Author's response to reviews

Title: Corticosteroid prescribing in palliative care settings: a retrospective analysis in New Zealand

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Author's response to reviews: see over
Corticosteroid prescribing in palliative care settings: a retrospective analysis in New Zealand

Response to Reviewers

We wish to thank the reviewers for the helpful and constructive comments concerning this submission. As a result of the reviewers’ comments we have substantially revised the manuscript, particularly the methods and results sections and we believe that the revised version is a much better manuscript. We have addressed all of the issues raised and are pleased to provide the following point-by-point responses to the reviewers’ comments.

Reviewer 1 comments

I read this paper with interest - the use of corticosteroids in palliative care is an important area. I think this is a useful paper, but have the following comments to make before a final decision on publication can be made:

Response: Thank you for these helpful comments; we have made all of the necessary revisions.

Major compulsory revisions:

P7. Give more information of how you sampled the 260 of 768 patients were included in the study.
Response: The methods section has been re-written, with a full description of how the 260 patients were sampled (page 8, sample size).

P8. No information is given concerning the patient sample - cancer / non-cancer, survival times, age + sex. Did all die in hospice or were some discharged to community and lost to follow-up?
Response: Additional comments on recording are provided in the methods section (pages 8,9, data collection), including a table describing the database (Table 2, page 22) and a table has been added on patient demographics (Table 5; page 25), with additional commentary in the results section (page 10).

One weakness of the study is that the only data available was that recorded in records - were some of the differences found related to different recording practices between hospices, or genuinely due to different prescribing practices? This needs to be addressed further in the discussion.
Response: A fuller description of data collection is provided in the methods section (pages 8,9, data collection), including a table describing the database (Table 2, page 22), and the issue of different recording practices is discussed more fully in the discussion (pages 15,16).

Minor essential revisions

P5. Expand on the impact of these drug interactions on drug effects, and add zopiclone as mentioned later.
Response: On reflection, we don’t feel the information on drug interactions adds much to the manuscript, so we have removed this section.

P7. Insert 95% confidence interval of 2.8%.
Response: Corrected
Only inpatient notes were accessed - did the data therefore only relate to periods spent as an inpatient? If so, that limits the data considerably.

**Response:** This limitation is acknowledged and a fuller description of data collection is given in the methods (pages 8,9, data collection) and further commentary is provided in the discussion (pages 15,16).

Please report all statistical analyses undertaken to permit assessment of potential for Type 1 errors.

**Response:** A fuller description of data analysis is provided in the methods section (page 9, data analysis).

Adverse effects - how were these defined and documented? No data is given concerning these at all.

**Response:** A definition of adverse effects is provided in the methods (page 9, data collection) and further commentary is provided in the results (page 12) and discussion (page 15).

No data given re dose ranges, just a statement that they were similar.

**Response:** A table has been added to show dose ranges (Table 7, page 27) and there is further commentary in the results (page 11) and discussion (page 14).

Suggest you describe the hospice sampling as purposive. Good to see the pilot data were used to generate sample size calculations.

**Response:** 'Purposive' has been added (page 7, Study sites). Thank you for the comment about pilot data.

I am surprised by the comment that steroids are low risk for causing GI side effects / haemorrhage in this population in the absence of NSAIDs. What is the evidence for this assertion?

**Response:** The section on drug interactions has been removed.

It is stated that the results are mirrored in the international literature - so what is new about this paper to convince an editor that it should be published?

**Response:** Statements have been added to the discussion and conclusion (Pages 13, 16) that this large, multi-site study confirms and adds weight to the findings in the international literature concerning the prescribing of corticosteroids in palliative care, and highlights some important considerations such as abrupt stopping in this setting.

**Reviewer 2 Comments**

General impression:

This article reports the findings of a retrospective review of corticosteroid prescribing across 6 hospices in New Zealand. This appears to be the first review of its kind in New Zealand, though numerous reports of corticosteroid prescribing practices in the palliative care setting have been published from other countries, including a UK prospective study by Hardy et al. (2001), a Canadian retrospective analysis by Pikey et al (2008) and a large cross-sectional Swedish survey of 30 hospices by Lundstrom et al (2008). To my knowledge, this appears to be the first multi-site retrospective analysis to be reported and it is possibly the largest of its kind to date. For this reason, the study merits some recognition. While the study does not appear to add new information to the literature, it does confirm previous literature findings and its large sample size lends further weight to
these findings. My overall impression is that this is a large-scale piece of work, which has been conducted rigorously within the constraints of a retrospective study design. My main concern is that the quality of the reporting within this article does not adequately reflect the rigor with which I suspect the study has been conducted. I would, therefore, like to suggest the following revisions in order to improve the quality of the paper.

Response: Thank you for these helpful and perceptive comments; we agree that the first draft of the paper did not do justice to the rigour with which the study was conducted and we did not present the findings in the best light. The methods and results sections have been substantially re-written to incorporate your suggestions and those of the other reviewers. We have incorporated your comments about the wider significance of the study in the discussion.

Major compulsory revisions:

1) Recommendations relating to methodological reporting:
   • The method of identifying patient records for corticosteroid prescribing and thereby including records for review is not clearly described. In practice, some patients are on corticosteroids prior to admission and others are commenced on corticosteroids during admission. It is necessary to define which of these cohorts is being studied or whether both are included. It is difficult to interpret the authors’ reported frequency of corticosteroid prescribing without this information. Related to this, no distinction is made between number of inpatient admissions and number of patients. Presumably, some patients had more than one admission. Therefore, a statement indicating that x number of patients had y number of admissions in 2007 would be helpful in order to determine the denominator.
   Response: A fuller description of both the cohort (sample) and data collection is provided in the methods section (pages 8, 9, sample size, data collection), including a table describing the database (Table 2, page 22). In addition, a table has been added (Table 4, page 24) to show the determination of proportions of patients receiving corticosteroids in the sample hospices. While there were multiple re-admissions, most patients continued a prior course of corticosteroids when re-admitted and this was recorded as a continuation event. A new course of corticosteroids on re-admission was recorded as a new event. As described in the results (page 10), there were 312 new prescribing events recorded for the sample of 260 patients.
   • I would recommend that the first paragraph of the ‘statistical analysis’ section be recorded as a ‘data collection’ section as the contents of this paragraph do not corticosteroids during admission. Within this ‘data collection’ section, more detail about the exact parameters of corticosteroid prescribing selected for evaluation should be included. The authors include some further information about the selected parameters in the results section but, arguably, these parameters should all be defined in the ‘data collection’ section. In particular:
     o What information about the dose was recorded? E.g. starting dose or average dose over time or cumulative dose?
   Response: The first section of statistical analysis has been re-named data collection (page 8) and the latter section re-named as data analysis (page 9). The data collection section (page 8) includes a table describing the database (Table 2, page 22) that describes the various parameters recorded. With respect to dose, a table has been added to show dose ranges and median start and finish doses (Table 7, page 27) and there is further commentary in the results (page 11) and discussion (page 14). We tried to record cumulative dose but this proved very difficult due to gaps in the patient records.
   o How was an abrupt withdrawal defined?
Response: A definition of abrupt stopping is provided in the methods (page 9, data collection) and further commentary is provided in the results (page 12) and discussion (page 14). Table 9, page 29 lists further details of abrupt stopping.

- How was a 'drug review' defined?
  \textbf{Response:} A definition of drug review is provided in the methods (page 9, data collection) and further commentary is provided in the results (page 12) and discussion (page 15). Table 10, page 30 lists further details of abrupt stopping.

- How was an 'adverse effect' defined?
  \textbf{Response:} A definition of adverse effects is provided in the methods (page 9, data collection) and further commentary is provided in the results (page 12) and discussion (page 15)

- What indications were recorded and how were they defined? (perhaps refer to table 1 at this point).
  \textbf{Response:} A full description of indications and how they were recorded is provided in the methods section (page 9, data collection), including a table describing the indications (Table 3, page 23). Table 6, page 26 in the results section describes corticosteroid prescribing by indication.

- Were certain things not recorded due to complexity e.g. preferred tapering schedule?
  \textbf{Response:} Apart from one hospice that had a separate corticosteroid prescribing chart, details of tapering schedules were recorded in the patient notes and these proved very difficult to accurately track for the majority of patients.

2) Recommendations relating to results reporting:

- The authors confine the results reporting to corticosteroid prescribing parameters and do not provide demographic or clinical data. This does not allow the results to be contextualised and, thus, restricts the degree to which the reader can assess the generalisability of the results. Given the heterogeneity of the palliative care population, I consider this to be a significant omission and would recommend that a description or a table of demographic and clinical details be provided. Regarding clinical details, in particular, it would be interesting to know the ratio of cancer to non-cancer patients in the population, review to know the primary tumour site and to have some indication of prognosis (e.g. were patients admitted for terminal or symptom-control, how many patients died during admission and how many were discharged, what was the median admission length etc?)
  \textbf{Response:} Additional comments on recording are provided in the methods section (pages 8,9, data collection), including a table describing the database (Table 2, page 22) and a table has been added on patient demographics (Table 5; page 25), with additional commentary in the results section (page 10). 95% of patients in this study had a cancer diagnosis and the four most common types are reported in the results section (page 10).

- The authors have omitted to report some data which I feel would actually be of interest to palliative care practitioners and which, arguably, are essential to the report if the primary objective of reporting prescribing patterns is to be fulfilled. For example, what was the most common start-dose for dexamethasone? What was the dose-range used (referred to in the article but not actually stated)? What was the median duration of corticosteroid use (range provided rather than median)? What was the cumulative dose per patient (if this was possible to record)? These parameters are most related to corticosteroid toxicity and, therefore, they are, arguably, the most important parameters to include in a review of prescribing patterns. While it is interesting to compare prescribing practices between
hospices (as this highlights the need for consensus guidelines, at minimum), it is preferable to report essential descriptive data in advance of comparative analysis reports.

Response: We fully accept that the emphasis on prescribing practices between hospices in the first draft was incorrect. Additional tables relating to corticosteroid dosing (Table 7, page 27) and course duration (Table 8, page 28) have been added and there is commentary on these in the results (pages 11 and 12) and discussion (page 14). As discussed previously, it was not possible to record cumulative dose accurately.

Discretionary revisions:

• The method of selecting 260 inpatient records from a total of 768 inpatient records for further review is not particularly clear. The authors explain that 1 in 3 were selected sequentially but it is not clear to me what this means. Does this mean that every third record from a list of all records was selected for review? Alternatively, was a random sequence generated to randomly select records?

Response: The methods section has been re-written, with a full description of how the 260 patients were sampled (page 8, sample size).

• Though I understand what the authors mean, I do not fully agree with the terminology used in the sentence describing the study aim in the background of the abstract section. Arguably, there is no consensus on 'international best practice' and I would suggest substituting this phrase with 'international practice' or 'international experience'. To compare the results to 'international best practice', a clear description of this practice would need to be provided; this, however, is not possible.

Response: This is a very good point and we have changed the terminology to 'international experience'.

• The authors provide a thorough review of the literature in the background. I feel that it would be helpful if the authors acknowledged the differences in terminology used across the literature with respect to both palliative care patients (some corticosteroid studies relate to 'advanced cancer' or 'pre-terminal cancer' patients) and with respect to the categorisation of corticosteroid indications. This is a limitation to the interpretation of the literature. The authors do define 'non-specific' in the second paragraph of the background section but it might be better to define this when the term is first used in the first paragraph. In addition, definitions for 'non-specific' appear to be variable across the literature and it would be helpful if the authors acknowledged this when providing their definition. Personally, I would limit 'non-specific' to cachexia-anorexia-related symptoms (anorexia, fatigue, weight loss) but, clearly, other studies have included nausea, pain and breathlessness within this category (as the authors have cited). Additionally, the authors provide 'bowel obstruction' as an example of 'soft tissue infiltration' in the first paragraph of the background section, and I am not sure that this is a very sensible example (as bowel obstruction can be caused by a range of pathologies). I would suggest reviewing this so that it does not detract from the article.

Response: We fully accept that there are different interpretations of the term ‘non-specific’ indications and have added a paragraph to this effect in the background (page 4). Additionally, we have further highlighted this issue in the methods (page 9, data collection), results (page 11) and discussion (pages 13 and 14) so as to make it clear that the proportion of ‘non-specific’ prescribing is open to interpretation according to the definition used.

• In the methods section, again, I would suggest that the definition for ‘non-specific’ be clearly defined. I notice that ‘non-specific’ and ‘other’ are separate categories in table 1 but paragraph 4 of the discussion sections suggests that these categories were amalgamated (‘non-specific indications in this study was the residual category’) for the analysis. If this is
the case, this needs to be explained in the methods section (not the discussion). The definition for ‘non-specific’ needs to be consistent throughout the text, whilst acknowledging that variable definitions exist.

Response: As discussed in the previous response, this has been addressed in the methods section (page 9, data collection). In addition we make it quite clear that ‘non-specific’ and ‘not clear/other’ indications are quite separate and the latter was only used when there was an indication that could not be otherwise classified, or where there was insufficient information concerning the indication in the patient notes.

- The finding that 49% of patients had their steroids stopped abruptly is perhaps the most interesting finding for me. It would be interested to know what percentage of these patients had their steroids stopped because they were no longer able to swallow; this is considered to be acceptable practice, in my experience, though it is clinically and ethically questionable. Steroid withdrawal in the last days of life has already been reviewed in a UK palliative care setting (Gannon et al. 2002) and abrupt withdrawal when the patient was unable to swallow occurred in 98% of cases. There is very limited further literature on this, however, and I would suggest highlighting this more as one of your main findings.

Response: We agree that the findings re ‘stopping abruptly’ are interesting and should be highlighted. An additional table has been added (Table 9, page 29) with further details. In addition there is commentary on this issue in the results (page 12), discussion (page 14), conclusion (page 15) and abstract (page 2).

Reviewer 3 Comments

This is a large case-note review considering an important topic. Corticosteroids are widely prescribed in palliative care, without a clear evidence base to support this practice. However, I am concerned that this review does not advance current knowledge in this field to warrant publication in its current form. The main finding is that approximately two third of patients in these hospices are prescribed steroids, but it is clear form the first paragraph in the discussion that this has already been established.

Response: Thank you for these helpful comments; we agree that the first draft of the paper did not present the findings in the best light and we highlighted differences between the hospices at the expense of more useful and interesting data. The methods and results sections have been substantially re-written to incorporate your suggestions and those of the other reviewers and we believe that the paper is now far more informative. Additional tables relating to corticosteroid dosing (Table 7, page 27) and course duration (Table 8, page 28) have been added and there is commentary on these in the results (pages 11 and 12) and discussion (page 14).

Other findings are not of particular interest because of the inherent limitations of the study. For example:

1) The results relating to the indication for prescription are limited by the fact the categories are not mutually exclusive (eg. soft tissue infiltration can also include cerebral tumours, capsular stretching by liver metastases and so on, eg. use for pain is defined as a non-specific indication and yet relates to most of the other categories too).

Response: We fully accept that there are different interpretations of the term ‘non-specific’ indications and have added a paragraph to this effect in the background (page 4). Additionally, we have further highlighted this issue in the methods (page 9, data collection), results (page 11) and discussion (pages 13 and 14) so as to make it clear that the proportion of ‘non-specific’ prescribing is open to interpretation according to the definition used. The reason that we used a ‘broad’ definition of
non-specific was to allow useful comparisons with other published studies where this definition is used.

2) The data relating to steroid stopping does not define 'stopping abruptly', and does not apparently consider whether the stopping related to the patient dying or being moribund (it is not usual practice to convert to the parenteral route in the last days of life).

Response: An additional table has been added (Table 9, page 29) with further details of those patients whose corticosteroids were stopped abruptly. In addition there is commentary on this issue in the results (page 12), discussion (page 14), conclusion (page 15) and abstract (page 2). We argue that while it may be usual practice to not switch to the parenteral route when a patient cannot swallow or is moribund in the last days of life, this may not be ethically or clinically sound and should be further debated.

3) Recording of adverse effects is, as correctly stated in the results, impossible to interpret because of poor documentation.

Response: This is a good point; we have acknowledged this in both the results (page 12) and discussion (page 15); our commentary now extends to a general comment about the need for better recording practices.

4) Data was collected four years ago, and I agree with the authors' concern that practice may have changed since then.

Response: We acknowledge this point in the limitations of the study. We also comment that the actual data collection occurred in 2009 (at which time all patients had died). The data from this study was used in part during interviews with prescribing clinicians from the hospices in 2010/2011 to ascertain their perspectives on prescribing of corticosteroids in palliative care. At the time of those interviews, there were very few actual changes in practice. This study is reported in a paper currently under review so we did not feel it appropriate to include this comment.

As well as these fundamental concerns, major compulsory revisions that would be needed before the paper could be considered for publication include:

1) Statements need to be amended that are not apparently supported by the data. For example a) in the abstract results, ‘Adverse effects tended to be undifferentiated from the dying process’, does not seem to relate to data in the main text of the paper, and b) in the abstract and main conclusion, the need for reappraisal or reconsideration of their use in palliative care is not well supported by the data presented.

Response: Phrase a has been removed and phrase b has been modified to “These findings are consistent with the international literature in this area and this large, multi-site study adds weight to the findings and the need for ongoing discussion about the place of these drugs in palliative care.”

2) 'International best practice' needs to be defined. This is referred to in several places (eg end of introduction) but it is not clear what it is.

Response: This is a very good point and we have changed the terminology to ‘international experience’.

3) There are inconsistent statements about the method of hospice selection early in the methods ‘a balance of rural and urban hospices’, and later in the methods ‘for ease of access’.

Response: Additional comments on hospice selection are provided in the methods section (page 7, study sites), including a table describing the sampled hospices (Table 1, page 21)
4) In the last two paragraphs of the results, there is no explanation for why phenytoin and zopiclone are being considered, and the relevance of this whole section is unclear. The statement about the different proportion of patients prescribed NSAIDs also appears to be relevant.  
Response: On reflection, we don’t feel the information on drug interactions adds much to the manuscript, so we have removed this section.

5) The bar charts are hard to interpret as ‘n’ is not clearly defined eg in figure 2, does it relate to the number of patients in the hospice, or the number of patients on steroids, or the number of patients on steroids for non-specific indications.  
Response: All bar graphs have been removed and replaced by tables which represent the data far more clearly.

Minor but essential revisions should include a number of statements that are unclear or wrong. Examples include the last sentence of the ‘sample size’ section; the statement that abrupt cessation of steroids ‘may lead to adrenal suppression’; and the phrase with the statistical analysis section ‘the clustering of data where patients had more than one record’.  
Response: All of these phrases or statements have been removed or corrected.

Reviewer 4 Comments

This has been a well written and well researched paper. It is of interest to the palliative care field and springboards the ongoing discussion for critical review of corticosteroid prescribing and guidance for use in the sector. In its current form, I believe that it is at a level and standard to be published. I believe that the authors have appropriately addressed the question posed and has provided sound use of data and its analysis with appropriate follow up discussion and conclusions. Limitations to the work are discussed. The style, format and referencing are fine. There is no particular need for any discretionary revisions from my point of view.  
Response: Thank you for these positive comments, as you will see from the responses to the other reviewers we have made a number of revisions to improve the manuscript.

Anne Denton and John Shaw

21 October 2013