

## **Giving Opioids with a Potentially Life-Shortening Effect: Experiences and Perceptions of Dutch Physicians<sup>1</sup>**

### **Abstract**

In the palliative care provided for patients with a terminal disease, physicians sometimes prescribe opioids in dosages that may be considered to have a life-shortening effect by physicians. Empirical information on the experiences and perceptions of such actions is lacking. The objective of this study is to report the frequency, intentions, patient characteristics, and other aspects of decisions made by Dutch physicians to give or increase opioids, taking into account or (partly) with the intention of a possible life-shortening effect. Method was a nationwide survey of physicians with written questionnaires (1) and face-to-face interviews (2) that was conducted in 1995-1996. Participants were (1) attending physicians of a random sample of 6060 patients who died in 1995; (2) random sample of 405 physicians. In 17% of the deaths, physicians had given dosages of opioids they regarded as possibly life-shortening. In 13%, they had only taken the shortening of life into account, in 3% they had partially intended to shorten life, and in 1% this was the explicit intention. Physicians estimated the amount of time by which life had been shortened as 'probably none' in 48% of the cases, less than 24 hours in 72%, and less than a week in 94%. The dosages of opioids used were less than 50 milligram in 39%, 51-100 milligram in 30%, 101-200 milligram in 21%, 201-500 milligram in 8%, and above 500 milligram in 3% of the cases. Physicians often take a life-shortening effect of opioids into account and sometimes partly or explicitly intend it. Indications were found that physicians attribute stronger lethal effects to opioids than can be warranted. The double effect rule is rarely relevant and has several shortcomings.

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Palliative care provided for patients in the terminal stage of disease often necessitates giving increasing dosages of opioids, which physicians and patients may associate with shortening life. The rule or doctrine of the double effect states that life-shortening effects of opioids would be morally wrong if caused intentionally but permissible if foreseen but unintended.<sup>1</sup> The double effect rule has recently been subject to

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renewed debate<sup>2-6</sup> and it is explicitly condoned in the United States in the pending Pain Relief Promotion Act.<sup>7</sup> However, in an extensive literature search we found only one publication reporting empirical data.<sup>8</sup>

In this paper, the frequency is reported with which Dutch physicians reported to have given or increased dosages of opioids, taking into account or (partly) with the intention of hastening death. Furthermore, data are presented about their intentions, the characteristics of the patients, the estimated amount of time by which life had been shortened, the extent to which giving opioids is discussed with the patient, the family and colleagues, the opioid dosages used, and the opinions of physicians. The results are based on a nationwide study on euthanasia and other medical decisions concerning the end of life, which was conducted in 1995 and 1996.<sup>9,10</sup>

## Methods

During the period 1995-1996 a nationwide study took place in the Netherlands focusing on the incidence and circumstances of euthanasia and other end-of-life decisions. The study consisted of two main parts: a death certificate study to provide reliable quantitative information, and an interview study to provide more in-depth case-related information.

### *1995 death certificate study*

Questionnaires were sent to the physicians who had attended a stratified random sample drawn from all approximately 43,000 deaths that occurred in the Netherlands from 1 August through 1 December, 1995. For this purpose all cause-of-death forms regarding this period were examined by two physicians and assigned on clinical grounds to one of five strata with an increasing probability that a medical decision concerning the end of life could have been made. A case was assigned to stratum 0 if no such decision had been possible (for instance, sudden death). These cases were retained in the sample, but no questionnaires were sent to the physicians. When the likelihood was deemed high that there had been a medical decision that might have hastened death, the case was assigned to stratum 4. The final sample contained 50% of the cases in stratum 4, 25% of the cases in stratum 3, 12.5 % of those in stratum 2, and 8.3 % of the cases in each of strata 1 and 0. A procedure was devised to ensure that both the physician and the deceased person would remain completely anonymous. Of the 6060 questionnaires mailed, 77% were returned.

The questionnaire contained 24 questions about medical decisions concerning the end of life, patients' and decision-making characteristics, and drug dosages. Three questions concerned opioids and their (presumed) life-shortening effects (see Box).

### *1995 interview study*

We interviewed a stratified random sample of 405 physicians, which included 124 general practitioners, 74 nursing home physicians, and 207 physicians from five clinical specialties (cardiology, surgery, internal medicine, pulmonology, and neu-

### BOX 1 Questions concerning the use of opioids

4. Did you or a colleague take one or more of the following actions (or ensure that one of them was taken), taking into account the probability or certainty that this action would hasten the end of the patient's life:
- 4a. withholding a treatment\*?
  - 4b. withdrawing a treatment\*?
  - 4c. intensifying the alleviation of pain and/or other symptoms using morphine or a comparable drug?

\* In this study, 'treatment' includes tube-feeding.

5. Was hastening the end of life partly the intention of the action indicated in 4c?

6. Was death caused by one or more of the following actions, which you or a colleague decided to take with the explicit intention of hastening the end of life\*?
- 6a. Withholding a treatment\*\*?
  - 6b. Withdrawing a treatment\*\*?

\* 'Hastening the end of life' may also be understood as 'not prolonging life'.

\*\* In this study, 'treatment' includes tube feeding.

7. Was death caused by the use of a drug\* prescribed, supplied or administered by you or a colleague with the explicit intention of hastening the end of life (or of enabling the patient to end his or her own life)?

\* This may mean one or more drugs; morphine is also sometimes used for this purpose.

rology). Such physicians attend 87% of all deaths in the Netherlands occurring in hospitals and almost all deaths occurring elsewhere. In order to achieve the desired number of 405 interviews, 559 physicians were sampled. Eighty-three did not meet the criteria for selection, and a further 21 were ill or could not be located. Fifty physicians (11% of those who met the selection criteria) declined to take part in the study. Approximately 30 experienced physicians, who were trained intensively for this purpose, conducted the interviews from November 1995 through February 1996. During the interviews, detailed questions were asked about the most recent case in which a physician had been involved in any medical decision that he or she thought could have hastened the death of the patient, and also about opinions and attitudes concerning such decisions and their legal status.

For this article, we selected cases in which physicians reported having given opioids in a dosage that might have shortened life. We excluded cases in which death had been the consequence of either withholding or withdrawing a treatment or in which opioids were given in combination with more potent lethal drugs, for instance, barbiturates or neuromuscular relaxants. To extrapolate the findings to all deaths in

the Netherlands, we calculated weights. For the death certificate study, the weights were based on the stratification procedure. For the interview study, they were based on the percentage of physicians from the various specialties who were represented in the sample. Interview data were corrected for the 13% of in-hospital deaths that are attended by clinicians from other specialties than the five sampled. Univariate and multivariate logistic regression analyses were performed to calculate odds ratios and their 95% confidence intervals (95% CI). P-values less than 0.05 were considered to indicate statistical significance. We calculated dosages as milligrams of oral morphine by using an equianalgesic table.<sup>10</sup>

## Results

The death certificate study showed that physicians reported that they had given dosages of opioids which they considered to be (possibly) life-shortening preceding 17% of all deaths; they no more than took into account the possibility of shortening life in 13%, while shortening life was partly their intention in 3%, and explicitly their intention in 1% of all deaths. Table 1 shows that, independent of the intention, decisions to give opioids that in the perception of the physician possibly hastened the end of life concerned cancer patients in more than half of the cases. Physicians estimated the amount of time by which life had been shortened as 'probably none' in almost half of all cases, but almost never when life-shortening had been their explicit intention. They estimated the shortening of life to be less than 24 hours in 72% of all cases, and less than a week in 94% of all cases; these percentages did not significantly differ according to the intention. Univariate logistic regression showed that an explicit intention more frequently (65%) involved an estimated shortening of life by more than a day, compared to cases in which life-shortening was only taken into account (21%) (odds ratio, 6.0; 95% CI 3.7-9.8). Multivariate logistic regression analysis with the patient's age and diagnosis and the physician's specialty as independent variables, showed that an explicit intention was significantly associated with specialty: compared to clinical specialists, nursing-home physicians administered opioids less frequently with the explicit intention of shortening life (43% versus 10%) (odds ratio, 0.24; 95% CI: 0.10-0.57). There was no statistically significant relationship with the patient's diagnosis ( $p = 0.20$ ) or age ( $p = 0.99$ ).

Table 1 also shows that discussion of the decision with colleagues, family and nursing staff occurred most often in cases in which there had been an explicit intention to shorten life. General practitioners and nursing home physicians were less likely to consult their colleagues than clinical specialists (odds ratio, 0.1, with 95% CI, 0.01-0.2; and odds ratio, 0.4, with 95% CI, 0.2-,0.7, respectively).

Data on the extent to which giving opioids in a dosage that the physician considered possibly life-shortening, had been discussed with the patient are presented in Table 2. Discussion with the patient had taken place in 78% of the cases when shortening life was the explicit intention; in 77% of these cases, the physicians reported that they had received an explicit request from the patient for shortening life. When shortening life was partly intended discussion had taken place with 54% of the

Table 1. Characteristics of giving opioids with the possible effect of shortening life, related to the physician's intention (1995 death certificate study, weighted percentages).

Hastening of death was	Only taken into account (n = 765) %	Partly intended (n = 169) %	Explicitly intended (n = 94) %	Total (n = 1028) %
<b>Diagnosis</b>				
Cancer	52	64	71	55
Circulatory disease	12	15	32	11
Respiratory disease	8	4	6	7
Infections (incl. AIDS)	1	3	-	1
Neurological disease	8	6	7	7
Other	20	8	13	18
<b>Age of patient (years)</b>				
20-49	6	8	9	7
50-64	15	21	22	16
65-79	38	37	38	38
≥ 80	41	34	32	39
<b>Sex of patient</b>				
Male	51	48	40	50
Female	49	52	60	50
<b>Estimated shortening of life</b>				
> 6 months	-	1	-	0
1-6 months	1	1	2	1
1-4 weeks	4	8	5	4
1-7 days	16	33	58	22
< 24 hours	22	34	32	24
Probably no shortening	58	24	2	48
<b>Specialty</b>				
General practitioner	36	50	48	39
Clinical specialist	32	37	43	34
Nursing home physician	29	13	10	25
Other	3	-	-	2
<b>Discussed with*</b>				
One or more colleagues	34	36	59	36
Nursing staff	32	35	54	35
Family	54	66	74	57
Other	2	3	-	2
Nobody	20	15	6	19

\* More than one answer could be given

patients (69% of those who had made an explicit request), and with 40% when it was only taken into account (42% explicit request). Patients with whom the decision had not been discussed had (clearly or less clearly) expressed a previous wish for their death to be hastened in most cases (34%) when the physician explicitly intended to

Table 2. Giving opioids with the possible effect of shortening life and discussion with patient, competence, request (death certificate study, weighted percentages).

Hastening of death was	Only taken into account (n = 765) %	Partly intended (n = 169) %	Explicitly intended (n = 94) %	Total (n = 1028) %
Discussed with patient*				
Shortly before giving opioids	18	21	30	20
Some time before	21	33	48	25
Not discussed	60	46	22	55
When discussed with the patient (shortly or some time before):	(n = 305)	(n = 93)	(n = 74)	(n = 472)
Explicit request from patient	42	69	77	52
No explicit request from patient	58	31	23	48
When not discussed with the patient:	(n = 427)	(n = 71)	(n = 20)	(n = 518)
Had patient ever expressed a wish for hastening of death?				
Yes, clearly	6	14	20	8
Yes, not very clearly	7	10	14	7
No	87	76	66	85
Was patient competent at the time of giving opioids?				
Yes	20	7	4	18
Not fully	19	20	22	20
No	61	72	72	63
Reason for not discussing decision with patient†				
Patient unconscious	31	58	50	35
Dementia	29	17	33	28
Clearly the best for patient	22	19	33	22
Would do more harm than good	7	7	6	7
Mental disorder	3	4	11	4
Mentally handicapped	1	-	-	0
Other reasons	23	11	11	21
Explicit request from family	4	15	29	6

\* Data on discussion with the patient were missing in 38 cases (4%).

† More than one answer could be given.

shorten life. Of the patients with whom giving or increasing opioids had not been discussed, 83% were not (fully) competent at that time; the percentage of competent patients, among those with whom the decision had not been discussed, was highest (20%) when the physician had only taken the shortening of life into account. When

Table 3. Dosages of opioids given in the last 24 hrs (calculated as milligram of oral morphine\*), related to estimated shortening of life and to request, discussion with patient and intention of physician† (1995 death certificate study, weighted percentage).

Dosage	Intention				Estimated shortening of life			Request from the patient	Total
	Only taken into account	Partly intended	Explicitly intended	Probably none	< 24 hours	1-7 days	> 7 days		
0 -50 milligram (n = 306), %	86	12	2	62	21	13	4	14	39
51-100 milligram (n = 252), %	79	14	7	43	32	22	4	19	29
101-200 milligram (n = 174), %	66	24	10	39	27	27	7	36	21
201-500 milligram (n = 70), %	60	21	19	24	31	34	10	44	8
> 500 milligram (n = 24), %	43	24	33	9	9	73	9	48	3

\* Parenteral opioids are considered to be twice as strong as oral opioids.<sup>22</sup> To calculate equivalent dosages from other opioids to morphine, an equianalgesic table has been used.<sup>10</sup>

† Data on dosages or method of administration are missing for 196 cases (24%); they could not be calculated as equivalent of morphine in six cases (1%).

life-shortening had been explicitly intended this was 4%. The most frequently mentioned reasons for not discussing the decision with the patient were that the patient was unconscious (35%) or had dementia (28%), or that the physician thought that the decision was clearly the best for the patient (22%). The latter reason was mentioned as the only one in 7% of all cases in which the decision had not been discussed with the patient.

In 95% of the cases in which the physician considered the dosage of opioids to be possibly lethal, they were the only drugs given; in 2% a benzodiazepine was the second drug. In the remaining 3%, various secondary drugs were used. Opioid dosages in the last 24 hours varied between 0.83 and 8000 milligram as an equivalent of oral morphine (24% missing data on dosages or method of administration; dosages could not be calculated as an equivalent of morphine in 1%). Table 3 shows that the reported dosages of opioids were 50 milligram or less in 39% of all cases, between 50 and 100 milligram in 29%, between 100 and 200 milligram in 21%, between 200 and 500 milligram in 8%, and over 500 milligram in 3%. When the dosage was 50 milligram or less, the shortening of life had only been taken into account in 86% and had been the explicit intention in 2%; when the dosage had been over 500 milligram these percentages were 43% and 33%, respectively. In the lowest dosages (50 milligram or less), physicians estimated life-shortening as 'probably none' in 62%, and less than one week in 13%, but when the dosage was over 500 milligram these percentages were 9% and 73%, respectively. In a univariate logistic regression analysis with the dosage as independent variable, an estimated life-shortening of more than a day was more likely in dosages of over 500 milligram compared to a dosage of 50 milligram or less (odds ratio, 20.3; 95% CI 6.6-62.1). There was an explicit request in more cases when a high dosage was given than when a low dosage was given.

The interview study provided information about previous opioid use and more details about the motives and attitudes of physicians. Table 4 shows that 80% of the patients who had received opioid dosages that the physician thought might shorten their life had already been taking opioids before. Of the 20% opioid-naïve patients, 42% received 50 milligram or less in the 24 hours preceding death, 24% received between 50 and 100 milligram, 30% between 100 and 200 milligram, and 4% between 200 and 500 milligram (not shown in table). When asked to specify what they meant by 'partly intending to hasten the end of life', physicians in 15% of the cases said that another intention, usually the alleviation of pain, had been equally important, and that in 48% of the cases life-shortening was a secondary intention. In the remaining 37% of cases, physicians said that life-shortening was more their hope than their intention, or that, after all, it was not intended. The majority of the physicians stated that they would act in a similar way with a similar patient in similar circumstances (93%) and that their decision had improved the quality of the dying process (95%).

Table 5 shows that those physicians who had ever given opioids in dosages that they thought could hasten death could more often conceive of situations in which they would be willing to perform euthanasia or assist with suicide (90% versus 77%) or had already done so (56% versus 30%), than those who had never given opioids in



Table 4. Other aspects of giving opioids with the possible effect of shortening life (1995 interview study, weighted percentages).

Hastening of death was	Only taken into account (n = 117) %	Partly intended (n = 130) %	Explicitly intended (n = 73) %	Total (n = 320) %
Was patient treated with opioids before giving opioids in a possibly life-shortening dosage?	82	89	73	80
Would physician act in a similar way with a similar patient in similar circumstances?*	95	93	92	93
Has action improved quality of dying process?				
Considerably	68	63	64	67
Somewhat	28	31	27	28
Not	4	6	8	5

\* Percentage that answered "yes".

Table 5. Opinions of physicians (1995 interview study, weighted percentages).

	Physicians who had ever given opioids with the possible effect of hastening death (n = 362) %	Physicians who had never given opioids with the possible effect of hastening death (n = 72) %
Could conceive of situations in which she would perform euthanasia or assist in suicide	90	77
Ever performed euthanasia or physician-assisted suicide	56	30
Considers herself religious	45	62
Agrees with following statement:		
'everybody has a right to decide about his own life and death'	65	53
'adequate pain treatment and terminal care make euthanasia avoidable'	31	38

such dosages. Physicians who had never given opioids with a possible life-shortening effect more frequently stated that they belonged to a religious denomination or adhered to a specific philosophy of life.

## Discussion

Dutch physicians gave opioids thinking that this might have hastened death in approximately one sixth of all deaths. The 1990 Rummelink Study found almost the same.<sup>12</sup> In approximately one fifth of these cases, there was a partial or explicit intention to hasten death. In an American study of hospitalized pancreatic cancer patients, this percentage was estimated to be considerably higher: out of a total of 118 comatose patients, 54 (46%) were given narcotics (three of them in combination with major sedatives) in the last four hours of their life, which, according to the authors, has a 'recognized life-shortening potential'.<sup>6</sup>

The diagnoses of patients receiving opioids with a possible life-shortening effect differ from those in euthanasia: 55% had cancer, compared with 80% in cases of euthanasia.<sup>7</sup> Decisions to give opioids with an alleged possible life-shortening effect often involved incompetent patients. The more explicit the intention to shorten life, the more likely it was that the physician had discussed the decision with the patient. However, an explicit intention was occasionally not discussed with a competent patient. A few physicians mentioned as the only reason for not discussing their decision that it was 'clearly the best for the patient'. Giving an assumedly potentially lethal dosage of opioids was discussed with colleagues in less than half of the cases, even if life-shortening was the explicit intention. We conclude that decision-making should be improved, both in order to prevent unjustified attributions of lethality and to increase transparency for the patient and others involved.

An important question is whether physicians are right in attributing a life-shortening effect to the opioids they gave. Opioids can be taken in large dosages for long periods,<sup>10,13</sup> and it is unclear whether an increase in opioid dosage really hastens death (and if so, to what extent), especially in patients who are already taking opioids,<sup>14,15</sup> as was the case in 80% of the patients in our interview study. The role of the patient's clinical condition is another uncertain factor. Physicians are not very accurate in estimating the length of survival of patients, with a tendency to overestimate it in terminal patients.<sup>16,17</sup> Therefore, the estimated life-shortening effects in our study (less than a day in 24% of cases, less than a week in 22%, and more than a week in 5%) are more likely to be overestimations than underestimations. Moreover, physicians thought that there had been no life-shortening in 48% of the cases. Thus, they took hastening the end of life into account about twice as often as they (with hindsight) thought that such an effect had actually occurred. The reported opioid dosages were generally not high (less than 100 milligram in 70% of the patients in the death certificate study), an explicit intention to shorten life was not always reflected in high dosages, and the highest dosages did not always result in the largest estimated effects in terms of shortening life. From this, we infer that there probably was a considerable overrating of the lethal effect of opioids. Therefore, the results of

our study could be yet another indication that physicians have a lack of knowledge about opioids that needs to be addressed in their professional education.<sup>18-21</sup>

If it is true that physicians over-estimate the lethal effects of opioids, the rule of the double effect, that is based on a distinction between foreseen and intended effects, loses part of its relevance. However, a life-shortening effect of opioids cannot be totally excluded. Various authors have pointed out that the distinction between foreseen and intended is vague and malleable.<sup>1,3</sup> Our data indicate a number of additional shortcomings of the double effect rule. Firstly, intentions of physicians are more differentiated than the 'yes' or 'no' that the double effect rule allows for. We distinguished three types of intentions, but even that is probably too crude a classification. Secondly, the ethical focus has been almost exclusively on allowability issues and not on the moral quality of 'double effect' actions. As a consequence, questions such as whether physicians should discuss possible life-shortening effects (if these are probable) with patients and families, or whether living wills or advance directives have significance for actions with a double effect, are left unanalyzed. Moreover, possible safeguards that are needed to prevent both abuse and unjustified attributions of lethality are not addressed in the double effect theory. Thirdly, in addition to their intentions, the reasons and motives physicians have for giving possibly or presumably lethal dosages of opioids (for instance, unbearable suffering, respect for autonomy) are important aspects which are not accounted for in the double effect rule.

One limitation of our study is that the data are retrospective and are derived from the self-reports of physicians. Moreover, there were 25% missing data on dosages. It is unclear whether this has biased our results, but if so, it seems likely that the physicians tended to forget the lower dosages. More detailed prospective clinical studies are needed to address additional questions, such as the role of the patients' clinical condition and previous opioid use, and also studies among physicians about these decisions that are very closely related to palliative care and occur much more frequently than euthanasia. Those studies should, in particular, address the uncertainty of the lethal effects of opioids. Knowledge about these types of decisions would profit from international comparisons, because it is probable that the frequencies and circumstances of these decisions are dependent on the predominant religion, the culture and the juridical situation in various countries. In a country in which termination of a human life is forbidden under all circumstances, physicians might be more likely to increase dosages of opioid, taking into account or even intending to shorten life. The legal and cultural climate might also influence the extent to which the decision is discussed with the patient and the family, and the extent to which physicians consider it ethical to discuss or not to discuss such decisions. On the other hand, it would also be important to relate the decision-making to national regulations concerning the prescription of opioids, and to the views and attitudes of physicians and lay people with regard to these drugs. Research should, for instance, address the relationship between the fear of addiction, the idea that opioids are 'drugs of last resort' and that their prescription is an indication of imminent death, views about maximum dosages, and the frequency with which physicians prescribe or increase opioids with a perceived life-shortening effect. One final important aspect of international comparison would be the extent of the education physicians receive concerning opioids and their

experience with prescribing them in relation to the frequency of attributing lethal effects to opioids. Do well-educated physicians with extensive experience in prescribing opioids less often consider an increase in the dosage of opioids to be lethal than those who are less informed about opioids, or less experienced in prescribing them?

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