

Anorexia-cachexia syndrome

— pharmacological management

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Management of anorexia-cachexia syndrome centres around treating the symptoms. This article describes evidence for the drugs currently used to manage these symptoms and those that look promising for the future



Eicosapentaenoic acid has shown to be beneficial in ACS patients

Anorexia-cachexia is a complex syndrome commonly seen in cancer patients, as discussed in the first part of this special feature (p249). Because the exact mechanism of the syndrome is not completely understood, management focuses on controlling the symptoms it produces, rather than targeting the causes. This article describes the drugs used to treat the main symptoms of ACS, which are summarised in Panel 1 (p258).

— Loss of appetite

Corticosteroids The mainstay of appetite stimulation in palliative medicine has long been corticosteroids. Several double blind randomised controlled trials have demonstrated symptomatic benefit from different corticosteroids in patients with cancer cachexia.^{1,2} However, the beneficial effects (which included increased appetite and sensation of well-being) were limited to two to four weeks. Patient review is therefore recommended within two weeks

of starting corticosteroid treatment. Most studies have failed to demonstrate a significant gain in body weight, so steroids are not recommended to treat weight loss alone. The first-line choice of corticosteroid has not been established but dexamethasone, methylprednisolone, prednisolone and hydrocortisone have all been found to be effective. Optimal doses are also unclear but equivalent daily doses of prednisolone 20mg to 40mg have been used. Dexamethasone 4mg is often used to minimise tablet burden for patients. Its use at this dose in palliative medicine is well established.

Steroids are well tolerated for brief periods. They have proven benefit in ACS, particularly in more unwell patients and those with a poor prognosis. If steroids are to be used long-term, the course of treatment should be monitored closely.

The precise mechanism of action of corticosteroids is unclear but it is thought to be due to inhibition of the release of metabolic products (eg, prostaglandins) by the tumour or the host immune system. They also have a non-specific central euphoriant effect. There is evidence to show that steroids inhibit tumour necrosis factor (anti-inflammatory) action and are involved in the TNF-induced muscle proteolysis characteristic of cachexia.

Corticosteroids also have antiemetic and analgesic properties and can relieve compression secondary to oedema.

Progestational drugs A systematic review of megestrol acetate in the treatment of ACS found that, compared with placebo, megestrol acetate increased appetite in oncology patients, encouraged weight gain and improved quality of life.³ There were no differences between lower (<800mg/day) and higher doses of the drug. One study in the review found a dose-related benefit on appetite, caloric intake, body weight gain (mostly fat) and sensation of well-being, with an optimal dose of around 800mg.

However, side effects are also dose dependent. Side effects may include thromboembolism, breakthrough bleeding, oedema, hyperglycaemia, hypertension, cushingoid symptoms, alopecia and adrenal suppression. Studies suggest that the starting dose of megestrol acetate could be lower (the most frequently studied dose was 480mg per day). Therefore to minimise side effects a dose of 160mg *tds* is recommended, with a review after two weeks and titration according to clinical response.

The exact mechanism of action of megestrol acetate is unclear but it is likely to be related to glucocorticoid or anabolic activity. It is also thought to affect cytokine release, possibly inhibiting interleukin-1, interleukin-6 or TNF- α . Research suggests megestrol acetate may also act centrally via stimulation of neuropeptide Y in the hypothalamus.⁴

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Panel 1: Managing the symptoms of anorexia-cachexia syndrome

Symptom	Drug options	Suggested dose/frequency
Loss of appetite	Dexamethasone Megestrol acetate (with ibuprofen)	4mg <i>om</i> 160mg <i>tds</i> 400mg <i>tds</i>
Weight loss	Thalidomide Eicosapentanoic acid	50mg <i>bd</i> , titrated to effect >2g per day
Early satiety	Metoclopramide	10mg <i>tds</i> (max 120mg per day)
Oral candidiasis	Fluconazole	50mg <i>om</i> for 7–14 days
Sore mouth (unknown cause)	Benzylamine mouthwash	15ml every 1.5–3 hours as required
Dry mouth	Pilocarpine Sugar free chewing gum Artificial saliva (mucin-based)	5m–10mg <i>tds</i> Regularly Apply to lips and oral mucosa <i>qds</i>
Altered taste	Zinc	Solvazinc (zinc sulphate monohydrate 125mg) 1 <i>tds</i>
Nausea and vomiting	Metoclopramide	10mg <i>tds</i>

Few serious adverse events have been recorded while using megestrol acetate in ACS. In trials patients have rarely needed to discontinue the drug because of side effects. However, one study of patients with non-small cell lung cancer showed that megestrol acetate might decrease survival and increase the rate of thromboembolic disease.⁵

NSAIDS A trial comparing megestrol acetate plus ibuprofen with megestrol acetate and placebo found that patient appetite increased in both groups, and found significant weight gain and improvement in quality of life scores in the megestrol acetate/ibuprofen group.⁶ It is therefore worth considering the combination of megestrol acetate and ibuprofen.

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce mediators of inflammatory response such as interleukin-6. Ibuprofen has been shown to decrease resting energy expenditure and acute phase protein production in cancer patients. Animal studies have found that inhibition of prostaglandin synthesis by the use of NSAIDs may attenuate tumour progression and decrease cachexia.

NSAIDs have significant side effects, including nausea, peptic ulcers, renal toxicity and exacerbation of asthma and heart failure.

Many patients with ACS will be frail and have co-existing morbidities which may mean these drugs are contraindicated or should be used with careful monitoring.

— Weight loss

Thalidomide A number of small studies have supported the use of thalidomide in patients with ACS. For example, one study of 37 patients with advanced cancer cachexia found that thalidomide significantly improved patients' appetite, nausea and sensation of well-being.⁷ Further studies confirmed either weight gain or attenuated weight loss in patients with pancreatic and oesophageal cancer taking thalidomide.⁸

Thalidomide inhibits TNF- α and has complex effects on other cytokines. This action has proved useful in the management of a range of symptoms seen in patients with palliative stage disease, including insomnia, sweating, nausea and neuropathic pain.

Due to the risk of teratogenesis, thalidomide was withdrawn from use in the UK and is now only available on a named patient basis via the System for Thalidomide Education and Prescribing Safety. Other potential side effects include neuropathy (in which case the drug should be withdrawn immediately), drowsiness, allergic reactions, haematological effects and drug interactions.

Eicosapentanoic acid (EPA) Much research has been done into the use of EPA in ACS. It has been shown to inhibit the production and effect of various inflammatory factors, including cytokines and proteolysis inducing factor.⁹ A trial of 200 patients with pancreatic cancer taking nutritional supplement drinks with or without EPA found a reduced rate of weight loss in both groups.¹⁰ There was no overall difference in

survival or quality of life. However, patients who managed the recommended intake of EPA (1.5–2 supplement cartons a day, 1.1g EPA per carton) had a significant gain in weight and lean body mass. This study emphasises the importance of ensuring that the recommended dose of EPA is achieved if benefit is to be seen.

The supplements were given for up to eight weeks, at which point benefit was seen in terms of weight gain (lean body mass) and quality of life. It is recommended to check patient tolerance and perceived benefit at four-weekly intervals.

The most common side effect of EPA is diarrhoea, and this is dose-dependent. Other side effects may include an abnormal taste, abnormal body smell, belching and flatulence.

If patients are not achieving the correct dose due to side effects it is advisable to try switching to a different form of EPA. If supplement drinks cannot be tolerated then Omacor capsules can be given (840mg of EPA and docosahexanoic acid per 1g capsule).

— Early satiety

Feeling full quickly is thought to be a result of both central and peripheral effects, although the exact pathophysiology remains unclear. Central influences may include taste changes and food aversion. Peripheral changes are thought to include poor gastric accommodation, delayed gastric emptying and altered sensory signals.

Prokinetic drugs Metoclopramide is the most widely used prokinetic drug for ACS. It also has a prokinetic effect that promotes gastric emptying. It is therefore particularly effective for patients with chronic nausea due to autonomic failure and delayed gastric emptying. These problems typically respond well to metoclopramide, improving appetite and food intake.

The main side effects of metoclopramide are extrapyramidal effects, neuroleptic malignant syndrome and occasionally drowsiness, restlessness, depression and diarrhoea. Extrapyramidal effects are rare but more common in young women and also in patients taking the drug for prolonged periods of time at high doses. Therefore it is recommended that metoclopramide is reviewed regularly and not continued long-term where possible.

Domperidone is an alternative to metoclopramide. There is evidence to show that doses above the maximum stated in the British National Formulary can be beneficial and current palliative care textbooks reflect this.

— Dry mouth

Dry mouth may be caused by a decrease in saliva secretion, an alteration in saliva composition or a combination of both. In

Panel 2: Treatment of mouth sores

Ulcers Topical corticosteroids are the treatment of choice for ulcers in the oral mucosa. However, they are more effective in preventing the development of further lesions than treating those already established. There is no difference in efficacy between the lozenges and paste so the formulation should be chosen according to patient preference. The treatment should be reviewed after five days. Occasionally use of topical corticosteroids can cause an exacerbation of local infections and may promote oral candidiasis. Again, the need for good oral hygiene should be emphasised.

Oral candidiasis Oral candidiasis is the most common oral infection in palliative care and may be present in several different clinical forms. Management begins with the treatment of any predisposing factors such as dry mouth (see below). Good denture care should be ensured. Subsequent management involves treatment with an antifungal agent. Evidence of the superiority of individual antifungal drugs or systemic versus topical therapies in patients with advanced cancer is weak. Treatment with a systemic agent is generally recommended because compliance is better than with topical antifungal treatment regimens, and they have the added advantage of efficacy in widespread disease.

Fluconazole is suggested first line because it has fewer side effects than otherazole drugs. Resistance to theazole drugs is an increasing problem in palliative care, so a swab of the oral mucosa should be sent for culture and sensitivity if the infection persists.

Side effects include nausea, abdominal discomfort, diarrhoea, flatulence, headache and rash. Treatment should be discontinued if these occur. Fluconazole does have significant drug interactions and so drug combinations should be checked before starting treatment.

Prevention of the recurrence of oral candidiasis can be achieved with good oral hygiene including thorough toothbrushing, careful denture care and use of chlorhexidine mouthwash (10ml).

Unknown cause Benzydamine mouthwash has a broad spectrum of activity and so is useful when the cause of mouth soreness is unknown. It is effective in a range of painful oral conditions in advanced cancer.³³ Benzydamine contains an atypical non-steroidal anti-inflammatory drug and has analgesic, anaesthetic and antimicrobial properties. The main side effects are numbness and stinging or burning. This may be alleviated by diluting the mouthwash with an equal volume of warm water.

cancer patients this is commonly caused by irradiation of the salivary glands, drug therapy (anticholinergics, antidepressants, opioids, sedatives, diuretics and chemotherapy agents), dehydration, breathing through the mouth and oxygen therapy. It is important to review the patient's treatment and drug history, promote good oral hygiene, and review their diet. Patients should be advised to avoid products that are acidic in nature (eg, fruit juice) which can cause dental caries and increase oral infections.

The next step is to try and stimulate the saliva. This can be done using several agents.

Pilocarpine Pilocarpine is a choline ester which acts via the parasympathetic nervous supply to the salivary glands. It has been shown to improve saliva production with minimal side effects but does need residual functioning salivary tissue to do so.¹¹ In a trial comparing a mucin-based artificial saliva to pilocarpine, 76 per cent of patients chose to continue with pilocarpine and found it to be more effective than the artificial saliva (improvement of dry mouth was seen in 90 per cent of patients).¹² Side effects of pilocarpine are usually those resulting from parasympathetic stimulation, commonly sweating, urinary frequency, headache, flushing, nausea, dizziness, dyspepsia, fatigue. These appear to be dose-dependent.

Chewing gum Chewing gum has been shown to be effective for dry mouth in a variety of patients. It increases the flow of the saliva by stimulating the chemoreceptors and, to a lesser extent, the mechanoreceptors. Evidence shows that it is more effective than saliva substitutes and better tolerated by patients.¹²

If stimulating the saliva does not work or is not acceptable to patients then a saliva substitute can be used.

Artificial saliva Artificial saliva substitutes are commonly prescribed for dry mouth. Several types have been developed, differing in type of lubricant, formulation and additives present.

A number of trials have reported that patients find mucin-based artificial saliva (eg, AS Saliva Orthana spray) more effective and better tolerated than cellulose-based artificial saliva.¹³ In a separate study, patients also reported that gel-based artificial saliva (eg, Biotene Oralbalance gel) was more effective than spray-based.¹⁴

Treatment of mouth sores is described in Panel 2.

— Altered taste

Zinc The most common enzyme in the membrane of the taste bud is alkaline phosphatase, for which zinc is the co-factor. Zinc (and other metals) also affects the conformation of the protein that regulates the passage of tastants through the taste bud pore. A deficiency in zinc has been linked to altered taste in several groups of patients including those with cancer. Drugs that chelate zinc have also been associated with taste disturbance. However, the exact role of zinc in the control of taste is not fully known. Many trials have been conducted in patients undergoing radiotherapy and it is not clear if the data can be applied to patients with taste disturbances due to other causes. Zinc supplements may be helpful in patients with altered taste which remains unresolved by good oral hygiene and is

affecting their quality of life. Since zinc can accumulate in patients with renal impairment it is recommended that patients have their renal function checked before initiating this therapy.

— Nausea and vomiting

Metoclopramide has been found to be particularly effective for the chronic nausea associated with ACS. It has a short half-life so needs to be given frequently. If patients are vomiting, a continuous subcutaneous infusion (syringe driver) may give optimal results. Metoclopramide is a dopamine (D2)-receptor antagonist and 5HT₄-receptor agonist and in higher doses it has 5HT₃ antagonist activity. It is probably most useful in the nausea and vomiting caused by ACS due to its prokinetic effect (see p258).

— Future developments

Much work is being done internationally to establish the exact mechanism of the anorexia-cachexia syndrome, with the aim of being able to target treatment to the cause. The following drugs show promise for the future.

Melatonin Studies have shown links between cytokine activity and immunomodulating neurohormones such as melatonin. Melatonin appears to influence cytokine activity during tumour growth by reducing circulating levels of TNF.¹⁵ In one study of 100 patients with untreatable metastatic solid tumours, lower weight loss was reported by those taking melatonin than by those who had best supportive care. Melatonin has also been shown to benefit patients undergoing chemotherapy, in terms

The role of the pharmacist in anorexia-cachexia syndrome

It is well established that anorexia-cachexia syndrome (ACS) is under-managed. Staff do not ask about it and patients do not report it. The symptoms listed in this article illustrate the large physical and psychological burden of ACS. This symptom burden requires polypharmacy, often using medicines "off-label". These medicines will usually be in addition to an already complex drug regimen, increasing the likelihood of drug interactions. Managing the symptoms of ACS in cancer patients is not just the role of the specialist pharmacist. Throughout their cancer journey, patients spend time on a variety of different wards. All hospital pharmacists can help identify, assess and manage cancer patients with ACS, playing a key role in the holistic care of these patients.

of reduced toxicity and increased survival time. The drug is generally well tolerated, with the main side-effect being drowsiness.

Cannabinoids Cannabinoids are thought to act via endorphin receptors or by inhibiting prostaglandin synthesis. It has also been suggested that they may work by inhibiting cytokine production or secretion. Appetite stimulation and increased body weight are well recognised side effects of chronic marijuana use, so this group of drugs is known to have an effect on weight gain.

In an open pilot study of 42 cancer patients, patients continued to lose weight when taking dronabinol, but the rate of weight loss decreased and there was a symptomatic improvement in mood and appetite.¹⁶ However the drug was discontinued in 10 patients due to intolerable side effects. In another study of dronabinol in advanced cancer, patients showed a significant weight gain at one week.¹⁷ Again, a number of patients did not complete the trial due to side effects. In contrast, a recent study comparing megestrol acetate and delta-9-tetra-hydro-cannabinol (dronabinol, THC) found that a greater percentage of patients in the megestrol acetate group had improvements in appetite and weight gain. THC and megestrol acetate in combination was no better than megestrol acetate alone.¹⁸

It appears that the potential of cannabinoids may be limited because of their side effects. These include euphoria, dizziness, somnolence and confusion. These side effects are particularly problematic in patients taking drugs such as opioids and psychotropics.

Cyproheptadine Cyproheptadine attempts to block serotonin activity in cancer cachexia. It is a serotonin antagonist with antihistaminic properties, still used in Latin American and some European countries as an appetite stimulant. Preliminary studies suggested both weight and appetite enhancing effects, but cyproheptadine did not prevent progressive weight loss in patients with advanced malignant disease.¹⁹ This drug is likely to have limited potential due to its side effects, which include sedation.

Pentoxifylline Pentoxifylline was originally used to reduce blood viscosity. It inhibits TNF synthesis and has been shown to reduce chemotherapy toxicity, but not to improve appetite or increase the weight of cachectic patients.²⁰ This might suggest that TNF suppression alone is not sufficient to reverse the activation of the various pathways involved in ACS.

Other drugs showing potential in the treatment of ACS include gherlin, hydrazine sulphate, amino acids and nucleotides, anabolic steroids, adenosine triphosphate, creatine, 5'deoxy-5-fluorouridine, and proteasome inhibitors.

However, it should be remembered that management of ACS is not confined to pharmacological therapies. Non-pharmacological interventions (see p249) such as nutritional supplementation, moderate exercise programmes, and advice are also important. Pharmacological management should always form part of a multidisciplinary approach to caring for these patients.

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