The use of opioids and sedatives at the end of life

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Opioids and sedative drugs are commonly used to control symptoms in patients with advanced cancer. However, it is often assumed that the use of these drugs inevitably results in shortening of life. Ethically, this outcome is excused by reference to the doctrine of double effect. In this review, we assess the evidence for patterns of use of opioids and sedatives in palliative care and examine whether the doctrine of double effect is needed to justify their use. We conclude that patients are more likely to receive higher doses of both opioids and sedatives as they get closer to death. However, there is no evidence that initiation of treatment, or increases in dose of opioids or sedatives, is associated with precipitation of death. Thus, we conclude that the doctrine of double effect is not essential for justification of the use of these drugs, and may act as a deterrent to the provision of good symptom control.

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There is a widespread consensus that physicians have an ethical obligation to relieve patients with advanced cancer of pain and other distressing symptoms.[1] However, opioids and sedatives—two vital classes of drugs for symptom control at the end of life—have become tainted with the implication that they hasten death.

High profile court cases involving the legal or illegal use of morphine attract much attention.[2,3] Billings and Block, described the use of a morphine drip (figure 1) as "slow euthanasia".[4] And, in a statement about physician-assisted suicide, the US Supreme Court described this treatment as pain relief that advances death. Wall believes these views perpetuate myths surrounding the use of morphine, despite the fact that claims about its addictive potential and safety have now been successfully challenged. He concludes that "we must help patients to be absolutely clear that their treatment for pain is just that, it is not an alternative route to an early grave".[5]

Despite the progress that has been made in palliative medicine with regards to symptom control, there are still patients who have symptoms that prove intractable, either because treatment is ineffective or the treatment itself is intolerable. The response in these circumstances is to use sedative medication to reduce the patient's awareness of their symptoms and hence relieve distress. In addition to physical symptoms, mental syndromes such as agitated delirium, severe anxiety, and fear are also present near the end of life. In very ill patients, delirium may prove to be untreatable, and the patients's energy and ability to concentrate may be insufficient to cope with talking through their concerns. In this situation, sedation is also the therapeutic response.

The use of sedation at the end of life has attracted suspicion in the same way that the use of opioids has done.

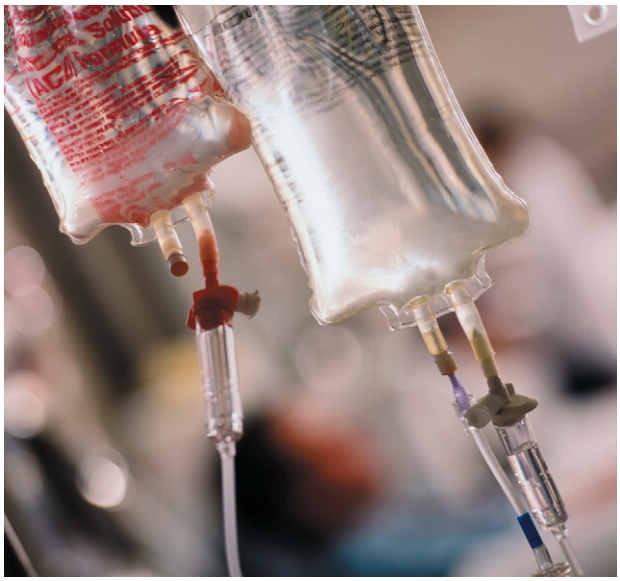

Figure 1. Opioids and sedatives can be given in increasing doses at the end of life.

The practice has been dubbed slow euthanasia or terminal sedation;[4] both these terms suggest that patients' lives are shortened by treatment. Such use of opioids and sedatives can be defended ethically on the basis of the doctrine of double effect.[6] The doctrine of double effect applies to a medical treatment if the following conditions are met:

- the treatment is potentially beneficial but may also have harmful effects
- the clinician intends the beneficial effect but not the harmful effect, although the harmful effect may be foreseen
- the harmful effect is not necessary in order to achieve the beneficial effect
- the symptoms are severe enough to constitute a compelling reason to expose the patient to the risk of a harmful outcome.

However, critics of this argument say that it is too difficult to know a person's true intentions.[7] The potential danger of conceding to these criticisms is that effective symptom control is withheld from dying patients for fear of accusations of malpractice.

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We aim to review current practices of opioid and sedative use, focusing particularly on evidence that life is shortened through use of these drugs.

Opioids

We identified 17 studies which examined the use of opioids at the end of life,[8–24] and analysed them for patterns of opioid use, types of opioid used, mean doses, and effect of opioid use on survival.

The use of opioids in palliative care

Opioids are commonly used in palliative care for the treatment of pain,[25] dyspnoea,[26] and cough (figure 2). Higher doses of opioids are required in some clinical situations such as neuropathic pain, advancing disease, metabolic variation, and in younger patients.[27] Such factors may explain some interindividual variation in the effectiveness of opioids, but the use of adjuvant analgesics and attention to non-physical factors, which may be exacerbating pain, need to be considered alongside dose escalation.

Inappropriate increases in opioid doses will probably result in myoclonus, hallucinations, and delirium. Although respiratory depression is the most feared and often quoted side-effect of strong opioids, it occurs late because tolerance to the effects on respiration develops with chronic use.[28] Fohr concluded that when opioids are used appropriately for pain relief, the risk of respiratory depression is more myth than fact.[29] However, the risk remains real when opioids are used inappropriately. Tolerance to the analgesic effect of opioids does not seem to be a significant problem.[27]

Opinion is divided over the issue of increasing opioid doses as symptoms increase and death approaches, because studying such circumstances is difficult. Those studies which have been published showed great variation in reported responses; probably due to differences in definitions, patient groups, and timing of assessments. Pain at the end of life is reported to occurr in up to 51% of patients, and dyspnoea is present in up to 38%. There is some evidence that pain becomes less over the last few weeks of life, but dyspnoea is known to worsen.[16,30]

Opioid use at the end of life

Frequency

The reported frequency of opioid use in the last few days of life varies from 25% to 99%.[14,18] Generally, patients receiving community palliative care seem to be given less opioids. Goldberg and colleagues reported that 66% of patients being cared for at home received opioids compared with 78% of hospice patients.[19] Patients receiving conventional care (ie, care without specialist palliation) received less opioids than either of the other two groups, possibly confirming the presence of anxieties among general physicians about their use. Mercadante reported a minimum use of opioids of 25% in his community group.[18] He suggests that this low percentage is due to a wide selection of patients in contrast to studies in specialist palliative-care units that treat more complex cases. McCormack, by contrast, found that 89% of patients received opioids in his community group.[20] This figure is similar to other in-patient studies that showed 70–90% of patients received opioids.

Figure 2. Opioids are derived from opium poppies (P somniferum).

Changes in dose

Studies of dose alterations show great variation in the methods used. Different time periods have been analysed and different percentage changes considered significant. Four studies showed an increase in the proportion of patients receiving opioids as death approached (table 1). Goldberg and colleagues reported only minor changes in the proportion of patients receiving opioids near death, but in conventional-care patients the proportion dropped from 68% to 57%.[19]

Five studies reported that the mean dose also increased over the last few weeks or days of life (table 2). Morita and colleagues[9] and Fainsinger and colleagues[15] found a decrease in opioid dose during the last few days of life after an initial increase. Furthermore, eight studies reported that some patients required a marked increase in the last 24–48 hours of life.[9,11,12,14,16,17,21,22] The percentage of these patients varied considerably from occasional individuals[21] to 32% (20% of which received less than 25 mg of parenteral morphine per day)[22] and 40%.[17]

Doses of opioids used

Mean doses of opioid used at the time of death vary widely between studies: 52–659 mg[14,21] with a weighted average of 192 mg. Patients in the USA and Canada reportedly receive higher doses than elsewhere. These differences have been suggested to be because of different rates of use of adjuvant

Table 1. Patients receiving strong opioids at study entry and before death

Patients receiving opioids at start of study (%)	Patients receiving opioids before death (%)	Ref
42	87	9
61	89	12
69	66	19
76	78	
68	57	
68	85	20

Table 2. Change in mean opioid dose in parenteral morphine equivalents from study entry to death

Mean opioid dose on entry to study (mg)	Mean opioid dose before death (mg)	Ref
49	139	9
42	55	12
125	460	13
493	659	14
184	180	15
45	75	24

analgesics, variations in psychological care, and differences in the type of opioids used.[31] In two studies by Fainsinger and colleagues, there is a marked difference in mean opioid dose.[14,15] This variation may be because of an increased rotation between different opioids and the use of methadone suppositories.

Types of opioids

Morphine is by far the commonest strong opioid used in studies that report on the frequency of opioid use (table 3).

Effect on survival

Five studies have looked at the effect of opioid use on survival, although they used different methods.[8,9,10,12,32] None of the studies reported that opioids had shortened life. However, this aspect does not seem to have been as frequently examined with opioids as it has been with sedatives.

Bercovitch and colleagues found no difference in survival between patients receiving high doses and those receiving low doses.[8] Furthermore, there were no cases of respiratory depression. Morita and colleagues found no significant difference in the survival of patients receiving different doses of opioids.[10] However, the studies comparing mean doses of opioids may be misleading because the rate of change of dose has been suggested to be a more important factor.[28] We reported, however, that there was no significant difference in the rate of increase in dose in relation to survival.[12] In the same study, we also analysed the distribution of large increases in opioid dose during the last week of life. We found that such increases were no more likely to occur in the last 48 hours of life than earlier in the study period. Regnard and Badger compared patients who were given a double dose of opioid at night with those who received a single dose; they reported that those in the double dose group were no more likely to die at night.[32] Respiratory depression seems to be an issue of concern only in experimental situations.[33]

Guidelines for opioid use at the end of life

Guidelines on the use of opioids in palliative care advocate the careful titration of opioid according to the patient's pain. They also offer reassurance that the appropriate use of morphine should not shorten life and that there is no reason to withhold opioids in the last few days.[34,35]

The evidence we report in this review supports these guidelines. Although studies generally report a gradual increase in opioid dose up until the end of life, there is no apparent shortening of life when higher doses are used or, as reported by our study, when the rate of administration of opioids is increased. Cases in which opioid doses given to patients increase substantially are rare even in specialist palliative-care units where more difficult pain problems may occur. Clinicians who are treating patients that need large increases in opioid dose should be encouraged to seek specialist help, particularly if the dose increases are greater than 100% per day or the clinician feels they risk shortening a patient's life. This message is reinforced in the UK's Royal College of Physicians guidance information that reminds doctors of the professional obligation to seek advice when the limits of their skills have been reached.

Sedation

We identified 17 studies (including 2 yet to be published by Morita and colleagues, and Scholes and colleagues, respectively) that addressed the use of sedatives in the care of cancer patients in the final stages of life.[10,14,22,36–47] In addition, we included a systematic review that analysed three studies published in Spanish.[48]

Definitions of sedation

In a survey of palliative physicians, Chater and colleagues defined sedation as "deliberately inducing and maintaining deep sleep for the relief of intractable physical or mental symptoms", but specified that their definition did not include the management of delirium.[49] Only 40% of respondents agreed with this definition and there were several alternative views. There is evidence that heavy sedation is more likely to be used by physicians who are less confident in psychological care and have higher levels of professional burnout.[50]

Table 3. Percentage of patients given strong opioids at the end of life

Morphine	Buprenorphine	Tramadol	Hydromorphone	Methadone	Diamorphine	Other	Ref
100	..	..	..	..	..	..	8
77	20	..	..	..	..	..	10
62	8	11	..	..	..	10	11
59	..	..	39	5	11	..	14
57	..	..	38	6	2	4	15
36	..	..	22	11	..	2 (oxycodone)	16
19	..	..	14	8	..	9	19
44	..	..	9	1	..	..	20
100	..	..	..	..	..	..	24

Table 4. Characteristics of sedation used

Type of study	n	Type of care	Mode of sedation	Frequency of sedation (%)	Length of sedative use (days)	Survival (days)	Ref
Retrospective	209	Palliative-care unit	Proportional	60	..	Overlapping Kaplan-Meier curves	10
Retrospective	100	Palliative-care unit	Proportional	16	..	..	14
Prospective	50	Palliative-care unit	Proportional and hospital	88	..	..	22
Prospective	154	Home care	Proportional	52	2*	25* (sedated) 23* (non-sedated) (p=ns)	36
Prospective	20	Hospital	Proportional	25	2·5	..	37
Retrospective	143	Palliative-care unit	Proportional	48	3·9	..	38
Retrospective	115	Palliative-care unit	Proportional and hospital	26	1·3	18·6 (sedated) 19·1 (non-sedated) (p=ns)	39
Retrospective	278	Palliative-care unit	Sudden	1	1·5	..	40
Retrospective	76	Palliative-care unit	Proportional	30	2·5	..	41
Prospective	157	Palliative-care unit	Proportional	45	3	..	42
Prospective Multicentre	401	Home and hospital	..	7–60	..	..	43
Prospective Muticentre	150	Palliative-care unit and hospital	Sudden	4–10	2·6	..	44
Prospective Multicentre	387	Palliative-care unit	Sudden	15–36	1·9–3·2	..	45
Prospective	251	Palliative-care unit	Proportional	28	5*	28·5 (sedated) 24·7 (non-sedated) (p=ns)	46
Retrospective	237	Palliative-care unit	Proportional	48	..	38·6 (sedated) 14·2 (non-sedated) (p<0·001)	47
Retrospective	284	Palliative-care unit	Proportional	22	2·5* (midazolam only)	..	†
Prospective	40	Palliative-care unit	Proportional	..	2·8 (levomepromazine) 1·0 (midazolam)	..	‡

*Median; †Morita et al, unpublished data; ‡Scholes et al, unpublished data; ns, not significant.

Clearly, many, perhaps most, palliative physicians do not aim to induce deep sleep by use of sedative drugs in very ill patients, other than in a situation where the patient experiences a catastrophic event, which is likely to cause an imminent, distressing death.[51] Instead, the sedative dose is titrated against the distress response, just as opioid doses are titrated against a pain response. Sedation should be classed as adequate if distress is relieved and the patient remains conscious. Sales described this approach as "proportional", distinguishing it from the act of deliberately inducing deep sleep which he termed "sudden".[48] We have used these terms in the analysis of the studies in table 4. However, in some cases it is unclear which approach was used and we do not agree with Sales about the interpretation of some of the studies. Also, few studies provide a definition of sedation, and the depth of sedation has either not been measured (many investigations are retrospective) or assessed in an objective way to allow a comparison with other reports.

Definitions of symptoms

Pain, dyspnoea, and vomiting are fairly unequivocal symptoms, but some studies use different terms, and other symptoms can be harder to characterise. Existential or familial distress is a fairly common reason for sedation in some countries, notably Spain, but apparently entirely absent in others.[45] How much does this category overlap with what another group has labelled mental anguish?[39] Is the classification the same as the restlessness reported by McIver and colleagues,[37] or the same as what most others studies define as delirium?

Some of these differences may be cultural, with identical behaviours given different interpretations in different countries. However, it has been suggested that some of the differences in perceived levels of existential distress may be genuine, and may be a reflection of the limited disclosure of information about cancer, which is common in some countries. The result of this practice may be a level of psychological distress that grows as the patient realises the seriousness of his or her condition through physical deterioration.[45] Although there is general agreement about the most common indications for use of sedatives at the end of life, such differences need to be explored further.

Patterns of sedative use

Table 4 shows the frequency and length of sedative use in various studies and table 5 describes the types of drug and indications for sedation. The prevalence of sedation varies widely, from 1% to 88% among the populations analysed. This variation is partly due to differences in definitions of sedation. Studies reporting a proportional use of sedation show a mean use of 45%, whereas the small number of studies using so-called "sudden" sedation report a mean use

of 16%. It is fair to expect that sedation to unconsciousness is a less common procedure than more moderate sedation.

Another influence on studies of sedation is the type and geographical location of the units where the studies were done. Units that have more complex and challenging palliative-care problems seem to use sedation more freely than those that are less specialised. This situation was the case in Canada where the specialist palliative-care unit had a sedation rate of 10% compared with 4% reported in other units.[44] Similarly, in a UK hospice, 31% of patients experienced some degree of sedation compared with only 21% of patients in hospital.[39] However, Peruselli and co-workers analysed data from at least 58 different centres across Italy and reported large differences in sedation frequency.[43] These results are likely to reflect differences in the definition of sedation by different doctors, rather than actual use of sedative drugs. Because of the variability inherent in this study it is impossible to classify the mode of sedative use (table 4).

Fainsinger and colleagues found that sedation was used more than twice as often in a Spanish palliative-care unit than in a comparable Israeli centres, with two South African centres having values inbetween.[45] This finding raises the possibility that the triggers for sedation are culturally determined. However, none of the uses of sedatives reported in this international multicentre study fell outside the range of values reported from studies in English-speaking countries.

There is a general agreement across the studies that a syndrome of delirium and agitation in an extremely ill patient with cancer is the most common indication for sedative use, with a weighted mean of 65% (table 5). After this, breathlessness is the next most frequent reason (weighted mean 26%). Pain, perhaps surprisingly, is a much less common reason for sedation (weighted mean 14%).

The drugs used in this patient group vary between countries, but midazolam was the most common, used in 8 of the 13 studies that reported medications, and was the second most used sedative in three other studies. Psychotropic drugs are used frequently, sometimes in conjunction with benzodiazepines. However, they are the most favoured drug category in only three reports—two citing haloperidol and the other chlorpromazine. Given the inefficiency of opioids as sedatives it is surprising to find their inclusion—in one case at the top of the list—in

Table 5. Types of sedative used and the indications for sedation

Type of sedative	Percentage of patients treated	Reason for sedation	Percentage of patients with symptoms	Ref
Haloperidol	43	..	..	10
Midazolam	23	..	..	
Hydroxyzine	15	..	..	
	..	Delirium	63	14
	..	Pain	37	
Midazolam	..	..	..	22
Clonazepam	..	..	..	
Lorazepam	..	..	..	
Diazepam	..	..	..	
Diazepam	..	Dyspnoea	41	36
Chlorpromazine	..	Pain	39	
Haloperido	..	Delirium	14	
	..	Vomiting	6	
Chlorpromazine	100	Dyspnoea	55	37
	..	Restlessness	45	
Midazolam	55	Dyspnoea	49	38
Morphine	55	Pain	39	
Haloperidol	33	Malaise	38	
Diazepam	15	Agitation	23	
Scopolamine	13	Nausea	10	
Midazolam	80	Delirium	60	39
Haloperidol	37	Mental anguish	27	
Levomepromazine	33	Pain	20	
Phenobarbitone	3	Dyspnoea	20	
Midazolam	100	Delirium	100	40
Midazolam	91	Delirium	96	41
Chlorpromazine	9	Dyspnoea	4	
Lorazepam	9	..	..	
Opioids	37	Delirium/ restlessness	42	42
Midazolam	31	Dyspnoea	41	
Haloperidol	31	Pain	13	
Diazepam	13	Vomiting	1	
Scopolamine	10	Psychological distress	1	
Midazolam	50	Delirium	91	44
Levomepromazine	30	Dyspnoea	9	
Lorazepam	10	..	..	
Diazepam	10	..	..	
Midazolam	71	Delirium	61	45
Haloperidol	9	Dyspnoea	26	
Lorazepam	8	Pain	7	
Phenobarbitone	3	Existential distress	7	
Levomepromazine	1			
Haloperidol	50	Delirium	57	46
Midazolam	24	Dyspnoea	23	
Morphine	13	Pain	10	
		Insomnia	7	
Midazolam	82	..	..	47
Levomepromazine	22	..	..	
Haloperidol	2	..	..	
Phenobarbitone	..	..	..	
Midazolam	100	Delirium	63	†
	..	Dyspnoea	44	
	..	Pain	13	
	..	Insomnia	13	
	..	Myoclonus	5	
Levomepromazine	50	Agitation	100	‡
Midazolam	50			

† Morita et al, unpublished data; ‡ Scholes et al, unpublished data.

two studies from the Southeast Asia.[38,46] Barbiturates and propofol are reported as sedative drugs to be used as a last resort.

Effect of sedation on survival

The most important ethical question is whether the use of sedatives shortens the life of terminally ill patients. A definitive answer to this question could only be obtained from a randomised controlled trial in which patients were randomly allocated to sedation or non-sedation groups. But this solution is ethically impossible.

Ten studies have estimated the average duration for which sedation was used (table 4). The weighted mean duration from these studies is 2·8 days, a figure that could either imply that sedative use results in death within 72 hours, or that sedation is used to control symptoms that occur as death approaches. To distinguish between these possibilities, five studies have reported the use of sedation in relation to survival from admission to death for in-patient centres or from commencement of service involvement to death for domiciliary-based teams (table 4). In each case survival of patients receiving sedation was not significantly different from that of patients who were not given sedatives, and in one case there was a difference in favour of sedation.[47] Patients who received sedatives for over a week before death had better survival than those who did not receive sedation; patients who had only 2 or 3 days of sedatives had the same survival as those who never received sedation. This finding may be explained by the role of delirium in initiating breakdown of care at home and consequent admission to a specialist palliative-care unit. Delirious patients would have been admitted at an earlier stage of their illness than those who did not experience this syndrome before being close to death.

Conclusion

Sedatives are used commonly in patients with cancer at the end of life. In most cases they are not given with the intention of inducing sleep. Instead, the dose is titrated against the relief of a specific symptom, most often an agitated delirium, to the point where the symptom is adequately relieved. The impairment of consciousness is not an objective but an accompaniment to the use of the medication, and varies in its extent.

Sedation is generally used over a short period and most of the evidence suggests that in the context of specialist palliative care it is not associated with shortening of life. Generally, sedative use is a response to symptoms that are part of the dying process, and for the same reason are untreatable by other means. Thus, concerns about hydration and feeding that have been raised are not generally relevant.[52,53]

Search strategy and selection criteria

Searches of Medline, Embase, CancerLit, CINAHL, and Cochrane databases were done with the search terms "palliative care", "hospice", "cancer", "opioids", "sedatives", "euthanasia", "ethics", and "double effect". Manual searches of reference lists of articles were also done. The Halley Stewart Library at St Christopher's Hospice was also searched. Papers were limited to detailed retrospective or prospective studies of the use of opioids or sedatives or both in the palliative care of cancer patients. Only papers published in English were selected.

Guidance

Cherny and Portenoy have produced guidelines for the use of sedatives for symptom control.[1] Sedation should be used appropriately for specified symptoms once therapeutic alternatives have been considered and found ineffective or inapplicable to the present situation. As agents of symptom control, not of life shortening, sedative drugs should be given in doses that are titrated against the response to balance relief of symptoms with the distress they cause.

Benzodiazepines are the most favoured class of sedatives in palliative care worldwide. In particular, midazolam can be administrated by continuous subcutaneous infusion, and has anticonvulsant and muscle relaxant as well as anxiolytic properties.[54] The psychotropic drugs haloperidol, levomepromazine, and chlorpromazine may be more appropriate for the specific management of delirium, but they can lower the fit threshold and may precipitate myoclonus in severely ill patients.[55] Psychotropics can be used in combination with benzodiazepines. Phenobarbitone and propofol have been reported on a case-series basis to be of use in severe agitation which is unresponsive to other sedatives.[56,57]

The doctrine of double effect

The doctrine of double effect is used as an ethical justification for the specific risk of foreseeable life shortening as a result of a medical treatment. However, we suggest that there is no evidence that the use of opioids or sedatives in palliative care requires the doctrine of double effect as a defence. We have specifically examined the role of this doctrine in relation to symptom control and found that in 238 patients in a specialist palliative-care unit (89% receiving strong opioids and 48% receiving sedation) there was no evidence that that the doctrine needed to be invoked in relation to any morphine therapy.[12] In fact, the doctrine was only possibly relevant to two patients who were treated with sedatives.[47] In each case the condition of the patient had already been noted to be deteriorating and they were very disturbed.

Thus, although the doctrine is a valid ethical device, it is, for the most part, irrelevant to symptom control at the end of life. To exaggerate its involvement perpetuates a myth that satisfactory symptom control at the end of life is inevitably associated with hastening death. The result can be a reluctance to use medication to secure comfort and a failure to provide adequate relief to a very vulnerable group of patients.[29]

Conflict of interest

None declared.

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