Pharmacovigilance in palliative care

SUMMARY

Patients receiving palliative care are at high risk of adverse effects from drugs. As these effects can be difficult to distinguish from the symptoms of the terminal illness, harm from medicines is often not recognised.

Adverse effects can contribute to the burden of symptoms, at a time when good control of symptoms is paramount. Adding another drug to treat the adverse effects can compound the problem.

Patients should be asked about their symptoms as they may not volunteer the information or recognise the link with their medicines. Reviewing their treatment may prompt a change in dose, drug or lead to some treatments being stopped.

Little is known about the prevalence of adverse drug events in palliative care. These patients have a high risk of adverse events because they are often elderly with multiple concomitant drug therapies, both for symptom control and for management of the terminal disease and other chronic conditions. They may experience significant weight loss, diminished oral intake, and altered organ function each of which can change a drug’s pharmacokinetics and pharmacodynamics. The burden of advancing disease and multiple morbidities often results in progressive increases in the number of drugs prescribed. Many patients will also be using non-prescribed treatments, including over-the-counter and complementary medicines, increasing the risk of interactions.

The adverse effects of drugs may have significant functional consequences for patients and their families. There are also associated burdens for patients, carers and families in managing the cost and complexity of medication regimens.

Decision making

Information from the patient, their families and carers about their goals and values is vital for informing decisions about treatment. Adverse effects may be weighed differently by patients and their families. Patients may have a
strong preference for having an opportunity to gain a sense of completion in their lives, of being able to say goodbye, resolve unfinished business and complete last tasks.6 While good pain control is essential, in one study physicians considered mental awareness to be much less important than pain control in contrast with patients who strongly valued being mentally aware. This study suggests that patients may be less willing to sacrifice lucidity for analgesia than doctors think.6

Treatments should be altered as symptoms change with time, reflecting changes in the patient’s condition. The expected benefits may diminish and the likely harms increase so the original therapeutic goals will need to be reset.7

Chronic diseases should be managed differently in patients who have little life remaining. The number needed to treat for one patient to benefit will tend to increase as death approaches because of the shortened prognosis, and the number needed to harm will fall as adverse effects become more frequent. The focus of prescribing should be on improving the quality of life while preventing avoidable harms.4,8 For example, there is little point in continuing a lipid-lowering drug in someone who is dying.

Symptom cascades

Drugs play an important role in relieving common symptoms, but there is a need to be vigilant for the ‘symptom cascades’ that result from adverse effects. Some of these symptom cascades are expected, such as constipation in patients starting opioids. Other examples of symptoms resulting from adverse effects are shown in Table 1.9

Common symptoms

There can be a tenfold difference between the number of symptoms volunteered by patients and those identified using systematic assessment.10 A study revealed that 69% of severe symptoms and 79% of distressing symptoms were not volunteered. This makes it difficult to identify symptoms that may be drug-related or exacerbated by drugs. Symptom assessment by nurses or other proxies only modestly correlates with the patient’s assessment and can significantly under-represent the patient’s actual symptom burden.11 Drugs may be either the primary cause, or exacerbate an underlying cause, of many common symptoms. Medicines that are used to treat a particular symptom may also cause that symptom, for example antipsychotics and benzodiazepines can trigger delirium.9

<table>
<thead>
<tr>
<th>Table 1 Common drug-related symptoms in palliative care 9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
</tr>
<tr>
<td>fatigue</td>
</tr>
<tr>
<td>anxiety</td>
</tr>
<tr>
<td>dry mouth</td>
</tr>
<tr>
<td>depression</td>
</tr>
<tr>
<td>hiccups</td>
</tr>
<tr>
<td>delirium</td>
</tr>
<tr>
<td>insomnia</td>
</tr>
<tr>
<td>constipation</td>
</tr>
<tr>
<td>drowsiness</td>
</tr>
<tr>
<td>restlessness</td>
</tr>
<tr>
<td>diarrhea</td>
</tr>
<tr>
<td>sweating</td>
</tr>
<tr>
<td>nausea</td>
</tr>
<tr>
<td>vomiting</td>
</tr>
</tbody>
</table>
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Drug-induced symptoms are usually a diagnosis of exclusion of other causes, but this is not always possible in palliative care. Some symptoms are also discontinuation effects when a drug is not taken, such as when agitation results from missed antidepressant doses.

**Deliurn**

Deliurn is a common neuropsychiatric complication in palliative care. It can result from a combination of predisposing baseline risk factors and superimposed precipitating factors. The prevalence is 26–62% for palliative care inpatients and up to 88% in the last days and hours of life.

Many drugs used for symptom control in palliative care (for example, benzodiazepines, corticosteroids, anticholinergics, opioids, antipsychotics) can exacerbate or cause neuropsychiatric adverse effects, including delirium. Opioids can cause delirium, but so can uncontrolled pain.

There are many similarities between the clinical presentation observed in terminal restlessness and delirium. This has led to the suggestion that terminal restlessness may actually be a potentially reversible acute delirium. A study of the occurrence, precipitating factors, and reversibility of delirium in patients with advanced cancer found that it was reversible in 49% of episodes.

**Management options**

An individualised approach is required which takes account of the level of investigation needed to identify reversible causes and the intensity of the therapeutic intervention to control delirium.

Initial management includes the identification of reversible causes. Many cases can be reversed if the delirium was precipitated by drugs, electrolyte abnormalities (which may also be drug induced) or infection. Non-drug strategies such as maintaining calm and quiet surroundings may be appropriate in some circumstances. Antipsychotics, specifically haloperidol, are widely used although there is limited evidence in palliative care. Benzodiazepines lack evidence to support their use for delirium in palliative care. Importantly, both antipsychotics and benzodiazepines can also cause delirium.

**Constipation**

Altered bowel habit is very common during palliative care. There are likely to be numerous concurrent risk factors, but opioids are often responsible. The relative contribution of different factors will change over time and it is often difficult to attribute constipation to opioids alone. For example, the catabolic state of cachexia, decreasing mobility and oral intake, and drugs with anticholinergic adverse effects are all likely to contribute. Opioids and other drugs may simply ‘tip the balance’.

Observational studies report that up to 60% of patients admitted to palliative care units are already receiving laxatives with the majority taking more than one type of laxative. However, constipation is still often underdiagnosed and undertreated in palliative care.

The consequences of constipation can contribute significantly to the patient’s symptom burden. This may result in prescribing cascades to treat the complications, with further potential for drug-related adverse effects. This includes the potential for harm from laxatives, such as the salt and water retention associated with some macrogol formulations which have a high sodium content, or pain associated with stimulant laxatives in people who have hard or impacted stools. Bowel perforation is a rare but important severe adverse effect.

**Management options**

In addition to addressing and modifying reversible causes of constipation, including drugs, laxatives are usually required. Current clinical guidelines such as Therapeutic Guidelines: Palliative Care recommends that, if it is safe to do so, the initial prescription should be an oral stool softener and a stimulant laxative. Rectal interventions may also be necessary when impaction has occurred, particularly if myopathy or neuropathy is contributing to the problem. After excluding bowel obstruction, methylnaltrexone can be tried in opioid-induced constipation which has failed to respond to laxatives.

**Box Potential consequences of drug-induced constipation**

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Impaction, obstruction, megacolon, faecal incontinence, rectal prolapse, haemorrhoids, bloating, anorexia and vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac and vascular</td>
<td>Arrhythmias, vasovagal episodes, angina</td>
</tr>
<tr>
<td>Urological</td>
<td>Retention, incontinence, urinary infection</td>
</tr>
<tr>
<td>Other</td>
<td>Delirium, anxiety, analgesic failure (opioid dose-limiting constipation), worsening pain, impaired quality of life</td>
</tr>
</tbody>
</table>

Adapted from reference 18
**Urinary symptoms**

Many medicines can contribute to urinary symptoms (see Table 2). Anticholinergic effects contribute to and worsen urinary symptoms particularly urinary retention and overflow incontinence. Complementary medicines can also cause problems. For example, St John’s wort has been associated with voiding difficulty, and guarana or large amounts of caffeine can increase diuresis, aggravate detrusor instability and worsen urge incontinence.

Many patients experience urinary symptoms, but often do not disclose them. If they are not asked directly, urinary incontinence may go unrecognised by clinicians. The causes are likely to be multifactorial and fluctuate so the contribution to symptom burden will vary. Urinary incontinence and faecal incontinence can sometimes be the ‘last straw’ for managing a person at home.

Urinary incontinence can impair participation in daily activities, physical functioning, psychological well-being, and overall quality of life. Patients with urge incontinence are almost twice as likely to fall than other patients. Incontinence can also put patients at increased risk of skin and urinary tract infections. Drug-related urinary retention is potentially reversible. Agitation and restlessness may be the result of a full

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Type of incontinence caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>cough</td>
<td>stress</td>
</tr>
<tr>
<td>Diuretics</td>
<td>diuresis (polyuria)</td>
<td>urge</td>
</tr>
<tr>
<td>Verapamil</td>
<td>impaired emptying (retention), voiding difficulty, constipation, dependent oedema (nocturnal polyuria)</td>
<td>overflow, urge</td>
</tr>
<tr>
<td>Alpha adrenergic agonists (pseudoephedrine)</td>
<td>increase urethral and prostate capsule smooth muscle tone (obstruction and retention)</td>
<td>overflow</td>
</tr>
<tr>
<td>Alpha adrenergic antagonists (prazosin, tamsulosin, terazosin)</td>
<td>sphincter relaxation</td>
<td>stress</td>
</tr>
<tr>
<td>Anticholinergics (oxybutynin, solifenacin, tolterodine)</td>
<td>reduce detrusor activity (retention), bladder outlet obstruction, constipation, sedation, dry mouth (polydipsia), blurred vision, confusion, delirium</td>
<td>overflow, functional, urge</td>
</tr>
<tr>
<td>Some antihistamines, biotropium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>selective serotonin reuptake inhibitors</td>
<td>increase detrusor activity, sedation</td>
<td>urge, functional</td>
</tr>
<tr>
<td>tricyclic antidepressants</td>
<td>anticholinergic effect, sedation, confusion</td>
<td>overflow, functional</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>anticholinergic effect, sedation, confusion, impaired mobility, parkinsonism, constipation</td>
<td>overflow, functional, stress</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>sedation, confusion, impaired mobility</td>
<td>functional</td>
</tr>
<tr>
<td>Opioids (oxycodone, morphine, fentanyl, codeine, tramadol)</td>
<td>impair voiding reflex (retention), reduce detrusor activity, constipation, sedation, confusion</td>
<td>overflow, functional</td>
</tr>
<tr>
<td>Alcohol</td>
<td>diuresis (polyuria), lowers central inhibition</td>
<td>urge, functional</td>
</tr>
<tr>
<td>Caffeine</td>
<td>diuresis (polyuria)</td>
<td>urge</td>
</tr>
<tr>
<td>Beta agonists</td>
<td>impair emptying (retention)</td>
<td>overflow</td>
</tr>
<tr>
<td>Cholinergics (donepezil, galantamine, rivastigmine, bethanecol)</td>
<td>increase detrusor activity</td>
<td>urge</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>dependent oedema (nocturnal polyuria)</td>
<td>urge</td>
</tr>
<tr>
<td>Rosiglitazone, pioglitazone</td>
<td>dependent oedema (nocturnal polyuria)</td>
<td>urge</td>
</tr>
<tr>
<td>Lithium</td>
<td>polydipsia (polyuria)</td>
<td>urge</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>dependent oedema (nocturnal polyuria)</td>
<td>urge</td>
</tr>
</tbody>
</table>
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and distended bladder and resolution of the problem
 can bring much relief.

Management options

Management of incontinence and urinary retention
includes assessment of underlying causes. It may
not be possible to change or alter effective drugs,
for example analgesics, but careful review may
identify drugs which are exacerbating incontinence
and contributing to symptom burden. Some can
be stopped or have their adverse effects managed,
for example improved management of constipation
may relieve urinary retention. A trial of simple
catheterisation, repeated if necessary or leading to a
permanent indwelling catheter, may be appropriate
depending on the underlying aetiology of the
urinary symptoms.19

Dry mouth

A dry mouth may be caused by underlying disease,
surgery, radiotherapy, fluid restriction and many
drugs. It is a common symptom, but patients do not
often complain about it. A study of 200 patients
revealed that dry mouth was only volunteered by
1.5% of them, however when systematically assessed
65.5% had the symptom.10 It can result in a very
painful, sore mouth which impacts on the ability to
eat, drink, take medicines or talk.

A hospice study found that dry mouth can contribute
to the risk of falls as patients may struggle to get
water to quench their thirst, particularly marginally
ambulant patients who feel uneasy about asking for
help or losing independence.24

Commonly used medicines for symptoms such
as pain, nausea, agitation, delirium and confusion
may contribute to dry mouth. Many medicines for
comorbid conditions also contribute to a cumulative
anticholinergic burden.25,26

Fluid intake for some patients needs to be
carefully balanced, for example in heart failure,
while for others increasing fluid intake to relieve
dry mouth can contribute to increased urinary
frequency. Moving more frequently to the toilet
may exacerbate painful movements and trigger
other symptom cascades for which additional drugs
may be prescribed. If movement is not possible,
additional toileting can increase the burden on
patients and carers.27

Management options

Carmellose spray and hypromellose gel for dry
mouth and benzydamine for painful mouth are
available through the palliative care section of the
Pharmaceutical Benefits Scheme.28 A few treatment
options advocated for dry mouth can worsen or
exacerbate painful mouths in some people, for
example lemon and glycerine mouth swabs. It is
important to individualise treatment and monitor
outcomes to enable timely changes in management.

Pharmacovigilance and research

There are very few studies of adverse drug events
in palliative care.29 In addition, the impact of adverse
effects, such as urinary and faecal incontinence,
anorexia, confusion, restlessness and agitation, on
patients and their carers has not been well studied.

There is a need to be aware that drugs may
contribute to symptom clusters or cascades in
palliative care. Identifying an adverse drug event
presents an opportunity to effect a ‘cure’ by
lowering the dose, stopping the drug or changing
to a less ‘toxic’ treatment.30 Stopping treatment
is an integral part of good prescribing and should
be reflected in conversations with the patients and
their carers.

The discipline of palliative care aims to improve its
evidence base for clinical prescribing. In Australia
randomised controlled trials of drugs in palliative
care are being conducted as part of the Palliative
Care Clinical Studies Collaborative (PaCCSC).28,31,32

A need to encourage the reporting of adverse
drug events has prompted the development of the
PaCCSC Rapid Pharmacovigilance studies, with more
than 90 centres in 18 countries now participating.33

Adverse events should be reported to
the Office of Product Review of the Therapeutic Goods
Administration.

Conclusion

The increasing use of drugs for chronic disease and
symptom management in palliative care increases
the risk of adverse effects. There is a need to review
the patient’s symptoms to see if they are caused or
exacerbated by drugs. Unnecessary medicines should
be stopped safely and non-pharmacological options
should be considered.

As patients often do not volunteer their symptoms,
ask about problems which may be adverse effects
of treatment. Pharmacovigilance does not end when
palliative care begins.<

Conflict of interest: none declared
Dental note

Managing the adverse effects of drugs used in palliative care

Very few patients actually complain of oral dryness (1.5%), yet on questioning, this is the second highest reported symptom of concern (67%) in patients receiving palliative care.1 A study assessing end-of-life care found that of the 96 patients with an estimated life expectancy under three months, mouth pain was reported by 67%, problems with food intake by 56%, and dry mouth by 78%.2 What is disappointing is that 78% of these patients said that they had received no information about oral adverse effects of cancer treatment.2

In an interview-focused study of 14 palliative care patients, from a mid-sized hospital in regional Australia, it was found that a range of oral problems significantly impacted on their physical, social and psychological well-being to varying degrees, sometimes over extended periods of time.3 The participants reported a lack of oral assessment and virtually no input from dental experts to assist with palliating oral problems.3

These problems are not new. In the 1990s many terminally ill patients were found to have oral problems resulting from therapy and poor oral care during lengthy illnesses. It was suggested that by including a dentist in the palliative care team, the dental needs of dying patients would be likely to be managed more effectively.4 Dental assessments may well identify dental disease, to not only reduce the microbial load, but also decrease the risk of oral pain and infection.5 Including a dentist in the multidisciplinary approach to palliative care may also improve the patient’s ability to speak, eat or swallow.5

Unfortunately, there is no single panacea for oral palliative care. There have been many suggested strategies, based on the limited clinical trial data available.6 Simple mouthwashes using bicarbonate7 may well be as effective as complex, over-the-counter and expensive topical products. These simple mouthwashes will not alleviate pain from dental disease, such as oral candidiasis, periodontal disease, tooth pain or abscesses, however dentists are excellent at dealing with specific physical curative treatment, that often has almost instantaneous results. Examples are the repair of a fractured tooth, the removal of an infected tooth, or the perfection of a smile with dental aesthetics.

REFERENCES