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Access to opioids for patients with advanced disease

Abstract

Pain at the end of life is common in both malignant and non-malignant disease. It is feared by patients, their families and carers, and professionals. Effective pain control can be achieved for the majority of patients at the end of life using a multimodal approach. Pharmacological management relies predominantly on strong opioids. In spite of this, evidence suggests that under treatment of pain is common resulting in unnecessary suffering. Multiple barriers to use of opioids have been identified. Patient barriers include reluctance to report pain and to take analgesics. Professional barriers include inadequate pain assessment and lack of specialist knowledge and confidence in opioid therapy. Fear of side effects including respiratory depression affects patients and professionals alike. The impact of the “opioid epidemic”, with increasing prescribed and illicit opioid use around the world, has also led to increasingly stringent regulation and concern about under prescribing in palliative care. System barriers to use of opioids at the end of life result from limited opioid availability in some countries and also inconsistent and limited access to palliative care. Multiple interventions have been developed to address these barriers, targeted at patients, professionals and systems. There is increasing evidence to suggest that complex interventions combining a number of different approaches are most effective in optimising pain outcomes for patients at the end of life.

Key words: Access to opioids, advanced disease, pain, palliative care, treatment.

Introduction

Pain at the end of life is one of the most feared symptoms by members of the public and doctors alike (1). It is common in cancer, confirmed in a recent large systematic review which found pain affects more than 50% of all cancer patients and 66.4% of those with advanced/metastatic/terminal disease (2). It is also prevalent in non-cancer illnesses, affecting more than 50% patients with non-cancer terminal disease (3, 4).

Pain at the end of life, along with other palliative care needs, is becoming an increasing clinical challenge (5). In 2018, it is estimated that cancer will be responsible for 6.9 million deaths worldwide (6), a significant proportion of whom will experience pain. This is set to increase further, with increasing global population (7), life expectancy (8, 9) and multimorbidity (10, 11). There is also increasing recognition of the important role that palliative care can play in life-limiting non-malignant disease (12, 13), widening the remit of palliative care still further. For example, a UK study estimates that 160,000 more people in England and Wales will need palliative care by 2040 and this will largely be driven, not only by cancer, but also dementia (5).

There are multiple mechanisms leading to pain in both cancer and non-cancer illness at the end of life. The presence and nature of pain in cancer can be affected by the histologic type of cancer, the location of the primary tumour and the location of any metastatic disease (14). It can also result from cancer treatment (e.g. chemotherapy, surgery), treatment-related procedures (e.g. thoracocentesis), and co-morbid conditions (15). Pain in cancer can be classified according to the underlying mechanism, either nociceptive or neuropathic. Nociceptive pain is caused by tissue damage, resulting in either somatic (e.g. bone) or visceral (e.g. gut) nociceptive pain (15). Neuropathic pain results from damage or dysfunction of the nervous system (e.g. spinal cord compression from metastatic disease) (16, 17).

Pain in non-cancer illnesses is common in many conditions including dementia (18), chronic obstructive pulmonary disease (COPD), end-stage renal disease, acquired immune deficiency syndrome (AIDS), Parkinson's disease, Motor Neuron Disease, Multiple Sclerosis (18) and end-stage heart failure (19). Pain mechanisms in these groups vary depending on the diagnosis. For example, in COPD a systemic inflammatory process may contribute to chronic and neuropathic pain, along with musculoskeletal pain from chest wall hyperinflation and osteoporosis, and inactivity aggravating pre-existing conditions such as osteoarthritis (20, 21). In people with dementia, pain may result from other common conditions that affect the elderly such as osteoporosis and arthritis, but there may also be altered perception of pain intensity and the affective components of pain associated with the condition (22).

Access to opioid analgesics

Access to pain relief, including in palliative care, is now recognised as a fundamental human right (23, 24). A multimodal approach to pain relief at the end of life is increasingly advocated, comprising pharmacological and non-drug interventions (25). Current "best practice" for pharmacological management is generally based upon the World Health Organisation (WHO) analgesic ladder (26, 27), first introduced in 1986. It was developed in response to perceived lack of recognition of existing guidelines for pain in cancer , lack of government concern, limited availability of opioids, fears around "addiction" to opioids and lack of systematic education of medical professionals about management of pain in cancer (27).

The analgesic ladder recommends initial use of non-opioids (paracetamol or non-steroidal anti-inflammatory drugs). If pain control is not achieved then mild opioids such as codeine, dihydrocodeine or tramadol should be added. If this is not sufficient then strong opioids such as morphine should be used. Importantly patients presenting with moderate to severe pain should be started on strong opioids from the outset, instead of moving through the earlier steps of the ladder. It has been suggested this point is often overlooked (28). Additional agents known as "adjuvants" may also be used at all stages. These might include antiepileptics or antidepressants for neuropathic pain (15, 29, 30). Disease-modifying therapy, nerve blocks and nondrug measures may also be used (28).

Precise estimates vary, but in cancer patients with pain treated according to the analgesic ladder, pain can be reduced or eliminated in the large majority (28, 31). More recent evidence suggests that effectiveness of the analgesic ladder rests predominantly on strong opioids (32). This is reflected in most current international guidance for cancer pain, questioning the role of weak opioids in treating pain in cancer, and suggesting that, for moderate to severe pain, strong opioids should be used first-line (15, 30, 33, 34).

There are multiple different formulations of opioids (35). These enable treatment to be tailored to best meet patients' needs. They include immediate and sustained-release preparations for maintenance treatment and immediate-release preparations for breakthrough pain. Drugs can be administered orally, transdermally, subcutaneously and intravenously. Concomitant prescription of antiemetics and laxatives with strong opioids is important (30, 35) to try to offset common side effects including nausea, vomiting and constipation.

Despite increased recognition of the importance of treating pain at the end of life and clear guidance for optimal treatment with opioids, there is evidence of ongoing under treatment (2). This results from both late and inadequate prescribing. In cancer, an updated systematic review of pain prevalence in cancer showed no decrease in prevalence over the last 10 years (2, 36). Another systematic review of management of pain in cancer showed some improvement over recent years, but that despite this one in three patients still do not receive pain relief which matches their reported level of pain (37).

As management of pain in cancer is so heavily dependent on opioids, study of opioid prescribing is important in ascertaining reasons for under treatment. A UK study showed that 48% of patients who died from cancer received a prescription for a strong opioid in the last year of life and the median interval between first prescription and death was 9 weeks (38). This does not match epidemiological studies suggesting higher pain prevalence and earlier onset, likely to require earlier and more frequent treatment with strong opioids (36, 39). Similar findings have been reported by other groups. Another UK study showed 43.6% of patients dying from cancer received at least one prescription for opioids in the last 3 months of life (40). A Dutch study found 51% of people dying from both cancer and non-cancer were prescribed a strong opioid over the same period (41). The Dutch study was notable in including both cancer and non-cancer patients, there being a paucity of data in the literature for the latter group. In this study 27% of all patients in general practice receiving palliative care were not prescribed any analgesics. A Canadian study found that 58.8% of cancer patients appeared to be receiving minimal doses of opioids up to 2 weeks prior to death (42).

Under-prescribing of opioids contributes to under-treatment of pain in cancer, but the way in which opioids are used may also be a factor. A Norwegian study examined how prescribing adhered to the analgesic ladder. They showed higher prescribing overall, with up to 60% of patients who died of cancer receiving strong opioids prior to death, though evidence of inadequate prescribing for breakthrough pain in a quarter of patients (43).

Under–treatment of pain in cancer is a particular problem in the community. The UK National Survey of Bereaved People (VOICES) survey in 2015 showed that in the last three months of life, just 18.6% people cared for at home had their pain relieved “completely, all of the time”, in contrast to 63.5% of those cared for in a hospice (44). This is consistent with the findings of the Ziegler study which found that patients who died in hospital were 60% less likely to have received a strong opioid while they were at home compared with those who died in a hospice, and were more likely to start strong opioids late (38). The authors suggested this might reflect poor pain management leading to admission and advocated earlier pain assessment at home. This is particularly relevant in the UK where there is increasing emphasis at a policy level on palliative care being delivered by generalists in the community (45).

Barriers to effective use of opioids

Considerable research has been done to identify barriers to use of opioids at the end of life leading to under treatment. These can be grouped into professional, patient and health care system barriers (29, 46, 47).

Professional barriers to opioid use include clinicians' reluctance to prescribe or administer, due to lack of specialist knowledge and confidence in opioid therapy, or fears about side effects including respiratory depression (48). This has been exacerbated by the case of Harold Shipman in the UK leading to GPs being even more apprehensive about using opioids (48, 49). Shipman was a General Practitioner who was convicted of murdering 15 patients by injecting them with lethal doses of diamorphine, but was thought to have been responsible for at least 200 more deaths (50). The Shipman effect may well have been compounded by another more recent report about Gosport War Memorial Hospital in Portsmouth, UK, where the lives of over 450 people, admitted for rehabilitation or respite, were shortened as the direct result of prescribing and administering opiates which were not clinically indicated or justified (51).

Inadequate assessment of pain is another important and frequently cited professional barrier to adequate opioid prescribing at the end of life (52, 53). Inadequate knowledge and training in palliative care for generalists, along with poor access to specialist support, also contribute. Aside from fears of side effects, professionals also report concern regarding tolerance and addiction to opioids (52). Professionals' fears of legal or administrative constraints may play a role (52, 53).

Patient barriers to opioid prescribing were examined by Ward et al in 2001 (54). They noted that patient reluctance to report pain and to take analgesics was frequently cited as a barrier to effective pain management, and explored reasons behind this. These included fear of addiction; fear of tolerance; fear of side effects being worse than pain itself; fatalism about the possibility of effective pain control; perception that “good “patients do not complain about pain; fear of distracting their physician from treatment; belief that progression of pain indicates disease progression; fear of injections. Misconceptions towards the interval of taking analgesics, belief that medications are better given as required rather than around-the-clock, and religious fatalism (52) have been cited as contributory factors, as have poor adherence to pain medication, psychological distress and inability to pay for analgesia also (53).

Despite considerable patient and professional fear about opioids hastening death, there is little evidence to suggest this occurs in clinical practice. A recent systematic review of 10 articles found no statistically significant difference in patient survival with higher opioid doses, with increased dosing in the last few days of life or of double dosing at night (55). However, clinical decisions to use strong opioids at the end of life are also supported by the doctrine of double effect (56, 57). This states that the administration of drugs which may hasten death is lawful and ethical when the patient is terminally ill and the use of drugs is in their best interests, if the intention in using opioids is to relieve pain and distress, and the doses used are commensurate with this aim (29, 56).

The emphasis on use of opioids in palliative care is also set in the context of a growing “opioid epidemic” in some countries including the US and UK (58). This describes increasing use of prescribed and illicit opioids (59), in the US resulting in increased fatal and non-fatal overdoses (58), and enormous societal costs. This has resulted in increasingly stringent regulation of opioids but also concern, as a consequence, that some patients may suffer from under prescribing, including in palliative care (60). Various strategies to offset the risk of opioid abuse or diversion, while maximising patient safety and pain management, have been proposed for patients with cancer (60). These include assessment of risk factors for opioid abuse, increased vigilance for those at risk and co–management with substance abuse specialists for patients who have both cancer and substance misuse.

Risks and side effects of long term opioid use (61) are increasingly relevant to the palliative care population as the characteristics of this group change. Traditionally patients with “advanced disease” were those in the last weeks and months of life. However, with improving treatment for both cancer and non-malignant disease the final phase of life can last much longer, sometimes years. While opioids can be essential for these patients, consideration of alternative treatment options and efforts to minimise risks and side effects are also particularly important.

Multiple health care system barriers have been identified around the world resulting from both opioid availability and regulation. Opioid availability is not universal. Indeed Cherny et al (2013) showed that most of the world’s population do not have access to opioids for effective cancer pain management and palliative care (62). This results from both formulary and regulatory constraints. In some countries national formularies may be severely limited such that they do not include drugs deemed “essential” by the World Health Organisation (63, 64). The costs to cancer patients of opioids can also vary, in some countries being completely subsidised and in others not at all (64). Along with limited availability of opioids in different parts of the world, there are myriad regulatory barriers also. These include physicians needing special authority to prescribe, patients needing to register for opioid eligibility, requirements for duplicate prescriptions and special prescription forms, prescription limits, dose limits, use of pejorative or stigmatising terminology in regulations and limits on prescribing in emergency situations or where there is a technical error on the prescription (64). These factors may conspire to make opioids completely unavailable or prohibitively expensive or impractical to use for many patients.

Alongside limitations to use of opioids, system barriers to accessing palliative care are also important. The World Health Organisation (WHO) estimate that, of the 40 million people in need of palliative care per year, only about 14% receive it (65).

Alongside many of the previously cited factors, this may also result from national health policy decisions which do not include palliative care at all, perhaps because of misconceptions as to what palliative care is and that it is not restricted just to those with cancer (65).

Where palliative care services do exist, system barriers can still limit access to these. For example, difficulties in accessing specialist support, poor coordination between providers and limited access to alternative methods of pain management can impact on patient care (53). Geographical limitations and inadequate time for consultations can also contribute (53). Poor access (66) and late referral to palliative care for patients with non–cancer terminal illness can be a factor (67).

In response to increasing recognition of the barriers contributing to inadequate pain outcomes at the end of life, different strategies to address these have been developed. These are targeted at patients, professionals and at system barriers.

Patient education programmes have been designed to reduce patient-related barriers and improve communication with healthcare professionals. The effect of these on pain is variable (68). A recent systematic review of 26 randomised controlled trials (RCTs) examined the effect of educational interventions on cancer pain intensity (69). Most were targeted at patients but three studies included both patients and their carers. Interventions included face to face and remote support, on single or multiple occasions, and some included additional materials such as videos or booklets. They found that a significant improvement in pain intensity in less than one third of studies and less than 20% of all included patients. A statistically significant improvement of 66% in patients' knowledge of pain was also found but the studies were too heterogeneous to prove any effect of self–efficacy and medication adherence.

Interventions targeted a professionals include professional education, guidance on pain assessment and treatment protocols (52). A 2009 systematic review of these could not identify any such interventions which unequivocally resulted in clinical improvements in pain outcomes (52). However it is also increasingly recognised that complex interventions combining a number of different approaches are more likely to be effective than those applied in isolation (70). For example, a US RCT examined the effect of automated symptom monitoring, combined with telephone-based care management, according to evidence-based guidelines (71). They found a significant improvement in pain scores over a 12 month period by comparison with usual care. A Dutch group studied the effect of a pain consultation combined with a patient education programme on pain and interference by pain with daily functioning (72). They also found in the study group a significant reduction in pain intensity and daily interference, by comparison with the usual care group over an 8 week period. Another RCT is currently underway in the UK assessing the effect of a complex intervention comprising referral to community palliative care, supported self–management education and electronic pain monitoring on outcomes including pain severity (70).

At an international level, system barriers to opioids and palliative care are well-recognised. The WHO has recommended that health system policies integrate palliative care into national health care systems. The have emphasised the importance of training existing and new professionals, volunteers and the public, and increasing capacity. They have also re–emphasised the importance of medicines policy which ensures availability of medicines for patients at the end of life, particularly opioids (65).

Different approaches have been developed at a national level to realise these objectives. For example in the UK it is recognised that there is ongoing variation in provision and funding of palliative care. In response to this, all four UK nations have developed national strategies to improve palliative care (29), including an emphasis on integrated care and recognition of the importance of palliative care for people with non-malignant conditions. Non–medical prescribing in palliative care by nurses and pharmacists (73), additional training for non-specialists (29) and specific guidance on pain relief for children and those with impaired communication (29) are other examples of UK strategies to optimise palliative care and particularly pain relief at the end of life.

Summary

Pain at the end of life is common, debilitating and distressing. In the majority of patients, pain can be adequately treated and this predominantly rests on the effect of strong opioids. Despite this, there is abundant evidence of under treatment and hence unnecessary suffering. With increasing understanding of the barriers to opioid treatment come increasing opportunities to intervene successfully, and to improve pain outcomes for patients at the end of their lives.

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