

- 36 Mino M, Nishino H. Fetal and maternal relationship in serum vitamin E level. *J Nutr Sci Vitaminol* 1973; **19**: 475–82.
- 37 Schiff E, Friedman SA, Stampfer M, Kao K, Barrett PH, Sibai BM. Dietary consumption and plasma concentrations of vitamin E in pregnancies complicated by preeclampsia. *Am J Obstet Gynecol* 1996; **175**: 1024–28.
- 38 Stratta P, Canavese C, Porcu M, et al. Vitamin E supplementation in preeclampsia. *Gynecol Obstet Invest* 1994; **37**: 246–49.
- 39 Gulmezoglu AM, Hofmeyr GJ, Oosthuizen MM. Antioxidants in the treatment of severe pre-eclampsia: an explanatory randomised controlled trial. *Br J Obstet Gynaecol* 1997; **104**: 689–96.
- 40 Nishikimi M. Oxidation of ascorbic acid with superoxide anion generated by the xanthine-xanthine oxidase system. *Biochem Biophys Res Commun* 1975; **63**: 463–68.
- 41 Jialal I, Grundy SM. Effect of dietary supplementation with alpha-tocopherol on the oxidative modification of low density lipoprotein. *J Lipid Res* 1992; **33**: 899–906.
- 42 Fuller CJ, Grundy SM, Norkus EP, Jialal I. Effect of ascorbate supplementation on low density lipoprotein oxidation in smokers. *Atherosclerosis* 1996; **119**: 139–50.
- 43 May JM, Qu ZC, Whitesell RR, Cobb CE. Ascorbate recycling in human erythrocytes: role of GSH in reducing dehydroascorbate. *Free Radic Biol Med* 1996; **20**: 543–51.
- 44 Higgins JR, Walshe JJ, Halligan A, et al. Can 24-hour ambulatory blood pressure measurement predict the development of hypertension in primigravidae? *Br J Obstet Gynaecol* 1997; **104**: 356–62.

Will to live in the terminally ill

Harvey Max Chochinov, Douglas Tataryn, Jennifer J Clinch, Deborah Dudgeon

Summary

Background Complex biomedical and psychosocial considerations figure prominently in the debate about euthanasia and assisted suicide. No study to date, however, has examined the extent to which a dying patient's will to live fluctuates as death approaches.

Methods This study examined patients with cancer in palliative care. Will to live was measured twice daily throughout the hospital stay on a self-report 100 mm visual analogue scale. This scale was incorporated into the Edmonton symptom assessment system, a series of visual analogue scales measuring pain, nausea, shortness of breath, appetite, drowsiness, depression, sense of well-being, anxiety, and activity. Maximum and median fluctuations in will-to-live ratings, separated by 12 h, 24 h, 7 days, and 30 days, were calculated for each patient.

Findings Of 585 patients admitted to palliative care during the study period (November, 1993, to May, 1995), 168 (29%; aged 31–89 years) met criteria of cognitive and physical fitness and agreed to take part. The pattern of median changes in will-to-live score suggested that will to live was stable (median changes <10 mm on 100 mm scale for all time intervals). By contrast, the average maximum changes in will-to-live score were substantial (12 h 33.1 mm, 24 h 35.8 mm, 7 days 48.8 mm, 30 days 68.0 mm). In a series of stepwise regression models carried out at 12 h, 24 h, and 1–4 weeks after admission, the four main predictor variables of will to live were depression, anxiety, shortness of breath, and sense of well-being, with the prominence of these variables changing over time.

Interpretation Among dying patients, will to live shows substantial fluctuation, with the explanation for these changes shifting as death approaches.

Lancet 1999; **354**: 816–19

Introduction

A patient's state of mind is the single most important factor in understanding of a request for physician-hastened death. Euthanasia and physician-assisted suicide raise critical issues about the psychological underpinnings of death-hastening requests. This study is part of a programme of research that has addressed various psychiatric dimensions of palliative care.^{1–4} The defining characteristic of this research has been that dying patients have served as the key informants. These studies have helped establish the prevalence of clinical depression among the terminally ill¹ and the extent to which dying patients may endorse a desire for death.² A limitation of the latter study was its largely cross-sectional design, with very little information on whether there are fluctuations in patients' will to live over the course of a terminal disease. Thus, although we now know that occasional or fleeting thoughts of a desire for death are common among the terminally ill and that some of these patients express a genuine desire for death, little is known about how these thoughts may change over the course of time.² Although the stability and determinants of will to live in a palliative-care setting are fundamental issues, they have received surprisingly little critical attention.

No previous studies have specifically examined the issue of will to live per se, but a few have addressed constructs that may serve as its proxy. Some studies, using responses to hypothetical scenarios before and after treatment, have documented the extent to which treatment of depression can favourably influence a patient's endorsement of life-sustaining therapy.^{5,6} Other studies have shown a strong association between interest in physician-assisted suicide and depression,^{2,4,7,8} pain,^{2,7,9–11} and other distressing symptoms.^{7,9–13} To date, only one small study reported that a desire for death may fluctuate over a brief period in a palliative-care setting.² Our study prospectively addressed the temporal stability of will to

Department of Psychiatry (H M Chochinov FRCPC) and **Faculty of Nursing** (D Tataryn PhD), **University of Manitoba**; **St Boniface Hospital Research Foundation** (J J Clinch MA), **Winnipeg, Manitoba**; and **Department of Medicine, Queen's University, Kingston, Ontario** (D Dudgeon FRCPC), **Canada**

Correspondence to: Dr Harvey Max Chochinov, Department of Psychiatry, University of Manitoba, PX 246-771 Bannatyne Avenue, Winnipeg, Manitoba, R3E 3N4, Canada (e-mail: chochin@cc.umanitoba.ca)

live and its correlates in a large cohort of terminally ill patients.

Methods

Patients

The ethics review committee of the University of Manitoba Faculty of Medicine approved this study. Before participation, all patients gave written acknowledgment of informed consent. Patients were recruited from the Riverview Palliative Care Unit in Winnipeg, Manitoba, Canada. This unit admits patients on a voluntary basis for various palliative-care needs, primarily including symptom management, respite for patients and families, and terminal care. All patients admitted to the hospital during the study period (November, 1993, to May, 1995) had a primary diagnosis of terminal cancer. After admission, each patient was given 24–48 h to become used to the ward routine before being approached for the study. The patient's medical status was reviewed with the ward staff. Patients who were too cognitively impaired, weak, or ill to complete the daily assessments were classified as ineligible and not approached for the study. When informed consent was obtained, patients completed Folstein's mini-mental status examination¹⁴ (MMSE). Those scoring 21 or higher out of 30 (a cut-off point recommended in routine screening for cognitive impairment in the elderly¹⁵) were enrolled in the study.

Procedures

Data were collected by means of the Edmonton system assessment system¹⁶ (ESAS). The ESAS is a self-report instrument consisting of a series of visual analogue scales designed specifically for patients in palliative care; it assesses pain, anxiety, depression, sense of well-being, dyspnoea, nausea, activity, drowsiness, and appetite. For the purpose of this study, we added an additional will-to-live visual analogue scale (with

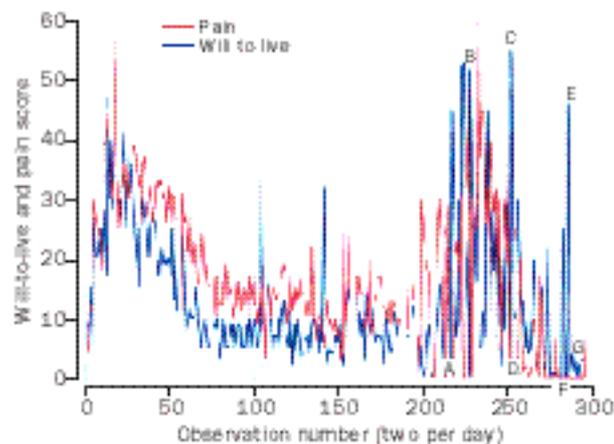


Figure 1: Will-to-live and pain scores in an 82-year-old woman with colorectal cancer

Maximum 12 h change=C–D; maximum 24 h change=E–F; maximum 7-day change=A–B; maximum 30-day change=B–G.

“complete will to live” and “no will to live” as the extremes). Each patient's subjective sense of constipation was also recorded once daily as being present or absent. To maintain consistency across the different items with visual analogue scales, a high score on any ESAS variable reflects high symptom distress. Thus, a high will-to-live score indicates a low endorsement of will to live. All participants were asked to make a vertical mark indicating the intensity of the particular symptom, at that point in time. For all participants, symptom distress was measured twice daily (morning and late afternoon) from the time they entered the study until they could no longer provide data (even with the assistance of a research nurse), they died, or they were discharged from the unit. The MMSE was administered on entry to the study, and once a week thereafter. This instrument enabled monitoring of cognitive status as well as providing a validity check of all ESAS data.

Statistics

Unless otherwise indicated, statistical significance was set at a probability level of 0.05. The will-to-live visual analogue scores were used to examine the temporal stability of this construct. Temporal stability addresses the consistency with which will to live is held by an individual patient across time. Maximum and median changes (differences) in will to live were calculated for each individual over consecutive 12 h, 24 h, 7-day, and 30-day intervals. Thus, the 7-day fluctuations in will to live were calculated between morning assessments of days 1 and 8, 2 and 9, 3 and 10, and so on; the calculations were repeated for the evening assessments across the same intervals.

Stepwise multiple regression procedures were used to predict will to live at six temporal cross-sections of the data (12 h, 24 h, 1 week, 2 weeks, 3 weeks, and 4 weeks after admission to the study). All variables for the revised ESAS, and constipation, were allowed to enter the model in a stepwise fashion. The criterion for entry was a significance level of $p < 0.1$, and the criterion for deletion from the model was set at $p > 0.05$ in a two-tailed test.

Results

There were 585 admissions during the data-collection period. 153 (26.2%) patients were not referred to the study because the initial screening showed that they were cognitively impaired or too weak or ill to participate. 39 (6.7%) other patients were found to be ineligible, since they scored below the critical threshold of 21 on the MMSE. 148 (25.3%) patients admitted to the unit refused to take part in the study. 77 (13.2%) were otherwise unavailable (away from the ward at the time of data collection, or too brief a stay to allow enrolment in the study). The remaining 168 participants, ranging in

	Non-participants	Participants	p
Number of admissions			
1	346 (83.0%)	146 (86.9%)	0.591
2	54 (12.9%)	19 (11.3%)	
3	9 (2.2%)	3 (1.8%)	
4	5 (1.2%)	0	
5	2 (0.5%)	0	
6	1 (0.2%)	0	
Sex			
Male	221 (53.0%)	83 (49.4%)	0.431
Female	196 (47.0%)	85 (50.6%)	
Marital status			
Married	199 (47.7%)	80 (47.6%)	0.805
Widowed	126 (30.2%)	50 (29.8%)	
Divorced	32 (7.7%)	15 (8.9%)	
Single	37 (8.9%)	15 (8.9%)	
Other	18 (4.3%)	8 (4.8%)	
Unknown	5 (1.2%)	0	
Living arrangements			
With spouse	203 (48.7%)	81 (48.2%)	0.402
With child	38 (9.1%)	13 (7.7%)	
Alone	134 (32.1%)	63 (37.5%)	
Other	42 (10.1%)	11 (6.5%)	
Primary diagnosis			
Lung cancer	107 (25.7%)	61 (36.3%)	0.009
Gastrointestinal cancer	99 (23.7%)	44 (26.2%)	
Genitourinary cancer	55 (13.2%)	19 (11.3%)	
Breast cancer	26 (6.2%)	12 (7.1%)	
Gynaecological cancer	16 (3.8%)	9 (5.4%)	
Head and neck cancer	14 (3.4%)	7 (4.2%)	
Melanoma	15 (3.6%)	2 (1.2%)	
Brain cancer	22 (5.3%)	1 (0.6%)	
Other diagnosis	63 (15.1%)	13 (7.7%)	
Median (IQR) age at entry to study	73 (65–81)	70 (58.5–76)	0.0017
Median (IQR) survival (days)			
After study	..	1 (1–2)	
Total from admission	15 (5–46)	31.5 (15–64)	0.0018

Demographic and clinical characteristics of participants and non-participants

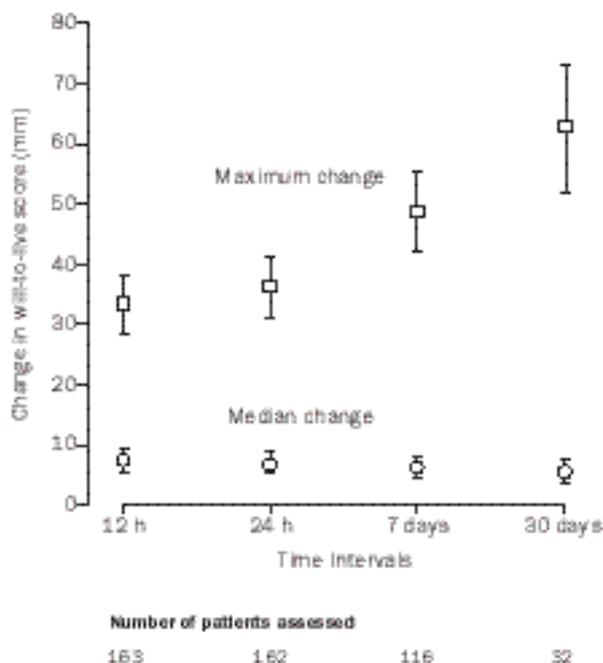


Figure 2: Average median and maximum changes in will to live. Error bars=95% CI.

age from 31 to 89 years, represent 29% of the total possible sample.

Since more than 55% of the non-participants died before the study started or were too ill or cognitively impaired to participate, there were significant differences in age and survival time between participants and non-participants (table); those participating were slightly younger and lived an average of 18 days or 50% longer than those who did not participate (median survival 31.5 vs 15 days, $p=0.0018$). Participants and non-participants were similar in diagnosis at time of admission, with the exceptions of lung, brain, and other tumours. The higher prevalence of brain tumours among the non-participants is related to the adverse effect of such tumours on cognitive function. The two groups differed substantially in status at the end of the hospital stay: 68% of participants compared with 81% of non-participants had died ($p<0.001$). The two groups were similar in distributions of sex, marital status, and previous living arrangements.

Among participants, the median length of time followed within the study was 12 days (IQR 5–27; mean 21.6 days [SD 27.1]). Complete ESAS data were collected to within 1 day (median) of death. As an example, figure 1 shows the profile of will-to-live scores in an 82-year-old woman with colorectal cancer. This unusually long data record was selected to provide a clear illustration of how will to live was tracked, and demonstrate the way in which the maximum time interval fluctuations were calculated. In the first 2 weeks after admission, her will to live weakened, peaking at a score of 55 mm. It then gradually improved, such that by day 60 most of her will-to-live scores were between 0 and 10 mm. Her scores remained stable until day 100 (observation 200). As death approached and pain became more difficult to control, her will-to-live score became very changeable.

Figure 2 shows the distribution of the average maximum and median fluctuations in will-to-live scores. The pattern of median changes in will to live over various

time intervals suggest that will to live was stable. On a 100 mm scale, median changes in will-to-live score were less than 10 mm across all time intervals. However, the maximum fluctuation in each individual patient's will-to-live score shows a different pattern. For example, the average maximum change in score was 33.1 mm (95% CI 28.4–37.8) for the 12 h time interval and 35.8 mm (30.8–40.7) for the 24 h interval. Wider time intervals showed greater fluctuations in will-to-live score (7 days 48.8 mm [42.2–55.3]; 30 days 63.0 mm [52.2–73.7]). For each of these time intervals, the greatest will-to-live score fluctuation was 100 mm, indicating extreme changes within some individuals over even the shortest time period examined. These large fluctuations suggest that will to live is highly unstable.

To clarify the relation between will to live and various common sources of symptom distress among dying patients, we constructed several multiple regression models. These models examined cross-sectional data at 12 h, 24 h, 1 week, 2 weeks, 3 weeks, and 4 weeks since entry to the study, with will-to-live score as the outcome variable. Initially, all ESAS variables (and constipation) were allowed to enter in a stepwise way. Sense of well-being was highly significant ($p<0.0001$) in four of the six regression equations (all but the 2-week and 3-week models). Since sense of well-being is not a well-circumscribed symptom that can be specifically targeted by palliative interventions, a second series of models was constructed in which this variable was omitted. As a result of attrition due to medical deterioration or death, the number of patients entering each model decreased with the broadening time interval examined in each subsequent model. Anxiety entered the 12 h model first ($r=0.4$, $F=29.2$, $df=1,157$, $p<0.0001$) followed by dyspnoea ($r=0.46$, $F=21.3$, $df=2,156$, $p<0.0002$) and activity ($r=0.5$, $F=17.3$, $df=3,155$, $p<0.0001$). In the 24 h model, only anxiety entered as a predictor variable of will to live ($r=0.3$, $F=14.43$, $df=1,139$, $p<0.0002$). In the 1-week model, depression was the factor accounting for most of the variance in will to live ($r=0.37$, $F=13.90$, $df=1,89$, $p<0.003$), as it did also in the 2-week model ($r=0.49$, $F=20.73$, $df=1,64$, $p<0.0001$). The 3-week and 4-week models reflective of a time frame approaching death, showed the critical role of dyspnoea ($r=0.37$, $F=5.46$, $df=1,42$, $p<0.02$; and ($r=0.33$, $F=4.11$, $df=1,33$, $p<0.05$). These findings suggest that, as death drew nearer, psychological variables were replaced by physical mediators of variation in will to live.

Discussion

The findings of this study suggest that will to live is highly unstable among terminally ill cancer patients. Although median changes in will-to-live score suggest less fluctuation, the maximum changes showed substantial variation over even the shortest time intervals studied. These findings are perhaps not surprising, given that only 10–14% of individuals who survive a suicide attempt commit suicide during the next 10 years, which suggests that a desire to die is inherently changeable.¹⁷

The regression models begin to offer some insight into the potential influences on the will to live of dying patients. These models show that factors accounting for variance in will to live change as death approaches. Initially, anxiety was the most significant predictor of will to live. Since most of the patients were enrolled in the study within 24 h of admission, these models may be

addressing the transitional phase while the patient adapts from community to inpatient palliative care. In later models, depression replaced anxiety, and in the final models dyspnoea was the most important variable. The prominent place of the psychological determinants of will to live in the earlier models was taken by more physically mediated distress as death approached.

Although the findings of this study may be relevant to the debate on euthanasia, there are limits to which they can be generalised. The patients studied were mostly elderly, and all were in an advanced stage of terminal cancer. We cannot say what would be found for younger populations or for patients dying from other illnesses, such as AIDS, progressive neuromuscular disorders, or advanced cardiac and respiratory disorders. The study group was also restricted to individuals who were mentally competent and well enough to fill out the self-report measures twice daily. This group was a minority of patients admitted to the participating palliative-care unit. However, the issue of euthanasia is largely concerned with the rights of competent individuals to specify the timing and circumstances of their death. As such, the patients involved in the study appear to be representative of those at the centre of the euthanasia debate.

For jurisdictions considering legislation enabling physician-assisted suicide or euthanasia, the likely transience of a request to die is one of the most important considerations. For the reasons confirmed in this study, demonstration of a sustained wish to die must be part of evaluating any death-hastening request. This study provides empirical, prospective data, showing the changing pattern of will to live in the palliative-care setting. Understanding of the temporal patterns of will to live and its correlates represents an important step toward improving care for dying patients. The ability of clinicians and researchers to understand and track will to live as an outcome measure in this vulnerable population will no doubt lead to better palliative care for patients approaching death.

Contributors

Harvey Chochinov devised and designed the study protocol, supervised all phases of the study including recruitment of patients, data management and evaluation, and the writing of the paper. Douglas Tataryn contributed to the concept of the study, designed the data collection and management strategy, evaluated the data, and was involved in writing of the paper. Deborah Dudgeon and Jennifer Clinch contributed to the concept of the study and protocol development and reviewed the paper.

Acknowledgments

We thank Tom Harrigan and Raymond Poirier for computer programming and analysis assistance; Bryan Mueller for text and figure

preparation; and the research nurses in this study—including Sheila Lander, Susan McClement, Gerri Anderson, Marilyn Kilpatrick, Marriette Chartier, Michelle Lobchuk, and Pauline Steinberg—for their conscientious attention to the data collection protocol. The study was supported by grants from the National Cancer Institute of Canada with funding from the Canadian Cancer Society and the Open Society Institute, Project on Death in America.

References

- 1 Chochinov HM, Wilson KG, Enns M, Lander S. Prevalence of depression in the terminally ill: effects of diagnostic criteria and symptom threshold judgments. *Am J Psychiatry* 1994; **151**: 537–40.
- 2 Chochinov HM, Wilson KG, Enns M, et al. Desire for death in the terminally ill. *Am J Psychiatry* 1995; **152**: 1185–91.
- 3 Chochinov HM, Wilson KG, Enns M, Lander S. Are you depressed? Screening for depression in the terminally ill. *Am J Psychiatry* 1997; **154**: 674–76.
- 4 Chochinov HM, Wilson KG, Enns M, Lander S. Depression, hopelessness, and suicidal ideation in the hopelessly ill. *Psychosomatics* 1998; **39**: 366–70.
- 5 Ganzini L, Lee MA, Heintz RT, et al. The effect of depression treatment on elderly patients' preferences for life-sustaining medical therapy. *Am J Psychiatry* 1994; **51**: 1631–36.
- 6 Hooper SC, Vaughan KV, Tennant CC, Perz JM. Major depression and refusal of life-sustaining medical treatment in the elderly. *Med J Aust* 1996; **165**: 416–19.
- 7 Breitbart W, Rosenfeld BD, Passik SD. Interest in physician assisted suicide among ambulatory HIV-infected patients. *Am J Psychiatry* 1996; **153**: 238–42.
- 8 Brown JH, Henteleff P, Barakat S, Rowe CJ. Is it normal for terminally ill patients to desire death? *Am J Psychiatry* 1986; **142**: 208–11.
- 9 Foley KM. The treatment of cancer pain. *N Engl J Med* 1991; **153**: 217–29.
- 10 Foley KM. The relationship of pain and symptom management to patient requests for physician-assisted suicide. *J Pain Symptom Manage* 1991; **6**: 289–97.
- 11 Seale C, Addington-Hall J. Euthanasia: why people want to die earlier. *Soc Sci Med* 1994; **39**: 647–54.
- 12 Jorm AF, Henderson AS, Scott R, Korten AE, Christensen H, MacKinnon AJ. Factors associated with the wish to die in elderly people. *Age Aging* 1995; **24**: 389–92.
- 13 Portnenoy RK, Thaler HT, Inturrisi CE, et al. Symptom prevalence, characteristics and distress in a cancer population. *Qual Life Res* 1994; **3**: 183–89.
- 14 Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–98.
- 15 MacKenzie DM, Copp P, Goodwin GM. Brief cognitive screening of the elderly: a comparison of the Mini-Mental State Examination (MMSE), abbreviated mental test (AMT) and the mental status questionnaire (MSQ). *Psychol Med* 1996; **26**: 427–30.
- 16 Bruera E, Kuehn N, Miller M, et al. The Edmonton symptom assessment system (ESAS): a simple method for the assessment of palliative care patients. *J Palliative Care* 1991; **7**: 6–9.
- 17 Diekstra R. An international perspective on the epidemiology and prevalence of suicide. *J Affect Disord* 1995; **36**: 11–20.