Ir J Med Sci (2013) 182:107–112
DOI 10.1007/s11845-012-0841-6

ORIGINAL ARTICLE

Pharmacological management of co-morbid conditions at the end of life: is less more?

S. McLean · B. Sheehy-Skeffington · N. O'Leary · A. O'Gorman

Received: 7 January 2012 / Accepted: 14 July 2012 / Published online: 29 July 2012

Abstract
Background Co-morbid conditions (CMCs) are present in over half of patients with cancer over 50 years of age. As life-limiting illnesses progress, the benefits and burdens of treatments for CMCs become unclear. Relevant issues include physiological changes in advanced illness, time-to-benefit of medications, burden of medications, and psychological impact of discontinuing medications. Optimal prescribing is unclear due to lack of evidence.
Objectives The objectives are to determine prescribing practice, for CMCs, in a single SPC service.
Methods Patients referred to a single specialist palliative care (SPC) service, who died between 1/8/2010 and 30/9/2012, were identified. Medical notes were reviewed, and data collected on prescribing at 3 months, 1 month, and 1 week prior to death.
Results Fifty-two patients with a median age of 74.5 years were identified; 41 patients (79 %) had a malignant condition. 50 % died in hospital. Patients had a mean of three CMCs. A mean of 4.6 medications for CMCs were prescribed to patients over 65. A mean of 10 medications in total were prescribed at 1 week before death. One week before death, one-third of patients continued to be prescribed aspirin, and over one-quarter a statin.
Conclusions Total medication burden increases as time to death shortens, due to continuation of medications for CMCs, and addition of medications for symptom control. There is a need for research to demonstrate the impact of polypharmacy at the end of life, in order to formulate a framework to guide practice.

Keywords Palliative · Co-morbid · Polypharmacy · Prescribing · End of life

S. McLean · B. Sheehy-Skeffington · N. O'Leary · A. O'Gorman
Specialist Palliative Care Service, Dochas Centre, Our Lady of Lourdes Hospital, Drogheda, Co. Louth, Ireland

S. McLean (✉)
St Francis Hospice, Station Road, Raheny, Dublin 5, Ireland
e-mail: smclean81@yahoo.com

Introduction

As life expectancy in the general population increases, increasing numbers of older people are living to be diagnosed with cancer. In Europe, 50 % of patients diagnosed with cancer are over 70 years of age [1]. The incidence of non-malignant life-limiting illness, such as renal failure, congestive heart failure, and stroke, also increases with age. Patients with such life-limiting conditions may require input from specialist palliative care (SPC) services for symptom management, or end of life care.

Older patients have higher rates of chronic conditions such as cardiovascular disease and diabetes mellitus, and often require multiple medications to manage these co-morbid conditions. As a life-limiting illness such as cancer, progresses, the benefits and risks of continuing pharmacological treatments for co-morbid conditions are uncertain. Optimal prescribing is unclear due to a lack of evidence, and clear recommendations.

Co-morbidities at the end of life

It has been demonstrated that the number of co-morbid conditions increases with age, and over half of patients over the age of 60 diagnosed with cancer have at least one co-morbid condition [2]. The most common co-morbid conditions seen in patients with cancer are cardiovascular

disease, hypertension, chronic obstructive pulmonary disease (COPD), and diabetes mellitus (DM) [2].

Polypharmacy

Polypharmacy—the simultaneous prescribing of multiple drugs—is an increasingly well-recognised phenomenon in older people. The occurrence of prescribing of inappropriate, or potentially inappropriate, medications increases with the number of medications prescribed, and with patient age [3]. Irish studies have demonstrated that at least one inappropriate or potentially inappropriate medication is prescribed to between 18.3 % and 50 % of older patients in the primary care setting [3, 4]. It has been shown that, at the time of referral to SPC services, 20 % of patients are prescribed 8 or more medications.

Considerations in prescribing

The rationale for medications for co-morbid conditions may change as a life-limiting illness progresses, and prognosis shortens. Medications may have been prescribed for primary prevention, such as aspirin; secondary prevention, such as anti-hypertensives or statins; or tertiary prevention, such as oral hypoglycaemics to manage DM, or digoxin to manage atrial fibrillation. As an underlying illness such as cancer progresses, the need for primary prevention will be less relevant, as expected time to benefit from medication is likely to exceed predicted life-expectancy. This is especially important for medications with a long time-to-benefit, such as statins, where time to risk reduction is 3–6 years [5]. However, other medications, such as digoxin for rate control in atrial fibrillation, may need to be continued up to the end of life in order to prevent distressing symptoms arising from an arrhythmia [6].

As cancer, or other life-limiting illness progresses, the burden of medications may increase, and the burden-to-benefit ratio of interventions may change. Some medications, which were previously acceptable due to their long-term beneficial effects, may become burdensome as prognosis shortens.

Changes in the bioavailability and metabolism of drugs often occur towards the end of life, due to altered protein binding, volume of distribution, and altered liver and renal function [7]. These physiological and metabolic changes may affect the need for certain medications. Patients who are cachectic and dehydrated may no longer require anti-hypertensive medication to control their blood pressure. Indeed, distressing adverse side effects such as postural hypotension and falls may result if such medication is continued. Similarly, if oral intake is very poor, an oral hypoglycaemic agent previously required to control blood sugars in a diabetic patient, may precipitate symptomatic hypoglycaemia. Medication side effects become more pronounced where a patient is frail, for example, myopathy and nausea secondary to statins are more common in older patients, those with low albumin, renal or hepatic impairment [8].

Furthermore, routes of administration and dosing schedules may require review, as the oral absorption of medications may be compromised [7]. The burden of medications may increase due to difficulty swallowing tablets due to weakness, dysphagia, or nausea [7]. The taking of medications has been described as a ‘daily struggle’ for some patients and their carers [9]. Injections may become more difficult to tolerate where there is cachexia [7].

Discontinuing medications for co-morbid conditions

It has been shown in the medicine for the elderly literature that many medications for chronic or co-morbid conditions can be safely discontinued without adverse effects. Garfinkel et al., using the validated Good Palliative-Geriatric Practice Algorithm for Drug Discontinuation, were able to discontinue 311 drugs in 64 older patients. A mean of 4.2 drugs were discontinued per patient, most commonly anti-hypertensives, aspirin and statins. Two percent of discontinued drugs were recommenced because of recurrence of the original indication, but successful discontinuation was achieved in 81 % of patients, without significant adverse effects [10].

Discontinuing medications for cardiovascular conditions can lead to concern that an acute cardiac event may be precipitated. It has been shown that, in one centre, over half of patients with recognized life-limiting conditions received statins during the last year of life [8]. It has been demonstrated that, unless a statin is withdrawn immediately following an episode of acute coronary syndrome [11], there is no short-term increase in the risk of acute cardiac events on statin discontinuation [12].

The psychological and emotional impact of discontinuing medications for chronic conditions has not been well researched. Prescribing is seen as fundamental to the clinician-patient relationship, and patients may have been told they will require certain medications ‘for life.’ There is evidence that withdrawal of treatment, or perceived changes in levels of support, can cause adverse psychological consequences [13]. Decisions to withdraw medications, along with the rationale for doing so, should be discussed with patients and their carers to avoid distress.

In determining optimal prescribing towards the end of life, Stevenson et al. [7] propose an approach that considers the original therapeutic intent (primary, secondary,

or tertiary prevention), and the likely benefit of the intervention as reflected in the number needed to treat. Holmes et al. [14] propose a 4-part decision-making process analysing:

- remaining life expectancy from underlying illness;
- time to benefit of the intervention for the co-morbid condition,
- overall goals of care,
- the treatment target.

Optimal prescribing for co-morbid conditions remains unclear, however, and we aimed to determine current practice in one palliative care service, in order to guide future practice.

Aims

We aim to evaluate the prevalence of co-morbidities in patients with a life-limiting condition referred to a specialist palliative care service; to determine current prescribing practice for co-morbid conditions; to compare prescribing practice in the acute hospital and community settings; and to evaluate the decision-making and communication process regarding discontinuation of medications for co-morbid conditions.

Methods

The SPC service in which this study was carried out is an integrated service, comprising an acute hospital, and community team, in a rural region of Ireland.

Patients referred to the SPC service, and who died between 1/8/2010 and 30/9/2010 were identified. A retrospective review of their hospital and home care notes was performed, and data was extracted using a pro-forma developed specifically for this purpose. GP records were not reviewed. Data collected included demographic details, primary diagnosis, co-morbid conditions and medications prescribed at 3 months, 1 month, and 1 week prior to death, and at the time of death. Medications were classified according to treatment intention, i.e. treatment of underlying life-limiting condition, treatment of co-morbid conditions, symptom control, supportive purposes, and prophylaxis. When identifying medications for co-morbid conditions in patients with a non-malignant condition such as stroke, medications used for secondary prevention of stroke such as aspirin or anti-hypertensives, were considered as treatments for the primary, life-limiting condition and not counted as medication for co-morbid condition. Data were analysed using descriptive statistics.

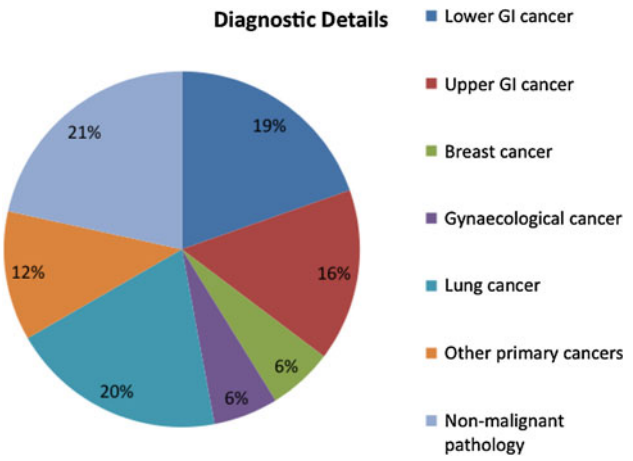

Fig. 1 Diagnostic details by cancer type and proportion with non-malignant pathology. Other cancers: malignant melanoma, renal cell carcinoma, multiple myeloma, primary brain tumour (one patient each), prostate cancer (2 patients)

Results

Demographics

Fifty-two patients who died during the study period were identified. The median age of patients was 74.5 years (range 36–91 years). 49 (94 %) patients ordinarily resided at home, and three patients in a nursing home. Twenty patients (38 %) died at home; 26 (50 %) died in hospital; and six (12 %) died in the nursing home setting. The mean duration of time between referral to SPC team and death was 10.8 weeks.

Diagnoses

Forty-one patients (79 %) had an advanced malignant condition (Fig. 1) with the remaining 11 patients having a life-limiting non-malignant condition: COPD (three patients), stroke (four), CCF (one), Alzheimer's dementia (one), end-stage renal failure (one), peripheral vascular disease (one patient).

The median number of co-morbid conditions per patient was 3 (range 0–7). Forty-five patients (87 %) had one or more co-morbid conditions. Seven patients (13 %) had no co-morbidity. The most common co-morbid conditions were hypertension, ischaemic heart disease, dyslipidaemia, and diabetes mellitus (Table 1).

Prescribing patterns: prescribing for co-morbid conditions

The most common medications prescribed for co-morbid conditions were those for cardiovascular diseases (aspirin, statins, anti-hypertensives); corresponding to the prevalence

Table 1 Co-morbid conditions

Co-morbid condition	Number of patients (%)
Hypertension	27 (52)
Ischaemic heart disease	20 (38)
Dyslipidaemia	11 (21)
Diabetes mellitus	9 (17)
Atrial fibrillation	8 (15)
COPD/Asthma	7 (13)
Depression	6 (12)
Osteoarthritis/osteoporosis	6 (12)

Table 2 Medications prescribed for co-morbid conditions at 3 months, 1 month, and 1 week prior to death (ACE I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker)

Medication prescribed	At 3 months prior to death Number of patients (%)	At 1 month prior to death Number of patients (%)	At 1 week prior to death Number of patients (%)
Aspirin	22 (42)	23 (44)	19 (36)
Beta-blocker	18 (35)	18 (35)	14 (27)
Diuretic	15 (29)	18 (35)	11 (21)
Statin	15 (29)	15 (29)	12 (23)
ACE I/ARB	13 (25)	13 (25)	8 (15)
Ca^{2+} channel blockers	11 (21)	11 (21)	8 (15)
Digoxin	5 (10)	5 (10)	5 (10)
Calchichew/ Fosamax	13 (25)	11 (21)	9 (17)

of ischaemic heart disease and dyslipidaemia in the cohort (Table 2).

Patients younger than 65 years had a lower burden of co-morbid conditions and at 3 months prior to death were prescribed a mean of 1.7 medications for co-morbid conditions as compared to a mean of 4.6 medications for co-morbid conditions in patients over the age of 65.

Medications for primary or secondary prevention were continued up to death in a significant proportion of patients. At 1 week prior to death, over one-third of patients were prescribed aspirin, and one-quarter of patients were each prescribed a beta-blocker, and/or a statin. It appears unlikely that a specific rationale existed for the use of aspirin or statins at the end of life, and their use may have contributed to side effects or tablet burden with minimal demonstrable benefit.

Prescribing patterns: prescribing for symptom control

As time to death approached, although the number of medications for co-morbid conditions fell slightly, the total number of medications prescribed increased, due to the addition of medications for symptom control (Fig. 2). At 3 months prior to death, patients were prescribed a mean of 2.2 regular, oral medications for symptom control, increasing to 4.6 at 1 week before death. The most commonly used medications for symptom control were opioids, paracetamol and non-steroidal anti-inflammatory drugs, anti-emetics, laxatives, anxiolytics and steroids. When 'as needed' and subcutaneous medications for symptom control were included, a mean of 4 medications for symptom control were prescribed at 3 months prior to death, increasing to 7.2 medications at 1 week prior to death.

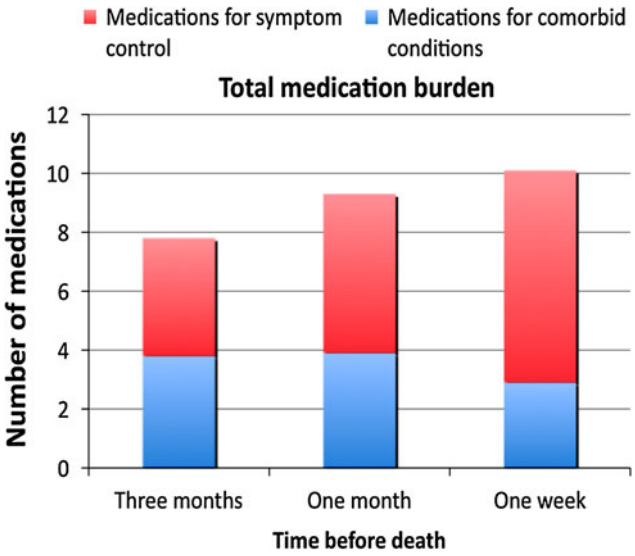

Fig. 2 Total medication burden at 3 months, 1 month, and 1 week prior to death

Prescribing patterns: total medication burden

Total medication burden was considerable, with a mean of 10 medications prescribed at 1 week prior to death (Fig. 2). Diuretics were more frequently prescribed as time to death shortened, peaking at 1 month prior to death and falling again at 1 week prior to death. This is likely due to their use in order to manage symptoms such as dyspnoea secondary to pulmonary oedema. Oral hypoglycaemics were prescribed in eight patients up to 1 week prior to death, and one patient received long-acting insulin up to the day before death. Prophylactic low molecular weight heparin (LMWH) was prescribed in six patients at 1 week prior to death, but was discontinued prior to death in all six patients, indicating that the burden of injections compared to the benefit of preventing a thromboembolic event at the end of life was appropriately considered.

Patients in the community (home and nursing homes) settings were prescribed more medications for co-morbid

conditions towards the end of life than in the hospital setting. A mean of 4.4 medications in the community compared to 3.2 medications in the hospital setting were prescribed at 3 months prior to death; and a mean of 3.4 medications compared to 2.2 medications were prescribed at 1 week prior to death. This was possibly due to more regular review of medications in the acute hospital setting.

Forty-five patients (86 %) required a syringe driver for control of symptoms at the end of life, indicating recognition of frailty and difficulty swallowing medications. Despite this, oral medications for symptom control continued to be prescribed at death in 22 patients (42 %), and for co-morbid conditions in 10 patients (19 %).

Documentation

There was limited documentation of decision making around discontinuing medications in both the community and hospital settings. In the community setting, the decision to stop medications was made in all cases by the general practitioner, in two cases prompted by the SPC home care nurse. In the hospital setting, the decision to stop medications was made in 80 % of cases by the SPC team. The specific rationale for discontinuing medications was not clearly described in the medical records, and in no case was there documentation of a discussion with the patient or their carer around the decision.

Discussion

Our small study describes current practice in one SPC service over a short period of time, but is likely to be representative of prescribing practice elsewhere in Ireland. In an Australian study, Currow et al. [15] previously demonstrated that total medication burden increases towards the end of life due to the addition of multiple medications for symptom control, but ours is the first Irish study to look at this issue.

There is only limited data on the actual burden of the prescription of multiple medications for co-morbid conditions at the end of life. Potential adverse consequences of drugs and drug–drug interactions are multiple. Side effects include falls and postural hypotension as a result of inappropriate use of anti-hypertensives; and myopathy secondary to statins. In addition, the 'tablet burden' of time and effort expended in taking tablets by fatigued patients who have difficulty swallowing, has been shown to be considerable. This burden can be alleviated somewhat by consideration of formulations of medications, for example prescribing liquids and capsules rather than tablets where possible [9]. In addition, better explanation of the purpose of medications to patients and their carers has been shown to allow prioritisation of medications for symptom control or important medical conditions, if ingestion of tablets is becoming difficult. The management of multiple medications has been demonstrated to be time consuming; a practical difficulty; and a source of significant distress and anxiety for the carers of patients who are approaching the end of life [9].

The financial considerations of prescribing for chronic conditions are considerable. While there is an abundance of evidence supporting the use of medications to reduce the risk of adverse disease outcomes in healthy populations, where the prognosis is short, the cost-effectiveness of such interventions may be low. Furthermore, much of the cost-effectiveness of palliative care input lies in the avoidance of hospital admissions towards the end of life. Polypharmacy increases the risk of drug side effects and drug–drug interactions, which may lead to unnecessary hospital admissions.

There is a clear need for the development, prospective evaluation, and validation of frameworks and guidelines to guide prescribing in this population. Such tools have been developed and validated for older people without a specific life-limiting diagnosis, such as the Medication Appropriateness Index [16], the Beers Criteria [17], and the STOPP (Screening Tool of Older Person's Prescriptions) criteria [3]. As some medications which may be inappropriate in the older population as a whole, such as short-acting benzodiazepines, tricyclic antidepressants, and non-steroidal anti-inflammatory drugs (NSAIDS), may be used expertly and appropriately in the palliative care setting for symptom control, the tools described would require adaptation in order to be applicable in the palliative care population. Such adapted guidelines would potentially be applicable to all patients with life-limiting illnesses even if not under the care of an SPC service.

In the absence of formal guidelines, prescribing in patients at the end of life should aim to maximise quality of life by optimizing symptom control, while minimizing medication burden, adverse drug side effects and drug–drug interactions.

As described by Stevenson, and Holmes et al. [7, 14], the physiological and metabolic changes that occur in advanced illness should be taken into account when prescribing. The original therapeutic intent of a medication should be considered, and where the expected time to benefit is longer than expected survival, consideration should be given to discontinuing the medication. The patient, family and multidisciplinary team should be involved in discussions regarding rationalising medications towards the end of life in order to avoid psychological distress. As with all interventions in life-limiting illness, priority should be given to maximising quality of life for the longest duration possible, and ensuring any intervention provides an acceptable benefit to burden ratio.

Conflict of interest None.

References

1. Coebergh JWW, Janssen-Heijnen MLG, Post PN et al (1999) Serious co-morbidity among unselected cancer patients newly diagnosed in the southeastern part of the Netherlands in 1993–1996. J Clin Epidemiology 52(12):1131–1136
2. Feinstein AR (1985) On classifying cancers while treating patients. Arch Int Med 145:1789–1791
3. Ryan C, O'Mahony D, Kennedy J et al (2009) Potentially inappropriate prescribing in an Irish elderly population in primary care. B J Clin Pharmacol 68(6):936–947
4. Walsh EK, Cussen K (2010) "Take ten minutes": a dedicated ten minute medication review reduces polypharmacy in the elderly. Ir Med J 103(8):236–238
5. Amarenco P, Labreuche J, Lavallee P (2004) Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke 35:2902–2909
6. Uretsky BF, Young JB, Shahidi FE et al (1993) Randomised study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED investigation group. J Am Coll Cardiol 22(4):955–962
7. Stevenson J, Miller C, Abernethy AP et al (2004) Managing comorbidities in patients at the end of life. BMJ 329:909–912
8. Silveira MJ, Segnini Kazanis A, Shevrin MP et al (2008) Statins in the last six months of life: a recognizable life-limiting condition does not decrease their use. J Pall Med 11(5):685–693
9. Sheehy-Skeffington B, McLean S, Bramwell M, O'Leary N, O'Gorman A (in press) Caregivers experiences of managing medications of palliative care patients at the end of life—a qualitative study
10. Garfinkel D, Mangin D (2010) Feasibility study of a systematic approach for discontinuation of multiple medications in older adults. Arch Intern Med 170(18):1648–1654
11. Heeschen C, Hamm CW, Laufs U et al (2002) Withdrawal of statins increases event rates in patients with acute coronary syndromes. Circulation 105:1446–1452
12. McGowan MP, for the Treating to New Target Study Group (2004) There is no evidence for an increase in acute coronary syndromes after short-term abrupt discontinuation of statins in stable cardiac patients. Circulation 110:2333–2335
13. Arnold EM (1999) The cessation of cancer treatment as a crisis. Soc Work Health Care 29:21–38
14. Holmes HM, Cox-Hayley JT, Alexander GC et al (2006) Reconsidering medication appropriateness for patients late in life. Arch Intern Med 166:605–609
15. Currow D, Stevenson J, Abernethy A et al (2007) Prescribing in palliative care as death approaches. J Am Geriatr Soc 55:590–595
16. Hanlon JT, Schmader KE, Samsa GP et al (1992) A method for assessing drug therapy appropriateness. J Clin Epidemiol 45:1045–1051
17. Beers MH, Ouslander JG, Rollingher I et al (1991) Explicit criteria for determining inappropriate medication use in nursing home residents. Arch Intern Med 151:1825–1832