

Conference on ‘Malnutrition matters’

Symposium 8: Drugs and nutrition

Drugs and nutrition: how side effects can influence nutritional intake

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There are many factors that can influence nutritional intake. Food availability, physical capability, appetite, presence of gastrointestinal symptoms and perception of food are examples. Drug therapy can negatively influence nutritional intake through their effect on these factors, predominantly due to side effects. This review aims to give a brief overview of each of these factors and how drug therapy can affect them. Specific examples are given for each section and an indication of the impact on nutritional status. This article aims to assist the clinician in the identification of the effects of drug therapy on nutritional intake and provides advice on appropriate intervention. A drug history and side effect review should form an integral part of nutritional assessment. Early identification and effective therapeutic use of alternative drug therapy can also positively influence nutritional intake.

Drug therapy: Side effects: Nutritional intake: Drug–nutrient interactions: Taste disturbances: Smell disturbances

It is only in recent years that research has revealed the breadth of factors that can influence nutritional intake and nutritional status. There is an increasing interest in drug–nutrient interactions and an ever-growing body of evidence in this field; however, there appears to be less focus on the overall effect that medication can have on nutritional intake.

This paper does not aim to review specific drug–nutrient interactions, readers are directed to the literature already available^(1,2), but focuses on how drug therapy can influence nutritional intake, both positively and negatively, through effects on appetite, gastrointestinal (GI) symptoms and food perception. It will identify the associated drug therapy and define high-risk patients.

In the broadest sense, the effects of drug therapy may begin with reducing the patient’s ability to gather and prepare food. There are many medical conditions that can affect a patient’s mobility or cognitive function and these are well recognised; however, drowsiness induced by drug therapy can have the same effect. There are other side effects that may affect mobility, such as continence issues for patients taking alpha blocker therapy⁽³⁾ or diuretics who are reluctant to leave the house or patients who are

unsteady on their feet due to drug-induced orthostatic hypotension^(4,5).

Food avoidance

Many medicines have specific dosing recommendations with respect to food intake in order to optimise their absorption (Table 1). For example, tetracycline should not be taken with milk as this can significantly reduce the absorption; even the small amounts added to tea or coffee can have a clinically important effect⁽⁶⁾. For this reason, many patients alter their usual food intake to comply with dosing guidelines and may reduce their overall intake.

The oral bisphosphonates, alendronate and risedronate have a very low oral bioavailability and therefore to maximise absorption they should be taken 30 min before breakfast with water only⁽⁷⁾. In a susceptible population, such as older adults, this may cause them to delay or even omit breakfast.

Medication counselling offers an opportunity to ascertain any possible change to the patients’ usual dietary intake as a result of the dosing requirements. Tailored

Abbreviation: GI, gastrointestinal.

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Table 1. Examples of medication with specific dosing instructions

30 min before food or on an empty stomach
Phenoxymethylpenicillin
Itraconazole
Not to be taken with indigestion preparations
Ketoconazole
Not to be taken with iron, zinc or indigestion preparations
Ofloxacin
Levofloxacin
Doxycycline
Lymecycline
Penicillamine
Not to be taken with milk, iron, zinc or indigestion preparations
Ciprofloxacin
Norfloracin
Tetracycline

advice could then be given to ensure that dietary intake is optimised.

Anorexia and weight loss

Anorexia is a commonly reported side effect of several frequently prescribed drugs (Table 2); however, the lack of reports indicates that this is not clinically significant in most cases. Recent research is only just beginning to explore the mechanisms by which drug therapy can cause weight loss.

Weight loss in Parkinson's disease is related to levodopa therapy⁽⁸⁾; however, this weight loss can also be attributed to disease severity and the effect of movement disorders on food preparation and intake.

The weight loss attributed to amantadine has been therapeutically exploited in the management of patients with antipsychotic-associated weight gain⁽⁹⁾. The weight loss associated with topiramate is due to increased energy metabolism⁽¹⁰⁾.

Patients with pre-existing malnutrition should be closely monitored when initiating medicines associated with anorexia and regular reviews should be undertaken to ensure that any weight loss is quickly identified and corrective action taken.

Increased appetite and weight gain

Weight gain secondary to drug therapy can be clinically important, and is associated with many commonly used drugs (Table 3). Weight gain is a major consideration in the treatment of psychosis and depression, as it is associated with poor treatment adherence in addition to reduced quality of life⁽¹¹⁾. Clinical consequences of drug-associated weight gain are also a concern, due to the negative effects on glucose tolerance, lipid profile and blood pressure, which may contribute to morbidity and mortality.

Weight gain associated with antipsychotic therapy can affect up to 80% of patients⁽¹²⁾. This can be 10–15 kg in patients taking olanzapine. Other antipsychotics, such as risperidone and haloperidol, are associated with a lower magnitude of weight gain. Interventions, such as dietary

Table 2. Drugs associated with anorexia or weight loss

Amantadine
Digoxin
Fluoxetine
Levodopa
Lithium
Metformin
Penicillamine
Topiramate
Nortriptyline

Table 3. Drugs associated with weight gain

Phenelzine ⁽³⁹⁾
Tri-cyclic antidepressants (excluding nortriptyline)
Valproate
Beta blockers
Oral contraceptives
Antipsychotics
Steroids
Anabolic steroids

counselling, exercise programmes and behavioural therapy, aimed at attenuating this weight gain are only effective over a short period of time⁽¹³⁾.

In addition to their original licensed indication, several drugs associated with weight gain are used in the management of migraine⁽¹⁴⁾, particularly amitriptyline, propranolol and valproate. This is a particular problem in this group of patients as there is evidence that overweight and obese patients with migraine have an increased severity and frequency of attacks when compared to normal-weight patients⁽¹⁵⁾. Prescribers should be aware of the risks of weight gain when prescribing drugs for this group of patients.

Drug therapy associated appetite stimulation and weight gain has been exploited in the management of cachexia syndromes associated with cancer and AIDS, and more recently in the management of the anorexia–cachexia syndrome in the elderly⁽¹⁶⁾.

Megestrol acetate is licensed in the USA for the treatment of anorexia, cachexia or unexplained weight loss in patients with AIDS; however, the data supporting its use in cancer cachexia is more robust⁽¹⁷⁾, with demonstrable effects on appetite, weight gain and health-related quality of life⁽¹⁸⁾.

Synthetic anabolic steroids are increasingly being used to attenuate the catabolism and weight loss experienced by critically ill patients. There is a growing body of evidence to support the use of oxandrolone in thermal injury⁽¹⁹⁾.

A multimodal approach is required when attempting to promote weight gain. Sound dietary advice should be given and drug therapy utilised only when dietetic measures have been demonstrated to be ineffective.

Nausea and vomiting

Nausea and vomiting is one of the most common side effects of drug therapy; it usually occurs early in treatment and symptoms may resolve despite continued treatment.

Table 4. Drugs commonly associated with nausea and vomiting

Action on chemoreceptors in gastrointestinal tract
Cytotoxics
Potassium
Iron preparations
Antibiotics
Action at chemoreceptor trigger zone
Cytotoxics
Anaesthetics
Opiates
Nicotine
Levodopa
Selective serotonin reuptake inhibitors (antidepressants)

Nausea and vomiting can have a profound effect on nutritional intake; however, there is an arsenal of effective anti-emetics which when correctly selected can minimise or even remove this adverse effect.

Understanding how drugs can cause nausea and vomiting can help to target therapy.

The mechanisms by which drug therapy can cause vomiting are by a direct effect on the chemoreceptors in the GI tract (serotonin/5HT₃ receptors); a direct effect on the chemoreceptor trigger zone (serotonin/5HT₃ and dopamine receptors) or where both pathways converge at the vomiting centre in the medulla (muscarinic cholinergic) (Table 4). By understanding the likely receptor stimulation, an appropriate anti-emetic can be selected.

However, care should be taken as drug-induced nausea can be an indication of drug toxicity as in the case of digoxin or theophylline. Anti-emetic choice should not negate the desired therapeutic effect of the original therapy; for example, using metoclopramide in nausea associated with the levodopa therapy will worsen Parkinson's symptoms due to central dopamine blockade.

Decreased gastrointestinal motility

A reduction in GI motility is associated with bloating, fullness and constipation and this can potentially reduce oral nutritional intake. Drugs blocking anticholinergic and those stimulating opiate receptors in the gut are the most common cause of slow transit and bloating; for many drugs this is a dose-related effect and may be attenuated through the use of modified release preparations or dose reduction (Table 5).

A syndrome of abdominal distension, pain, constipation, nausea and vomiting is a well-recognised effect of opiate therapy, and affects over 50% patients. Opiates have both a central and local component to their effect on the gut⁽²⁰⁾. Opioid receptors are expressed throughout the GI tract, reducing motility and secretory processes. Constipation caused by opioid therapy can be a side effect which is difficult to manage. Traditionally therapy has been targeted using stimulant laxatives, such as senna or bisacodyl, to counteract the effect on GI motility⁽²¹⁾. Transdermal opioid delivery systems appear to have a reduced incidence of constipation⁽²²⁾, perhaps due to the lack of topical action in the GI tract.

Table 5. Medication associated with decreased gastrointestinal motility

Anticholinergic effect
Tricyclic antidepressant
Oxybutynin
Propantheline
Opiates
Morphine
Codeine
Ondansetron

Table 6. Drugs associated with diarrhoea

Erythromycin
Metoclopramide and domperidone
Broad spectrum antibiotics
Auranofin (affects 50%)
Misoprostil (affects 8%)
Proton pump inhibitor (affects 1–3%)
Antivirals, adefovir, tenofovir, lamivudine
Antiretrovirals
Magnesium salts
Iron
Lithium (sign of toxicity)
Digoxin (sign of toxicity)
Acarbose
Sevelamer
Metformin
Colchicine (sign of toxicity)

Specific peripherally acting opioid antagonists are under investigation, which may offer an effective means of managing opioid-induced constipation without affecting the analgesic potential⁽²³⁾.

Dietetic management includes the provision of adequate oral or enteral fluid therapy and the supplementation of fibre. A multidisciplinary approach is necessary to manage constipation which can have a significant adverse effect on the quality of life of patients.

Diarrhoea

Diarrhoea is one of the most frequently reported side effects of drug therapy, with hundreds of drugs being implicated. Drug therapy can cause diarrhoea through a variety of mechanisms: increase in GI motility, alteration of gut flora and disturbance of mucosal surface. For some drugs, this can be a debilitating side effect; patients may reduce their oral intake in an attempt to reduce the frequency of diarrhoea (Table 6).

Anti-microbials are responsible for over 25% drug-induced diarrhoea. This can range from mild diarrhoea to life-threatening pseudo-membranous colitis. Penicillins and cephalosporins account for the vast majority of cases of pseudo-membranous colitis. Prompt corrective action is necessary; removal of the implicated antibiotic and initiation of metronidazole or vancomycin therapy⁽²⁴⁾. Erythromycin acts directly on motilin receptors to increase GI motility; this side effect has been exploited in the

Table 7. Drugs associated with dry mouth (incidence >10%)

Anticholinergic drugs	Sedatives
Atropine, Oxybutynin, hyoscine, benztropine	Diazepam, temazepam
Antidepressant and antipsychotic drugs	Muscle relaxants
SSRI – citalopram, fluoxetine, paroxetine, sertraline, venlafaxine	Orphenadrine
	Analgesics
Tricyclic – amitriptyline, imipramine	Codeine, methadone, tramadol
Atypicals – phenelzine, olanzipine	Ibuprofen, naproxen
Diuretics	Antihistamines
Furosemide, chlorothiazide	Astemizole, chlorphenamine, loratidine
Antihypertensives	Others
ACEI – captopril, enalapril, lisinopril	Carbamazepine, tolterodine, carbidopa/levodopa, ipratropium
Clonidine	
Methyldopa	

SSRI, selective serotonin reuptake inhibitor; ACEI, angiotensin converting enzyme inhibitor.

management of diabetic gastroparesis and other motility disorders.

Antiretrovirals are also associated with diarrhoea⁽²⁵⁾ particularly combinations of lopinavir and fosamprenavir with ritonavir; if significant, consideration should be given to changing to another combination.

Several chemotherapy regimens are associated with significant diarrhoea⁽²⁶⁾ which can lead to dehydration; loperimide is used routinely in the management of this side effect.

Consideration should also be given to the excipients used in liquid drug formulations; excessive intake of sorbitol from liquid medicines can cause diarrhoea⁽²⁷⁾, and excess maltitol causes bloating.

For most drugs, diarrhoea is self-limiting or ceases on discontinuation of the offending drug. Taking the drug with food or increasing the dose may gradually reduce symptoms, and is particularly effective with diarrhoea associated with metformin and iron preparations. Corrective action should be taken before reduced oral intake leads to weight loss.

Perception of food

Perception of food can dramatically change intake and enjoyment, and is influenced by image, texture, smell and taste⁽²⁸⁾. Side effects of drug therapy can affect all aspects of food perception but are predominantly due to effects on the perception of texture, taste and smell.

Dry mouth

Saliva has many functions. It enhances taste, facilitates speech and swallowing and irrigates, lubricates and protects the mucous membranes of the upper GI tract.

Salivary stimulus is affected by both the parasympathetic and sympathetic pathways. Parasympathetic stimulation increases the volume of saliva produced and sympathetic stimulation decreases volume and increases viscosity.

Many drugs have an action at the receptors that influence saliva production, causing a dry mouth and therefore affecting the perception of food texture and taste (Table 7). The most common cause of dry mouth is due to parasympathetic blockade by drugs with anticholinergic or

antimuscarinic activity, and sympathetic stimulation caused by alpha agonists. There are many drugs that act non-specifically at these receptors. The prevalence of dry mouth is unsurprisingly influenced by the number of drugs taken per day⁽²⁹⁾.

Management of dry mouth caused by drug therapy can be achieved in several ways. For many drugs, it is a dose-dependent side effect and therefore flattening the pharmacokinetic profile of the drug by using a modified release preparation or splitting the dose may reduce the severity of symptoms. An alternative drug within the same class may achieve the desired therapeutic effect with less dry mouth symptoms. If discontinuing the offending drug is not an option, it may be possible to adjust dose times to minimise the effect on oral intake and meal times. Salivary stimulants and artificial saliva products may be appropriate in severe cases.

Taste disturbances

Perception of taste is determined by the proportion of the five constituents: sweet, salt, bitter, sour and umami. Bitter and sour tastes tend to elicit an adverse effect on intake⁽³⁰⁾, because most toxins are bitter and food that has 'gone off' is sour; it is a protective mechanism and the reaction is more pronounced in children than in adults. Most drugs are toxic, particularly in large quantities, and most have a bitter taste.

Disturbances in taste due to medication are well documented and acknowledged as a common side effect; however, the implications for the effect on nutrient intake both in quantity and profile can be overlooked.

Taste disturbances can be categorised into four main types. Ageusia, a complete loss of one of the taste sensations, is rarely associated with drug therapy; however, hypogeusia, a reduction in the overall sense of taste, is more commonly associated with drug therapy (Table 8). Dysgeusia is an altered perception of taste, often described as bitter or metallic and is commonly associated with drug therapy (Tables 9 and 10). Parageusia is a bad taste in the mouth, in the absence of a source of taste and is rarely associated with drug therapy.

Management of drug-induced taste disturbances should include an investigation into other causes such as dry

Table 8. Drugs associated with ageusia or hypogeusia

ACEI	Clopidogrel	Methotrexate
Amphetamines	Colchicine	Methyldopa
Amiloride	Corticosteroids	Metoclopramide
Amphotericin	Didanosine	Metronidazole
Ampicillin	Diltiazem	Nifedipine
Aspirin	Furosemide	Penicillamine
Azathioprine	Glycopyrrolate	Phenytoin
Baclofen	Gold salts	Propranolol
Benzodiazepines	Hydralazine	Spironolactone
Candesartan	Hydrochlorothiazide	Sucralfate
Carbamazepine	Hydroxychloroquine	Terbinafine
Cephalosporins	Levodopa	Triamterine
Chlorhexidine	Losartan	Tricyclic antidepressants
Clarithromycin	Metformin	Venlafaxine
Cimetidine	Methimazole	Vincristine

ACEI, angiotensin converting enzyme inhibitors.

Table 9. Drugs associated with dysgeusia – bitter

Acetazolamide
Aspirin
Carbamazepine
Clarithromycin
5-Fluorouracil
Isosorbide mononitrate
Lamotrigine
Levodopa
Metolazone
Risperidone

Table 10. Drugs associated with disgeusia – metallic

Allopurinol
Captopril
Ethambutol
Gold salts
Lithium
Metformin
Methyldopa
Metronidazole (12%)
Nifedipine (6%)
Pentamidine (32–72%)
Sartans
Sulphasalazine

mouth or depression⁽³¹⁾ and where identified, corrective action taken. Where a clear association with a particular drug is identified, discontinuation of the offending drug should be considered.

If discontinuation of the offending drug is not possible, masking techniques using mouth sprays and lozenges containing local anaesthetics can be useful for dysgeusia.

The evidence supporting zinc supplementation in the therapeutic management of taste disturbances due to drug therapy is not conclusive and should only be recommended in patients with a proven zinc deficiency⁽³²⁾.

Drug-induced olfactory disturbance

The larger proportion of what we call flavour is contributed by odour and not taste, although the exact proportion is

Table 11. Drugs associated with olfactory disturbance

ACEI – angiotensin converting enzyme inhibitors, amikacin ⁽⁴⁰⁾ amiodarone ⁽⁴¹⁾ , amoxicillin ⁽⁴⁰⁾ , amphetamines, beta blockers, calcium channel blockers ⁽⁴²⁾ , chlorhexidine, cimetidine, cocaine ⁽⁴³⁾ , corticosteroids, decongestants, doxycycline ⁽⁴⁴⁾ , flubiprofen, gemfibrozil, gentamicin, inhaled corticosteroids, isotretanoin, levodopa, methotrexate, pentamidine, quinolones, sildenafil ⁽⁴⁵⁾ statins, streptomycin ⁽⁴⁰⁾ , sumatriptan, terbinafine, tobacco
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still debated, and smell is 10,000 times more sensitive than taste⁽³³⁾.

We respond in an involuntary way to odour, because smell is the only sensory pathway routed through the limbic system. The limbic system deals with emotion, motivation and the association of emotions with memory. The Proust phenomenon links autobiographical memory to odour⁽³⁴⁾. This can be a problem with trauma or medical treatments as they can be associated with the meal that was eaten prior to the event.

Smell is linked to appetite and satiety and is the first part of the cephalic phase. Food odour triggers an increase in salivation, gastrin and insulin release⁽³⁵⁾.

Patients suffering from anosmia (a complete lack of sense of smell) tend to prefer a texture-centred diet to facilitate food enjoyment. A reduction in the sense of smell and therefore taste can cause overeating due to the search for something 'tasty' or a reduction in intake⁽³⁶⁾.

Drug-induced olfactory disturbances are rarely considered in clinical practice and yet a reduction or alteration in our sense of smell can clearly have a profound effect on nutritional intake (Table 11).

Recent research in cancer patients has identified that chemotherapy causes a transient reduction in both sense of taste and smell, which is more pronounced in elderly patients⁽³⁷⁾. A recent review highlighted the potential impact on appetite, nutritional intake and weight loss and provided suggestions to improve nutritional intake in this group of patients⁽³⁸⁾.

Identifying patients at risk

Numerous studies demonstrate a direct correlation between the number of medications that a patient is taking and the incidence of side effects^(4,29). The consequences of these side effects can be compounded by the physical condition of the patient due to age, disease or malnutrition.

The older adult patient is at particular risk, due to declining organ function which may affect drug metabolism potentially increasing side effects coupled with a declining sensory function. Polypharmacy is particularly prevalent in this patient group.

An increased awareness of drug side effects that can affect nutritional intake in addition to the use of effective nutritional screening tools will assist in the early identification of drug side effects that adversely affect nutritional intake and allow corrective action to be taken.

It is increasingly important that the whole of the multi-disciplinary team involved in the nutritional care of

patients is aware of the potential impact, both negative and positive, that drug therapy can have on nutritional status. Any nutritional assessment should include a review of the patient's drug therapy and consideration should be given to any opportunity to optimise this therapy in collaboration with the pharmacist and prescriber.

There have been several publications advocating a role for both pharmacists and dietitians in the counselling and management on drug nutrient interactions; there are also many publications on the benefits of side effect counselling on concordance; however, many other ways in which drug therapy can affect nutritional status are yet to be widely acknowledged. There is a need for both patient- and professional-oriented educational materials to raise the awareness of these issues.

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