COMMENTS AND RESPONSES

Justifying Different Levels of Palliative Sedation

TO THE EDITOR: We read with great interest the article by Quill and colleagues (1), which presented and discussed 3 categories of palliative sedation: ordinary sedation, proportionate palliative sedation (PPS), and palliative sedation to unconsciousness (PSU). One notion shared by these practices, and by all attempts to justify sedation, is that the degree of sedation should match the symptoms—proportionality.

The prominence of proportionality in this and other discussions of palliative sedation suggests a simpler and ethically clearer classification. Instead of "ordinary," "proportionate," and "unconscious" sedation, we suggest that all palliative sedation be classified as PPS. This is not a confusion of types of palliative sedation, as Quill and colleagues suggest, but a helpful reconception. Under the notion of proportionality, all types of palliative sedation are given only to the extent demanded by symptoms. Low demands imply minimal sedation, and higher demands imply greater sedation. In this way, prognosis does not change the rationale or the practice of sedation, but it places limits on the degree of acceptable sedation. The closer the patient is to death, the higher the level and duration of acceptable sedation (although low levels of sedation will sometimes still be sufficient).

The classification presented by Quill and colleagues is reasonable and helpful, but our amendment improves simplicity and ethical clarity. Considering all palliative sedation as PPS avoids the inevitable difficulties of distinguishing among ordinary, proportionate, and unconscious sedation, particularly when palliative sedation is titrated to the point of near or total unconsciousness. Classifying some sedation as PSU also risks blurring the importance of intention to the practice of palliative sedation (2). Considering all palliative sedation as proportionate underscores the ethical imperative that the intention in using sedation is to palliate and not to hasten death.

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TO THE EDITOR: We are curious about the repeated invocation by Quill and colleagues (1) of double-effect reasoning regarding palliative sedation. Double-effect reasoning crucially involves the distinction between what one foresees and what one intends, as well as the ability to make a proportionate judgment about the good and bad outcomes of an action (2, 3). Inexplicably, 2 of the authors have elsewhere rejected double-effect reasoning at the end of life (4); nonetheless, they explicitly cite this article to support the application of double effect to palliative sedation. They now write, "Occasionally, PPS requires sedation to unconsciousness, which is considered a foreseen but unintended side effect when lesser degrees of sedation were ineffective" (1). Yet, they previously rejected the distinction between the intended and the foreseen, stating that ". . . the analysis of intention used in the rule of double effect is problematic. . . . Even philosophers and theologians sympathetic to the distinction between intended and foreseen consequences have failed to find an unambiguous way to draw the distinction in many difficult cases" (4).

In the current article, they use double-effect reasoning to argue that what they have called PSU can be distinguished from euthanasia. They state, "Although the purpose of PSU is to relieve otherwise intractable suffering, the patient is always rendered unconscious as an end point and therefore cannot take food and fluids by mouth, which may have the unintended effect of hastening a patient's death" (1). Yet their reference for this sentence is the very article in which they previously rejected double-effect reasoning and came to the opposite conclusion, stating that "[a]lthough the overall goal of terminal sedation is to relieve otherwise uncontrollable suffering, life-prolonging therapies are withdrawn with the intent of hastening death" (4).

We agree that PPS is often an appropriate application of double effect at the end of life. In our view, however, Quill and colleagues were previously correct in judging that PSU involves the intention to hasten death and therefore is not permitted by double effect and would be better described as "sedation to death" (5).

Do the authors now accept the ethical importance of double effect? Have they simply misapplied it here? Do they err in citing their previous article? In the face of this apparent self-contradiction, their vigorous endorsement of the ethical propriety of intentionally sedating patients to the point of unconsciousness seems premature.

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IN RESPONSE: We generally agree with Dr. Cellarius and Mr. Henry that the main justifications for the different levels of palliative sedation are proportionality and informed consent. For mild levels of distress, mild sedation is appropriate. For more severe distress, heavier sedation (even to the level of unconsciousness) may be needed. With PPS, the level of sedation and the pace of increase are directly related to the severity of otherwise unrelieved suffering. The level of sedation used will be the least amount that can relieve the distress. Although PPS may end with the patient being unresponsive, that is not the intended end point.

We also agree with Dr. Sulmasy and colleagues that the double effect can generally justify PPS (for clinicians who endorse the rule). Relief of suffering is the clinician's primary intent, and although there may be a foreseen risk for hastening death, this is not the clinician's intent (1, 2). However, we do not agree that PPS can only be justified by double-effect reasoning and would not justify it that way ourselves. Intent can distinguish PSU from euthanasia but does not mark the difference between the morally permissible and impermissible, as proponents of double-effect reasoning claim. Death may or may not be intended by patient or clinician in PSU; in some circumstances, intent may be only to relieve suffering and to respect the patient's right to refuse nutrition and hydration, whereas in others intent may be more multilayered (3). How intent applies to PSU is more controversial than how it applies to PPS, but this is less important to us than to Dr. Sulmasy and colleagues in distinguishing between permissible and impermissible actions.

Proportionate palliative sedation is adequate to deal with most but not all intractable end-of-life suffering. We stand by our assertion that PSU will still be needed from the outset in certain compelling cases in which lesser levels of sedation would be insufficient. Consider these real examples:

A terrified patient with advanced oropharyngeal cancer is bleeding from a progressively rupturing carotid artery.

A patient with advanced pulmonary fibrosis is prepared to die rather than be intubated for the third time in 1 month, provided that we promise to aggressively manage his dyspnea. He is now extremely short of breath and agitated, with a carbon dioxide level of 90 mmol/L.

A patient with amyotrophic lateral sclerosis wants to be taken off his mechanical ventilator but is very afraid of suffocation.

For us, these cases are more difficult to justify by using strict double-effect reasoning because death can be both foreseen and to some extent intended by both patient and clinician (4). Stopping at less than total sedation made no sense to the patients, their families, or the clinicians caring for them, and prolonging the patients' extreme suffering by continuing other life-prolonging therapies would have been inappropriate. In each case, the criteria of proportionality were met, informed consent was obtained, and the clinician's primary intent was to relieve the patient's severe suffering; however, to say that assisting these patients to die was completely unintended seems false (3). Rather than relying exclusively on a rule from a particular religious tradition with sometimes unrealistic requirements about intention, it seems better to develop clear guidelines that include ways of responding to some of the most challenging cases.

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Cost-Effectiveness of Biologics in Early Rheumatoid Arthritis

TO THE EDITOR: We appreciate Boers' (1) ideas about our cost-effectiveness study (2), but some require comment. He says, "Curiously, the investigators shy away from a firm conclusion, instead stating that the cost-effectiveness of early biologics is still uncertain." We feel that the case cannot be closed for at least 3 major reasons.

First, the long-term effects of very early initiation of aggressive antirheumatic therapy, and biologic therapy in particular, are largely unknown. These include long-term effects on mortality, the need for joint replacement, and the rate of disability decades after starting these therapeutic strategies.

Second, other variables profoundly affect the cost-effectiveness ratio of these therapies, the major ones being the availability of effective alternatives after failure of several biologics, the price of these agents, the induction of long-term drug-free remission, and the ability to identify responders to biologics before treatment initiation. Because of these uncertainties, a firm conclusion is not justified. Rather, our findings support the use of aggressive disease-modifying anti-inflammatory drugs (DMARDs) before biologics in very early rheumatoid arthritis from a cost-effectiveness perspective. Our study identifies the key variables that are uncertain and that drive the results, and these variables should be studied to improve future decisions.

We calibrated estimates of the published literature against real patients from the National Data Bank for Rheumatic Diseases. Such calibration techniques are appropriate and are commonly applied in cost-effectiveness studies. Calibration in another unrelated data set would further validate the model. However, at present, significant

circularity is unlikely, because the patient populations used to derive most of the variables and those used to calibrate the model are largely different.

Finally, Boers takes issue with the model and its treatment of glucocorticoids and believes that including them in only the nonsteroidal anti-inflammatory drug strategy group is "medically inappropriate." Glucocorticoids are effective and clinically useful. In the doses originally used for rheumatoid arthritis, the benefits were outweighed by serious and sometimes fatal long-term effects, such as increased susceptibility to infection, osteoporosis, obesity, hypertension, or glucose intolerance. The long-term risk–benefit ratio of lower doses is debated (3), and in North America, lower doses are more likely to be used to put out "fires" than for long-term treatment. Adding steroids to the DMARD strategy would, as Boers points out, probably be a conservative bias with respect to the findings (4).

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IN RESPONSE: I think the authors and I agree on most of the issues, but we differ in the wording of our conclusions. It is wise to avoid firm conclusions in the face of shaky evidence. A model can never fully replace reality, and we probably need another 10 years of additional experience with biologics to be fully certain of their cost-effectiveness. Nevertheless, when we trust the model, and it points unmistakably in 1 direction, we shouldn't be afraid to clearly communicate what it shows. This is especially important in the area of biologics in rheumatoid arthritis, where intense marketing pressure pushes opinions in the other direction. In their reaction, Dr. Finckh and colleagues use a whole paragraph to describe the uncertainties inherent in modeling and conclude with the sentence I wanted to see in the original article: "Our findings support the use of aggressive DMARDs before biologics in very early rheumatoid arthritis from a cost-effectiveness perspective." It would have been even better if they had said, "our findings *clearly* support . . . ".

In their response to the glucocorticoid question, Dr. Finckh and colleagues are side-stepping my point that not modeling glucocorticoids is an unfortunate omission in the study. To say that glucocorticoids "in the doses originally used" (that is, high doses) have many side effects is stating the obvious. Dr. Finckh and colleagues misrepresent our review on the published evidence of the safety of low-dose glucocorticoids (1) when they use it to conclude that "the long-term risk–benefit ratio of lower doses is debated." In fact, we showed that the popular conviction on the unacceptable harm of long-term low-dose glucocorticoid therapy in rheumatoid arthritis is based on poor-quality or no data, and that the admittedly limited good-quality data that are available actually support the contrary view that harms are limited and manageable. Together with the strong evidence of benefit, it follows that the role of this class of drugs in rheumatoid arthritis should no longer be ignored. Thus, the study's value would have been greatly enhanced by including glucocorticoids explicitly in the model.

In contrast to the authors' belief, data show that practitioners in the field have already got the message: Current glucocorticoid use in rheumatoid arthritis in North America is dynamic, but these drugs are being used not only to "put out fires" but for extended periods in many patients (2).

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Clinical Observations

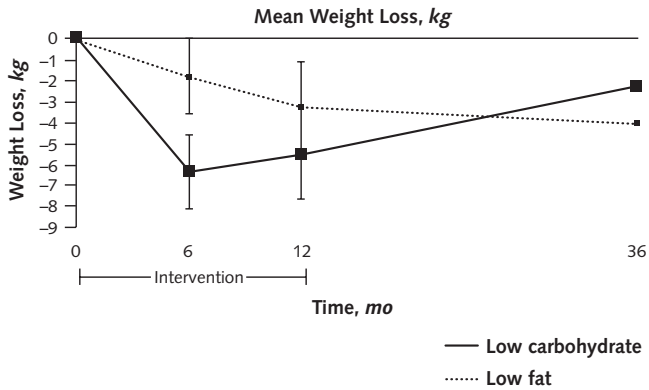
Long-Term Effects of Low-Carbohydrate Versus Low-Fat Diets in Obese Persons

Background: We reported elsewhere (1) the results of a randomized, controlled trial that found greater weight loss at 6 months with a low-carbohydrate diet (<30 g/d) than with a calorie-restricted, low-fat diet (deficit of 500 kcal/d with <30% kcal from fat) in 132 participants with a mean weight of 130.9 kg (SD, 25.2) and a high prevalence of diabetes and the metabolic syndrome. We subsequently reported (2) no significant differences in weight loss between groups at the end of the trial (12 months).

Objective: To assess outcomes after 36 months.

Methods: No further intervention occurred after 12 months. At 36 months, we invited all participants to return for a follow-up visit; 40 participants in the low-carbohydrate group and 48 in the low-fat group returned (66.7%). From the hospital's electronic medical records, we obtained weights within 3 months of the expected

Figure. **Difference in weight loss between the low-carbohydrate group and the low-fat group.**



$P = 0.003$ for comparisons between diet groups at 6 months. The difference in weight loss between groups was not significant at 36 months ($P = 0.071$ before and 0.056 for the interaction between visit and dietary assignment after adjustment for baseline variables). Error bars represent 95% CIs.

follow-up for 19 additional participants (11 from the low-carbohydrate group and 8 from the low-fat group). Thus, we had weights for 81.1% of participants: 51 from the low-carbohydrate group (mean, 37.4 months [SD, 3.2]) and 56 from the low-fat group (38.4 months [SD, 3.1]). Data were missing for 13 participants from the low-carbohydrate group and 12 from the low-fat group. We used random-coefficient models to assess changes in weight (primary outcome) and metabolic and dietary data (secondary outcomes). These models included all available data for participants with a baseline measurement and at least 1 of the assessments at 6, 12, or 36 months. Covariates included variables for time, diet group, and interaction of diet group by time. We performed separate analyses to adjust for baseline differences by adding covariates for age; race; sex; baseline body mass index and caloric intake; weight loss at 12 months; and the presence of hypertension, diabetes, smoking, sleep apnea, and lipid-lowering therapy. We performed a final analysis by using all available data to determine whether baseline characteristics or weight loss differed between participants with all data and those with missing data. The study was approved by the institutional review board of the Philadelphia Veterans Affairs Medical Center.

Results: At 36 months, persons in the low-carbohydrate group weighed 2.2 kg (SD, 12.3) less than at baseline compared with 4.3 kg (SD, 12.2) less in the low-fat group (**Figure**). The difference in weight change between groups was not significant (2.1 kg [95% CI, −2.1 to 6.4 kg]; $P = 0.323$ before and $P = 0.411$ after adjustment for baseline variables). From months 12 to 36, the mean difference in weight change was not significant ($P = 0.071$), although the low-carbohydrate group regained weight and the low-fat group did not. Changes in lipids, glycemic control, insulin sensitivity, and dietary intake did not differ significantly.

Discussion: A recent large, 2-year randomized trial that compared weight loss with similar diets (3) found no significant differences between the diets. We observed similar findings at 36 months, but the pattern of weight change from 12 to 36 months differed. Although participants in the low-carbohydrate group lost more weight at 12 months, they regained more weight during the next 24 months. In contrast, participants in the low-fat group maintained their weight loss. The difference in weight regain between groups probably reflects initial weight loss, because greater weight loss from baseline to 12 months was associated with greater weight regain from 12 to 36 months ($P = 0.001$). Carbohydrate restriction during the first 12 months did not cause detrimental effects on lipid levels or renal function at any time during the 36 months.

Conclusion: No significant differences were found in weight change, metabolic outcomes, or dietary intake between the 2 diet groups at 36 months. Both groups maintained a modest weight loss from baseline. Participants who lost more weight during the first 12 months tended to regain more weight by month 36.

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Varenicline and Pheochromocytoma

Background: Varenicline is a widely used smoking-cessation therapy. It acts as an $\alpha_4\beta_2$ nicotinic acetylcholine receptor (nAChR) partial agonist to diminish the symptoms of nicotine withdrawal.

Objective: To report a case of varenicline-triggered pheochromocytoma crisis.

Case Report: A 55-year-old woman who smoked about 15 cigarettes a day for decades had hypertension, hypothyroidism, and an 8-year history of palpitations. She was prescribed varenicline. Her medications included stable doses of telmisartan and L-thyroxine.

The patient took one 0.5-mg varenicline tablet without ill effects, but after taking the second varenicline tablet the next day, she experienced diarrhea, stomachache, and palpitations. She described the symptoms as being unlike anything she had had before. They steadily worsened, and she started having chest pain the next morn-

ing. She took propranolol for the palpitations that morning; it did not help with the palpitations but did not cause any adverse effects.

In the emergency department, the patient was at first stable with mild hypertension, but her condition deteriorated rapidly. She was intubated and transferred to the intensive care unit, where she was treated with milrinone, levosimendan, norepinephrine, and antibiotics for suspected sepsis. Chest computed tomography showed severe pulmonary edema. Echocardiography revealed systolic dysfunction, with an ejection fraction of 0.32. Coronary angiography showed no evidence of occlusive coronary artery disease. Urine metanephrine and normetanephrine levels and serum chromogranin levels were highly elevated, and magnetic resonance imaging showed a left-sided adrenal mass (47 × 34 mm). A subsequent metaiodobenzylguanidine scintiscan was consistent with adrenal pheochromocytoma, which was later removed successfully. The pathoanatomical diagnosis was pheochromocytoma without malignant features.

Discussion: Pheochromocytoma is a catecholamine-releasing tumor that usually arises from the adrenal medulla. The sympathetic nervous system and nAChRs regulate the release of catecholamines from the adrenal gland. Most adrenal nAChRs are $\alpha_3\beta_4$ and $\alpha_3\beta_2$ subtypes, but $\alpha_4\beta_2$ receptors are also found (1, 2). Although the nAChRs subtypes expressed in human pheochromocytomas are unknown, the PC12 cell line, derived from rat pheochromocytoma, expresses α_3, α_4, α_7, β_2, and β_4 subunits (3, 4). Varenicline is a potent partial agonist at $\alpha_4\beta_2$, an agonist at α_7, and a high-efficacy (but low-affinity) agonist at $\alpha_3\beta_4$ receptors (5, 6). Although varenicline has a lower affinity for $\alpha_3\beta_4$ receptors than for $\alpha_4\beta_2$ receptors, it is a more potent $\alpha_3\beta_4$ agonist (lower in vitro half maximal effective concentration value) than nicotine (6), which might explain why varenicline could trigger pheochromocytoma crisis, whereas nicotine derived from smoking did not.

One full day and night after symptom onset, the patient took propranolol (a nonselective β-blocker), which could have exacerbated her condition. She had used propranolol occasionally for the palpitations with no adverse effects, although not in the past several months. She had had a documented visit to the emergency department for palpitations 6 years before the current admission, suggesting that she may have had pheochromocytoma for years without crises. This emphasizes the importance of the temporal relation of varenicline exposure to the crisis. Because pheochromocytoma is a rare condition and varenicline a novel medication, to our knowledge no other studies have reported on the tolerability of varenicline in patients with pheochromocytoma.

Conclusion: Pheochromocytoma should be considered in the differential diagnosis when encountering patients with severe varenicline-associated symptoms. Varenicline should be avoided in patients with suspected or known pheochromocytoma.

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