EDITORIAL

Appropriate pharmacotherapy at the end of life: prescribing safely and only what is needed as part of whole-person care

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by Grądalski,
see p. 659

Most patients with chronic progressive diseases are treated with several drugs to modify their life-limiting illness(es), if still possible, and to relieve any symptoms caused by it (them).[1] According to a European survey, patients with advanced cancer who are taking opioids for moderate or severe pain are given 7.8 medications on average, and approximately 45% of patients receive unnecessary or potentially unnecessary drugs.[2] Polypharmacy defined either by the use of 5 or more medications (including over-the-counter medicines) or by the inappropriateness of the prescription[3] raises risks of serious adverse effects and drug–drug interactions (DDIs).[4,5]

A recent systematic review of studies reporting clinically significant DDIs involving medications used for symptom control, other than opioids given for pain management, in adults with advanced cancer pointed to alterations in CYP450-dependent metabolism and overstimulation of serotonin receptors in the central nervous system as the main mechanisms.[4] Clinical manifestations of identified DDIs included, among others, sedation, respiratory depression, serotonin syndrome, neuroleptic malignant syndrome, delirium, seizures, ataxia, liver and kidney failure, bleeding, cardiac arrhythmias, rhabdomyolysis. Similarly, systematic reviews reporting clinically significant DDIs involving opioid analgesics used for pain management also highlighted the need to avoid polypharmacy (if possible) because of the higher risk of serious adverse effects.[5]

There is evidence of the use of many unnecessary medications in palliative care even among patients being in the final weeks of life,[6,7] many of which can lead to harms in this frailest of patient populations. Therefore, for those who will not benefit from some medications prescribed for them, the concept of deprescription has been developed.[3,8] Deprescription is defined as a systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patients' goal, current level of functioning, life expectancy, values, and preferences.[9] Appropriate deprescribing is one of the most important aspects of appropriate pharmacological management at the end of life.

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Grądalski[10] reports his findings from a cross-sectional study assessing polypharmacy, overprescribing, and the incidence of potential pharmacological errors in patients at the time of referral to single Polish center of palliative care. All patients consecutively admitted to the palliative outpatient clinic and the free-standing 42-bed hospice that predominantly provided the care for the people close to dying between August 1, 2016 and December 31, 2017 were enrolled. During the first appointment, the consultant in palliative medicine evaluated the current medications in the relation to age, prognosis, length of care, and functional capacity, and documented all inconsistencies between the patients' clinical condition, the goals of care, symptoms profile, and the medications taken. Medications were defined as unnecessary or inappropriate if the time needed to obtain a clinically meaningful benefit was longer than the remaining survival time, or the therapeutic target did not align with the preferences expressed by the patient regarding the goals of care, or the harm caused by the treatment outweighed the expected benefit, especially if the risks arose before the benefit. Medications were reviewed also based on the commonly known DDIs checklists. During the first appointment, the adjustment of the therapy, including deprescription, was initiated and

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the numbers of drugs / tablets used prior to admission compared with those prescribed during the first palliative care consultation were counted. The median number of drugs used at referral to palliative care was 7.0 (and 9.0 tablets) per day and polypharmacy (defined as ≥5 medications) was found in 78.6% of patients. In about 70% of patients, at least one inappropriately prescribed medication was found, most frequently due to unnecessary treatment in the setting of limited prognosis. Omission of key medications was also noted such as no coprescription of a laxative when opioids were prescribed (24%). Interestingly, the patients with the shortest prognosis took more medications and tablets per day on referral (median number 8.0 and 10.0, respectively) while bed-bound patients, with the shortest life expectancy, or discharged from hospital more often had one or more potentially inappropriate medication. Evaluation of the deprescription initiated during first appointment revealed that number of medications / tablets was diminished on palliative care consultation by a median of 1.0 / 2.0, while the subgroups with higher numbers of medication errors had a greater reduction in the number of medications.

All these observations from a single Polish center of palliative care are in accordance with the studies showing the high burden of unnecessary medicines at the end of life, even during the dying phase. A framework for considering the changing balance for net effects of medications (benefits and harms) as a person's life-limiting illness progresses was proposed 15 years ago.[11] Based on that, every prescriber is asked to be clear about why a medication was commenced, what is the realistically expected benefit, the time frames to that benefit, and the time frames to any likely harms were it to be ceased. This framework seeks to apply the principles of primary, secondary, and tertiary prevention to prescribers' thinking about the continued prescription of long-term medications. Many physicians seeing a patient for the first time will have difficulty establishing the therapeutic intent of many of the medications for comorbid disease. Systematically understanding the net effects of every medication prescribed, whether it is for the long-term management of comorbid disease or for symptom control, is a necessity for every person writing a prescription, dispensing the prescription, or administering the medications.[12] When measured prospectively, the immediate and short-term harms of symptom control medications have been systematically underestimated in palliative care.[13,14] Pharmacists, nurses, and doctors all have the responsibility to reduce the burden of iatrogenic harm in people with life-limiting illnesses.

Why is polypharmacy such a frequent phenomenon among palliative care patients? There are many potential reasons, such as multiple comorbidities usually treated by different specialists, according to guidelines usually recommending pleiotropic treatment for every progressive disease, that may not be necessarily applicable in patients with a short life expectancy, unrealistic expectation of patients and families (and clinicians), or the presence of side effects of the medication recognized as problems requiring more medications. Some medications that do not offer any substantial benefit (like nitrates) or are no longer clinically indicated (such as diuretics / oral hypoglycemic agents in people with massive weight loss and poor oral intake) remain on medication lists and will only cause harm late in life.

Prophylactic medications are considered for discontinuation. For example, stopping aspirin in the primary prevention rarely causes any clinical controversy. However, it does not mean that we always should stop all prophylactic medicines in every patient at his or her end of life.[15] For example, anticoagulants can be used either as primary (in immobilised people at risk of lung emboly or preventing stroke in people with atrial fibrillation at risk of ischemic stroke) or secondary (in people at risk of recurrence of above mentioned complications) prevention. Continuing both kinds of prophylaxis with anticoagulants, even in people approaching death, can help prevent a new clinical complication that could abruptly decrease quality of life (like severe breathlessness in nonfatal lung emboli or hemiplegia in nonfatal stroke). What is more, the strategy of deprescribing should not be to stop all disease-modifying medications for comorbid conditions as they can contribute substantially to maintaining quality of life. For example, angiotensin converting–enzyme inhibitors in heart failure can help prevent breathlessness by limiting pulmonary congestion in lungs. Likwise, bronchodilatators can help minimize exacerbations in people with chronic obstructive lung disease.[16,17]

One of the most important principles of medicine is not to cause harm. Palliative care should offer medical care to a person in full recognition of her or his individual needs, aims, and values. Thus, removing unnecessary medications is ethically permissible and medically indicated as it can improve quality of life, and reduce avoidable morbidity.[18,19]

Lastly, a more general reflection. Dame Cicely Saunders, one of the greatest founders of modern palliative care, developed her theory of total pain based on patients' narratives on facing the end of life. Her view was that a failure to recognize the contribution of spiritual, psychological, and social domain to the well-being of the patients may result in overwhelming suffering. We should remember that this kind of suffering experienced by a person as a whole could not be relieved solely through medications.[20]

To conclude, there is a growing number of studies demonstrating that polypharmacy is a frequent problem among patients even at the end of their life. Polypharmacy often does not assure better quality of life. On the contrary, it can lead to other symptoms / adverse events and increase the costs of treatment. Grądalski[10] showed that

polypharmacy and increased risk of drug inappropriateness affect particularly older people with a poor prognosis and poor condition, and those referred to a hospice by hospitals. There is an urgent need to introduce education within nonspecialist palliative care on appropriate pharmacotherapy for patients approaching death. Pharmacists, nurses, and doctors all share the responsibility to reduce the burden of iatrogenic harms in people with life-limiting illnesses. It is also high time to introduce into healthcare system and clinical practice attitudes which allow clinicians to recognize the key role of biopsychosocial and spiritual model of care especially for people facing end of their life.

ARTICLE INFORMATION

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CONFLICT OF INTEREST MK reports personal fees from Stada, Pfezier and Angellini, outside the submitted work; in addition, she is a head of a foundation which is supported in its educational activities by different pharmaceutical companies, outside the submitted work. DCC reports he is an unpaid member of an advisory board for Helsinn Pharmaceuticals, is a consultant to Specialised Therapeutics and Mayne Pharma, and received intellectual property payments from Mayne Pharma. PS declares no conflict of interest.

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