Polypharmacy and the Elderly

Reducing adverse drug events in the elderly can be achieved by making precise diagnoses and by using treatment based on specific literature. When extrapolating from studies of younger patients, physicians should consider the physiology of aging, as well as ethical issues relevant to the elderly.

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Problems related to polypharmacy are most often associated with the elderly. It appears, however, that the number of medications prescribed *per se*, has only a weak influence on the health of the elderly. The phenomena of adverse drug events are found more frequently in the older population. Such terms as “inappropriate prescribing” or “potentially inappropriate prescriptions” and “adverse reactions,” versus “adverse drug events” (which includes adverse
reactions, difficulties of compliance and errors) are now used more frequently, describing more relevant concerns about the quality of the medications used by the elderly population.

Data concerned with polypharmacy and adverse drug events are variable. Among the limitations noted are unrecognized cases, and difficulties in determining a cause-and-effect relationship between the medication(s) and the multiple conditions of the elderly. Limitations also include lists of medications to be avoided by older individuals. These are not consistent from one study to another and do not take into consideration the specific medical conditions of each patient.

Adverse drug events can be the cause of falls, fractures, cognitive dysfunction, postural hypotension, electrolyte disorders and cardiac failure and are responsible for up to 23% of hospital admissions in the elderly.1

### The Number of Drugs

Many drugs are associated with a greater potential for drug interactions and side effects. In a recent study conducted in southern Quebec, Allard demonstrated that individuals over the age of 75 took an average of six different medications.2 Drug interactions are responsible for 15% to 20% of adverse drug reactions,3 and, according to some researchers, the incidence of adverse drug reactions increases exponentially with the number of medications used by an individual.4

According to many studies, the rate of adverse events is related to the number of medications. For example, 4% of adverse events per year are reported when less than five drugs are prescribed, however this rises to 54% if more than five medications are prescribed.3

Conversely, in a study of hospitalized patients, Bates found an insignificant association

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**Summary**

**Polypharmacy in the Elderly**

The physiology of normal aging and pharmacokinetic (i.e., renal and hepatic metabolism, distribution volume) and pharmacodynamic (i.e., receptor site response) changes explain a portion of the adverse drug reactions observed in the elderly. Nevertheless, the majority of these reactions are probably explained by the comorbidity and polypathology often associated with aging.

Studies have shown poor use of medications in the older population, where only a small proportion of patients take the recommended medication, or use low, non-recommended doses or undertreatment. This results in poor control of medical conditions.

Limiting the number of prescriptions will help patients remain compliant. Other strategies include synchronizing drugs, simplifying the medication schedule, keeping PRN medications to a minimum, prescribing slow-release drugs, being attentive to the size of caplets and using syrups, cellophane packaged medication and pill boxes.

Weaning patients from certain drugs can be difficult. One must be prudent with all neurotropics, anticonvulsants, opioids, benzodiazepines, antidepressants and antihypertensive agents.
between the number of drugs that patients received and the presence of adverse drug reactions.\textsuperscript{5} Therefore, even the relationship between multiple medication use and adverse events is a debatable question. The number of drugs would then only have a link to adverse events by being proof of the severity of illness.

Age

Adverse drug reactions are more frequent in the older population (2% to 10% identified in a younger group \textit{versus} 20% to 25% in an elderly population).\textsuperscript{6} A relationship between increasing age and an increased number of medications is clearly described, which again, seems to be explained by the prevalence of chronic conditions seen in the elderly population. The direct effects of age on the incidence of adverse drug events is controversial and, according to Bates, even disappear when polypathology and comorbidity are considered. Age appears to be responsible for more hospital admissions due to adverse drug reactions.\textsuperscript{7} Adverse drug events lead to 3% to 23% of hospital admissions in the older population, and 6% to 10% are reported more frequently in research studies.\textsuperscript{1,6}

Physiology or Pathology

The physiology of normal aging and pharmacokinetic (\textit{i.e.}, renal and hepatic metabolism, distribution

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### Table 1

**Pharmacokinetic Changes in Relation to Aging**

- **Absorption:** Few changes except for some secondary achlorhydria.
- **Distribution:** Decrease of distribution volume of hydrosoluble drugs, increase of distribution volume of liposoluble drugs.
- **Hepatic metabolism:** Decrease of hepatic mass and blood flow 30% to 40% with reduction in metabolism particularly on first-pass. Decrease of phase I metabolism, oxidation, reduction, hydrolysis, stability of phase II.
- **Renal excretion:**
  
  Cockcroft-Gault formula: Creatinine clearance = \((140—\text{age}) \times \text{weight (kg)} \times 1.23\)
  
  \[
  \text{Cockcroft-Gault formula: Creatinine clearance} = \frac{(140—\text{age}) \times \text{weight (kg)}}{1.23}
  \]
  
  Baltimore study on aging demonstrated that clearance is under-estimated nearly in 1/3 of elderly.
- **Half-life:** Function of distribution volume and clearance \(t \frac{1}{2} = 0.693 \times \text{Vd/Cl}\), especially pertinent for psychotropes (\textit{e.g.}, flurazepam 74 \textit{versus} 160 hours in the elderly).

### Table 2

**Pharmacodynamic Changes in Relation to Aging**

- **Diminished response to beta agonists and beta blockers.**
- **Increased response to opiates and benzodiazepines, possibly warfarin.**
volume) and pharmacodynamic (i.e., receptor site response) changes explain a portion of the adverse reactions observed in the elderly. Nevertheless, the majority of these reactions are probably explained by the comorbidity and polypathology often associated with aging (Table 1) (Table 2).

### Definition of Potentially Inappropriate Prescriptions

Different authors and groups have proposed lists of potentially inappropriate prescriptions (PIP). The contents of these lists, however, are often debated. In 1990, up to 52% of elderly persons in Quebec experienced one or more situations of what is called high-risk prescribing. PIP lists and other similar nomenclatures for lists of potentially hazardous drugs for the elderly define, more or less precisely, classes or specific drugs. They do not consider particular medical conditions, they show a variety of opinions between authors and they are subject to changes in medical literature updates.

PIP lists, above all, do not consider the necessity of appropriate treatments related to particular, and often less frequent, diagnoses. For example, alpha blockers, tricyclic antidepressants and intermediate-acting benzodiazepines still have a place in the treatment of the elderly. Nortriptyline is an appropriate drug for certain cases of incontinence and depression in patients with weight loss. Centrally-acting alpha blockers are recommended in the treatment of orthostatic hypotensions with dysautonomia, and benzodiazepines are used to treat anxiety disorders and certain situations of drug withdrawal. A drug frequently cited on these lists can sometimes be seen in a patient receiving excellent medical supervision.

Despite these restrictions, the use of long-acting benzodiazepines, some opiates, nonsteroidal anti-inflammatory drugs (NSAIDs), and prescribing more than one drug in the same class are, in most cases, not recommended for elderly people (Table 3).

### Treatment

Current literature concerned with pharmacological interventions and the elderly addresses the undertreatment of this population, and derives from a per-
spective of available data taken from controlled randomized studies. Studies have shown poor use of medications in the older population where only a small proportion of patients take the recommended medication, or they use low, non-recommended doses, or undertreatment, resulting in poor control of medical conditions (e.g., cases of hypertension in patients, even while they are being treated). This literature becomes more substantive where studies have demonstrated a reduction of mortality and morbidity, particularly in the elderly. For example, the use of beta blockers in post-infarction patients over the age of 75 and 85 was 14% and 44% lower, as compared to those aged 65 to 74. The use of angiotensin-converting enzymes (ACE) inhibitors in cardiac failure has been reported at 31%. A lower use of opiates in cancer patients and undertreatment of hypertension is also described. Rochon stated that “the fewer-the-better approach to drug therapy in the elderly does not work when drugs with proven efficacy in elderly patients are available.”

**Absence of Literature**

Only a small portion of evidence-based medical literature has shown interest in the population over the age of 75 years, however, a high percentage of medications are prescribed for this particular age group. Studies on primary prevention of hyperlipemia have excluded people over 65 years of age, and large scale studies in secondary prevention excluded people over the age of 75. In Quebec, however, nearly 80% of hypolypemic medications are administrated to people over the age of 65. Patients suffering from multiple chronic conditions, which are often encountered in family practice, are excluded from these studies. Finally, literature that places a particular emphasis on mortality without giving a priority to morbidity is less relevant for the very old with a poor prognosis.

Polypharmacy is less of a problem in geriatric medicine than is the use of certain classes of medication, or, above all, the inadequate use of certain medications in specific clinical situations.

Many preventable problems are encountered where non-medical treatments could have been used (e.g., behavioral, surgical).

All too often, in the same patient, polypharmacy unrelated to a specific diagnosis coexists with an underuse of clinically indicated beneficial medications.

**Prescribing Medication For The Elderly**

When prescribing a new medication, caution is always needed. Being knowledgeable of the limitations discussed earlier, it is preferable to keep the numbers of prescriptions to a minimum, if possible. It is important to remember the conditions that frequently present in the elderly, such as renal failure. Other variables to keep in mind include the low weight of many older individuals and the changes in distribution volume and organ receptors.

Many mistakes occur, causing adverse events, simply because of a lack of knowledge concerning the medications already being taken by a patient (Table 4).
Start drugs cautiously. Purely symptomatic treatments are to be avoided. Avoid NSAIDs, diuretics, digoxin, antidepressants and cholinesterase inhibitors, unless there has been a formal diagnosis (Table 5). A cautious approach is encouraged with new medications, such as selective serotonin reuptake inhibitors SSRIs, cyclo-oxygenase-2 (COX-2) inhibitors and NSAIDs. The side effects of these medications are initially described as benign, but then are used on a large scale without valid data from studies conducted, specifically in elderly patients, with comorbid conditions. Overmedicating should be avoided, for example, when using neuroleptics, including new generation drugs, such as risperidone followed by levodopa for the treatment of secondary parkinsonism. One must be on the alert for side effects specific to the elderly, such as delirium, orthostatic hypotension, falls, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and anorexia.

Compliance. Specific compliance problems are encountered when treating the elderly. The total number of concurrently prescribed medications is in inverse ratio to medication compliance. Limiting the number of prescriptions will help patients remain compliant. Other strategies include synchronizing drugs, simplifying the medication schedule, keeping PRN medications to a minimum, prescribing slow-release drugs, being attentive to the size of caplets, and using syrups, cellophane packaged medication and pill boxes. It is also beneficial to recommend frequent deliver-
ies by the pharmacy, instruct the caregiver and consider using new electronic devices, such as clocks. Be aware of cognitive impairment. Take a realistic approach and discuss this at great length with your patients.

Weaning. Weaning patients from certain drugs can be difficult (Table 6). One must be prudent with all neurotropics, anticonvulsants, opioids, benzodiazepines, antidepressants and antihypertensive agents. Special attention must be given to neuroleptics and benzodiazepines (e.g., using substitutions, a different half-life, and using only one drug per class). In a study of 134 patients, Graves withdrew a minimum of one drug in 60% of patients, with undesirable reactions observed in 26% of patients, and 36% of the latter needing medical consultation.13 Higher percentages were reported when more drugs were stopped and when beta blockers and benzodiazepines were weaned. This study acts as a reminder that close follow-up is mandatory. Studies regarding approaches to inappropriate prescriptions demonstrate the limitations of consultative efforts.2 To reduce adverse events and polypharmacy, the patient’s own family doctor’s motivation seems necessary.

Table 6
Weaning

| Many specific situations for weaning patients and stopping inappropriate medications are found. Among them, the following examples are frequently seen: |
| - Over-treated diastolic cardiac failure (or treated as systolic). |
| - Convulsions treated as epilepsy. |
| - Oral hypoglycemic agents are no longer required after starting insulin in long-term care, or in a regimen that is not made simpler by such care. |
| - “Forgotten” steroids in stabilized situations (COPD, rheumatoid arthritis). |
| - Lipid-lowering agents as a primary prevention in the very old. |
| - Theophylline prescribed as monotherapy for obscure pulmonary conditions. |
| - Palliative situations where primary and secondary prevention medications are still administered (often with insufficient treatment of pain). |
| - Newly diagnosed probable adverse events (e.g., delirium, falls, orthostatic hypotension, SIADH). |
| - Physiological and pathological changes in a patient receiving a drug for a number of years; development of renal failure, dementia. Do not allow the use of inappropriate drugs simply because they previously were tolerated by the patient. |

COPD=chronic obstructive pulmonary disease; SIADH=syndrome of inappropriate secretion of antidiuretic hormone

Summary
Few studies have demonstrated current medication efficacy for patients over the age of 75. Because of age or associated conditions, the
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The elderly are often systematically excluded from research studies.

A large portion of prescriptions, therefore, have a limited evidence base, in spite of the fact that the elderly have a particular physiology and numerous conditions that interfere with drug therapy.

The elderly also represent a large portion of those who use prescription medication. Although they account for about 15% of the population, they receive about 40% of all medications.15 Not surprisingly, as a result, they suffer from the majority of adverse events. In addition, they continue to be undertreated for many well known conditions.

Reducing adverse drug events in the elderly can be achieved by making precise diagnoses and by treating medical conditions according to recommendations strictly based on the specific literature. When extrapolating from studies of younger patients, physicians should consider the physiology of aging, as well as ethical issues relevant to the elderly. Simply reducing the number of multiple medications has no value, nor does the withdrawal of all potentially inappropriate drugs. Proposed lists of hazardous medication have limitations. Respecting the individual needs of individual patients is the preferred approach.14

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References: