ried out a variety of sensitivity analyses. Significant heterogeneity was found only with 2 specific studies on quinidine sulfate and sotalol hydrochloride in relation to their results for mortality and withdrawals. All that was explained in detail, and the particularities of those 2 trials were discussed. No significant heterogeneity appeared between pooled studies for any of the remaining comparisons performed. In sensitivity analysis, with the only exception of the aforementioned 2 studies, selectively pooling the best-quality studies or those studies with more patients did not modify the overall results.

Any meta-analysis pools together studies that are, to some extent, heterogeneous in design. The matter is to evaluate if this heterogeneity between studies is high enough to avoid to combine them. This was not the case in our review. Despite the dissimilarities in design, the heterogeneity and the differences between studies actually observed were not important, and the results obtained proved to be consistent.

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1. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Mahe I, Bergmann JF. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. *Arch Intern Med*. 2006;166:719-728.

Morphine Is Not a Sedative and Does Not Shorten Life

Rietjens et al[1] compared the practices of palliative sedation and euthanasia in the Netherlands. Two conclusions deserve further attention. In 36% of the patients, palliative sedation was performed with morphine only. The estimated life shortening due to sedatives (including morphine) was 1 to 4 weeks in 21% and more than 1 month in 6%.

Palliative sedation is considered to be an effective treatment for dispelling refractory symptoms in patients near death. Benzodiazepines such as midazolam are proper sedatives for palliative care for patients with refractory symptoms such as delirium and terminal agitation. Palliation of pain or dyspnea first requires opioids. Although many palliative patients receive opioids prior to the initiation of palliative sedation, opioids are empirically not effective at producing sustained sedation.

Delirium is one of the distressing symptoms at the end of life, requiring palliative sedation. Terminal delirium has multiple causes, and recent studies suggest that accumulations of toxic morphine metabolites might also contribute to the development of delirium in terminally ill patients.[2] This makes morphine unsuitable as a sedative for treating delirium because of the possibility that delirium is induced instead of treated.

Sedation is also given to relieve the stress of dying. This stress can be divided into 3 components: stress from the experience of physical discomfort (pain and dyspnea); psychological stress from the anxiety regarding the prospect of death; and stress from the experience of organ failure and bodily deterioration. The mechanism of stress is not well understood, although it is known that stress increases cortisol levels. Erkut et al[3] hypothesized that the administration of high-dose morphine during the last premortem period would suppress the rise in cortisol level induced by physical discomfort and psychological stress. Postmortem cortisol levels indicate, however, that levels are not suppressed by high-dose morphine during dying.[3]

Morphine is not appropriate to relieve suffering from refractory symptoms such as exhaustion, depression, delirium, anxiety, agitation, and psychological suffering. Rather, it induces delirium and hallucinations. "Sedation" with morphine is nothing more than unprofessional inadequate practice. Morphine is a first choice for the treatment of pain and dyspnea in patients near death but a "no choice" for sedation. Palliative sedation must only be considered near death, in our experience within a week before death, and when used as an appropriate tool, it does not shorten life.[4,5] In the Netherlands, this is stated in the recently released national guidelines on palliative sedation.[6]

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1. Rietjens JAC, Van Delden JJM, van der Heide A, et al. Terminal sedation and euthanasia: a comparison of clinical practices. *Arch Intern Med*. 2006;166:749-753.
2. Jackson KC, Lipman AG. Delirium in palliative care patients. In: Lipman AG, Jackson KC, Tyler LS, eds. *Evidence Based Symptom Control in Palliative Care: Systemic Reviews and Validated Clinical Practice Guidelines for 15 Common Problems in Patients With Life Limiting Disease*. New York, NY: Pharmaceutical Products Press; 2000:5970.
3. Erkut ZA, Klooker T, Endert E, Huitinga I, Swaab DF. Stress of dying is not suppressed by high-dose morphine or by dementia. *Neuropsychopharmacology*. 2004;29:152-157.
4. Bercovitch M, Waller A, Adunsky A. High dose morphine use in the hospice setting: a database survey of patient characteristics and effect on life expectancy. *Cancer*. 1999;86:871-877.
5. Good PD, Ravenscroft PJ, Cavenagh J. Effects of opioids and sedatives on survival in an Australian inpatient palliative care population. *Intern Med J*. 2005;35:512-517.
6. Koninklijke Nederlandse Maatschappij tot bevordering der Geneeskunst. *KNMG-Richtlijn Palliatieve Sedatie*. Utrecht, the Netherlands: Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst; 2005.

In reply

We fully agree with Kompanje et al that morphine is not an appropriate drug for terminal sedation. Nevertheless, this is the practice that we encountered when we asked physicians to describe the last time they had administered drugs to keep a patient in deep sedation or coma until death, without