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EDITORIAL

Deprescribing in older people: why it matters in routine clinical practice

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Polypharmacy in older people presents a real threat to the health and welfare of older people globally, because of the close cause-and-effect relationship with inappropriate prescribing and adverse drug reactions (ADRs) and adverse drug events (ADEs). Given the phenomenon of population aging both in developed and developing countries, it is clear that the heightened risk of ADRs and ADEs from polypharmacy represents a major global public health problem.

Polypharmacy is traditionally defined (somewhat arbitrarily) as the intake of 5 or more daily drugs, with major polypharmacy usually meaning consumption of 10 or more daily drugs. The cause of polypharmacy in old age is clearly multimorbid illness, that is, more chronic medical conditions leading to more drugs being prescribed.[1] The difficulty is that the risk of ADRs or ADEs rises in parallel with increasing medication, so that the risk of an older person experiencing drug adversity of one kind or another when taking 10 daily drugs is about 100%. It is therefore in older patients' best interest to restrict the number of daily drugs they are prescribed. The difficulty for prescribers is that there is no agreed "safe limit" for the number of daily drugs. Most prescribers appreciate that it is very easy to add more drugs to the prescription of older persons with multimorbidity; it is much more difficult to remove drugs (or "deprescribe") from their prescription list.

In the present issue of this journal, Bień and Bień-Barkowska[2] retrospectively examine the changes in the prescriptions of 301 older people from admission to discharge from a specialist geriatric medicine unit in one hospital in Białystok, Poland. The mean age of the patients was 82.4 years and two-thirds were female, as expected for a geriatric hospital cohort such as this. They found a significant reduction in the number of drugs prescribed per patient from admission (average 7.53 drugs per patient) to discharge (average 6.25 drugs per patient) and that 57% of the patients experienced a reduction in medication. The patients who experienced the most deprescribing were those who had ADRs, recent falls, and diabetic patients with episodes of hypoglycemia. From a wide range of predictive factors, the number of drugs on admission, the number of comorbid conditions, age, solitary living status, and incident ADRs were the factors that in a multiple logistic regression model accounted for the significant deprescribing in these patients. Low body mass index also had a positive influence: the lower the BMI, the greater the degree of deprescribing by the attending physicians. The authors conclude that in-patient specialist geriatric assessment achieved significant deprescribing. Because of the retrospective nature of the study, it was not possible to determine what (if any) effect the deprescribing had on patients' cognition or physical function or quality of life.

The findings of Bień and Bień-Barkowska[2] may not be surprising. Specialist geriatricians are trained to examine multimorbid older patients' medication lists carefully, given that polypharmacy engenders inappropriate prescribing and ADRs or ADEs.[3] Deprescribing in specialist geriatric medical units arises through careful medication review, which has always been an integral part of comprehensive geriatric assessment, the cornerstone of specialist geriatric medical practice. Careful medication review and optimization in the context of comprehensive geriatric assessment (or "geriatric evaluation and management" in the study by Bień and Bień-Barkowska) in turn depends on specialist training and wide knowledge of drug-related problems in old age as well as the various and often nonspecific manifestations of ADRs and ADEs in older people. Geriatricians will also be keenly aware of "prescribing cascades", that is inappropriate prescribing of new medication for presenting symptoms in multimorbid older people that are misinterpreted as symptoms of new medical conditions in these patients. For example, an older person with

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dementia who receives a neuroleptic antipsychotic for night-time agitation develops parkinsonism. The patient is referred to another physician regarding the parkinsonism and is subsequently commenced on levodopa. The patient becomes hypotensive on levodopa and subsequently suffers a fracture injury due to a syncopal fall relating to inappropriately prescribed levodopa.

Several explicit potentially inappropriate medication (PIM) lists exist in the literature that were designed specifically for the growing older person population. The most commonly cited among the explicit PIM lists are Beers criteria (now in its 5th iteration[4]) and STOPP criteria (now in its 2nd iteration[5]). There are also several implicit PIM lists designed for the geriatric population, most notably ACOVE criteria and the Medication Appropriateness Index. Although implicit PIM criteria sets are undoubtedly useful as research tools, none has entered routine clinical practice as a deprescribing tool, probably because they are too time-consuming to deploy. In contrast, Beers criteria and STOPP criteria are now used in several countries as routine medication review tools. Beers criteria have been endorsed by the American Geriatrics Society for several years. STOPP criteria are recommended in the recent UK National Institute for Clinical Excellence guidelines for structured medication review in older people with polypharmacy as a practical means of deprescribing (https://www.nice.org.uk/guidance/ng5).

Despite the multiplicity of explicit deprescribing criteria sets, few randomized clinical trials (RCTs) exist in which deprescribing criteria have been used as an intervention and compared with standard pharmaceutical care. Only STOPP criteria have been tested by an RCT; currently, there are 3 RCTs involving STOPP in the hospital setting and 1 RCT in a large nursing home facility. All 4 RCTs are single-center and none was double-blinded. Two of these RCTs took place in our center; the primary outcomes in these RCTs were medication appropriateness and incident ADRs, respectively.[6,7] The total average number of drugs per patient was not significantly reduced in the intervention groups compared with controls in these 2 trials, most probably because whatever deprescribing was achieved through application of STOPP criteria was likely counterbalanced by addition of new medications through application of START criteria. In the RCT reported by Frankenthal et al,[8] undertaken in 359 frail nursing home residents in Israel, application of STOPP/START criteria did achieve significant reduction in the number of daily drugs in the intervention cohort (mean [SD], 8.1 [3.2]) compared with the control cohort (mean [SD], 9.0 [3.3]). Although the proportion of intervention patients with PIMs at hospital discharge was significantly less than controls in the RCT by Dalleur et al,[9] the impact of STOPP/START criteria on the average number of daily medications in the intervention cohort was not documented.

The challenge now facing researchers in this area is how to implement PIM criteria in the routine clinical care of older patients with polypharmacy. Researchers generally agree that meeting this challenge depends on sufficiently robust software to apply PIM criteria and to present the relevant PIM criteria that apply to individual patients to their physicians accurately and quickly. To this end, 2 important RCTs have recently been funded by the European Commission: SENATOR[10] and OPERAM.[11] The software interventions tested in these trials are based primarily on STOPP/START version 2 criteria.[5] The SENATOR trial has been completed this year and OPERAM is expected to finish randomization later in 2018. SENATOR has randomized over 1500 patients to standard pharmaceutical or once-off software-driven application of STOPP/START criteria as well as drug-drug and drug-disease interactions. OPERAM is expected to randomize over 1800 patients in a cluster randomized design to standard pharmaceutical care or single-time point application of STOPP/START criteria using a different software engine. These multicenter trials will determine whether software-driven deprescribing reduces ADRs (SENATOR) and drug-related unscheduled hospitalizations (OPERAM).

Are there any practical guidelines to help physicians deprescribe drugs effectively and safely, specifically in very frail older multimorbid patients with poor survival prognosis who represent a very important and growing population of older people globally? In these patients, the focus of pharmacotherapy should be on symptom relief as distinct from long-term primary or secondary disease prevention. In this context, drugs that would be generally appropriate (eg, statins, calcium supplements) become potentially futile. Scott et al[12] have recently proposed a protocol for assessing individual medications in older people burdened by polypharmacy. A follow-up small-scale open-label study of 50 older multimorbid patients (mean age, 82.5 years) by the same group showed that a median number of 10 medications at hospital admission could be reduced to a median of 7 medications at discharge, with less than 2% of deprescribed drugs needing to be represcribed at follow-up (median, 78 days).[13] A small-scale RCT involving 47 older intervention patients and 48 control patients in 4 nursing homes in Western Australia using the same deprescribing algorithm showed a mean (SD) reduction of 1.9 (4.1) drugs per patient compared with a slight mean (SD) increase of +0.1 (3.5) drugs in the control group at 1-year follow-up.[14] In contrast to the implicit deprescribing algorithm of Scott et al[12] are the recently published 27 explicit deprescribing STOPPFrail criteria.[15] An RCT involving STOPPFrail criteria as the intervention compared with standard pharmaceutical care in frail, multimorbid older people with poor survival prognosis is being conducted in our center. While the results of all these clinical trials are awaited, physicians should nevertheless

seek to deprescribe medication in frail multimorbid older people.

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