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REVIEW ARTICLE

Palliative Sedation in End-of-Life Care and Survival: A Systematic Review

Marco Maltoni, Emanuela Scarpi, Marta Rosati, Stefania Derni, Laura Fabbri, Francesca Martini, Dino Amadori, and Oriana Nanni

See accompanying editorial on page 1258; listen to the podcast by Dr Cherny at www.jco.org/podcasts

Marco Maltoni, Emanuela Scarpi, Dino Amadori, and Oriana Nanni, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola; and Marta Rosati, Stefania Derni, Laura Fabbri, and Francesca Martini, Azienda Unità Sanitaria Locale di Forlì, Forlì, Italy.

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Corresponding author: Marco Maltoni, MD, I.R.S.T., Via Piero Maroncelli 40, 47014 Meldola (FC), Italy; e-mail: ma.maltoni@ausl.fo.it.

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ABSTRACT

Purpose
Palliative sedation is a clinical procedure aimed at relieving refractory symptoms in patients with advanced cancer. It has been suggested that sedative drugs may shorten life, but few studies exist comparing the survival of sedated and nonsedated patients. We present a systematic review of literature on the clinical practice of palliative sedation to assess the effect, if any, on survival.

Methods
A systematic review of literature published between January 1980 and December 2010 was performed using MEDLINE and EMBASE databases. Search terms included palliative sedation, terminal sedation, refractory symptoms, cancer, neoplasm, palliative care, terminally ill, end-of-life care, and survival. A manual search of the bibliographies of electronically identified articles was also performed.

Results
Eleven published articles were identified describing 1,807 consecutive patients in 10 retrospective or prospective nonrandomized studies, 621 (34.4%) of whom were sedated. One case-control study was excluded from prevalence analysis. The most frequent reason for sedation was delirium in the terminal stages of illness (median, 57.1%; range, 13.8% to 91.3%). Benzodiazepines were the most common drug category prescribed. Comparing survival of sedated and nonsedated patients, the sedation approach was not shown to be associated with worse survival.

Conclusion
Even if there is no direct evidence from randomized clinical trials, palliative sedation, when appropriately indicated and correctly used to relieve unbearable suffering, does not seem to have any detrimental effect on survival of patients with terminal cancer. In this setting, palliative sedation is a medical intervention that must be considered as part of a continuum of palliative care.

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INTRODUCTION

There is a widespread consensus that physicians have an ethical obligation to relieve pain and other distressing symptoms in patients with advanced cancer.[1] Despite the progress made in palliative medicine in terms of symptom control, there are still many patients who have intractable symptoms, because the treatment is either ineffective or intolerable. In these circumstances, sedative drugs are commonly prescribed to control refractory symptoms and relieve unbearable suffering in those with advanced cancer. However, palliative sedation (PS) at the end of life has aroused concern in the same way as that of opioids.[2] Some authors have suggested that these drugs may shorten life, thereby confusing the boundaries between PS and euthanasia.[3] Indeed, PS has been dubbed by some as slow euthanasia or terminal sedation, both terms suggesting that patients' lives are shortened by treatment.[3] This has sparked a wide debate in the palliative care world.

Here we present the results of a systematic review of literature published over the past 30 years concerning the clinical practice of PS. The aim of this review was to evaluate the effect of sedation on survival, when appropriately indicated and correctly used to relieve unbearable suffering. In particular, we wanted to determine if there is a significant difference in survival between sedated and nonsedated patients and if the use of sedatives is associated with anticipation of death.

METHODS

Study Design and Search Strategy

According to the review protocol approved by the medical scientific committee of our institute (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori), a systematic review of literature published between January 1980 and December 2010 was performed using MEDLINE and EMBASE databases. Because the global definition of PS at the end of life is not generally accepted, we adopted the following search terms: palliative sedation, terminal sedation, refractory symptoms, cancer, neoplasm, palliative care, terminally ill, end-of-life care, and survival. A manual search of the bibliographies of electronically identified articles was also performed. Studies were included in the analysis if they reported on the length of survival of terminally ill adult patients with cancer referred or not referred for PS therapy. The previous end point was crucial in excluding or including the articles in our systematic literature review (references not included in the review are listed in the Appendix, online only). Only articles published in English were selected. Case studies, letters, reviews, editorials, and studies focusing on euthanasia and assisted suicide, ethical aspects, or opinions were excluded, as were articles that did not report the length of survival of each sedated and nonsedated group of patients. The following study characteristics were recorded: first author, year of publication, sample size, type of study (randomized clinical trial or prospective, retrospective, or cohort study), study location (hospice, hospital, home care), number of patients sedated, reasons for sedation, length of PS (days), type of sedative used, mode of sedation (primary/secondary, intermittent/continuous, proportional/sudden, mild/deep), mean and/or median length of sedative use (days), and mean and/or median overall survival (days).

Selection of Trials and Data Collection

Two reviewers (M.M., E.S.) independently assessed the eligibility of the studies identified by the search. The same reviewers extracted the data independently using a data collection form predefined in the study protocol. All data were checked for internal consistency, and any disagreements in interpretations were resolved by a discussion and consensus approach. All selected articles had to present a reliable measurement of outcome. Length of survival of sedated and nonsedated patients was collected and tabulated for each case series. The methodologic quality of each study was assessed according to the criteria proposed by Hawker et al.[4] Each part of the study was appraised as good, fair, poor, or very poor. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for building reviews were strictly followed.

Statistical Methods

The main outcome measure for this systematic review was length of survival for sedated and nonsedated patients. Because the study designs, participants, interventions, and reported outcome measures varied markedly, we decided to focus on describing the studies, their results, and their limitations and on a qualitative synthesis rather than combining the data in a meta-analytic statistical approach.

RESULTS

Fifty-nine articles were identified through an electronic and manual literature search strategy summarized in Figure 1. Of these, 48 were excluded for the following reasons: reviews (n = 4), guidelines (n = 2), case reports (n = 2), surveys (n = 8), letters (n = 1), ethics articles (n = 3), and articles not presenting survival comparisons between sedated and nonsedated patients (n = 28; Fig 1; excluded articles are described in the Appendix, online only).

Of the 11 articles that matched the inclusion criteria,[5-15] there were no randomized trials; seven studies were retrospective,[6,7,9-13] and four were prospective.[5,8,14,15] All involved consecutive patients except for one prospective matched cohort study presented by our group, in which the sedated group was consecutively recruited, and the nonsedated group was simultaneously recruited and matched for age, sex, reason for hospice admission, and Karnofsky performance status.[15]

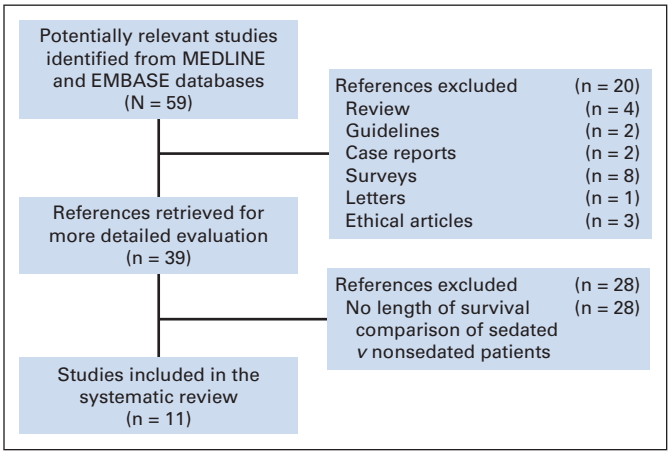

Fig 1. Search results.

Although most of the studies were designed to evaluate the prevalence and type of symptoms in terminally ill patients, the study methodologies were found to be heterogeneous in terms of inclusion criteria, data collection, and care setting. Sample size varied considerably between studies, with 76 patients in the study by Fainsinger et al[7] and 548 in that by Muller-Busch et al.[9] Ten studies involved hospitalized patients from palliative and/or acute care units, and one involved patients receiving home care.[5] Study characteristics are listed in Table 1.

There was great variability in the number of patients receiving sedation (range, 14.6% to 66.7%). Of 1,807 consecutive patients enrolled onto 10 studies, 621 (34.4%) were sedated. Although delirium was the most common indication for PS, there was wide interstudy variability (range, 13.8% to 91.3%). Other frequent reasons for sedation were dyspnea (range, 8.7% to 63.0%) and pain (range, 9.5% to 49.2%). Of the 10 studies reporting the main refractory symptoms requiring sedation (Fig 2),[5-9,11-15] seven reported psychological distress as one of the main reasons for prescribing PS.[6,9,11-15] Mean or median duration of sedation varied from 0.8 to 12.6 days. We also found a significant difference in type of drug used, not only among countries but also among care units in the same country. Midazolam was the most common drug prescribed in nine of the studies (Fig 3).[6-8,10-15] Psychotropic drugs were also frequently used, sometimes in conjunction with benzodiazepines. However, they were the most favored drug category in only two reports, one citing haloperidol, and the other, chlorpromazine and lorazepam (administered intravenously and/or subcutaneously).

PS characteristics are listed in Table 2. Proportional sedation was the most common method of drug administration; few patients received sudden sedation (deliberately rapid loss of consciousness, inducing deep sleep). Furthermore, only four studies reported results of sedation in terms of relief of distress.[7,8,12,14] In most studies, survival was defined as the number of days from hospice/hospital admission or from the start of home care to death. Survival from the start of sedation therapy was also reported in two studies.[6,8] Median survival of sedated and nonsedated patients varied from 7 to 36.5 days and from 4 to 39.5 days, respectively; this was not statistically different between the two patient groups (Table 3).

DISCUSSION

Despite the huge progress made in palliative medicine in terms of symptom control, many are intractable (refractory symptoms),

Table 1. Study Characteristics

Study	Total No. of Patients	Type of Study	Location of Study	Patients Receiving Sedation		Sedation*		Quality of Study
				No.	%	Reason	%	
Ventafridda et al[5]	120†	Prospective	Home care	63	52.5	Breathlessness, dyspnea	52.4	Fair
						Pain	49.2	
						Delirium	17.5	
						Vomiting	7.9	
Stone et al[6]	115	Retrospective	Hospital, hospice	30	26.0	Agitated delirium	60.0	Fair-poor
						Mental anguish	26.7	
						Pain	20.0	
						Breathlessness	20.0	
						Other	3.3	
Fainsinger et al[7]	76	Retrospective	Hospice	23	30.3	Pain	0	Fair-poor
						Nausea	0	
						Breathlessness	8.7	
						Delirium	91.3	
Chiu et al[8]	251‡	Prospective	Hospital, hospice	70	27.9	Agitated delirium	57.1	Fair
						Breathlessness	22.8	
						Severe pain	10.0	
						Insomnia	7.2	
						Severe itching	2.9	
Muller-Busch et al[9]	548	Retrospective	Hospital	80	14.6	Anxiety, psychological distress	40.0	Fair-poor
						Breathlessness	35.0	
						Delirium	13.8	
						GI	7.5	
						Pain	2.5	
						Bleeding	1.3	
Sykes et al[10]	237	Retrospective	Hospice	114	48.0	NR		Fair
Kohara et al[11]	124	Retrospective	Hospital	63	50.3	Breathlessness	63.0	Fair-poor
						Restlessness	40.0	
						Pain	23.0	
						Agitation	21.0	
						Nausea, vomiting	6.0	
Vitetta et al[12]	102	Retrospective	Hospice	68	66.7	Anxiety, depression	25.5	Fair
						Delirium	38.0	
Rietjens et al[13]	157	Retrospective	Acute PCU	68	43.0	Terminal restlessness	62.0	Fair-poor
						Breathlessness	47.0	
						Pain	28.0	
						Anxiety	6.0	
						Other	15.0	
Mercadante et al[14]	77	Prospective	PCU	42	54.5	Breathlessness	59.5	Fair
						Delirium	57.1	
						Psychological distress	11.9	
						Pain	9.5	
Maltoni et al[15]	518	Prospective, multicenter, matched cohorts	Hospice	267	25.1§	Delirium	78.7	Fair
						Breathlessness	19.5	
						Pain	11.2	
						Vomiting	4.5	
						Psychological and physical distress	18.7	
						Psychological distress only	6.0	

Abbreviations: NR, not reported; PCU, palliative care unit; PS, palliative sedation.
*Percentage refers to sedated patients only.
†154 enrolled.
‡276 enrolled.
§Percentage refers to the overall prevalence of PS in patients admitted to participating hospices.

either because the treatment is ineffective or because the treatment itself is intolerable.[1,2] PS, aimed at offering relief from unbearable suffering, is therefore the only reasonable option left to control these symptoms. A recent systematic review addressed the feasibility of PS in the residential setting, showing it to be a realistic treatment option for those who choose to die at home.[16] In a survey of European oncologists, Cherny et al[17] reported that although PS should be an integral part of the professional skills of medical oncologists, few of those interviewed felt sufficiently confident in their ability to manage PS. Some authors have suggested a negative impact of PS on survival, becoming a kind of slow euthanasia.[3,18] However, the European Association for Palliative Care Ethics Task Force has clearly stated that PS is a medical intervention, totally different from euthanasia in aim, procedure, and result (or success [ie, attainment of expected outcome]).[19] Overall, despite

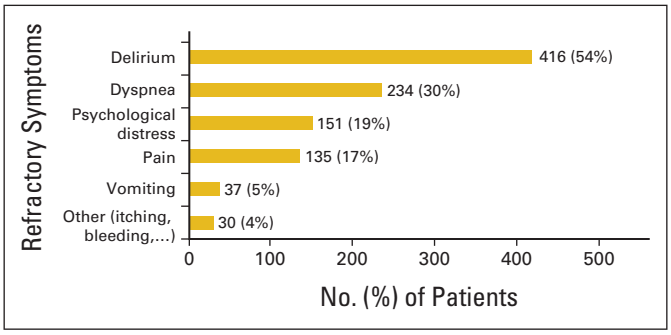

Fig 2. Main refractory symptoms requiring sedation in 774 sedated patients from 10 studies.[5-9,11-15]

some interstudy variability, a common concept in many PS definitions is "the use of sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness."[20(p67),21]

The most common refractory symptoms requiring sedation are reported in Figure 2. Delirium and dyspnea are fairly unequivocal, frequently present at the end of life, and prognostic for death in a short time.[22,23] However, many other symptoms are much harder to characterize. For example, although psychological distress is reported to be a common reason for PS in several studies,[6,9-12] it is seemingly entirely absent in others.[5,8] Indeed, PS as a means to treat psychological suffering is particularly delicate and controversial, presenting some irregularities. First, it may occur early in the disease trajectory, not just in the terminal phase. Second, it has little chance of being alleviated by supportive and/or psychological interventions, so many people should be sedated if their psychological suffering cannot be controlled. Last, although it tends not to be progressive, such as the suffering caused by physical symptoms, it often fluctuates and is unpredictable. For all these reasons, PS should be used with extreme caution, together with regular multidisciplinary discussions, specialist psychological support and spiritual assistance, and intermittent or relief sedation instead of continuous sedation.[24,25] Sedation, as evidenced in this study, may be superficial or deep, continuous or intermittent, gradual or rapid, and primary or secondary.[26] As already noted, the prevalence of PS to control refractory symptoms varies considerably. This could be a reflection of the uncertain definition of the term PS, with some authors focusing on the most extreme continuous deep sedation and others on any type of sedation. The use of different patient case mixes in albeit similar palliative care programs could also be an important factor in this uncertainty. Sedation is generally used over a short period, and most

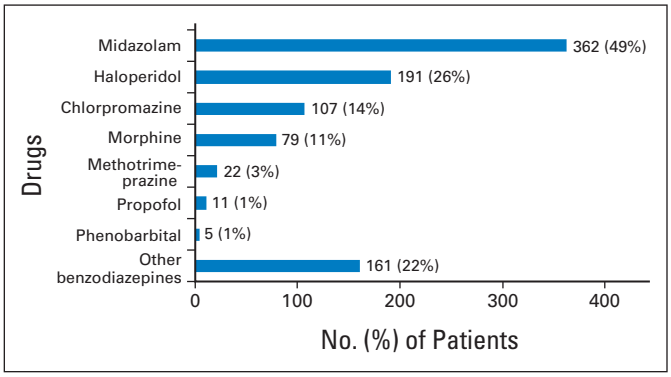

Fig 3. Sedative drugs administered to 745 patients from nine studies.[5-7,9-14]

evidence shows that in the context of specialist palliative care and when correctly used for symptom relief, it is not associated with shortening of life. In this way, from an ethical point of view, the theory of double effect does not apply. Morita et al[27] argue this case, reporting a possible negative impact on survival (in which the theory of double effect is rooted) in only 3.9% of sedated patients. Naturally, PS has to be performed with great accuracy, because a voluntary or involuntary abuse of drugs could lead to iatrogenic overdose and acceleration of death. This unwelcome event could have dramatic consequences, especially in nonterminal and respite sedations. For this reason, the effects of PS need to be accurately monitored patient by patient, and a correct approach in decision making and in performing PS is mandatory. Guidelines and frameworks have recently been published to help the clinician in this difficult and delicate area.[24,25]

Length of survival cannot be considered the only outcome measure of PS; other real outcomes such as ability to control symptoms and probability to survive after discontinuation of PS could be important aspects in this setting. Nevertheless, we decided to focus our review primarily on the former aspect, being an ethically sensible topic.

Our review reports the data across studies to estimate the length of survival in both sedated and nonsedated patients with more precision than is possible in a single study. However, our review has several limitations, the most important being the quality of the studies, because randomization is ethically implausible. As a consequence, only prospective cohort and retrospective studies, not always of good quality, are able to provide the highest level of evidence with the well-known risk of bias. Our quality evaluation of the studies was performed according to Hawker's method, which offers the possibility of reviewing disparate data systematically.[4] According to this method, the quality of evidence was quite low: fair to poor in five studies, and fair in six studies.

Other limitations include the heterogeneity of the patient inclusion criteria and of the definitions of PS and differences in clinical setting and type of drug used. Incomplete data on study design, patient population, and criteria for the choice of nonsedation control may hamper interpretation and synthesis of the included studies. These limitations make the presentation of data in a statistical meta-analytic, evidence-based approach almost impossible.

Although the studies included in this review assessed all types of sedation, there were no reports comparing the effects of nonsedation and continuous deep sedation. In each study, there was no significant difference in overall survival between patients who received sedation or those who did not, although in five studies there was a trend in favor of sedation.

Sedation should be appropriately used for the control of specific symptoms once all other therapeutic alternatives have been considered and found to be ineffective or inapplicable. As agents to control symptoms, not to shorten life, sedatives should be provided in doses that are titrated against the response to achieve relief of symptoms. Benzodiazepines remain the most favored class of sedatives in the palliative care world. Midazolam is the most commonly used drug; it is administered by continuous subcutaneous infusion, and it has anticonvulsant, muscle relaxant, and anxiolytic properties. However, the psychotropic drugs haloperidol, levomepromazine, and chlorpromazine may be more appropriate for the specific management of delirium and can be used in combination with benzodiazepines.

In conclusion, the key drawback of this study is the lack of evidence from randomized controlled trials, in which patients are randomly allocated to sedation or nonsedation groups, but this is an impossible task, because it cannot be ethically justified. However, our

Table 2. Palliative Sedation Characteristics

Study	Sedative		Sedation		Duration of Sedation (days)		Length of Sedative Use (days)	
	Type	Patients Treated (%)	Mode	Patients Treated (%)	Mean	SD	Median	Range
Ventafridda et al[5]	Diazepam	NR	Proportional		2.1	2.7	2	0.1-16.7
	Chlorpromazine	NR	Continuous					
	Haloperidol	NR						
	Morphine	NR						
	Methadone	NR						
Stone et al[6]	Midazolam	80	Proportional		1.3	1.4	NR	
	Methotrimeprazine	33						
	Haloperidol	37						
	Other	3						
Fainsinger et al[7]	Midazolam	61	Proportional		2.5	NR	1	0.2-0.5
	Benzodiazepine	30	Intermittent/continuous					
	Chlorpromazine/lorazepam	9						
Chiu et al[8]	Midazolam	24	Intermittent	52.9	12.6	19.6	5	
	Chlorpromazine	3	Continuous	37.1				
	Haloperidol	50	Intermittent/continuous	10				
	Other benzodiazepines	10						
	Morphine, rapidly increasing dose	13						
Muller-Busch et al[9]	Midazolam	NR	Proportional		2.6	2.4	NR	
	Analgesics	NR	Intermittent	60				
	Comedication	NR	Continuous	40				
Sykes et al[10]	Midazolam	80	Proportional		NR		NR	
	Methotrimeprazine	11						
	Haloperidol	1						
	Propofol	1						
	Phenobarbital	4						
Kohara et al[11]	Midazolam	98	Proportional		3.4	NR	NR	
	Haloperidol	84	Continuous	69				
	Scopolamine	10	Intermittent/continuous	30				
	Hydrobromide	5						
	Chlorpromazine	2						
	Flunitrazepam	2						
	Ketamine	NR						
Vitetta et al[12]	Haloperidol	43	Proportional		NR		NR	
	Midazolam	61	Continuous/intermittent					
	Clonazepam	18						
Rietjens et al[13]	Midazolam	75	Continuous/deep	100	0.8	NR	NR	
	Midazolam and other	10						
	Propofol	15						
Mercadante et al[14]	Midazolam	100	Intermittent/definitive	28.3	6.6	4.6	0.9	2-160
			Continuous	66.7				
Maltoni et al[15]	Lorazepam	38	Primary	86	4	6	2	0-43
	Chlorpromazine	38	Secondary	14				
	Midazolam	8	Intermittent	56				
	Prometazine	24	Continuous	44				
	Haloperidol	23	Mild	62				
	Diazepam	9	Deep	38				
	Other	4	Proportional	88				
	Morphine	26	Sudden	12				

Abbreviations: NR, not reported; SD, standard deviation.

systematic review seems to show that apart from observational clinical studies, a certain level of evidence on the absence of an impact of PS on survival can be affirmed, and PS can therefore be considered as an integral part of the palliative medicine approach to end-of-life care.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

Table 3. Survival in Days From Admission: Sedated Versus Nonsedated Patients

Study	Sedated Patients					Nonsedated Patients					*P*
	Mean	SE/SD	Median	Range	90%/95% CI	Mean	SE/SD	Median	Range	90%/95% CI	
Ventafridda et al[5]			25	NR				23	NR		.57
Stone et al[6]	18.6	NR				19.1	NR				> .2
Fainsinger et al[7]	9	5	8	2-16		6	7	4	1-33		.09
Chiu et al[8]	28.5	36.4				24.7	30.9				.430
Muller-Busch et al[9]	21.5	20.3	15.5	1-109		21.1	23.6	14.0	0-199		NR
Sykes et al[10]											.23
48-hour sedation	14.3		7.0	1-182	11.2 to 17.4	14.2		7.0	1-80	12.7 to 15.7	
7-day sedation	36.6		34.5	7-86	31.5 to 41.7	14.2		7.0	1-80	12.7 to 15.7	
Kohara et al[11]	28.9	25.8				39.5	43.7				.10
Vitetta et al[12]	36.5				20.4 to 52.7	17				2.2 to 31.8	.1
Rietjens et al[13]			8	0-38				7	0-38		.12
Mercadante et al[14]	6.6	4.6				3.3	2.8				.003
Maltoni et al[15]			12		10 to 14			9		8 to 10	.330

Abbreviation: NR, not reported.

AUTHOR CONTRIBUTIONS

Conception and design: Marco Maltoni, Emanuela Scarpi, Dino Amadori
Administrative support: Emanuela Scarpi, Dino Amadori
Provision of study materials or patients: Emanuela Scarpi, Marta Rosati, Stefania Derni, Laura Fabbri, Francesca Martini
Collection and assembly of data: All authors
Data analysis and interpretation: Marco Maltoni, Emanuela Scarpi, Dino Amadori
Manuscript writing: All authors
Final approval of manuscript: All authors

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CORRECTIONS

Author Corrections

The April 20, 2012, review article by Maltoni et al, entitled "Palliative Sedation in End-of-Life Care and Survival: A Systematic Review" (J Clin Oncol 30:1378-1383, 2012), contained errors.

In Figure 2, incorrect data were given for all refractory symptoms. The corrected figure is reprinted here in its entirety.

The online version has been corrected in departure from the print. The authors apologize for the mistakes.

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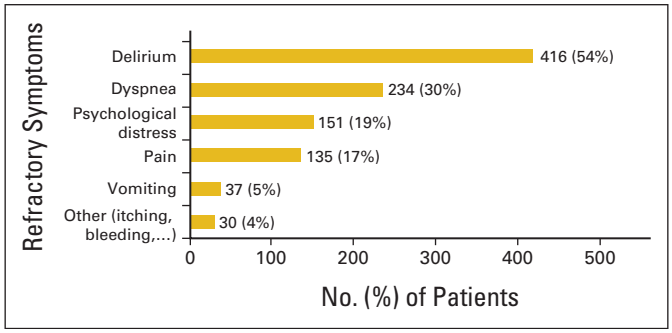

Fig 2. Main refractory symptoms requiring sedation in 774 sedated patients from 10 studies.[5-9,11-15]

The July 10, 2012, article by Garderet et al, entitled "Superiority of the Triple Combination of Bortezomib-Thalidomide-Dexamethasone Over the Dual Combination of Thalidomide-Dexamethasone in Patients With Multiple Myeloma Progressing or Relapsing After Autologous Transplantation: The MMVAR/IFM 2005-04 Randomized Phase III Trial From the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation" (J Clin Oncol 30:2475-2482, 2012), contained an error.

In the Affiliations section, the affiliation of Francesco Onida was given as University Hospital Milano, Milano, Italy, whereas it should have been Maggiore Policlinico Hospital, University of Milano, Milano, Italy.

The authors apologize for the mistake.

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