harms were not reported, but it is vital to know about toxicity when proposing a prophylactic treatment (potentially for the benefit of family and staff rather than the patient)[4-6] where a significant number of people would never develop noisy RTS (40% in comparator arm of present study) but nevertheless have now been exposed to a drug with a significant harm profile (including dry mouth, constipation, and urinary retention).[2,3] In particular, anticholinergics are known to contribute to delirium—of concern in this high-risk population.[7] To make clinical judgments, we must be able to evaluate the net-benefit (harms-benefit balance) of exposing patients to a medication they might not need but might cause clinically important harms. Furthermore, we cannot identify and target patients at higher risk of developing RTS.[8]

These data are useful to inform a subsequently adequately powered double-blinded randomized placebo-controlled trial, but until high quality data are available (of both effectiveness and harms), a change in practice cannot be recommended.

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References

1. Mercadante S, Marinangeli F, Masedu F, et al. Hyoscine butylbromide for the management of death rattle: Sooner rather than Later. J Pain Symptom Manage 2018.

2. Mercadamte S. Death rattle: critical review and research agenda. Support Care Cancer 2014;22:571−575.

3. Star A, Boland JW. Updates in palliative care - recent advancements in the pharmacological management of symptoms. Clin Med (lond) 2018;18:11−16.

4. Wee BL, Coleman PG, Hillier R, Holgate SH. The sound of death rattle I: are relatives distressed by hearing this sound? Palliat Med 2006;20:171−175.

5. Wee B, Coleman P, Hillier R, Holgate S. Death rattle: its impact on staff and volunteers in palliative care. Palliat Med 2008;22:173−176.

6. Campbell ML, Yarandi HN. Death rattle is not associated with patient respiratory distress: is pharmacologic treatment indicated? J Palliat Med 2013;16:1255−1259.

7. Hosie A, Davidson PM, Agar M, Sanderson CR, Phillips J. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. Palliat Med 2013;27:486−498.

8. Likar R, Michenthaler MC, Traar R, Molnar M, Neuwersch S. Clinical factors influencing death rattle breathing in palliative care cancer patients: Non-interventional study. Z Gerontol Geriatr 2017;50:332−338.

Author's Response

Dear Editor

Thanks again for the further comments. The debate continues and I'm happy that this paper has raised such interest, giving me the occasion to further clarify its meaning.

The colleagues emphasize that the natural history of respiratory tract secretions, presumably how death rattle has developed in time, is poorly described. Possibly it is right, but I did not have access to any information of this type in literature published on this topic. The reason probably relies on the individual differences that are unlikely to be reported in a trial.

The second point regards the power calculation. In methods, they partially have the answer: "for sample size for each arm of the research a 'small' Cohen effect size was used. The sample size estimation was affected by an expected drop out in group 1 because of the drug administration inclusion criteria, of 65%, so that we had to adjust for this unbalancing in our study arms." To complete this information, we compared the failure rates according to the study estimates using few lines of code on **R**: > pA=0.60, pB=0.06, kappa=1.6, > alpha=0.05, (Power=pnorm(z-qnorm(1-alpha/2))+ pnorm(-z-qnorm(1-alpha/2) [1] 0.800001. Thus, the power 1-b achieved is 80%. Original data are available.

They also stress that a proportion of patients who receive an early medication may not develop death rattle and consequently are exposed to unnecessary harms. From a clinical point of view, I have many doubts that patients may perceive the effects feared by authors, such as dry mouth, constipation, and urinary retention. I recognize that dying patients having a progressive decrease of the level of consciousness did not complained of these problems or, better, were able to do that. It is surprising to note that, according to authors' opinion, dying patients with a low level of consciousness may not feel death rattle, but they may feel such unpleasant adverse effects.

They quote a paper in which anticholinergic drugs are included in a list of drugs triggering delirium. Again, this is not the clinical context in which offending drugs may be stopped to improve patient's cognitive condition. It would be like suggesting to discontinue opioids because in the last hours they could induce delirium, constipation, or whatever (i.e., potentially true), or sedative drugs because they could induce drowsiness (and this is true too), and so on. But I guess that no clinician would suspend these drugs in the last hours of life for these fears. In every clinical situation, advantages and disadvantages are balanced for the patient's best interest.

It is unclear to me what is the practice that cannot be changed because I'm unaware of standard current practices, unless they would refer to the use of anticholinergics once death rattle occurs (that they have correctly stated to be ineffective). Unless they would propose to "normalize" death rattle with a good communication with relatives. But this is another story, already discussed in a previous correspondence.

I agree that adequate powered double-blind randomized placebo controlled study trials may help solve such a difficult question, although the use of placebo in these cases may be questionable and, for what concerns me, little useful and probably unacceptable for most ethical committees in Italy.

From my study, one can only conclude that 60% of patients who could develop death rattle will be unlikely to develop that with a timely administration of hyoscine butylbromide. This is a considerable outcome if confirmed in other studies. Furthermore, 40% patients who possibly will not develop death rattle may receive this medication, but without relevant harms clinically evident or reported (i.e., unlikely) by patients. I would like invite colleagues to use a scientific approach based on common clinical sense rather than on twisted methodological aspects that are hard to be translated and applicable in clinical practice.

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