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In this issue

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Editorial

The *AJCN* aims to provide a forum where debate and the exchange of views can take place. We welcome papers on contemporary professional policy or practice issues of concern and interest to cancer nurses.

Notes for contributors

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The CNSA is committed to achieving and promoting excellence in cancer care through the professional contribution of nurses.

To achieve our mission of promoting excellence in cancer care, the CNSA will act as a resource to cancer nurses around Australia, no matter what their geographical location or area of practice.
The CNSA will be the link between cancer nurses in Australia, the consumers of cancer nursing services and other health professionals involved in cancer care.

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The Australian Journal of
Cancer Nursing

Editorial

End-of-life care

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In this palliative care themed issue of the *Australian Journal of Cancer Nursing* it is timely to revisit the goals of palliative care and how these goals are achieved in the Australian health care context.

Palliative care focuses on relieving suffering and achieving the best possible quality of life for patients and their caregivers. Palliative care services integrate the expertise of a team of providers from different disciplines to address the complex needs of seriously ill patients and their families. In order to achieve this goal it requires the collaborative efforts of the interdisciplinary team. This should include professionals from medicine, nursing and allied health including social work, chaplaincy, nutrition, rehabilitation, pharmacy and other support services as indicated. It involves the assessment and treatment of symptoms; support for informed decision-making by the patient and family; practical aid for patients and their caregivers; initiation of the appropriate community resources in order to provide optimum home support; and implementation of a collaborative model of care across hospital, home, nursing home and hospice.

Palliative care can be provided within a designated hospice palliative care service and outside of this service by incorporation of the principles of palliative care into other speciality services. It can then be provided in conjunction with life-prolonging and curative therapies for persons living with serious, complex and life-threatening illness. Hospice palliative care becomes appropriate when curative treatments are no longer beneficial; when the burdens of these treatments exceed their benefits or when patients are entering the last weeks to months of life.

The four articles in this issue include the management of cancer-related fatigue; to a literature review on the support provided to caregivers of people with advanced cancer; a Cochrane review on the effects of end-of-life pathways and do they improve patient outcomes; to a discussion on terminal delirium illustrated by case studies.

Raymond Chan and colleagues, in their review article, describe the distressing symptom of cancer-related fatigue, which is frequently experienced by patients with cancer. Whilst the aetiology, impact and current management of cancer-related fatigue is discussed, it is noted that advances in management have primarily been made in patients undergoing primary or adjuvant treatment. Further research is required in patients with advanced cancer; however, there are several effective strategies currently available that can reduce the severity of cancer-related fatigue in this cohort of patients.

In their review of caregiving literature, Anna Ugalde and colleagues again focus on the support of people with advanced cancer. The caregiving role is fraught with anxiety, depression, strain and reduced quality of life. These emotions, however, can be counterbalanced by the knowledge that the role of caregiving makes a positive difference to the patient. As health professionals, it is important that we assist caregivers by enquiring how they are coping and then providing the appropriate support to assist them to consider their own needs and begin to care for themselves.

John Robinson's paper describes the management of terminal delirium and is illustrated by two case studies and a review of patients' notes. The setting for these case studies is a tertiary metropolitan hospital; however, the importance of accurate assessment in the management of these distressing symptoms applies to the home and hospice setting as well. The author concludes with the statement that delirium may be classed as a natural end-of-life symptom rather than a psychiatric disorder.

The final paper by Raymond Chan and Joan Webster is a Cochrane review on the effects of end-of-life pathways and the question, do they improve patient outcomes? The aim of the review was to assess the effects of these pathways compared with usual care (no pathway), or with care guided by a different end-of-life pathway. As a result of the review, the authors were unable to find any effect or harm with the use of end-of-life pathways; however, they conclude that without sufficient evidence for improving patient outcomes, organisations should await further high-quality evidence before the roll-out of an end-of-life pathway.

All four articles reflect contemporary palliative care practice and provide us with questions for discussion within our workplace environment.

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The aetiology, impact and management of cancer-related fatigue in patients with advanced cancer

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Abstract

Cancer-related fatigue (CRF) is a distressing symptom frequently experienced by patients with advanced cancer. While there have been some advances in the understanding of the management of fatigue associated with cancer treatment, CRF associated with advanced cancer remains a phenomenon that is not well-managed. The aetiologic factors associated with CRF, the impacts of CRF and the current management of CRF are discussed in this review article in relation to patients with advanced cancer. The paper concludes that, while further research is required in the area, there are several potentially effective strategies currently available that can reduce the severity of CRF in patients with advanced cancer.

Introduction

Fatigue is one of the most frequently experienced[1-3] and distressing symptoms[4,5] reported by patients with advanced cancer. The prevalence and impact of fatigue in this population, however, is not often acknowledged or understood by health professionals[6,7]. The likely reasons for this are that health professionals tend to focus more on pain or other, more obvious symptoms[8]; and health professionals' and patients' lack of awareness of effective treatments for this symptom[7]. Over the past few decades, however, for patients at all stages of the cancer trajectory, there has been a substantial body of research that has enhanced our understanding of the pathophysiology of fatigue, patients' experiences of this symptom and potentially effective interventions for patients who report cancer-related fatigue (CRF). It should be noted, however, that most of this research does not pertain to patients with advanced cancer[1,2]; it has focused to date largely on patients undergoing active treatment. The purpose of this paper is to review the state of knowledge regarding CRF in patients with advanced cancer. In this paper, we review the evidence pertaining to the aetiologic factors associated with fatigue, the impact of fatigue on the patient with advanced cancer and current trends in its management.

Aetiologic factors associated with fatigue in patients with advanced cancer

The aetiology of CRF is complex and remains unclear in patients with advanced cancer[9]. The literature indicates that aetiologic factors associated with CRF could comprise (but are not limited to) cachexia, infection, anaemia, neurological changes, psychological distress, metabolic and endocrine disorders, over-exertion, medications, side effects of antineoplastic treatment and paraneoplastic neurological syndromes[10]. In recent years, the role of a number of biological response modifiers (for example, interferon, tumour necrosis factor, IL-1 and IL-6)[11,12], and the patient's genetic make-up[13] in CRF have also been explored. Although these studies have focused on people experiencing cancer treatment-related fatigue, there is preliminary evidence to indicate relationships between genetic make-up, cytokine markers and symptoms in oncology patients and their family caregivers[13]. One recent study, for example, reported an association between a functional promoter polymorphism in the TNF-α gene with the severity of both sleep disturbance and morning fatigue[13].

The evidence further indicates that the aetiologic factors associated with CRF could vary between those in the earlier stages of the cancer trajectory compared to those who are at the more advanced stage. For example, although it is repeatedly reported that anaemia is associated with fatigue in patients undergoing treatment, it is also reported that there is no association between haemoglobin levels and fatigue in patients with advanced cancer[14,15]. For another example, although fatigue is thought to be a common side effect of antineoplastic treatment in cancer patients, antineoplastic treatments received by patients with advanced cancer normally aim to improve symptom control and quality of life and can, in some cases, alleviate their fatigue and other symptoms[16,17].

One UK observational study of 122 patients with advanced cancer provided further empirical evidence of potential differences in contributors to CRF[15]. The study reported no relationships between the level of fatigue and age, sex, diagnosis, presence or sites of metastases, anaemia, dose of opioid or steroid, or a range of haematological markers or biochemical indices (except urea), but did identify significant associations between fatigue, pain and dyspnoea scores[15]. Recent studies which have investigated the interrelationship between and coexistence of fatigue and other symptoms[18,19], similarly emphasise the greater significance of symptom burden as a contributor to fatigue in patients with advanced cancer.

The impact of fatigue for patients with advanced cancer

Fatigue is associated with impaired health-related quality of life in patients with cancer at all stages of cancer, but particularly for those whose disease is more advanced[20-23]. For example, a study of 40 patients with advanced cancer admitted to an academic palliative care unit reported a high correlation between fatigue within 24 hours of admission and individual quality of life scores at seven days[23]. Moreover, the experience and impact of fatigue in patients with advanced cancer is likely to have some unique characteristics that have implications for management strategies. One qualitative study of patients with advanced cancer described how fatigue affects the physical, psychological, social and spiritual aspects of their lives[24]. These individuals often find that they are unable to do much and they particularly struggle to manage fatigue[8,25,26]. The perception of "nothing can be done" for their fatigue is often shared among families and health professionals[25]. As a result, the effect of fatigue on patients can be tremendous, which they express in terms of the burden they impose on others, their inability to participate in family and other social activities, and cognitive impairments such as memory loss and loss of ability to concentrate[8,24-27]. Moreover, patients with advanced cancer are more likely to associate fatigue with the process of adjusting to living with a terminal illness and, ultimately, death[24,27]. Individuals with advanced disease may, thus, perceive fatigue in different ways to those individuals who experience fatigue primarily associated with curative treatment for their disease[28,29].

In 1996, Sutcliffe-Chidgey and Holme's cross-sectional survey offered insights into perceived distress levels associated with fatigue in patients with advanced cancer, where 49% (n=100) of participants perceived fatigue as a distressing symptom[4]. This study also reported that the level of perceived distress varied among patients, professionals and bereaved carers, with only 9% of professional carers (n=60) and 17% of bereaved carers (n=30) perceiving fatigue as a distressing symptom[4]. Such findings suggest that people other than the patient may have limited insight into such a subjective experience.

For some patients with advanced cancer, fatigue could also be perceived as "necessary" or unavoidable in the terminal phase of life[30]. Some have suggested that treatment of fatigue is no longer indicated at end of life, as fatigue may provide protection and shielding from suffering[30]. While there is some agreement that fatigue negatively influences quality of life among patients with advanced cancer, the association between fatigue and quality of life and negative emotions could change during the last days and weeks of life[31]. However, while attitudes towards fatigue might change over time, it is still a burdensome symptom even during the last week of life[32] and, therefore, worthy of further investigation.

Other studies involving patients with advanced cancer report that the decline in performance status that is associated with advanced cancer is associated with increased fatigue levels. For example, one study reported that as performance status declined, fatigue interfered with subjects' physical activities such as walking (36.3%, n=157), normal work (31.8%), mood (21.7%) and enjoyment of life (19.1%)[33]. Other studies report that fatigue is highly and negatively correlated with performance status[34-38]. One Japanese longitudinal study offered some insights into the specific physical and psychological factors correlating with fatigue in terminally ill patients with cancer over three time points[33]. At time 1 (the second visit to the palliative out-patient department), greater fatigue was significantly correlated with psychological distress, lower performance status, dyspnoea and appetite loss. At time 2 (a week after time 1), greater fatigue was significantly correlated with higher psychological distress and lower performance status at time 1. Fatigue was also positively correlated with deterioration in psychological distress, performance status and dyspnoea severity during the period between times 1 and 3. Another study that attempted to differentiate factors that affected fatigue and physical function in lung cancer patients did so cross-sectionally[39]. Using multiple regression analysis, the researcher identified that performance status scores, weakness and depression scores were correlated independently with fatigue. Hence, while studies report that CRF is almost universally a distressing and disruptive symptom, the experience and impact of fatigue for people with advanced cancer, as compared to early-stage cancer has some unique dimensions. These unique features are associated with the particular meanings and declining performance characteristic of progressive and life-limiting disease.

The management of CRF in people with advanced cancer

The management of CRF in patients with advanced cancer is complex and may involve a range of treatment measures associated with pharmacologic and non-pharmacologic strategies[9]. These measures aim to target potentially reversible aetiologic factors that are known to contribute to CRF[9].

Pharmacological management

A range of pharmacologic agents is used for the treatment of CRF. These agents include psychostimulants (for example, methylphenidate), paroxetine and progestational steroids (for example, megestrol acetate). The effectiveness of each class of medication and related concerns are discussed below.

Psychostimulants

Research on symptomatic treatment of fatigue in patients with advanced cancer has concentrated on stimulant drugs such as methylphenidate and donezepil. Methylphenidate is reported as effective in several uncontrolled trials or retrospective studies that investigated fatigue in patients with advanced cancer[40-42]. In 2005, one randomised, placebo-controlled trial of 152 patients with breast cancer reported favourable results for methylphenidate, which was significantly more effective than placebo in improving fatigue after chemotherapy. However, this study did not report on the staging of the disease of this sample of women with breast cancer. In 2006, another randomised, placebo-controlled trial of 112 patients with advanced cancer receiving palliative care reported no difference between placebo and methylphenidate[43]. In light of these equivocal findings, a systematic review concluded that the two methylphenidate trials for CRF did not provide sufficient evidence to recommend its use in practice; however, a later meta-analysis favoured the use of a dose of 10 to 20 mg per day titrated to response[44]. This review concluded that serious adverse effects were minimal but contraindications should be reviewed before prescribing[44]. In 2010, a retrospective analysis reported that the side effects of methylphenidate (10–20 mg/d) are well tolerated in patients with advanced cancer[45]. According to the information retrieved from the international trial registries, more trials are now under way to determine its effects in patients with advanced cancer.

With respect to donezepil, the effects are still not certain in patients with advanced cancer. Although donezepil was reported as effective in the treatment of opioid-induced sedation in an uncontrolled trial[46], one recent randomised, placebo-controlled trial of 142 patients with advanced cancer also reported that it was not superior to placebo[47]. Another recent randomised, double-blinded, placebo-controlled trial conducted with 39 patients with advanced cancer reported potential benefits of using dexamphetamine[48]. Specifically, the use of 10 mg twice daily for eight days was well tolerated with minimal side effects and improved fatigue levels on day two, but not at the end of the study. These results suggest uncertainty about the effectiveness of dexamphetamine beyond day two. With the consideration that the current tested dosing was well tolerated, further investigations with higher dosing may be warranted.

Paroxetine, progestational steroids and Acetyl-L-Carnitine

In 2010, two meta-analyses were conducted in a Cochrane systematic review[49]. The meta-analysis of two studies (n=625) was conducted for paroxetine and indicated no difference between paroxetine and placebo for the treatment of CRF in patients with advanced cancer[49]. Similarly, the meta-analysis of four studies (n=587) investigating the effect of progestational steroids on CRF also reported that it was not superior to placebo[49]. Acetyl-L-Carnitine was compared against placebo in a double-blind, randomised-controlled trial (RCT) with patients with advanced cancer and was not superior to placebo[50].

Non-pharmacological management

A range of non-pharmacological management strategies are used in the management of CRF[51]. This section discusses the evidence base for each of the non-pharmacologic management strategies as recommended by the National Comprehensive Cancer Network (NCCN), and their potential application for patients with advanced cancer[52]. Due to the lack of direct evidence for patients with advanced cancer, some of the recommended strategies in the NCCN guidelines are based primarily on evidence for patients with early-stage cancer[52] and their application to patients with advanced cancer is yet to be

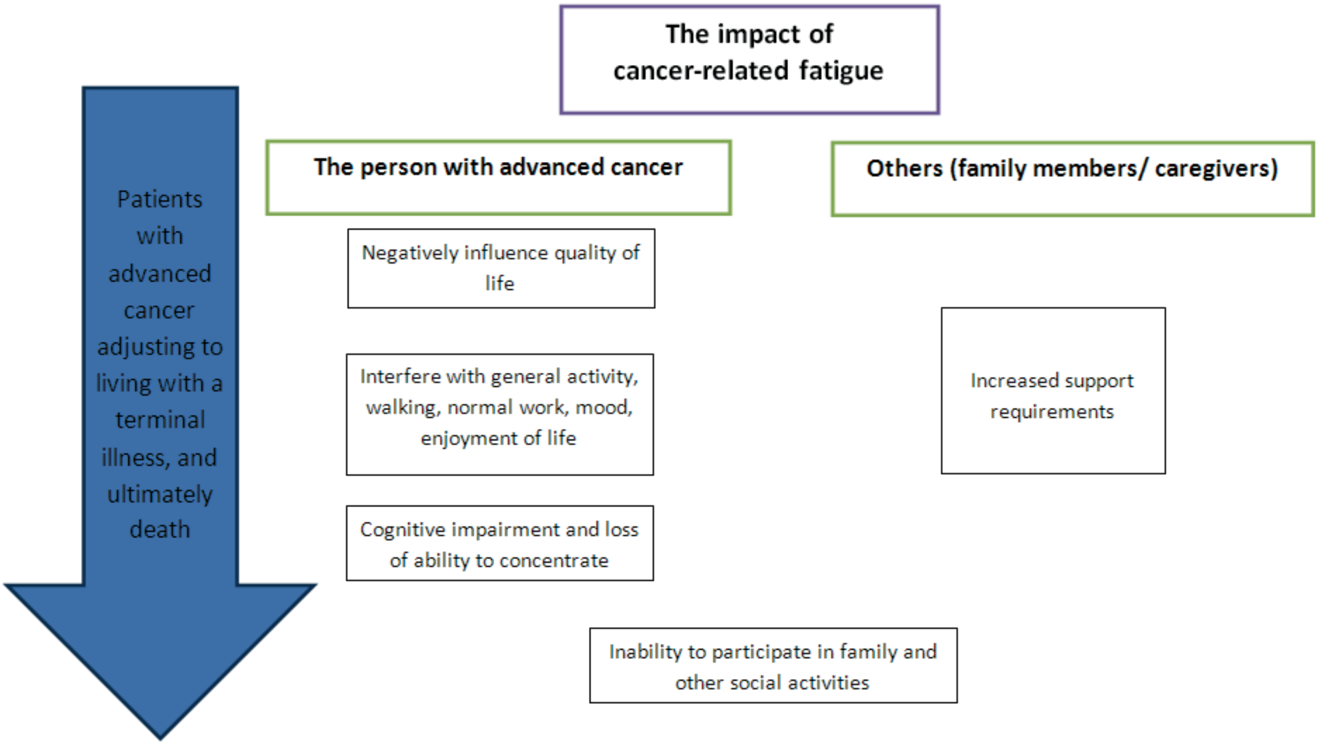

Figure 1. The impact of CRF on patients with advanced cancer and others.

tested in randomised trials. The key strategies reviewed in this section include exercise, sleep and rest, energy conservation, complementary therapies and psychosocial interventions.

Exercise

A Cochrane review by Cramps and Daniel of 28 RCTs that studied patients with cancer of all stages concluded that moderate exercise appears to have benefit in the management of CRF both during and after active cancer treatment[53], particularly in patients with breast cancer and prostate cancer. However, there is not sufficient evidence to determine the best type or intensity of exercise for reducing CRF[53]. Further, this review only identified few studies that included samples with patients who had advanced cancer[53].

The few available studies suggest that at least some groups of patients with advanced cancer may also benefit from exercise-based interventions. One Norwegian study of 63 patients with advanced cancer receiving palliative care pilot-tested an exercise program and reported that the exercise participants had significantly less physical fatigue and increased walking distance[54]. This program consisted of two 50-minute sessions twice a week for six weeks. A combination of strength building, standing balance and aerobic exercise was used in this program. Another small pilot study was conducted by Porock and her research team to evaluate an exercise program for nine patients with advanced cancer who were enrolled in a home hospice program[55]. In this intervention, a physical therapist guided participants to perform a range of strategies throughout the day (for example, walking, performing arm exercises with resistance, marching in place, and dancing). All participants were able to increase their activity level over a two-week period without increased fatigue. There was also a trend towards increased quality of life and decreased anxiety. In 2003, a 12-week exercise program was tested in 82 men with locally advanced/metastatic prostate cancer receiving androgen deprivation therapy, as compared to a wait-list control group[56]. Patients who were in the exercise group reported less interference of fatigue with daily activities (p=0.002) and better quality of life (p=0.001). In addition, they also demonstrated high levels of upper body (p=0.009), and lower body (p<0.001) muscular fitness than men in the control group.

Although there is some preliminary evidence now suggesting the benefits of exercise in patients with advanced cancer, the evidence is not yet conclusive due to the lack of RCTs. Two recent RCTs of patients with advanced cancer[57,58] reported contradictory results with regard to the benefits of exercise for patients with advanced cancer. One possible explanation may be that the more effective intervention evaluated by Headley *et al.* required patients to participate in a less intense program (a 30-minute seated exercise program, three times a week, with one week break between sessions)[57], as compared to the less effective intervention of Brown *et al.* (2006) that asked patients to perform stretching, strength, balance and gait training over eight 90-minute sessions in four weeks[58]. Although it is suggested that a 30-minute seated exercise regimen is a feasible management strategy for patients with advanced cancer, further RCTs are needed to duplicate these results in the various populations of patients with advanced cancer. While health professionals need to be informed by high-quality trials that can support specific, effective exercise regimens for this patient group, research efforts should also be directed to understanding what patient responses are to these recommendations for exercise therapy, what are their confidence level with regard to carrying out the exercises and the factors that may influence the use of exercise.

Sleep and rest

In general, patients with cancer can experience disruptions in both the quantity and the quality of their sleep[59,60]. Due to the close relationship between sleep disturbance and fatigue[61], health care professionals commonly recommend strategies for improving sleep quality to patients with CRF[62] and they may be the most frequent self-management activities patients perform[51,63,64]. Although there is compelling evidence suggesting the effectiveness of sleep hygiene programs in insomnia[65-68], there are limited trials testing non-pharmacological strategies in managing sleep disturbance in patients with advanced cancer. In one RCT, 46 patients with advanced cancer receiving hospice care were allocated to three groups: massage group, aromatherapy group and control group in the hospice setting in the UK[69]. The results of this study demonstrated significant clinical improvements in sleep disturbance and depression scores. However, the sample was too small to detect statistically significant differences in sleep disturbance.

There is also now some preliminary evidence that shows the potential benefits of an eight-week Carlson's Mindfulness-based Stress Reduction program in patients with early-stage cancer[70]. The components of the program included body scan meditation, sitting, walking, meditation and hatha yoga. The number of participants with total sleep scores over eight (≥5 indicates sleep disturbance with the use of PSQI) was reduced from 70% at baseline to 49% post-intervention. Other than the structured programs mentioned above, the literature has documented a list of strategies undertaken by palliative/cancer care professionals. These range from avoiding stimulating substances (such as caffeine, nicotine) before bedtime to light exercise during the day time[60,71]. These interventions have not yet been formally tested in this population, despite a prevalence of sleep alterations in patients with advanced cancer of approximately 71%[72-74]. A recent UK study using comprehensive patient reports and objective measures such as actigraphy reported the manifestations for patients with advanced cancer are high levels of sleep fragmentation and movement during sleep, rather than the length of sleep[75]. It is important that appropriate sleep therapies are formally evaluated in patients with advanced cancer.

Energy conservation

Energy conservation is defined as "the deliberate, planned management of an individual's personal energy resources to prevent their depletion"[76]. The goal of energy conservation is to balance rest and activity during times of high fatigue so that valued activities and goals can be maintained. Energy conservation involves a number of strategies: taking additional rest periods, priority setting, delegation, pacing oneself and planning high-energy activities at times of peak energy. A multisite RCT of 396 patients with various cancers at different stages undergoing chemotherapy and radiotherapy reported that the intervention group using these strategies experienced a greater decrease in fatigue over time compared with the control group ($p<0.01$)[76]. A further recent study reported the experiences and outcomes of a fatigue clinic in a comprehensive cancer centre[62]. This study reported that energy conservation was recommended to 98.5% of patients with CRF (n=260), regardless of cancer stage. However, the authors also reported that they faced challenges in encouraging patients to delegate tasks to family or hired help. While some patients were reluctant to seek help, families were enthusiastic about participating in treatment plan recommendations[62]. The NCCN guideline for CRF recommends energy conservation as a "general strategy for management of fatigue" for patients with advanced cancer and their caregivers. However, there is a lack of research suggesting its effectiveness in patients with advanced cancer who are not undergoing treatment.

Complementary therapies

Complementary therapies such as massage therapy[77,78], yoga[79], breathing exercises[80,81], muscle relaxation[82,83] and mindfulness-based stress reduction[70,84-86] have been evaluated in pilot studies. The preliminary data suggest that these therapies may have an effect in reducing fatigue in patients with cancer. These strategies have also been recommended for the management of CRF in a number of clinical guidelines for the management of CRF[9,30,87]. However, these interventions were either supported by indirect evidence[88,89] or a case report[90], or tested with benefits in patients who were not in their advanced stage of disease[82].

Psychosocial interventions

The NCCN guideline for CRF management recommends that patients should be counselled about coping and educated on how to deal with anxiety and depression, which are commonly known to be associated with fatigue during cancer treatment[52]. A recent Cochrane systematic review in 2009, involving 27 studies of a total of 3324 participants, reported limited evidence that psychosocial interventions are effective in reducing fatigue during active treatment in patients with cancer[91]. Of these studies, only five were designed with the focus of fatigue, with four being effective ($p<0.05$). The five interventions were brief, consisting of three individual sessions provided by oncology nurses. The general content of these interventions included education about fatigue, self-care or coping techniques, and learned activity management. Only three of these studies reported sustained effects at follow-up. To date, there is scant evidence suggesting the effectiveness of psychosocial interventions in patients with advanced cancer[92].

Summary

Despite the fact that many advances have been made in

Table 1. Current evidence for the management of CRF in patients with advanced cancer.

Interventions	Benefits for reducing CRF in patients with advanced cancer	NHMRC Level of evidence	The directness of evidence for patients with advanced cancer	Remarks
Pharmacological				
Methylphenidate	Potential benefits	Level I	Direct evidence	A meta-analysis favoured the use of a dose of 10 to 20 mg per day titrated to response[44]
Donezepil	Not superior to placebo	Level II	Direct evidence	
Dexamphetamine	Potential benefits	Level II	Direct evidence	The results of a RCT suggest uncertainty about the effectiveness of dexamphetamine beyond day two[48]
Paroxetine	Not superior to placebo	Level I	Direct evidence	
Progestational steroids	Not superior to placebo	Level I	Direct evidence	
Acetyl-L-Carnitine	Not superior to placebo	Level II	Direct evidence	
Non-pharmacological				
Exercise	Potential benefits	Level II	Direct evidence	The most appropriate intensity of exercise yet to be determined patients with advanced cancer[57,58]
Sleep/rest	Potential benefits	Level II	Indirect evidence	
Energy conservation	Potential benefits	Level II	Indirect evidence	
Complementary therapies	Potential benefits	Level III or level IV	Indirect evidence	
Psychosocial interventions	Potential benefits	Level I	Indirect evidence	

understanding and managing fatigue in patients with cancer, these advances have primarily been made for patients with cancer undergoing primary or adjuvant treatment. Prevalence data for CRF suggests that this symptom is not well managed in patients with advanced disease. While the evidence base relating to management of cancer treatment-related fatigue is a useful starting point for identifying strategies for managing fatigue associated with advanced cancer, differing aetiologies and experiences means that management strategies may need to be tailored for this population.

Researchers have tested a number of interventions, both pharmacological and non-pharmacological, with the aim of reducing the severity and impact of CRF. While there have been many efforts to test pharmacological agents in patients with advanced cancer in the management of CRF, a number of non-pharmacological management strategies are recommended for patients with advanced cancer, in spite of the fact that they are not well tested in patients with advanced cancer (Table 1). Most of these interventions require patients to respond with a number of health behaviours (for example, taking medications, exercising, delegating tasks). These responses may have a direct impact on the efficacy of some of these interventions in relieving CRF. For patients with advanced cancer, further research is required to investigate the effectiveness of these interventions with good-quality, controlled trials and investigate how patients respond to evidence-based recommendations.

Recommendations for nursing practice

It is important for nurses to encourage patients with advanced cancer or their caregivers to openly discuss their fears, concerns and experience of CRF.

The literature shows that patients often are not aware of treatment options. Nurses can support the self-management of patients by providing evidence-based information in relation to fatigue management.

Preliminary research indicates some benefits of exercise in the management of fatigue in patients with advanced cancer. Although more research is warranted to determine the most effective intensity and mode of exercise, low-intensity, seated exercise appears to be appropriate for this population.

Evidence pertaining to patients with early-stage cancer indicates the potential benefits in a number of management strategies such as energy conservation and sleep hygiene behaviours. These strategies can be recommended for use in patients with advanced cancer as appropriate.

Although more trials are currently under way, the use of methylphenidate could be discussed with medical staff for consideration in managing CRF in some patients with advanced cancer.

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Supporting informal caregivers of people with advanced cancer: a literature review

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Abstract

Informal carers are people who provide care without a specific professional role. They provide diverse caregiving supports including disease-related problems, side effects of treatment and psychosocial impacts. This paper reports on a comprehensive review of caregiving literature, focusing specifically on cancer caregivers. The paper presents five observations drawn from the literature in order to make recommendations about how caregivers of people with advanced cancer can best be supported. The observations are: 1) caregivers are a heterogeneous group; 2) they have unique needs that differ to the patient; 3) their role includes more than attending to physical caregiving tasks; 4) they may feel unable to take a break from the role and 5) they need their own support which may be beneficial to their capacity to continue in the caregiving role. Recommendations for how health professionals can assist in supporting caregivers in their role are discussed.

Introduction

With an ageing Australian population and a tendency for care to be delivered in community and home settings, informal caregivers are increasingly central to the delivery of health care. As a consequence, carers of people with cancer are expected to take on often complex, technical care requirements for which they lack the necessary training or resources[1]. The elements of care provided by informal caregivers have been described as being similar in complexity to that provided by a nurse[2,3]. In addition, providing care for people with advanced cancer is associated with several negative impacts for the caregiver, including anxiety, depression, strain and reduced quality of life[4-8]. However, studies have also demonstrated that caregivers experience several positive aspects to their role, including demonstrating love and knowing their caregiving is making a positive difference to the patient[9,10].

In this paper, the term caregiver is used to describe an informal caregiver, usually a family member or friend of the patient, rather than a health professional. The paper explores the caregiving role through a comprehensive review of the literature, in order to make recommendations about how health care professionals can best support caregivers in their role.

Exploring the literature

An in-depth literature review was conducted. The focus of this review was on caregivers of people with advanced cancer, but papers that reported on caregivers in other groups were also considered. Five main observations were identified from the literature. These include: 1) caregivers are a heterogeneous group; 2) caregivers have unique needs that are distinct from patient needs; 3) the caregiving role is broader than attending to physical caregiving tasks; 4) caregivers may feel unable to take a break from their role and 5) support for caregivers may be beneficial in helping them continue with their caregiving role and ensure carer wellbeing.

Main findings

Caregivers are a heterogeneous group

Studies often refer to informal caregivers as partners or spouses of people with cancer. There is often an assumption within the literature that this is the person who always takes on the carer's role. A retrospective study of 56 people who provided end-of-life care to people with a range of illnesses found that if the spouse was available to care, they most commonly took on this role[11]. When spouses are not available to provide care, adult children often become the caregiver, with evidence suggesting this is more often a daughter[12]. However, importantly, other studies have reported that caregivers are not always related to the patient. In a study of 988 terminally ill patients (with a range of diagnoses, including cancer, heart disease and chronic obstructive pulmonary disease), the primary caregiver was a family member 96% of the time[13], indicating that a small but significant number of carers were non-family members. In a study of 677 caregivers of lung and colorectal cancer patients, 25% had a different relationship than spouse or adult child of the patient[1], indicating diversity in who takes on this role and challenging commonly held assumptions about caregiver and patient dyad relationships.

Caregivers typically live with the person they care for, but once again, there are exceptions. In an Australian study of 136 caregivers of patients with advanced cancer, one fifth of carers did not live with the person they cared for[14]. In a qualitative study of 13 active caregivers of patients with advanced cancer, two did not live with the patient[15]. In addition to relationship and living circumstances, caregivers also differ in the amount of care they provide. Education, experience and understanding of cancer can also vary. In an Australian study of 136 caregivers of people with incurable cancer (including diagnoses of breast, lung, gastrointestinal and others), carers were asked about various aspects of the advanced cancer patients' illness. Less than half the caregivers understood that treatment was not curative[14].

This evidence indicates that it is important to recognise that caregivers are a diverse group and that, although the majority will be related to the patient, there is a small but significant percentage who are not. When engaging caregivers, it is important to gauge their understanding of the patient's diagnosis and treatment in order to understand what level of care they are able to provide and to provide carers with individualised information to help them understand the likely trajectory and how this impacts the time frame of the caregiving role.

Caregivers may have unique needs that differ from the patient

Identifying and addressing unmet patient need is recognised as a component of excellent cancer care. However, the literature indicates that caregivers may have needs that differ from patients and are important to address. Specifically, caregivers' information needs often relate to how best to provide care[16]. A large survey of 1149 caregivers of chronically disabled adults at the end of life reported that the majority of supportive services accessed by caregivers was directed towards the care recipient[17]. In a study of 100 advanced cancer caregivers, unmet information needs and unmet symptom management needs were reported as being the most common, indicating the importance of greater support (and information provision in particular) for caregivers[18].

Despite the recognition of unmet carer needs, studies indicate that caregivers of patients with advanced disease do not readily identify themselves as caregivers and are ambivalent about identifying where they would like help[19]. Evidence indicates that, for some, this is because they do not want to shift the focus of care from the patient[20] or they do not want to bother formal services with their own concerns[21]. In a qualitative study of carers of people with advanced cancer, caregivers struggled to recognise caregiving as a discrete role and, yet, appeared to experience loss of self-identity as a consequence of taking on the caregiving role[15]. Therefore, it appears to be important to directly engage caregivers in considering their own needs as a carer and to encourage them to consider where they need help.

Recognising that caregiver needs differ to that of the patient is a first important step in considering how to address any unmet needs. Asking caregivers where they need help and assistance is likely to be helpful in encouraging caregivers to ask for help and to indicate to carers that health professional recognise that they may need help to provide care.

The caregiving role includes more attending to physical caregiving tasks

The scope of the role that caregivers take on is largely dependent on patient need. A retrospective study of 56 bereaved caregivers (patients had a range of chronic diseases, including but not limited to lung disease, cardiac disease or diabetes) defined the role as consisting of personal care, household care and management care[11]. Most caregivers provide personal care including, but not limited to, helping with dressing, getting in and out of bed, going to the toilet and giving medication. Household tasks included errands, dishes, laundry and other jobs around the house. Most caregivers also carried out management and coordination tasks including visiting the doctor, attending appointments, filling out forms, attending to financial affairs and arranging care[11]. More than half the caregivers in this sample (n=30 of 55) had a role in all three aspects of care provision and 90% had a role in at least two aspects of care provision[11]. In a large study of 1149 caregivers of disabled adults at the end of life, the majority of informal caregivers were found to assist with shopping and transport (85%), household tasks (83%), personal care (65%) finances (52%), administration of medication (51%) and indoor mobility (39%)[17]. This was supported by qualitative data from a study of 28 family members of people with advanced cancer. This study found that caregivers exhibited nine types of caregiving tasks relating to: activities of daily living, ambulation, bowel management, bladder management, comfort care, dietary control, pain management, wound and skin care and special techniques (such as oxygen management, tube-feeding measures or injection procedures)[22]. Qualitative data indicates that caregivers of terminally ill cancer patients perceive different aspects of caregiving: physical caregiving tasks, emotional caregiving tasks and outside demands[23]. In addition, medication management has been identified as central to caregiving, but this is a complex task and their role is not only to administer but also to make decisions about medication use[24]. Successful medication management is based on the ability to liaise with health professionals, organise and store medications, recognise and interpret symptoms, understand basic administration and respond to patients' needs[25]. Clearly, the instrumental aspects of the caregiving role are extensive and complex.

The role has been shown to be heavily defined by the patient: caregivers have more physical tasks when the patient has more symptoms[2]. Caregivers of cancer patients report needing, but not receiving, training for several aspects of care including: managing fatigue, administering medications, managing nausea, managing pain, changing wound bandages or managing other symptoms[1]. The list of carer tasks is extensive, but evidence indicates a dominant focus on physical caregiving tasks. But caregivers are also often involved with the coordination and dissemination of information within and across family members and friends and with treatment decision-making and emotional care for the patient. In addition, caregivers also have their own emotional needs that arise in responses to the patient's diagnosis; their own fears and anxieties and burden of instrumental tasks.

In summary, when considering the role caregivers take on and enquiring about any caregiving tasks they may find difficult, it is necessary to consider all aspects of care provision, not just physical tasks. Discussing the nature and extent of emotional support they provide to the patient and others should also be explored, as these are equally important to address, if the negative impacts of caregiving are to be minimised and carer wellbeing sustained.

Caregivers may feel unable to take a break

The review of the literature demonstrated that caregivers expect little help from professionals; rather, they report feeling fully responsible for daily care tasks[26]. Although frequently not realised when they begin caregiving, the role requires significant sacrifice to personal time and frequently paid work time. Specifically, a study with 124 bereaved caregivers who had cared for someone with cancer indicated that they had provided 10.8 hours a day of direct care and 8.9 hours a day of companionship[27]. An interview study with 21 female caregivers of advanced-stage cancer patients supported this substantial role; they estimated an average of 16.6 hours daily spent providing care[28].

Despite the impact of caregiving on daily life, caregivers are very committed to care provision[29]. They provide care in a belief that it will benefit the patient[26], which is often the case[30]. In a qualitative study with both active and bereaved caregivers (n=17), all caregivers were entirely committed to the caregiving role; however, many reported being unable to take a break and some had not considered that as a possibility[15].

Caregivers should be encouraged to consider whether they need a break. Having a break from caregiving can range from establishing alternative care arrangements to securing some quiet time away from the role within the care environment[31]. The type of break caregivers may find useful is likely to vary with what is feasible and desired. Nonetheless, all caregivers should be encouraged to think about ways they can take time to best look after themselves in their role. The importance of respite care has been demonstrated, with evidence that respite brings normality to caregivers and allows them to continue caring[32]. Consequently, if caregivers are aware of respite options and feel able to take up these services if required, this is likely to be of benefit. If a longer term break can't be achieved or is desired, encouraging caregivers to consider short breaks or some time to themselves should be proposed as a way of assist them to sustain their role.

Caregivers can benefit from support directed at them

Studies repeatedly demonstrate the importance of social support for caregivers. A literature review published in 2003 on the psychological impact on partners of cancer patients reported that being involved in the care of a cancer patient may place someone at higher risk of psychological morbidity or experience relationship difficulties if they do not have support[33]. In a more recent interview study of 29 caregivers of people with varying cancer diagnoses, the quality of the relationship between the carer and patient was suggested as a factor that might contribute to a caregiver coping well with the role[34]. In a study of patients with early-stage cancer and family caregivers, caregivers with higher levels of social dependence (defined as those needing help from other people in order to conduct tasks) were found to have more physical caregiving tasks but also higher self-esteem[2].

Support may come from several sources. Caregivers of patients with advanced cancer were shown to have higher quality of life if they were employed[5]. While this finding could indicate that work is a form of support, it may also indicate that patients aligned with these specific caregivers may not have been as unwell, as the caregiver was able to continue working. Other studies have provided evidence of the importance of relationship between the carer and patient. In a study of 101 advanced cancer patients and spousal caregivers, martial dissatisfaction was associated with depression[35]. The notion that support from family, friends and neighbours is important has been supported in quantitative studies with people currently providing care[36] and also from studies of bereaved caregivers[37]. Support may come in the form of having a break through the involvement of others, but also through simply participating in usual and valued activities. When the ability to engage in valued activities has been limited, family caregivers of advanced cancer patients have been shown to experience higher levels of distress than those who experience less lifestyle interference, as demonstrated with an structured interview study with 44 caregivers of advanced cancer patients[38]. Compared with caregivers that have higher social support, poorly supported caregivers have lower quality of life[39] and higher burden[40]. Evidence indicates that if caregivers feel supported, they may be better able to meet patient needs: whereas caregivers who do not have support are more likely to have a patient with unmet needs[41].

Health care professionals have a role to play in reducing the burden of caregiving through provision of caregiver support[42]. Caregivers of patients with advanced cancer are more likely to report reduced carer burden if they have a good relationship with the family, but also with the health care professionals involved in the patient's care[43], indicating that clinicians have a central role in providing support to caregivers. A large interview study of 1858 bereaved cancer carers reported that support from district nurses resulted in reduced levels of bereavement-related, psychological problems and an increase in viewing the caregiving role positively[44]. These findings were supported by data from a sample of bereaved caregivers who regretted not seeking out more resources and support to assist them with their caregiving role[45].

It is, therefore, important that caregivers are well supported in their role. They should be encouraged to access and consider support from a range of sources including friends, other family and clinical services. Asking caregivers to consider where they need help may help legitimise their need for support in a role acknowledged to be complex and challenging. Making sure carers have someone to talk about their needs may encourage and enable a caregiver to access support for themselves.

Recommendations

This literature review has resulted in several key observations relevant to assisting caregivers. Firstly, as caregivers are a diverse group made up of family members, friends or neighbours, exploring who is involved, their capacity to care and their understanding of the disease and treatment is important. Secondly, caregivers should be encouraged to consider their own needs and recognise when and where they need help to sustain the caregiving role and to ensure their wellbeing. Thirdly, it should be acknowledged that the caregiving role consists of more than attending to physical chores, medication management, symptom management and transport. Rather, it is a complex role that demands attention to emotional and non-physical aspects of patient need and this diversity of caregiving requires acknowledgement and consideration. Caregivers should be encouraged to consider the patient and carer-related benefits of taking a short break as needed and they should be helped to identify supports from various avenues including family, friends, health professionals, support groups and community-based cancer help services.

When providing advice such as the need for a break or accessing support, evidence indicates that caregivers are unlikely to be focused on or receptive to discussions about their own needs[20.] As such, health care professionals must be aware that carers may have difficulty identifying or be unprepared to respond to questions about their own needs and coping capacity. As such, it is suggested that caregivers should be asked regularly how they are coping and be encouraged to consider accessing support for themselves as carer tasks differ or as new needs emerge. Where carers choose not to access support, exploration of support needs and provision of information should be followed up and reinforced, as caregivers may wish to take up these opportunities later. When offering support and assistance, being familiar with national and local resources is important to identify what may be appropriate to each person.

In an attempt to engage with caregivers, it is important that health professionals recognise that carers may not think of themselves in this way[15]. However, asking them how they are coping and whether there is anything in particular they are finding difficult may be one way in which help can be provided. Providing contact details and letting carers know that professionals expect they will need help at some stage during their caregiving role may help legitimise their need for support and assistance. The contacts established between health care professionals and carers should be followed up over time and offers of assistance extended at differing stages.

Conclusions

The caregiving role is broad and varied and dependent on patient need. Caregivers are vital to the support of people with advanced cancer and, in turn, need support from clinicians. This paper outlines key findings from the literature in order to provide health professionals with important considerations when engaging caregivers. Most importantly, by simply asking caregivers how they are and whether they need help, is likely to encourage and enable caregivers to consider their own needs and to begin the essential work of taking care of themselves in this important role.

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Terminal delirium

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Abstract

Delirium is common in terminally ill patients and is associated with increased morbidity and mortality. Often misdiagnosed and poorly managed due to the similarity in presentation with pain and other psychological disorders such as dementia and depression, it is a distressing symptom for patients, their families/caregivers and health care professionals.

The pathogenesis of delirium is multifactorial, complex and poorly understood and no single cause has been identified to date. Management of delirium requires accurate assessment and investigation of potential causes and may include both non-pharmacological and pharmacological strategies. Palliative sedation may be required in some cases, but this strategy remains controversial.

Difficulties identified included a lack of awareness and poor recognition of delirium, a paucity of definitive assessment tools for both delirium and pain at the end of life and the underuse of assessment tools that are available. The routine use of medications at the end of life may cause or exacerbate delirium.

Introduction

Delirium and pain are common symptoms at the end of life. Delirium is a complex psychiatric syndrome that reaches prevalence of greater than 80% in the final days of life[1-4]. It is associated with increased mortality and morbidity[5] and may be the first sign that heralds the "difficult road to death"[6]. It is an independent predictor of mortality in advanced cancer and irreversible delirium heralds a poor prognosis[7]. Pain is reported to have a 70–80% prevalence in advanced terminal illness, regardless of the underlying diagnosis and it has been found that 40% of patients had "severe pain most of the time" in the last three days of life[3].

This paper focuses primarily on terminal delirium, identifying causative factors and examining appropriate management. It discusses the difficulties faced in assessing terminal delirium, comparing presenting features with those of pain at the end of life when a patient is unresponsive, requiring visual assessment by the health professional (Table 1). Two case studies and a review of patients' notes will also be presented.

Terminal delirium

Delirium is common in patients with advanced illness nearing death, often presenting as confusion, restlessness and/or agitation, with or without day/night reversal[8]. Delirium is subdivided into three subtypes: hyperactive, hypoactive and mixed (Table 2). Agitated (hyperactive) terminal delirium can be very distressing for the family and caregivers who do not understand it, although it is reported that the hypoactive and mixed subtypes are more commonly encountered in palliative care (~70%) and hypoactive delirium may often initially be misdiagnosed as depression[1,9].

Communication between the patient, their family/caregiver and health professionals may be difficult, compromising patient autonomy, treatment decisions and symptom assessments[10]. Whilst terminal delirium may be reversible in approximately 50% of cases, it is a condition that is often under-diagnosed and poorly managed[4,10]. Agitated terminal delirium is often misdiagnosed as pain[11,12] and, whilst Emanuel *et al.*[8] state that "it is a myth that uncontrollable pain suddenly develops during the last hours of life when it has not previously been a problem", Twycross *et al.*[2] claim that pain is, in fact, a common development at the end of life.

Table 1. Comparison of presenting features in non-communicative patients[32,33,52,55,56].

Pain	Delirium
Vocalisation • Whimpering; groaning; crying	Vocalisation • Moaning; groaning; mumbling
Facial expressions • Looking tense; frowning; grimacing	Facial expressions • Variable, but may look disturbed or frightened; twitching
Changes in body language • Fidgeting; rocking; guarding; withdrawn	Changes in body language • Increased, decreased or mixed; fidgeting; withdrawn
Behavioural changes • Increased confusion; refusing to eat; alteration in usual patterns	Behavioural changes • Increased confusion; pulling out IV lines or urinary catheters; trying to climb out of bed; picking at object in the air; may be worse at night; reversed sleep/wake cycle
Physiological changes • Temperature, pulse or blood pressure outside normal limits; perspiring; flushing or pallor	Psychological changes • Perseverate in answers; forgetful; altered alertness, attention and orientation (may fluctuate); reduced consciousness; hallucinations; delusions
Physical changes • Skin tears; pressure areas; arthritis; contractures	Speech • Often incoherent; slow or rapid; may call out repeatedly or repeat the same phrase

Table 2. Delirium subtypes: frequency and manifestations[1].

Hyperactive (~15%)	Agitation; anxiety; insomnia; hallucinations; nightmares; combative/violent behaviours; loud, abnormal speech patterns
Hypoactive (~19%)	Decrease in physical activity; lethargy; somnolence; apathy; depression; withdrawn; mental clouding
Mixed (~52%)	Combined features of both hyperactive and hypoactive delirium

Causative factors

There are many potential causes of delirium and an understanding of these, as well as its assessment, is essential for the palliative care clinician.

Polypharmacy[13-19]. Medication is reported to be implicated in 12–40% of all patients with delirium[15]. Generally, patients taking three or more medications are at greater risk of medication-induced delirium, especially those medications with psychoactive effects and high anticholinergic potential[18,20]. Medications with psychoactive effects have been linked with the occurrence of delirium in 15–75% of cases[18]. Interestingly, a study by Gaudreau *et al.*[21] found no association between anticholinergic medications and delirium, though only a very short list of anticholinergics was recorded and no dose weighting was described.

Metabolic disturbances[13-16,18,19,22,23]. It is understood that the cholinergic system is involved in arousal, attention, memory and rapid-eye-movement (REM) sleep[18]. It is believed that impairment of central cholinergic transmission may result in delirium with reduced levels of acetylcholine in plasma and cerebrospinal fluid (CSF) found in some patients with delirium[15,18]. Electrolyte, glucose and renal abnormalities are risk markers and causes of delirium[13-15,22].

Uraemia secondary to renal failure is known to cause delirium[13,24].

Dehydration[18,19,23] may cause cognitive dysfunction and delirium in a number of ways: by causing intracellular changes leading to cytokine concentrations, pharmacokinetics and anticholinergic burden; intravascular volume depletion, causing reduced cerebral perfusion, thromboembolic disorders and cardiac ischaemia; extravascular changes that may lead to water and electrolyte imbalances, contraction alkalosis and renal failure; damage to neuronal mitochondria and glutamate hypertransmission[18]. Dehydration may also cause deranged concentrations of drugs and/or their metabolites and decreased elimination of drugs, metabolites and toxic waste by the kidneys[18].

Immobility[15,19]. Animal studies have demonstrated that widespread acetylcholine reduction may be caused by immobility.

Malnutrition[17,19]. Reduced nutritional intake may result in lowering of serum protein and blood glucose levels as well as micronutrient deficiencies (vitamins, minerals, trace elements and antioxidants). However, low serum protein and polypharmacy may present the highest risk factors for delirium, as many medications bind to proteins and a reduction in serum protein level is likely to cause an increase in the serum drug levels[17]. Conversely, re-feeding syndrome, a potentially fatal complication in the treatment of malnourished patients, has also been shown to be a risk factor in the development of delirium[25].

Infection[13,19,23,24] is known to increase arterial ammonia levels. Spontaneous bacterial peritonitis is an infection of ascitic fluid where no secondary source (such as perforated viscus) is identified and is almost always seen in the setting of end-stage liver disease. Altered mental state is one of its manifestations. It is claimed that nearly 60% of all patients with compensated cirrhosis will develop ascites[24].

Opioid medications[7,18,19,26]. Opioids may cause delirium by increasing dopamine and glutamate activity and decreasing acetylcholine activity. Opioids are implicated in the development of delirium in nearly 60% of patients with advanced cancer[18].

Hypoxic encephalopathy[13,14,18,19,22]. One delirium hypothesis, the 'oxygen deprivation hypothesis' proposes that cerebral dysfunction occurs because of various neurotransmitter system abnormalities, caused by decreased oxidative metabolism in the brain[18]. Hypoxia is implicated in impairment of cholinergic neurotransmission, discussed previously[18].

Pain[19]. The relationship between pain and delirium is complex. Although under-treated pain causes agitation and confusion, opioid use often precipitates delirium that can be reversed by adjusting dosage[19].

Sleep deprivation and sleep pattern disruption[18] may be both a causative and an exacerbating factor of delirium. Delirious patients are often reported to have irregular melatonin release patterns[18,27].

Constipation[26,27] may cause delirium due to increasing of ammonia levels and pain[27].

The pathogenesis of delirium, however, is often multifactorial[11], complex and poorly understood[12]; indeed, the 'cause-and-effect' mechanistic approach to diagnosis may fail to explain many cases of delirium[13] and it is claimed that the cause for delirium can only be found in as few as 44% of patients[29]. No single cause for delirium has, to date, been identified; therefore, investigations and management should be based on a thorough history and consideration given to the stage of disease, prognosis and likelihood that a reversible cause can be found[7,14,29].

Case study 1

Mr A was a 68-year-old gentleman admitted as an emergency under a general surgical team with anaemia, renal failure and worsening abdominal pain. He had no significant past medical history and was not taking any medications prior to admission. In the emergency department he was prescribed morphine as required (PRN) for the abdominal pain.

Investigations showed a caecal mass and he underwent a right hemicolectomy. He had an eventful postoperative recovery, with transfer to the intensive care unit (ICU) following a cardiac arrest on the ward five days after his surgery. In ICU he was intubated and a tracheostomy was performed 11 days later. He was in ICU for 21 days and was successfully weaned off the ventilator two days before discharge from ICU.

Two days before discharge from ICU he was described in the nursing notes as "anxious at times, easy to reassure" and suffering from "night time awakening". The next day the nursing notes recorded that he was becoming "agitated when being washed"; it was also recorded that he "denies any pain". On the day of discharge from ICU he is described as being "aggressive, confused, agitated".

Although no formal assessment tools were used, Mr A was prescribed and given morphine PRN for distress/agitation. He was given morphine and hyoscine hydrobromide (hyoscine) for "anxiety and increased resps [sic]". He was reported, six days before death, to be "unresponsive", though was given morphine "for discomfort" at which stage he was prescribed morphine 50 mg, clonazepam 2 mg, hyoscine hydrobromide 1200 mcg over 24 hours via a continuous subcutaneous infusion device. He was also prescribed intravenous (IV) fluids "to make the family feel better". He continued to receive escalating doses of PRN morphine (and occasionally hyoscine) for "breakthrough", "agitation", "moaning" and "distress", the last injection given less than one hour before he died.

Case study reflection

It appears that a lack of formal assessment and management tools contributed to the suboptimal management of Mr A's condition. Clinicians frequently do not recognise and, therefore, misdiagnose delirium. It is recommended that delirium should be presumed until proven otherwise, given the high prevalence of delirium in populations such as ICU patients, cancer patients, the hospitalised elderly and the terminally ill[1]. Research by Gaudreau *et al.*[21,26] showed that the use of psychoactive drugs, such as opioids and benzodiazepines, increases the risk of developing delirium. Undesirable effects of hyoscine may include central antimuscarinic (anticholinergic) syndrome including agitated delirium, confusion, restlessness and drowsiness[20,30]. Yennurajalingam *et al.*[31] claim that it is likely that nurses and physicians misinterpret agitation in patients with agitated delirium as an expression of pain and that delirium may be aggravated when the diagnosis of delirium is not considered and, therefore, treated as pain with the administration of increasing doses of opioids. Cognitively impaired patients may, conversely, be at risk of inadequate pain control due to their inability to communicate information about their pain[32]. This is a particularly challenging situation and ascertaining whether the patient's distress is due to pain or delirium may guide the clinician as to the most appropriate treatment, whether it be an analgesia or an antipsychotic[7].

This was a distressing time for Mr A's family as they had no understanding of delirium. The possibility of a diagnosis of delirium was only considered after being seen by palliative care nurses on the day of his death, by which time it was not possible to improve the situation. Misdiagnosed or poorly managed delirium has the potential to cause distress for the family and their memory of the patient's death may be that of a very unpleasant experience[11].

Assessment

Comprehensive assessment on an ongoing, consistent basis is essential for the effective management of delirium. A literature review reveals that the main consideration should be a structured and holistic assessment that includes interview, physical assessment, medication review, medical review (with appropriate diagnostic investigations), sleep patterns, psychosocial review and review of the physical environment[10].

The diagnosis of delirium is usually based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria (Table 3).

Table 3. DSM-IV criteria for diagnosing delirium due to a general medical condition[28].

A	Disturbance of consciousness (that is, reduced clarity of awareness of the environment) with reduced ability to focus, sustain and shift attention
B	A change in cognition (that is, memory deficit, disorientation, and language disturbances) or perception disturbances not better explained by a pre-existing established or evolving dementia
C	The disturbance develops over a short period of time (usually hours or days) and tends to fluctuate during the course of the day
D	There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition

A number of instruments are available for the assessment of delirium, of which the most commonly used are the Mini-Mental State Exam (MMSE), the Memorial Delirium Assessment Scale (MDAS), the Delirium Rating Scale (DRS) and the Confusion Assessment Method (CAM)[28,33]. A recently developed instrument that is gaining popularity due to its ease-of-use is the Nursing Delirium Screening Scale (Nu-DESC)[7,34]. These instruments are outlined in Table 4.

Table 4. Delirium assessment instruments[1,7,9,28,34,52].

MMSE	Screens for cognitive impairment, but does not distinguish between delirium and dementia. Measures severity of cognitive impairment. Assesses five general cognitive areas: orientation; registration; attention/calculation; delayed recall; language. Routine use to identify and monitor delirium is inappropriate.
MDAS	Ten-item delirium assessment tool. A good diagnostic screening tool as well as assessing delirium severity. Has replaced the MMSE in some institutions for examination and monitoring of delirium. Validated in advanced cancer patients in a palliative care unit.
CAM	Nine-item diagnostic scale. Ninety-four per cent sensitivity and 89% specificity for diagnosing delirium, but only when applied by specialists. Not validated for use by health professionals in palliative care setting.
DRS	Most widely used instrument. Useful in assessment of delirium in terminally ill. Has the best results for screening severity. Lacks administrative ease for clinicians. No literature available on its use by nurses.
Nu-DESC	Observational five-item scale. Gaining popularity. Easy to use. Validated to screen and monitor patients with delirium. Eighty-six per cent sensitivity and 87% specificity when used by nurses (comparable to MDAS).

The Delirium Index is a seven-item instrument that measures the severity of symptoms of delirium based solely on observation of the patient. It was designed to be used with the MMSE, at least the first five questions of which comprise the basis of observation. This may cause a considerable problem in the terminally ill patient, as described in Table 4.

A retrospective review of deceased patients' notes

Following a literature review on terminal delirium, a retrospective review of the medical records of nine deceased patients, all of whom had been referred to the palliative care nurses with difficult-to-manage "pain", was undertaken by the author to examine their end-of-life symptom management. Approval to conduct and publish this audit was sought and obtained through the Nursing Quality and Research Department in the hospital in which the author is employed. Only information recorded from the patients' final admission was collected, in order to confine the audit to the management of the patients' end-of-life phase.

Seven male and two female patients with an average age of 75 (range 46–94, eight over 60) were reviewed. They were being treated by a wide range of disciplines, though the majority were under the care of general medical physicians (4). The remainder were under the care of surgical, oncology, gastroenterology, orthopaedic and vascular teams (one each).

The primary diagnoses identified were dementia (4), cancer (2) and non-malignant diseases in the remaining three. In three cases the reason for admission was a fractured neck of femur (following a fall) and "increasing confusion" was recorded as a co-admitting symptom in four cases.

All patients were recorded as having multiple comorbidities including depression, dementia or Parkinson's disease, either alone or a combination. One patient had had a recent admission for "severe delirium". All of the patients, except one (case study 1) were taking multiple medications prior to admission and five were taking at least one opioid.

No formal delirium assessment tool was used at any time for six patients and, of those that were used, none were used within one week before death. In one case an abbreviated Mental Test (AMT 4) score of 2 out of 4 (indicating a high degree of cognitive impairment) was recorded 19 days before death with no further assessment recorded. Another patient had a score of 4 out of 4 on admission (normal cognition) 16 days before death and 1 out of 4 one week before death. These were the only assessment scores recorded for this patient. No formal pain assessment tools were used on any of the nine patients.

Descriptors used for reporting in the medical records included "agitated", "aggressive", "confused" (Table 5). All cases were treated with escalating doses and/or frequency of morphine (Table 6). In seven cases a continuous subcutaneous infusion was used and in all but one of these (case study 2) morphine was included at doses ranging from 30 mg/24 hours to 100 mg/24 hours. A benzodiazepine (midazolam or clonazepam) and another drug (haloperidol, metoclopramide or hyoscine hydrobromide) was included in these six.

The apparent "pain" was poorly controlled in all but two patients until death as evidenced by the continued use of "breakthrough" morphine and descriptors used until death

Table 5. Symptom descriptors used in patients' medical records.

Agitated
Aggressive
Confused
Restless
Pulling at IDC
Pain
Drowsy
"Moans and groans"
Encephalopathic
Unsettled
Totally disorientated
Drowsy but rousable
Confused and distressed
"Mumbling/screeching incomprehensible sounds, trying to climb out of bed"
"Confused at times, unresponsive with some moans and groans"

Table 6. Management strategies as recorded in patients' medical records

"IVT to make family feel better" (nurse report)
Subcutaneous fluids increased from 40 to 60 ml/hour due to decreased urine output one day before death
"Adjust Graseby to ongoing pain management" (doctor report)
"Morpine PRN as unsettled" (nurse report)
One day before death, nurse reports: "PRN morphine only providing quick/short acting relief"

(Table 5). In these two patients haloperidol was used with midazolam (one with 30 mg of morphine, one without) in a continuous subcutaneous infusion.

Treatment of delirium

Maldonado[18] recommends a multilevel approach in the treatment of delirium that addresses the many pathways leading to the development of delirium. This may give a better chance of effectively preventing and treating delirium. Caraceni and Simonetti[28] claim that:

> *… providing safety, companionship, orientation, a quiet environment, emotional support to both the patient and the care-givers, and a caring relationship can avoid pharmacological and eventually physical restraint in many patients with mild to moderate symptoms, and will probably improve the outcome of therapy in all cases.*

Non-pharmacological and environmental strategies are under-utilised and tend to be used as a response to behavioural disturbances rather than to the degree of cognitive impairment[15,16]. Strategies for providing support and orientation, an unambiguous environment and maintaining competence are given by Attard *et al.*[16] Bourne *et al.*[35] state that most recommendations for management of delirium are based on the treatment of the underlying condition and non-pharmacological supportive care. The process of delirium may be reversible even in patients with advanced illness, though it may not be reversible in the last 24–48 hours of life, most likely due to irreversible processes such as multiple organ failure occurring at this time[36]. A shift in focus from being classed as a psychiatric disorder to that of a natural end-of-life syndrome may, therefore, be appropriate.

Attard *et al.*[16] recommend that pharmacological treatment should only be considered in patients whose delirium symptoms may threaten their own safety, or that of others. However, delirium in the last few hours or day or two of life is, by definition, irreversible and the management of the symptoms should be the focus of care[8]. Harlos[3] and Glare[37] state that at this stage there may be no purpose attempting to find and reverse possible causes for delirium, although there may still be a role for intervention, after consideration of the benefit versus burden[7] and a simple blood test to assess hypercalcaemia, electrolytes, glucose and white cell count may be warranted as these may be easily diagnosed and treated[3,37]. When pharmacological management is appropriate, the use of antipsychotic medication (usually haloperidol) is recommended[14,19,22] though its use is not well supported by evidence and it is unclear whether newer, atypical antipsychotics are superior to haloperidol[38].

The hospital in which this author is employed (medium/large, acute, metropolitan) utilises a delirium algorithm that recommends the use of pharmacological interventions only after all other prevention and management strategies have been employed[39], although this may not be appropriate during the dying phase[8]. In the author's experience, if delirium is recognised at this time, the first-line treatment is usually administration of haloperidol with or without a benzodiazepine (most often with morphine included), via a continuous subcutaneous infusion. This pharmacological approach is supported by Emanuel *et al.*[8]

There may be a role for sedation in refractory delirium when all other treatment options have failed. The aim of palliative sedation is the comfort of the patient and relief of suffering. Lowering of consciousness is a means to achieve this[40]. Chang[33] also states that palliative sedation may be required at the end of life as terminal delirium, by definition, does not respond to conventional pharmacological management. Palliative sedation is reported as safe in the majority of patients (80%) and many empirical studies confirm that sedation has no apparent effects on patient survival[41].

A complete assessment and critical analysis of the patient, the symptom and the health care environment should be performed before a decision to sedate is made. This should include the likely aetiology of the symptom and the risks and benefits of any investigation and intervention[42].

When all other treatment options have been exhausted, full discussion with the patient (where possible), family and carers should be carried out to confirm the desired level of care[43]. A consensus is sought on the individualised goals of care that is based upon the disease and comorbidity, prior level of functioning and quality of life, level of distress and the patient's prior expressed wishes[7].

Case study 2

Mr B was a 78-year-old gentleman with metastatic bladder cancer. He was referred to the palliative care service for consultation as the treating medical team were unable to control his pain, despite prescribing large amounts of opioids. A review of his medical record revealed that this gentleman had received morphine regularly over the previous 48 hours, totalling around 200 mg each 24 hours. Descriptors used by nurses and medical staff included "pain +++", "distress", "agitation" and "confusion", for which morphine was given. His medical history included alcoholic liver disease. A CT scan of the abdomen revealed a very large, cirrhotic liver with multiple metastases. On examination, Mr B was noted to be jaundiced with a very large, tightly distended abdomen. He was unresponsive to verbal stimulus and in obvious distress, writhing around and trying to climb out of bed, calling out incomprehensible words and pulling at an indwelling catheter (IDC), peripheral IV lines and bed sheets. He showed no obvious signs of pain on palpation of his abdomen. His vital signs were generally unremarkable. Five family members were present in the room, crowding the bed and distraught at the current situation, claiming nothing was being done for his pain and distress. No formal assessment tools were used by nursing or medical staff, who had acted on the family members' requests for analgesia.

The palliative care nurse instigated assessment using the Delirium Index, which gave a score of 18 out of 21. This revealed a high probability for delirium and, as such, a change of focus for management of delirium was initiated. This included educating family members as well as nursing and medical team. Family members were advised that crowding around his bed was not recommended and that only one or two people should be close to the bedside at any time (though others could be in the room) and that gentle touch and quiet reassurance was appropriate.

Following long discussion with family members, pharmacological management was determined to be the best option as Mr B's prognosis appeared to be so short. They were advised that this management plan may result in the sedation of Mr B to alleviate his suffering and they agreed to this. This was recorded in his medical record. He was commenced on haloperidol 1 mg hourly PRN as per Health Department guidelines for management of terminal agitation[44]. Mr B required this dose for the next four hours, whereupon he was started on a continuous, subcutaneous infusion of haloperidol 5 mg and midazolam 10 mg over 24 hours. This is slightly more than the guidelines stipulate, though it was deemed appropriate due to his level of agitation. Twycross *et al.*[2] state that doses of 10–20 mg/24 hours for haloperidol and 10–60 mg/24 hours of midazolam may be appropriate. He was also prescribed haloperidol 1 mg hourly PRN of which he required only three further doses before his agitation resolved. Mr B died two days later with no further obvious agitation, distress or discomfort. His family members were present throughout and were grateful for his comfortable, dignified death.

Case study reflection

This case shows the importance of accurate assessment in the management of symptoms. It was reasonable to assume that Mr B may have had pain due to his hugely distended liver and abdomen and an empirical trial of morphine was appropriate[33]. Risks exist, however, when pain management continues without relief, as opioids and other medications used in the terminal phase can cause or exacerbate delirium[7,18,19,26,45].

Delirium was suspected based on clinical judgement and the use of the Delirium Index helped confirm the diagnosis, enabling a refocus to more appropriate management.

O'Malley *et al.*[46] and Breitbart and Alici[47] found that "76% of spouses/caregivers and 73% of nurses reported severe distress related to delirium". Distress levels were higher for spouses and caregivers than for nurses or patients themselves. Namba *et al.*[48] found that, whilst many families were distressed by delirium, others felt the delirium was a relief from real suffering.

Mr B's family was certainly distressed at first, feeling that nothing was being done to help him, although when provided with an explanation and information about delirium and the change in management, they were much more reassured.

In order to ensure that the needs of the patient are treated and not the pressure of family or staff, it is important for the palliative care clinician to explain the medical nature of delirium, as well as potential treatment options, including palliative sedation[47]. Multidisciplinary interventions and supportive and psycho-educational approaches are needed to alleviate family distress related to a misconception that agitation is a sign of extreme pain or that the patient is "losing their mind"[49,50].

A study by Brajtman[51] concluded that treatment decisions have implications involving many personal, emotional and ethical challenges for the interdisciplinary team and that informal and formal support for team members is required to meet the complex care needs of this patient and family population.

Bruera and Dev[52] suggest that brochures and other written materials can improve communication between health care providers and patients and families, though this depends on their understanding, which may be limited. This author's hospital provides written information, in the form of patient information and advice booklets that aim to provide some level of education for patients and the families/carers. One of the booklets focuses on delirium, providing information about symptoms and causes and includes advice on how to care for someone with delirium[53]. Another booklet gives information on the dying process, including terminal restlessness[54]. Anecdotally, these booklets have proven to be invaluable for families/carers to alleviate some of the fear around delirium and the dying process and as an education tool for staff members. Education for nursing, medical and allied health staff is provided, both formally as part of study days and in-service and informally during consultations. It includes an emphasis on recognising and managing delirium and appears to have had a positive effect (anecdotal) on staff who now at least talk about terminal delirium. Further research is required into this area and a follow-up audit is planned in the near future to determine whether there has been a change in practice.

Conclusion

Delirium is a common symptom in the terminally ill patient. Agitated delirium, whilst being the most familiar subtype, actually occurs in the minority of cases. Hypoactive and mixed subtypes occur in about 70% of cases.

Delirium is frequently misdiagnosed and poorly managed due to similar presentations with pain and other psychiatric disorders, including depression and dementia. No definitive assessment instrument exists at this time, though some show promise.

The pathogenesis of delirium is often multifactorial and investigation of the aetiologies, correction of any identifiable causes and management of symptoms, including non-pharmacological and pharmacological approaches, are recommended, though this may be inappropriate at the end of life, when delirium is likely to be irreversible. Delirium may be classed as a natural end-of-life syndrome, rather than a psychiatric disorder.

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A Cochrane review on the effects of end-of-life care pathways: Do they improve patient outcomes?

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Abstract

Clinical pathways for end-of-life care management are used widely around the world and have been regarded as the gold standard. The aim of this review was to assess the effects of end-of-life care pathways (EOLCP), compared with usual care (no pathway) or with care guided by a different end-of-life care pathway, across all health care settings (for example, hospitals, residential aged care facilities, community). We searched the Cochrane Central Register of Controlled Trials (CENTRAL), the Pain, Palliative and Supportive Care Review Group Specialised Register, MEDLINE, EMBASE, review articles and reference lists of relevant articles. The search was carried out in September 2009. All randomised controlled trials (RCTs), quasi-randomised trials or high-quality, controlled, before and after studies comparing use versus non-use of an EOLCP in caring for the dying were considered for inclusion. The search identified 920 potentially relevant titles, but no studies met criteria for inclusion in the review. Without further available evidence, recommendations for the use of EOLCP for the dying cannot be made. There are now recent concerns regarding the big-scale roll-out of EOLCP despite the lack of evidence; nurses should report any safety concerns or adverse effects associated with such pathways.

* This paper is based on a Cochrane Review published in The Cochrane Library 2010, Issue 1 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

Introduction

It is well recognised that populations in developed countries are ageing[1]. As populations age, the pattern of diseases that people die from also changes[2]. With advanced ageing, there is an increased risk of death from chronic diseases such as cancer and heart failure[3]. For example, cancer was estimated to account for about seven million deaths (12% of all deaths) worldwide in 2000[3]. Therefore, palliative care has been identified as one of the worldwide public health priorities due to the ageing population[2]. Palliative care is concerned with "the quality of life of patients and families who face life-threatening illness, by providing pain and symptom relief, spiritual and psychosocial support from diagnosis to the end of life and bereavement"[4]. End-of-life care focuses on the last days and hours of life[5] and the need to provide high-quality care at this time is essential. The needs of dying people may include, but are not limited to, knowing when death is coming, understanding what can be expected, being able to maintain a sense of control and having their requests given preference, having access to information and excellent care, and having access to spiritual and emotional support as required[6]. Quality end-of-life care may vary from person to person and may be difficult to define and accurately measure. However, such care should at least include the following domains: quality of life, physical symptoms, emotional and cognitive symptoms, advanced care planning, functional status, spirituality, grief and bereavement; satisfaction and quality of care, as well as caregiver wellbeing[7]. Obstacles to quality end-of-life care have also been identified and may include failure to recognise treatment futility, lack of communication among decision-makers, no agreement on a course of end-of-life care, and failure to implement a timely end-of-life plan of care[8]. In recent years, there has been a variety of initiatives developed worldwide to target such issues by developing systematic approaches towards end-of-life care. These initiatives include programs such as the National End of Life Care Strategy[9], Gold Standards Framework in Care Homes[10] and the Liverpool Care Pathway (LCP)[11,12].

Integrated care pathways are documents that outline the essential steps of multidisciplinary care in addressing a specific clinical problem. They can be used to introduce clinical guidelines and systematic audits of clinical practice[13]. The LCP is an example of an integrated care pathway specifically for the dying phase of palliation.

Historically, dying patients receiving general hospital care tended to lack adequate attention from senior medical staff and nursing staff[14]. The quality of symptom control and basic nursing care were considered to be inadequate[14]. It was thought that much could be learned from the way patients were cared for in the hospice movement[14]. The LCP is a model of best practice developed by the Royal Liverpool University Trust and the Marie Curie Centre Liverpool[11,12], based on the care received by those in the hospice setting. Other objectives of the pathway were to promote cost-effective health care by appropriate prescribing, and avoiding crisis interventions and inappropriate hospital admissions. The document is patient-centred and focuses on the holistic needs of people who are dying. It incorporates the physical, psychological, social, spiritual and religious aspects of care[15]. The LCP defines 19 goals considered essential in the management of dying patients and for the care of their relatives/carers after death[11,12]. These goals were established with the issues identified from surveys, focus groups, expert opinion and consensus best practice.

Later, several other groups developed care pathways for the dying based on the concept of Ellershaw and colleagues[16-18]. Whilst the professional conjecture is that end-of-life care pathways (EOLCP) promote best possible patient outcomes[15], recent speculations have suggested possible adverse effects. These adverse effects included premature use of the pathway, leading to death due to the premature diagnosis of imminent death, the care pathway masking the signs in improvement in patients and causing carers' dissatisfaction[19,20]. Therefore, a systematic review is warranted to substantiate claims as to whether the EOLCP are beneficial or harmful for dying patients and their carers.

Methods

The primary objective of this review was to assess whether EOLCP improve outcomes of the dying across all health care settings (hospitals, residential aged care facilities, community). In particular, we aimed to assess the effects on symptom severity and quality of life of people who are dying and/or those related to the care such as families, caregivers and health professionals.

Search strategies

The standard methodology of the Cochrane Collaboration was used. We searched the Pain, Palliative and Supportive Care Review Group Specialised Register (September 2009), the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 4, 2009), Medline, EMBASE, CINAHL and PsycINFO. All databases were searched in September 2009). The following search terms were used: "palliative care"; "end-of-life"; "terminally ill"; "hospice$"; "end-stage"; "dying"; "critical pathways"; "guidelines"; "protocol"; "professional standard"; "care plan$ or map$"; "clinical or critical or care path$". The dollar sign was used to retrieve all possible derivations of the root words. Hand searching of palliative care journals and relevant conference proceedings was performed. There was no restriction by language or date of publication. Reference lists of all retrieved articles were searched for additional studies.

Inclusion and exclusion criteria

Two authors reviewed each paper independently. We considered randomised controlled trials (RCTs), controlled clinical trials and controlled before and after studies as meeting explicit inclusion and quality criteria used by the Cochrane Effective Practice and Organisation of Care (EPOC) group. To be eligible for review, controlled before and after studies had to include: (1) contemporaneous data collection; (2) appropriate choice of control site; and (3) a minimum of two intervention sites and two control sites. We did not plan to include any non-controlled studies[21]. Participants in the included studies were to be patients and families who received care guided by an EOLCP. Participants included may have had different diseases such as cancer or organ failure. However, participants who received interventions must have been receiving care guided by an EOLCP for their last days and hours of life. There was to have been no restriction on the age of the patient, diagnosis or setting (hospital, home, nursing home). There was to have been no age limit for participants included in this review.

Results

In total, 920 titles and abstracts were retrieved in electronic format and assessed.

Included studies

No studies fulfilled the study eligibility criteria.

Table 1. Characteristics of excluded experimental studies.

Excluded studies	Reasons for exclusion	Other characteristics
Bailey 2005, USA[22]	Before and after study (without control)	**Participants:** pre=108, post=95 (patients with cancer and end-stage disease). **Pathway:** End-of-life care plan. **Main outcomes:** Increased mean number of documented symptoms, number of care plans, opioid medication availability, do-not-resuscitate orders, and the use of restraints in the post-intervention group. **Notes:** Changes in the proportion of deaths that occurred in intensive care units and the use of nasogastric tubes were not statistically significant. The end-of-life care plan was part of a larger intervention with a focus of improving processes of care.
Bookbinder 2005, USA[16]	Controlled before and after study: non-contemporaneous data collection, non-comparable sampling	**Participants**: Pre=101, post=156 **(**patients with cancer and end-stage disease). **Pathway:** The Palliative Care for Advanced Disease pathway (PCAD). **Main outcomes:** Patients in the experimental units were more likely to have do-not-resuscitate orders, the comparison units were more like to have morphine infusions and cardiopulmonary resuscitation.
Luhrs 2005, USA[24]	Controlled before and after study: non-contemporaneous data collection, non-comparable sampling and does not have at least two intervention and two control sites	**Participants:** pre=28, post=29 (patients from a medical and an oncology unit). **Pathway:** The Palliative Care for Advanced Disease pathway (PCAD). **Main outcomes:** Patients on the PCAD were more likely to have documentation of care goals and plans of comfort care, fewer interventions and more symptoms assessed, more symptoms managed as per guidelines.
Okon 2004, USA[25]	Controlled before and after study: does not have at least two intervention and two control sites	**Participants**: 54 internal medicine residents (medical officers). **Pathway:** Integrated end-of-life clinical pathway: the PEACE tool. **Main outcomes:** Mean end-of-life care knowledge scores of the internal medicine residents were 46% higher in the intervention group compared to the control group.
Taylor 2007, New Zealand[37]	Before and after study (without control)/audit	**Participants**: pre=20, post=10 (patients in a residential aged care facility). **Pathway:** Liverpool Care Pathway. **Main outcomes:** There was an increase in pre-emptive medication prescription within one residential aged care facility. **Notes**: The pre-post comparison included only medication prescriptions.
Thompson-Hill 2009, UK[38]	Before and after study (without control)/audit	**Participants**: 20 patients. **Pathway:** Supportive care plan. **Main outcomes:** Increased documentation and discussion of place of preferred death.
Veerbeek 2008, Netherlands[27]	Before and after study (without control)	**Participants:** pre=219, post=253 **(**patients with cancer and end-stage disease). **Pathway:** Liverpool Care Pathway. **Main outcomes:** Documentation of care was significantly more comprehensive compared with the baseline period, and the average total symptom burden was significantly lower in the intervention period.
Veerbeed 2008, Netherlands[23]	Before and after study (without control)	**Participants:** pre=131, post=141 (patients with cancer and end-stage disease and relatives). **Main outcomes:** The relatives had declined levels of bereavement. **Pathway:** Liverpool Care Pathway. **Notes:** Only 59% of relatives filled in the questionnaires. Relatives who filled in the questionnaires may be those who had higher satisfaction with the use of the pathway and the service.

Excluded studies

Twenty-eight papers were retrieved in full text and were excluded because the study designs did not meet the criteria for included studies. Twenty papers were audits, letters or reviews, and were not experimental studies. Eight experimental studies were excluded because they did not meet the minimum criteria to be included in this review. Table 1 summarises the characteristics of the excluded studies.

Discussion

No RCTs, quasi-experimental studies or controlled, before and after studies meeting our eligibility criteria were identified for this review. The results of a number of case series and non-eligible controlled before-and-after studies indicate that EOLCP may have the potential to improve symptom management[22,23], clinical documentation and assessment[16,23,24], knowledge of end-of life care amongst internal medicine students[25], prescription of medications for end of life[22,26], and bereavement levels of relatives[27]. However, the effects of pathways are difficult to ascertain from these designs. It is also worth noting that no studies reported adverse effects of any EOLCP.

In the UK, the registered users of the LCP reached over 1800 health care institutions across all settings including hospitals, hospices, care homes and community services[28]. Further, a publication endorsed by the Australian Government, titled *Supporting Australians to live well at the End of Life – National Palliative Care Strategy 2010*, recommended a national roll-out of EOLCP across all sectors (primary, acute and aged care) in Australia[29]. The use of EOLCP has been accepted as the gold standard/national end-of-life care policy, despite the fact that there is a lack of sound evidence supporting such practice[30]. This may be because of the ethical issues around randomising patients to a study arm that does not include an intervention, which many clinicians, irrespective of the lack of RCTs, believe to be effective. However, it is important for policy makers and clinicians to note that such a large-scale roll-out of the EOLCP will make good-quality research ethically impossible[30].

Designing and conducting trials involving the dying is difficult and challenging due to methodological and ethical issues[31,32]. These issues may include difficult patient recruitment due to the patient being too ill to participate or unable to give informed consent, or the heterogeneous nature of palliative populations[33]. However, a range of other strategies may be considered to make clinical trials possible. These include designing shorter term studies, limiting the number of outcomes, undertaking frequent follow-ups, advanced consent and proxy consent where appropriate for studies involving this population[34].

Although there have not yet been any formal reports of harm associated with the EOLCP, there is no guarantee, unless formal measurement has occurred, that implementing EOLCP does not cause harm[35]. Therefore, palliative care researchers should attempt to investigate end-of-life interventions with the most rigorous research methodology possible. It is encouraging to note that one Italian cluster randomised trial is now under way to investigate the effects of the EOLCP on patients[36].

Implications for practice and research

This review was unable to find any evidence of effect or harm with the use of EOLCP for the dying. Without sufficient evidence for improving patient outcomes, organisations should await further high-quality evidence before the roll-out of the EOLCP. With the recent concerns regarding potential harms associated with the use of the EOLCP, it is important that clinical nurses document and report any suspected safety concerns or adverse effects associated with the pathways to their nursing directors or the safety and quality committee in their organisations. Until further formal investigation is conducted, documented harms in an organisation may suggest further quality and safety measures or discontinuation of the pathways. RCTs or other well-designed, controlled studies are needed for the evaluation of the use of EOLCP in caring for dying people. In future studies, outcome measures should include the outcomes of interest in this review in relation to patients, families, caregivers and health professionals. These may include patients' symptom control, harms, communication between health care team and families, caregivers' wellbeing, grief and bereavement, staff and caregivers' satisfaction, staff confidence, cost of intervention, cost of care, medication use and harms. Further, investigations of the effects of such pathways for specific populations are warranted. These specific populations may include, but are not limited to, children and patients with end-stage organ failure or dementia.

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