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Opioid Use and Survival at the End of Life: A Survey of a Hospice Population

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Abstract

Concern that opioids hasten death may be among the reasons that pain is treated inadequately in populations with advanced illness. Studies that assess the true risks are needed. To determine whether survival after last opioid dose change is associated with opioid dosing characteristics and other factors, data from the National Hospice Outcomes Project, a large prospective cohort study involving 13 U.S. hospice programs, were analyzed. Of 1,306 patients, 725 received opioids and underwent at least one dose change before death. Subsamples based on maximum opioid dose compared patients receiving usual doses with those receiving high-dose therapy. Spearman rank correlations examined bivariate associations between survival after final dose change and other variables, including dose in morphine equivalent mg and percentage dose increase. Multivariate least squares regression analyses determined associations between survival and other variables, including those significant in bivariate analyses. The mean ± SD number of days between final dose change and death was 12.46 ± 23.11. Multivariate models demonstrated a significant association between shorter survival and higher opioid dose, a cancer diagnosis, unresponsiveness, and pain of <5 on a 0–10 scale, but none of these models explained >10% of the variance in time till death. Analyses of subsamples did not reveal additional effects of dose. This analysis revealed that opioid dosing was associated with time till death, but this factor would explain very little of the variation in survival. In a hospice population, survival is influenced by complex factors, many of which may not be measurable. Based on these findings, concern

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about hastening death does not justify withholding opioid therapy. J Pain Symptom Manage 2006;32:532–540.

Key Words
Hospice, terminal illness, death and dying, opioids, risk of hastened death

Introduction

Although pain is highly prevalent in populations with advanced illness and the need for aggressive opioid therapy is widely accepted, undertreatment is common.[1] Factors that contribute to undertreatment are complex[2] and may include clinician reluctance to prescribe because of concern about the potential for serious adverse drug effects, which may hasten death. The critical balance between the need to reduce suffering through aggressive pharmacotherapy and the potential to do harm has been discussed extensively in both the medical and ethics literature.[3–12]

Ideally, ongoing discussion surrounding the risks, benefits, and ethical foundation for the use of opioids at the end of life should be informed by empirical observations that specifically assess opioid-related risk in terms of the key concern—the potential to hasten death when these drugs are used to treat pain. Remarkably, there is very little evidence of this type. The few studies extant suggest that opioids actually pose little risk of hastened death in populations with advanced illness.[13–16] Additional studies are needed.

The National Hospice Outcomes Project (NHOP), a prospective longitudinal survey of patients admitted to hospice programs, collected extensive data pertaining to clinical outcomes during end-of-life care. These data were analyzed to explore the relationship between opioid use and survival.

Methods

The NHOP was conducted by the National Hospice and Palliative Care Organization during 2001–2003. Data were collected from 1,306 patients admitted to 13 hospices across the United States. Based on clinical practice improvement methodology, the survey included a review of hospice medical records and direct patient assessments by clinicians. Methodological details are described elsewhere.[17]

Case Definition

From 1,163 patients who received an opioid drug (89% of the total sample), 725 patients (55.5% of the total sample) who underwent at least one recorded opioid dose change prior to death were selected for study. The interval between the last opioid dose change and death was the key variable of interest. This interval was analyzed in relation to characteristics of the opioid regimen and a variety of other factors.

Subsamples based on maximum daily opioid dose administered during hospice admission were selected to provide more interpretable information about patients who are commonly encountered in practice and to separately analyze subgroups that received high-dose opioid therapy. Patients were taking different opioids, and for all analyses, opioid doses were converted into milligrams equivalent to intravenous morphine.[18] Total daily dose was the sum of the fixed scheduled dose plus "as needed" doses.

One subsample was defined to include 640 patients (88.3% of 725) who received a maximum dose of ≤200 intravenous morphine equivalent mg per day (IVME). This maximum dose, which is roughly equivalent to ≤600 oral morphine equivalent mg per day,[18] is within the range of doses widely encountered in the U.S. hospice community.[13,14] In bivariate analyses, this group was compared to the remaining group of 85 patients (11.7% of 725), who received a maximum dose of >200 IVME.

Another subsample isolated a small group of 19 patients (2.6%) who required extremely high opioid doses and was defined to include those who were receiving >600 IVME (roughly equivalent in oral dosing to >1800 mg morphine per day[18]). These patients were

compared with the remaining subsample of 706 patients (97.4% of 725), who received ≤600 IVME.

Measures

Data included demographics and disease-related information, signs and symptoms, treatments and processes of care, and patient and family outcomes.[17] In addition to opioid dosing information, the present study evaluated hospice length of stay, demographics, type of disease, disease severity score (determined with the Comprehensive Severity Index, which yields higher scores in patients with greater disease severity[19,20]), pain and level of consciousness at the time of last opioid dose change, and last recorded performance status (measured with the Palliative Performance Scale (PPS), on which higher scores indicate better functioning[21]).

Statistical Analyses

The goal of the analyses was to determine the extent to which opioid dosing characteristics or other clinical factors (the independent variables) were associated with time till death after last opioid dose change (the dependent variable). Relevant variables were first compared across the entire sample and defined subsamples. Analysis of variance, Wilcoxon rank sum tests, and Spearman rank correlations were used to examine bivariate associations between survival after final dose change and other variables. Opioid variables that were analyzed included opioid dose in morphine equivalent mg and percentage increase in dose. These analyses were performed on the total sample and each of the subsamples.

Multivariate least squares regression analyses then were applied to determine associations between the interval between last opioid dose change and death, and a variety of independent variables, including variables that had significant associations in bivariate analyses. We allowed the algorithm in the maximum R^2 selection procedure for ordinary least squares regressions to select independent variables to enter and leave each model. Separate models were constructed in an effort to explore the relationship between opioid dosing characteristics and survival, and to optimize their explanatory value (R^2).

All analyses were performed with SAS statistical software Release 8.2 (SAS Institute, Cary, North Carolina).

Results

Patient Characteristics

Characteristics of the entire sample ($n = 725$) and each subsample are presented in Table 1. Maximum daily opioid dose varied significantly by length of stay in hospice and by patient age. Mean ± SD length of stay in hospice was 30.25 ± 37.8 days. Patients receiving >200 IVME had a length of stay significantly longer than those receiving less than this amount (46.6 ± 45.4 days vs. 28.1 ± 36.1, $P = 0.0005$), and patients receiving >600 IVME had a length of stay longer than those receiving less (54.7 ± 48.8 vs. 29.6 ± 37.3, $P = 0.0042$).

Mean ± SD age for the entire group was 76.6 ± 13.4 years. Those patients receiving >200 IVME were younger than those receiving ≤200 IVME (67.1 ± 16.8 vs. 77.9 ± 12.4 years, $P < 0.0001$), and those receiving >600 IVME were younger than those receiving less than this dose (69.2 ± 15.8 vs. 76.8 ± 13.3 years, $P < 0.0150$). Maximum daily opioid dose did not vary by other demographic factors (Table 1).

Forty-two percent of the sample population had cancer. The proportion with this diagnosis was significantly higher in the subsamples defined by a total daily dose of >200 IVME and >600 IVME, respectively.

Mean disease severity scores did not vary significantly among subsamples and ranged from 17.4 ± 21.4 to 20.2 ± 22.0 (Table 1). Mean ± SD PPS score for the entire sample was 33.2 ± 14.1 and was significantly higher in subsamples distinguished by relatively high opioid doses (Table 1). Thirty-six percent of the total sample was unresponsive at the time of last opioid dose change and this proportion was similar across subsamples defined by maximum daily dose.

Opioid Doses

Table 1 also depicts the interval in days between the time of last opioid dose change and death, the maximum opioid dose prior to death, and the percentage by which the dose had been changed to achieve this final dose. For the entire sample, the mean ± SD number of days between final dose change and death was 12.46 ± 23.11 (median 5 days; range 0–231 days). Patients

Table 1
Patient Characteristics

Variable	Total Sample	Patients w/max IVME of up to 200	Patients w/max IVME of 200 and above	*P*-value	Patients w/max IVME of up to 600	Patients w/max IVME of 600 and above	*P*-value
No. of patients	725	640 (88.3)	85 (11.7)		706 (97.4)	19 (2.6)	
Age	76.6 ± 13.4	**77.9 ± 12.4**	**67.1 ± 16.8**	<0.0001	**76.8 ± 13.3**	**69.2 ± 15.8**	0.015
Gender							
Female	421 (58)	380 (59)	41 (48)	0.0609	408 (58)	13 (68)	0.4811
Male	304 (42)	260 (41)	44 (52)		298 (42)	6 (32)	
Ethnicity							
White	626 (86)	552 (86)	74 (87)	0.1301	608 (86)	18 (95)	0.5736
Black	32 (4)	25 (40)	7 (8)		31 (4)	1 (5)	
Other	8 (1)	8 (1)	0 (0)		8 (1)	0 (0)	
Unknown	59 (8)	55 (9)	4 (5)		59 (8)	0 (0)	
Length of stay in hospice (days)	30.25 ± 37.8	**28.1 ± 36.1**	**46.6 ± 45.4**	0.0005	**29.6 ± 37.3**	**54.7 ± 48.8**	0.0042
Disease severity score, last	19.9 ± 21.9	20.2 ± 22.0	17.4 ± 21.4	0.259	20.0 ± 22.0	17.7 ± 19.1	0.6633
Diagnosis							
Cancer	307 (42)	**248 (39)**	**59 (69)**	<0.0001	294 (42)	13 (68)	0.1026
CHF/COPD	132 (18)	**127 (20)**	**5 (6)**		131 (19)	1 (5)	
Mental alt	105 (14)	**102 (16)**	**3 (4)**		104 (15)	1 (5)	
Combinations of cancer, CHF/COP, and/or mental alt	181 (25)	**163 (25)**	**18 (21)**		177 (25)	4 (21)	
Maximum total IVME dose	164.3 ± 1221	**65.7 ± 45.6**	**906.3 ± 3493**	0.0292	89.5 ± 91.7	2944 ± 7159	0.0993
Change from maximum dose to final	−40.6 ± 951.7	−1.9 ± 9.6	−332 ± 2776	0.2764	−2.6 ± 16.5	−1450 ± 5854	0.2955
Days from dose change to death	12.5 ± 23.1	12.7 ± 23.9	10.8 ± 16.2	0.3538	12.5 ± 23.4	10.1 ± 11.2	0.3723
Final dose before death	123.7 ± 363.7	**63.8 ± 45.1**	**574.5 ± 944.3**	<0.0001	**86.8 ± 90.5**	**1494 ± 1722**	0.0022
Final dose change percent[a]	291.9 ± 1240, $n = 448$ (61.7)	188.4 ± 300.1, $n = 374$ (58.5)	815.3 ± 2937, $n = 74$ (87.1)	0.0707	243.8 ± 1038, $n = 433$ (61.3)	1682 ± 3706, $n = 15$ (78.9)	0.1554
PPS score (last)	33.2 ± 14.15, $n = 511$ (70.5)	**32.7 ± 13.9**, $n = 459$ (71.7)	**37.5 ± 15.45**, $n = 52$ (61.2)	0.0197	**32.9 ± 14.05**, $n = 499$ (70.7)	**44.2 ± 14.4**, $n = 12$ (63.2)	0.0063
Level of consciousness							
No. of patients	615 (84.3)	540 (84.4)	75 (88.2)		599 (84.8)	16 (84.2)	
Full	171 (28)	150 (28)	21 (28)	0.7353	167 (28)	4 (25)	0.3760
Drowsy	97 (16)	82 (15)	15 (20)		92 (15)	5 (31)	
Confused	127 (20)	113 (21)	14 (19)		124 (21)	3 (19)	
Unable to respond	220 (36)	195 (36)	25 (33)		216 (36)	4 (25)	

Data are presented as mean ± SD or number (percent).
w/max = with maximum; IVME = intravenous morphine equivalent mg per day; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; Mental alt = mental alteration; PPS = Palliative Performance Scale.
Bold numbers indicate $P \leq 0.05$.
[a]Sample size decreases due to known dose change but unknown previous dose ($n = 123$) or previous dose was 0 ($n = 154$).

receiving a maximum daily dose of >600 IVME had an interval slightly shorter than those receiving less than this dose (10.1 ± 11.2 vs. 12.5 ± 23.4, $P = 0.3723$).

Overall, patients received 123.7 ± 363.7 IVME (range 5.0–6400 mg) immediately prior to death. In many cases, the final dose before death was not the maximum dose administered during the time in hospice. Patients in the entire sample received a mean ± SD maximum opioid dose of 164.3 ± 1,221 IVME. Mean ± SD maximum dose of opioid analgesic varied from 65.7 ± 45.6 mg per day in the group receiving a maximum daily dose <200 IVME to 2,944 ± 7,159 mg per day in the group receiving a maximum daily dose of >600 IVME. For the total sample, final dose before death averaged 40.6 ± 951.7 morphine equivalent mg less than the maximum dose administered at any point during the hospice admission; there were no significant differences between maximum dose and final dose across the various subsamples.

Bivariate Analyses

To depict the relationship between opioid dose and survival after last dose change, the sample was divided into two sets of deciles, the first based on final opioid dose and the second based on percent final dose change. These deciles were compared in terms of mean survival and the proportion of patients who died within two days of the last dose change (Table 2). The only significant relationship was that patients in the lowest decile of final dose had a significantly longer mean time till death than the other nine deciles.

In other bivariate analyses, the interval between final dose change and death was significantly related to race/ethnicity and several disease-related variables (Table 3). Caucasian race was associated with a relatively shorter survival after last dose change in the subsample receiving <200 IVME ($P = 0.011$) and a relatively longer survival in the group receiving more than this amount ($P = 0.041$). Length of stay in hospice was positively associated with survival after last dose change in the total sample and the subsamples with maximum daily doses of ≤200 IVME and ≤600 IVME, respectively ($P \leq 0.001$). Last recorded PPS score and a full level of consciousness were each significantly associated with longer survival for the entire sample and each subsample, except the group receiving >600 IVME. Being unable to respond was correlated with shorter survival in all groups (Table 3).

Higher final opioid dose was significantly associated with shorter time till death in the total sample ($P = 0.010$) and in subsamples receiving ≤200 IVME ($P = 0.001$) and ≤600 IVME ($P = 0.008$), respectively. Absolute dose change and percent dose change were not associated with survival.

Table 2

Relationships Between Deciles of Last Opioid Dose (Absolute and % Change), and Mean Time Till Death and Proportion of Deaths During Days 1–2 After the Final Dose Change

	Final Dose				% Final Dose Change			
Decile	*n*	Range of IVME Dose	Mean (SD) Time till Death[a]	% Patients Who Died Within 0–1 Days[b]	*n*	Range of % Change	Mean (SD) Time till Death[c]	% Patients Who Died Within 0–1 Days[d]
1	61	5–17	26.5 (43.1)	16.4	45	−87 to −7	10.5 (16.6)	37.8
2	70	20–25	11.5 (21.6)	24.3	44	−6 to 16	12.0 (16.7)	20.5
3	73	27–32	14.1 (21.9)	16.4	47	17–33	7.5 (7.9)	17.0
4	83	33–47	14.8 (29.7)	19.3	44	34–56	8.7 (10.5)	11.4
5	66	48–58	13.9 (22.2)	22.7	44	57–87	10 (18.6)	22.7
6	81	59–78	7.4 (9.1)	29.6	46	88–120	9.1 (15.7)	32.6
7	71	80–97	9.7 (19.7)	18.3	44	125–177	8.8 (11.3)	18.2
8	75	97–128	8.9 (13.8)	24.0	45	183–279	8.9 (13.9)	33.3
9	73	129–210	9.3 (15.7)	24.6	44	280–490	7.9 (13.3)	31.8
10	72	216–6,400	11.1 (17.1)	20.8	45	500–20,000	11.4 (19.7)	13.3

IVME = intravenous morphine equivalent mg per day.
[a]ANOVA *P*-value = 0.0001.
[b]Wilcoxon rank sum test *P*-value = 0.3545.
[c]ANOVA *P*-value = 0.9171.
[d]Wilcoxon rank sum test *P*-value = 0.7984.

Table 3
Bivariate Analyses Between Patient and Opioid Treatment Characteristics, and Time Between Final Dose Change and Death

	Patients w/o Maximum IVME Limitation ($n=725$)		Patients w/max IVME of <200 ($n=640$)		Patients w/max IVME of > 200 ($n=85$)		Patients w/max IVME of <600 ($n=706$)		Patients w/max IVME of >600 ($n=19$)	
Variable	*n*	*r* and *P*	*n*	*r* and *P*	*n*	*r* and *P*	*n*	*r* and *P*	*n*	*r* and *P*
Age	725	[a]	640	[a]	85	[a]	706	[a]	19	[a]
Gender, female	725	[a]	640	[a]	85	[a]	706	[a]	19	[a]
Ethnicity										
White	725	[a]	640	**−0.10**, 0.011	85	**0.22**, 0.041	706	[a]	19	[a]
Black	725	[a]	640	[a]	85	[a]	706	[a]	19	[b]
Other	725	[a]	640	[a]	85	[b]	706	[a]	19	[b]
Length of stay	725	**0.52**, <0.001	640	**0.56**, <0.001	85	[a]	706	**0.53**, <0.001	19	[a]
Disease severity	725	**−0.09**, 0.018	640	[a]	85	[a]	706	**−0.09**, 0.014	19	[a]
Diagnosis										
Cancer	725	[a]	640	[a]	85	[a]	706	[a]	19	[a]
CHF/COPD	725	[a]	640	[a]	85	[a]	706	[a]	19	[a]
Mental alt	725	[a]	640	[a]	85	[a]	706	[a]	19	[a]
Combinations of cancer, CHF/COPD, and/or mental alt	725	[a]	640	[a]	85	[a]	706	[a]	19	[a]
Final dose before death	725	**−0.10**, 0.010	640	**−0.13**, 0.001	85	[a]	706	**−0.10**, 0.008	19	[a]
Final dose change, absolute	602	[a]	523	[a]	79	[a]	585	[a]	17	[a]
Final dose change, % change	448	[a]	374	[a]	74	[a]	433	[a]	15	[a]
Last PPS score	511	**0.24**, <0.001	459	**0.23**, <0.001	52	**0.28**, 0.045	499	**0.23**, <0.001	12	[a]
Level of consciousness										
Full	615	**0.32**, <0.001	540	**0.30**, <0.001	75	**0.49**, <0.001	599	**0.32**, <0.001	16	[a]
Drowsy	615	[a]	540	[a]	75	[a]	599	[a]	16	[a]
Confused	615	**0.09**, 0.011	540	**0.11**, 0.004	75	[a]	599	**0.1**, 0.01	16	[a]
Unable to respond	615	**−0.23**, <0.001	540	**−0.22**, <0.001	75	**−0.33**, 0.002	599	**−0.23**, <0.001	16	**−0.59**, 0.008

Bold numbers indicate $P \leq 0.05$.
w/o = without; w/max = with maximum; IVME = intravenous morphine equivalent mg per day; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; Mental alt = mental alteration; PPS = Palliative Performance Scale.
[a] *P*-value greater than 0.056.
[b] No patients in the group with race designation.

Multivariate Analyses

Examination of sample characteristics and the bivariate analyses did not reveal meaningful differences in the groups receiving relatively higher doses. Indeed, there was no significant relationship between high-dose opioid treatment (i.e., in the sample receiving >200, or >600, IVME) and the interval between final dose change and death. Accordingly, multivariate analyses were performed on the subsample that received a maximum daily dose of <200 IVME, the group that both most reflected the opioid dose range commonly encountered in practice and demonstrated a relationship between final dose and shorter survival ($r=-0.13$, $P=0.001$, Table 3).

In the first multiple regression model constructed, the variables entered included all those found to have significant bivariate relationships with survival, plus age and pain level at time of final dose change. The latter variables were included because of clinical observations suggesting that they are likely to influence the potential for adverse effects during opioid therapy. Of 640 patients receiving <200 IVME, 360 (56.25%) could provide data on all these variables. The model (Table 4) demonstrated that a pain score of <5 on a 0−10 numeric scale (associated with longer survival) and lack of consciousness (associated with shorter survival) remained significant when controlling for other variables, but together explained only about 10% of the variance in time till death after final dose change ($R^2=0.0999$).

Because PPS score was not associated with survival in the initial model, and missing values for this variable had reduced the sample size for analysis, it was deleted to provide access to a larger sample ($n=523$ or 81.7% of 640

Table 4
Multiple Regression Analyses of Time to Death After Final Dose Change in Patients Receiving <200 IVME

Model Information	Variable	Coefficient	*t*-value	*P*-value
$n = 360$, $R^2 = 0.0992$	Age	−0.074	−0.79	0.4272
	Final dose change	0.005	0.1	0.8795
	Final dose in IVME	−0.054	−1.72	0.0861
	Last PPS score	0.123	1.58	0.116
	Diagnosis			
	Cancer	−3.801	−1.37	0.1730
	CHF/COPD	−3.545	−1.18	0.2377
	Mental alt	1.748	0.52	0.6008
	Level of consciousness = unable to respond	**−4.969**	**−2.14**	**0.0333**
	Pain <5	**11.042**	**3.36**	**0.0009**
$n = 360$[a], $R^2 = 0.0836$	Final dose of IVME	**−0.059**	**6.3**	**0.0125**
	Level of consciousness = unable to respond	**−5.218**	**5.51**	**0.0195**
	Pain <5	**12.147**	**14.61**	**0.0002**
$n = 523$[b], $R^2 = 0.0586$	Final dose in IVME	**−0.048**	**5.59**	**0.0185**
	Diagnosis			
	Cancer	**−3.821**	**3.88**	**0.0493**
	Level of consciousness = unable to respond	**−5.958**	**8.71**	**0.0033**
	Pain <5	**8.200**	**7.97**	0.0049

Bold numbers indicate $P \leq 0.05$.
IVME = intravenous morphine equivalent mg per day; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; Mental alt = mental alteration; PPS = Palliative Performance Scale.
[a]Only three variables included.
[b]PPS score removed, constructed to maximize R^2.

patients receiving <200 IVME). When the variables used in the initial model (Table 4) were forced into this regression model, final opioid dose, cancer diagnosis, and unresponsiveness were significantly correlated with shorter survival, and pain score <5 was significantly associated with longer time till death. This model, however, accounted for only 7% of the variation in survival time.

To further explore the impact of opioid dose, another analysis entered only the two variables that were predictive in the initial model, plus final opioid dose (Table 4). All three variables were significantly predictive of survival, but together explained only about 8% of the variance ($R^2 = 0.0836$). In this model, higher final opioid dose and being unresponsive at time of final dose change were associated with shorter time till death, and a pain score of <5 was associated with longer survival.

Finally, in an attempt to improve the ability to explain the variance in survival after final opioid dose change, a multiple regression analysis evaluated final opioid dose, diagnosis, lack of consciousness, and a pain score <5 in 523 patients (Table 4). All were significant, but explained only 6% of the variance in survival ($R^2 = 0.059$).

Discussion

Although pain due to advanced illness usually can be managed with an opioid regimen, undertreatment is common.[1] Clinician concern about the potential for serious toxicity in medically frail patients may contribute to undertreatment. Although a robust literature has generally endorsed the application of the ethical principle of double effect as the moral justification for aggressive therapy,[3,5,6] this may not allay concerns. This literature typically assumes a substantial risk of hastened death due to the opioid.

Opioid use at the end of life also has been discussed in the literature on physician-hastened death.[5,8,9,12] These writings also assume that opioid toxicity is substantial during end-of-life care and that these drugs may be used intentionally to shorten life.

These assumptions contrast with the common clinical experience of specialists in pain management or palliative medicine, who typically use opioid drugs in whatever doses are needed to achieve analgesia and rarely encounter a scenario consistent with a primary opioid-related death. This sanguine experience is supported by a small number of studies[9,13–15] that together suggest a relatively low risk of serious opioid toxicity.

To reconcile these opposing views, studies must specifically assess the extent to which opioid use affects survival among those with advanced illness. The NHOP analyses demonstrate that final opioid dose, but not percent change in dose, was one of several factors associated with survival, but the association is very weak, and in multivariate analyses, this and other relevant factors explain only a very small percentage of variation in survival. The implication that opioid dose poses an extremely small risk of hastened death in this population was supported further by the relatively long intervals between final dose change and death, and the lack of higher opioid risk in subsamples receiving high doses.

These findings resonate with clinical experience and findings of other surveys.[13,14] Although experienced clinicians are aware that serious toxicity, including risk of hastened death, could be produced by rapid dose escalation, the usual approach to opioid therapy incorporates incremental dose changes that, on balance, appear relatively safe even if patients are near the end of life, require relatively high doses, or need frequent dose increases.

These findings have several limitations. The results apply to a hospice population, and although the methodology incorporated systematic prospective data collection, the study was not primarily designed to address the question of opioid risk. Given missing data and data collection by treating nurses, the possibility of observer bias, and referral and selection biases, must be acknowledged. Finally, variation in opioid regimens may have limited the ability to identify the "signal" of opioid toxicity during a complex interplay of many other relevant phenomena.

These limitations notwithstanding, this analysis suggests that the timing of death in populations with far advanced illness involves a complex interplay of variables, including important factors that were not assessed in this study, and that opioid therapy should not be the focus of future research of this type. Equally important, these data should help advance the appropriate use of opioids for symptom control. Undertreatment of pain is a far more pressing concern than is the risk of hastened death in those with advanced disease, and physicians should be encouraged to use opioids effectively to relieve suffering at the end of life.

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