Peer Review File

Article information: https://dx.doi.org/10.21037/apm-23-507

REVIEWER A

Comment 1: *Introduction: line 53. Consider focusing on the prevalence that was identified in 2 prospective studies that found ~50% of patients developed DR (Wildiers, 2002; Campbell, 2013) which is stronger evidence than largely retrospective reports.*

Reply 1: *Thank you for this helpful insight. We have modified our references and provided new prevalence data, based on three prospective studies (Campbell, 2013; Yamaguchi 2012; Morita 2005). Initially, we wanted to use both of your suggested references. However, we found that Wildiers, 2002 is a retrospective analysis. Based on the fair comment of prospective studies being scientifically stronger we only included prospective designs to describe the prevalence of death rattle (DR). We hope this adjustment is sufficient to resolve your comment.*

Adjustments in text: *We adjusted our text based on your insight. See page 3, line 54.*

Comment 2: *Discussion: lines 199-200: The RDOS has strong validity, reliability and cut-point determination psychometrics and is not subject to investigator interpretation although that can be true about the DRIS.*

Reply 2: *We've adjusted the discussion section of our manuscript in which we now have added evidence on the validity and reliability of RDOS. (Zhuang et al., 2019).*

Adjustments in text: *We have modified our text based on your insight and have added extra data to our discussion section. See page 12, lines 179 – 184.*

Comment 3: *Discussion: lines 245+ Consider adding the ethical conundrum of treating relatives distress by medicating the patient, in other words, non-maleficence. See the recent paper in J of Pain and Symptom Management by Van Esch et al that discusses this controversy.*

Reply 3: *We highly appreciate your suggestion as we think the addition of this ethical discussion is an improvement to our discussion section. Therefore, we have taken more time to elucidate these ethical considerations and have modified our discussion section based on your suggested reference. We hope you find these adjustments of added value to our manuscript.*

Adjustments in text: *We have modified our text based on your suggestion and have added extra data to our discussion section. See pages 14 – 15, lines 235 – 261.*

REVIEWER B

Comment 4: *The authors note one of the aims of the review is to "describe the effectiveness of non-pharmacological interventions in DR management yet it does not appear that any of the studies they included were designed to do this. I do think this supports their conclusion that further research is needed but I think it tempts the reader to believe there will be some great data to digest which is not the case.*

Reply 4: *The phrasing of our aims was changed in an attempt to prevent any misconceptions about the amount of data that will be discussed in the result section.*

Adjustments in text: *We adjusted our text based on your insight. See page 2, lines 29 – 33 and page 4, lines 74 – 75.*

Comment 5: *The authors also state regarding the patient experience "it is generally assumed they do not experience any distress" and I disagree with this. In their editorial, Lowe and Hansen state that "we should embrace humility and acknowledge that the internal experience of the dying, nonverbal patient cannot be fully known, but when in doubt regarding comfort, it is best to try treatment" I would agree that it is difficult to conclude that patients experience no discomfort or distress from the pooling of secretions in pharynx based on observational tools. We often explain to families that hearing is preserved through the dying process but then try to convince them the patient is not aware of a loud death rattle. The authors have cited works that detail the distress that families experience when they hear death rattle so I think it is reasonable to think treatment of this problem could have significant value if an effective approach was developed. Mercadante also strongly advocates for the treatment of death rattle.*

Reply 5: *Thank you for these additional insights which made us consider adjusting our introduction and discussion section with more nuanced phrasing about your viewpoints being raised here.*

To start, we realize there is no complete certainty about patients' experiences regarding DR. As stated by Lowe and Hansen, we should indeed acknowledge we do not fully know the internal experience of the dying. However, in most of the studies it is stated that the general assumption most health professionals have is that patients are not aware of the noise because of their decreased consciousness (Bradley et al., 2010). In addition, a recent review by Star et al., 2018 stated that there is no evidence supporting the association between respiratory secretions and respiratory distress. As we are aware this remains a difficult ethical topic within the DR management topic, we have discussed these ethical considerations more deeply in our discussion section with the help of the suggested editorial of Lowe and Hansen and an additional reference about the preserved hearing at the end of life. We hope you find these adjustments sufficient.

Second, we do agree that when in doubt regarding a patient's comfort it is best to try treatment. However, since the experienced distress in the patient itself remains unclear, we believe a first and more suitable treatment option could be a non-pharmacological one, such as repositioning the patient or educating the relatives. This is because of the adverse effects caused by anticholinergics and the 'primum non nocere' principle.

Third, when considering treatment for death rattle we believe it is very important to be aware of the existing ethical dilemma. As patients' distress related to DR is unknown and evidence exists on relatives' experienced distress, we are not completely sure if the best way to treat

relatives' distress is by medicating the patient. We do agree treatment of the problem could have significant value. However, "the problem" that needs "treatment" should be clarified more. In our opinion, the problem that is most often addressed is the DR-related distress of relatives. Therefore, we suggest treatment options directly focused on the relatives, rather than on the patients. When in doubt about the comfort of the patient, it is obviously necessary to treat the patient. When treating the patient, both pharmacological and non-pharmacological interventions should be considered. However, when the choice for a pharmacological treatment is made we believe this entails another ethical consideration. As anticholinergics seem to be more effective when started prophylactically, we tried to focus more on these ethical consideration in our discussion section.

We hope these additions are of added value to our manuscript and our sufficient enough to answer to your concerns raised here.

Adjustments in text: *We adjusted both our introduction and discussion section based on your insights. See page 3, lines 56 – 59 and lines 66 – 69. Page 12, lines 172 – 177 and line 185. Pages 14 – 15, lines 235 – 261.*

Comment 6: *The authors state regarding anticholinergics in line 63, "current evidence does not support their effect" and I think the study by van Esch et al clearly provides evidence for their effect if started before the onset of death rattle.*

Reply 6: *There is indeed existing evidence for the effectiveness of anticholinergics when started prophylactically. However, our aim was to address the evidence-base gap when administering anticholinergics the moment DR is already present. We can agree with your statement and acknowledge the fact we need to be more clear about the gap we want to address. Therefore we made adjustments to our manuscript. We hope this adjustment is sufficient to resolve your comment.*

Adjustments in text: *We adjusted our text based on this statement. See page 3, lines 66 – 69*

Comment 7: *Also in lines 245-6 "causes a controversiality into" seems to be an awkward if not grammatically incorrect phrase.*

Reply 7: *Based on another comment we have revised this section of our manuscript and removed this grammatical error.*

Adjustments in text: *We adjusted our text based on comment 3.*

Comment 8: *So in summary I think many clinicians would disagree with the central themes that pharmacologic treatment is ineffective and patients experience no distress.*

Reply 8: *We have adjusted our manuscript in an attempt to clarify some statements that we have made about patients' experienced distress and the (in)effectiveness of pharmacological treatment. We agree some of our statements were not specific enough leading to general conclusions, when in fact a lot of aspects within the DR topic cannot be generalized. We hope we have resolved your disagreement by our adjustments and additions to our manuscript.*

Adjustments in text: *We adjusted our text based on this statement, together with the statements made in comment 5. See page 3, lines 56 – 59 and lines 66 – 69. Page 12, lines 172 – 177 and line 185. Pages 14 – 15, lines 235 – 261.*

REVIEWER C

Comment 9:

- Abstract: line 40: Change ‘other’ to ‘additional’.

- Results: line 132: add ‘also’.

- Discussion: line 193: Change ‘part of the’ to ‘Some’.

- Discussion: line 209: Delete ‘Unfortunately’.

- Discussion: line 227: Change ‘role’ to ‘efficacy’.

Reply 9: *All spelling and grammatical errors pointed out were highly appreciated and have been corrected in the manuscript.*

Adjustments in text: *We adapted the text as the reviewer suggested.*

Comment 10: *figure 1 is unnecessary and doesn't add value beyond what was already described.*

Reply 10: *Thank you for this suggestion. We understand that using a figure and describing it again in our written text is an unnecessary repetition. Therefore, we adjusted our manuscript and removed any repetition from our written text as we wanted to retain our figure for more transparent reporting. In addition, we believe this figure has an added value in mentioning the total articles screened (n = 102) and the course of the screening process. We hope these adjustments are sufficient enough to resolve your suggestion.*

Adjustments in text: *We adjusted our text based on this suggestion. See page 4, lines 83 – 87.*

Comment 11: *Table 1 is also unnecessary and the information was already described.*

Reply 11: *Thank you for this suggestion. The use of Table 1 is suggested in the ‘Author Instruction’ of the APM journal system (see link below). In section ‘2.2.3 Narrative Review (Also Called Literature Review)’ it is stated that ‘The Methods section should include a completed table as follows: …’. However, we did remove any repetition that occurred in the written text and we have adjusted the order in which Table 1 and Figure 1 appear in the text to maintain a logical order. As the final format of the manuscript should follow the author's instruction requirements, we hope you understand we did not remove Table 1 from the manuscript. (https://apm.amegroups.com/pages/view/guidelines-for-authors)*

Adjustments in text: *We adjusted our text based on this suggestion. See page 4, lines 83 – 87*

Comment 12: *Results: line 155: This paragraph needs information on the observed effectiveness of repositioning.*

Reply 12: *We understand the importance of mentioning this information in this paragraph. Unfortunately both included studies (Hirsch et al., 2013 and Matsunuma et al., 2020) do not report on the observed effectiveness of repositioning. In both studies, repositioning was mentioned as a secondary end-point in which no information about effectiveness of repositioning was provided. As we reread our manuscript, we came to the conclusion this was not stated as clear as possible. Hence, we added some extra information in our manuscript. We hope this additional information is an answer to your comment.*

Adjustments in text: *Based on this suggestion, we provided our manuscript from an additional explanation. See page 8, lines 128 – 130.*

Comment 13: *Discussion: line 208: Explain 'self-developed questionnaire'.*

Reply 13: *Thank you for this suggestion. As we agree with this statement, we tried to explain 'self-developed questionnaires' in a more comprehensive way. We hope you find this adjustment sufficient enough.*

Adjustments in text: *Based on this statement, we adjusted a phrase in our manuscript. See page 13, lines 192 – 195.*

Comment 14: *Discussion: lines 219+: This recommendation conflicts with the finding in this review that there is insufficient evidence for the efficacy of pharmacological and non-pharmacological interventions for the rattle. If the interventions are unsupported then a recommendation to intervene "as soon as possible" is meaningless. Delete.*

Reply 14: *Thank you for this valuable insight. As we agree to this contradiction we brought into our manuscript, we have indeed removed a part of our recommendation. We do think it is important for health professionals to become aware of these contributing factors to identify relatives more at risk of experiencing DR-related distress. Since there are no (non-)pharmacological interventions proven to be effective in reducing DR-related distress in relatives, we removed this part of the recommendation. We hope this adjustment is sufficient to resolve your comment.*

Adjustments in text*: We have deleted a part of the text in our discussion section. See page 13, lines 206 – 207.*

Comment 15: *Discussion: line 222+: How? This needs further explanation, especially since it is one of the main topics of the paper*

Reply 15: *As we agree with this statement, we provided our discussion section with a better explanation concerning how some of the contributing factors to relatives' distress levels could be alleviated or prevented. We hope these additions are sufficient to resolve your comment.*

Adjustments in text: *We have provided our discussion section from additional information. See page 13, lines 209 – 213.*

Comment 16:

- Discussion: line 245-246: Change 'causes a controversiality' to 'introduces a controversy'.

- Discussion: line 246: Change 'Especially' to 'This is especially the case'.

Reply 16: *Due to revisions of our manuscript these two grammatical errors were not applicable anymore.*

Adjustments in text: *We adapted our manuscript based on a previous comment, see comment 3.*

Comment 17: *Discussion: line 247: A sentence should be added before or after this sentence which briefly discusses the risks associated with pharmacological treatments.*

Reply 17: *Thank you for your suggestion. This section has been adjusted based on previous comments by another reviewer. However, we did take into account your suggestion. Hence, a sentence which briefly describes the associated risks (adverse effects) of pharmacological treatments has been added to this section.*

Adjustments in text: *We have added additional data in our manuscript based on this suggestion. See page 14, line 241.*

REVIEWER D

Comment 18: *Please clarify why the authors limited the review to papers within the last 10 years*

Reply 18: *Thank you for your suggestion. This decision was based on the availability of the systematic review of Lokker et al., (2014) in which articles published up to August 2012 were included. This narrative review aimed to provide researchers and health professionals with new or additional insights into DR management. We understand the importance of clarifying this limitation. Therefore we adjusted the discussion section of our manuscript and provided you with the reason why we limited this narrative review to papers within the last 10 years.*

Adjustments in text: *We adjusted our text based on this suggestion. See page 16, lines 286 – 290.*

Comment 19: *The following article on the association between hydration volume and death rattle development might be included, because this observational study approached the causal relationship between the two by adjusting for confounding through propensity score weighting: Yokomichi N, et al. J Palliat Med. 2022 Jan;25(1):130-134.*

Reply 19: *Thank you for your input. This article is definitely an added value to our manuscript. Therefore, we included this article to strengthen the discussion section of our manuscript.*

Adjustments in text: *We have added additional data to the discussion section of our manuscript based on this suggestion. See page 15, lines 265 – 269.*

REVIEWER E

Comment 20: *Bronchial secretions may also accumulate with loss of cough reflex, not only for infection. Of course, it is impossible to state that patients presumably do not experience distress.*

Reply 20: *We are aware of the fact that bronchial secretions may also accumulate due to loss of cough reflex and not only for infection. The different types of DR 1 and 2 do not refer to the mechanism of accumulation (that is incorporated in the definition itself), but are based on the origin, so whether they are "salivary" or "bronchial" secretions (Wildiers et al., 2002) We feel this explanation covers with nuance the two types of DR and made no adjustments to our manuscript. In addition, based on comment 5 by reviewer B, we have addressed and adjusted our statements about patients' experienced distress. We hope these adjustments in our manuscript are sufficient to resolve your comment.*

Adjustments in text: *For changes in text, please see comment 5.*

Comment 21: *Current evidence does not support the effect of anticholinergics. This is not true, as most recent papers reported, given that these drugs should be used pre-emptively.*

Reply 21: *There is indeed existing evidence for the effectiveness of anticholinergics when started prophylactically. We can agree with your statement and acknowledge the fact we need to be more clear about the gap we want to address. Based on the feedback of other reviewers we have made adjustments to our manuscript to clear this out. We hope these adjustments are sufficient to resolve your comment.*

Adjustments in text: *For changes in text, please see comment 5.*

Comment 22: *There is no minimal data regarding non-pharmacological interventions in DR management (repositioning of the patient, suctioning of secretions, reducing hydration levels, and communication about DR with relatives). So the scope of this review is debatable.*

Reply 22: *Unfortunately, there is indeed only limited data available about non-pharmacological interventions. Their use in DR treatment is described in studies rather than investigated thoroughly. To our knowledge there were no studies focusing on their effectiveness before the start of our review. Therefore we conducted this review to see if non-pharmacological interventions were studied more* in detail in the last ten years. However, we are aware of the limitations of using only one database predominantly focusing on medical literature. We believe that presenting this minimal data is valuable, as it can lead to set priorities for further research. We agree that DR is a symptom that needs adequate management and treatment for patients, relatives and health professionals. We also believe in a holistic approach focusing on the opportunities non-pharmacological interventions could provide in order to be able to prevent and/or treat this symptom and its related distress the best way possible.

Adjustments in text: *No changes in the manuscript were carried out.*

Comment 23: *Among the included studies, strangely there is not some valuable papers that anyone involved should know, regardless of the method of data base research*

Reply 23: *We do not fully understand this comment, but we believe the reviewer highlights the gap in evidence there is for non- pharmacological interventions, which we commented upon in the previous comment.*

Adjustments in text: *No changes in the manuscript were carried out.*

Comment 24: *The discussion is not appropriate in many points.*

Reply 24: *Based on the feedback of the other reviewers we have adjusted our discussion on several points, hopefully meeting your concerns.*

Adjustments in text: *We have added additional data to the discussion section of our manuscript. See Page 12, lines 172 – 177 and line 185. Pages 14 – 15, lines 235 – 261.*