The use of corticosteroids in reducing cancer-related fatigue: assessing the evidence for clinical practice

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Fatigue has a lasting effect on the quality of life of people with advanced cancer (Barnes and Bruera, 2002). It is reported in 60–90% of those with advanced cancer and has been ranked as the most disruptive symptom to everyday life (Hofman et al, 2007). There are many definitions of fatigue, which is a ‘subjective feeling of tiredness, weakness or lack of energy’ (Radbruch et al, 2008). Cancer-related fatigue (CRF) is a ‘distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning’ (National Comprehensive Cancer Network, 2003). There is limited quality research in relation to treatment of CRF and corticosteroids (Radbruch et al, 2008), which may lead to nurses being uncertain about research recommendations (Grol, 1997).

Strategies to combat fatigue are diverse and include non-pharmacological and pharmacological approaches. Thus, a multidisciplinary approach is required to manage both the physical and psychological aspects of fatigue (Radbruch et al, 2008). One strategy to treat fatigue in palliative care is the use of corticosteroids but, despite being frequently prescribed, evidence of their effectiveness has not been well demonstrated (Radbruch et al, 2008).

Inadequate screening and reporting of CRF is also an issue (Mock, 2001). To treat CRF nurses need to understand, assess and manage the symptom (Mock, 2001). This includes examining the severity and features of the symptom, exacerbating and relieving factors, and the impact of fatigue on quality of life (QoL) (Barnes and Bruera, 2002).

Many assessment tools for CRF exist (Mock, 2001). Palliative care guidelines recommend that patients are screened for fatigue at their first visit to an oncologist, nurse practitioner or other clinician, and then at regular intervals after this (Mock, 2001). The influence of secondary factors causing fatigue, such as anaemia, infection, dehydration and depression, must also be eliminated (Barnes and Bruera, 2002).

The primary supporting factor for the use of corticosteroids in CRF is the prevalence of the symptom among cancer patients and the effect on QoL (Walsh et al, 2000). In a US study of 1000 patients in a palliative care programme:

- 84% reported fatigue
- 66% reported weakness
- 61% reported lack of energy (Walsh et al, 2000).

In addition, the significant impact of CRF on QoL is well documented by Curt et al (2000), who found it to be one of the most frequently anticipated symptoms of patients with advanced cancer. CRF has also been widely expressed as the most distressing symptom after treatment, and has a greater negative impact on QoL and daily activities than any other cancer-related symptom (Vogelzang et al, 1997). CRF not only affects physical functioning, but also...
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psychological wellbeing, and the majority of patients with CRF report loss of emotional control, feelings of social isolation and feelings of dejection (Curt et al, 2000). Consequently, it is of paramount importance that CRF be addressed by health professionals working in cancer care and palliative care settings.

Oncology and palliative care nurses frequently witness the negative impact of CRF. The specific aetiology of fatigue is often unclear, multifactorial and difficult to treat (Hofman et al, 2007). Despite the aspiration to incorporate evidence-based practice (Grol, 1997; Rodgers, 2000), clinical staff commonly use only anecdotal evidence to recommend corticosteroids to reduce levels of fatigue.

This paper explores the evidence behind a commonly used intervention in cancer and end-of-life care: whether the use of corticosteroids improves levels of CRF in patients with advanced cancer. The paper examines studies addressing this topic, and discusses associated barriers for wider practice.

Methodology
A systematic approach was used to explore literature to determine the evidence for whether the use of corticosteroids improves levels of CRF in people with advanced cancer. Electronic databases accessed and searched during 2014 were Medline, CINAHL and Cochrane, as they are regarded as the main sources of clinical articles. The Medical Subject Headings terms used were:

- Advanced cancer
- Terminal
- Palliative care
- End-stage disease
- Fatigue
- Lethargy
- Weakness
- Cancer-related fatigue
- Corticosteroids
- Dexamethasone
- Prednisolone
- Methylprednisolone.

The initial search yielded 12 relevant studies, of which 6 were excluded as they examined CRF in patients receiving chemotherapy. This left six papers, but two were excluded because of old publication dates (Della Cuna et al, 1989; Popeila et al, 1989), leaving four that were used to explore the research question.

All patients in the included studies had advanced cancer, ranging from pre-terminal (no longer having active treatment) to terminal (days-weeks from death). Studies included differing corticosteroids—either dexamethasone or methylprednisolone.

Each of the four studies measured fatigue differently. When discussing each study, a description of how fatigue was measured is provided, and these were:

- Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) subscale
- Edmonton Symptom Assessment Scale (ESAS)
- Hospital Anxiety and Depression scale (HADS)
- Functional Assessment of Cancer Therapy–Anorexia–Cachexia (FACCT).

Results
Yennurajalingam and Bruera (2014) conducted a literature review of placebo-controlled double-blinded randomised studies that examined the effect of corticosteroids on CRF. The authors systematically searched peer-review literature of studies conducted before 2012 and retrospective audits and surveys. The search yielded two papers—Paulsen et al (2014) and Yennurajalingam et al (2013), which is a limitation, as older, but relevant, randomised controlled trials were excluded due to the very specific exclusion criteria. This weakens the authors’ conclusions, as only two articles were included.

The authors concluded that corticosteroids were an effective treatment for CRF but recommended that only short-term treatment (up to 2 weeks) be used (Yennurajalingam and Bruera, 2014). There was insufficient evidence to recommend a specific dose of dexamethasone and long-term use of corticosteroids was not indicated, because of concerns about side effects, such as myopathy and glucose intolerance (Yennurajalingam and Bruera, 2014). The authors recommended further studies be conducted, especially to investigate the long-term effect of corticosteroids on CRF.

The key study that addressed the research question was a double-blind randomised control trial in which patients were recruited from oncology/palliative care outpatient clinics (Yennurajalingam et al, 2013). This was the only randomised control trial about corticosteroids in which measuring fatigue was the primary goal. Eligible participants were those with advanced cancer, who had experienced more than three symptoms during the previous 24 hours. Some 132 participants were randomly assigned to receive either dexamethasone 4 mg, or a placebo, twice a day (Yennurajalingam et al, 2013). Fatigue levels were measured three times, at days

- 0
- 8
- 15.
FACIT-F subscale, ESAS, HADS and FACCT (Yennurajalingam et al, 2013).

At days 8 and 15 the dexamethasone group reported significantly less fatigue than the placebo group, and at day 8 the FACIT-F total score had a greater mean improvement than the placebo group (13.37 with SD 13.22 vs 7.5 SD 14.04) (p=0.008) (Yennurajalingam et al, 2013), which was a statistically significant result. Some 95% confidence intervals (CI) were not included in the analysis. At day 8 the 95% CI for the dexamethasone group mean was 9.42 to 17.32 and 3.2 to 11.8 or the placebo group. As these two confidence intervals overlapped it was not possible to say, based on these alone, whether the test was statistically significant; thus, the chi squared test was also used.

At day 15 the FACIT-F sub-scale score (measure of primary outcome) had greater mean improvement than the placebo group (9 with SD of 10.3 vs 3.1 with SD of 9.59) (p=0.008) (Yennurajalingam et al, 2013). The p value demonstrates that this result was statistically significant and not due to chance. The standardised mean difference between the groups at the primary end point was 5.9 in favour of the dexamethasone group. At day 15, the 95% CI for the FACIT-F subscale score for the dexamethasone group was 5.92 to 12.08 and 0.16 to 6.04 for the placebo group (Yennurajalingam et al, 2013). Again, these two CIs overlapped, so it is not possible to say whether the test was statistically significant and so again, the chi squared test was applied. These findings were clinically significant as the results demonstrated that after 15 days, a substantial improvement in fatigue was found in comparison to those on the placebo (Yennurajalingam et al, 2013).

The major limitation of the study was the percentage of participants (23% in both groups) lost-to-follow-up. This limits the positive findings of the study, as those lost-to-follow-up may have had different outcomes. (Yennurajalingam et al, 2013). Excluding the non-compliant patients from analysis impaired the unbiased comparison provided by randomisation (Guyatt et al, 2001). Intention to treat analysis was not included. All participants entered into the trial were accounted for in its conclusion. The clinical bottom line of this study was that use of low dose dexamethasone in patients with advanced cancer improves CRF.

A recent randomised placebo-controlled study published by Paulsen et al (2014) examined the effect of methylprednisolone on pain as a primary outcome, and on fatigue as a secondary outcome in 50 patients with advanced cancer. The participants were given 16 mg methylprednisolone twice daily for 7 days. Fatigue was measured by the ESAS at the baseline and then at day 7. At the completion of the study statistically and clinically significant improvement was measured in fatigue (-17 points vs 3 points) (p=0.01) but not pain (Paulsen et al, 2014).

Unlike the other studies of the population with advanced cancer, this study obtained their target number to treat and had minimal loss-to-follow-up (Paulsen et al, 2014). Although not the primary outcome, the improvement in fatigue observed was clinically significant. A limitation of the findings was the large number of patients screened (592 over 45 months) to reach the 50 eligible for the study. The authors explained that many patients screened were already on corticosteroids, hence were ineligible for the study (Paulsen et al, 2014). The large number of patients screened opens the study to selection bias. The 7-day length of the study was also a limitation (Paulsen et al, 2014).

Hardy et al (2001) conducted a prospective survey of the use of dexamethasone in a palliative care unit. Some 106 patients with advanced malignant disease were commenced on dexamethasone as inpatients or outpatients, and then followed over the course of 8 months (Hardy et al, 2001). Changes in symptoms, side effects and the reasons for stopping the steroids were documented. Every 2 weeks the patients were asked to use a non-validated symptom assessment tool to self-assess their symptoms. The survey found that 50% of the patients had an improvement in their fatigue (Hardy et al, 2001). No statistical analysis was provided.

While a good overview of the use of corticosteroids in a major tertiary hospital, this study provided little evidence of the effectiveness of corticosteroids to improve fatigue. This was an uncontrolled study, which did not take into account any concurrent treatment or provide statistical analysis (Hardy et al, 2001). There is inherent bias in the study as the decision to start dexamethasone was entirely physician-led (Hardy et al, 2001).

Discussion

All studies reported improvements in patient-reported fatigue, as a result of taking corticosteroids; although the quality of the results varied and only a few were deemed to have statistically significant results. While not the primary outcome, Paulsen et al (2014) had the most clinically and statistically significant result.

Although not the primary outcome, the improvement in fatigue observed was clinically significant.
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Yennurajalingam et al (2013) also had a statistically significant improvement in fatigue but had a high loss-to-follow-up. Two out of six of the studies were published in 1989. Evidence for the use of corticosteroids in fatigue exists and a definite trend is emerging but requires larger studies to achieve statistically significant results.

In synthesising the studies, exploring the potential harm versus benefit to patients is also paramount. This highlights one area of disagreement across the studies. The major potential/actual harm to patients in the examined studies was the potential side effects of proximal myopathy, increased appetite, increased risk of infection and insulin resistance noted in four of studies. Yennurajalingam et al (2013) and Paulsen et al (2013) both found no significant difference between the steroid group and placebo group, but this may be because both studies were relatively short in duration. Hardy et al (2001) found oral candida was the most common side effect, affecting 34% of patients. Yennurajalingam S et al (2008) describe similar side-effect, some of which may actually aggravate the experience of fatigue.

Gaps across the examined studies still leave uncertainty about the exact details of corticosteroid prescription and at the time that this article was published, no guidelines were in place. Thus, there remains uncertainty around the exact dose, duration of course of corticosteroids, and exactly which patient group experiences positive effects. However, Bruera et al (2008), representing an expert reference group of clinicians, report their anecdotal experience that low dose prednisolone (up to 10 mg per day) can alleviate fatigue for a short period (1 to 2 weeks); this may be to align with an individual’s goals, like enabling them to have a holiday with family. There is still ambiguity about the benefits and burdens of using corticosteroids for CRF a week before death, and further research is needed to address these gaps.

It makes economic sense to use corticosteroids to treat CRF as it is cost efficient and clinically effective. Corticosteroids are cheaply and widely available for treatment of CRF (Pilkey et al, 2012), with dexamethasone and prednisolone available by prescription in many countries (Commonwealth of Australia, 2014). Encouraging the use of corticosteroids for this population among general practitioners has very little economic cost and the benefit far outweighs the small cost of corticosteroid drugs (Therapeutic Guidelines, 2010), in alleviating the distress resulting from CRF and the impact of fatigue on QoL (Peuckmann et al, 2010).

Implementing the evidence into clinical practice

There are a number of barriers that inhibit the implementation of evidence into clinical practice. A meeting of expert palliative care practitioners in the European Association for Palliative Care (EAPC) concluded that from clinical practice experience, corticosteroids, such as dexamethasone and prednisolone, are frequently used as effective treatment of CRF for short periods (Radbruch et al, 2008). However, as noted, more evidence is required that corticosteroids may improve CRF. While the evidence is still growing, it is important to address implementation strategies to enable evidence-based clinical practice change.

Research use by nurses has been widely investigated over many years, resulting in a number of seminal publications (Rogers, 1995; 2000; Grol, 1997; Parahoo, 1999). The main recurring issues in the literature are:

- Problems in interpreting and using research outcomes
- Lack of organisational support
- Nurses feeling that researchers lacked credibility
- Nurses lack of skills and/or motivation to use research (Rycroft-Malone et al, 2004).

Presenting the research evidence and managing the knowledge translation is thus a significant challenge, and there is not necessarily a defined or logical approach to research dissemination.

To overcome this barrier an extensive education and exposure strategy is required. Rycroft-Malone et al (2004) found that nurses appreciate a broad base in looking for evidence, which is inclusive of clinical practice, and that research findings are more likely to be adopted if they accord with existing organisational policies and structures. Implementation will more likely be successful if a multidisciplinary team focus is used, and a clear lead person is vital to the uptake of new practices arising from research (Rycroft-Malone et al, 2004).

As noted, inadequate screening and reporting of CRF may be an obstacle to the uptake of using corticosteroids for CRF (Mock, 2001). Education strategies would need to take this into consideration and as suggested (above), adopt a wide-ranging approach. This would include informing nurses of tools to screen and measure CRF, as well as non-pharmacological activities that can be used in conjunction with pharmacological interventions.

While nurses may be resistant to using corticosteroids for CRF, there may also be resistance across other disciplines like allied
Conclusion and implications

This paper has described that CRF is an issue relevant to every cancer and palliative care clinician, because of the distress it causes and the impact of fatigue on QoL for many patients. There is good evidence in the literature suggesting that CRF is the foremost factor hindering patients’ QoL; hence it is paramount that nurses equip themselves with the latest broad-based evidence to assist patients with managing this symptom (Radbruch et al, 2008). In examining the literature there is some evidence supporting the use of corticosteroids in the short term (even though limited by high loss-to-follow-up rates, low study numbers and limited duration of the studies) and clinical guidelines would assist with their use.

While there are promising signs that corticosteroids can improve CRF, particularly in the short-term, more research is required to further demonstrate this effect as well as monitor side-effects and to weigh up the benefits and burdens.

In examining key strategies to implement and change practice, one needs to address the barriers to implementation of the evidence. At the heart of care is the overriding nursing goal to improve people’s quality of life.

Declaration of interests

The authors have no interests to declare.


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