

In Focus

Drugs in the elderly with chronic kidney disease: beware of potentially inappropriate medications

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In this issue of *NDT*, Kondo *et al.* [1] address a clinically relevant topic, which has been rarely studied so far in the chronic kidney disease (CKD) population: the use of potentially inappropriate medications (PIMs). In particular, they studied the frail subset of elderly haemodialysis subjects, who are more exposed to the potentially severe adverse effects of medication errors, especially when multiple therapies are prescribed.

The study of Kondo refers to 1367 elderly patients with a median age of 72 years and a range of 65–98 years [1], reflecting the European prevalent dialysis population, including many old or very old patients.

Elderly people are at higher risk of side effects even for a single drug for many pharmacokinetic reasons. A healthy 40-year-old subject has a total body water content of 55% of body weight (women) or 60% (men), progressively declining to 50% in men and even less in women by the age of 75 years and more [2]. Consequently, the same dose of a drug given to a healthy adult, in a very old person will reach higher blood concentrations, thus increasing the risk of side effects. In addition, the elimination of hydro-soluble drugs through the kidney is reduced in the elderly due to decreased renal mass [3], cortical blood flow [4] and glomerular filtration rate [5]. Although these considerations do not apply to the patients studied by Kondo, all on haemodialysis and therefore functionally anephric, they must be considered when treating elderly persons with reduced or even apparently normal kidney function.

On the contrary, the fat-soluble drugs have a greater volume of distribution in older people due to a higher percentage of body fat. The liver plays a major role in fat-soluble drug clearance and ageing has been reported to reduce hepatic blood flow and the clearance capacity, particularly for those drugs that undergo oxidation by the microsomal cytochrome

P450 isoform CYP3A-dependent monooxygenase system [6]. Moreover, we do not have any formulae to measure liver function like those available for kidney function.

Another point to be considered when examining the potential risk of adverse effects of drugs is that the elderly are often malnourished or at risk of malnutrition: when their serum albumin concentration is reduced, the capacity to bind drugs is also reduced, increasing their free fraction. Consequently, more drug becomes available to reach receptors, thus increasing the pharmacologic effect in an elderly individual.

Loss of attention and memory of elderly people not adequately assisted by partners or caregivers who give a further contribution to increase the risk of under but also over ingestion of drugs.

An increased risk of adverse drug reactions (ADRs) in the elderly also derives from two other factors: the exclusion of elderly patients from large randomized controlled trials testing new medications and the high number of drugs prescribed to the elderly, which can be difficult to discontinue for the presence of multiple comorbidities. Therefore, the pharmacology of many medications has not been studied sufficiently in elderly adults and, not surprisingly, the risk of developing an ADR is estimated to be ~20% and ADRs requiring hospitalization is ~10.7% for elderly patients, when compared with 5.3% for the general population [7]. Table 1 shows the main classes of drugs, which most commonly determine adverse events. Comparisons should be approached with caution, due to different classification criteria used by the different authors [8–10]. In fact, the ranked lists of the individual groups of drugs are quite different: heparin, insulin/hypoglycaemic agents, warfarin and digoxin [11]; cardio-tonic glycosides, adrenal corticosteroids, anti-neoplastic agents, anticoagulants and analgesics [9]; loop diuretics, opioids, steroids, antibiotics,

Table 1. Drugs most likely determining adverse events

	Ref. [8]	Ref. [9]	Ref. [14]
	Percentage of all ADRs	Percentage of all ADRs	Percentage of hospitalizations due to ADR
Analgesics, antipyretics and anti-rheumatics	8.0	13.3	NR
Endocrine agents	11.0	14.1	22.8
Cardiovascular drugs	21.6	11.5	9.8
Oral anticoagulants	7.4	10.3	42.3
Anti-neoplastic and immunosuppressive	8.1	10.1	2.9
Antibiotics	4.7	6.3	3.8
Central nervous system drugs	7.5	4.3	9.7

ADR, adverse drug reaction; NR, not reported.

oral anticoagulants and beta-agonist inhaled [12], non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, anticoagulants, angiotensin-converting-enzyme (ACE) inhibitors/angiotensin-receptor blockers, opiates and digoxin [13] and oral anticoagulants, insulin, anti-platelets, oral hypoglycaemic agents and opioids [9].

The most common causes of ADR in elderly patients are the unwanted interactions among the many medications taken, due to the high number of diseases or co-morbidities, such as ischaemic heart disease, peripheral and cerebral vascular disease and diabetes. Various studies have documented a direct correlation between the number of medications and the risk of an ADR. The potential drug interaction risks when patients are taking 2–3, 4–5 and 6–7 medications are 39, 89 and 100%, respectively [14], also as a consequence of pharmacokinetic and pharmacodynamic changes. Thus, elderly patients are inevitably at risk of numerous ADR [7, 15–17].

The most common negative drug interactions reported in the literature are the following: hyperkalaemia due to ACE inhibitors/angiotensin-receptor blockers and potassium-sparing diuretics or sulfamethoxazole-trimethoprim or quinolones, hypotension and shock with calcium-channel blockers plus macrolide antibiotics, increase digoxin toxicity with macrolide antibiotics lithium toxicity due to association with ACE inhibitors or diuretics or NSAIDs [18–20].

Because of the difficulties in defining the correct dose of drugs for elderly patients, inadequate interventions of the physician can result in inappropriate dosing, duration of therapy, lack of attention to other prescribed drugs, leading to clinically significant ADR, drug–drug and drug–disease interactions [21].

Moreover, in elderly CKD and haemodialysis patients, the presence of many co-morbidities, each of them requiring specific therapies, leads to the possible prescription of a high number of drugs. Some of them could be indicated for one co-morbidity but contraindicated in the presence of another one. Thus, the composition of a list of PIMs is complex, but necessary to avoid the risk of many ADRs. Moreover, haemodialysis patients have the big problem of a quite different pharmacokinetics due to the lack of the excretory renal function and the intermittent clearing effect of dialysis.

Drugs are considered appropriate if their expected benefits outweigh the potential risks. The elderly, and even more elderly patients affected by CKD, are particularly prone to drug-related adverse events. Thus, lists of drugs have been proposed for avoiding medications whose risks outweigh benefits among the elderly. These drugs, also defined as ‘medications with no clear evidence-based indication, and which carry a substantially higher risk of adverse side-effects or are not cost-effective’, correspond to the term ‘potentially inappropriate medication’ [22].

The most commonly used list derives from the Beers criteria, originally developed by geriatrician Mark Beers [23, 24], which have been recently updated and revised by the American Geriatrics Society [25]. Fifty-three medications or medication classes encompass the final updated criteria divided into three categories: PIM and drug classes to avoid in older adults, PIM and drug classes to avoid in older adults with certain diseases and syndromes that the drugs listed can exacerbate and finally medications to be used with caution in older adults.

In Europe, the STOPP (Screening Tool of Older People’s potentially inappropriate Prescriptions) [22, 26] and START (Screening Tool to Alert doctors to the Right Treatment) criteria [27] have been developed, because of lack of significant and consistent associations between Beers criteria for PIMs and adverse drug events. STOPP and START criteria appear to be more appropriate in the clinical setting, as they address not only potentially inappropriate drugs, but also under-treatment due to lack of prescribing necessary medications.

STOPP comprises 65 clinically significant criteria for potentially inappropriate prescribing in elderly people [22, 26]. Each criterion is accompanied by a concise explanation as to why the prescribing practice is potentially inappropriate. START consists of 22 evidence-based prescribing indicators for commonly encountered diseases in older people.

Kondo *et al.* [1] applied the Beers criteria to elderly haemodialysis patients, focusing on the three most frequently prescribed PIMs: H₂ blockers, anti-platelet agents and α -blockers, and tried to determine which characteristics of either the patient or the facility were associated with PIM prescriptions. Teaching hospitals and facilities conducting multidisciplinary rounds were associated with a lower prevalence of PIM. While the initiative of Kondo *et al.* should be applauded, we feel that their findings are just the tip of the iceberg, because many drugs are potentially inappropriate in dialysis patients, but they are not listed in the Beers criteria. Several drugs may be more problematic in dialysis patients for one or more of the following reasons: inability to be excreted by the kidneys (either as basal drug or its metabolites); higher probability of clinically relevant drug interactions; adverse reactions more common in patients in renal failure and renal failure affects drugs transport, altering their bioavailability [28]. In CKD patients, one area that deserves special attention is pain management, as both under-treatment and misuse of drugs are frequent [29, 30].

In the cohort studied by Kondo *et al.*, selected PIMs were prescribed to more than half of the patients, indicating the need for further investigations on a larger number of drugs in elderly people receiving haemodialysis. The same is probably

Table 2. PIMs in haemodialysis: recommendations for the nephrologist

Drug handling in CKD and dialysis patients is an underestimated issue among physicians. There is a high risk of prescribing PIMs. Practicing nephrologists should be familiar with the concept of PIM. Kondo *et al.* highlighted some of them (H2 blockers, anti-platelet agents and α -blockers), but the peculiar pharmacokinetic and pharmacodynamics features of drugs in dialysis patients may widen the number of problematic drugs in this patient population. Analgesic drugs are a typical example of a class with important prescribing limitations and side effects for some of them. STOPP [22, 26] and START [27] criteria, which could be adapted to the dialysis population, should be considered by the practicing nephrologist, as they address not only potentially inappropriate drugs, but also potential under-treatment due to lack of prescribing necessary medications.

true for patients with CKD not on dialysis. Jones and Bhandari [31] found that in elderly patients with CKD (mean estimated glomerular filtration rate 17.2 mL/min/1.73 m²; range 4–44), prevalence of PIM according to the Beers criteria was 13%, lower than that reported in dialysis patients, but still relevant. Some of the consequences of PIM can be severe, such as drug-induced falls.

The main limitations of the study by Kondo *et al.* are the lack of data about the association of PIM and clinical outcomes, as well as the lack of generalizability since all patients were Japanese and were followed in selected centres participating to the Dialysis Outcome Practice Pattern Study in Japan.

In the USA, ADRs result in over 700 000 visits to hospital emergency rooms and 120 000 hospitalizations each year [32]. Costs of ambulatory (non-hospital settings) ADR are also significant, and at least 40% of them may be preventable [33]. The seriousness of ADR-related public health problems led the Centers for Disease Control and Prevention to establish a medication safety programme (<http://www.cdc.gov/medicationsafety/>). In elderly dialysis patients, ADRs and the use of PIMs might be an even greater problem. In this respect, we highlight some practical considerations in Table 2.

In conclusion, we strongly support the notion that more studies are needed on the problem of PIMS in dialysis patients, especially in the elderly. As many adverse drug events can be prevented, it could be extremely useful to develop specific PIM criteria for dialysis patients, identifying those medications that could be withdrawn, thus reducing the pill burden and, at the same time, increasing the safety of our patients.

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