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From research to reality: A review of three clinical problems in the last days of life ☆

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ABSTRACT

All of us will one day die. For most of us, death will be anticipated, usually following a period of ill health. The opportunity to anticipate and manage clinical conditions associated with the agonal process is an essential part of advance care planning.

Guidelines exist for the palliation of most symptomatic events at the end of life, although many recommendations are based on low-quality evidence or consensus. Furthermore, when potentially practice-changing data emerge, there is an inevitable lag time before clinical practice changes.

In this paper, we shall discuss the management of three challenging scenarios faced by teams looking after patients at the end of life: delirium, terminal haemorrhage and noisy upper airway secretions. We aim to critically evaluate the utility of current evidence, pharmacological and non-pharmacological, and how it translates into clinical practice.

Introduction

Every human life on this planet is furnished with its own tranche of genetic, epigenic and lifestyle-associated risk factors, which will influence their predisposition to disease. Our increasing understanding of these factors has led to developments in a more targeted approach to the diagnosis and earlier treatment of those at greatest risk. This individualised approach has resulted in improved outcomes, including overall survival for some. However, despite healthcare developments among our highly heterogenous population, there remains one clinical commonality which unites us; the fact that every one of us will die. There is sad irony, therefore, that management of the dying person is informed by such a limited evidence base. It is beyond the scope of this article to explore reasons for the limited evidence base, and the challenges of undertaking research at the end of life have been recognised for some time.[1] However, with appropriate funding, expertise and infrastructure, it is possible to research the most fundamental of clinical end-of-life questions.[2,3]

Without a strong evidence base, common end-of-life problems will continue to be managed by consensus, with guidelines basing their recommendations on low-level data. Few end-of-life medicines have been evaluated through prospective randomised control trials (RCT), leaving us to manage some clinical problems based on little more than agreed ritual. On the rare occasions that adequately powered RCTs have been conducted, their outcomes have been variably received, particularly when they challenge current dogma.

In this paper, we shall describe the management of three events that may manifest near to or during the dying process. We shall critically evaluate the evidence base upon which the management of these important presentations are based to explore if current palliative care evidence translates to optimal end-of-life care.

Delirium in the last days of life

Delirium is a global impairment of cognition, perception and consciousness, characterised by memory dysfunction, disordered thinking and sleep–wake cycle reversal. Delirium can be hyperactive, defined by restlessness, agitation and hallucinations; hypoactive, where patients become slow and withdrawn; or mixed, with patients exhibiting features of both types. Delirium at the end of life can range from mild to severe and uncontrolled. Severe hyperactive delirium at the end of life is sometimes recognised as a form of terminal agitation, though it is important to note that individuals may exhibit signs of agitation without delirium, for example secondary to breathlessness, existential distress, or a sudden and rapid decline in their condition.

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Table 1
Common potentially reversible causes of delirium in the advanced cancer patient.[6]

Reversible causes	Notes
Pain	Analgesia
Bladder and bowel issues	Constipation: laxatives Urinary retention: catheter Irritation from urinary catheter: repositioning or removal
Infection	Identify source Antibiotics and supportive measures
Opioid toxicity	Reduce opioid dose if pain levels allow, opioid switch, change to non-opioid analgesics, treat precipitating factors eg renal impairment, dehydration
Hypercalcaemia	Correct dehydration/renal impairment first with IV fluids, then treat with IV bisphosphonates
Cerebral irritation	Consider treatable/modifiable intracerebral pathology eg raised intracranial pressure, chronic subdural, encephalitis
Accumulation of drugs	Cachexia may lead to reduced protein binding of medicines, leading to higher concentrations of free drug eg anticonvulsants Renal impairment may lead to accumulation of renally excreted medicines eg morphine, digoxin

Table 2
Suggested medication doses for the management of delirium at the end of life (adapted from *Oxford Textbook of Palliative Medicine* [2021]).[12]

Medication	Route of administration	PRN dose	Syringe driver/24 hours dose[a]
Haloperidol	Subcutaneous	0.5 mg 2 hourly, max 5 mg/day	Uptitrate as needed to max 5 mg/day
Levomepromazine	Subcutaneous	12.5–25 mg hourly, max 50 mg/day	Uptitrate as needed to max 50 mg/day
Midazolam	Subcutaneous	2.5–5 mg hourly, max 60 mg/day	Uptitrate as needed to max 60 mg/day

[a] Starting doses should be based on PRN use and maximum doses may be higher only with SPC input.

The first step in the management of delirium at the end of life is to establish the diagnosis. The 4AT is an objective rapid screening tool that has been validated for use in the diagnosis of delirium in the hospice setting.[4] Similarly, the nursing delirium screening scale has been validated for rapid and continuous screening of delirium.[5]

The next priority is to identify any precipitating causes of delirium and whether they may be reversible. Common reasons are listed in Table 1; it is important to note that there are often multiple causes. Furthermore, each pathology may concurrently complicate other causes. For example, as hypercalcaemia progresses, it will lead to renal impairment and dehydration. Renally excreted medications such as morphine can accumulate, worsening delirium.

It is important to ascertain the patient's wishes around escalation and investigation when they are well enough to make these decisions. For patients who wish to have investigations carried out, and where it is practical to do so, it may be appropriate to consider all reversible causes. In patients where investigations would not be appropriate, some reversible causes can still be elicited and acted upon. Subjecting a patient to investigations such as CT brain or lumbar puncture is often inappropriate and should only be undertaken if the patient is well enough to undergo treatment with a sustained period of improvement.

Management of irreversible delirium at the end of life

Irreversible delirium can be diagnosed where no reversible cause can be identified, a patient has not responded to treatment, or the ceiling of treatment has been reached. While delirium can be managed with non-pharmacological techniques such as communication, reorientation and reassurance, this is not always a feasible option in the dying patient.[7] Pharmacological measures are often used to reduce patient distress. It is important to acknowledge the support needed for loved ones who may find delirium at the end of life distressing to witness.

Pharmacological management

Medications should first be trialled on a PRN basis, with a view to commencing a continuous dose via syringe driver if required. A first-generation antipsychotic such as haloperidol or levomepromazine is recommended as first-line treatment.[8] Benzodiazepines such as midazolam can be used for rapid delirium control, but should be used cautiously, as they can cause paradoxical agitation.[8] They may be an appropriate second-line intervention to use alongside an antipsychotic.[9] Pharmacological management of delirium should begin at the lowest possible dose with slow titration to minimise side-effects. Specialist palliative care (SPC) services should be involved early in the management of delirium at the end of life.

Objective assessment of the use of antipsychotics for delirium in palliative care make for interesting reading. In a double-blind, parallel arm RCT, palliative care patients with delirium were randomised to receive risperidone, haloperidol or placebo, titrated according to symptom severity. Additional supportive measures and subcutaneous midazolam were provided for distress or safety. The placebo group had lower delirium scores than the risperidone and haloperidol arms. In addition, patients receiving haloperidol had lower overall survival. Not surprisingly, the authors concluded that individualised management of delirium precipitants and supportive strategies resulted in lower delirium scores and shorter duration of distressing delirium symptoms than when using risperidone or haloperidol.[10] Despite these interesting findings, antipsychotics, rather than benzodiazepines, remain the first-line pharmacological agent to manage delirium.[11] This most likely represents clinicians' interpretation of the data to be that the safest interventions for delirium are non-pharmacological or supportive measures.

Severe and uncontrolled delirium at the end of life

Delirium causing uncontrolled distress in a dying person despite use of the above measures is a medical emergency requiring urgent SPC input. Such patients may need to be managed with continuous palliative sedation for symptom control. This option must consider previous wishes of the patient and involvement of their loved ones.

Terminal haemorrhage

For the purposes of this article, terminal haemorrhage is defined as 'a major haemorrhage, from an artery, which is likely to result in death within a period of time that may be as short as minutes'.[13] While thankfully rare, the experience of a poorly managed terminal bleed leaves an indelible impression on anyone who bore witness. Clinical guidelines recommend identifying those at risk of terminal haemorrhage and ensuring that they are pre-prescribed 'crisis medicine'. The classic scenario of a terminal haemorrhage consists of a patient with progressive head and neck cancer with a tumour in close anatomical proximity to an artery such as the carotid. The risk is increased if the patient has received

radiotherapy to the locality, which makes the surrounding tissue more friable.[14] Events are often preceded by small herald bleeds. Other cancers at risk of terminal haemorrhage with associated visible blood loss are pulmonary, upper gastrointestinal and uterine. Statistically, the risk is greater in the presence of thrombocytopenia or coadministration of anticoagulants or antiplatelets, but in the presence of an arterial bleed, such cofactors are moot.[15]

Crisis medicines refer to administration of a parenteral anxiolytic such as midazolam, with the aim to reduce distress from the sight of rapid blood loss and/or the symptoms of decompensation from exsanguination.[13,16] A suggested dose of 5–10 mg intravenous midazolam is recommended if the patient has a cannula in place, or 5–10 mg subcutaneously if not. Some guidelines have suggested the use of opioids, although this introduces additional delays in accessing medicines stored as controlled drugs. A further recommendation is to have green sheets/towels to hand, since these will mask the colour of blood and hopefully be less distressing.

It comes as no surprise that these recommendations are based on consensus and not prospective research, due to the scarcity of events and other clinical and ethical challenges around conducting prospective studies. However, qualitative interviews with healthcare professionals (HCPs) who have witnessed or managed terminal haemorrhage offer interesting insights as to the utility of current guidelines.[13,16,17] Significant findings are reported below.

1. *Vivid memories of the event*
   Acute terminal haemorrhage is, thankfully, extremely rare. However, those who have borne witness to such an event remember it in detail. This adds to the veracity of their recollections and illustrates the marked impact that such an event has.
2. *We are poor predictors of those at risk of terminal haemorrhage*
   Patients identified at being at risk of haemorrhage rarely, if ever, progressed to a terminal bleed. Those who had a terminal haemorrhage were rarely predicted and hence not prepared for. Similarly, those charted for crisis medicine never required it. This might challenge the benefits of warning families or patients of the risk of terminal bleed if this event does not happen.
3. *Death is rapid*
   Witnesses suggested the time from initial bleed to loss of consciousness was less than a minute, with death following quickly after. Midazolam is reported to induce sedation within 2–2.5 mins when given intravenously, 5–10 mins subcutaneously and 15 mins intramuscularly.[18] This would suggest that even if a patient had a cannula in place and the drug was ready to hand, the patient would, in the very least, be unconscious before its effects were noticeable.
4. *Patients frequently left alone to get crisis medicine*
   At the sign of a terminal haemorrhage, staff would immediately rush to get the prescribed crisis medicine. This process took at least several minutes, if not longer. This usually resulted in the patient being left alone to bleed to death, usually terrified.

These observations listed above suggest that the prescribing of crisis medicine does more to reassure HCPs that 'something is being done', rather than offer any real form of symptom control or solace to the patient. In addition, it introduces a strong likelihood that the patient may die alone, should staff prioritise accessing medicine over remaining with the patient. In view of this, the most important advice for anyone witness to a terminal bleed is to stay with the patient and maintain a calm environment. If there is someone with the patient, the next step is to call for help. The team can gather necessary equipment and medications. Non-pharmacological interventions include applying external pressure on a visualised site of bleeding and using dark towels to conceal the extent of blood loss.[13] If the patient is bleeding orally, lying them in the lateral decubitus position towards the site of bleeding may reduce the risk of aspiration and suffocation.[19]

The above recommendations are of help to HCPs caring for an inpatient, but not all patients experiencing terminal haemorrhage do so as inpatients. Many patients identified to be at risk of a fatal bleed will be discharged or residing at home, and the decision to discuss the risks of bleeding and the associated outcomes pose considerable ethical dilemmas for the team. Respecting the patient's autonomy should take precedent over the other major ethical principles, but this should be approached in a sensitive, unrushed approach in order to ascertain how much information a patient wants regarding their condition and possible complications. Any way of establishing the likelihood of the patient having a bleed, such as previous bleeds or evidence of tumour encroachment on an artery, will help establish whether a frank discussion, while following a duty of candour to the letter, might be causing unnecessary distress to an already vulnerable patient and family.

Finally, as with any distressing clinical or ethical scenario, the importance of a team debrief and opportunity for support cannot be overemphasised. Similarly, the consequences of such an event on loved ones will be profound and highly likely to contribute to a complex bereavement.[20]

Noisy upper respiratory tract secretions in the last days of life

Respiratory secretions are common at the end of life and are reported in up to 92% of anticipated deaths.[21] Secretions predominantly occur when the patient's level of consciousness is too depressed for them to swallow or expectorate and are thereby a harbinger of imminent death.

Terminal secretions are rarely distressing for the patient as they are usually deeply unconscious. Some loved ones who bear witness to this final stage of life see the presence of secretions as a reassuring sign, indicating an imminent end to a distressing situation; however, others can be distressed by the presence of sounds perceived as 'choking' or 'drowning'.[22]

The first-line management for terminal secretions is education and reassurance for loved ones. Simple measures, such as repositioning, can also be helpful. If these interventions do not help, a trial of parenteral antimuscarinics may be considered.[23] Hyoscine butylbromide, hyoscine hydrobromide or glycopyrronium bromide can be used when treating secretions.[12] There is no one preferred medication to use and the correct option should consider patients' comorbidities, risk of side-effects and concurrent medications. If a single dose of one of these medications has some positive effect on secretions, a syringe driver may be considered. Antimuscarinics do not clear existing secretions. It is also important to monitor the patient for unwanted side-effects, such as dry mouth, urinary retention and constipation. These can lead to confusion, which may present as terminal delirium. Additionally, hyoscine hydrobromide crosses the blood–brain barrier, which can also precipitate confusion.[24]

Despite the numerous guideline recommendations to the use of antimuscarinics for terminal secretions, systematic reviews have identified a paucity of high-quality research to justify the recommendations. A Cochrane review found no evidence to show that any intervention, pharmacological or non-pharmacological, is superior to placebo in the treatment of terminal secretions.[25] The authors acknowledged that in the face of heightened emotions when death is imminent, staff will feel a pressure to intervene in some way. This may well account for the continued use of antimuscarinics as a therapeutic option.

Conclusion

This brief review of three conditions that occur at the end of life highlights the limited evidence base that informs our current clinical guidelines and consequently our practice. While this might be understandable in the context of rare conditions such as terminal haemorrhage, guidelines for management of common conditions such as terminal secretions and delirium recommend strategies that, at best, are based on minimal supportive evidence and, at worst, in contradiction to the more robust of the published research evidence. For the research base to improve, we need to nurture the current specialist in training to pursue every

opportunity to gain formal research training. The number of research-focused clinical academics across all specialties is in decline, with palliative medicine academics making up a tiny proportion of the university workforce. It is impossible to say whether this situation is likely to change soon. In palliative medicine, we often use the term 'Hope for the best, but prepare for the worst'.

Here's hoping.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Tasneem Wadee: Writing – review & editing, Writing – original draft, Conceptualization. **Simon Noble:** Writing – review & editing, Writing – original draft, Conceptualization.

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