Statistics: Canberra, 2001.

This was an inadvertent error in referencing- data were weighted to the Stage 2 data was reweighted using the 2004 Estimated Resident Population, incorporating participation in the three components, whilst retaining the original weight in the calculation. (see Reference ???, Grant et al, Int J Epidemiol 2009). The correct reference has been added, i.e. Australian Bureau of Statistics. Population by Age and Sex, South Australia, June 2004. Canberra: ABS, 2005.

4. In Results 2nd paragraph
“Over 30% of people taking NSAIDs had Stage 3 or higher chronic kidney disease.” This sentence lacks clarity. What percentage over 30% - 40%, 70% etc??? While technically correct, the statistic was 30.8%. It would be clear to say 31% or approximately a third, so as not to artificially imply a higher percentage. I would be even more concerned if e.g. 75% of patients with significant renal impairment were taking NSAIDs.

This has been changed to “Thirty-one percent …”

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

5. Discussion, 2nd paragraph line 5
Philosophical point only- As is appropriate, most results included in the discussion go onto to have a follow-on sentence “This suggests …” However there is no discussion point in relation to “Unlike COX-2 inhibitors, there was no association of increasing use of ns-NSAIDs with advancing age. Also there was no association with education level and COX-2 use, as distinct from ns-NSAIDs where a tertiary education was associated with less use of ns-NSAIDs.” It would be more appropriate for this sentence to move to the results section.

As per the suggestion of the other reviewer, these sentences have been deleted and replaced with, “There were clear differences in the trends of use of ns-NSAIDs and COX-2 inhibitors with the socio-demographic characteristics examined.”

Overall comments:
# The question posed by the authors is well defined – i.e. what is the prevalence of NSAID use, any presence of chronic conditions and any contraindications to NSAID use in a representative population sample of Australian adults?
# The methods are clearly described
  o The robustness if the NWAHS as a representative biomedical population is justified.
  o Risk factors and chronic diseases of interest are defined.
# Data is basically sound
  o While the demographic profile of the cohort participants gathered in 2004-06 are well described (& previously published), data has been weighted using 2001 census data.
Appropriate comparative data were gathered - clinical measurements, information on health behaviours, health service utilisation, doctor diagnosed comorbidities, symptoms of joint pain & all medication.

Statistical analysis is appropriate for the data gathered and associations described.

The manuscript does appear to adhere to relevant standards for reporting and data deposition.

All results are tabulated.

While the Discussion is generally well balanced, it does over extrapolate findings in relation to consideration of risk when prescribing to all NSAIDs, when this can only be justified from data presented to COX-2 inhibitors (as n-NSAID use has not been sub-classified by the proportion of used that was OTC/self managed vs prescribed use). Similarly, the implications of findings in relation to consideration of risk to NSAID users cannot really be substantiated without this sub-categorisation.

While most limitations of the work are clearly stated, the lack of sub-classification of n-NSAID use by was prescribed vs self-managed is a clear limitation to being able to clearly extrapolate study results (as described above & below).

The authors have clearly acknowledged key published works upon which they built on. I cannot comment on unpublished works in the field.

The title and abstract accurately convey what has been found.

The writing is acceptable.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** I declare that I have no competing interests