Prognostic Factors in Advanced Cancer Patients: Evidence-Based Clinical Recommendations—A Study by the Steering Committee of the European Association for Palliative Care

Marco Maltoni, Augusto Caraceni, Cinzia Brunelli, Bert Breckoaert, Nicholas Christakis, Steffen Eychmueller, Paul Glare, Maria Nabal, Antonio Viganò, Philip Larkin, Franco De Conno, Geoffrey Hanks, and Stein Kaasa

ABSTRACT

Purpose
To offer evidence-based clinical recommendations concerning prognosis in advanced cancer patients.

Methods
A Working Group of the Research Network of the European Association for Palliative Care identified clinically significant topics, reviewed the studies, and assigned the level of evidence. A formal meta-analysis was not feasible because of the heterogeneity of published studies and the lack of minimal standards in reporting results. A systematic electronic literature search within the main available medical literature databases was performed for each of the following four areas identified: clinical prediction of survival (CPS), biologic factors, clinical signs and symptoms and psychosocial variables, and prognostic scores. Only studies on patients with advanced cancer and survival \( \leq 90 \) days were included.

Results
A total of 38 studies were evaluated. Level A evidence-based recommendations of prognostic correlation could be formulated for CPS (albeit with a series of limitations of which clinicians must be aware) and prognostic scores. Recommendations on the use of other prognostic factors, such as performance status, symptoms associated with cancer anorexia-cachexia syndrome (weight loss, anorexia, dysphagia, and xerostomia), dyspnea, delirium, and some biologic factors (leukocytosis, lymphocytopenia, and C-reactive protein), reached level B.

Conclusion
Prognostication of life expectancy is a significant clinical commitment for clinicians involved in oncology and palliative care. More accurate prognostication is feasible and can be achieved by combining clinical experience and evidence from the literature. Using and communicating prognostic information should be part of a multidisciplinary palliative care approach.

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INTRODUCTION

Besides being one of the core skills in the practice of medicine,\(^1,2\) prognostication in advanced cancer has special importance. In advanced phases of the disease, prognostication cannot be based on the same information as in earlier stages, when it is typically based on tumor stage.\(^3,5\) However, accurate prediction of survival is still necessary for clinical, organizational, and ethical reasons, especially in helping to avoid harm, discomfort, and inappropriate therapies in vulnerable patients\(^6\) and, conversely, in planning specific care strategies. Additionally, important personal decisions are influenced by
The WG reviewed several sources describing the clinical guidelines development process, and the following steps were adopted: (1) defining group membership; (2) identifying the target population; (3) defining the key questions; (4) systematically searching the literature; (5) assigning the level of evidence to the selected literature; and (6) formulating and grading the final recommendations.

**Methods**

The WG members were identified on the basis of their clinical experience in palliative care and in prognostic cancer studies (M.M., A.C., N.C., S.E., P.G., M.N., and A.V.). Members with epidemiologic and statistical expertise were also enlisted (C.B., P.G., and A.V.), and the contribution of an experienced nursing person was ensured (P.L.). Practical and ethical considerations determined the exclusion of patients. Sociologic and philosophical points of view were available (B.B. and N.C.). Finally, the group conclusions were submitted to external reviewers (F.D.C., G.H., and A.V.), and the contribution of an experienced nursing person was ensured (P.L.). Practical and ethical considerations determined the exclusion of patients. Sociologic and philosophical points of view were available (B.B. and N.C.). Finally, the group conclusions were submitted to external reviewers (F.D.C., G.H., and A.V.), and to the Steering Committee of the European Association for Palliative Care Research Network.

**Defining Group Membership**

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**Identifying the Target Population**

Accepted criteria for staging advanced cancer patients are lacking. Some authors have attempted to describe, with subjective criteria, inception cohorts, whereas others have examined patient populations referred to a palliative care program. However, many studies have shown that the median survival in populations of advanced cancer patients undergoing palliative care is less than 90 days. For these reasons, only populations homogeneous by survival (survival cohort) were included by selecting studies in which the median survival of the group was ≤90 days, excluding surgical series.

**Defining the Key Questions**

The WG defined six key questions, which developed into recommendations, that were assigned to different pairs of group members to carry out a literature search and analyze the available evidence about the usefulness of an accurate prognostication of life expectancy in advanced cancer patients, the prognostic role of clinical signs and symptoms, psychosocial characteristics, laboratory parameters, and prognostic scores.

**Systematic Literature Search**

Systematic reviews were performed for each area of interest. The search for relevant articles was performed on the Medline and Embase databases. The search strategy is presented in Table 1. A hand search of the References section of electronically identified articles was also performed. Articles not based on original data (unless formal meta-analyses) were excluded.

**Table 1. Literature Search Strategy**

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<tr>
<th>Limits: human full article studies and English language publications</th>
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<tr>
<td>1. Strategy used to search for articles on advanced cancer patients (Neoplasms (Mesh term all subheadings) OR cancer (tw) OR tumor (tw) OR tumour (tw) OR oncolog* (tw) AND (terminal care (Mesh term all subheadings) OR terminally ill (Mesh term all subheadings) OR palliative care (Mesh term all subheadings) OR hospices (Mesh term all subheadings)) AND (human full article studies AND English language publications))</td>
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<td>2. Strategy used to search for articles on prognosis (incidence (Mesh term) OR mortality (Mesh term all subheadings) OR follow-up studies (Mesh term) OR mortality (subheading) OR prognosis* (tw) OR predict (tw) OR course (tw) OR predict (tw) OR course (tw))</td>
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<td>3. One of the following strategies used to search for articles on a specific topic (Prediction (Mesh term and tw) OR Symptoms (Mesh term and tw) OR Performance status tw OR Biological factors (Mesh term and tw) OR Prognostic score (tw) OR prognostic index (tw))</td>
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**Table 2. Checklist of Quality Criteria for Study Evaluation**

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<th>Checklist</th>
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<td>1. Prospective study design</td>
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<td>2. Well-defined cohort of patients assembled at a common point in the course of their disease</td>
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<td>3. Random patient selection</td>
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<td>4. Percentage of patients lost to follow-up ≤20%</td>
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<td>5. Ratio between the number of events (death) and the number of potential predictors ≥10</td>
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<td>6. Prognostic variables fully defined, accurately measured, and available for all or a high proportion of patients</td>
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<td>7. Reliable measurement of outcome (date of death)</td>
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*High quality (or low probability of bias) is attributed to studies fulfilling at least five of seven criteria.*
A formal meta-analysis was not conducted because of the great heterogeneity of the combinations of different prognostic factors examined, poor quality of published studies, and frequent lack of minimal standards in reporting results. The prognostic strength of each predictor examined was described considering the hazard ratios and their CIs. A detailed report of all the hazard ratios and their CIs will be presented elsewhere.

Assigning the Level of Evidence to the Selected Literature

The level of evidence attributed to the results from each study was based on the methodologic quality of the study and on the study type. A quality assessment checklist, based on the existing literature, was formulated (Table 2). When evaluating meta-analyses, homogeneity of results was required to ensure quality. The study type classifications are listed in Table 3. Quality and study type classification levels were combined to give the final level of evidence (Table 4, modified from the Centre for Evidence Based Medicine Web site). Each study was evaluated independently by at least two group members.

Formulating and Grading the Final Recommendations

The evidence available for each topic, graded as shown in Table 4, was developed into draft recommendations by a writing committee, circulated to the full WG and to the external reviewers, and finalized into the present format.

RESULTS

The literature review produced a list of publications, which are listed in Table 5, that show the quality and characteristics of the evidence that was used to formulate the following recommendations (listed in brief in Table 6).

Recommendations

Recommendation 1. In the management of the patient with advanced cancer, physicians should base their decisions about therapeutic interventions and the place and type of care on the preferences and expectations of patients and their care givers as well as the life expectancy of the patient. Prognosis will sometimes determine access to specialist services, and an accurate estimate of life expectancy will generally facilitate decision making both for professional care givers and for patients and their families (grade D).

There is no study on prognostic factors aimed at evaluating whether an accurate prediction of survival can improve actual clinical care; that is, there is no impact study concerning the role of prognostic tools in improving decision making in the palliative care of advanced cancer. Despite this, it is the opinion of the WG that increased prognostic accuracy would assist health professionals to improve their care strategy and help patients and families to make more informed choices.

Recommendation 2. The Clinical Prediction of Survival (CPS) is a generally useful and valid tool but is subject to a series of factors that limit its accuracy. CPS could be defined as clinical prognostic judgment;
### Table 5. Results of the Literature Review Used for Developing the Recommendations

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<th>Prognostic Factor Area Considered</th>
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<th>No. of Articles Identified</th>
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<th>No. of Patients</th>
<th>No. of Quality Criteria Points Fulfilled*</th>
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NOTE. Some articles have a certain level of evidence for a given parameter and another level for a different factor. Abbreviations: Inv, investigative; Expl, explorative; Conf, confirmative.
*TThere are seven quality criteria points (listed in Table 2). Five of seven points is considered to be the minimum level acceptable for a low risk of bias.
it is subjective and depends on the clinician’s assessment of the individual patient at the bedside or in the clinic. The prognostic value of CPS has received a great deal of criticism in the literature because of the characteristics previously mentioned and because of its inherent nonreproducibility.

Our systematic review of the literature on CPS resulted in the selection of 27 articles, 11 of which were excluded. In the 16 eligible studies, the correlation coefficient of CPS/actual survival varied between 0.2 and 0.65. In all the studies examined in a review published in 2000, CPS was reported as having an independent effect when used with most other prognostic factors or tools. When using CPS, physicians need to be aware that it is subject to a series of features and shortcomings that limit its prognostic capacity. CPS is more than twice as likely to be overoptimistic versus overpessimistic and to overestimate the length of actual survival by a factor of between 3 and 5 (grade A). CPS is subject to the Horizon Effect, which is a term taken from the language of weather forecasting and used in clinical prognostication to mean the greater accuracy of short-term predictions over long-term predictions. Therefore, repeated evaluations of CPS at fixed intervals may be opportune (grade A). Considering CPS as a probability rather than a temporal value would ensure a more experienced professional could be useful (grade D). A second opinion could also be worth obtaining if the first physician has a close relationship with the patient (grade B).

Clinicians should consider using CPS in combination with other prognostic factors or scores to improve the accuracy of their predictions (grade A). Training in prognostication could improve the accuracy of CPS (grade D).

Recommendation 3. Certain clinical signs and symptoms have proven to be prognostically significant in this patient population, the most important of which are performance status (grade B), some symptoms of the cancer anorexia-cachexia syndrome (CACS; grade B), dyspnea (grade B), and delirium or cognitive failure (grade B). Factors linked to the patient or to the primary/metastatic site and biologic characterization of the tumor do not seem to be prognostically important in advanced cancer, as defined in this review.

Conversely, a correlation between some clinical signs and symptoms and survival has been confirmed in numerous multivariate analyses. In this section, of the 80 works analyzed, the 20 studies considered show that performance status and various indices of activity and functional autonomy are prognostically significant. In particular, low performance status is considered a reliable prognostic factor to predict short-term survival. However, initially high scores are not necessarily predictive of a long survival, whereas their deterioration often indicates a serious worsening of the prognosis.

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pulse, and respiratory rate), polymorbidity, opioid therapy, and therapeutic and diagnostic interventions have occasionally proven to be significant, mainly in less advanced stages of the disease. However, these symptoms have not been confirmed in multivariate analysis, especially in the far advanced patient population.

The prognostic capacity of subjective indicators of quality of life or other psychological parameters is somewhat contradictory. Although they are certainly relevant in the earlier stages of disease, the prognostic relevance of multidimensional tools in patient populations with a median survival of 90 days or less seems to be attributable to the physical-symptomatic component of the test.

**Recommendation 4.** There is some evidence that abnormalities in certain laboratory tests (particularly leukocytosis, lymphocytopenia, and elevated C-reactive protein) have prognostic significance (grade B). The need for a blood sample also needs to be weighed against the likely clinical advantage for the individual patient (grade D). Biologic parameters have not been as widely investigated as clinical parameters in this population of patients, and a more accurate evaluation of these variables in relation to prognosis is undoubtedly warranted.

In the present review, a total of 23 biologic factors were studied in the nine works selected for assessment. Laboratory parameters that proved significant in at least one multivariate analysis were low pseudocholinesterase, high vitamin B$_{12}$, and high bilirubin. Statistical significance in more than one study was observed for elevated C-reactive protein, lymphocytopenia, and leukocytosis. The same biologic parameters also proved to be prognostically valid in other heterogeneous populations of patients with less advanced disease. This positive relationship was, conversely, lost by some factors, such as albumin and prealbumin levels, which could be attributed to a close correlation with other CACS characteristics that maintain their significance, to the detriment of weaker factors.

**Recommendation 5.** A number of prognostic scores or indices have been developed that are easy to use and permit a rapid estimate of life expectancy by placing patients into broad groups that differ significantly in survival (grade A). Some authors have built and validated prognostic scores for patients in palliative care programs. These scores are constructed on the basis of prognostic factors that have proven to be significant in multivariate analysis and have been validated quantitatively on the basis of their individual prognostic weight.

Only eight of the 24 studies identified satisfied the review requirements. Of these studies, four involved construction and development of scores, whereas four concerned the validation of two of the scores, the Palliative Prognostic (PPI) and the Palliative Prognostic Index (PPI). The PaP Score (Table 7) was built and validated in two independent multicenter population studies and is the only measure to include some simple biologic factors that require a blood sample. It has been validated in several countries, in various settings, and in different disease phases. This score includes CPS, which means that it is used together with, rather than instead of, clinical judgment. The PaP Score was not constructed to include hematologic malignancies and, therefore, cannot be used in this patient population. Furthermore, the score does not include delirium, which was subsequently demonstrated to subdivide each population categorized by the PaP Score into two further prognostic subgroups.

The PPI does not include CPS, and one study specifically aimed at evaluating the impact of PPI on CPS showed a significant improvement in prognostication. No studies have ever been conducted to compare the efficacy of different scores.

**Recommendation 6.** Establishing an accurate prognosis is part of the therapeutic alliance. Patients have a right to be informed of their prognosis or, if they prefer, not to be informed. Using and communicating prognostic information...
should be within the context of a comprehensive, individualized, patient-centered approach (grade D).

A number of principles should be applied to this clinical situation. First, do not be a burden to the patient. From an ethical point of view, it is important that prognostic tools do not impose an additional burden on the patient, be it directly or indirectly (ie, by being time consuming and, thus, leaving less time for other aspects of patient care).

Second, use prognostic information within an ethically valid approach. It is important to understand that a prognosis is established, used, and communicated. Although our recommendations concentrate on establishing a prognosis, we should not forget that, once established, a prognosis should be used in an appropriate way. Treatment decisions should be based on a number of variables, including prognosis, and all these variables should receive due attention. The fact that prognostic information is, by definition, probabilistic, and that even the best prognostication will be dramatically inaccurate for a significant number of patients provides an additional reason for never losing sight of the patient and his or her individual trajectory and personal history. Prognostication that is not deeply embedded in an open, flexible, patient-centered, and dialogic approach is potentially dangerous.

Third, communicate prognosis when requested and in an appropriate way. Patients have a right to be informed about their prognosis, but they also have the right to refuse to be informed. When prognosis is communicated, ethical, cultural, religious, and psychological considerations are of fundamental importance to avoid inflicting additional harm to the patient.

Fourth, place emphasis on a holistic therapeutic approach beyond time limits. It is only by working within the realms of multidisciplinary palliative care and by continuing to consider the individual value of the patient’s residual life that life expectancy prognostication can improve and further personalize the care of advanced cancer patients.

**DISCUSSION**

The recommendations made here are confined to a population of patients with advanced cancer and a median survival of no more than 90 days. The WG demonstrated that, given the available literature evidence, prognostication of life expectancy in advanced cancer patients is feasible and facilitated by the use of clinical tools such as signs and symptoms, laboratory examinations, and prognostic scores. In particular, strong evidence of prognostic significance has emerged for CPS, performance status, clinical symptoms of CACS (anorexia, weight loss, dysphagia, and xerostomia), dyspnea, delirium, some biologic factors (leukocytosis, lymphocytopenia, and C-reactive protein).

<table>
<thead>
<tr>
<th>Factors for which a definite correlation with prognosis has been identified</th>
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<tr>
<td>Clinical prediction of survival</td>
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<td>Performance status</td>
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<tr>
<td>Signs and symptoms of cancer anorexia-cachexia syndrome (anorexia, weight loss, dysphagia, and xerostomia)</td>
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<tr>
<td>Delirium</td>
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<td>Dyspnea</td>
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<td>Some biologic factors (leukocytosis, lymphocytopenia, and C-reactive protein)</td>
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<td>Prognostic scores</td>
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<th>Factors for which a correlation has been indicated but not confirmed or for which a statistical significance has been identified in patient populations with less advanced disease or for which contradictory data have emerged</th>
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<tr>
<td>Pain</td>
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<td>Nausea</td>
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<td>Tachycardia</td>
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<td>Fever</td>
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<td>Neoplastic pattern (primary and secondary sites)</td>
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<td>Comorbidity</td>
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<td>Anemia</td>
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<td>Serum calcium level</td>
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<td>Serum sodium level</td>
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<tr>
<td>Lactate dehydrogenase and other enzymes</td>
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<td>Patient characteristics (age, sex, and marital status)</td>
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<th>Factors with controversial indications</th>
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<tr>
<td>Multidimensional quality-of-life questionnaires; it is possible that their prognostic capacity is a result of the identifying component of physical symptoms contained within them</td>
</tr>
</tbody>
</table>
lymphocytopenia, and C-reactive protein level), and prognostic scores (Table 8).

More research is needed to deepen our understanding of the processes leading to clinical prediction and of how it can be improved and refined by the help of other explicit, objective evaluations.79,80 The lack of evidence from impact studies supporting the usefulness of better prognostic tools for advanced cancer patients should also be underlined as an urgent area for research. Therefore, health workers involved in the care of advanced cancer patients are encouraged to use their clinical skills, together with evidence-based recommendations, to elaborate their own prediction of individual patient survival. The systematic use of prognostic scores can teach clinicians to focus their attention on prognosis and, at the same time, help in the clinical management of the patient. Therefore, these scores can be considered useful tools for health workers in clinical practice.

It is important to point out that prognostic information should not be limited to palliative care populations, but it can also be used to gain a better understanding of patient survival before referral for palliative care. More studies on well-defined inception cohorts are needed to improve our knowledge in this field.

Finally, it is clear to the WG that ethical considerations regarding prognostication at the end of life are indeed of fundamental importance. The failure to prognosticate or to prognosticate accurately can, in some circumstances, be as harmful as a mistaken diagnosis or therapy. The fallibility of prognosis alone highlights its moral dimensions.

Acknowledgment

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Appendix

Members of the Steering Committee of the Research Network of the European Association of Palliative Care who also contributed to this study include the following: F. De Conno (Chair), H. Huyer Abu-Saad, A. Caraceni, N. Cherny, C.J. Furst, J. Ferraz Gonçalves, G.W. Hanks, S. Kaasa, P. Klepstad, M. Lloyd Williams, S. Mercadante, J.M. Nunez Olarte, P. Poulain, L. Radbruch, C. Ripamonti, F. Strasser, and A. Tuca i Rodriguez.

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Terminal Withdrawal of Life-Sustaining Supplemental Oxygen

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John Hansen-Flaschen, MD

A new influential report released in 1983 defined life-sustaining therapies as "all health care interventions that have the effect of increasing the life span of the patient." This definition is highly inclusive: aspirin for stable coronary artery disease, intravenous antibiotics for osteomyelitis, and mechanical ventilation for respiratory failure all qualify. However, when considering withholding or withdrawing life-sustaining interventions, clinicians commonly refer to a more discrete group of therapies intended to forestall impending death by augmenting or replacing a vital bodily function. A hallmark of life-sustaining therapies, therefore, is that withholding or withdrawing them leads to physiologic decompensation foreseeably to cardiac arrest.

Supplemental oxygen has not commonly been considered a life-sustaining therapy. Yet it clearly serves this purpose for spontaneously breathing patients in whom pulmonary gas exchange is so impaired that the needs of vital organs cannot be met with ambient air alone. Supplemental oxygen may be lifesaving, as in the acute treatment of severe pneumonia or pulmonary embolism, or life-sustaining, as in the subacute or long-term management of patients with advanced pulmonary fibrosis, extensive intrathoracic cancer, or cardiovascular conditions causing right-to-left shunting of venous blood.

As cardiopulmonary diseases associated with hypoxemia increase in incidence, and as new technologies are available to provide high-flow oxygen to patients living at home, physicians are more commonly caring for patients whose lives are sustained by supplemental oxygen. Although improvements in oxygen delivery systems have led to improved functional capacity for some patients, the quality of life associated with long-term oxygen dependence may remain unacceptable. As a result, some patients have asked their physicians for assistance with or acquiescence to their plans to withdraw supplemental oxygen.

Informed patients with decision-making capacity have well- established rights to forgo any and all forms of lifesustaining therapy. Although these rights clearly extend to supplemental oxygen, requests to remove this form of lifesustaining therapy raise difficult questions. Should physicians help patients remove such a minimally invasive and...
often comforting intervention when death is the expected result? If so, should oxygen be replaced with palliative sedation? Should such sedation be administered before oxygen is removed in anticipation of distress, or afterward in response to manifest discomfort? These and other concerns may prevent some physicians from heeding requests for the withdrawal of life-sustaining oxygen as readily as they may heed requests that other therapies be withdrawn. As the Association of Palliative Medicine noted, "once oxygen has been given to a patient it is often difficult to stop its use." In this commentary, we discuss these concerns and suggest strategies for physicians to overcome them.

Concerns About Balancing the Burdens and Benefits of Supplemental Oxygen

When discussing the possibility of terminal withdrawal of life-sustaining interventions with patients or family members, physicians often point to the discomfort, invasiveness, and functional impairment associated with continuation of a therapy that is no longer serving an intended purpose. Patient comfort and dignity are improved by removing (or not inserting) indwelling catheters and by eliminating life-supporting machines that limit patient movement and interfere with family access to the bedside. Compared with discontinuation of invasive life-sustaining treatments, such as mechanical ventilation or hemodialysis, the benefits of discontinuing supplemental oxygen may seem less clear.

In the past, dependence on high-flow oxygen imposed pragmatic constraints on patients, such as effectively prohibiting transfer from the hospital to a preferred location for terminal care (e.g., home or a skilled nursing facility). Dependence on tightly fitting reservoir oxygen masks also limited movement and inhibited patients’ abilities to eat and speak clearly. However, newer oxygen concentrators that generate flow rates up to 10 L/min effectively overcome some of these burdens. One or 2 such concentrators can reliably supply adequate oxygen in any location with electrical wall outlets. Furthermore, high-flow, humidified nasal cannulae and tracheal catheters can deliver oxygen at flow rates that are sufficient to replace a reservoir mask in many instances, thereby facilitating eating and speaking.

Thus, although some supplemental oxygen devices are inconvenient, oxygen is less burdensome than many other forms of life support. In addition, it may be beneficial by alleviating dyspnea. Although explanations for this benefit remain unclear and include the possibility that airflow rather than oxygen per se contributes importantly to palliation, most physicians believe that oxygen improves dyspnea. More clearly, supplemental oxygen sustains cognitive function for patients with severe hypoxemia at rest, and thereby preserves their ability to interact meaningfully with others. Physicians and other caregivers observe these benefits whenever unintended displacement or interruption of supplemental oxygen results in patient confusion, air hunger, or panic.

Balancing benefits against burdens for high-flow supplemental oxygen is further complicated by the potential for pulmonary oxygen toxicity. Continuous inhalation of 100% oxygen at atmospheric pressure causes injury to airways and consequent chest pain in healthy volunteers after as little as 16 hours. Pulmonary edema typically follows after several days. Considerably less is known about the tolerance of patients with severe lung disease to inhalation of variable concentrations of oxygen in clinical settings. Thus, the burden of high-flow supplemental oxygen may change over time and in an unpredictable fashion for patients who are dependent on this therapy.

Concerns About Appearing Neglectful

Another difficulty in removing supplemental oxygen is that oxygen is often perceived as meeting a basic bodily need, and so its use may comfort family and friends by suggesting that caregivers are actively attending to the dying patient. Perhaps for this reason, some physicians regularly provide oxygen via face mask or nasal cannula after terminating withdrawing mechanical ventilation, even for those patients who are deeply sedated and unresponsive. Thus, unlike the withdrawal of most other forms of life support (although similar, for some, to artificial feeding), the unexplained withholding or withdrawal of oxygen can appear neglectful or callous.

Concerns About the Patient’s Decision-Making Capacity

Many illnesses for which oxygen is used are accompanied by acute impairments of cognitive function due to sleepiness, hypercarbia, hypoxemia, or the administration or accumulation of sedating drugs. Therefore, physicians may wonder whether patients who wish to end their lives by removing oxygen are, in fact, competent to make such choices. The challenge of testing decision-making capacity in this circumstance may be compounded if patients’ abilities to communicate are limited by rapid breathing or exertional dyspnea.

Concerns About Using Sedation in Lieu of Oxygen

Some physicians will also be concerned about withdrawing a life-sustaining and potentially palliative intervention, only to replace it with analgesic or sedative medications. Doses of opioid and benzodiazepine medications that are sufficient to alter consciousness can also suppress ventilation, particularly when used in combination. Although administration of opioids and benzodiazepines does not seem to influence the time until death after palliative withdrawal of mechanical ventilation in an intensive care unit, such drugs could easily hasten death among spontaneously breathing patients who are only marginally able to sustain adequate ventilation.
The religious and ethical doctrine of double effect has frequently been invoked to address such situations. The doctrine holds that outcomes that would be morally unacceptable if caused intentionally might be acceptable if caused as a byproduct of some other intended effect. Although this doctrine has clear philosophical limitations, it has been explicitly accepted by the Supreme Court and remains an integral concept in end-of-life decision making. Accordingly, if competent patients wish to discontinue supplemental oxygen therapy and dyspnea results, it becomes acceptable and humane to relieve this dyspnea pharmacologically.

Even physicians who accept this justification, however, may be unsure about how to administer sedatives and analgesics in this situation. It is unclear what physiological changes occur after abrupt replacement of high-flow oxygen with ambient air, how patients experience these changes, and at what pace they occur. In light of such uncertainty, should clinicians sedate fully conscious patients prior to oxygen withdrawal? Will clinicians be able to titrate medications effectively and responsibly if distress develops suddenly after oxygen is discontinued? As difficult as these questions may be for physicians faced with requests for oxygen withdrawal among hospitalized patients, they become even more challenging when patients request that oxygen be withdrawn at home.

**Concerns About the Patient’s Motivation for Discontinuing Oxygen**

If high-flow supplemental oxygen is minimally invasive, widely available, and palliative to both patient and family, why would rational patients ask that it be discontinued? The answer to this question will be unsettling for some clinicians: these patients may be seeking relief from the burden of life itself.

Some patients never complain about the discomfort or expense associated with administration of supplemental oxygen, and yet wish to have it removed. For many terminally ill patients, progressive loss of functional capacity and sense of self lead to substantially reduced opportunities for happiness and satisfaction.

Such limited benefits to ongoing life may be dominated by steadily increasing burdens. In addition to the dyspnea that may result from such commonplace activities as eating, bathing, or defecating, living near the threshold of dependency on mechanical ventilation may cause anxiety, despondency, and other forms of emotional distress. For some patients, fear of suffocation is ever present and episodes of panic arise whenever breathing is compromised, such as with mucous plugging. Patients are also burdened by their increasing dependence on others for transportation and hygiene.

A comparable situation confronts some patients who are dependent on hemodialysis. Voluntary withdrawal of dialysis is a common prelude to death for patients with end-stage renal disease, contributing to approximately 1 of every 4 deaths among patients with end-stage renal disease in the United States. The burden of dialysis does not fully explain this phenomenon. An unacceptable overall quality of life and the desire not to remain a burden to others commonly contribute to patients' decisions to discontinue dialysis.

Physicians may be concerned that by condoning a patient's plan to end his or her own life and providing sedative medication to make the withdrawal of oxygen or dialysis more comfortable, the physician may be criticized for assisting in the patient's suicide. However, when a competent patient requests that a physician discontinue life support, this is not equivalent to a request for assisted suicide. The distinction between assisting in a patient's death and removing a life-sustaining treatment holds even if the life-sustaining treatment is obtrusive and potentially palliative. Importantly, the fact that the primary purpose of such requests may be to escape the burden of life itself, rather than the burden of therapy, does not absolve physicians of their duty to heed patients' requests for therapy withdrawal.

**Recommendations**

Although it may be difficult for physicians to overcome all of these concerns, the following 4-step approach may be helpful.

First, physicians should assure themselves, other health care professionals involved in the patient's care, and the patient's family members or close friends that supplemental oxygen is a form of life-sustaining medical treatment. As such, requests to discontinue oxygen should be honored with the same judiciousness as requests to withdraw other forms of life support. The physician should further recognize that requests to discontinue this intervention are not inherently irrational. Even if the practical burdens of oxygen are minimal and the palliative benefits real, the patient's dissatisfaction with his or her current quality of life may justifiably underlie such requests.

Second, physicians should ensure that patients requesting the terminal withdrawal of oxygen are free from undue influences, including family members' wishes, economic considerations, or treatable depression. Physicians should search for sources of distress or unfulfilled needs that can be addressed in other ways. For example, problems related to oxygen supplementation, such as an ill-fitting mask or overly restrictive apparatus, may be resolved by consulting physicians who more commonly use new technologies for supplying and conditioning high-flow oxygen.

Third, physicians should ensure that the patient has the capacity to make medical decisions. Patients should be required to show consistency by conveying the same preference on at least 2 separate occasions; to show understanding by acknowledging the alternatives to and consequences of their decision; and to show rationality by explaining why their decision serves their goals.
And fourth, physicians should ensure that patients and their family members understand the difficulty of predicting patients’ experiences after oxygen withdrawal. Although hypoxia may often produce unconsciousness without discomfort, increased dyspnea, anxiety, and agitation are also possible results. Physicians should further explain that pharmacotherapy is indicated if dyspnea or anxiety do occur, but that such therapies may be difficult to titrate; sedation may enable distress and oversedation may limit the quality of patients’ final interactions with loved ones.

In an acute care facility, patients who choose to discontinue oxygen may be administered opioids and benzodiazepines to alleviate dyspnea and anxiety. In some instances, a recent temporary interruption of oxygen therapy will allow prediction of the patient’s subjective response after palliative withdrawal. If such an experience predicts rapid onset of patient distress, sedation can be provided in anticipation of oxygen withdrawal, as is recommended in anticipation of withdrawing mechanical ventilation. When the patient’s response is less certain, sedating drugs should be reserved but readily available for administration as needed after withdrawal. Dosing will be inexact, but the presence of a clinician who is experienced in the palliative titration of intravenous or oral opioids and benzodiazepines will help to optimize this difficult process.

Some patients will request physicians’ assistance in withdrawing supplemental oxygen at home. In certain cases, patients provided with prescriptions for sedatives and analgesics can manage their own end-of-life care with the assistance of family members. However, a hospice nurse or a visiting physician may provide more skilled assessment, titrated dosing of medications, comfort to others who are present, and appropriate documentation of this legitimate medical service.

Regardless of whether supplemental oxygen is withdrawn in a hospital or at home, physicians should explain that the patient’s major recourse in the event of uncontrolled distress is to reapply their oxygen. The plan can then be reconsidered in light of the experience gained. False starts and ambivalence have been described in the context of withdrawing dialysis and also may occur after withdrawal of supplemental oxygen.

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ABSTRACT

In recent years a better understanding of the pharmacologic and pharmacokinetic properties of methadone, including equianalgesic ratios has led to its increased use as a second line opioid for the treatment of pain in patients with cancer. Methadone may be an important alternative for those who have side effects related to the use of other opioids because it has no known active metabolites, is well absorbed by oral and rectal routes, and also has the advantage of very low cost. However, it has a long, unpredictable half-life, which can result in accumulation and toxicity in some patients. In addition, rotation to methadone as a second line agent is more complex than with other opioids because of its increased potency in those patients who are opioid tolerant, particularly those who have been on higher doses of other opioids. Future research should address the use of methadone as a first-line agent in the management of cancer pain, its use in patients with neuropathic pain, and in those who develop rapid tolerance to other opioids. In some patients with cancer the long half-life of methadone offers the advantage of extended dosing intervals to 12 and even 24 hours, further research is also needed in this area.

INTRODUCTION

OVER THE PAST 10 YEARS interest in the use of methadone for treatment of pain has increased. Several studies have shown methadone to be an effective analgesic in cancer-related pain.\(^1\)\(^-\)\(^3\) Better understanding of the pharmacologic and pharmacokinetic properties of methadone, including equianalgesic ratios has led to its increased use as a second-line opioid for the treatment of cancer-related pain.

In this paper we outline pharmacologic characteristics and clinical uses of methadone in palliative care. In addition, we identify some future potential indications for its use and areas requiring further research.

PHARMACOLOGIC ASPECTS

Methadone is a synthetic opioid agonist and was developed over 40 years ago.\(^4\) The chemical structure of methadone is not related to the alkaloid-type structure of the opium derivatives. In addition to opioid agonist activity, methadone has been found to be a relatively potent \(N\)-methyl-D-aspartate (NMDA) receptor antagonist.\(^5\)\(^,\)\(^6\)

It is a basic and lipophilic drug and is subject to considerable tissue distribution.\(^7\) This peripheral reservoir sustains plasma concentrations during chronic treatment.\(^8\) Methadone has relatively high lipid solubility, is highly bound to \(\alpha\)-1-acid-glycoprotein, and is extensively metabo-
lized in the liver to inactive metabolites via N-demethylation.\textsuperscript{9}

In the United States methadone is available as methadone hydrochloride powder, which can be used for the preparation of oral, rectal, and parenteral solutions. In many countries, methadone is commercially available in these formulations. It is generally available in racemic form. In some countries such as Germany, \(L\)-methadone is available and its analgesic effect is approximately twice that of the racemic form.\textsuperscript{10} Methadone is almost completely absorbed in the gastrointestinal tract. Its oral bioavailability is generally high and considered to be about three times that of other oral opioids such as morphine, it ranges from 41% to 99%, and is usually considered to be in the region of 80%.\textsuperscript{11,12} Oral morphine has a larger interindividual variation in bioavailability than oral methadone.\textsuperscript{12}

There is large interindividual variation in the pharmacokinetics of methadone. Methadone is characterized by a rapid and extensive distribution phase (half-life, 2–3 hours). This is followed by a slow elimination phase (\(\beta\) half-life, 15–60 hours). Elimination phase half-lives with a range of 4.2–130 hours have been reported in some individuals.\textsuperscript{13} This extended elimination phase is of clinical importance because it may result in drug accumulation and toxicity.\textsuperscript{14,15} Most of the drug is excreted by the fecal route and only minor amounts are eliminated in the urine. Renal elimination is influenced by urinary pH; increased renal clearance is seen below the urinary pH of 6.\textsuperscript{4,16}

There are many potential drug interactions involving methadone. Administration of amitriptyline can increase the concentration of \(\alpha\)-1-glycoprotein, this may explain the decreased methadone clearance associated with concomitant use of amitriptyline therapy.\textsuperscript{17} The cytochrome P450 (CYP) system is involved in the metabolism of methadone, hence drugs that interfere with this system can alter the metabolism of methadone causing either accumulation or increased inactivation with important clinical consequences. The CYP system involves several isoenzymes. The CYP 3A3/4 isoenzyme appears to be the most important with respect to methadone metabolism.\textsuperscript{18,19} Drugs that inhibit or activate these isoenzymes have the potential to cause clinically important interactions when combined with methadone. Table 1 outlines inhibitors and activators of the CYP system that may affect the metabolism of methadone. Probable interac-

<table>
<thead>
<tr>
<th>Table 1. Drugs That Affect the CYP-450 System and Can Potentially Interact with Methadone</th>
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<tr>
<td>3A4 Isoenzyme Inhibitors</td>
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<tr>
<td>Antibiotics</td>
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<tr>
<td>Erythromycin and other macrolides\textsuperscript{20}</td>
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<tr>
<td>Ketoconazole and other imidazoles\textsuperscript{20}</td>
</tr>
<tr>
<td>Ciprofloxacin and other quinolones\textsuperscript{19}</td>
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<tr>
<td>Antidepressants</td>
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<tr>
<td>Selective serotonin reuptake inhibitors (in particular fluvoxamine)\textsuperscript{62,63}</td>
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<tr>
<td>Atypical antidepressants (e.g., nefazodone)\textsuperscript{20}</td>
</tr>
<tr>
<td>Diazepam\textsuperscript{64}</td>
</tr>
<tr>
<td>Antiviral drugs</td>
</tr>
<tr>
<td>Ritonavir, nevirapine\textsuperscript{66}</td>
</tr>
<tr>
<td>3A4 Isoenzyme Inducers</td>
</tr>
<tr>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Phenytoin, carbamazepine, and phenobarbital\textsuperscript{67}</td>
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<tr>
<td>Rifampicin\textsuperscript{20}</td>
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<tr>
<td>Corticosteroids\textsuperscript{68}</td>
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Inhibitors of the relevant CYP isoenzymes have the potential to increased levels of methadone with resulting sedation and respiratory depression. Drugs that activate the relevant CYP isoenzymes increase the inactivation of methadone and can result in poor pain control or the development of symptoms of withdrawal. Methadone itself can inhibit the CYP 450 system.\textsuperscript{20,24} Methadone metabolites are capable of inhibiting the CYP 450 system more than the parent drug.
and can hence result in rising levels of methadone, this may be important in palliative medicine.\textsuperscript{20} Although methadone is not metabolized by the 2D6 isozyme, one study suggests that it could partially inhibit the system\textsuperscript{24} and might affect the levels of drugs metabolized by this isozyme such as dextrometorphan, codeine, hydrocodone, secondary tricyclic antidepressants, haloperidol, phenothiazines, and $\beta$-blockers.

In summary, methadone undergoes extensive metabolism in the CYP 450 microsome and all agents metabolized by this system could potentially interact with this drug. More clinical research is needed to better understand these interactions, in the meantime it is advisable to limit the use of agents metabolized in the 3A4 and possibly the 2D6 isoenzymes in patients using methadone. If this is not possible, increased clinical monitoring of side effects may be required in patients receiving such agents in combination with methadone.

**CLINICAL USES**

The use of methadone as a maintenance treatment in the management of individuals with opioid dependence has resulted in reluctance on the part of some physicians to prescribe methadone and some patients to accept it as an analgesic agent. In addition, a number of early studies of the analgesic effects of methadone reported toxicity with respiratory depression\textsuperscript{15,32} and reduced survival in cancer patients taking oral methadone when compared to those taking diamorphine/codeine.\textsuperscript{33} With better understanding of the pharmacokinetics (particularly the long half-life) of methadone it has subsequently been found to be a safe and effective alternative to other opioids when prescribed by physicians experienced in its use.\textsuperscript{34–37} In one randomized controlled trial, Mercadante et al.\textsuperscript{35} compared methadone to morphine for the treatment of pain in advanced cancer patients. Twenty patients were treated with oral liquid methadone and 20 patients were managed with commercially available sustained release morphine preparations, both drugs were given 2 to 3 times per day according to need. Doses of both drugs were kept as low as possible and titrated to achieve acceptable analgesia with minimal adverse effects. Pain control and side effects were similar in both groups. Opioid escalation was significantly less in those patients treated with methadone than in those treated with morphine. In addition, more stable analgesia over time was seen in patients treated with methadone.

The unique pharmacologic and pharmacokinetic characteristics of methadone result in both clinical advantages and disadvantages over other opioids; these are summarized in Table 2. Methadone is currently used for two main indications in palliative care: as a second line agent in opioid rotation and for the treatment of opioid resistance and neuropathic pain.

**Opioid rotation**

Methadone has no known active metabolites. Active metabolites of other opioids such as morphine appear to be involved in the development of opioid induced neurotoxicity.\textsuperscript{38} In addition, methadone does not tend to accumulate in patients with renal impairment as its excretion is primarily by the fecal route. These two features of methadone mean that it has the potential to be an excellent alternative in patients in whom opioid rotation is required due to opioid induced neurotoxicity (see below). Its excellent absorption by the oral and rectal route also makes it a convenient choice for many patients.

More than 80\% of cancer patients require opioid analgesics for pain at some point before death.\textsuperscript{39,40} With current practice, patients with cancer are receiving opioid analgesics earlier and for longer periods of time than they were 10 years ago. This is a highly desirable consequence of improved education about cancer pain. However, the use of higher doses of opioids has resulted in the identification of new side effects, probably the most problematic of these are neurotoxic side-effects (opioid induced neurotoxicity). These are most likely caused by an accumulation of active metabolites of opioids. The parent compound may also have a significant role in its development.\textsuperscript{41} Table 3 summarizes the features of opioid induced neurotoxicity. Some of the specific features of this syndrome include excitatory side effects as opposed to the traditionally described sedative side effects of opioids. The recent finding that accumulation of active opioid metabolites occurs in patients receiving such common opioids as morphine, hydromorphone, fentanyl and oxycodone has prompted a number of authors to suggest that opioid rotation should be attempted in most patients who develop opioid in-
duced neurotoxicity, or in whom side effects are limiting doses.\textsuperscript{41–53}

Several prospective studies, retrospective studies, and case reports have been published describing successful rotation from other opioid analgesics to methadone in patients experiencing side effects or inadequate analgesia from other opioids.\textsuperscript{1,2,36,44–51} Mercadante et al.\textsuperscript{44} in a prospective study of 52 consecutive patients with cancer pain with uncontrolled pain and/or moderate to severe opioid side effects switched opioid from oral morphine to methadone. In patients switching for uncontrolled pain and morphine-related adverse effects, a significant improvement was seen in pain intensity, nausea and vomiting, constipation, and drowsiness.\textsuperscript{44} In another prospective multicenter study of 108 patients with cancer pain treated as outpatients it was found that rotation to methadone from other opioids resulted in a significant improvement in pain scores. Rotation to methadone was completed in 103 patients and it was concluded that a regime of oral methadone every 8 hours was safe and effective for the management of cancer pain.\textsuperscript{37}

A major problem encountered when rotating to methadone from another opioid is that clinical experience has found large interindividual variations in the equianalgesic ratio of methadone to other opioids.\textsuperscript{1,45} Methadone becomes relatively more powerful with increasing prior exposure to other opioids and can be up to 10 times more potent in patients given greater than 500 mg/d of morphine than in patients given less than 100 mg/d.\textsuperscript{1} This large variation prevents the use of simple equianalgesic tables to calculate the required dose of methadone. There are three possible explanations for this observation.

### Table 2. Potential Advantages and Disadvantages of Methadone Over Other Opioids in Palliative Care

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Oral, rectal and intravenous routes at administration with very good oral bioavailability</td>
<td>Subcutaneous route is associated with local reactions</td>
</tr>
<tr>
<td>No known active metabolites</td>
<td>Long and variable elimination half-life, may lead to accumulation and adverse effects in some patients</td>
</tr>
<tr>
<td>Excretion mainly by fecal route, does not accumulate significantly with renal impairment</td>
<td>Rotating to methadone is difficult due to dramatic variation in dose ratio of methadone to other opioids depending on the extent of previous exposure to opioids</td>
</tr>
<tr>
<td>Inexpensive (15–20 times cheaper than other opioids)</td>
<td>Stigmatization because of its traditional use in the management of opioid addiction</td>
</tr>
<tr>
<td>NMDA receptor antagonism, hence may have role in opioid resistant and neuropathic pain</td>
<td>Methadone inadequately studied as a first-line agent</td>
</tr>
<tr>
<td>Extended dosing interval, 2–3 times/day and or even daily may be possible in selected individuals\textsuperscript{55}</td>
<td>Dose ratios for rotation from methadone to other opioids has not been systematically researched</td>
</tr>
<tr>
<td>Constipation may develop more gradually\textsuperscript{58}</td>
<td>Drug interactions at the CYP 450 3A4 and 2D6 levels</td>
</tr>
</tbody>
</table>

NMDA, N-methyl-D-aspartate.

### Table 3. Features of Opioid-Induced Neurotoxicity (OIN)

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe sedation</td>
</tr>
<tr>
<td>Cognitive failure\textsuperscript{a}</td>
</tr>
<tr>
<td>Hallucinosis/delirium</td>
</tr>
<tr>
<td>Myoclonus/grand mal seizures</td>
</tr>
<tr>
<td>Hyperalgesia/allodynia</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Cognitive failure denotes abnormality in attention, memory, orientation and/or psychomotor skills and is assessed by simple cognitive tests such as the Mini Mental State Examination.
1. Decreased cross-tolerance of opioid receptors: The chemical characteristics and configuration of methadone may result in a different type of binding to opioid receptors as compared to other opioids. This different manner of receptor binding could result in only a partial development of cross-tolerance to methadone.

2. NMDA receptor antagonism: Methadone has been found to be a relatively potent inhibitor of NMDA receptors. \(^5,6\) Excitatory amino acids such as NMDA have been shown to play a major role in the development of opioid tolerance and in the opioid resistance of neuropathic pain. \(^5,6,52\) NMDA receptor antagonists have been found to reverse opioid tolerance in animal models. \(^52\) It is possible that methadone exerts a similar effect in reversing previously developed opioid tolerance in patients with cancer pain.

3. Elimination of active metabolites: It is possible that the increased potency of methadone may be related to the elimination of proalgesic active opioid metabolites, such as morphine-3-glucuronide, normorphine or other unidentified products. \(^41\) However, rapid changes in the concentrations of neurotoxic opioid metabolites would occur when patients are rotated not only to methadone but also to other

FIG. 1A. The relationship between dose ratio and previous opioid dose of morphine and hydromorphone expressed as morphine-equivalent daily dose. (Reprinted with permission from PRR, Inc., Bruera E, Neumann C: Role of methadone in the management of pain in cancer patients. Oncology 1999;13:1275–1282.)
opioids. Such a dramatic difference in dose ratio has not been observed when patients are switched to other opioids such as hydromorphone.\textsuperscript{47,53,54} Figure 1A shows the relationship between dose ratio and previous opioid dose for morphine and hydromorphone in 74 patients with cancer. Figure 1B shows that the relationship between equianalgesic ratios of other opioids and methadone in 103 patients was highly correlated with total opioid dose before rotation.

The process of switching from another opioid agonist to methadone is complex and should be attempted only by physicians who are experienced in cancer pain management. Even when methadone is administered by experienced physicians serious toxicity can occasionally occur.\textsuperscript{14} Contrary to what would be expected with other opioids, toxicity appears to occur more frequently in patients previously exposed to high doses of opioids than in patients who have received low doses. These findings suggest that greater caution is needed when patients are switched to methadone from higher doses of other opioids. A number of strategies for rotating to methadone from other opioids have been used by various groups. Mercadante et al.\textsuperscript{36} reported a method of rapid switching from morphine to methadone using a fixed conversion ratio of 5:1, with subsequent doses adjusted according to clinical need. Switching took place in an outpatient setting and was effective in 19 of 24 patients. More than half the patients in this study were receiving 90 mg/d of morphine or less and the mean morphine dose for all patients was 125 mg/d. The authors concluded that an appropriate system of patient monitoring was necessary because of the clinical need in some patients to change doses. A similar approach for patients with poor pain control and/or adverse effects has been used with titration of the ratios of methadone to morphine depending on morphine dose prior to the switch. Table 4 summarizes this approach to methadone rotation. Only three patients were receiving greater than 300 mg of morphine. Using this method a significant increase in the methadone dose was required to improve analgesia (average 20%) for those patients switched because of poorly controlled pain. The authors commented that caution in switching to methadone is particularly important for physicians treating patients with higher doses of morphine than were used in their study.\textsuperscript{44}

Reports on patients receiving high-dose opioids suggest that the changes to methadone should occur in an inpatient setting over 3 to 6 days. Nauck et al.\textsuperscript{10} switched 33 patients from high-dose morphine (> 600 mg oral equivalent)
to L-methadone. This method of rotation to methadone is summarized in Table 5. Another method of rotation to methadone is summarized in Table 6. Patients receiving morphine equivalent daily doses of less than 100 mg have their previous opioid discontinued and are commenced on methadone 5 mg every 8 hours and 5 mg every 2 hours as needed for additional pain. Patients receiving equivalent daily doses of morphine of greater than 100 mg are switched to methadone over 3 days. This method was used in the prospective multicenter study of 108 patients previously discussed.37

Although the above studies mainly deal with rotation from morphine to methadone identical approaches can be used for rotation of other opioids to methadone by first calculating the morphine equivalent daily dose of the opioid to be changed.37,47

The best rotation method has not been defined. However, careful monitoring of side effects particularly sedation and cognition should take place at least once a day. Monitoring should continue for many days after successful rotation because of the possibility of late toxicity due to methadone accumulation.

<table>
<thead>
<tr>
<th>Morphine</th>
<th>Methadone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Stop 4:1 morphine &lt; 90 mg/d 8:1 morphine 90–300 mg/d 12:1 morphine &gt; 300 mg/d</td>
</tr>
<tr>
<td></td>
<td>Rescue dose: one sixth of daily dose up to 3 allowed per day</td>
</tr>
</tbody>
</table>

*Methadone dose divided and administered every eight hours. Ratio given is for morphine : methadone ratio.

Opioid-induced tolerance and neuropathic pain

Excitatory amino acids such as NMDA have been implicated in the development of neuropathic pain and the development of opioid tolerance.5,6,52 Both neuropathic pain and opioid tolerance are independent poor prognostic indicators in patients with cancer pain.55,56 Methadone has recently been recognized as an NMDA receptor antagonist. Hence, it is possible that methadone may be particularly effective in patients with neuropathic and opioid tolerance. This could lead to the hypothesis that equianalgesic ratios of methadone to other opioids may be different in patients who do and do not have neuropathic pain. However, in a retrospective study of 40 rotations from morphine or hydromorphone to methadone for side effects in 34 patients, 22 rotations took place in patients with neuropathic pain, 18 rotations took place in patients with nonneuropathic pain. There was no difference between the overall ratios in those with and without neuropathic pain.57 Currently, available evidence justifies randomized controlled trials to assess the role of methadone in patients with opioid tolerance.

**ROUTES OF ADMINISTRATION**

Methadone can be given by the oral, rectal, and intravenous routes. Methadone is not suitable for subcutaneous administration because of the frequency of local reactions with redness and pain at the injection site.58

**Rectal administration**

An alternative to oral administration of opioids is needed in patients who experience nausea,
vomiting, dysphagia, bowel obstruction, or mal-absorption. The rectal route has certain advantages over repeated injections or continuous infusions. It avoids the discomfort of repeated injections and may be preferable for those patients who have bleeding disorders or immunologic deficiencies.

Rectal administration of opioids can also prevent the need for analgesic infusion systems such as syringe drivers or spinal catheters. Disadvantages of the rectal route include local discomfort and the limited dose ranges for most commercially available rectal opioid preparations. In addition frequent administration of rectal drugs is inconvenient. Methadone has an advantage in this regard because of its long half-life and the resulting need for less frequent administration.

Ripamonti et al. looked at pharmacokinetics of rectal methadone in six opioid-naïve cancer patients. Ten milligrams of methadone hydrochloride liquid was administered rectally as a microenema. Pain relief was statistically significant as early as 30 minutes and up to 8 hours after administration. Pain relief may have lasted longer than 8 hours as the intensity of symptoms was not assessed between 8 and 24 hours after administration and 5 of the 6 patients did not request additional pain medication until 24 hours after the initial dose of rectal methadone. No significant side effects were reported. Similar to intravenous administration the pharmacokinetics of rectal methadone showed a rapid, extensive distribution phase followed by a slow elimination phase with wide interindividual variation. In a prospective study 16 cancer patients with poor pain control were rotated from high dose hydro-morphone to custom made methadone suppositories every 8 hours. Pain intensity decreased significantly with the change to rectal methadone and the total cost of treatment was significantly lower $86 \pm 128$ Canadian dollars per day for methadone as compared to $1531 \pm 2423$ Canadian dollars per day for previous opioid treatment. The mean daily rectal methadone dose was $469 \pm 267$ mg. All patients experienced mild sedation, two developed proctitis (one of whom required discontinuation of methadone). In six patients plasma levels were determined after at least 2 days of stable methadone dose. Large interindividual variation was seen in the ratio of methadone level to dose, however, stable blood levels were observed in individual patients. The clinical results and stable blood levels suggest that custom-made suppositories are safe and effective even at high doses.

### Parenteral administration

Methadone can be administered intravenously either by intermittent injections or a continuous infusion through an intravenous line or catheter. Unfortunately the racemic preparation available in most countries is generally not well tolerated for subcutaneous infusion.

### FREQUENCY OF ADMINISTRATION

The relatively long half-life of methadone when compared to morphine and many other opioids means that administration every 8 hours

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce by 30%-50%</td>
<td>Reduce by further 30%-50% of original dose of opioid</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

Replace opioid using 10:1 morphine to methadone ratio
Increase dose of methadone if moderate to severe pain. Transient pain managed with rescue doses of short acting opioids
Maintain methadone every 8 hours
Rescue dose: 10% of daily methadone dose
Titrating methadone dose daily

aMEDD less than 100 mg immediate change to methadone 5 mg every 8 hours and every 2 hours as needed.
bMethadone dose is divided and given every 8 hours.
provides adequate analgesia for the majority of patients. A recent pilot study in cancer pain suggests that oral methadone can be safely administered in extended dose intervals of every 12 hours in almost two thirds of patients or even every 24 hours in up to one third of patients.66

**SIDE EFFECTS**

The general adverse effects of opioids such as sedation, nausea, and respiratory depression apply also to methadone. Opioid rotation to methadone is not straightforward because of varying equianalgesic ratios as mentioned above and problems with respiratory depression have been reported.14,67 The long and variable half-life can lead to accumulation and side effects in some patients. In addition, subcutaneous administration of methadone is problematic because of local reactions at the injection site. A recent report outlines three patients who developed ventricular arrhythmias while on high doses of methadone (600 mg/d). In two of the cases patients had some degree of previous cardiac impairment. In all three cases drug interactions involving methadone and the CYP3A4 isoenzyme system were a possible cause.68 Possible drug interactions involving methadone have been discussed in the section on pharmacologic aspects of methadone. Methadone has some potential advantages over other opioids in terms of side effects. With its dual effect on opioid receptors and NMDA receptors, methadone may produce tolerance less frequently than do other opioids. Another possible benefit is suggested by preliminary data which suggests that constipation may develop at much slower pace in patients receiving methadone than in those given other opioid agonists.69,70

**Future research**

A number of issues related to the use of methadone require further clarification through research. With its numerous advantages and the difficulties encountered in rotation to methadone from other opioids it could be an alternative first line agent in the treatment of cancer pain. In addition its extremely low cost (it is 15–20 times cheaper than other opioids4,71 makes it an appealing drug from the perspective of developing countries. At least one international multicenter trial is planned to look at the possibility of using methadone as a first-line agent.

There have not been enough reported cases of opioid rotation from methadone to other opioids to either confirm or reject the assumption that the dose ratio is the same in both directions, this needs to be clarified especially if methadone is to be used as a first line agent in the future. The issue of how best to rotate to methadone in various clinical situations should also be further researched.

Studies are needed to evaluate the role of methadone further in patients with poorly responsive pain syndromes such as neuropathic pain and in those who develop rapid tolerance to other opioids. More evidence is also required in the area of extending dosing intervals to every 12–24 hours.55

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Supporting Family Caregivers at the End of Life

“They Don’t Know What They Don’t Know”

Michael W. Rabow, MD
Joshua M. Hauser, MD
Jocelia Adams, RN

THE PATIENT’S STORY
Mr R was a 70-year-old man, legally blind from retinitis pigmentosa, who was diagnosed as having pancreatic cancer in January 2002. He underwent a Whipple procedure at an urban academic medical center and then received radiation therapy and chemotherapy with fluorouracil and gemcitabine. To alleviate intermittent bowel obstructions, he had a ventilating gastrostomy tube placed for decompression of his abdomen. Over the next 9 months, he was admitted to the hospital several times for infections at the site of his gastrostomy tube, diarrhea, vomiting, and dehydration.

He lived at home with his wife, Mrs R, who was also his partner in the marketing firm he had founded. He had one daughter, Ms L, a psychologist who lived locally, and a son, a history professor, who lived far away but visited every few weeks. Both children were active caregivers over the course of their father’s illness. Despite Mrs R’s own severe rheumatoid arthritis and other health issues, she was determined to care for her husband at home with the assistance of a home care nurse, Ms P, and a housekeeper to aid with daily chores.

As Mr R’s health deteriorated, a close friend of Ms L’s advised her about a local in-hospital palliative care unit. In November 2002, when Mr R’s pain and nausea became so severe that they could not be managed at home, he was admitted to the palliative care unit. At admission, Mr R was alert and oriented but bed bound due to weakness. He and his family hoped his symptoms could be quickly controlled so that he could return home. He received intravenous hydromorphone and dexamethasone for pain and intravenous haloperidol and frequent gastrostomy tube flushings for his nausea. His symptoms initially improved and discussions ensued about his transition home. Although scheduled to go home with hospice care, his condition then declined rapidly to a point where his family did not think they could care for him at home, even with intensive medical care for serious and life-threatening illness, family caregiving is typically at the core of what sustains patients at the end of life. The amorphous relationship between physicians and the families of patients at the end of life presents both challenges and opportunities for which physicians may be unprepared. Families play important roles in the practical and emotional aspects of patient care and in decision making at the end of life. At the same time, family members may carry significant burdens as a result of their work. Through the perspectives of the wife, daughter, and home care nurse of a patient who died from pancreatic cancer, we illustrate the range of family caregiver experiences and suggest potentially helpful physician interventions. We describe 5 burdens of family caregiving (time and logistics, physical tasks, financial costs, emotional burdens and mental health risks, and physical health risks) and review the responsibilities of physicians to family caregivers. Based on available evidence, we identify 5 areas of opportunity for physicians to be of service to family members caring for patients at the end of life, including promoting excellent communication with family, encouraging appropriate advance care planning and decision making, supporting home care, demonstrating empathy for family emotions and relationships, and attending to family grief and bereavement. In caring well for family caregivers at the end of life, physicians may not only improve the experiences of patients and family but also find greater sustenance and meaning in their own work.

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creased assistance. They struggled to find a balance between the level of nursing care he could receive in the palliative care unit and his initial desire to be at home. After 7 days in the palliative care unit, he died, with his family at his bedside.

**PERSPECTIVES**

In December 2002, shortly after Mr R’s death, a Perspectives editor separately interviewed Mr R’s wife (Mrs R), daughter (Ms L), and home care nurse (Ms P).

Mrs R: I knew I would take care of him myself because we had always done things together. We worked together for 30 years. We played together, we did everything together since I was 18 years old. Because he had been legally blind since the early 1970s, I had always been by his side. There was never a question that I wouldn’t continue to be [with him] during this period.

Ms L: I think that physicians need to be as aware as they can as to how alone and ignorant the family and the patient feel. For example, Dad’s physician was sort of ominously saying with raised eyebrows, “The bilirubin is going up, the bilirubin is going up.” But we had no context for that. We knew it was bad, but we didn’t know if that meant that in 6 months he was going to be in trouble, or in a week he might be in trouble.

Ms P: When they go into the hospital, they become patients, but they’re really people. In the hospital you can forget: they’re all in the same kind of rooms; they’re all in the same kind of gowns; they all have tubes and things hooked up to them. But at home, they’re people. They’re in their house, they’re surrounded by their photographs, the things they’ve worked for all their life. They’re people first, and then they’re patients.

As with Mr R, the story of a dying patient is often also a story about loving family members. Increasingly, death in the United States is preceded by family caregiving—informal support and lay medical care provided by family members, partners, and friends. About one quarter of adults in the United States report providing informal caregiving, including helping with transportation, shopping, homemaking, emotional support, nutritional care, nursing care, personal care, and financial management. Family members, almost always women, provide nearly all of the care patients receive at home. The prevalence of chronic family caregiving is likely to increase with the aging US population and the increasing number of diseases managed over many years in the outpatient setting.

In light of the pervasiveness and importance of family caregiving, the physician’s relationship with family caregivers is an important facet of the patient-physician relationship. Mr R’s illness richly illustrates both the joys and the challenges of family caregiving. We describe the burdens of family caregiving, outline basic physician responsibilities in the support of family caregivers, and identify 5 areas in which physicians can be of service to family members caring for patients at the end of life.

**BURDENS OF FAMILY CAREGIVING**

**Time and Logistics**

Mrs R: To me, it just never stopped. It wasn’t the care, it was the whole commitment. It never went away.

Caregiving can take as little as a few hours per week, but, commonly, it is equivalent to a full-time job, with 20% of caregivers providing full-time or constant care. Mrs R reported spending about 10 hours a day tending to her husband, but the sense of responsibility was never-ending. The length of a patient’s illness before death and the trajectory of functional decline (and concomitant caregiving need) are difficult to predict, particularly in noncancer conditions. The administrative and logistical needs can be enormous: families typically must coordinate numerous medications, treatments, clinical and social services, as well as the needs of multiple family members. At times, families may feel as if they are “reinventing the wheel,” with each individual family trying to identify local services even though many in their community have struggled with the very same issues.

**Physical Tasks**

Laborious caregiving is often performed by people who are themselves elderly, ill, and disabled. In this case, Mrs R has severe rheumatoid arthritis. Caregivers usually have no training in moving, lifting, or turning seriously ill adults, yet they routinely perform these strenuous physical activities. As a result, family caregivers are at significant risk of physical injury. Fortunately, Mrs R realized that her husband “couldn’t move and I wasn’t strong enough to help him” and asked her daughter and the nurse for help.

**Financial Costs**

Caregiving creates an uncompensated financial burden for family members, both in outright expenses and in lost income and benefits. In the United States, yearly family caregiving costs range from $3 billion to $6 billion for diabetes, more than $6 billion for stroke, and $65 billion for patients with Alzheimer disease. The economic disruption of family caregiving can be profound: 20% of family caregivers must quit work or make major life changes and 31% lose most or all of their family savings as a result of caregiving. African American and Hispanic caregivers are more likely to experience economic disruption compared with whites. The economic burden is similar within both managed care and fee-for-service health care systems. Government support for family caregiving is limited: the Family Medical Leave Act of 1993 guarantees only unpaid leave to care for a seriously ill spouse, son, daughter, or parent; only a few states allow those eligible for Medicaid’s personal care benefit to receive a cash allowance to purchase their own care and hire friends or family to provide it.

Patients and family members may feel differently about the intense costs of caregiving. Patients often fear being a burden to their family, despite the family’s willingness to provide care. Family economic hardship is associated with
a preference for “comfort only” care over life-extending care.22 Substantial caregiving needs have even been associated with an increased likelihood of patients considering euthanasia or physician-assisted suicide.23,24

Caregiver Emotional Burdens and Mental Health Risks
Caregivers often bear an incalculable emotional burden for their work. Although many enjoy a profound sense of privilege and derive deep satisfaction in this role, sadness, guilt, anger, resentment, and a sense of inadequacy are also common and understandable reactions. Exhaustion, financial strain, disrupted usual activities, and continuous caregiving contribute to significant mental health morbidity, including anxiety and depression.23 Although selection bias may lead to overestimates of the prevalence of caregiver depression, a number of studies document that as many as one half of all caregivers experience clinical depression, with 61% of intense family caregivers (those providing at least 21 hours of care per week) experiencing depression.26,27 Caregiver wives appear to be more likely than caregiver husbands to have depression.28

Health Risks for Caregivers
Mrs R: My health isn’t red hot, but I didn’t worry about it at all. Family caregivers tend to put the needs of the ill person ahead of their own, minimizing the severity of their own problems and foregoing or delaying their own health care.20 Caregiving is associated with poor sleep30 and even with increased cancer risk.31 Caregivers are at particular risk for worsened health if they have poor baseline health or limited education and if caregiving means significant loss of social and leisure time.3,12 Notably, caregiving is also associated with increased caregiver mortality.8 In a 4-year study of 392 caregivers and 427 noncaregivers older than 66 years, caregivers who experienced mental or emotional strain had a mortality risk 63% higher than noncaregiving controls.31

THE PHYSICIAN’S RESPONSIBILITIES TO FAMILY
Given the significant risks of family caregiving and the goal of comprehensive patient care, physicians clearly have a role to play with the families of patients at the end of life. In clinical practice, however, physicians may be uncertain about their relationship and responsibility to the family. Sensitively negotiating family issues can be difficult for physicians, but it is intensified when families challenge the physician’s authority, are plagued by their own disagreements, raise the specter of litigation, or are culturally or religiously diverse from the physician.34,35 Physicians must also be alert to the fact that their own patients, even those with advanced illness, may actually be serving as the caregiver for even more seriously ill relatives.36,37

A physician’s legal obligation is to the patient; legal obligations to the family are minimal. Physicians are required to address the wishes of appropriate patient surrogate decision makers and to report patients they believe are being abused or neglected. However, the physician’s role should extend beyond what is required by law to provide the best possible care for the patient. The Council on Scientific Affairs of the American Medical Association argues that family caregivers and physicians are interdependent and should create a care partnership.38 The patient’s primary care physician has a key linkage role, assessing the caregiver as well as the patient in a comprehensive home-based approach that includes training caregivers, validating the caregiver’s role, and case management.38 Physicians must recognize that family caregivers provide an instrumental component of patient care and support them sufficiently. Physicians can assess family caregivers with a simple screening question such as, “How is the caregiving going for you?” or “How is the family doing?” Vulnerable caregivers should be evaluated for their ability to provide care without putting their own health at risk.39,40 and physicians should refer overwhelmed caregivers to support services and to the caregiver’s own physician. Even well-meaning hospitalists and palliative care specialists can contribute to discontinuity of medical care at the end of life, and all clinicians must pay particular attention to ensuring clear communication with each other and with family during handoffs between physicians and across care settings.40

PHYSICIAN OPPORTUNITIES TO SERVE FAMILIES
Beyond the basic responsibilities, working both individually and as part of an interdisciplinary team, there is great potential for physicians caring for patients at the end of life to provide important and perhaps even life-sustaining support to family caregivers. Empirical research and the clinical experiences of experts suggest that there are at least 5 areas of service that physicians may offer to families.

Excellent Communication With Family
Mrs R: [We moved him] almost more to avoid having to worry about not having a doctor who we could talk to than because he was in such bad shape.

Ms L: It’s always hard to present a family with all of the gory details. [Although my mother did not], I personally would have wanted a clearer sense of perspective about the actual prognosis.

Families want to know that their loved one’s physician is comfortable talking about death and dying.41 The needs of family members for timely and clear information are significant but are frequently underappreciated.1,21 Communication with families is complex due to the multiplicity of perspectives held by family members, as Ms L’s observation makes clear. Physicians should provide proactive guidance, particularly when the patient is no longer able to make decisions about his or her own health care, including sharing data on the efficacy of feeding tubes and cardiopulmonary resuscitation in relevant situations, describing the possibility and process of withdrawal of interventions, and explaining the role and benefits of hospice.3,33,44 Recently, using a large population-based sample of elderly persons,
hospice was associated with a significant reduction in the risk of death of the hospice patient’s bereaved spouse, even when hospice was used only for a median of 3 to 4 weeks.43

Careful listening is paramount for physicians to understand the diverse perceptions family members may have regarding decisions about life-sustaining treatment, dying at home, and talking about the meaning of death.22 Physicians can elicit a family’s views with open-ended queries,46 providing answers to a family’s cognitive questions, but offering empathic responses to their primarily affective expressions.57,58 Ultimately, physicians have a role in helping families come to understand what their loved one’s medical care signifies—including the particular family’s definitions of doing everything, giving up, or letting go.99

Informal family communication may occur spontaneously at the bedside, in clinic, in the hallways of hospitals or nursing homes, or by telephone. Formal communication typically occurs in a family meeting or conference.50 With appropriate documentation in the medical record, physicians can bill for this service, particularly if it takes place in the presence of the patient. Time spent can be used to determine the evaluation and management coding level if more than 50% of the encounter is spent counseling and relaying information. Family meetings take on increased importance at the end of life because many patients have lost their decision-making capacity.49,51 Recommendations for conducting productive family meetings are presented in the BOX. There are limited data about the efficacy of family meetings but one study of intensive family communication showed a 1-day reduction in median length of stay in the intensive care unit among patients who died.52

The Health Insurance Portability and Accountability Act (HIPAA) has generated significant concern among physicians with regard to privacy regulations, but the impact of HIPAA on physician-family communication is not yet known. As before, some have urged physicians to try to obtain patients’ consent when talking with family members,53 but this consent may often be presumed. The Office of Civil Rights Privacy Rule, as well as interpretation from the Web site of the Department of Health and Human Services, suggest that unless individuals have indicated that they do not want information shared with family members, HIPAA regulations allow it.54,55 However, to provide good patient-centered care, for patients who are able, physicians should explore with them their willingness to have their care discussed with family members.

**Advance Care Planning and Clear Decision Making**

Mrs R: The first decision was to absolutely follow his lead. I didn’t know until we got to the hospital and he said, “Oh, I feel better here.” He felt safer there. He had always said he wanted to die in his own bed. But that was not in terms of this illness.

Advance care planning is an essential component of end-of-life care. It includes discussing preferences, values, and contingencies for end-of-life care, as well as preparing legal advance directives, such as naming a health care proxy or executing a living will. Exploring patient wishes regarding after-death issues may be useful as well, including plans for autopsy, organ donation, funerals, and disposition of possessions. Although clear proof of the beneficial impact of advance directives themselves on costs, decision making, and clinical interventions has been elusive,50-58 there is growing consensus that engaging in the process is important for patients, families, and clinicians.59-60 Advance care planning is not a static document or a set of instructions, but rather is an ongoing process, and an opportunity to engage with patients and families. Even when advance care planning has begun early in a patient’s illness, as it should, patient and family preferences may change, and it is critical for physicians to follow up and modify plans as the illness progresses.60

Patients develop treatment preferences, consider truth-telling, and undertake decision making within a cultural and ethnic heritage. In a study of 200 elderly people from 4 ethnic groups, 57% of Korean Americans and 45% of Mexican Americans believed that the family should be the primary decision maker, compared with 24% of African Americans and 20% of European Americans.61 But even with the goal of honoring cultural background, patients and families must not be stereotyped because there is wide variation of beliefs within cultures, and personal characteristics may be as important as cultural influences. For physicians, cultural sensitivity is likely to be as important as cultural competence.62

For patients lacking decision-making capacity who have not previously identified a surrogate decision maker, it is generally appropriate to turn to the family.63 Notably, though, predicting patient preferences is difficult for both family and clinicians. In one study, given only demographic and clinical information, clinicians were only slightly better than chance in predicting a patient’s preferred code status.64 In another study of actual patient-surrogate pairs using hypothetical scenarios, surrogates’ predictions were accurate only 66% of the time.65 Surrogate-patient agreement is often limited, even in cases in which patients and surrogates have discussed preferences beforehand.56,67

Even in the presence of an advance directive, family members may have conflicts of interest or disagree with one another. Strategies for achieving consensus among disagreeing family members include focusing on the known medical facts of the patient’s conditions and continually re-focusing on what is known about the patient’s values and preferences.63 Directing the family through the precept of substituted judgment, physicians can encourage each family member (both appointed surrogates and others) to imagine and discuss what the patient would want done for himself or herself—which is not always equivalent to what the family member would want done for the patient.99

Distant family and the unpredictability of physician and family schedules can combine to make decision making
Box. Recommendations for Conducting a Family Meeting When the Patient Is Unable to Participate

Prepare for the Meeting
Review medical issues and history.
Coordinate health care team.
Discuss goals of meeting with team.
Identify a meeting leader among the health care team.
Discuss which family members will be present.
Arrange a private, quiet location with seating for all.
Try to minimize distractions: set aside adequate time and seating, turn off pager if possible.

Open the Meeting
Introduce all in attendance.
Review the medical situation.
Establish the overall goal of the meeting, by saying something like: “Today I’d like to make sure everyone understands how [the patient] is doing and answer all the questions that you have,” or “We wanted to meet today to discuss how [the patient] will be cared for at home.”
Be prepared for the goals of the meeting to change based on family’s desires.

Elicit Family Understanding
Ask family members questions, such as “What have you been told about [the patient’s] condition?”
After hearing from the family, a helpful follow-up question is “Is there anything that isn’t clear that we can help to explain?”

Elicit Patient and Family Values and Goals
Elicit goals of all those present, especially if multiple perspectives are held.
Begin with an open-ended question, such as, “Given what’s gone on, what are your hopes for [the patient]?” This may be followed by more specific suggestions for the family: “Sometimes getting home is an important goal for someone. Sometimes seeing a certain family member or friend is an important goal: are there things like this that you imagine are important for [the patient]? I’d like for you to please help me to understand what I need to know about [the patient’s] beliefs and practices to take the best care of [the patient]? “
Maintain focus on the patient’s perspective. Often this can help to relieve guilt that family members may feel over making decisions. Such questions could include “What do you imagine [the patient] would have done or wanted in this situation?” or “Our goal is not so much to think about what you would want or not want but to use your knowledge of [the patient] to understand what he or she would want in this situation.”

Deal With Decisions That Need to Be Made
Achieve a common understanding of the issues.
Find out if the patient had made his or her wishes about the decision known by asking, “Had [the patient] ever discussed what he would want or not want in this kind of a situation?”
Reassure family members that they are making a decision about what is in the best interests of the patient, not necessarily what is in their own best interests.
Begin with open-ended assessments and then turn to specific interventions if necessary.
Offer clear recommendations based on patient and family goals, by suggesting, for example, “Given our understanding of the medical situation and what you’ve told us about [the patient’s] goals, I would recommend not pursuing dialysis.”
Seek consensus whenever possible, agreeing on the decision or on the need for more information.
Use summary statements, such as “It sounds like we are coming to an understanding that [the patient] would not want to continue on the ventilator. Is that how everyone understands his or her wishes?”
Consider the possibilities of seeing the decision as a “therapeutic trial” or as a health care team recommendation that requires only family assent.
Check for understanding of the decisions made, by saying something like, “I want to make sure everyone understands that we’ve decided to . . . .”

Close the Meeting
Offer a brief summary of what was discussed.
Ask for any final questions.
Offer a statement of appreciation and respect for the family: “I appreciate how difficult this must be, but I respect everyone for trying so hard to do right by [the patient],” or “I want to thank everyone for being here and for helping to make these difficult decisions.”
Make a clear follow-up plan, including plans for the next family meeting and how to contact the health care team.

Follow up on the Meeting
Document the meeting in the chart.
Follow up with any information or reassessment agreed upon during the meeting, by saying, “When we last met, you were going to talk with your brother about our meeting. How did that go?”

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even more difficult. In such cases, telephone communication and conference calls may be pursued. As with in-person meetings, having a clear goal for the call and a discussion leader are key. Although e-mail and Web-based systems may be easy methods for families to circulate updates, the inability to foster real-time, synchronous interaction generally limits their utility for family decision making. Families should be mindful that these modes of communication carry the potential for breaches in patient-physician confidentiality.

Support for Home Care

MRS R: The home caregiver doesn’t know what they don’t know. I didn’t know questions to ask doctors. . . . I never talked to the doctor without my husband there. So, it was not always easy to ask a blunt question.

MS L: It was never presented to us what it would entail, in terms of taking care of him.

MS P: It’s incredible what people at home can do and what they want to do just to keep people at home . . .

Although family caregivers are important to the care of patients in the hospital and nursing home, the family caregiver role is a central element of home-based patient care. At home, the success of the care plan may depend on the physician’s relationship with the patient’s caregiving network. Family caregivers are medical team representatives in the home, providing medical services and assessments, including complex decisions about when to call the physician or bring the patient to the emergency department, with little preparation, training, or compensation. A 1998 national survey of 1002 informal caregivers found that one fifth of all caregivers help with dressing changes and nearly 40% administer medications. Among caregivers administering medications, half are responsible for managing 5 or more, and 1 in 6 caregivers must administer medications non- orally, including via injection. Mr R was taking 10 medications, all of them managed by Mrs R. A number of medications, such as lorazepam for anxiety and haloperidol for insomnia, were given as needed, creating an additional responsibility for Mrs R to make dosage and administration decisions. This became an overwhelming responsibility for her as Mr R’s health declined.

Physicians’ medication orders should provide the patient and caregiver with specific guidelines for their use and administration at home, especially for medications given by family caregivers on an as-needed basis. Evidence suggests that medications for breakthrough pain are underused in home care and physicians, along with other members of the home care team, can help clarify the use of such treatments. Additionally, family caregivers require clear instructions about when and whom to call for help. Family caregivers require 24-hour-a-day access to professional advice. E-mail, online, handheld, and wireless communication technologies can supplement routine telephone access. Even for families who wish to continue to care for their loved one at home, caregivers require direction about which developments (such as sudden, massive, uncontrolled bleeding) might best be addressed by calling an emergency contact number (eg, 911) directly, and seeking care emergently in the emergency department or inpatient palliative care unit. Caregivers also should be instructed as to how to convey their loved one’s wishes about advance directives when calling for emergency help.

Physicians are part of the interdisciplinary home care team that provides family caregivers with orientation, information, training, and support. Especially for patients not enrolled in hospice, physicians play a role in initiating and orchestrating, along with home health social workers and agencies, the multidisciplinary referrals and training family caregivers may require. Beyond their role as organizers and supervisors, physicians can make home visits and be reimbursed for this service. Physician home visits have been shown to improve patient quality of life and delay nursing home admissions. Additionally, the multiple roles physicians play in supporting home care create important opportunities for medical student and house staff education about palliative care and working within a clinical team.

Physicians can help prepare family caregivers by orienting them to the expected natural history of the patient’s condition, the care needs that might arise, and the options for the caregiver’s response. Physicians should also educate families about their options when dying at home is not desired and describe the range of services provided by an institutional hospice or a hospital-based palliative care unit. Unfortunately, when Mr R’s condition deteriorated to the point that he could no longer be cared for safely at home, the referral to the palliative care unit came from a concerned family member, not from Mr R’s physician, and the family members initiated admission on their own.

Empathy for Family Emotions and Relationships

MS L: [The burdens] just brought us closer. I felt very privileged to be able to be helpful to him and to be helpful to my mother. And it occasioned a lot of the most precious moments of connection that I’ll always remember.

MRS R: Giving care at home made me feel useful. It only became scary for me at night when there were just 2 of us here, and I realized that if anything untoward occurred, I wouldn’t be able to do anything for him.

MS P: The patient needs can be taken care of. There’s more anguish for the family. I think it’s harder on the family than it is on the patient.

Family caregiving can both strengthen and strain personal well-being and family relationships. As in this case, adult children frequently assume responsibilities for ill parents and may have to adjust the expectations within their own nuclear families. Amid the challenge of integrating illness into family dynamics, family members may find themselves reacquainted with long-estranged relatives during the period of end-of-life care and bereavement.
Addressing family caregiver emotions and recognizing family dynamics may be a necessary prerequisite to optimum care of the patient. The personal characteristics and emotional strain of family caregivers may create barriers to placement of patients in appropriate care settings, leading family inappropriately to insist on or reject care in the intensive care unit, long-term care setting, home, or institutional hospice. Caregiver attitudes and burden directly impact the rate of patient hospitalization and institutionalization. In a study of 40 caregivers of patients with mild to moderate dementia, caregiver depression negatively affected their assessment of the patient’s quality of life, which may bear on the caregiver’s ability to serve as an appropriate surrogate decision maker.

Although family caregiving holds the promise of promoting patient autonomy and dignity, conditions such as diarrhea, hair loss, open wounds, and incontinence can sometimes lead to loss of privacy, embarrassment, or resentment for the patient. Preparing the family and patient for these contingencies, emotional troughs, and the inevitability of loss is critical. Physicians can be helpful in recognizing and validating common feelings and reassuring family members about the quality of their care. Empathic responses, such as saying, “This must be a very difficult time for you,” communicate respect and support during an emotionally stressful, even traumatic, time. In a study of 988 terminally ill patients and 893 caregivers, caregivers of patients whose physician listened to the caregivers’ needs and opinions had significantly less depression (27.6%) than caregivers of similar patients with nonempathic physicians (42.0%). Adult day care, respite care, home care, social work services, and caregiver education and psychological support demonstrably improve caregiver satisfaction, quality of life, and burden. Helping family caregivers identify support resources may be especially important for families of patients ineligible for the comprehensive services provided by hospice.

Attention to Grief and Bereavement

Grief worsens both physical and mental health, and it has been associated with increased depression, insomnia, substance abuse, suicidality, and mortality. Research suggests that the caregiving experiences of family members influence their adjustment to the patient’s eventual death. Caregiving support may be even more important than grief support: a study of 73 adult family caregivers showed that caregiving support prior to the patient’s death accounted for 29% of the variance in personal bereavement difficulties while bereavement support after the death accounted for only 2%. Bereaved family members highly value a physician’s empathy and support. Caregivers may help sustain physicians. A physician’s empathy and compassion may be more readily elicited in the company of those who love the patient and who have known the patient in both health and illness.

Nationally, education and compensation reform should enhance physician opportunities to be of service to family caregivers. Legislation must improve and integrate family caregiver policy, so families do not have to needlessly duplicate effort. The experience of caring for loved ones as they approach death can be one of deep fulfillment or significant trauma. In recognizing the burdens of family caregiving, communicating well, assisting with decision making, supporting home care, helping with caregiver emotions, and acknowledging bereavement, physicians have much to offer and much to gain. The appreciation and well-being of family caregivers may help sustain physicians. A physician’s empathy and compassion may be more readily elicited in the company of those who love the patient and who have known the patient in both health and illness.

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ADDITIONAL CAREGIVER RESOURCES

American Association of Retired Persons (AARP) Caregiving Resources
http://www.aarp.org/inthemiddle

Alzheimer's Disease Education and Referral Center
http://www.alzheimers.org/careguide.htm

The Alzheimer's Store
http://www.alzstore.com
“A Guide to Alzheimer's-Proofing Your Home”

The American Gerontological Society Online Caregiver Guide
http://www.healthinaging.org/public_education/eldercare/

Caregiver Resource Directory
http://www.stoppain.org/caregivers/resource_form.html
Online service of Beth Israel Hospital, New York

Caregivers Marketplace
http://www.caregiversmarketplace.com

Caregivers USA
http://www.caregivers-usa.org

Caregivers in Action
http://www.lastacts.org
Family Caregiver Chat Hour, an online chat with others who serve as caregivers for their families. Tuesdays, 9:30 PM (Eastern time).

Center for Caregiver
http://www.caregiving101.org
Offers caregivers basic, practical skills and strategies they need to care for their loved ones

Last Acts Family Committee
http://www.lastacts.org
Consumer and family resources for end-of-life care

Local Red Cross Chapter Caregiving Classes
http://www.redcross.org

National Alliance for Caregiving
http://www.caregiving.org

National Council on Aging
http://www.ncoa.org
http://benefitscheckup04.governmentguide.com

National Family Caregiver Assn
http://www.nfcacares.org

Today's Caregiver Magazine
http://www.caregiver.com

US Administration on Aging, National Family Caregiver Support Program

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Original Article

A Randomized, Double-Blind, Crossover Trial of the Effect of Oxygen on Dyspnea in Patients with Advanced Cancer

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Abstract

Dyspnea is a common symptom in palliative care. Despite this, there is uncertainty regarding the role of oxygen to treat the symptom in patients with advanced illness. This randomized, double-blind, crossover trial examined the effect of oxygen versus air on the relief of dyspnea in patients with advanced cancer. Following the blinded administration of air and oxygen via nasal prongs, 51 patients rated dyspnea and indicated preferences for the blinded treatments. On average, patients improved symptomatically with both air and oxygen, and there were no significant differences between the treatments. The subgroup of 17 hypoxic patients overall did not demonstrate a significant difference between air and oxygen, despite having improved oxygen saturations when administered oxygen. Hypoxia was corrected in 13 of 17 patients using the treatment dose of 4 L/min of oxygen. The experience of dyspnea is a complex, multifactorial phenomenon, with oxygen tension not correlating with the subjective experience. The administration of either air or oxygen via nasal prongs on average confers improvement of the symptom. J Pain Symptom Manage 2006;32:541–550.

Key Words

Dyspnea, cancer, oxygen, palliative care

Introduction

Dyspnea is a common symptom in patients with advanced cancer, rated as a moderate or severe problem in 46% of those admitted to a palliative care program, and affecting 70% of hospice inpatients.1,2 At the Peter MacCallum Cancer Center, the incidence of dyspnea among all patients with a cancer diagnosis was 33%.3 The presence of dyspnea indicates a poor prognosis for patients with pancreatic...
Dyspnea is one of the most distressing symptoms experienced by patients. It is a combination of a “sensation” (neural activation resulting from stimulation of a receptor) and a “perception” (reaction of the individual to that sensation). A consensus statement of the American Thoracic Society has defined dyspnea as “a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioral responses.”

The development of dyspnea is a complex phenomenon and is related to activation of sensory systems involved with respiration. The main mechanisms involve feedback from chemoreceptors, mechanoreceptors, and vagal afferents in the lung and chest wall, which project to higher brain centers to provide a direct review of the chemical state of the body and the mechanical state of the lungs. Efferent copies of brainstem respiratory motor output also appear to be transmitted to higher brain centers and result in a conscious awareness of the motor command. Behavioral style and emotional state influence the perception of the stimulus. These factors all play a role in shaping the perception of dyspnea, and, therefore, this symptom, like pain, should be understood to be a multidimensional experience.

The management of dyspnea involves attention to the etiology of the symptom and where possible, correction of causative factors. Management of the symptom itself may include behavioral approaches, pharmacological agents, and the use of airflow and oxygen. A number of small studies have demonstrated the benefit of behavioral techniques, while the body of literature supporting pharmacological management, principally opioids, is well established.

Oxygen plays an important role in the management of the hypoxic patient with chronic obstructive pulmonary disease (COPD), being associated with improvements in survival, quality of life, and neuropsychologic function. There have been few studies addressing the role of oxygen in hypoxic and normoxic dyspneic patients with advanced cancer. Bruera et al. conducted a randomized, double-blind, crossover trial in 14 patients with advanced cancer and hypoxemia, defined as oxygen saturation of less than 90% on pulse oximetry. These patients received oxygen or air at 5 L/min by mask and then were twice crossed over to the other treatment. The average dyspnea score, measured by visual analogue scale (VAS), was significantly less when patients received oxygen ($P < 0.001$), and 12 of 14 patients consistently preferred oxygen ($P < 0.001$). The blinded investigator also chose oxygen for 12 of 14 patients. According to a global well-being scale, patients felt little or no benefit with air but moderate to much benefit when receiving oxygen. The authors concluded that hypoxic patients with cancer receive symptomatic benefit from oxygen therapy. In 1994, Booth et al. did not obtain these findings when they conducted a single-blind, crossover trial of oxygen and air administered in random order to 38 hospice patients who reported dyspnea at rest. These patients completed a VAS for dyspnea, oxygen saturation measures, and limited lung function tests before and after 15 minutes on each gas. On average, dyspnea improved significantly with both treatments, with the air group having a reduction of dyspnea from a mean of 59 to 48 mm on a 100 mm scale ($P < 0.001$) and the oxygen group having a reduction of dyspnea from a mean of 59 to 45 mm ($P < 0.001$). While the average response to oxygen was quantitatively better than the response to air, there was no statistically significant difference between the treatments. It is noteworthy that the analysis performed in this study did not appear to make use of statistical methods appropriate for crossover trials. The discrepancy between these two studies may, therefore, be explained by the different patient groups (hypoxic versus mixed hypoxic and normoxic patients on no routine inhaled treatment) or the analysis methodology, or may be a spurious result due to the small numbers in each study.

We proposed, therefore, to clarify the role of oxygen when used to relieve dyspnea in patients with advanced cancer, focusing on the clinically relevant group of patients who...
present with the symptom and, therefore, including both hypoxic and normoxic patients.

Methods

The primary aim of this randomized, double-blind, crossover study was to determine blinded patient preference for oxygen or air, following 15-minute administration of both. Secondary aims were to compare the response to oxygen and air in hypoxic and normoxic patient groups, and to identify factors other than hypoxia that may affect the experience of dyspnea and the response to oxygen.

The study took place in two centers in Australia (The Alfred Hospital and the Peter MacCallum Cancer Center) and recruited both inpatients and outpatients. Patients were eligible if they had a diagnosis of cancer, were dyspneic and had a main etiology for dyspnea that was clinically deemed to be related to cancer, had a dyspnea intensity score of at least 30 mm on a 0–100 mm VAS, were on stable medication doses (including opioids), had normal cognitive status defined according to the Blessed Orientation Memory & Concentration mental status examination, were over 18 years of age, had no contraindications to oxygen, and signed a written informed consent. Patients were ineligible if they had evidence of acute respiratory distress, were thought to be unable to complete the trial, or were oxygen dependent.

Eligible patients completed a VAS for dyspnea and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 dyspnea measurement, providing verbal ratings of intensity, and underwent oxygen saturation pulse oximetry. The investigator collected demographic data and determined the most likely pathological causes of the symptom, to a maximum of three causes. Patients were then randomized to receive either air or oxygen at 4 L/min via nasal prongs for 15 minutes, following which dyspnea intensity ratings and oximetry were repeated. Then, following a 30-minute interval without gas, repeat measurements were taken with crossover to the other gas for a further 15 minutes. Measurements of symptom intensity and oximetry were then repeated, and the blinded patient and investigator nominated the preferred gas. Patients were asked to select qualitative descriptors of their experience of dyspnea according to the Dyspnea Assessment Questionnaire. The results of these qualitative data will be presented elsewhere.

Four-liters-per-minute of gas administration is generally the maximum amount that is tolerated for longer-term use when given via nasal prongs and is also the maximum amount that can be achieved via standard home oxygen therapy delivery systems. Thus, 4 L/min was chosen for practical reasons and because this closely mimics the clinical situation for patients at home. Since the trial was attempting to answer the clinical problem of improvement of dyspnea, gas flows required to correct hypoxia were not conducted for patients prior to trial enrollment.

Institutional ethics committee approval was granted at both centers. The trial was registered with the Clinical Trials Registry. All data were collected on study-specific case record forms and entered into a Microsoft Access database. Data consistency checks were made at the time of data entry and prior to statistical analysis.

Statistical Methods

A sample size of 50 was chosen based upon the primary objective of the study, which was to determine patient preference for oxygen or air. Given a two-sided significance level of 0.05, the study had 90% power to detect a significant difference between the two gases if 60% of patients preferred oxygen, 20% preferred air, and 20% had no preference.

Descriptive statistics of baseline patient characteristics were computed for all patients and by randomized gas sequence. For all patients and the subgroup of hypoxic patients, the change in VAS score and oxygen saturation from pre- to postadministration of gas was analyzed using analysis of variance for a 2 × 2 crossover design. In a 2 × 2 crossover trial, it is necessary to consider the effects of carryover and period. Carryover refers to the possibility that the effect of the treatment given in the first period (e.g., oxygen) may be carried over to the second period when the next treatment is given (e.g., air), and so might influence response to the second treatment. The period effect refers to the possibility that the response in the first treatment period may...
tend to be different from the response in the second period irrespective of the treatment given. In the analysis of variance, an estimate and test for the carry-over effect, the period effect, and the treatment effect were undertaken. Treatment comparisons were then made allowing for the effects of carry-over and period. Results are presented according to the gas received first in accordance with appropriate statistical analysis for a 2 × 2 crossover design. Pearson’s Chi-squared test was used to assess if the change in EORTC verbal rating was dependent on the gas used, both before the first and the second gas. Patient preference for oxygen or air was compared using Prescott’s test. Cohen’s kappa statistic was used to measure agreement between patient and investigator assessment of gas preference. The Spearman rank correlation coefficient was computed between VAS score and oxygen saturation after administration of the first and second gas.

Two-tailed P-values were reported for all statistical tests. Hypoxic patients were defined as those with oxygen saturation <90% prior to commencing treatment. Statistical analysis was performed using Genstat for Windows 7th edition (VSN International, UK, 2003) and StatXact 6.0 (Cytel Software Corporation, USA, 2003) software.

Results

A total of 51 eligible patients were accrued to the study between August 13, 2001 and January 12, 2005, 17 from The Alfred Hospital and 34 from the Peter MacCallum Cancer Center. Twenty-seven patients (53%) were randomized to the “Air first” arm and 24 (47%) to the “Oxygen first” arm. The patient baseline characteristics are outlined in Table 1. All patients had been exposed to intermittent oxygen therapy prior to trial enrollment.

For 47 patients (92%), cancer was directly responsible for dyspnea. Of these, cancer was deemed to be solely responsible for the symptom in 29. The remaining patients had other causes of dyspnea related either to complications of cancer, such as pneumonia (five patients), or to the treatment of cancer, such as radiation pneumonitis (two patients). Fifteen patients (29%) had unrelated causes contributing to dyspnea, including 11 with COPD. In total, 32 patients had a single cause of dyspnea, 17 had two causes, and 2 had three or more causes.

Response to Gas—VAS

Descriptive statistics are presented in Table 2 of VAS scores prior to and after 15 minutes on each gas. For the “Air first” arm, the median change was an improvement in VAS score of 3 mm (range, −19 to 70 mm) after air and 10 mm (range, −19 to 63 mm) after oxygen. For the “Oxygen first” arm, the median change was an improvement of 11.5 mm (range, −20 to 45 mm) after air and 7 mm (range, −33 to 71 mm) after oxygen. After allowing for carry-over and period effects, there was no significant difference between the two gas types in the mean change in VAS score (P = 0.622, air = 8.7 mm, oxygen = 10.5 mm).

Mean VAS scores before and after administration of the first and second gas are shown in Fig. 1.

Response to Gas—EORTC Verbal Rating

A summary of EORTC verbal ratings before and after administration of each gas is presented in Tables 2 and 3. According to the EORTC descriptors, patients were assessed as having “improved,” “stayed the same,” or “worsened” in their shortness of breath from pre- to post-intake of gas. After the first gas, 12 patients (44%) who received air reported an improvement in their shortness of breath, compared to 10 (42%) of those who received oxygen (P = 0.888). After the second gas, 9 patients (38%) improved with air and 7 patients (26%) with oxygen (P = 0.767) (Fig. 2).

Response to Gas—Oxygen Saturation

Oxygen saturation levels pre- and post-administration of gas are shown in Table 2. The change in oxygen saturation levels from pre- to post-intake of gas was computed for all patients after they received each of the two gas types. There is a significant difference between the two gas types in the mean increase in oxygen saturation (P < 0.001, air = 0.94%, oxygen = 5.43%). There was no evidence of a significant correlation between VAS score and oxygen saturation. The Spearman rank correlation coefficient was 0.019 (P = 0.895)
after the first gas and 0.056 ($P = 0.695$) after the second gas.

Gas Preference

Twenty-one patients (41%) expressed a preference for oxygen, 15 (29%) expressed a preference for air, and 15 (29%) expressed no preference. There was no evidence of a significant difference in patient preference for air or oxygen ($P = 0.357$). The investigator assessment of patient preference was 20% for air, 35% for oxygen, 43% no preference, and one patient was not assessed. Using Cohen’s kappa statistic, the agreement between patient and investigator in their assessment of gas preference was significant ($P < 0.001$, kappa = 0.501, 95% confidence interval: 0.305–0.697).

Hypoxic Patients

In the subgroup of 17 hypoxic patients, mean change in VAS score did not differ significantly between air and oxygen ($P = 0.812$, air = 15.4 mm, oxygen = 13.3 mm) but mean oxygen saturation levels increased significantly more for oxygen than for air ($P = 0.005$, air = 2.7%, oxygen = 10.7%). Following oxygen administration, hypoxia was corrected in 13 of the 17 patients. Of the 17 hypoxic patients, 35% expressed a preference for air, 24% expressed a preference for oxygen, and 41% expressed no preference.

Discussion

A number of authors have commented upon the difficulties in conducting clinical research in palliative care. The problems encountered have included the difficulties of recruitment and attrition of patients.\textsuperscript{25,26} Having enrolled patients, difficulties arise with the problems of isolating the effect of a single intervention from the complexities of an ever-changing disease state and the heterogeneity of the patient group.\textsuperscript{27,28} In an attempt to circumvent some of these difficulties encountered by other researchers, the intervention in this trial was simple and brief, with the data collection completed within 2 hours of enrollment. In addition, the symptom examined was one that is common in a cancer population. Despite this, recruitment continued for almost 5 years until the required 50 participants were enrolled. A significant component of this related to the clinical fragility of the patients. Many patients were screened and complained of dyspnea, and for reasons of accessibility, these were largely inpatients. But unless patients identified as eligible were able to be enrolled in the trial within 24 hours, most deteriorated, with cognitive impairment or increasing oxygen

### Table 1

<table>
<thead>
<tr>
<th>Characteristic Category</th>
<th>Overall (n = 51)</th>
<th>Air First (n = 27)</th>
<th>Oxygen First (n = 24)</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Sex</td>
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<td>61</td>
</tr>
<tr>
<td></td>
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<td>39</td>
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<tr>
<td>Age (years)</td>
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<td>33–82</td>
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<td></td>
</tr>
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<td>25</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>37</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
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<td>NSCLC</td>
<td>22</td>
<td>43</td>
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<tr>
<td></td>
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<td>6</td>
<td>12</td>
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<tr>
<td></td>
<td>Breast cancer</td>
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<td>16</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer</td>
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</tr>
<tr>
<td></td>
<td>Other\textsuperscript{a}</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Time since diagnosis of cancer (months)</td>
<td>Median</td>
<td>10.7</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.1–247.4</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Other diagnoses include lymphoma, melanoma, sarcoma, carcinoid tumors, and cancers from skin, bladder, and pharyngeal origins.

NSCLC = non-small-cell lung cancer.
requirements, to the point where they were unable to participate in the study. Despite this study being specifically designed to cater to this particular group of patients, it nevertheless proved difficult for them to participate in the intervention. The experience of the researchers was that dyspnea in an inpatient cancer population indicated an extremely poor prognosis. This was confirmed by the Eastern Cooperative Oncology Group (ECOG) Performance Status, with the majority of patients (73%) having an ECOG performance status rating of 3. In addition, they had extensive malignant disease, with nearly half of the participants having multiple causes for the complaint of dyspnea. However, it is a particular strength of this trial that it did in fact study the palliative care population of interest.

The improvement of oxygen saturation when oxygen was administered indicated effective delivery of oxygen within the short study time of 15 minutes. While hypoxia was not corrected in all cases, with four patients remaining hypoxic despite oxygen administration, the oxygen flow mimicked the standard application of oxygen administered in the domiciliary setting. Under these conditions, the improvement of mean oxygen saturations did not correlate with a reduction of mean VAS ratings of dyspnea. Instead, average VAS scores improved with both interventions. It should not be anticipated that there would be a linear relationship between oxygen saturations and

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Overall (n = 51)</th>
<th>Air First (n = 27)</th>
<th>Oxygen First (n = 24)</th>
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<tr>
<td>Breathlessness immediately before first gas</td>
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<td>31–78</td>
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<tr>
<td>Breathlessness after 15 minutes on first gas</td>
<td>Median 43</td>
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<td>34.5</td>
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<tr>
<td>Range</td>
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<td>0–68</td>
</tr>
<tr>
<td>Breathlessness immediately before second gas</td>
<td>Median 53</td>
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<td>42</td>
</tr>
<tr>
<td>Range</td>
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<td>15–88</td>
<td>10–70</td>
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<td>Breathlessness after 15 minutes on second gas</td>
<td>Median 34</td>
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<td>0–90</td>
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<tr>
<td>Shortness of breath immediately before first gas</td>
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<tr>
<td>Not at all</td>
<td>43</td>
<td>37</td>
<td>12</td>
</tr>
<tr>
<td>A little</td>
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<td>48</td>
<td>10</td>
</tr>
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<td>7</td>
<td>2</td>
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<tr>
<td>Very much</td>
<td>4</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Not recorded</td>
<td>1</td>
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<td>0</td>
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<td>Shortness of breath minutes after first gas</td>
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<td>11</td>
<td>3</td>
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<tr>
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<td>16</td>
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<tr>
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<td>26</td>
<td>5</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Very much</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shortness of breath immediately before second gas</td>
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<td>4</td>
<td>0</td>
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<tr>
<td>Not at all</td>
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<td>17</td>
<td>18</td>
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<tr>
<td>A little</td>
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<td>63</td>
<td>75</td>
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<tr>
<td>Quite a bit</td>
<td>29</td>
<td>33</td>
<td>6</td>
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<tr>
<td>Very much</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Shortness of breath minutes after second gas</td>
<td>37</td>
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<td>74</td>
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</tr>
<tr>
<td>Quite a bit</td>
<td>10</td>
<td>15</td>
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</tr>
<tr>
<td>Very much</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Oxygen saturation immediately before first gas</td>
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<td>30</td>
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<tr>
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<td>8</td>
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<tr>
<td>Oxygen saturation after 15 minutes on first gas</td>
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<td>71–98</td>
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<td>93</td>
<td>93</td>
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<tr>
<td>Range</td>
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<td>69–98</td>
<td>73–100</td>
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<tr>
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<td>97</td>
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<td>93</td>
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<tr>
<td>Range</td>
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<td>Hypoxic prior to first gas</td>
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<td>8</td>
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<td>Hypoxic prior to second gas</td>
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<td>8</td>
</tr>
<tr>
<td>Hypoxic after second gas</td>
<td>24</td>
<td>15</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 2

Patient Responses Pre- and Post-administration of Gas
complaints of dyspnea in view of the subjective nature of symptom reporting, the multiple factors contributing to the generation of dyspnea, and the complexity of the physiology of oxygen-hemoglobin binding, which does not occur according to linear dynamics. Nevertheless, the lack of correlation between oxygen saturation and dyspnea complaints is an important finding of this study to disseminate, since much practice in acute hospitals revolves around “treating” dyspnea by responding to oxygen saturation levels. Other authors have similarly demonstrated that standard clinical tools, such as forced expiratory volume in one second and forced vital capacity, do not correlate with the experience of dyspnea in patients with advanced cancer. The results of this study add further weight to the statement that dyspnea is a subjective symptom and its adequate management requires full inquiry of the patient, not simply responding to abnormal investigations. Appropriate management of patients with advanced cancer must include an evaluation of the burden of symptoms irrespective of the results of investigations.

Consistent with the results of Booth et al., patients on average improved with gas administration. Air was not considered a placebo arm in this trial, with air administration on average conferring considerable benefit. The benefits of air and oxygen were not significantly different. Since hypoxia was not corrected with oxygen in 4 of the 17 patients, the lack of significant difference between the gases in this group needs to be interpreted with caution. But this finding has clinical implications, because while using the equivalent of standard domiciliary oxygen flow, patients demonstrated no difference in response between air and oxygen. Importantly, no clear preference expressed for either treatment arm according to the criteria set for the trial. It appears that the act of treatment is important, with treatment in this study consisting of gas administration via nasal prongs. The mechanism by which this improvement is achieved is not clear.

The possibility of a placebo response to any treatment including air must be considered. Since all these patients had previously been exposed to gas administration, it is not treatment naïveté informing the results. The trial was conducted over a short treatment period, and it may be that the initial response to air would lessen during longer-term administration, as would be expected in a placebo response.

Another possible explanation for the lack of differential response is that mechanoreceptors

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th>Same</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>First gas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td>12</td>
<td>44</td>
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</tr>
<tr>
<td>Oxygen</td>
<td>10</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td>Second gas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td>9</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Oxygen</td>
<td>7</td>
<td>26</td>
<td>1</td>
</tr>
</tbody>
</table>

*One patient was not assessed prior to first gas.
are stimulated by gas administration, bringing about a reduction in the sensation of dyspnea. In studies on normal subjects, breathlessness has been found to be reduced by oral mucosal stimulation and cold facial stimulation, suggesting the mechanism by which open windows and fans may be useful. Others have suggested that wearing nasal prongs appears to bring about a reduction of breathlessness in patients with COPD. The role of the establishment of a therapeutic environment may also be important in this trial. The presence of an interested researcher throughout the intervention may lead to a reduction of anxiety and fear, which, in turn, may result in a reduction of symptom intensity.

There were limitations to this study that may influence the results. First, eligible patients had to record a dyspnea score at rest of 30 mm on VAS. A number of patients complained of significant dyspnea with activity but at rest did not reach this score, rendering them ineligible for study inclusion. In order to control for differing levels of activity, the study required patients to remain at rest for the study duration. It is possible that if gases were administered to patients during activity, there may have been a differential preference and response to the gases that were not apparent at rest. Second, the investigators defined a clinically significant response to oxygen to be a preference for oxygen chosen by 60% of patients. However, the exact nature of what constitutes a clinically significant improvement in this symptom is uncertain. While there has been some discussion and attention to this issue in pain research, the same remains to be established for other symptoms, including dyspnea. If a clinically significant improvement occurred at lower increments of improvement, then this study may not have been adequately powered. The study methodology and response criteria were informed by the considerable clinical experience of the investigators, and, therefore, this study represents the best available evidence at the time.

Conclusion

In agreement with the findings of Booth et al., this study established that both oxygen and air administered intranasally improve the mean sensation of dyspnea for patients with advanced cancer. There is no significant difference between the gases in either VAS or preferences expressed. This is despite oxygen significantly improving mean oxygen saturation measures. Nor did the group of hypoxic patients show mean greater improvement with, or preference for, oxygen. Notably, oxygen saturation measures do not correlate with ratings of dyspnea, which is in keeping with the knowledge that dyspnea in advanced cancer is the expression of multiple sensations and experiences, and not simply related to oxygen tension.

This study has highlighted the need to establish what constitutes a clinically significant
improvement of the symptom of dyspnea. This requires investigation as a matter of urgency such that future studies may be designed and powered to reflect clinically relevant outcomes. Once established, the role of oxygen to relieve dyspnea in advanced cancer may require further investigation, with particular attention given to longer-term studies. Until such time, the current state of evidence suggests that the administration of intranasal gas, either air or oxygen, improves the sensation of dyspnea in advanced cancer.

Acknowledgments

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References


