EDITORIAL

Preventing Death Rattle With Prophylactic Subcutaneous Scopolamine Butylbromide

Jared R. Lowe, MD; Laura C. Hanson, MD, MPH

Among the signs that accompany impending death, one that evokes controversy in end-of-life care is noisy breathing. Commonly referred to as the *death rattle*, this is the sound of respirations caused by secretions and muscle relaxation in the upper airway. In a 2014 review of 29 studies involving 7908 patients and assessing the prevalence of the death rattle in the dying phase, audible respirations accompanied decreased consciousness during the final hours or days of life for 35% of patients.[1] The specificity of this finding to the dying phase allows it to be used in prognostication, as one study involving 203 patients found the presence of the death rattle has a positive likelihood ratio of 9 of impending death within 3 days.[2]

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Although the patient experience of noisy breathing is unclear, family members and other observers may be distressed by these noisy airway sounds and interpret them as the patient having distress or discomfort.[3] Clinicians typically manage noisy breathing with patient repositioning and administration of anticholinergic medications to reduce airway secretions, yet many question the benefit of these practices. Prior studies have been small, methodologically limited, focused on treating rather than preventing death rattle, and have had mixed results.[4-6]

In this issue of *JAMA*, van Esch and colleagues[7] report findings from a double-blind, placebo-controlled randomized clinical trial of prophylactic subcutaneous scopolamine butylbromide for the death rattle in patients at the end of life. The authors enrolled 162 patients with diverse diagnoses from 6 hospice units in the Netherlands. Eligible patients had a life expectancy of at least 3 days and were able to provide advance informed consent upon hospice admission. When patients entered the dying phase, as determined by a multidisciplinary team, they were randomly assigned to receive scheduled subcutaneous scopolamine butylbromide (20 mg) or placebo 4 times a day. Patients in the dying phase underwent structured symptom assessments every 4 hours, including grading of the death rattle based on a standardized scale.[8] The primary end point was the occurrence of a grade 2 or higher death rattle, meaning audible from standing at the end of the bed or further, at 2 consecutive time points.

Of the 162 enrolled patients, 157 were accurately identified as being in the dying phase and were included in final analyses. Significantly fewer patients who received scopolamine butylbromide developed a death rattle than did patients who received placebo (13% vs 27%; difference, 14%; 95% CI, 2%-27%; P = .02). The authors also found no differences in the secondary outcomes involving potential anticholinergic adverse effects, including restlessness, dry mouth, and urinary retention. Other exploratory end points demonstrated no difference in the use of opioids, haloperidol, or sedatives between the 2 groups.

The SILENCE (Scopolamine Butylbromide Given Prophylactically for Death Rattle) trial provides the most rigorous available evidence that prophylactic subcutaneous scopolamine butylbromide is effective in reducing noisy breathing for dying patients. These data support the clinical approach of prophylactic anticholinergic medications, with the goal of reducing upper airway secretions before they form. Investigators employed a systematic approach to patient monitoring, and the absence of adverse effects associated with anticholinergic medications suggests the risks associated with this intervention were minimal.

Perhaps even more significant for clinicians who care for dying patients, the research methods employed by the SILENCE investigators offer confirmation that high-quality end-of-life research is feasible. Clinical trials of palliative care and hospice care are relatively rare, and investigators must overcome major ethical and practical challenges in design. Several design features of this trial are exemplars for overcoming these challenges.

First, because many patients nearing death are typically unable to provide informed consent, obtaining advance consent for research is novel but essential, as done successfully in this trial. Second, screening and eligibility procedures must account for the vulnerability and rapidly changing health status of seriously ill patients. To enroll their target sample size, SILENCE investigators screened 1097 hospice admissions, expected only half of eligible patients to consent, and accounted for drop-outs due to rapid death and failure to enter the dying phase of illness.

Third, the study team used structured symptom distress outcome measures relevant for this population. Patients in the dying phase are typically unable to report on their experiences, and assessing therapeutic response is dependent on clinician- or caregiver-reported outcomes. This approach provides a model of data gathering that can guide future clinical trial design in end-of-life care. Fourth, because most patients prefer to die in home and community settings, SILENCE demonstrates the value of research partnerships with hospice organizations. Similar community partnerships have generated other practice-changing research findings.[9]

Since 2010, the Palliative Care Research Cooperative has been funded by the National Institute for Nursing Research to improve clinical science in palliative and end-of-life care. One of its primary objectives is to foster the development of

a growing cadre of investigators to lead rigorously designed clinical trials to improve serious illness care and outcomes.

Despite the significant findings of this well-conducted randomized clinical trial, the results may have limited applicability to change current practice, particularly in the United States. The intervention required intermittent subcutaneous medication administration, which is generally restricted to inpatient settings and would not be applicable for the many patients who receive end-of-life care at home. The study medication, scopolamine butylbromide, is a compound distinct from scopolamine administered transdermally, and it is not approved in the United States. Scopolamine butylbromide is a quaternary ammonium derivative that does not cross the blood-brain barrier, whereas transdermal scopolamine is a tertiary amine that does cross the blood-brain barrier and has central effects.[10] This suggests that the adverse effect profile of these products differs, and the safety demonstrated in this study may not generalize to other formulations.

Additionally, although dose equivalency data are limited, an estimated 5 to 8 transdermal patches might be necessary to achieve the dosing of subcutaneous scopolamine used in this study and others investigating therapies for the death rattle.[11] Other anticholinergic medications such as atropine, glycopyrrolate, or parenteral hyoscine are used for the death rattle, but these are not clearly more effective than scopolamine butylbromide.[1] Additional research on the efficacy and safety of prophylactic administration of the medications available in a given country is needed before these results can change standard practice there, such as in the United States.

The primary controversy of the clinical question addressed by van Esch et al is that many clinicians question whether the death rattle should be treated. One argument is that there is no evidence to suggest this sign is distressing to a patient, and interventions may be costly and burdensome.[12] One counterargument is to 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. Another reason to consider treatment for a death rattle is that the patient's noisy respiration can have negative effects on family members and other observers.

Although the patient is the primary focus of clinicians, consensus palliative care practice guidelines define the unit of care as both the patient and their family.[13] As most people move toward death, they are deeply supported by their close personal relationships. Hospice and palliative care clinicians assess the needs of the patient and those who support them, and attend to the distress and discomfort of both. Witnessing a death rattle can be disturbing and interpreted as choking or air hunger.[3,14] In a 2003 study that involved 76 caregivers of patients receiving hospice care, such negative experiences among caregivers were associated with downstream effects of worse social functioning and complex grief, including increased odds of depressive and posttraumatic symptoms.[15] Clinicians should care about family-centered care at the end-of-life, and this trial is a step forward in understanding how best to do so.

The SILENCE trial is a well-executed randomized clinical trial that can serve as a model for research to improve end-of-life care. The findings provide a strong grounding for future investigation into prophylactic anticholinergic medicines for noisy breathing. Clinicians should still consider repositioning for patients with a death rattle and provide supportive counseling to address family concerns about this sign. For patients who are not actively dying, other strategies such as humidified air and expectorants may be more effective. While the SILENCE trial findings support use of subcutaneous scopolamine butylbromide when available, the findings are not sufficient to indicate that transdermal scopolamine should be used for this indication. Nonetheless, the results suggest that when used, anticholinergics may be more effective if used earlier as prophylaxis rather than as treatment once the death rattle commences. The SILENCE trial focuses on improving an outcome important to family and other caregivers. This study is a powerful reminder that evidence-based hospice and palliative care requires new research to deepen the understanding of best practices for end-of-life care.

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Ninth International Congress on Peer Review and Scientific Publication
Call for Abstracts

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In 2019, before the COVID-19 pandemic, we highlighted the unprecedented promise and peril surrounding the quantity, quality, and integrity of scientific research.[1] The pandemic has been a crash test for scientific publishing, emphasizing the great successes and failures, and the promise and perils of current systems. In 2020, because of the pandemic, we announced a postponement of the Ninth International Congress on Peer Review and Scientific Publication. We now confirm plans to hold the meeting September 8-10, 2022, and we announce the official call for abstracts.

The aim of the Congress is to encourage research into the quality and credibility of peer review and scientific publication and to further the evidence base on which scientists can improve the conduct, reporting, and dissemination of scientific research. As with the previous 8 Congresses,[2] the ninth Congress will feature 3 days of presentations of original research about processes, policies, problems, and innovations related to peer review, scientific publication, and research dissemination. Participants will include editors and publishers of scientific peer-reviewed journals, researchers, funders, bibliometric and informatics experts, information innovators, librarians, journalists, policymakers, ethicists, scientific information producers and disseminators, and anyone interested in the progress of the scientific information enterprise and the quality of scientific evidence. The Congress embraces a wide range of disciplines, including (but not limited to) biomedicine, health and life sciences, applied sciences, basic sciences, physical and chemical sciences, mathematics, computer sciences, engineering, economics, and social sciences. New and emerging disciplines are also welcome.

The Congress program will be determined by the abstracts submitted by researchers, representing the interests and work of their scientific communities, with priority given to novel, data-driven studies. As noted in the call for research 2 years ago,[1] we are interested in studies that evaluate and test the processes and policies used by researchers, authors, editors, peer reviewers, publishers, funders, universities, and any other stakeholders to improve the conduct, reporting, quality, integrity, and dissemination of scientific research. We encourage new ideas and rigorous evaluations of both old and new processes. We have a continued special interest in studies of bias and how biases can be identified and managed. As the world is emerging from a lethal pandemic that created a stimulating, contentious, and challenging interface between science, society, and policy, this is a most opportune time to test, challenge, and improve the standards of peer review and scientific publication. Meaningful improvements are more likely to happen in the current volatile environment, which is hopefully more receptive to change.

Abstracts summarizing original, high-quality research on any aspect of peer review and publication and the conduct, reporting, assessment, and dissemination of scientific research are welcome. Illustrative examples and suggested topics of interest are included in the **Box**, but we will consider any novel research relevant to the conduct, peer review, reporting, and dissemination of research. A broad range of study designs will be considered, with preference given to well-developed studies with more generalizable results (eg, prospective, multiyear trials and controlled studies from collaborative researchers, journals, publishers, funders, and information disseminators). Retrospective studies, systematic reviews, meta-analyses, bibliometric and other data analyses, surveys, modeling studies, and other types of studies will also be considered. Abstracts that report new research and findings will be given priority and we also encourage studies that build on previous related research. We particularly encourage research that crosses disciplines and work that aims to provide valuable insights across disciplines. Abstracts of research previously published are not permitted unless they include new unpublished analyses. Abstracts describing narrative reviews, recommendations, and opinion will not be considered.

The abstract submission site will be open December 1, 2021, and the deadline for abstract submission is January 31, 2022. Instructions for preparing and submitting abstracts[3] and programs and abstracts of research presented at the previous