Pharmacotherapy at the end-of-life

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Abstract

Older people reaching end-of-life status are particularly at risk from inter-related adverse effects of pharmacotherapy, including polypharmacy, inappropriate medications and adverse drug events. These adverse effects of pharmacotherapy may be highly detrimental, as well as highly expensive. End-of-life pharmacotherapy is sometimes perceived to be complex and challenging, probably unnecessarily. This relates in part to the poorly developed evidence base and lack of high-quality research in this area. In this article, we deal with some of the key issues relating to pharmacotherapy in end-of-life patients, namely (i) the guiding principles of drug selection, (ii) the main drugs and drug classes that are best avoided, (iii) the benefits of ‘oligopharmacy’ (i.e. deliberate avoidance of polypharmacy) in end-of-life patients.

Keywords: end-of-life, pharmacotherapy, elderly

Introduction

The syndrome of advancing frailty and impending death is often referred to as ‘end-of-life’. Frequently, end-of-life is associated with complex polypharmacy which heightens the risk of serious adverse drug events (ADEs). Although frailer, older people are usually excluded from randomised controlled trials [1], prescribers often persist with evidence-based prescribing in end-of-life older patients. In turn, this evidence-based (evidence-biased?) approach of prescribing for all treatable medical conditions is unnecessarily expensive and ultimately of dubious benefit to the patient. The most important requirement for designing good-quality drug regimens for end-of-life patients is the a priori recognition of end-of-life itself. End-of-life is characterised by accumulating health problems over a period of weeks to months with failing homeostasis that is irreversible and inexorably leading to death. Recognition of reduced remaining life expectancy is challenging for physicians and requires repeated assessments over several days or weeks. The terminal phase of illness indicates imminent death within hours to days. Clearly, end-of-life is the forerunner of the terminally ill state. The pharmacotherapy of terminal illness is well-defined and evidence-based, with its focus clearly and appropriately on palliative symptom management. In contrast, there are few guidelines for physicians as to what constitutes appropriate pharmacotherapy in end-of-life patients [2].

Challenges of medication withdrawal

For some clinicians, once a medication is initiated it may be difficult to discontinue it. Factors to consider include (i) remaining life expectancy, (ii) goals of treatment: symptom control versus long-term prevention (iii) time-to-benefit of medicines prescribed, (iv) difficulties with administration and (v) dangers of withdrawing certain medications abruptly e.g. steroids, long-acting benzodiazepines. Patients view prescribing as an expression of the doctor–patient relationship. Consequently drug discontinuation may be misconstrued by patients and their families as a withdrawal of care. In order to avoid misunderstanding, clear communication is needed between physician, patient and close relatives. The key point of emphasis for the prescriber to convey is that the aim of pharmacotherapy shifts from prevention to symptom control.

Principles of prescribing in end-of-life patients

We propose the following guiding precepts:

- Life-extending drugs are usually not appropriate.
- Drugs for primary prevention have, in general, no place in the treatment of end-of-life patients, since the time-to-benefit usually exceeds life expectancy [2].
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- Drugs for secondary prevention require careful scrutiny and should be prescribed only where ongoing benefit is to be expected within a patient's life expectancy.
- In general, prescribing more than five regular daily drugs to a patient with end-of-life status should be avoided. Six or more daily drugs heighten the risk of ADEs [3, 4] as well as poor medication compliance [5] in older people.
- Defining treatment goals is of central importance and will usually direct the prescriber to the most appropriate pharmacotherapy. This process should be discussed between the physician and the patient and, where necessary the patients primary carer.
- Optimisation of the drug regime for an end-of-life older patient is a dynamic process. The drug regime may require several changes before medications have been rationalised effectively. Where drugs are best stopped, it is preferable to withdraw one drug at a time. In this way, adverse symptoms after particular drug discontinuations can be attributed more readily and the necessary corrective action taken.
- Fewer daily tablets and doses should be a core aim of drug regime review, including the use of once-daily, long-acting preparations.
- Close liaison with the patient's pharmacist is also important, particularly with regard to presentation of prescribed drugs to end-of-life patients e.g. blister packs arranged at times most convenient for consumption by the patient. Careful Medication Use Review [6] conducted by the pharmacist directly with the patients and/or primary carers should facilitate better compliance.

To illustrate application of these principles a case study is provided in the Supplementary data available in Age and Ageing online.

Potentially inappropriate medications in older people in general

Before considering inappropriate drugs at end-of-life, there are several drugs that are potentially inappropriate in older people in general. Until recently, Beers’ criteria for potentially inappropriate medications (PIMs) in old age [7] have dominated the literature. However, the lack of a consistent, significant association between Beers’ criteria PIMs and clinically significant ADEs [8, 9] has cast doubt on the relevance of Beers’ criteria in routine clinical practice. This led to the creation and validation of new criteria, called STOPP (Screening Tool of Older Persons’ Prescriptions) [10]. STOPP criteria are arranged according to physiological systems, and include reference to drug class duplication, drug–drug and drug–disease interactions. It focuses on commonly prescribed medicines in older people and the potential problems associated with prescription of such medicines in older patients. In a recent study comparing Beers’ criteria and STOPP in older hospitalised patients, ADEs associated with STOPP medications were judged to be the prime cause of acute admission in twice as many patients as ADEs arising from Beers’ criteria medications [11]. The STOPP criteria enable physicians to review patients’ medications in a systematic way and facilitate rationalisation of medications in an evidence-based manner. STOPP criteria when used in tandem with good clinical judgement can mitigate polypharmacy and its associated negative outcomes. This in turn should improve the quality-of-life that patients experience in the final months of their lives.

Drugs to be avoided in end-of-life patients

Most older people reach end-of-life status having been prescribed medicines for a variety of chronic medical conditions and polypharmacy is commonplace, even in patients with advanced dementia [12]. Identification of end-of-life should bring about a significant reduction in the number of daily drugs. While there is no clear consensus about which drugs are unsuitable for end-of-life older persons, nevertheless certain drugs are clearly not appropriate, principally because the time to clinical benefit exceeds life expectancy [2]. Thus, lipid-lowering drugs are almost always inappropriate in end-of-life. Similarly, the most medicines used for minimisation of fragility fracture risk in these patients are usually inappropriate. Likewise, ACE-inhibitors and angiotensin receptor blockers to prevent diabetic nephropathy or to reduce mortality from heart failure are of little value when a patient’s life expectancy is severely curtailed as a result of other irreversible disorders. In general, drugs prescribed to improve longevity can be avoided since the focus of pharmacotherapy in end-of-life is optimal symptom control for the remaining weeks or months of life. Best clinical practice would involve an open and frank discussion between physician and patient as to the reasons for withdrawal of preventive drug therapies. Such a discussion may in turn facilitate more in-depth dialogue about overall prognosis with the patient and his/her carers’. There is an important distinction to be made between drugs that should generally not be initiated and drugs that should be discontinued when encountered in end-of-life patients. For example, it would be generally considered inappropriate to commence methotrexate in an end-of-life patient for symptomatic active rheumatoid disease and more appropriate instead to opt for corticosteroids for symptom control, given the patient’s short-term life expectancy. Conversely, an end-of-life patient whose chronic rheumatoid disease is well controlled on a fixed dose of weekly methotrexate is probably best maintained on methotrexate, particularly if the patient has a history of relapse with its withdrawal. Another example is that of long half-life benzodiazepines. These drugs are best avoided in older people in general. However, subjecting older people at end-of-life to the onus of structured withdrawal of a long half-life benzodiazepine is generally not appropriate, given the risk of inducing major withdrawal symptoms.
Regrettably, most drug formularies do not include advice to the prescriber specific to end-of-life patients, probably as a result of the absence of an internationally accepted definition of end-of-life. A suggested list of commonly prescribed drugs that are generally better avoided in end-of-life older people is illustrated in the Supplementary data available in Age and Ageing online.

The benefits of ‘Oligopharmacy’ in end-of-life

Major polypharmacy, i.e. the consumption of ≥10 daily prescription drugs is a consistent independent predictor of ADEs in older people [13]. Frail older people, particularly nursing home residents, are at considerably higher risk of serious polypharmacy-related ADEs [4]. A recent study by Onder et al. [14] indicates that polypharmacy to the level of ≥8 regular prescription drugs daily is the strongest predictor of ADEs in hospitalised older people. Therefore, the conversion of major polypharmacy to ‘oligopharmacy’, i.e. ≤5 daily prescription drugs is likely to be beneficial to end-of-life patients in terms of serious ADE avoidance. One small-scale study from Israel showed that a deliberate policy of oligopharmacy in frail, disabled older people in nursing care units significantly reduced mortality, hospitalisation and drug costs [15]. This structured approach to palliative pharmacotherapy has also been shown to be applicable in community-dwelling frail older people as well as nursing unit residents [16].

Appropriate polypharmacy

Is polypharmacy always inappropriate? Paradigms for palliative care demonstrate that prescribing cascades not only occur but often reflect good clinical practice e.g. opiates often require concomitant prescription of laxatives and antiemetics to optimise patients’ symptoms. In the final days of terminal illness polypharmacy is often appropriate as the emphasis focuses entirely on symptom management.

Questions for future research

- What is the most reliable way to predict patient survival time in the pre-terminal end-of-life phase of their illness that is applicable in clinical practice?
- Does deliberate oligopharmacy reliably reduce ADEs and improve quality of life in older people with end-of-life status?
- Does routine pharmacist surveillance of pharmacotherapy for end-of-life older people significantly improve symptom control, avoid polypharmacy and ADEs?

Health care systems must adapt to ageing demographics which will be heavily populated by patients with progressive, incurable illness, many of whom have end-of-life status. In Ireland the annual cost to the State of supplying medicines exceeds €2.24 billion; a sixfold increase over a decade [17]. This level of expenditure is unsustainable. The imperative now is to provide models for optimal prescribing which facilitate reconsideration and rationalisation of medication use in end-of-life older patients.

Key points

- End-of-life, i.e. the pre-terminal phase of a person’s decline to death is well recognised by physicians in Geriatric Medicine but hitherto has been poorly defined and consequently poorly researched.
- The focus of pharmacotherapy in the rising numbers of end-of-life older people should be oligopharmacy, i.e. the deliberate avoidance of polypharmacy (the greatest risk factor for ADEs) and symptom control, rather than life-prolonging treatments.
- Drugs for secondary disease prevention are of no value in end-of-life patients if the time to therapeutic benefit exceeds estimated life expectancy.

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Conflicts of interest

None declared.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

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