Polypharmacy in patients with advanced cancer and the role of medication discontinuation

Thomas W LeBlanc, Michael J McNeil, Arif H Kamal, David C Currow, Amy P Abernethy

Polypharmacy is a well known problem in elderly patients in general, but its prevalence and effects in patients with cancer are less clear, particularly in end-of-life settings. This Review examines the existing literature on polypharmacy in advanced cancer and end-of-life settings by reviewing evidence-based approaches to reduce polypharmacy, and outlining the potential benefits of decreasing the number of drugs that patients with cancer can take, with emphasis on the need for thoughtful discontinuation initiatives in the context of life-limiting malignant disease. In view of the apparent burden of polypharmacy in patients with advanced cancer, we expect that greater attention to polypharmacy could lead to improvements in adverse drug events, cost, and possibly quality of life. However, few data for specific interventions in the advanced cancer population are available, and thus more research is warranted.

Lancet Oncol 2015; 16: e333–41

Duke Cancer Institute (T W LeBlanc MD, A H Kamal MD, Prof A P Abernethy MD), **Division of Hematologic Malignancies and Cellular Therapy, Department of Medicine** (T W LeBlanc), **and Division of Medical Oncology, Department of Medicine** (A H Kamal, Prof A P Abernethy), **Duke University School of Medicine** (M J McNeil BS), **Durham, NC, USA; Center for Learning Health Care, Duke Clinical Research Institute, Durham, NC, USA** (T W LeBlanc, M J McNeil, A H Kamal, Prof A P Abernethy)**; and Palliative and Supportive Services, Flinders University, Adelaide, SA, Australia** (Prof D C Currow BMed)

Correspondence to:
Dr Thomas W LeBlanc, Box 3961, Duke University Medical Center, Durham, NC 27710, USA
thomas.leblanc@duke.edu

Introduction

The term polypharmacy describes a patient's use of several drugs. Although the number of drugs that objectively constitutes polypharmacy has not been formally defined, a growing body of evidence links polypharmacy with negative outcomes, even in patients taking as few as four drugs at any given time.[1–4] In other published work, the term is used more generally to describe unnecessary drug prescriptions irrespective of the total number of drugs a patient takes. We prefer the more inclusive definition,[5–7] but will use both definitions in this Review in recognition of the heterogeneity of published studies, and acknowledge that harm can result from even one unnecessary or inappropriate drug.

Although polypharmacy is not well described in oncology, it is a well known problem in elderly patients and has been studied in patients cared for longitudinally in institutional settings, such as nursing homes.[2] As expected, the prevalence of polypharmacy in older patients (aged 65 years and older) is linked with comorbid illnesses, including cancer.[8,9] Research has focused on the development and testing of innovative approaches to reduce polypharmacy in this vulnerable population. In oncology settings, however, published reports remain descriptive. In a review by Lees and Chan,[5] the problem of polypharmacy specifically among elderly patients with cancer was discussed. Undesirable outcomes in that population include adverse drug events, drug–drug interactions, and reduced adherence to drugs thought to be essential. Not all patients with cancer are elderly, however, and some younger patients with advanced cancer will also experience polypharmacy in end-of-life scenarios, although this population is less well studied.

Several important questions need to be answered about patients with advanced cancer, especially those nearing the end of life. Comorbidities are common in patients with advanced cancer,[10] but if or when drugs to treat them should be discontinued remains unclear. For example, should a patient with advanced cancer continue to take a lipid-lowering drug to reduce the likelihood of cardiovascular disease years beyond his or her expected survival? If not, how and when should it be discontinued, and could discontinuation put the patient at risk of short-term negative outcomes? Such questions about the balance between benefit and harm are important and timely.[11,12] We searched several biomedical databases for articles reporting on prescriptions for comorbidities in patients with advanced cancer, published in the past 20 years (figure).

Advanced cancer

Table 1 lists some reported scientific literature that show the burden of polypharmacy in the cancer population. We focused on studies in which the frequency of patients with advanced disease was reported. Many studies did not include a definition of advanced cancer (in some studies patients' cancer stages were not reported), and we recognised that published reports on this topic are scarce.

The identified data confirm that polypharmacy is prevalent in the advanced cancer population, with one study reporting median number of drugs as less than 4·0 (the lowest published definitional threshold). The reported mean and median number of prescribed drugs ranged from 3·0 to 9·1. Older patients with cancer (aged 65 years and older) more often had polypharmacy than younger patients. For example, Jorgensen and colleagues[15] reported that 35% of patients in a large, population-based cancer registry in Denmark aged 70 years or older were taking at least five drugs at any given time. Furthermore, the number of prescribed drugs increased in the 6 months before a cancer diagnosis.

Several of the identified studies show a substantial potential for drug–drug interactions in patients with cancer. In a US study,[20] just under 50% of patients in outpatient clinics reported complementary and alternative medicine use. The potential for serious drug–drug interactions may increase with the increased use of over-the-counter products, complementary and alternative medicines, and oral targeted therapies, many of which require long-term use and can induce complex drug-interaction scenarios.[21] This topic merits further prospective studies.

Much polypharmacy in the cancer population involves drugs meant to treat long-term comorbidities, such as

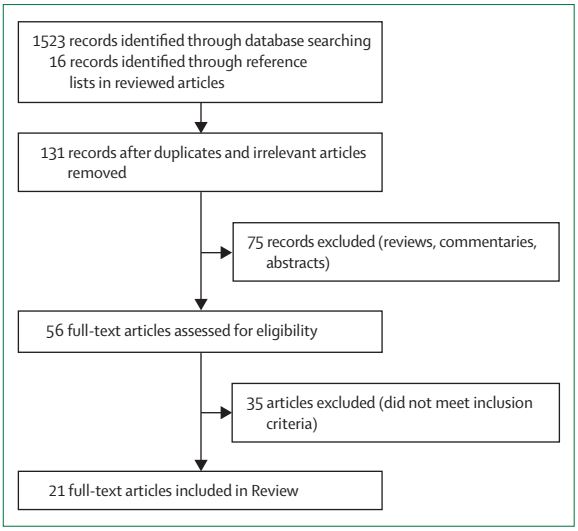

***Figure*: Study inclusion flow chart**

hypertension, hyperlipidaemia, or gastro-oesophageal reflux disease. In patients with advanced cancer and with short life expectancy, trade-offs between medication usefulness and the burden of possible drug-related adverse events must be balanced carefully.

End of life in patients with cancer

Although polypharmacy is prevalent in the elderly population and in patients with cancer, its prevalence in late-stage, end-of-life settings in patients with cancer is less well known. Ambulatory patients with advanced cancer are probably quite different from those who are much closer to the end of life, such as those receiving care in a hospice or other palliative care settings. Thus, we separately reviewed and summarised key findings in this population (table 2), with a focus specifically on studies that included patients with cancer. We focused on studies that included a substantial proportion of patients with cancer, although Maddison and colleagues[4] did a good review on polypharmacy in general end-of-life settings.

Polypharmacy is clearly common in patients with cancer nearing the end of life.[8,25,28] In one study of more than 4000 patients in hospices in 11 US states (35% of whom had cancer diagnosis),[23] all patients had been prescribed an average (mean) of 15 drugs at any one time. Out of all patients, more than 350 patients were prescribed 30 drugs or more. Across all participants, an average of 7·9 "as needed" drugs were prescribed, and an average of 8·3 regularly scheduled drugs. These results are important, confirmatory findings in an end-of-life population.

As patients approach death the number of drugs they take usually increases.[22] In an Australian study[22] using 260 consecutive patients (250 [96%] of whom had cancer) referred to a regional palliative care programme in Australia, the baseline mean number of prescribed drugs was 4·9, which increased by 1·5 drugs in a mean time of 107 days from referral to palliative care to death. This increase in prescribed drugs is related to addressing specific symptoms that occur near the end of life. Similarly, in a study of 138 patients in an inpatient hospice in Northern Ireland (91% of whom had cancer),[24] the mean number of prescribed medications at admission was eight, which increased to a mean of ten at the time of discharge to their homes. However, the mean fell to only two drugs in patients who were actively dying. Further evidence shows that, for patients dying in a hospice setting, the anticholinergic burden of drugs increases as death approaches and is associated with adverse effects including poor mental concentration, reduced quality of life, and worsening physical function.[29] Anticholinergic burden is a prominent cause of concern in terms of the frequency of adverse drug events experienced by the patient. Despite showing some interesting results, these three studies solely assessed the number of drugs prescribed and not the number of tablets, dosages, routes of administration, or frequency of drugs taken, all of which can affect regimen complexity and possibly quality of life.

Although drug burden increases in end-of-life settings, long-term drugs that were previously prescribed to manage comorbidities are often continued, despite possibly no longer being of benefit. In an Irish study of 52 patients seen by a palliative care service (41 [79%] of whom had advanced cancer), a mean of 4·6 drugs were prescribed for patients with comorbidities.[25] A mean of ten drugs in total were still being prescribed a week before death. These data point to a sizeable burden of polypharmacy in end-of-life settings, perhaps signifying that inadequate attention is given to drugs that were meant to prevent long-term complications and co-morbidities (eg, antihypertensives, lipid-lowering drugs) that can cause short-term problems. Antihypertensives, for example, can induce postural imbalances in patients who have lost substantial amounts of weight.

Interpretation

In view of our findings about the prevalence of polypharmacy in elderly, oncological, and end-of-life populations, we need to explore and address the specific consequences for patients with advanced, incurable cancer. Several of the concerns noted in our Review are of great importance for such patients. Most importantly, our findings imply that targeted action is needed to address polypharmacy in patients with cancer.

Drug–drug interactions were noted to be quite prevalent,[30–33] possibly as a result of the growing availability of targeted oral biological agents. Further study is warranted, particularly as models of concurrent palliative care emerge, wherein patients receive interventions to preserve and enhance quality of life through both cancer-directed therapies and palliative efforts simultaneously.[34] The proactive assessment and treatment of symptoms is an important part of concurrent